

# **Cognitive decline, dementia and air pollution**

## **A report by the Committee on the Medical Effects of Air Pollutants**

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## Foreword

It is estimated that 2 in 10 people over the age of 65 have mild cognitive impairment. Although the mild form of this condition often has little effect on daily life, 5 to 10% of people with it will develop dementia – one of the greatest, if not the greatest, global challenge for health and social care in the 21st century. Recognition that air pollution might accelerate the decline in cognitive function and contribute to the development of dementia came as a surprise when such an association was first postulated. However, in that both (a) the risk of dementia and cognitive decline and (b) long-term exposure to air pollution increases with age, such a link becomes more feasible. Following initial findings that poor air quality could have neurodegenerative effects, a huge amount of research has been undertaken to confirm earlier observations and understand the underlying causal mechanisms. This has by no means been a trivial exercise; for the health effects under discussion herein to ensue, a detrimental process must begin, eliciting alterations in the respiratory system that subsequently lead to harmful changes in the brain.

Gathering and assessing the various strands of evidence to produce this report was both challenging and rewarding. New avenues of thought were required to probe the possibilities of direct and/or indirect effects of particulate pollution on a delicate organ, well shielded by the blood-brain barrier. Evidence of a contribution by reactive gaseous pollutants, which themselves cannot possibly reach the brain, provided insight to a chain of reactions that may ultimately explain a causal link.

Clearly, an understanding of the magnitude of the effect of air pollution on neurodegenerative conditions is critical in terms of contributing to public health and this report is a key step in beginning the process of determining this information. Since the literature review exercise was completed for this work, it is pertinent that subsequently published evidence, within an ever increasingly literature base, both adds to and reinforces the views of COMEAP that are laid out in this report.

The contribution of this report to our understanding of the effects of air pollution on mental ability and dementia is a culmination of an immense amount of work conducted over several years. This coincided with other unprecedented challenges. Several Committee members and the Secretariat needed to focus on the ongoing coronavirus (COVID-19) pandemic and the increasing threat of climate change. Committee activity was also called upon to address other time-critical requests for advice as government prepared to introduce the new Environment Act within which air quality issues played a key part.

A working group under the direction of Bob Maynard undertook the majority of the work in the report. Given the extensive effort, maintained over several years, I am immensely indebted to Bob, not least for his continued and dedicated guidance post retirement. Bob was ably supported by Members: Jonathan Grigg and Gavin Shaddick, and co-opted members: Roxana

Carare, Nick Fox, Seth Love and Ian Mudway. Juana Maria Delgado-Saborit and Valentina Guercio also made substantial and valuable contributions. I am deeply grateful to all these individuals, to the Secretariat and other members of COMEAP who contributed their time so generously to bring this report to fruition.

Professor Frank Kelly

Chairman of the Committee on the Medical Effects of Air Pollutants

## Acknowledgements

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## Lay summary

Dementia is an umbrella term for a range of conditions that affect how the brain works, reducing the ability to remember, think and reason. It mainly affects older people, both men and women, and gets worse over time. A number of health and lifestyle factors, such as high blood pressure and smoking, are known to increase the risk of developing dementia. In recent years, there has been growing interest in the possibility that exposure to outdoor air pollution could increase the risk of dementia.

We have reviewed nearly 70 studies in human populations (epidemiological studies) which have examined the possible link between air pollutants and effects on mental ability and dementia. We think it is likely that air pollution can contribute to a decline in mental ability and dementia in older people. It is known that air pollution, particularly small particle pollution, can affect the heart and the circulatory system, including circulation to the brain. These effects are linked to a form of dementia (vascular dementia) caused by damage to the blood vessels in the brain. Therefore, we think it likely that air pollution contributes to mental decline and dementia caused by effects on the blood vessels.

Experimental studies suggest that air pollution might also stimulate the immune cells in the brain, which can then damage nerve cells. It is not clear whether this effect is important at the levels of pollution which occur in the UK today. It is also likely that some very small air pollution particles can enter the brain, and may cause direct damage. However, based on the current evidence, it does not seem likely that this is an important mechanism for the development of dementia.

We have not made recommendations of how to quantify the effects of air pollution on dementia. This is because we do not think that it is possible to combine the results of the currently available studies in an appropriate way, to produce a summary estimate of the relationships between pollutants and dementia. We have made recommendations for further research which we think would help develop the evidence on this important topic.

## Executive summary

The Committee on the Medical Effects of Air Pollutants (COMEAP) established a sub-group in 2017 to examine evidence linking exposure to air pollutants with cognitive decline and dementia. The terms of reference of the subgroup and its membership are set out in [Appendix 1](#) and [Appendix 3](#).

We have undertaken a review of the relevant epidemiological evidence and have also examined, more briefly, a number of aspects of the evidence related to possible mechanisms by which ambient air pollutants could cause, or contribute to, these effects.

The epidemiological evidence linking exposure to air pollutants with effects on the brain which manifest themselves as effects on cognition and the development of dementia has developed appreciably over the past 15 to 20 years. We have concluded that the evidence is now suggestive of an association between ambient air pollutants and an acceleration of the decline in cognitive function often associated with ageing, and with the risk of developing dementia.

There are a number of plausible biological mechanisms by which air pollutants could cause effects on the brain leading to accelerated cognitive decline and dementia. Some of these have been demonstrated in experimental studies. We think there is a strong case for the effects of air pollutants on the cardiovascular system having a secondary effect on the brain. COMEAP has already concluded that long-term exposure to air pollutants damages the cardiovascular system (COMEAP 2006, 2018) and we think it likely that such effects have an effect on the blood supply to the brain. That such an effect might well lead to damage to the brain seems, to us, likely. We therefore regard the association between exposure to air pollutants and effects on cognitive decline and dementia as likely to be causal with respect to this mechanism.

A number of mechanisms have been suggested by which air pollutants could have direct effects on the brain. These include the translocation of small particles from the lung to the blood stream and thence to the brain. The evidence suggests that a small proportion of very small particles that are inhaled can enter the brain, both from the blood and via the olfactory nerves leading from the nasal passages to the olfactory bulbs. What is much less clear is whether exposure to ambient concentrations of particulate material results in sufficient translocation to produce damage to the brain. Our study of the literature has suggested that particles which enter the brain are cleared from the brain only slowly, if at all. This is clearly a point in favour of the suggestion that particulate material which does enter the brain might produce detrimental effects. Animal and in vitro studies of ultrafine particulate material, diesel engine exhaust or ozone have all shown effects on the brain or brain cells. The mechanisms involved include the generation and release of free radicals within the brain and the induction of an inflammatory response; these 2 mechanisms seem likely to be linked. The experimental studies generally used exposure to higher than ambient concentrations and were conducted over short time periods, so it is not clear how informative they might be about effects in human populations

chronically exposed to lower concentrations. Nonetheless, they indicate that a number of common pollutants may affect brain function.

Our confidence in the likely causality of the association between exposure to air pollutants and effects on cognition as a result of effects on the cardiovascular system led us to consider whether the evidence was sufficient to allow quantification of the effect. We regard the current evidence base as inadequate for direct quantification of the effects of air pollutants on cognitive decline or dementia. This is partly because the available epidemiological studies are too heterogeneous to be suitable to allow meta-analysis to be used to derive a summary effects estimate.

Nonetheless, we considered whether the evidence base is sufficiently strong to allow a quantitative estimate to answer the question:

“If there is an effect, and if the effect were of a size predicted by the currently available evidence, would it make an important difference to a cost-benefit assessment of policies designed to reduce levels of air pollutants?”

We think there is a case for such an approach but point out that further work to identify a suitable coefficient would be necessary before it could be undertaken. Anyone intending to include such a quantification in an assessment should be aware of the uncertainties involved, for example: uncertainties regarding which pollutant is most closely associated with the effects, whether confounding factors such as noise may contribute to the reported associations, and uncertainty as to the extent to which effects on the brain contribute to neurodegenerative processes other than those known to be secondary to cardiovascular disease.

We think that consideration could be given to developing an indirect approach to quantification of the effects of particulate air pollution on vascular cognitive impairment or vascular dementia. This would require linking the quantification of the cardiovascular effects of particulate pollution with quantitative evidence linking these cardiovascular endpoints to neurological outcomes. We think that the possible effects of exposure to air pollutants on cognitive decline and dementia are potentially very important for public health in the UK. We therefore consider further research to reduce the current uncertainties to be a priority. We have recommended a number of approaches to future research that might be taken (see [Chapter 7](#)). We urge that steps to enact these recommendations should be taken as soon as possible.

We conclude that:

1. The epidemiological evidence is suggestive of an association between exposure to ambient air pollutants and both the risk of developing dementia and acceleration of cognitive decline. The epidemiological literature is inconsistent as to which pollutant is most associated with these effects.

2. There is evidence that air pollution, particularly particulate air pollution, increases the risk of cardiovascular, including cerebrovascular, disease. These diseases are known to have adverse effects on cognitive function. It is therefore our view that there is likely to be a causal association between particulate air pollution and effects on cognitive function in older people.
3. The evidence base is currently inadequate to allow direct quantification using a meta-analysis of epidemiological studies linking air pollution with cognitive decline or dementia. Direct quantification of cognitive decline or dementia associated with air pollution would therefore be subject to unknown uncertainty.
4. It may be possible to develop an indirect method of quantification of cognitive effects secondary to the effects of particulate pollution on cardiovascular disease. This would require a review of evidence regarding the quantitative link between cardiovascular endpoints and effects on cognition.



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# Chapter 1. Introduction to air pollution and possible effects on the brain

## 1.1 The development of studies of the effects of air pollutants on health

The modern era of research into the effects of air pollutants on health began in the 1950s. A great deal of work was done in the UK in the period 1952 to 1978. This work had been triggered by the London smog of 1952 and focused on the effects of exposure to the combination of particulate matter (smoke) and sulphur dioxide (SO<sub>2</sub>). The Clean Air Act (1956) reduced urban emissions of these pollutants and ambient concentrations fell dramatically. Work on the effects of air pollutants on health continued after 1978 in other countries and, in the USA, attention focused on emissions from traffic. These included particulate matter (PM), nitrogen oxides (NO<sub>x</sub>), carbon monoxide (CO) and lead (Pb). Ozone (O<sub>3</sub>), a secondary air pollutant produced from traffic emissions by the action of ultra-violet light, also attracted a good deal of attention: the oxidative smog of Los Angeles contained high concentrations of ozone, oxides of nitrogen and other oxidant species and had been identified as a problem in the early 1950s. All this research contributed to the World Health Organization (WHO) Air Quality Guidelines of 1987: an important landmark in air pollution research (WHO, 1987).

A new wave of research began in the late 1980s: work was undertaken in the UK, Europe and the United States as well as in other countries. Attention focused on PM and on sub-fractions of the ambient aerosol. Two sub-fractions were defined: PM<sub>10</sub> (particles of <10µm aerodynamic diameter)<sup>1</sup> and PM<sub>2.5</sub> (particles of <2.5µm aerodynamic diameter)<sup>2</sup>.

PM<sub>10</sub> was chosen to represent those particles that could pass the upper airways, the nasal passages and larynx, and enter the lung; PM<sub>2.5</sub> was chosen as a breakpoint between particles generated by combustion and formed by chemical reactions in the air and those produced by attrition of solid materials. PM<sub>2.5</sub> also represented, rather better than PM<sub>10</sub>, those particles likely to reach the gas exchange zone of the lung. It is important to remember that PM<sub>10</sub> includes PM<sub>2.5</sub>: PM<sub>2.5</sub> is a sub-fraction of PM<sub>10</sub>. PM<sub>10</sub> and PM<sub>2.5</sub> are expressed as mass concentrations. For example, the population-weighted annual average concentration of PM of <2.5µm aerodynamic diameter in England today is about 10µg/m<sup>3</sup>. The terms PM<sub>10</sub> and PM<sub>2.5</sub> refer to mass concentrations of size-defined particles. The move to PM<sub>10</sub> and PM<sub>2.5</sub> was important: in the USA Total Suspended Particulate matter (TSP) had been the standard

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<sup>1</sup> PM<sub>10</sub> is defined as the mass per cubic metre of airborne particles passing through the inlet of a size selective sampler with a transmission efficiency of 50% at an aerodynamic diameter of 10 µm. In practice, PM<sub>10</sub> represents the mass concentration of all particles of <10 µm aerodynamic diameter.

<sup>2</sup> PM<sub>2.5</sub> is defined as the mass per cubic metre of airborne particles passing through the inlet of a size selective sampler with a transmission efficiency of 50% at an aerodynamic diameter of 2.5 µm. In practice, PM<sub>2.5</sub> represents the mass concentration of all particles of <2.5 µm aerodynamic diameter.

measurement, in the UK Black Smoke (BS: measured using a reflectance technique) had been the standard. At the same time as these new definitions of PM were being introduced, methods for continuous monitoring of PM became available. This meant that correlations between the occurrence of events related to ill-health, for example deaths and hospital admissions, and daily average, or even hourly average, PM<sub>10</sub> and PM<sub>2.5</sub> could be explored. A new wave of epidemiological studies, the time-series studies, appeared. The results were surprising: even very low concentrations of PM were correlated with 'health events'. Careful examination of the evidence, and especially of the control for confounding factors such as variations in daily temperature, led to the conclusion that many of the reported associations were causal in nature. Time-series techniques were also applied to gaseous air pollutants (O<sub>3</sub>, NO<sub>2</sub> and SO<sub>2</sub>) and, again, effects were found.

A second wave of epidemiological studies involving a different design followed in the mid 1990s. These were cohort studies and focused on PM. It was found that the effects of long-term exposure to PM, measured as PM<sub>2.5</sub>, were even more striking than the effects of short-term variations in concentrations that had been revealed by the time-series studies. Indeed, in terms of the increased risk of all-cause mortality, the effect of long-term exposure was 10 times that of day to day variations (COMEAP, 2009). Effects were expressed in terms of increased risk of all, non-accidental, mortality per 10µg/m<sup>3</sup> increment in daily PM<sub>10</sub> (time-series studies) and long-term average PM<sub>2.5</sub> (cohort studies). The Hazard Ratio (HR) reported from cohort studies was 1.06. What this means is that a 10µg/m<sup>3</sup> increment in long-term average concentrations of PM measured as PM<sub>2.5</sub> is associated with a 6% increase in overall risk of death from non-accidental causes. It will be appreciated that this is by no means a small effect: it was, in fact, equivalent to 29,000 deaths in the UK in 2008 (COMEAP 2010)<sup>3</sup>. Of course, it should be remembered that the studies just described did not take into account the possible effects of other pollutants. We know, for example, that concentrations of PM measured as PM<sub>2.5</sub> are often correlated with concentrations of NO<sub>2</sub>. More work has been done on the possible effects of particulate matter than on those of gaseous air pollutants: although associations have been reported with long-term average concentrations of the common gaseous air pollutants, ozone and nitrogen dioxide, the extent to which these associations are causal is not yet clear (COMEAP, 2015, COMEAP, 2018).

Another striking discovery was that effects on the cardiovascular system appeared to dominate the effects of long-term exposure to PM. This was, at the time, surprising: earlier work had focused on the effects of air pollutants on the respiratory system. The discovery of such effects led to a search for mechanisms of effect and a large body of evidence, relating especially to PM, has accumulated (Donaldson and MacNee, 2001; COMEAP, 2018). This has been reviewed, many times, and has been found to be convincing (Brook et al, 2010). It is generally accepted that PM induces an inflammatory response in the lung and that markers of

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<sup>3</sup> In the light of newer evidence, COMEAP (2022) now recommends a HR of 1.08 per 10 µg/m<sup>3</sup> PM<sub>2.5</sub> for this pollutant-outcome pair ([Particulate air pollution: quantifying effects on mortality](#)).

this response can be detected in the blood. Effects on the development of atheromatous plaques in the walls of blood vessels and on the clotting of the blood have also been reported.

Whether PM crosses from the alveoli to the blood has been debated; in the case of very small particles (ultrafine particles, UFP, <100nm in diameter) this seems possible, though the percentage of those particles deposited in the lung that reach the blood is of the order of only 1% (Kreyling et al, 2002a) or substantially less (Miller et al, 2017a,b). That may seem a small fraction, but it represents many UFP and some of these have been shown to reach other organs including the brain (Oberdörster et al, 2004). Interest in UFP led to the hypothesis that UFP might be important in explaining the effects attributed to PM in general (Seaton et al, 1995, Oberdörster et al, 1995). Additionally, effects on the autonomic control of the heart have also been reported. The links in the chain leading from exposure to PM to effects on the heart and circulatory system are now well established. The possibility that materials carried on the surface of UFP could enter the blood and the brain should not be discarded without further study. The evidence for potentially similar effects of gaseous pollutants is at an earlier stage of development. Effects on the respiratory system are also well established.

## 1.2 Effects of air pollutants on the brain

Current interest in the possible effects of air pollutants on the brain began in about 2002 when Calderón-Garcidueñas and colleagues reported that dogs exposed to air pollution in Mexico City showed neuropathological changes of the type associated with Alzheimer's disease (Calderón-Garcidueñas et al, 2002). This work was an extension of studies undertaken in the 1990s on the effects of Mexico City air pollution on the olfactory epithelium of humans and dogs. More recently, interest in possible effects on the brain has been focused by epidemiological studies that suggest that exposure to air pollutants is associated with decline of cognitive function and the occurrence of dementia (Calderón-Garcidueñas et al, 2017a). As has often been the case in the air pollution field, the question of whether such associations are causal in nature, or perhaps the result of confounding factors (including, for example, smoking, poor diet and deprivation) or effect modification, has been debated.

Two lines of study have been influential in causing people to think that the associations reported in epidemiological studies and the early work on the dogs might be important. The first was the appreciation that ultrafine particles could reach the olfactory bulbs of the brain via the olfactory nerves (Oberdörster et al, 2009). The second concerned the protection of the brain by the blood-brain barrier. The blood-brain barrier is an effective barrier, or filter, against many circulating blood factors and consequently it had been thought that the brain is well protected against invasion by particles. This perception was based on 2 lines of thought.

First, it was thought that particles deposited in the lung did not readily pass into the blood stream. The mechanisms by which particles are dealt with by the lung were well known – clearance via the mucociliary escalator and to lymph nodes via macrophages taking up

particles in the gas exchange zone and migration across the epithelium to local lymphatic vessels. It was known that the lungs of people living in polluted cities were slate-grey in colour: particles were clearly being retained in the lung.

Despite the observation that particles - at least very small particles - could reach the blood, it was assumed that the blood-brain barrier would protect the central nervous system. To some, the idea that particles could cross that barrier in significant numbers seemed implausible. It was known that the endothelial cells of cerebral capillaries were not fenestrated and that they were joined by tight intercellular junctions. Some research workers have pointed out that not all cerebral capillaries were so impermeable: attention has focused on the circumventricular organs. Others wondered whether the blood-brain barrier could be made less impermeable by systemic inflammation, perhaps induced by exposure to air pollutants. The fact that the blood-brain barrier is less tight in the very young was also noted.

Once transport of particles along the olfactory nerves had been demonstrated, it was asked whether these particles had damaging effects on the neurons of the olfactory bulbs.

Neuropathological studies suggested that they had. It was also asked whether particles that reached the olfactory bulbs could, so to speak, migrate any further along the olfactory pathway. Further work is needed to address this issue. Clear demonstration that significant numbers of particles make their way beyond the olfactory bulbs is lacking though particles have been reported as being seen, by electron microscopy, in other parts of the brain. The route by which these particles travelled is unclear (see section 4.4).

Another important line of research has included studies of the microglial response to particles. This has been stressed by a number of workers including Block et al, (2007) and is discussed in Section 4.6 of this report. Furthermore, it has been shown that diesel particles can affect dopaminergic systems of the brain (Block et al, 2004). A link between exposure to particles and the type of neuropathological change seen in patients with Alzheimer's disease and with Parkinson's disease has been postulated (Block et al, 2004).

It is possible that effects on the brain might be secondary to effects of air pollutants on other organs and systems. For example, damage to the vasculature, or blockage by embolism, could lead to cerebral ischaemia and thus to damage to the brain. Similarly, it is conceivable that damage to the respiratory system could lead to hypoxia with, again, knock-on effects on the brain.

In developing our thinking in this area, we identified 2 important questions:

1. How reliable are the experimental models as regards predicting effects in humans?
2. Are the associations reported by epidemiologists likely to be causal in nature?

In some areas, for example the effects of air pollutants on the cardiovascular system, evidence of effects has been available from studies in human volunteers. This evidence has been invaluable in supporting the findings of work in animal models. In the current case we lack such evidence, at least as regards ambient pollutants.

We agreed that, when we looked at the results of the experimental work, we should ask whether the mechanisms shown in animals are likely to apply to humans. This is by no means a novel question: the problem of extrapolating from animal models to humans is as old as toxicology itself. An obvious starting point is to ask whether the anatomy, physiology, biochemistry and molecular biology of humans is sufficiently similar to that of the animals used. When this question is asked the answer is often that, where we have the necessary comparative data, the similarities have been found to be substantial. This may be the case as regards the current problem. Of course, if we had reason, for example, to think that marked differences in pathways within the brain could affect the reliability of extrapolation we should say so. It is certainly the case that the 'olfactory brain' of rodents is very different from that of humans.

Does this matter? Perhaps not: we know that the large pyramidal cells of the hippocampus, for example, are sensitive to anoxia and toxicants in both rodents and humans. What of the blood-brain barrier? Are there important species differences here or is it safe to assume that what crosses the blood-brain barrier of a rodent might well cross that of humans? And what of repair processes and processes by which particulate matter might be removed from the brain? Here very little is known. Dose-response relationships also need to be considered. The demonstration of damaging effects of chemicals, in animals, at high doses, is often possible. One should ask what is known of realistic doses. Do we know the dose as far as the human brain and its exposure to air pollutants is concerned? Again, information is lacking.

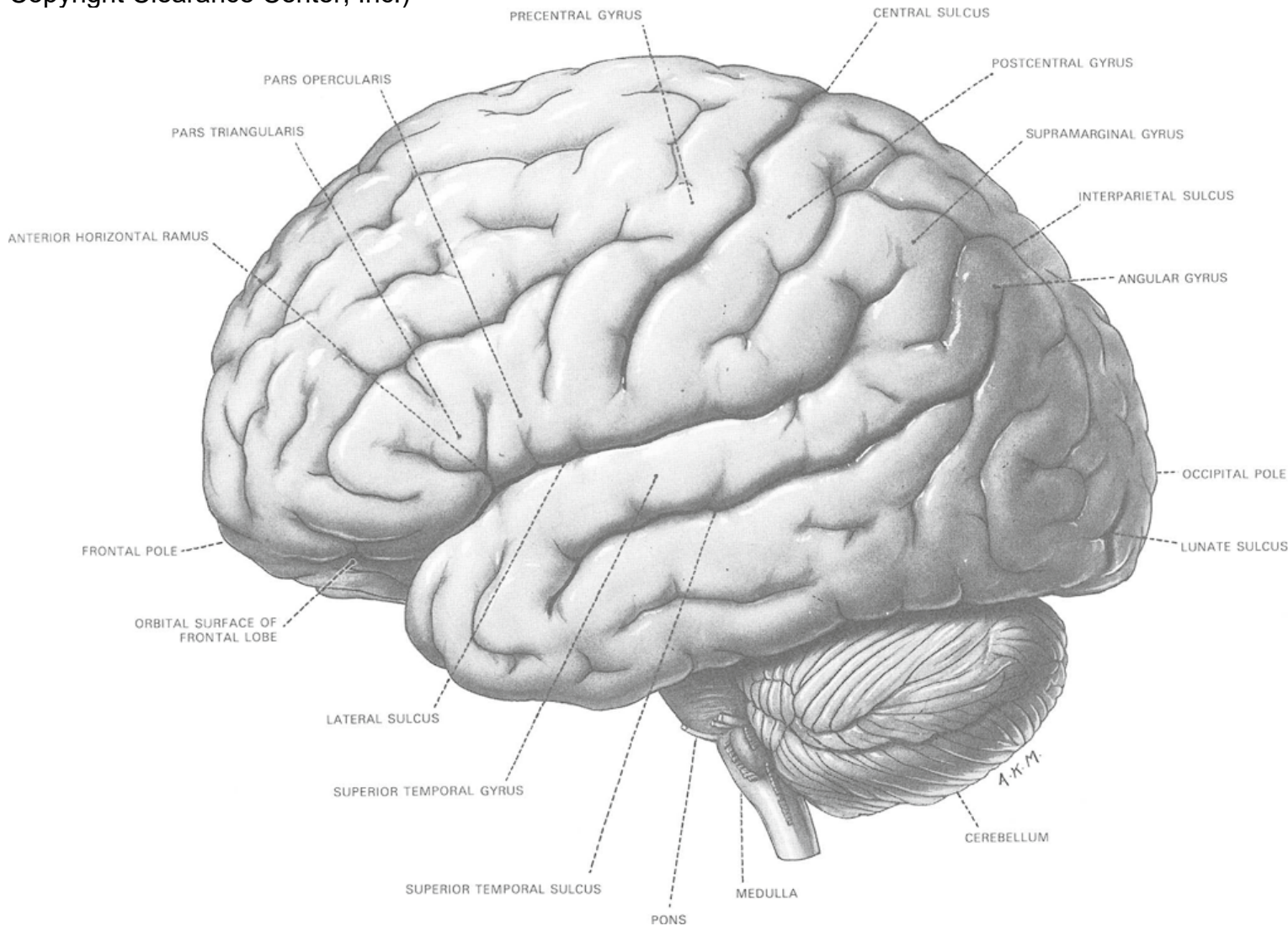
When we turn to the epidemiological evidence and the question of causality we are on familiar ground. Bradford Hill's features of causal associations are well known in the air pollution field (Hill, 1965). These features of causal associations have been examined with respect to the possible effects of air pollutants on the brain by Clifford et al, (2016), who concluded that there was coherence in the evidence linking exposure to a range of traffic-related pollutants but that the evidence was at that time insufficient to comment on consistency.

The brain is a complex organ, with specialised regions controlling functions such as reasoning memory, emotion, senses and motor skills. The effect of damage to the brain differs depending upon the area affected. Figures 1.1, 1.2 and 1.3 depict different areas of the brain, some of which are mentioned in the following chapters.



**Figure 1.1 The brain viewed from its lateral aspect**

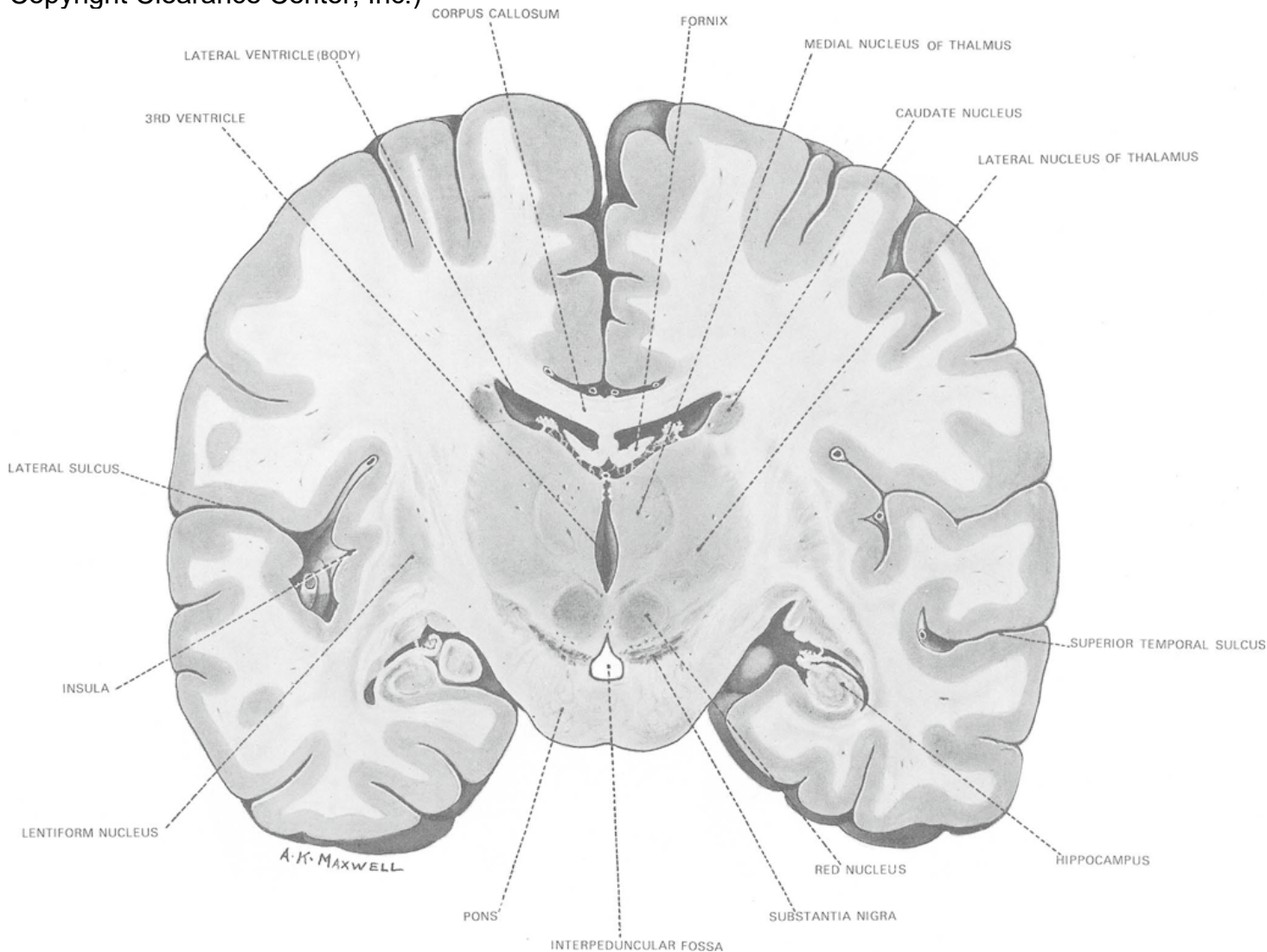
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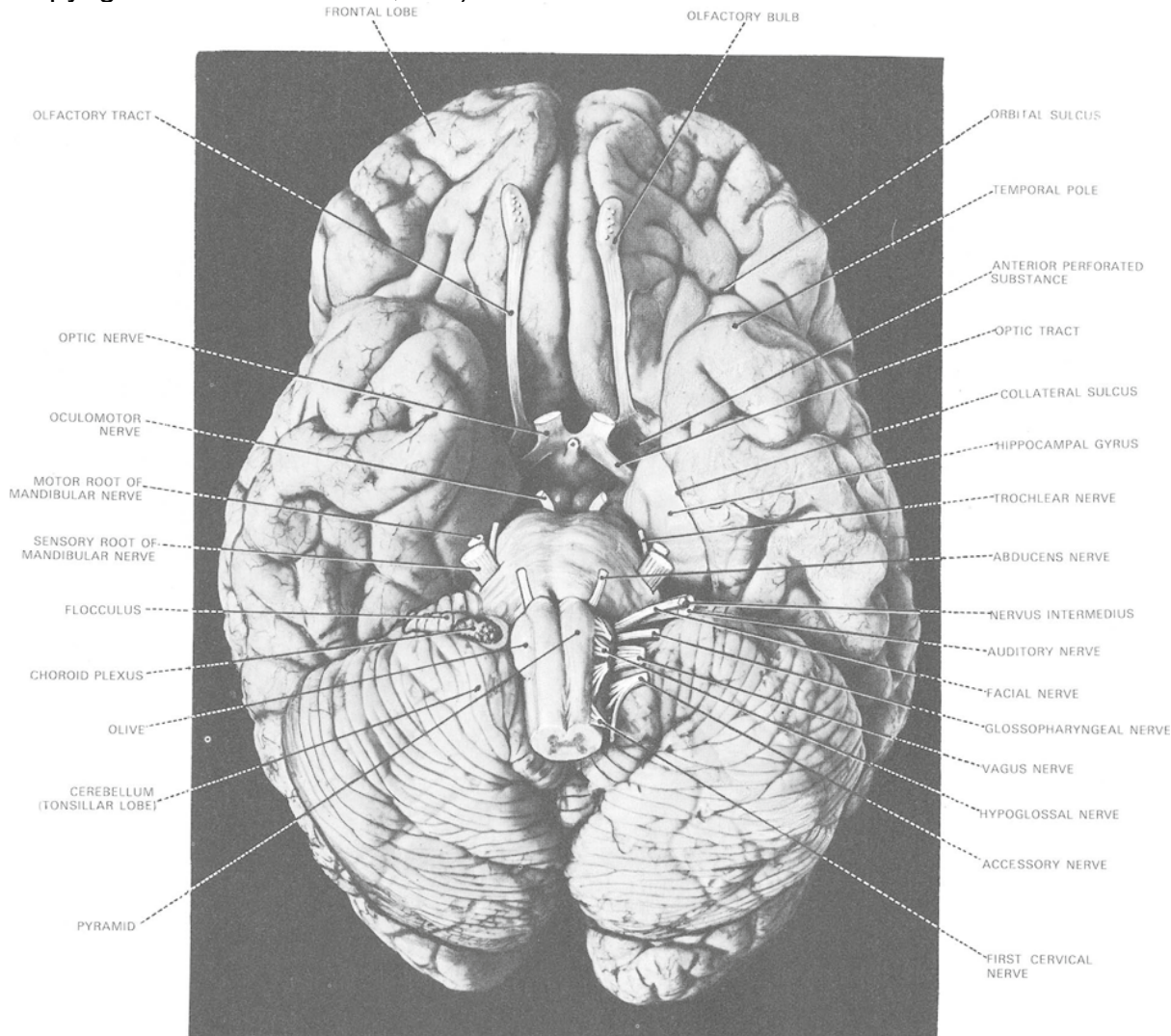
**Figure 1.2 Coronal section of the brain through the middle of the thalamus**

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**Figure 1.3 The brain viewed from its basal or inferior aspect**

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## 1.3 Further reading

The following sources may be consulted for further information on the history of research on the effects of air pollution on health and on more recent developments in the field.

Harrison R M. Pollution: Causes, Effects and Control. 5th edition, 2014. Royal Society of Chemistry Publishing.

Holgate S T, Samet J M, Koren H S, Maynard R L. (Eds) 1999. Air Pollution and Health. 1st Edition: Academic Press. Lippmann M. Environmental Toxicants. 3rd edition 2009, Wiley-Interscience.

Wayne R P. Chemistry of Atmospheres. 3rd edition, 2000. Oxford University Press.

World Health Organization (WHO). Air Quality Guidelines for Europe, 1987. First Edition. WHO Regional Office for Europe.

WHO. Air Quality Guidelines, Global Update, 2005. WHO Regional Office for Europe.

WHO. Global Air Quality Guideline: particulate matter (PM<sub>2.5</sub> and PM<sub>10</sub>), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide, 2021

## 1.4 Our approach to the problem

The above paragraphs provide a background to our work. COMEAP discussed the terms of reference for its work on the link between air pollution and cognitive decline and dementia at its meeting in June 2017, and agreed that the work should be undertaken by a sub-group. A small Sub-group on the effects of exposure to air pollutants on cognitive decline and dementia was established to assess the relevant evidence. The sub-group included a number of non-COMEAP members who were co-opted for their specialist expertise in this area. The terms of reference adopted by the sub-group are set out in [Appendix 1](#). The key questions which it considered are repeated here. The committee is asked to assess the strength of evidence for hazard. Based on the available epidemiological and mechanistic evidence, what is the committee's view on:

1. The strength and consistency of the epidemiological evidence for associations of air pollutants with cognitive decline and dementia?
2. Are there biologically plausible mechanisms by which air pollutants could contribute causally to cognitive decline and dementia?
3. How strong is the evidence that air pollutants act via these mechanisms to cause these effects?

4. Based on the available evidence, which pollutants are most likely to be causally related to these effects?
5. Does the evidence indicate at which points in the life-course exposure might be most relevant?
6. What future research work would the Committee recommend to increase the understanding of this topic?

The Committee is also invited to consider whether the evidence is sufficient to propose that a QUARK working group be established to consider quantification of cognitive decline and dementia associated with air pollution in the UK. In coming to this view, it may wish to consider:

1. For which pollutants and endpoints?
2. Any existing approaches which have been used, by others, to quantify these effects.

These are challenging questions.

It was agreed by the sub-group that it would not be possible to undertake a systematic review of all the evidence bearing on the questions set out above: this would have been beyond our resources. Instead we decided to undertake a critical review of the epidemiological evidence and to prepare a series of shorter reviews or essays dealing with specific issues which we think are important in reaching answers to the questions we were asked. The review of the epidemiological evidence and the shorter reviews of specific aspects of the problem form the main part of this report. A short statement of the importance of dementia as a current problem precedes these sections of the report.

Individual members of the sub-group and secretariat led the work on the reviews: their work was then considered by the whole sub-group. The lead authors of the individual reviews are listed below.

Chapter 1: Introduction to air pollution and possible effects on the brain: R. Maynard

Chapter 2: Introduction to dementia as a problem today: N. Fox

Chapter 3: Epidemiological evidence: J.M. Delgado-Saborit

Section 4.1: Aspects of potential mechanisms, Introduction: R. Maynard

Section 4.2: Translocation of inhaled particles to the blood: R. Maynard

Section 4.3: The Blood-brain barrier: R. Maynard and R. Carare

Section 4.4: Movement of particles through the olfactory bulb: A. Gowers

Section 4.5: The fate of particles which enter the brain: R. Maynard and R. Carare

Section 4.6: Biochemical mechanisms: A. Gowers and I. Mudway

Section 4.7: Effects on the brain secondary to other health effects: S. Love

Section 4.8: Possible influence of early life exposures: J. Grigg and S. Love

Dr Valentina Guercio (UK Health Security Agency) assisted in summarising the epidemiological studies. In addition, we consulted Professor Roy Harrison and Professor Peter Burney on specific points on which they are recognised authorities: we gratefully acknowledge, here, their assistance. They are, of course, not responsible for the conclusions we reached.

Having set out our thinking in the body of the report, we draw together our conclusions in the final Conclusions chapter. The executive summary provides an overview of our work and conclusions.

Drafts of the report were discussed at meetings of the full COMEAP Committee. The report was revised to take into account comments and suggestions made during these discussions. This final version of the report was agreed for publication by the chair of the sub-group and the COMEAP chair, and circulated to the full committee.

## Chapter 2. Introduction to dementia as a problem today

Dementia is arguably one of, if not the, most pressing public health challenges of our age. Its prevalence is strongly age-related: doubling every 5 to 6 years over the age of 65 years. There are currently an estimated 850,000 individuals living with dementia in the UK. As the UK population ages this number is projected to increase, to 1 million by 2025 and 2 million by 2050 (Prince et al; 2014). Dementia is now the leading cause of death in the UK.<sup>4</sup> It is also now the most feared medical condition in those over the age of 50.<sup>5</sup>

The impact of dementia on individuals and their families is devastating. Dementia usually involves a relentless loss of cognitive function that ultimately results in total dependence. Many of the diseases that cause dementia are chronic disorders, and most, but not all, are progressive. Onset is often insidious with relatively slow progression: survival from diagnosis is typically 5 to 8 years (for instance in Alzheimer's disease). Those living with moderate to severe dementia need considerable support with tasks such as dressing or eating. This protracted, progressive loss of functional independence combined with the growing numbers of those affected represents a major challenge for health and social care systems. The cost to the UK economy in 2014 was estimated at £26 billion with social care accounting for over £10 billion (Prince et al; 2014)<sup>6</sup>; these are costs that will only increase. People with dementia now account for 75% of those in residential care.

Dementia is defined as cognitive decline that is sufficient to interfere with independence in everyday activities<sup>7</sup>. Mild cognitive impairment (MCI) refers to cognitive decline that is not sufficient for a diagnosis of dementia – the boundary between these 2 definitions is often unclear. Dementia is a syndrome with many causes: the most common is Alzheimer's disease (AD) but vascular dementia (VaD) and dementia with Lewy bodies (DLB) are also common and frequently co-exist, especially in older individuals. The relative prevalence of different diseases that cause dementia varies with age and with geography. These causative diseases have different pathophysiologies and genetic risk factors, although some risk factors are shared.

Loss of neuronal connectivity, through synaptic and (eventual) neuronal loss, and through damage to the white matter, is the final common pathway for the different dementias. The distribution of this loss within the brain maps closely onto the appearance of symptoms. The sites of earliest loss and the associated cognitive decline and clinical features provide the initial basis for the clinical diagnosis. AD is typically associated with early hippocampal atrophy

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<sup>4</sup> [Deaths registered in England and Wales 2016: main points points](#)

<sup>5</sup> [Older people fear dementia more than cancer \(Saga\)](#)

<sup>6</sup> [Dementia UK Update](#)

<sup>7</sup> DSM-V criteria for major neurocognitive disorder (dementia)



and early memory deficits before progressing to widespread neocortical degeneration and the loss of cognitive function across multiple domains (for instance, language, calculation, visuo-perceptual and executive function). The early cortical abnormalities may be contrasted with the early damage seen in small vessel vascular dementia where subcortical, white matter deficits predominate. Although distinctions may be drawn between disorders that have an initial disproportionate impact on particular structures (for instance, the hippocampus) or cortical vs subcortical regions of the brain, most, in time, progress to cause widespread and generalised damage.

The particular predilection of different diseases for distinct cerebral regions, (and thereby for different patterns of cognitive decline), formed the traditional basis for clinical diagnosis. Increasingly these clinical diagnoses are supported by brain imaging or cerebrospinal fluid (CSF) biomarker evidence of the pattern and severity of loss across the brain, and the presence of particular molecular changes, for instance in amyloid- $\beta$  ( $A\beta$ ) or tau. Older epidemiological studies lack this support and often only assess associations with 'dementia' rather than the underlying, specific diseases.

Many of the neurodegenerative causes of dementia (AD, DLB, frontotemporal dementia) involve long presymptomatic phases, during which cerebral pathology gradually and progressively accumulates prior to discernible symptoms. In AD, the appearance of molecular pathology in the brain (for instance of  $A\beta$  plaques) predates symptoms by an estimated 20 years or longer. This long presymptomatic period is particularly relevant when considering the period over which potential environmental risk factors may be having an influence of the progression as well as the development of the pathophysiology of these diseases.

Although the overall prevalence of dementia continues to rise (due to ageing of populations) age-specific incidence appears to have been declining in a number of developed economies: studies from the US, the UK and other EU countries report significant age-specific declines over the last 2 or more decades. The reason for these declines is unclear; the decline has been attributed to improvements in health (for example, blood pressure control), lifestyle and other factors (for instance, education).<sup>8</sup> These changes highlight the importance of understanding potentially modifiable risk factors. This report seeks to address one such factor – with an assessment of the evidence linking exposure to air pollution with effects on cognitive decline and dementia.

Table 2.1 taken from Ferrari et al (2018) lists diseases that can cause dementia. However, while classifications of dementia can be useful, in most older people who have dementia, the dementia is caused by multiple disease processes (for example, Robinson et al, 2018; Coulthard and Love, 2018).

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<sup>8</sup> 2017, 2020 Lancet commissions on dementia

**Table 2.1 Diseases that can cause dementia**

(Adapted from ‘The diagnosis of dementias: a practical tool not to miss rare causes’, authors: Ferrari C, Nacmias B, Sorbi S, by permission from Springer Neurological Sciences 2018: volume 39, pages 615 to 627. Copyright (2018) Neurological Sciences)

|                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Neurodegenerative diseases</b>                                                                                                                                                                                                                                      |
| (a) Specific cognitive profile: Alzheimer disease, Fronto-temporal lobar dementia, Lewy Body Dementia, Corticobasal Degeneration, Progressive Supranuclear Palsy                                                                                                       |
| (b) Other neurodegenerative dementia with prominent frontal symptoms: Huntington disease, Autosomal Dominant Spino-Cerebellar Ataxia, Hereditary Spastic Paraparesis, FTAX                                                                                             |
| <b>Vascular dementia</b>                                                                                                                                                                                                                                               |
| (a) Large vessel disease                                                                                                                                                                                                                                               |
| (b) Small vessel diseases (hypertensive, sporadic cerebral amyloid angiopathy)                                                                                                                                                                                         |
| <b>Familial cause of vascular dementia</b>                                                                                                                                                                                                                             |
| CADASIL, CARASIL, COL4A1, RVCL, genetic form of cerebral amyloid angiopathy                                                                                                                                                                                            |
| <b>Adult-onset leukodystrophy</b>                                                                                                                                                                                                                                      |
| Adrenoleukodystrophy, Adult-onset leukoencephalopathy with axonal spheroid and pigmented glia, ovario-leukodystrophy, Cerebrotendinous Xanthomatosis, Pelizaeus-Merzbacher Disease, Alexander disease, Adult polyglucosan body disease, Vanishing white matter disease |
| <b>Lysosomal storage disorders</b>                                                                                                                                                                                                                                     |
| (a) with mainly primary neuronal dysfunction: Gaucher’s disease, Niemann-Pick Type C, Kuf’s disorder (Neuronal ceroid lipofuscinosis), Tay-Sachs disease                                                                                                               |
| (b) with primary glial dysfunction and leukoencephalopathy: Krabbe disease<br>Metachromatic leukodystrophy                                                                                                                                                             |
| (c) with vascular dysfunction: Fabry disease                                                                                                                                                                                                                           |
| <b>Mitochondrial pathologies</b>                                                                                                                                                                                                                                       |
| MELAS, MERFF, Kearn-Sayre Syndrome                                                                                                                                                                                                                                     |
| <b>Basal ganglia pathologies</b>                                                                                                                                                                                                                                       |
| (a) Degeneration: Wilson disease; Neuroacanthocytoses (Chorea-Acanthocytosis, McLeod Syndrome, HD-like syndrome)                                                                                                                                                       |
| (b) Accumulation pathologies: neurodegeneration with iron accumulation (pantothenate kinase-associated neurodegeneration, PLA2G6, Kufor-Rakeb, neuroferritinopathy, aceruloplasminemia), Fahr disease                                                                  |
| <b>Infective dementia</b>                                                                                                                                                                                                                                              |
| HIV, syphilis, borrelia, herpes simplex, VZV, prion diseases                                                                                                                                                                                                           |



|                                                                                                         |
|---------------------------------------------------------------------------------------------------------|
| <b>Metabolic dementia</b>                                                                               |
| hypo and hyperthyroidism, vitamin deficits, hyponatremia, hepatic encephalopathy, uremic encephalopathy |
| <b>Autoimmune dementia</b>                                                                              |
| Multiple sclerosis, vasculitis, limbic encephalitis, hashimoto encephalopathy, nmdar encephalitis       |
| <b>Neurosurgical causes</b>                                                                             |
| Neoplasm, normal pressure hydrocephalus, subdural hematoma                                              |

## 2.1 Further reading

Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N. 2020. '[Dementia prevention, intervention, and care: 2020 report of the Lancet Commission](#).' Lancet 18 August 2020: volume 18, issue 396, (10,248), pages 413 to 446

O'Brien JT, Thomas A. 'Vascular dementia.' Lancet 2015 October 24: volume 386, issue 10,004, pages 1,698 to 1,706

Alzheimer's Disease Facts and Figures. Alzheimer's Association Alzheimer's and Dementia 2018: volume 14, issue 3, pages 367 to 429

## Chapter 3. Epidemiological evidence

### 3.1 Summary

The epidemiological evidence reviewed fairly consistently reports associations between chronic exposure to air pollution and reduced global cognition and impairment in visuospatial abilities as well as cognitive decline and increased risk of dementia. Results are heterogeneous as regards to other cognitive domains such as executive function, attention, memory, language and mild cognitive impairment. The identified neuroimaging studies consistently report associations between exposure to air pollution and white matter atrophy. The impact of air pollution on hippocampal volume is not consistent among studies. Other effects reported by individual studies relate to reduced grey matter, larger ventricular volume, and smaller corpus callosum. Results on ischaemic (white matter hyperintensities or silent cerebral infarcts) and haemorrhagic (cerebral microbleeds) markers of cerebral small vessel disease are heterogeneous. The few studies available on neuroinflammation tend to report associations with exposure to air pollution.

Several effect modifiers have been suggested in the literature, but results are heterogeneous and more replication studies are required. Widely recognised confounding factors have been controlled, or adjusted, for in the reviewed studies. Additional confounding factors have also been included, but the inclusion of these varies among the different studies. Despite all the efforts to adjust for confounding factors, residual confounding cannot be completely ruled out, especially since the factors affecting cognition and dementia are not yet fully understood. The available evidence, which has been reviewed with reference to Bradford Hill's features of causal associations (see [Chapter 5](#)), is suggestive of an association between exposure to a range of air pollutants and a number of effects on the nervous system including the acceleration of cognitive decline and an increased risk of dementia.

However, the diversity of study designs, air pollutants and end-points examined precludes identification of which pollutant is most closely associated with these adverse effects and makes meta-analysis inappropriate.

### 3.2 Introduction

This review updates the body of evidence that had been already reviewed in the 6 literature reviews published between 2015 and 2016 (Clifford et al, 2016; Killin et al, 2016; Peters et al, 2015; Power et al, 2016; Tzivian et al, 2015; Xu et al, 2016), available at the start of the work of the Sub-group. These 6 reviews included 4 systematic reviews on the effects of air pollution on cognitive function, cognitive decline and dementia, and reviewed a body of evidence that spanned from 5 (Killin et al, 2016) to 20 (Xu et al, 2016) papers. We used these reviews as the starting point for our examination of the epidemiological evidence, and have assessed the

original research papers included in the published reviews. We identified more recently published studies by undertaking an extensive literature search using PubMed and Web of Science databases up to December 2019 and by hand-searching reference lists of published reviews found by the search.

Inclusion or exclusion eligibility criteria were developed: papers were included if they reported an association between either short- or long-term exposure to ambient air pollution (considering both exposure to specific air pollutants and traffic) and cognitive performance, mild cognitive impairment, incident cognitive impairment, dementia, hospitalisations due to neurological disease, brain imaging, or neurological biomarkers. All study designs were included. Only studies on adult populations were considered for inclusion. Abstracts and unpublished studies were not included. No studies were excluded a priori for weakness of design or data quality.

The papers were first screened by titles and abstracts. When the information provided in the abstract was not detailed enough full-text documents were also reviewed. The following information from the included epidemiological studies was collected: first author, year of publication, name of the study, location, study design, period of enrolment and follow up, sample size, sex and age, exposure assessment methodology, outcome, effect estimator used, and covariates adjusted for in the analysis.

This gave a total of 69 papers to review. The papers report evidence in the areas of global cognition (16)<sup>9</sup>, executive function (9), attention (6), memory (11), constructional praxis and coding ability (3), language (5), cognitive decline (9), mild cognitive impairment and incident cognitive impairment (7), dementia (16), hospitalisations (6), brain imaging (8) and neurological biomarkers (8). None of the newer literature reviews published is as comprehensive as the current one detailed in this report, which reviews evidence in 12 different areas related to cognitive decline and dementia; nor do any include as many papers as this one. For example, Kilian and Kitazawa (2018) reviewed 23 papers whilst this one includes 69 papers – the maximum number reviewed so far. The present review also includes more up-to-date published evidence than other currently available reviews, to December 2019).<sup>10</sup>

In the studies reviewed, chronic exposure to air pollution was modelled using several methods such as proximity models (for instance distance to nearest road), allocating concentrations from the nearest monitoring site, using geostatistical models (for example, kriging, inverse distance weighting), dispersion models, land use regression models) and hybrid models (for example, incorporating satellite measurements, chemical transport models, Bayesian models). Studies assessing effects of short-term air pollution on hospital admissions assessed daily

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<sup>9</sup> Numbers in brackets indicate the number of papers dealing with the specified aspects of the evidence.

<sup>10</sup> This review of the epidemiological literature has also been published as a journal paper: Delgado-Saborit and others (2021) [A critical review of the epidemiological evidence of effects of air pollution on dementia, cognitive function and cognitive decline in adult population - ScienceDirect](#)

exposures using district or region level mean concentrations calculated from available monitoring stations within the region of interest.

Cognitive performance outcomes have been assessed using a range of different neuropsychological tests. Dementia diagnosis has been assessed using information on health databases or medical records.

Several factors potentially acting as effect modifiers and/or confounders are identified in this chapter, and the strengths and limitations of the studies included in our review are also discussed. The main conclusions of the already published literature reviews up to 2016 are summarised at the end of this chapter. [Appendix 2](#) contains a glossary of terms and abbreviations used in this review.

The review of the epidemiological evidence has been conducted following the guidance offered by Bradford Hill (Hill, 1965) on the features of causal associations. The available evidence was reviewed with emphasis on strength of association, dose-response functions, temporality, reversibility, consistency of association and specificity of association. Biological plausibility is reviewed in detail in [Chapter 4](#). Our views on the extent to which the available evidence demonstrates these features are given in Section 5.1.

## 3.2 Review of associations reported in epidemiological studies on the effect of air pollution on cognitive decline and dementia

### 3.3.1 Global cognition

The effect of air pollution on global cognition has been assessed on the basis of the evidence presented in 16 papers. The characteristics of the epidemiological studies on air pollution and global cognition are reported in Table 3.1.

Sanchez-Rodriguez et al (2006) found that older residents in Mexico DC (aged over 60) had lower global cognition, measured with the Mini-Mental State Examination (MMSE), compared with residents in rural areas (MMSE:  $26.15 \pm 0.35$  vs  $27.16 \pm 0.28$ ,  $p > 0.05$ ) (Sanchez-Rodriguez et al, 2006). No formal assessment of air pollution exposure concentrations was made, only a simple urban-rural comparison.

Sun and Gu (2008) studied the association between air pollution and cognitive performance among participants of the Chinese Longitudinal Health Survey. They used the Air Pollution Index (API), which is a composite index accounting for sulphur dioxide, nitrogen dioxide, particulate matter of  $<10\mu\text{m}$  in diameter ( $\text{PM}_{10}$ ), carbon monoxide, and ozone concentrations. After adjusting for several meteorological, demographic, socio-economic, lifestyle and health factors, they reported that a 1-point increase in the API (in 1995) at the city level was

associated with a mean difference of 0.51 points in the MMSE test (as measured in 2002) indicating poorer cognitive function in older adults ( $86.3 \pm 11.4$  year old) (Sun and Gu, 2008).

Ranft et al (2009) studied the effect of air pollution on cognitive function and attention in elderly women in the SALIA cohort in the Ruhr valley accounting for demographics, lifestyle, health and education. They found that living within 50 metres of a busy road ( $>10,000$  cars per day) during the 20 years prior to the test was related to poorer performance in the CERAD test ( $\beta = -3.8$ , 95% confidence interval (CI)  $-7.8, 0.1$ ). The association was weaker when the average  $PM_{10}$  was calculated for the period when the tests were undertaken (2002 to 2006) ( $\beta = -0.6$ , 95% CI  $-1.4, 0.2$ ). The association reversed when  $PM_{10}$  exposures were estimated for the age when tests were conducted (55 years old) ( $\beta = 0.4$ , 95% CI  $0.0, 0.9$ ). In both cases, exposures were assigned using 5-year average concentrations measured at the nearest monitoring site. A follow up study on the SALIA cohort estimated exposures to  $NO_2$ ,  $NO_x$ , particulate matter of  $<2.5\mu m$  in diameter ( $PM_{2.5}$ ) and  $PM_{10}$  using a land use regression model (LUR). Schikowski et al (2015) found a statistically significant association between increased  $NO_x$  exposure and lower cognitive performance using the CERAD test ( $\beta = -1.35$ , 95% CI  $-2.59, -0.10$ ) and an association, but not statistically significant, using the MMSE test ( $\beta = -0.04$ , 95% CI  $-0.19, 0.12$ ). Increased traffic load,  $NO_2$ ,  $PM_{10}$  and  $PM_{2.5}$  showed no association with cognitive performance as assessed using both the CERAD and the MMSE tests.

Wellenius et al (2012) found that participants in the MOBILIZE Boston study younger than 78 years or who were college educated living near busy traffic roadsides had an increased risk of lower cognitive performance (MMSE  $<26$ ) with an odds ratio (OR) of 1.34 (95% CI 1.01, 1.76) and 1.54 (95% CI 1.10, 2.17) respectively, associated with an interquartile range (IQR) decrease (851.2 m) in residential distance to a major road. They also studied the effect of black carbon (BC), a diesel tracer, on the same population. An IQR increase in residential BC ( $0.11\mu g/m^3$ ) estimated using a LUR model was associated with an increased risk of lower cognitive performance (OR= 1.15, 95% CI 0.99, 1.34). Power et al (2011) reported that exposure to BC increased by a factor of 1.3 (95% CI 1.1, 1.6) the odds of having a MMSE score of  $<25$  for each doubling of BC concentration. The observed effect was similar to ageing by 1.9 years. The association between BC and cognitive function was affected by telomere length, systemic inflammation (Colicino et al, 2017) and microRNA (miRNA) expression in carriers of particular miRNA-processing single nucleotide polymorphisms (SNPs) (Colicino et al, 2016).

Gatto et al (2014) studied the effects of  $O_3$ ,  $NO_2$ , and  $PM_{2.5}$  in a cohort of healthy, mainly Caucasian, women aged  $60 \pm 8$  years. Despite results suggesting a positive association between exposure and lower global cognition, none of the associations reached conventional levels of statistical significance (Gatto et al, 2014).

Higher  $PM_{2.5}$  exposure ( $13.8$  to  $20.7\mu g/m^3$ ) was linked with worse cognitive function ( $\beta = -0.26$ , 95% CI  $-0.47; -0.05$ ) than that of subjects living in lower  $PM_{2.5}$  exposure areas ( $4.5$  to  $9.9\mu g/m^3$ ) in adults aged over 50 participating in the Health and Retirement Study (Ailshire and

Crimmins, 2014). Similar results were observed in the American's Changing Life's Survey, in which a higher number of cognitive errors was associated with increased PM<sub>2.5</sub> exposure (incidence rate ratio, IRR= 1.04, 95% CI 1.00, 1.08 per 1µg/m<sup>3</sup> of PM<sub>2.5</sub>) (Ailshire et al, 2017). Results of the Heinz Nixdorf Recall cohort study also report an association between an IQR increase of PM<sub>2.5</sub> (1.43µg/m<sup>3</sup>) and worse global cognition, achieving statistical significance in those subjects exposed to high noise levels ( $\beta$  = -0.48, 95% CI -0.72, -0.23) (Tzivian et al, 2017).

Similarly, an IQR increase in 1-year PM<sub>2.5</sub> (4.25µg/m<sup>3</sup>) and 2-year NO<sub>2</sub> (6.66 ppb) concentrations was associated with decreased cognitive function scores (PM<sub>2.5</sub>:  $\beta$ = -0.22; 95% CI -0.44, -0.01 and NO<sub>2</sub>:  $\beta$ = -0.26; 95% CI -0.45, -0.06) in participants of the National Social Life, Health and Aging Project cohort study, equivalent to ageing by 1.6 years (PM<sub>2.5</sub>) and by 1.9 years (NO<sub>2</sub>) (Tallon et al, 2017). A larger reduction was reported when a longer period was analysed. A 7-year IQR increase in PM<sub>2.5</sub> (4.33µg/m<sup>3</sup>) was associated with a decrease in cognitive function scores of -0.25 (95% CI -0.43, -0.06), whereas a 7-year IQR increase in NO<sub>2</sub> concentration (7.42 ppb) was associated with a decrease in cognitive function score of -0.27 (95% CI -0.48, -0.07) (Tallon et al, 2017).

Exposure to PM<sub>2.5</sub> was significantly associated ( $\beta$  = 0.10 per 10µg/m<sup>3</sup> increase; 95% CI 0.02; 0.18) with poor cognition using the WHODAS-2 test (higher score means greater disability) in participants of the Study on global AGEing and Adult Health in 6 low- and middle-income countries (China, India, Ghana, Mexico, Russia and South Africa) (Lin et al, 2017a).

A study in Chile compared MMSE scores in 4 groups of women aged 69.8 ± 4.3, living in Santiago de Chile (polluted environment) and Viña del Mar (clean environment), further subdivided according to engagement in a physical training programme. Active women in the clean environment (29 ± 1.3) had higher MMSE scores than did sedentary women (24.3 ± 2.9) or active women (28.4 ± 1.5) in the polluted environment (Molina-Sotomayor et al, 2019).

Exposure to PM<sub>2.5</sub> and PM<sub>10</sub> was associated with lower MMSE scores in adults aged 70 to 84 years in The Korean Frailty and Aging Cohort Study, whereas exposure to NO<sub>2</sub>, O<sub>3</sub> and CO was associated with higher scores (Shin et al, 2019).

### 3.3.2 Specific cognitive domains

#### 3.3.2.1 Executive function

A summary of the characteristics, exposure, adjustments and outcomes of the 9 epidemiological studies on air pollution and executive function reviewed is reported in Table 3.2.

Decreasing distance to a busy traffic roadside was associated with reduced executive function measured by the time required to complete the trail making test (TMT) part B and TMT interference, but not with part A of the TMT test (Wellenius et al, 2012). An IQR decrease in

residential distance to a major roadway (851.2 m) was linked with an increase of the scores on the TMT part B of 10.5 seconds (95% CI, 4.0, 17.1). These estimates were equivalent to ageing 4 years for those subjects living closer to major roadways. No associations were found between increased BC exposures and poorer executive function (Wellenius et al, 2012).

Gatto et al (2014) reported that exposure to high concentrations of O<sub>3</sub> (>49ppb) was associated, though not statistically significantly, with lower executive function ( $\beta = -0.66$ , 95% CI -1.35, 0.03). Reduced reasoning ability was associated with increased exposure to PM<sub>2.5</sub>, PM<sub>2.5 exhaust</sub>, PM<sub>10</sub> and PM<sub>10 exhaust</sub> in the Whitehall II study (Tonne et al, 2014).

No statistically significant association was found between traffic load, NO<sub>2</sub>, NO<sub>x</sub>, PM<sub>2.5</sub> and PM<sub>2.5 abs</sub> and executive function in the SALIA study (Schikowski et al, 2015).

Cullen et al (2018) found associations between air pollution, estimated from a 100 metres x 100 metres land use regression model, and executive function test performance that were inconsistent in direction and of very small magnitude in UK Biobank cohorts. An increase of 1µg/m<sup>3</sup> in PM<sub>10</sub> was associated with a better response in the reasoning test ( $\beta = 0.0111$ ; 95% CI 0.0054; 0.0169) on a scale 1 to 13. Increases of NO<sub>2</sub> (1µg/m<sup>3</sup>) were also associated with better reasoning scores ( $\beta = 0.032$ ; 95% CI 0.0013, 0.0050). No association was found between reasoning and either PM<sub>10-2.5</sub> or NO<sub>x</sub> (Cullen et al, 2018).

Cumulative exposure to air pollution, measured with the API averaged from 30-days to 3 years, was associated with worse mathematics test scores ( $\beta = -0.004 \pm 0.002^{11}$  for 30-day;  $\beta = -0.016 \pm 0.007$  for 3-year) in participants of a nationally representative longitudinal survey database in China. No associations were found for 1-day and 7-day API with mathematics tests. The longer the cumulative exposure, the higher the effect: an increase in the 30-day mean API by 1 standard deviation lowered the scores by  $0.068 \pm 0.011$ , whereas an increase in the 3-year mean API decreased the scores by  $0.211 \pm 0.033$  (Zhang et al, 2018).

Molina-Sotomayor et al (2019) found that a group of elderly women living in a clean area in Viña del Mar (Chile) had significant better scores in time and space orientation and calculation ability, although not adjusted for any confounding variables, than those in a polluted area in Santiago de Chile (Molina-Sotomayor et al, 2019).

Results from The Korean Frailty and Aging Cohort Study found that PM<sub>2.5</sub> was associated with worse scores in the Digit Backward Span test and the Frontal Assessment Battery. Sulphur dioxide (SO<sub>2</sub>) was also related to lower scores in the Digit Backward Span, whereas NO<sub>2</sub> was associated with worse performance in the Frontal Assessment Battery and O<sub>3</sub> with better scores (Shin et al, 2019).

A study conducted among the general population in Tehran found that exposure to high residential traffic, self-reported by participants in a questionnaire, was associated with worse

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<sup>11</sup> Regression coefficient  $\pm$  standard error.



scores on the TMT part B test compared with the scores in those participants reporting low residential traffic ( $\beta = 0.127s$ ; 95% CI 0.024s, 0.325s) (Rafiee et al, 2019).

### 3.3.2.2 Attention

Table 3.3 summarises the characteristics, exposure, adjustments and outcomes of the 6 epidemiological studies reviewed assessing associations between air pollution and attention. Ranft et al (2009) reported an association between long-term (20-years) exposure to traffic, measured as living within 50 m of a busy road, and decreased attention ( $\beta = -5.1$ , 95% CI -8.2, -2.0). Associations of attention with PM<sub>10</sub> exposures, assigned at different time points from concentrations measured at the nearest monitor site, did not show a clear pattern ( $\beta = 0.0$  or 0.2) and were not statistically significant.

In contrast, Chen and Schwartz (2009) analysed the effect of PM<sub>10</sub> and O<sub>3</sub> on attention on participants of the US Third National Health and Nutrition Examination Survey. They reported that PM<sub>10</sub> and O<sub>3</sub> had a negative impact on attention, with a larger effect for O<sub>3</sub> exposures. Each 10-ppb increase in 1-year average O<sub>3</sub> prior to examination increased the time to complete the serial-digit learning test (SDLT) test (measuring attention and short-term memory) by 0.52 seconds (95% CI 0.03, 1.01) and it increased the number of trials to achieve the set criterion ( $\beta = 0.26$ , 95 CI% 0.03, 0.48). This was equivalent to ageing 5.3 years. Each 10 $\mu\text{g}/\text{m}^3$  increase in 1-year average PM<sub>10</sub> prior to examination was associated with an increase in the number of trials to achieve the criterion of 2 correct repetitions of the learned number series 0.09 (95% CI 0.00, 0.17) and with an increase on the SDLT total scores of 0.12 seconds (95% CI -0.07, 0.31,  $p > 0.05$ ) (Chen and Schwartz, 2009).

No statistically significant associations were reported between traffic load, NO<sub>2</sub>, NO<sub>x</sub>, PM<sub>10</sub>, PM<sub>2.5</sub> or PM<sub>2.5 abs</sub> and attention in the SALIA study conducted in the North Rhine-Westfalia area (Germany) (Schikowski et al, 2015).

Analysis of the UK Biobank cohort suggested that exposure to PM<sub>2.5</sub> was associated with a reaction time rate ratio of 1.0032 (95% CI 1.0012, 1.0053 per unit ( $\mu\text{g}/\text{m}^3$ ), with values above 1 indicating relatively longer reaction time. No association was found with PM<sub>10</sub>, PM<sub>10-2.5</sub>, NO<sub>2</sub> or NO<sub>x</sub> (Cullen et al, 2018).

Shin et al (2019) reported that exposures to PM<sub>10</sub>, PM<sub>2.5</sub> and NO<sub>2</sub> were associated with worse scores in the digit forward span test, whilst CO, SO<sub>2</sub> and O<sub>3</sub> were associated with better scores in The Korean Frailty and Aging Cohort Study (Shin et al, 2019).

Rafiee et al (2019) reported worse attention scores in the TMT part A test for those subjects self-reported to live in an area with high residential traffic compared with subjects in areas with low residential traffic ( $\beta = 0.118s$  ; 95% CI 0.062s; 0.238s).



### 3.3.2.2 Memory

Eleven studies which provide evidence on air pollution and memory have been reviewed. A summary of their characteristics, exposure, adjustments and outcomes is reported in the Table 3.4.

Chen and Schwartz (2009) reported an association between exposure to 1-year average PM<sub>10</sub> and O<sub>3</sub> exposure prior to examination and reduced short-term memory, measured with the SDLT test as discussed in the previous section (Chen and Schwartz, 2009).

Wellenius et al (2012) found that an inter-quartile range decrease (851.2 metres) in residential distance to a major road was associated with reduced scores in the Hopkins Verbal Learning Test-Revised (HVLT-R) immediate recall. The associations were significant in participants aged 77 and younger ( $\beta = -0.6$ , 95% CI -1.1, -0.1) and in those with college education ( $\beta = -0.66$ , 95% CI -1.15, -0.17). They also reported that an IQR reduction in distance to main road was associated with reduced delayed memory in subjects  $\leq 77$  age ( $\beta = -0.59$ , 95% CI -0.87, -0.31) and subjects with college education ( $\beta = -0.4$ , 95% CI -0.7, -0.1). No associations were found with performance on the HVLT-R word recognition ( $\beta = 0.07$ , 95% CI -0.1, 0.2) or with reduced working memory ( $\beta = -0.04$ , 95% CI -0.15, 0.07). Overall, they reported these results to be equivalent to ageing 2 years. They also studied the effect of BC exposures and reported that an IQR increased in BC exposures (IQR = 0.11  $\mu\text{g}/\text{m}^3$ ) was associated with reduced HVLT-R immediate recall ( $\beta = -0.36$ , 95% CI -0.71, -0.01). No associations were found between BC exposure and delayed recall or working memory (Wellenius et al, 2012).

The US Health and Retirement study found a strong positive association between exposure in the third (12.185–13.796  $\mu\text{g}/\text{m}^3$ ) and fourth (13.797–20.661  $\mu\text{g}/\text{m}^3$ ) quartiles of PM<sub>2.5</sub> and reduction in episodic memory, an early marker of cognitive decline (Ailshire and Crimmins, 2014). They reported that the scores for episodic memory decreased  $\beta = -0.35$  (95% CI -0.51, -0.19) and  $\beta = -0.17$  (95% CI -0.33, -0.01) for the third and fourth quartile respectively. A 10  $\mu\text{g}/\text{m}^3$  increment of PM<sub>2.5</sub> was linked with an increased odds ratio of errors on working memory and orientation tests (OR=1.53, 95% CI 1.02, 2.30) in the American Changing Life survey (Ailshire and Clarke, 2015).

In the German SALIA study, Schikowski et al (2015) reported that traffic load, NO<sub>2</sub> and NO<sub>x</sub> were associated (non-significantly) with reduced episodic and semantic memory, whereas PM<sub>10</sub>, PM<sub>2.5</sub> and PM<sub>2.5 abs</sub> showed an opposite (non-significant) trend. Reduced memory was associated with increased exposure to PM<sub>2.5</sub>, PM<sub>2.5 exhaust</sub>, PM<sub>10</sub> and PM<sub>10 exhaust</sub> in the Whitehall II study, but results were not significant (Tonne et al, 2014).

Gatto et al (2014) reported that exposure to PM<sub>2.5</sub> was positively associated with lower verbal learning ( $\beta = -0.32$  per 10  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub>, 95% CI -0.63, 0.00) and with lower logical, visual and semantic memory (not significant). No significant associations were reported for O<sub>3</sub> and NO<sub>2</sub> (Gatto et al, 2014). Cullen et al (2018) found associations between NO<sub>2</sub> (1  $\mu\text{g}/\text{m}^3$ ) and worse visuospatial memory ( $\beta = 0.032$ ; 95% CI 0.0013, 0.0050) in the UK Biobank cohort. No

association was found between PM<sub>10</sub>, PM<sub>10-2.5</sub>, NO<sub>2</sub> and NO<sub>x</sub> with numeric or prospective memory, or between PM<sub>10</sub>, PM<sub>10-2.5</sub>, and NO<sub>x</sub> with visuospatial memory (Cullen et al, 2018).

PM<sub>2.5</sub> exposure was associated with raised odds of poorer cognitive performance on the 3-word memory test (OR =1.37; 95% CI 1.08, 1.74) in a nationally representative sample of older adults from the National Survey of Health and Nutrition in Mexico (Salinas-Rodriguez et al, 2018).

A group of physically active women living in a relatively unpolluted area in Chile had better recall scores than a group of sedentary women living in a polluted area in Santiago de Chile, but similar registration scores. No differences were observed between physically active groups in the 2 environments (Molina-Sotomayor et al, 2019).

In the Korean Frailty and Aging Cohort Study, PM<sub>2.5</sub> exposure was associated with worse Word List, Word List Recall, Recall Storage and Word List Recognition test scores. Exposure to CO was associated with lower Word List and Word Recall List test scores, and exposure to SO<sub>2</sub> with lower Word List Recall and Recall Storage test scores. NO<sub>2</sub> exposure was associated with better Word List test scores but worse scores in the Word Recall List. PM<sub>10</sub> levels were associated with better Word List scores, exposure to O<sub>3</sub> was associated with better Word List Recall and Recall Storage test scores (Shin et al, 2019).

#### 3.3.2.4 Constructional praxis and coding ability

Two studies assessed the associations of air pollution with constructional praxis and another study did so with coding ability. Table 3.5 summarises the characteristics, exposure, adjustments and outcomes of both studies.

Schikowski et al (2015) found a significant association between an inter-quartile (IQR) increase of exposure to NO<sub>2</sub> ( $\beta = -0.27$ , 95% CI -0.45, -0.10, IQR= 25.9 $\mu\text{g}/\text{m}^3$ ), NO<sub>x</sub> ( $\beta = -0.25$ , 95% CI -0.42, -0.08, IQR= 39.5 $\mu\text{g}/\text{m}^3$ ), and PM<sub>10</sub> ( $\beta = -0.15$ , 95% CI -0.29, -0.01, IQR= 26.4 $\mu\text{g}/\text{m}^3$ ) and reduced scores (that is, worse) in the Figure Copying test that assesses constructional praxis. Traffic load within a 100-m buffer (IQR= 211k car-km/day), PM<sub>2.5</sub> (IQR= 17.4 $\mu\text{g}/\text{m}^3$ ) and PM<sub>2.5abs</sub> (IQR= 1.3 m<sup>-1</sup> x10<sup>-5</sup>) also showed an association (non-significant)( $\beta = -0.19$  to -0.10) with reduced constructional praxis. Subjects with the APOE  $\epsilon 4$  allele had a stronger association between all the air pollutants considered and reduced constructional praxis (p-interaction <0.01) suggesting that carrying the APOE  $\epsilon 4$  was an effect modifier. Air pollution was associated with worse visuo-construction performance scores in the SALIA cohort study for PM<sub>10</sub> ( $\beta = -0.25$ , 95% CI -0.40, -0.11, IQR = 8.0 $\mu\text{g}/\text{m}^3$ ), PM<sub>2.5</sub> ( $\beta = -0.21$ , 95% CI -0.36, -0.06, IQR= 4.9 $\mu\text{g}/\text{m}^3$ ) and NO<sub>2</sub> ( $\beta = -0.26$ , 95% CI -0.50, -0.03, IQR = 13.8 $\mu\text{g}/\text{m}^3$ ) (Huls et al, 2018).

Chen and Schwartz (2009) found an association between annual PM<sub>10</sub> and O<sub>3</sub> exposures during the year prior to testing, and reduced coding ability, measured with the symbol-digit substitution test (SDST). A larger (and significant) effect on reduced coding ability was

reported for an increase of 10 ppb of O<sub>3</sub> ( $\beta = 0.11$ , 95% CI 0.00, 0.22) than for an increase of 10 µg/m<sup>3</sup> of PM<sub>10</sub> ( $\beta = 0.0$ , 95% CI -0.04, 0.05).

### 3.3.2.5 Language

Five studies have analysed the associations between air pollution and language skills. Table 3.6 presents a summary of their characteristics, exposure, adjustments and outcomes.

Wellenius et al (2012) found an association between decreasing IQR distance to a major road (851.2 metres) and poor performance in language, using letter ( $\beta = -1.4$ , 95% CI -2.7, -0.2) and category fluency ( $\beta = -0.7$ , 95% CI -1.1, -0.3) tests in the MOBILIZE study. This was equivalent to ageing by 4 years. Results from a nationally representative sample of older adults from the National Survey of Health and Nutrition in Mexico showed that exposure to PM<sub>2.5</sub> concentration is associated with lower number of valid animals named in the verbal fluency test ( $\beta = -0.72$ , 95% CI -1.05, -0.4) (Salinas-Rodriguez et al, 2018). In a nationally representative longitudinal survey database in China, language scores were associated with cumulative exposures to air pollution, measured with the API, averaged from 7-days to 3-years ( $\beta = -0.013 \pm 0.005^{12}$  for 7-day;  $\beta = -0.086 \pm 0.021$  for 3-year). No associations were found for 1-day API with verbal tests. The effect was higher for language test score than for mathematics test scores. As with mathematics scores, the longer the cumulative exposure, the higher the effect: an increase in the 7-day mean API by 1 standard deviation lowered the verbal scores by  $0.278 \pm 0.026$ , whereas an increase in the 3-year mean API decreased the verbal scores by  $1.132 \pm 0.108$  (Zhang et al, 2018).

On the other hand, no significant associations were found between language tests scores and BC exposures in the MOBILIZE study (Wellenius et al, 2012). This is consistent with the Whitehall II study conducted in London, which found non-significant associations between PM<sub>2.5</sub>, PM<sub>2.5</sub> exhaust, PM<sub>10</sub> and PM<sub>10</sub> exhaust with semantic and phonemic fluency (Tonne et al, 2014).

No differences in language scores were observed between women living in clean and polluted areas in Chile (Molina-Sotomayor et al, 2019).

### 3.3.3 Cognitive function decline

A summary of the characteristics, exposure, adjustments and outcomes of the 9 epidemiological studies on air pollution and cognitive function decline reviewed are reported in Table 3.7.

Weuve et al (2012) found associations between global cognitive decline and an increase of 10 µg/m<sup>3</sup> PM<sub>2.5</sub> ( $\beta = -0.018$ ; 95% CI -0.035, -0.002) and PM<sub>10-2.5</sub> ( $\beta = -0.020$ ; 95% CI -0.032, -0.008) on a 7-year follow up period equivalent to ageing by 2 years in the Nurse's Health Study (Weuve et al, 2012).

<sup>12</sup> Regression coefficient  $\pm$  standard error.

Cacciottolo et al (2017) reported that participants of the Women's Health Initiative Memory Study (WHIMS) living in areas with high PM<sub>2.5</sub> exposure ( $>12\mu\text{g}/\text{m}^3$ ) had a greater hazard ratio (HR) for accelerated cognitive decline (HR = 1.81; 95% CI 1.42, 2.32) during a 10-year follow up period. Greater hazard ratios were observed in carriers of the *APOE*  $\epsilon 4/\epsilon 4$  alleles (HR=3.64; 95% CI 1.36, 9.69) than in carriers of the *APOE*  $\epsilon 3/\epsilon 3$  alleles (HR = 1.65; 95% CI 1.23, 2.23), but these differences were not statistically significant (p-value interaction  $>0.05$ ).

Long-term exposure to air pollution showed a trend of association (non-significant) between an IQR increase of PM<sub>2.5</sub> (IQR=  $1.1\mu\text{g}/\text{m}^3$ ), PM<sub>2.5</sub> exhaust (IQR =  $0.27\mu\text{g}/\text{m}^3$ ), PM<sub>10</sub> (IQR =  $1.8\mu\text{g}/\text{m}^3$ ) and PM<sub>10</sub> exhaust (IQR =  $0.30\mu\text{g}/\text{m}^3$ ) and a decline in reasoning, memory, semantic and phonemic fluency over a 5-year period in participants of the Whitehall II Study. Associations for a yearly lag 4 IQR increase of PM<sub>10</sub> ( $\beta=-0.041$ ; 95% CI -0.079, -0.003) and PM<sub>2.5</sub> ( $\beta=-0.039$ ; 95% CI -0.073; -0.005) were associated with memory decline in those subjects who had never moved away from the greater London area (Tonne et al, 2014).

In the Chinese Longitudinal Healthy Longevity Survey, participants who lived all or part of their lives in rural environments showed faster cognitive decline than did participants who had always lived in urban environments. Xu et al (2017) suggested that the faster decline in rural subjects could be related to not having access to socioeconomic benefits, such as retirement pension and access to health care. Other confounding factors might be attributed to the 'healthy migrant effect' with healthier subjects moving to urban areas in search of better economic opportunities (Tong and Piotrowski, 2012) although this would not explain the faster decline found by Xu et al in participants who had moved from rural to urban areas, compared with those who had lived in urban areas from birth.

In participants of the Betula study (Sweden), living in an area with relatively low NO<sub>x</sub> exposures ( $21 \pm 16\mu\text{g}/\text{m}^3$ ), a longitudinal analysis assessing change of episodic memory and exposure to NO<sub>x</sub> over a 5-year period did not find any association ( $\beta = 0.01$ , 95% CI -0.02, 0.03) per  $1\mu\text{g}/\text{m}^3$  NO<sub>x</sub> increase (Oudin et al, 2017).

In a cohort of older Puerto Rican adults living in Greater Boston, in-year interquartile range moving averages of BC (IQR =  $53.0\text{ng}/\text{m}^3$ ), nickel (IQR =  $2.0\text{ng}/\text{m}^3$ ), sulphur (IQR =  $390\text{ng}/\text{m}^3$ ), silicon (IQR =  $11.0\text{ng}/\text{m}^3$ ) and PM<sub>2.5</sub> (IQR =  $1.75\mu\text{g}/\text{m}^3$ ) were associated with decline in several cognitive domains. Verbal memory was reduced for nickel ( $\beta = -0.25$ , 95% CI -0.40, -0.10) and BC ( $\beta = -0.38$ , 95% CI -0.46, -0.30) per 1-year IQR increase. In contrast, increased PM<sub>2.5</sub> exposure was associated with better verbal memory scores ( $\beta = 0.23$ , 95% CI 0.06, 0.41). Worse recognition scores were observed per 1-year IQR increase for all pollutants under consideration, ranging from  $\beta = -0.25$  (95% CI -0.36, -0.13) for silicon to  $\beta = -0.57$  (95% CI -0.76, -0.37) for nickel. Worse mental processing was associated with a 1-year IQR increase of BC ( $\beta = -1.14$ , 95% CI -1.55, -0.74) and nickel ( $\beta = -1.18$ , 95% CI -1.91, -0.45). Worse executive function was also associated with BC ( $\beta = -0.94$ , 95% CI -1.31, -0.56) and nickel ( $\beta = -1.94$ , 95% CI -2.62, -1.26). On the contrary, better visuospatial scores were associated with PM<sub>2.5</sub> ( $\beta = 0.33$ , 95% CI 0.10, 0.55), sulphur ( $\beta = 0.31$ , 95% CI 0.08, 0.54) and

silicon ( $\beta = 0.15$ , 95% CI 0.04, 0.26). The magnitude of the effect of BC increased for all cognitive domains when adjusted for PM<sub>2.5</sub> and in two-pollutant models including nickel, sulphur and silicon (for example, verbal memory changed from  $\beta = -0.38$  to  $\beta = -0.46$ ) (Wurth et al, 2018).

Higher regional ozone concentrations were associated with a faster rate of cognitive decline in individuals followed by the National Alzheimer's Coordinating Centre with normal cognition at baseline. The score in the cognitive dementia sum of boxes test was lower in the first tertile compared with the third tertile of ozone exposure ( $\beta = -0.27$ , 95% CI -0.4, -0.1) in the normal cognition group, with higher scores representing faster cognitive decline. Subjects who had one or more *APOE*  $\epsilon 4$  alleles experienced faster cognitive decline. No effect was observed for those subjects who entered the study with baseline cognitive impairment. No effect was observed for PM<sub>2.5</sub> exposure (Cleary et al, 2018).

No association was found between PM<sub>10</sub>, PM<sub>10-2.5</sub>, NO<sub>2</sub> and NO<sub>x</sub>, and cognitive decline in the domains of memory (numeric, visuospatial, prospective), reasoning, or reaction time in the UK Biobank cohort (Cullen et al, 2018).

Exposure to PM<sub>2.5</sub> over the preceding 3-year period (IQR= 2.81 $\mu\text{g}/\text{m}^3$ ) was associated with greater annual declines in immediate recall ( $\beta = -19.3\%$ , 95% CI -1.9%, -36.2%) and new learning ( $\beta = -14.8\%$ , 95% CI -4.4%, -24.9%) in participants of the Women's Health Initiative (WHI) Memory Study, who also participated in the subsequent ancillary studies: WHI Study of Cognitive Aging (WHISCA) and the WHI Memory Study of Magnetic Resonance Imaging (WHIMS-MRI). No association was found between 3-year average PM<sub>2.5</sub> exposure and decline in delayed-recall or composite scores (Younan et al, 2020).

### 3.3.4 Mild cognitive impairment and incident cognitive impairment

Table 3.8 presents a summary of the characteristics, exposure, adjustments and outcomes of the 7 epidemiological studies reviewed on air pollution and mild cognitive impairment and incident cognitive impairment.

The REGARDS study conducted across 48 contiguous US states reported that an increase of 10 $\mu\text{g}/\text{m}^3$  exposure to PM<sub>2.5</sub> resulted in an increased OR of incident cognitive impairment of 1.26 (95% CI 0.97, 1.64). The OR was attenuated to 0.98 (95% CI 0.72, 1.34) after adjusting for several confounding factors (Loop et al, 2015).

An IQR increase in PM<sub>2.5</sub> (3.9 $\mu\text{g}/\text{m}^3$ ) or diesel PM (0.35 $\mu\text{g}/\text{m}^3$ ) was not associated with mild cognitive impairment (MCI) in older women participating in the WHIMS study (Chen et al, 2017c). The authors reported a HR of 0.93 (95% CI 0.79, 1.09) for PM<sub>2.5</sub> and of 0.95 (95% CI 0.82, 1.11) for diesel PM exposures.

On the other hand, Zeng et al (2010) found that elderly residents in China with higher exposures to air pollution, measured as API, had a higher odds ratio (OR = 1.09; 95% CI 1.01, 1.18) for cognitive impairment (MMSE <18) (Zeng et al, 2010). Results of the Heinz Nixdorf Recall study also suggest an association between increased 1-year IQR exposure to PM<sub>2.5</sub> (1.44µg/m<sup>3</sup>) and overall MCI (OR=1.16; 95% CI 1.05, 2.24), especially with amnesic MCI (OR=1.22; 95% CI 1.0.8, 1.38) (Tzivian et al, 2016). The authors reported a synergic effect between PM<sub>2.5</sub> and noise, with higher odds ratio (OR=1.30; 95% CI 1.01, 1.67) for subjects exposed to higher noise levels (L<sub>DEN</sub> ≥60).

Sanchez-Rodriguez et al (2006) observed that the prevalence of older residents with cognitive impairment (MMSE <23 points) was higher in Mexico DC (18%) than in rural areas (11%), with an odds ratio (OR) of 5.67 (95%CI 1.14, 38.02)(Sanchez-Rodriguez et al, 2006). No formal assessment of air pollution exposure concentrations was made in their study beyond a simple urban-rural comparison.

In a study of participants of the Taiwan Longitudinal Study on Aging, Lo et al (2019) reported that long-term exposure to PM<sub>10</sub> and O<sub>3</sub> was associated with cognitive impairment. An increase of 10µg/m<sup>3</sup> of PM<sub>10</sub> was associated with an increased risk of cognitive impairment with an OR = 1.094 (95% CI 1.020, 1.174). Likewise, an increase of 10ppb of O<sub>3</sub> was associated with a larger OR=1.878 (95% CI 1.363, 2.56) for cognitive impairment. Two-pollutant models remained statistically significant (Lo et al, 2019).

IQR increases in 1-month (8.3µg/m<sup>3</sup>) and 2-month (7.9µg/m<sup>3</sup>) PM<sub>2.5</sub> were associated with worsening of symptoms related to mild cognitive impairment, as assessed during outpatient visits, in participants of the Clinical Research Center for Dementia of South Korea (CREDOS) Study. The risk was increased 40.7% (95% CI 18.3 - 67.3%) and 24.9% (95% CI -3.1 - 61.1%) for 1 and 2 month IQR increases. Two-pollutant models remained statistically significant for 1 month averages for aggravated symptoms of mild cognitive impairment (Lee et al, 2019).

### 3.3.5 Dementia, Alzheimer's disease

Sixteen studies have assessed the association between air pollution and dementia. Table 3.9 presents a summary of their characteristics, exposure, adjustments and outcomes.

Exposure to air pollution has been significantly associated with dementia in several studies. Residential proximity to traffic was related to incident dementia (ascertained from provincial health administrative databases with validated algorithms) in a cohort of over 2 million participants in Ontario (Canada) (Chen et al, 2017b). The hazard ratio (HR) was 1.07 (95% CI 1.06, 1.08) for people living within 50 metres of a major traffic roadside, and the HR decreased with distance from main traffic roads. The strongest HRs were found for residents of the main cities in Ontario (Canada) and for urban residents. Consistent results for PM<sub>2.5</sub> were reported in a follow-up study. An IQR increase in 5-year cumulative PM<sub>2.5</sub> exposure (4.8µg/m<sup>3</sup>) was positively associated with an HR of 1.04 (95% CI 1.03, 1.05) (Chen et al, 2017a).



Another population-based cohort study in Ontario, the National Population Health Survey and the Canadian Community Health Survey, reported only non-statistically significant associations between exposure to NO<sub>2</sub> and dementia incidence (HR = 1.10; 95% CI 0.99, 1.19 per 5ppb) and between exposure to PM<sub>2.5</sub> and dementia (HR = 1.29; 95% CI 0.99, 1.64 per 10µg/m<sup>3</sup>) (Ilango et al, 2020).

In the Women's Health Initiative Memory Study (WHIMS), consisting of 4500 older women across USA, a high residential exposure to PM<sub>2.5</sub> (>12µg/m<sup>3</sup>) averaged during the 3 years prior to the incident event, was associated with an increased hazard ratio (HR = 1.92; 95% CI 1.31, 2.80) (Cacciottolo et al, 2017).

However, a recent reanalysis conducted in the WHIMS cohort did not report an association between an interquartile increment (3.9µg/m<sup>3</sup>) of annual PM<sub>2.5</sub> exposures and the incidence of dementia in older women (HR = 0.99; 95% CI 0.81, 1.22), nor did they find significant associations between an IQR increment of diesel particulate matter exposure (0.35µg/m<sup>3</sup>) and dementia (HR = 1.02; 95% CI 0.83, 1.25)(Chen et al, 2017c).

An increase of exposure of 4.34µg/m<sup>3</sup> annual PM<sub>2.5</sub> was positively associated with an increased hazard ratio for Alzheimer's disease (physician-diagnosed) (HR = 2.38; 95% CI 2.21, 2.56) in a cohort of around 100k participants randomly selected from the National Health Insurance Research Database (NHIRD) of Taiwan in the year 2000 (Jung et al, 2015). Likewise, exposure to the highest tertile of PM<sub>10</sub> (≥49.23µg/m<sup>3</sup>) was linked with an increased odds ratio (OR) of vascular dementia (OR = 3.61; 95% CI 1.67, 7.81) and Alzheimer's disease (OR = 4.17; 95% CI 2.31, 7.54) compared to the lowest tertile (<44.95µg/m<sup>3</sup>), in a case-control study in Taiwan (Wu et al, 2015). In contrast, a nested case-control study within the Taiwan NHIRD database found no association between risk of incident vascular dementia and 3 year, 5 year or 7 year average exposure to PM<sub>10</sub> (Li et al, 2019).

Another study conducted using data from the NHIRD of Taiwan for the period 2000 to 2010 reported positive associations between exposure to NO<sub>2</sub> and dementia. Subjects exposed to the fourth quartile of NO<sub>2</sub> (>9,826ppb [*sic*]<sup>13</sup>) had an adjusted HR of 1.54 (95% CI 1.34, 1.77) compared with subjects exposed to NO<sub>2</sub> in the lowest quartile (<6,652ppb [*sic*]) (Chang et al, 2014). Li et al (2019) found an increase in the odds ratio of incident vascular dementia (OR=1.06; 95% CI 1.01, 1.11 per 1ppb) with 7-year average exposure to NO<sub>2</sub>, in a nested case-control study within NHIRD. A study in Ontario (reported above) also found an increased incidence of dementia was associated with long-term average concentrations of NO<sub>2</sub> (HR = 1.10; 95% CI 1.08, 1.12 per IQR increase of 26.7µg/m<sup>3</sup>)(Chen et al, 2017a).

A United States Veterans Health Administration (VA) study reported that an IQR increase in baseline PM<sub>2.5</sub> exposure was associated with dementia mortality (HR = 1.09; 95% CI 1.06,

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<sup>13</sup> Yearly averaged exposures calculated from the baseline to the date of dementia occurrence, the withdrawal of patients, or the end of the study period, and the data were categorized into quartiles. Units reported as in original paper.

1.12). Participants exposed to the highest PM<sub>2.5</sub> quartile (13.9 to 20.1 µg/m<sup>3</sup>) had a higher incidence of dementia (IR = 0.70; 95% CI 0.68, 0.72 per 1000 person-years) than participants in the lowest PM<sub>2.5</sub> quartile (4.8 to 10 µg/m<sup>3</sup>) (Bowe et al, 2019).

A positive association was also reported between NO<sub>x</sub> exposure and dementia incidence in the Betula study in Sweden (approximately 2000 participants). A 10 µg/m<sup>3</sup> increase in NO<sub>x</sub> was associated with a HR of 1.05 (95% CI 0.98, 1.12) of dementia. The association was stronger in a sub-analysis that excluded the younger population (HR = 1.08; 95% CI 1.00, 1.16) or when the highest quartile (>26 µg/m<sup>3</sup>) was compared with the lowest quartile (4.8 to 9 µg/m<sup>3</sup>) (HR = 1.60; 95% CI 1.02, 2.10) (Oudin et al, 2016). In a subsequent analysis, based on the same study population, in order to investigate the contribution to noise exposure to the impact of traffic-related air pollution on the risk of dementia, subjects exposed to the third (17 to 26 µg/m<sup>3</sup>) and fourth (≥26 µg/m<sup>3</sup>) quartiles of traffic-related NO<sub>x</sub> had a higher hazard ratio for developing dementia (HR<sub>3ile</sub> = 1.48; 95% CI 1.03, 2.12; HR<sub>4ile</sub> = 1.41; 95% CI 0.97, 2.03). The effect was not modified by modelled residential traffic noise levels (Andersson et al, 2018). In a recent analysis from the Betula study restricted to data from participants who were *APOE* ε4-positive, Oudin et al (2019) reported increased hazard ratio for incident dementia (AD or VaD) in the third (HR = 1.52; 95% CI 1.08, 2.12) and fourth (HR = 1.41; 95% CI 1.01, 1.98) quartiles of exposure compared to the lowest quartile. However, no significant association was found for 10 µg/m<sup>3</sup> increase in NO<sub>x</sub> (HR = 1.03; 95% CI 0.97, 1.10). For AD, hazard ratios were higher in the third (HR = 1.72; 95% CI 1.12, 2.65) but not the fourth (HR = 1.53; 95% CI 0.99, 2.36) quartile, with no significant association per 10 µg/m<sup>3</sup> NO<sub>x</sub> increase (HR = 1.04, 95% CI 0.96, 1.13) (Oudin et al, 2019).

A further analysis showed that PM<sub>2.5</sub> from local residential wood burning was associated with dementia incidence (HR = 1.55; 95% CI 1.00, 2.41) per each 1 µg/m<sup>3</sup> increase of wood burning-origin PM<sub>2.5</sub>. The hazard ratio was larger for those participants who were living in areas within the highest quartile of PM<sub>2.5</sub> from residential wood burning who also had a wood-burning stove at home (HR = 1.74; 95% CI 1.10, 2.75) compared to participants in any of the other quartiles without wood-burning stoves at home. PM<sub>2.5</sub> from traffic exhaust was also associated with increased risk of dementia incidence with hazard ratios of 1.66 (95% CI 1.16, 2.39) and 1.41 (95% CI 0.97, 2.23) for the third and fourth quartiles respectively (Oudin et al, 2018).

Carey et al (2018) found an increased incidence of dementia in London associated with NO<sub>2</sub> (HR = 1.15; 95% CI 1.04, 1.28; IQR = 7.47 µg/m<sup>3</sup>), PM<sub>2.5</sub> (HR = 1.06; 95% CI 1.01, 1.13; IQR = 0.95 µg/m<sup>3</sup>) and traffic related PM<sub>2.5</sub> (HR = 1.08; 95% CI 0.99, 1.18; IQR = 0.58 µg/m<sup>3</sup>) but not with O<sub>3</sub>. NO<sub>2</sub> exposure was also associated with higher risk of Alzheimer's disease (HR = 1.23; 95% CI 1.07, 1.43), vascular dementia (HR = 1.15; 95% CI 0.96, 1.39) and non-specific dementia (HR = 1.13; 95% CI 0.99, 1.28) per each IQR increase. Similar, but smaller, effects were observed for PM<sub>2.5</sub> and for traffic-related PM<sub>2.5</sub> (Carey et al, 2018).

O<sub>3</sub> exposure has also been associated with an increased risk of Alzheimer's disease. Studies conducted in Taiwan reported that an IQR increase of 10.91 ppb of O<sub>3</sub> was associated with a HR of 3.12 (95% CI 2.92, 3.33) for Alzheimer's disease (Jung et al, 2015). Another Taiwanese



study reported that participants exposed to the highest tertile of O<sub>3</sub> ( $\geq 21.56$ ppb) had an adjusted OR of 2.09 (95% CI 1.01, 4.33) for dementia and an OR of 2.00 (95% CI 1.14, 3.50) for Alzheimer's disease compared to the lowest tertile ( $< 20.20$ ppb) (Wu et al, 2015). On the other hand, no association was found between 3-year, 5-year or 7-year O<sub>3</sub> exposure and risk of incident vascular dementia in a nested case-control study of the NHIRD cohort in Taiwan (Li et al, 2019). Likewise, the study by Chen et al. in Ontario did not find increased dementia incidence linked with increased concentration of O<sub>3</sub> (IQR 12.4 $\mu$ g/m<sup>3</sup>) (Chen et al, 2017a); neither did the study in London by Carey et al (2018), assessing the effect of ozone on the incidence of any type of dementia.

Chang et al (2014) reported that participants randomly selected from the NHIRD study of people living in Taiwan exposed to the highest quartile of CO ( $> 297$  ppm) had a greater adjusted hazard ratio for dementia (adjusted HR = 1.61; 95% CI 1.39, 1.85) than did participants exposed to the lowest quartile ( $< 196$ ppm), consistent between men and women. A nested case-control study in the same NHIRD cohort found an increased odds ratio of incident vascular dementia for people whose 7-year average CO exposure was in the second (OR = 1.46; 95% CI 1.11, 1.93), third (OR = 1.53; 95% CI 1.10, 2.13) or fourth (OR = 1.53; 95% CI 1.03, 2.27) quartile compared to the first quartile (Li et al, 2019). No associations were found with SO<sub>2</sub> exposure in the same study.

IQR increases in 1-month (8.3 $\mu$ g/m<sup>3</sup>) and 2-month (7.9 $\mu$ g/m<sup>3</sup>) PM<sub>2.5</sub> were associated with worsening of symptoms related to Alzheimer's disease assessed during outpatient visits in participants of the CREDO Study. The risk increased 17.1% (95% CI 2.7, 33.5%) for a 1-month IQR PM<sub>2.5</sub> increase and 20.7% (95% CI 1.8, 43.1%) for a 2-month increase. The distress of Alzheimer's diseases carers was also evaluated, and increased 29% (95% CI 8.1, 53.9) and 36.1% (95% CI 9.1, 69.8%) for 1-month and 2-month IQR PM<sub>2.5</sub> increases. The PM<sub>2.5</sub> results remained statistically significant for worsening of Alzheimer's disease symptoms and caregiver distress for 1-month and 2-month exposures when adjusted in 2-pollutant models for NO<sub>2</sub>, SO<sub>2</sub> or O<sub>3</sub>, but not for CO (Lee et al, 2019).

### 3.3.6 Hospital admissions due to neurological disease

Table 3.10 summarises the characteristics, exposure, adjustments and outcomes in the 6 studies that have analysed the associations between air pollution and hospital admissions due to neurological disease.

Short-term exposure to PM<sub>2.5</sub> was not associated with an increase of hospitalisations due to Alzheimer's disease (0.20%; 95% CI -1.26%, 1.69%) or dementia (0.92%; 95% CI -0.44%, 2.30%) per each 10 $\mu$ g/m<sup>3</sup> increase in the 2 days preceding the episode, in a national case-crossover analysis of the hospitalisations among Medicare enrollees aged 65 and over in 121 US communities. On the other hand, age was found to be significant modifier ( $p$ -value<sub>interaction</sub> = 0.009) for Alzheimer's disease hospitalisation, with an increased risk of 3.48% (95% CI 0.83, 6.19) for subjects 65 to 75 years old. Short-term PM<sub>2.5</sub> exposure was associated with an

increased mortality risk among subjects with a previous hospitalisation for Alzheimer's disease (1.04%; 95% CI 0.36%, 1.72%) or dementia (0.94%; 95% CI 0.01%, 1.89%) (Zanobetti et al, 2014).

Kioumourtoglou et al (2016) estimated the effects of long-term city-wide PM<sub>2.5</sub> concentrations on first hospital admissions for dementia, Alzheimer's disease and Parkinson's disease (primary or secondary cause) in a group of 9.8 million elderly subjects across 50 north-eastern US cities over 11 years. They reported significant associations for all 3 outcomes, with HR of 1.08 (95% CI 1.05, 1.11) for dementia, HR of 1.15 (95% CI 1.11, 1.19) for Alzheimer's disease and HR of 1.08 (95% CI 1.04, 1.12) for Parkinson's disease per 1µg/m<sup>3</sup> increase in annual PM<sub>2.5</sub> concentration (Kioumourtoglou et al, 2016).

A similar study in Rome estimated the effects of long-term exposure to air pollution on first hospital admission for dementia. First hospital admission for vascular dementia was associated with PM<sub>10</sub>, PM<sub>2.5</sub>, PM<sub>coarse</sub>, PM<sub>2.5 abs</sub>, NO<sub>2</sub> and NO<sub>x</sub>, with hazard ratios ranging from 1.05 to 1.15 (p <0.05) for increments of 5µg/m<sup>3</sup> (PM<sub>2.5</sub>, PM<sub>coarse</sub>), 10<sup>-5</sup>/m (PM<sub>2.5 abs</sub>), 10µg/m<sup>3</sup> (PM<sub>10</sub>, NO<sub>2</sub>) and 20µg/m<sup>3</sup> (NO<sub>x</sub>), and with distance to heavy traffic roadside (HR = 1.17, 95% CI 1.10, 1.24 for <50m). In contrast, exposure to most of these pollutants was associated with reduced hazard ratios for first time hospitalisation for Alzheimer's disease or 'senile dementia', ranging between 0.91 and 0.96 (p<0.05). For first time hospitalisation related to dementia, the hazard ratio associated with long-term exposure to NO<sub>2</sub> was 0.97 (95% CI 0.96, 0.99) for 10µg/m<sup>3</sup>, whereas the hazard ratios reported for exposure to NO<sub>x</sub> and O<sub>3</sub> were 1.01 (95% CI 1.00, 1.02) for 20µg/m<sup>3</sup> and 1.06 (95% CI 1.03, 1.08) for 10µg/m<sup>3</sup> respectively (Cerza et al, 2019).

Short-term exposures to PM<sub>2.5</sub> were associated with a relative risk of daily Alzheimer's hospital admissions (primary cause) of 1.38 (95% CI 1.15, 1.65) at 2-day lag in Madrid for an increment in IQR 20µg/m<sup>3</sup> of PM<sub>2.5</sub> (Culqui et al, 2017). The relative risk of daily hospital admissions for dementia with a 10µg/m<sup>3</sup> increase in O<sub>3</sub> concentrations (lag 5) was 1.09 (95% CI 1.04, 1.15) (Linares et al, 2017). Excessive heat and noise were found also to affect Alzheimer's and dementia hospital admissions respectively (Culqui et al, 2017; Linares et al, 2017).

Qiu et al (2019) evaluated the risk of hospital admissions for dementia attributable to PM<sub>2.5</sub>, PM<sub>10</sub> and PM<sub>coarse</sub> in Sichuan Province by using electronic hospitalisation summary reports from all tertiary and secondary hospitals in the area. A 10µg/m<sup>3</sup> increase of PM<sub>coarse</sub> on lag 1, lag 2 and lag 0-2 was significantly associated with dementia hospitalisations, whilst PM<sub>10</sub> or PM<sub>2.5</sub> were not associated. The attributable fraction and number of hospitalisations were 7.22% (95% CI 0.063, 12.81%) and 66 (95% CI 0, 6,118 cases) respectively per 10µg/m<sup>3</sup> increase of PM<sub>coarse</sub> (Qiu et al, 2019).

### 3.3.7 Neuro-imaging

Eight studies on 4 different American cohorts have assessed the effects of air pollution on brain morphology, white matter lesions and small vessel ischaemic disease. A summary of the study characteristics, exposure, adjustments and outcomes is reported in Table 3.11.

A  $2\mu\text{g}/\text{m}^3$  increase of  $\text{PM}_{2.5}$  exposure was associated with smaller brain volume ( $\beta = -0.32\%$ ; 95% CI -0.59, -0.05) in the Framingham Offspring Study, equivalent to one year of brain ageing (Wilker et al, 2015). However, no association between brain parenchymal fraction and  $\text{PM}_{2.5}$  or distance to residential proximity to traffic roadsides was found in the Massachusetts Alzheimer's Disease Research Centre Longitudinal Cohort (Wilker et al, 2016).

Structural brain magnetic resonance imaging was conducted in 1400 community-dwelling older women participating in the WHIMS study and who did not suffer from dementia. Women had smaller white matter (WM) volumes ( $6.23 \pm 1.28^{14} \text{ cm}^3$ , 95% CI 3.72, 8.74) when total brain volume was analysed, and a reduction of  $4.47 \pm 1.12 \text{ cm}^3$  (95% CI 2.27, 6.67) in WM association areas ( $-2.04 \pm 0.59 \text{ cm}^3$  in frontal,  $-0.73 \pm 0.3 \text{ cm}^3$  parietal and  $-1.70 \pm 0.33 \text{ cm}^3$  temporal association regions) per inter-quartile ( $3.49\mu\text{g}/\text{m}^3$ ) increase in cumulative yearly  $\text{PM}_{2.5}$  (1999 to 2006) (Chen et al, 2017c; Chen et al, 2015).

Casanova et al (2016) used voxel-based morphometric analysis and also reported that long-term (3-year average)  $\text{PM}_{2.5}$  exposure preceding MRI scans in participants in the WHIMS study was associated with smaller volumes of subcortical WM, especially in the frontal lobe, with less marked associations in the temporal, parietal and occipital lobes.

The association between WM volume and exposure to diesel particulate matter (estimated by the U.S. EPA National-Scale Air Toxics Assessment (NATA) Program<sup>15</sup>) has been inconsistent. An IQR increase ( $0.31\mu\text{g}/\text{m}^3$ ) in the first to third quartiles of diesel particulate matter concentration ( $0.01\text{--}0.55\mu\text{g}/\text{m}^3$ ) was associated with reduction of frontal and temporal WM volume but an increase in WM volume was found for the fourth quartile of concentration ( $0.55\text{--}3.93\mu\text{g}/\text{m}^3$ ) (Chen et al, 2017c).

Unexpectedly, white matter hyperintensities (WMH), a marker of small vessel disease, were associated with increased residential distance to traffic and negatively associated with exposure to  $\text{PM}_{2.5}$  ( $\beta = -0.19$ ; 95% CI -0.37, -0.005) (Wilker et al 2016, and Wilker et al 2015). No convincing argument was proposed to explain these unexpected results. In a follow-up analysis restricted to subjects with probable Alzheimer's disease, Wilker et al (2016) did not find any association between WMH and residential traffic or a  $2\mu\text{g}/\text{m}^3$  increment in  $\text{PM}_{2.5}$ .

<sup>14</sup> Regression coefficients  $\pm$  standard error.

<sup>15</sup> The U.S. EPA National-Scale Air Toxics Assessment (NATA) Program estimates ambient concentrations of around 50 of the more prevalent and higher risk hazardous air pollutants from emission inventories using a blend of chemical transport models with a dispersion model (AERMOD).

Some studies have reported an association between air pollution and higher risk of covert brain infarcts (OR 1.46; 95% CI 1.10, 1.94) per  $2\mu\text{g}/\text{m}^3$  increase of  $\text{PM}_{2.5}$  (Wilker et al, 2015). On the other hand, no association was found between exposure to  $\text{PM}_{2.5}$  or living closer to a major road and microbleeds (Wilker et al, 2016); nor were differences in small-vessel ischaemic diseases with varying exposure to  $\text{PM}_{2.5}$  or diesel particulate matter found in total brain, brain association areas, WM or GM areas (Chen et al, 2017c).

No association was found between  $\text{PM}_{2.5}$  estimated over a 6-year period prior to MRI scanning and grey matter (GM) volume in older women participating in the WHIMS study (Chen et al, 2017c; Chen et al, 2015). A subsequent analysis of the same cohort using a 3-year average  $\text{PM}_{2.5}$  exposure prior to MRI scanning and Voxel-wise morphology to characterise brain volumes reported that increased  $\text{PM}_{2.5}$  exposure was related to smaller cortical GM volume, the effects being clustered in the bilateral superior, middle and medial frontal gyri (Casanova et al, 2016). A follow-up analysis of the WHIMS cohort found that exposure to diesel particulate matter was associated with lower GM volume (Chen et al, 2017c). The largest effect was reported for the association areas of the brain ( $-12.72 \pm 1.88$ ) followed by the frontal ( $-6.64 \pm 0.91$ ), parietal ( $-3.85 \pm 0.55$ ) and temporal ( $-2.23 \pm 0.63$ ) lobes when diesel PM exposure to the fourth quartile of concentration (median =  $0.78\mu\text{g}/\text{m}^3$ ) was compared with exposure to the first-to-third quartiles (median =  $0.29\mu\text{g}/\text{m}^3$ ) (Chen et al, 2017c).

In the Atherosclerosis Risk in Communities (ARIC) study, higher mean  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$  exposures 5 to 20 years prior to the MRI scans were associated with smaller deep-grey matter volumes ( $\beta = -0.02$  SD-unit brain volume; 95% CI -0.04, 0.0 per  $1\mu\text{g}/\text{m}^3$ ). Increased  $\text{PM}_{2.5}$  concentration was associated with smaller total ( $\beta = -0.09$  SD-unit brain volume; 95% CI -0.16, -0.01) and regional brain volumes ( $\beta$  -0.08 to -0.1) in Minnesota only, but not in the other 3 study regions. No other MRI marker (total brain, frontal, occipital, parietal or temporal brain volume, hippocampus or Alzheimer's disease 'signature'<sup>16</sup>) was associated with  $\text{PM}_{2.5}$  or  $\text{PM}_{10}$  exposure (Power et al, 2018).

No association has been found between exposure to air pollutants ( $\text{PM}_{2.5}$  or diesel particulate matter) and hippocampal volumes in any of the American cohort studies (Casanova et al, 2016; Chen et al, 2017c; Chen et al, 2015; Wilker et al, 2015). Mean annual concentrations of  $\text{PM}_{2.5}$  for the year 2010 were associated with smaller left hippocampal volume ( $-10.78 \text{ mm}^3$ ) in participants of UK Biobank (Hedges et al, 2019). No associations were observed for  $\text{PM}_{\text{coarse}}$ ,  $\text{PM}_{10}$ ,  $\text{NO}_2$  or  $\text{NO}_x$  with left or right hippocampal volumes.

Exposure to diesel particulate matter was associated with an increase in ventricular volume ( $0.96 \pm 0.43 \text{ cm}^3$ ) per IQR increase ( $0.31\mu\text{g}/\text{m}^3$ ), which suggests an overall atrophic effect on the ageing brain (Chen et al, 2017c). No association was found between  $\text{PM}_{2.5}$  and ventricular volume (Chen et al, 2017c).

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<sup>16</sup> Alzheimer's Disease signature region refers to multiple grey matter regions atrophied in Alzheimer's disease, such as parahippocampal, entorhinal, inferior parietal lobules, hippocampus, precuneus and cuneus.

An IQR increase ( $3.49\mu\text{g}/\text{m}^3$ ) in cumulative yearly  $\text{PM}_{2.5}$  (1999 to 2006) was associated with a reduction of corpus callosum volume ( $-0.12 \pm 0.04 \text{ cm}^3$ ) (Chen et al, 2017c; Chen et al, 2015), but this association was not observed by Casanova et al (2016).

No association was reported between exposure to  $\text{PM}_{2.5}$  or diesel particulate matter and changes in the basal ganglia in the WHIMS study (Chen et al, 2017c).

Younan et al (2020) reported that average exposure to  $\text{PM}_{2.5}$  over 3 years preceding an MRI scan was associated with an increased Alzheimer's Disease Pattern Similarity score ( $\beta_{\text{PM}_{2.5}} = 0.018$ , 95% CI 0.001, 0.034). This score is a structural brain MRI-based neuroanatomic biomarker reflecting grey matter atrophy in areas vulnerable to Alzheimer's disease neuropathology (Younan et al, 2020). It was derived using a voxel-wise supervised machine learning algorithm (Casanova et al, 2018; Casanova et al, 2013; Casanova et al, 2011).

It is worth noting that the regions of the brain showing morphological changes associated with air pollution are also associated with several higher cognitive functions such as working memory, episodic memory retrieval and executive function (Casanova et al, 2016).

### 3.3.8 Human studies on neuroinflammation

Table 3.12 presents a summary of the characteristics, exposure, adjustments and outcomes of the 8 studies assessing the associations between air pollution and markers of neuroinflammation.

Sanchez-Rodriguez et al (2006) found a higher proportion of elderly subjects with higher oxidative stress biomarker levels and cognitive impairment in urban areas (25%) than rural environments (9%). Subjects from urban areas had statistically significantly higher levels of lipoperoxides and lower levels of superoxide dismutase and glutathione peroxidase. The authors found that MMSE had significant negative correlations with lipoperoxides, total antioxidant status and age, and a significant positive correlation with superoxide dismutase. These results support the view that air pollution promotes oxidative stress which constitutes a risk factor for cognitive impairment.

Shaffer et al (2019) evaluated associations between vascular cell adhesion molecule-1 (VCAM-1)<sup>17</sup> and E-selectin<sup>18</sup> in cerebrospinal fluid (CSF) and short-term (7-day average) and long-term (1-year) preceding  $\text{PM}_{2.5}$  exposure. In cognitively normal adults,  $\text{PM}_{2.5}$  exposure over the preceding week was associated with elevated VCAM-1 ( $35.4\text{ng}/\text{ml}$ , 95% CI 9.7, 61.1  $\text{ng}/\text{ml}$  per  $5\mu\text{g}/\text{m}^3$ ) and E-selectin ( $53.3 \text{ pg}/\text{ml}$ , 95% CI 11.0, 95.5  $\text{pg}/\text{ml}$  per  $5\mu\text{g}/\text{m}^3$ ) in CSF;  $\text{PM}_{2.5}$  exposure over the preceding year was associated with elevated VCAM-1 only ( $51.8$

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<sup>17</sup> Vascular cell adhesion molecule-1 (VCAM-1) is expressed on cytokine-activated endothelium and helps regulate vascular adhesion and transendothelial migration of leukocytes (for instance macrophages and T cells) during inflammatory processes.

<sup>18</sup> E-selectin is expressed on endothelial cells after activation by interleukin 1 (IL-1), tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) or bacterial lipopolysaccharides and it is crucial to control leukocyte accumulation in inflammatory responses.

ng/ml, 95% CI 6.5, 97.1 ng/ml per 5 $\mu$ g/m<sup>3</sup>). No associations were found in individuals with mild cognitive impairment or Alzheimer's disease (Shaffer et al, 2019).

Bos et al (2011) reported that brain-derived neurotrophic factor (BDNF) did not increase after cycling near a 'major traffic road', whilst it did increase when cycling whilst breathing filtered air. BDNF increases brain plasticity and is thought to be linked to enhanced cognition and improved memory function. A failure to increase BDNF on exercise was seen as a potentially deleterious effect. Consistent results were found when comparing subjects training in urban and rural environments (Bos et al, 2013).

In a randomised controlled crossover study, Liu et al (2017) exposed 50 healthy non-smoking volunteers to coarse (mean 231 $\mu$ g/m<sup>3</sup>), fine (mean 238 $\mu$ g/m<sup>3</sup>) and ultrafine (mean 136 $\mu$ g/m<sup>3</sup>) concentrated ambient particles for 130 minutes. They found significant associations between levels of biological molecules such as endotoxin and  $\beta$ -1,3-D-glucan in the coarse and fine concentrated ambient particles, and blood C-terminal hydrolase L1 and astrocytic calcium-binding protein S100 $\beta$ , which are biomarkers indicative of damage to the blood-brain barrier. No association was found with ultrafine concentrated ambient particles (Liu et al, 2017).

In contrast, Cliff et al (2016) did not find any relationship between short-term exposure to diesel exhaust and several biomarkers of neurotoxicity such as S100 $\beta$ , the neuronal cytoplasmic enzyme neuron-specific enolase (NSE), and serum BDNF (Cliff et al, 2016).

Calderón-Garcidueñas et al (2013a) reviewed their work in children and youngsters in Mexico City and reported alterations in the brains of children and young adults similar to those in Alzheimer's disease. The authors documented upregulation of cyclooxygenase-2, interleukin-1 $\beta$  and CD14 mRNAs, clusters of mononuclear cells around blood vessels and activated microglia in the frontal and temporal cortex, subiculum and brain stem, as markers of neuroinflammation and vascular damage. They also reported production and deposit of protein aggregates (diffuse A $\beta$ 42 plaques, pre-tangle hyper-phosphorylated tau and  $\alpha$ -synuclein in frontal areas, and hippocampus), oxidative stress, cell damage and death of neurons. These, the authors regarded as markers of Alzheimer's and Parkinson's disease. Consistent with biochemical changes observed after short-term exposure, chronic exposure to air pollution in children from Mexico City lowered the concentration of BDNF (Calderón-Garcidueñas et al, 2016a).

### 3.3.9 Summary tables reviewing the evidence

The following tables summarise the reviewed epidemiological evidence on the effects of air pollution on neurological endpoints. As well as the tables mentioned above, Table 3.13 provides a summary of studies reporting the effect of air pollution on cognition as an effect equivalent to ageing. Table 3.15 summarises the consistency of the studies which used brain imaging techniques and Table 3.14 summarises the consistency of the reviewed literature on all other endpoints.



**Table 3.1. Summary of characteristics and outcomes of studies assessing the effect of air pollution on global cognition included in literature review**

| First author, year (Name of study)                                                                         | Location                                                  | Study design                                                     | Time recruitment/FU                    | N cases/cohort size or N Controls, Sex (age)                                                      | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Outcome                                  | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                      | Exposure                                                                                                                                                                                                                                                                           | Adjustments                                                                                                                                                                                                                                                               |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sanchez - Rodriguez et al, 2006                                                                            | Mexico City and Actopan, Mexico                           | Cross-sectional                                                  | Not Reported                           | 189 M+W (104 urban, 85 rural) (mean age urban: 66.8 $\pm$ 6.4 years; rural: 70.8 $\pm$ 8.4 years) | Air pollution exposure by residence in high (urban) and low (rural) polluted areas for 10 years or more.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Cognitive function (MMSE score)          | Average score (Standard Deviation)<br>Rural 27.16 (0.28)<br>Urban 26.15 (0.35)<br><b>p&lt;0.05</b>                                                                                                                                | Rural and urban                                                                                                                                                                                                                                                                    | Subjects were not smokers, without acute or chronic diseases and were not receiving prescription medications, physical activity was similar between the two groups                                                                                                        |
| Sun and Gu, 2008 (Chinese Longitudinal Health Longevity Survey, CLHLS)                                     | Nationwide China 735 districts in 171 cities (urban only) | Cross-sectional analysis using data from the third wave of CLHLS | 2002                                   | 7358 M+W (mean 86.3 $\pm$ 11.4 years)                                                             | Air pollution index<br>At the city level, shared by districts within the same city (graded from score 1- the lowest exposure- to 7- highest exposure) for the year 1995. This index assesses the concentration of 3 pollutants: SO <sub>2</sub> , NO <sub>2</sub> and inhalable particulates (PM <sub>10</sub> , CO and O <sub>3</sub> ). City air pollution indexes were obtained from national databases                                                                                                                                                                                         | Cognitive function (MMSE)                | <b><math>\beta</math> = -1.51 (95% CI - 2.16, -0.86) p&lt;0.001</b>                                                                                                                                                               | 1-point increase in Air Pollution Index (API)                                                                                                                                                                                                                                      | Temperature in January, age, sex, education, occupation, perceived economic condition, marital status, parity, smoking, alcohol, physical activity and leisure activities.                                                                                                |
| Ranft et al, 2009 (Study of the influence of Air pollution on Lung function, Inflammation and Aging SALIA) | Ruhr district, Germany                                    | Cross-sectional from cohort study                                | 2007-2009 (cohort enrolment 1985-1994) | 399 W (at enrolment 54-55 years; at present analysis mean: 74.1 $\pm$ 2.6, range: 68-79 years)    | Individual exposure to PM <sub>10</sub> was estimated from the nearest monitoring station (distributed over the Ruhr district in an 8-km grid) to the participants' residence averaged over the five years before the cohort enrolment (that is, 1980-1993) and over the 5 years from 2002-2006. PM <sub>10</sub> was calculated converting the TSP concentrations into PM <sub>10</sub> using a factor of 0.71. Residential traffic proximity was calculated as the distance of the address to the next busy road with 10,000 cars (traffic counts assessed in the year 2000). All women included | Cognitive function (CERAD plus, z score) | $\beta$ = -3.8 (95% CI - 7.8, 0.1) p<0.1<br><br>Stronger association among younger subjects (age $\leq$ 74 years) for unadjusted estimates<br><br>$\beta$ = 0.4 (95% CI 0.0, 0.9) p<0.1<br><br>$\beta$ = -0.6 (95% CI - 1.4, 0.2) | Residential Traffic proximity (<50 m for the last 20 years)<br><br>5-years average PM <sub>10</sub> background concentration in ambient air at age 55 years<br>5-years average PM <sub>10</sub> background concentration in ambient air 2002-2006 (28.3 in Ruhr district and 25 in | age, education, smoking, environmental tobacco smoking, indoor air pollution, depression, chronic respiratory diseases, diabetes, hypertension, high cholesterol, ever infarction, ever stroke, physical activity, obesity, traffic, PM <sub>10</sub> , traffic exposure. |



| First author, year (Name of study)                 | Location    | Study design                                                                           | Time recruitment/FU              | N cases/cohort size or N Controls, Sex (age)            | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Outcome                                                                                                                                                                                                                                                  | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                   | Exposure                                                               | Adjustments                                                                                                                                                                                                                                                                     |
|----------------------------------------------------|-------------|----------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                    |             |                                                                                        |                                  |                                                         | lived more than 20 years at the same residential address.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                | Rural county Borken $\mu\text{g}/\text{m}^3$ )                         |                                                                                                                                                                                                                                                                                 |
| Power et al., 2011 (Normative Aging Study)         | Boston, USA | Longitudinal (cohort, not all participants completed more than 1 cognitive assessment) | 1996-2007                        | 680 (M) (range: 51-97 years, mean: $71 \pm 7$ years)    | BC exposure was estimated at the residence of each participant using a spatio-temporal land-use regression model using daily average BC estimates from 83 monitoring sites including information on meteorological conditions, land use (for example, traffic density) and other descriptors. Annual daily estimate prior to the date of the first cognitive assessment completed on or after 1 January 1996, the first date of which computation of a prior 1-year average was possible.                                                                                       | Cognitive function (MMSE $\leq 25$ vs $> 25$ )<br><br>Global cognition (the digit span backward test, a verbal fluency task, constructional praxis, immediate recall of a 10-word list, delayed recall of a 10-word list, and a pattern comparison task) | <b>OR = 1.3 (95% CI 1.1, 1.6)</b><br><br><b><math>\beta = -0.054</math> (95% CI -0.103, -0.006)</b>                                                                                                                                                                                                                                                                            | Doubling BC (corresponding approximately to 0.69 unit change in ln BC) | Age, education, first language, computer experience, physical activity, alcohol, diabetes, dark fish consumption, race, income, indicator for first cognitive assessment and indicator for part-time resident.                                                                  |
| Wellenius et al., 2012 (MOBILE Boston Study (MBS)) | Boston, USA | Longitudinal (cohort)                                                                  | 2005-2008/ 16.8 months (mean FU) | 765 (M+W) ( $\geq 65$ years Mean: $78.1 \pm 5.4$ years) | ArcGIS was used to geocode participant address and calculate the Euclidean distance from residence to the nearest major roadway, defined as roads having US Census Feature Class Code A1 (primary highway with limited access) or A2 (primary road without limited access).<br><br>Daily outdoor BC levels (a marker of traffic pollution) at participant's address was estimated using a validated spatio-temporal land-use regression model. To create a metric of long-term BC, estimated residential BC was averaged over the 365 days preceding each cognitive assessment. | Cognitive function (MMSE $< 26$ vs $\geq 26$ )                                                                                                                                                                                                           | <b>OR = 1.34 (95% CI 1.01, 1.76)</b> (subject's age $\leq 77$ -year-old)<br><br>OR = 0.89 (95% CI 0.65, 1.21), (subject's age $> 77$ -year-old)<br>P for heterogeneity 0.056<br><br><b>OR = 1.54 (95% CI 1.10, 2.17)</b> (subjects with college education or more)<br>OR = 0.86 (95% CI 0.66, 1.12) (subjects with high school or less education)<br>P for heterogeneity 0.007 | Residential Traffic proximity IQR decrease (851.2 m).                  | Age, sex, race, history of stroke, history of smoking, physical activity, education, visit number, BMI, household income, season of home interview, percent of neighbourhood population that is non-white and percent of neighbourhood population with college degree or above. |

## Cognitive decline, dementia and air pollution: a report by the Committee on the Medical Effects of Air Pollutants

| First author, year (Name of study)                                                                               | Location                       | Study design                                               | Time recruitme nt/FU | N cases/cohort size or N Controls, Sex (age)         | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Outcome                                                                                                                                                             | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                          | Exposure                                                                                                                                                                                                                                                                                                                                                                                                    | Adjustments                                                                                  |
|------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------------------------|----------------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
|                                                                                                                  |                                |                                                            |                      |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Cognitive function (MMSE <26 vs $\geq 26$ )                                                                                                                         | OR = 1.15 (95%CI 0.99-1.34) p=0.063                                                                                                                                                                                                                                                   | BC IQR increase (0.11 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                                                                                                                                                            |                                                                                              |
| Ailshire and Crimmins, 2014 (Health and Retirement Study)                                                        | Nationwide, USA                | Cross-sectional                                            | 2004                 | 13,996 (M+W) (>50 years, mean 64.0 $\pm$ 10.4 years) | Annual average PM <sub>2.5</sub> exposure for the year 2004 was derived using 24-hour daily means reported by monitors within 60-km radius of each census tract centroid. The values from each monitoring station were weighted using the inverse of the distance from the census tract centroid.                                                                                                                                                                                                                                                                                                                  | Cognitive function (35-point scale that sums scores to measure memory, to measure working memory, to measure processing speed, measure of orientation and language) | $\beta$ = -0.26, (95% CI - 0.47, -0.05)                                                                                                                                                                                                                                               | PM <sub>2.5</sub> Highest (13.8–20.7 $\mu\text{g}/\text{m}^3$ ) vs lowest (4.5–9.9 $\mu\text{g}/\text{m}^3$ ) quartile                                                                                                                                                                                                                                                                                      | Age, sex, race, education, employment status, income, smoking                                |
| Gatto et al, 2014 (BVAIR, WISH, ELITE)                                                                           | Los Angeles, USA               | Cross-sectional analysis of 3 randomised controlled trials | 2000-2006            | 1496 (M+W) (mean age 60.5 $\pm$ 8.1 years)           | Annual average O <sub>3</sub> , PM <sub>2.5</sub> and NO <sub>2</sub> concentrations for 2000-2006 from monitoring stations were spatially interpolated to the subjects' residential addresses using inverse-distance-squared weighting in a GIS programme. Ambient air quality data were extracted from the Air Quality System, maintained by the US Environmental Protection Agency                                                                                                                                                                                                                              | Cognitive function (14 cognitive tests in the neuropsychological battery, z score)                                                                                  | $\beta$ = -0.08 (95% CI -0.45, 0.28)<br>p for trend=0.81<br><br>$\beta$ = -0.32 (95% CI -0.92, 0.28)<br>P for trend= 0.74<br><br>$\beta$ = -0.15 (95% CI -0.38, 0.08)<br>P for trend= 0.23                                                                                            | 8-hour O <sub>3</sub> highest (>49 ppb) vs lowest ( $\leq$ 34 ppb) tertile<br><br>24-hour NO <sub>2</sub> highest (>20 ppb) vs lowest ( $\leq$ 10 ppb) tertile<br><br>24-hour PM <sub>2.5</sub> highest (>17 $\mu\text{g}/\text{m}^3$ ) vs lowest ( $\leq$ 15 $\mu\text{g}/\text{m}^3$ ) tertile                                                                                                            | Age, race/ethnicity, sex, highest education level achieved, household income, mood and study |
| Schikowski et al., 2015 (Study of the influence of Air pollution on Lung function, Inflammation and Aging SALIA) | North Rhine-Westfalia, Germany | Cross-sectional from cohort study                          | 2007-2009            | 789 W (mean age 73.4 $\pm$ 3.05 years)               | Exposure to NO <sub>2</sub> , NO <sub>x</sub> , PM <sub>2.5</sub> , PM <sub>2.5abs</sub> and PM <sub>10</sub> was estimated at the participating home addresses by land-use regression (LUR) models. Pollutant levels were measured over a period of one year (2009-2010) and the exposure values to the years 1985-1994 were back-extrapolated by assuming proportional changes over time within city spatial patterns. Daily traffic load within a 100-metre buffer around the home was calculated as the sum of the products of the number of vehicles from all roads with the street section length in the 100 | Cognitive function (CERAD- Battery, z score)                                                                                                                        | $\beta$ = -0.40, 95% CI - 2.16, 1.36)<br><br>$\beta$ = -0.10, 95% CI - 2.37, 0.18)<br><br><b><math>\beta</math>= -1.35, 95% CI - 2.59, -0.10)</b><br><br>$\beta$ = 0.32, 95% CI - 0.68, 1.33)<br><br>$\beta$ = 0.31, 95% CI - 1.11, 1.72)<br><br>$\beta$ = 0.21, 95% CI - 0.65, 1.08) | Traffic load ( $\geq 50,000$ cars per day)<br><br>NO <sub>2</sub> IQR increase (9.6 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>x</sub> IQR increase (23.4 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10</sub> IQR increase (2.2 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> IQR increase (1.9 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> abs IQR increase (0.4 $10^{-6}$ x m <sup>-1</sup> ) | age, urban/rural living, SES, smoking, Environmental Tobacco smoke and APOE.                 |

| First author, year (Name of study)            | Location    | Study design                                                                                                       | Time recruitment/FU | N cases/cohort size or N Controls, Sex (age) | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Outcome                                                                                                                                                                       | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                  | Exposure                                                                                                                                                                                                                                                                                                                                   | Adjustments                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------|-------------|--------------------------------------------------------------------------------------------------------------------|---------------------|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                               |             |                                                                                                                    |                     |                                              | m buffer for the year 2000 and from 2007 for the follow-up investigation. Predictor variables on nearby traffic, population/household density and land use were derived from a Geographic Information System (GIS) programme and were evaluated to explain spatial variation of annual average concentrations.                                                                                                                                                                               | Cognitive function (MMSE)                                                                                                                                                     | $\beta$ = 0.04 (95% CI - 0.18, 0.26)<br>$\beta$ = 0.00 (95% CI - 0.16, 0.16)<br>$\beta$ = -0.04 (95% CI - 0.19, 0.12)<br>$\beta$ = 0.07 (95% CI - 0.06, 0.20)<br>$\beta$ = 0.07 (95% CI - 0.10, 0.25)<br>$\beta$ = 0.02 (95% CI - 0.08, 0.13)                                                                                                                                 | Traffic load ( $\geq 50,000$ cars per day)<br>NO <sub>2</sub> IQR increase (9.6 $\mu\text{g}/\text{m}^3$ )<br>NOx IQR increase (23.4 $\mu\text{g}/\text{m}^3$ )<br>PM10 IQR increase (2.2 $\mu\text{g}/\text{m}^3$ )<br>PM2.5 IQR increase (1.9 $\mu\text{g}/\text{m}^3$ )<br>PM2.5 abs IQR increase (0.4 $10^{-6} \times \text{m}^{-1}$ ) |                                                                                                                                                                                                                                                                                                                                                                                                       |
| Colicino et al., 2016 (Normative Aging Study) | Boston, USA | Longitudinal (cohort, multiple assessment, up to 4, of cognitive tests completed by most participants but not all) | 1995-2007           | 533 (M) (53-97 years, Mean age 72 $\pm$ 7)   | BC exposure was estimated at the residence of each participant using a spatio-temporal land-use regression model using daily average BC estimates from 148 monitoring sites including information on meteorological conditions, land use (for example, traffic density) and other descriptors.<br>Annual daily estimate prior to the date of the first cognitive assessment completed on or after 1 January 1996, the first date of which computation of a prior 1-year average was possible | Cognitive function (MMSE $\leq 25$ vs $> 25$ )<br>Global cognition (the digit span backward test, a verbal fluency task, constructional praxis, immediate recall of a 10-word | <b>OR=1.35 (95% CI 1.07, 1.70), p=0.01</b><br>All subjects<br>Stronger association among heterozygous carriers of rs11077 XPO5 compared to individuals with the major homozygous carriers (ORs 1.99 vs 1.20) and among individuals with minor variant carriers of GEMIN4 rs2740348 compared to homozygous minor variant carriers (ORs<br>$\beta$ = -0.01 (-0.06, 0.04) p=0.62 | A doubling increment in BC concentration is approximately equal to 0.69 unit change in ln(BC).                                                                                                                                                                                                                                             | age, education, alcohol, smoking, physical activity, obesity, BMI, dark fish consumption, computer experience, first language, percentage of the participants' census tract that is non-white, and percentage of the adult residents in the participants' census tract with at least a college degree, an indicator for first cognitive assessment, an indicator for a part-time residence in Boston. |

| First author, year (Name of study)                       | Location    | Study design                                                                                                                    | Time recruitment/FU | N cases/cohort size or N Controls, Sex (age)     | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Outcome                                                                                                                                      | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                      | Exposure                                                                                                          | Adjustments                                                                                                                                                                                                                                                        |
|----------------------------------------------------------|-------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                          |             |                                                                                                                                 |                     |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | list, delayed recall of a 10-word list, and a pattern comparison task)                                                                       | $\beta = -0.10$ (95% CI $-0.18, -0.02$ )<br>heterozygous carriers of GEMIN4 rs4968104<br><br>$\beta = -0.09$ (95% CI $-0.17, -0.02$ )<br>heterozygous carriers of GEMIN4 rs910924                                                                                                                                                                                                                 |                                                                                                                   |                                                                                                                                                                                                                                                                    |
| Colicino et al., 2017 (Normative Aging Study)            | Boston, USA | Longitudinal (cohort, cognitive assessment tested up to 3 times, but not all participants had more than 1 cognitive assessment) | 1999/2007           | 428 (M) (51-97 years, mean age $72 \pm 7$ years) | BC exposure was estimated at the residence of each participant using a spatio-temporal land-use regression model using daily average BC estimates from monitoring sites including information on meteorological conditions, land use (for example, traffic density) and other descriptors. Annual daily estimate prior to the date of the first cognitive assessment completed on or after 1 January 1996, the first date of which computation of a prior 1-year average was possible                                  | Cognitive function (MMSE $\leq 25$ vs $> 25$ )                                                                                               | <b>OR = 1.57 (95% CI 1.2, 2.05)</b><br><b>p = 0.001</b><br><br><b>OR = 3.23 (95% CI 1.37, 7.59)</b><br>Individuals with longer blood Telomere Length (5th quintile)                                                                                                                                                                                                                               | Doubling BC (corresponding to a 0.69 $\mu\text{g}/\text{m}^3$ increase in average $\ln(\text{BC})$ concentration) | Age, education, first language, physical activity, BMI, dark-meat fish consumption, alcohol, smoking, education, race, indicator for first cognitive assessment, indicator for part time resident, hypertension, diabetes, coronary heart disease, C-protein level |
| Tzivian et al., 2017 (Heinz Nixdorf Recall cohort study) | Germany     | Cross-sectional                                                                                                                 | 2006-2008           | 4814 (M+W) (45-75 years)                         | Long-term exposure to $\text{PM}_{10}$ , $\text{PM}_{\text{coarse}}$ , $\text{PM}_{2.5}$ , $\text{PM}_{2.5}$ absorbance, $\text{NO}_x$ and $\text{NO}_2$ was estimated at each participant's baseline address using LUR model combining measurement at sites (20 for $\text{PM}_{10}$ , $\text{PM}_{\text{coarse}}$ , $\text{PM}_{2.5}$ , $\text{PM}_{2.5}$ absorbance; 40 for $\text{NO}_x$ and $\text{NO}_2$ ) over 1 year (Oct 2008- Oct 2009) and predictor variables, derived from Europe-wide and GIS databases. | Global cognition (test battery assessing verbal fluency, immediate and delayed memory, problem solving/speed of processing and abstraction). | $\beta = -0.16$ , (95% CI $-0.33, 0.01$ ) (for low 24-h road traffic noise)<br><b><math>\beta = -0.48</math>, (95% CI <math>-0.72, -0.23</math>)</b> (for high 24h traffic road)<br><br>For the association between Global cognition and exposure to other pollutants ( $\text{PM}_{2.5\text{abs}}$ , $\text{PM}_{\text{coarse}}$ , $\text{PM}_{10}$ , $\text{NO}_2$ and $\text{NO}_x$ ), results | IQR increase of $\text{PM}_{2.5}$ ( $1.43 \mu\text{g}/\text{m}^3$ )                                               | Age, sex, SES, alcohol, smoking, environmental tobacco smoke, physical activity, BMI.                                                                                                                                                                              |

| First author, year (Name of study)                                          | Location                                             | Study design                        | Time recruitment/FU | N cases/cohort size or N Controls, Sex (age)    | Exposure assessment                                                                                                                                                                                                                                                                                                | Outcome                                                         | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                      | Exposure                                                                                                                                                                                                                                                         | Adjustments                                                                                                                                                                                                                                |
|-----------------------------------------------------------------------------|------------------------------------------------------|-------------------------------------|---------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                             |                                                      |                                     |                     |                                                 |                                                                                                                                                                                                                                                                                                                    |                                                                 | are reported in figure                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                            |
| Tallon et al., 2017 (National Social Life, Health and Aging Project cohort) | USA                                                  | Cross-sectional from a cohort study | 2010-2011           | 3377 (M+W) (57-85 years)                        | Exposure to PM <sub>2.5</sub> was estimated using GIS-spatio-temporal models combining data from EPA-AQS databases and interagency Monitoring of protected Visual environments network including 3 meteorological covariates (wind speed, temperature and total precipitation) from 2000 US census                 | Global cognition (Chicago Cognitive Function Measure, CCFM)     | $\beta = -0.22$ ; (95% CI - 0.44, -0.01)<br>$p < 0.05$<br><br>$\beta = -0.25$ ; (95% CI - 0.43, -0.06)<br>$p < 0.05$<br><br>$\beta = -0.13$ ; (95% CI - 0.34, 0.08)<br><br>$\beta = -0.27$ ; (95% CI - 0.48, -0.07)<br>$p < 0.05$ | PM <sub>2.5</sub> 1-year IQR increase (4.25 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> 7-year IQR increase (4.33 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>2</sub> 1-year IQR increase (8.37 ppb)<br><br>NO <sub>2</sub> 7-year IQR increase (7.42 ppb) | Age, sex, race, education, season, smoking, region, income.                                                                                                                                                                                |
| Lin et al., 2017a (SAGE Study on global AGEing and Adult Health)            | China, India, Ghana, Mexico, Russia and South Africa | Cross-sectional                     | 2007–2010           | 45,625 (M+W) (mean age 58.06 $\pm$ 14.88 years) | Exposure to PM <sub>2.5</sub> was estimated at participant's address combining 3 satellite-derived PM <sub>2.5</sub> sources to produce global PM <sub>2.5</sub> estimates at about 10km x 10 km. GEOS-Chem chemical transport model was used to represent local aerosol optical properties and vertical profiles. | Cognitive function (WHODAS 2)                                   | $\beta = 0.59$ (95% CI 0.38, 0.80)<br><br>$\beta = 0.10$ (95% CI 0.02; 0.18)                                                                                                                                                      | PM <sub>2.5</sub> High (>27.83 $\mu\text{g}/\text{m}^3$ ) vs low (>14.33 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> increase (10 $\mu\text{g}/\text{m}^3$ )                                                                                             | Age, sex, BMI, marital status, urbanity, education, income, consumption of fruits and vegetables, smoking, alcohol, domestic fuel type, ventilation and season of the survey.                                                              |
| Ailshire and Clarke, 2017 (Americans' Changing Lives survey)                | Nationwide, USA                                      | Cross-sectional                     | 2001-2002           | 779 (M+W) ( $\geq 55$ years)                    | Annual PM <sub>2.5</sub> levels were estimated using air monitoring data from US EPA monitoring sites within a 60-km radius of each census tract centroid for the year 2000. Daily monitor values were aggregated to create an annual average exposure using the inverse distance formula.                         | Cognitive function (Short Portable Mental Status Questionnaire) | IRR= 1.03, (95% CI 0.99, 1.07)                                                                                                                                                                                                    | PM <sub>2.5</sub> increase (1 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                         | age, sex, race, education, income, marital status, employment status, length of residence, neighbourhood socioeconomic context disadvantage and affluence, neighborhood stress BMI, smoking status, physical activity, hypertension, heart |

| First author, year (Name of study)                            | Location                                                                                    | Study design       | Time recruitment/FU      | N cases/cohort size or N Controls, Sex (age)                                                                                                                                                                                                                                      | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Outcome                                                 | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Exposure                                                                                                                                              | Adjustments                                                                                                                                                                                                                                 |
|---------------------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                               |                                                                                             |                    |                          |                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                       | disease, cancer, diabetes, lung disease.                                                                                                                                                                                                    |
| Molina-Sotomayor et al., 2019                                 | Santiago (highly polluted city) and Viña del Mar (city with low levels of pollution), Chile | Quasi-experimental | March 2013-December 2014 | 181 (W): 47 active/polluted air group (AP) (mean age 69.8 $\pm$ 4.3 years); 44 sedentary/polluted air group (SP) (mean age 68.3 $\pm$ 3.5 years); 45 active/clean air group (AC) (mean age 69 $\pm$ 1.2 years); 45 sedentary/clean air group (SC) (mean age 68.5 $\pm$ 2.4 years) | The participants were recruited from women living in a highly polluted city (Santiago) and women living in a city with low levels of pollution (Viña del Mar). They were divided into four groups: AP, SP, AC and SC combining Active (A) and Sedentary (S) Polluted (P) and Clean (C) city groups. The active groups performed a training programme consisting of low/moderate intensity walking on a horizontal plane, with progressive speed increases. The study duration was 24 months, with four training cycles of six months each and three 1-hour sessions per week. | Cognitive function (MMSE)                               | At the end of the experiment, a statistically significant decreasing rate (p,0.05) was observed in the SC and SP groups (-4% and 9.9% respectively). Results at the end of the experiment: M $\pm$ SD (95% CI)<br>AC: 29 $\pm$ 1.3 (28.3-29.6)<br>AP: 28.4 $\pm$ 1.5 (27.7-29)<br>SC: 26.6 $\pm$ 2.1 (25.9-27.2)<br>SP: 24.32 $\pm$ 2.85 (23.7-24.9)<br><b>p for intercomparison group=0.000</b><br><br>At the beginning of the experiment no statistically significant difference between groups (p>0.05) | Comparison between four groups: AP, SP, AC and SC combining Active (A) and Sedentary (S) Polluted (P) and Clean (C) city groups                       | No adjustments                                                                                                                                                                                                                              |
| Shin et al., 2019 (The Korean Frailty and Aging Cohort Study) | Korea                                                                                       | Cross-sectional    | 2016-2017                | 2,896 (M+W) (70-84 years, mean age 76 $\pm$ 3.9)                                                                                                                                                                                                                                  | The level of PM <sub>10</sub> , NO <sub>2</sub> , CO, SO <sub>2</sub> and O <sub>3</sub> were measured hourly at 268 nationwide surveillance stations located in residential areas by the Korean Air Pollutants Emission Service in 2013-2017. As PM <sub>2.5</sub> has only been measured in Korea since 2015, average concentrations of                                                                                                                                                                                                                                     | MMSE (Korean version) (log-transformed cognitive scale) | <b><math>\beta</math> = -0.010 (95% CI -0.019, -0.001)</b><br><br><b><math>\beta</math> = -0.035 (95% CI -0.050, -0.020)</b><br><br><b><math>\beta</math> = 0.044 (95% CI 0.032, 0.056)</b>                                                                                                                                                                                                                                                                                                                | PM <sub>2.5</sub> increase (1.5 $\mu$ g/m <sup>3</sup> )<br><br>PM <sub>10</sub> increase (4.6 $\mu$ g/m <sup>3</sup> )<br><br>CO increase (0.08 ppm) | Age, sex, body mass index, smoking, alcohol intake, physical activity, education, household income, marital status, Carlson's comorbidity index, length of time at same residence, meteorological data, residence area, PM <sub>2.5</sub> , |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls, Sex (age) | Exposure assessment                                                                                                                                                                                     | Outcome | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                              | Exposure                                                                                                      | Adjustments                                                                                                                                               |
|------------------------------------|----------|--------------|---------------------|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |          |              |                     |                                              | PM <sub>2.5</sub> in the data from 2015 to 2017 were applied. Pollutant levels were matched with the location of the participants' surveillance centres and the average concentrations were calculated. |         | $\beta = 0.007$ (95% CI - 0.005, 0.020)<br>$\beta = 0.012$ (95% CI 0.001, 0.025)<br>$\beta = 0.045$ (95% CI 0.027, 0.062)<br>ORs are reported in the figures in the paper | SO <sub>2</sub> increase (0.9 ppb)<br>NO <sub>2</sub> increase (7.7 ppb)<br>O <sub>3</sub> increase (4.3 ppb) | PM <sub>10</sub> , CO, SO <sub>2</sub> , NO <sub>2</sub> , O <sub>3</sub> were adjusted as fixed effects, and each centre was adjusted as random effects. |

### Abbreviations

FU, follow-up; M, men; W, women; SES, socioeconomic status; MMSE, mini mental status examination; CERAD, The Consortium to Establish a Registry for Alzheimer's Disease; CDR-SB Cognitive Dementia Rating Sum of Boxes; BC, black carbon, BMI, body mass index; HR, hazard ratio; OR, odds ratio; RR, relative risk; CI, confidence interval; M, mean; SD, standard deviation.



**Table 3.2. Summary of characteristics and outcomes of studies assessing the effect of air pollution on executive function included in literature review**

| First author, year (Name of study)                   | Location                        | Study design                                                   | Time recruitment/ FU             | N cases/cohort size or N Controls (age)                  | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Outcome                                                                                                                                        | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                   | Exposure                                                                                                                                                                                                                                                                                   | Adjustments                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------|---------------------------------|----------------------------------------------------------------|----------------------------------|----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wellenius et al., 2012 (MOBILIZE Boston Study (MBS)) | Boston, USA                     | Longitudinal (cohort)                                          | 2005-2008/ 16.8 months (mean FU) | 765 (M+W) ( $\geq 65$ years, mean: $78.1 \pm 5.4$ years) | ArcGIS was used to geocode participant address and calculate the Euclidean distance from residence to the nearest major roadway, defined as roads having US Census Feature Class Code A1 (primary highway with limited access) or A2 (primary road without limited access). Daily outdoor BC levels (a marker of traffic pollution) at participant's address was estimated using a validated spatio-temporal land-use regression model. To create a metric of long-term exposure, modelled residential BC was averaged over the 365 days preceding each cognitive assessment. | Executive function (TMT part B (higher scores indicate poorer performance))                                                                    | $\beta = 10.5$ (95% CI 4.0;17.1) $p=0.002$ (the association was stronger among subjects who were less highly educated and younger $\leq 77$ years)<br>$\beta = 15.2$ (95% CI -1.6;32) $p=0.025$<br>$\beta = 2.51$ (95% CI -2.91;7.94) $p=0.36$ | Residential Traffic proximity IQR decrease (851.2 m).<br><br>Residential distance to major roadway (<100 m vs >1000 m)<br><br>BC IQR increase ( $0.11 \mu\text{g}/\text{m}^3$ )                                                                                                            | Age, sex, race, history of stroke, history of smoking (ever vs never), physical activity, education (3 categories), visit number, BMI, household income (below vs above median) season of home interview, percentage of neighbourhood population that is non-white and percent of neighbourhood population with college degree or above. |
| Gatto et al., 2014 (BVAIR, WISH, ELITE)              | Los Angeles, USA                | Cross-sectional analysis of three randomised controlled trials | 2000-2006                        | 1496 (M+W) (mean age: $60.5 \pm 8.1$ years)              | Annual average $\text{O}_3$ , $\text{PM}_{2.5}$ and $\text{NO}_2$ concentrations for 2000-2006 from monitoring stations were spatially interpolated to the subjects' residential addresses using inverse-distance-squared weighting in a GIS programme. Ambient air quality data were extracted from the Air Quality System, maintained by the US Environmental Protection Agency                                                                                                                                                                                             | Executive function (Symbol Digit Modalities test, TMT-Part B, Letter-Number Sequencing, Shipley Institute of Living Scale-Abstraction Subset). | $\beta = -0.66$ (95% CI -1.35, 0.03) $p$ for trend 0.07<br>$\beta = -0.01$ (95% CI -1.13, 1.11) $p$ for trend 0.053<br>$\beta = -0.06$ (95% CI -0.49, 0.37) $p$ for trend 0.81                                                                 | 8-hour $\text{O}_3$ highest (>49 ppb) vs lowest ( $\leq 34$ ppb) tertile<br><br>24-hour $\text{NO}_2$ highest (>20 ppb) vs lowest ( $\leq 10$ ppb) tertile<br><br>24-hour $\text{PM}_{2.5}$ highest (>17 $\mu\text{g}/\text{m}^3$ ) vs lowest ( $\leq 15 \mu\text{g}/\text{m}^3$ ) tertile | Age, race/ethnicity, sex, highest education level achieved, household income, mood and study                                                                                                                                                                                                                                             |
| Schikowski et al., 2015 (Study of the influence)     | North Rhine-Westphalia, Germany | Cross-sectional from cohort study                              | 2007-2009                        | 789 (W) (mean age $73.4 \pm 3.05$ years)                 | Exposure to $\text{NO}_2$ , $\text{NO}_x$ , $\text{PM}_{2.5}$ , $\text{PM}_{2.5\text{abs}}$ and $\text{PM}_{10}$ was estimated at the participating home addresses by land-use regression (LUR) models. Pollutant levels were                                                                                                                                                                                                                                                                                                                                                 | Executive function (TMT-B)                                                                                                                     | $\beta = 0.13$ , 95% CI -0.05, 0.31)<br>$\beta = -0.07$ , 95% CI -0.20, 0.06)                                                                                                                                                                  | Traffic load ( $\geq 50,000$ cars per day)<br><br>$\text{NO}_2$ IQR increase ( $9.6 \mu\text{g}/\text{m}^3$ )                                                                                                                                                                              | Age, urban/rural living, SES, smoking, EST and APOE.                                                                                                                                                                                                                                                                                     |

| First author, year (Name of study)                               | Location                         | Study design                           | Time recruitment/ FU | N cases/cohort size or N Controls (age)    | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Outcome                                | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                             | Exposure                                                                                                                                                                                                                                                                                                                                                                                | Adjustments                                                                                                                                                                                                                                              |
|------------------------------------------------------------------|----------------------------------|----------------------------------------|----------------------|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| of Air pollution on Lung function, Inflammation and Aging SALIA) |                                  |                                        |                      |                                            | measured over a period of one year (2009-2010) and the exposure values to the years 1985-1994 were back-extrapolated by assuming proportional changes over time within city spatial patterns. Daily traffic load within a 100-metre buffer around the home was calculated as the sum of the products of the number of vehicles from all roads with the street section length in the 100m buffer for the year 2000 and from 2007 for the follow-up investigation. Predictor variables on nearby traffic, population/household density and land use were derived from a Geographic Information System (GIS) programme and were evaluated to explain spatial variation of annual average concentrations. |                                        | $\beta$ = -0.09, 95% CI -0.21, 0.04)<br>$\beta$ = 0.01, 95% CI -0.09, 0.11)<br>$\beta$ = -0.02, 95% CI -1.16, 0.12)<br>$\beta$ = 0.03, 95% CI -0.06, 0.12)                                                                                               | NO <sub>x</sub> IQR increase (23.4 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>10</sub> IQR increase (2.2 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5</sub> IQR increase (1.9 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5</sub> abs IQR increase (0.4 $10^{-6}$ x $\text{m}^{-1}$ )                                                                                                               |                                                                                                                                                                                                                                                          |
|                                                                  |                                  |                                        |                      |                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Executive function (TMT-B/A)           | $\beta$ = 0.07, 95% CI -0.11, 0.25)<br>$\beta$ = -0.01, 95% CI -0.14, 0.12)<br>$\beta$ = -0.02, 95% CI -0.15, 0.10)<br>$\beta$ = 0.01, 95% CI -0.09, 0.11)<br>$\beta$ = 0.03, 95% CI -0.11, 0.17)<br>$\beta$ = 0.05, 95% CI -0.04, 0.14)                 | Traffic load ( $\geq 50,000$ cars per day)<br>NO <sub>2</sub> IQR increase (9.6 $\mu\text{g}/\text{m}^3$ )<br>NO <sub>x</sub> IQR increase (23.4 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>10</sub> IQR increase (2.2 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5</sub> IQR increase (1.9 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5</sub> abs IQR increase (0.4 $10^{-6}$ x $\text{m}^{-1}$ ) |                                                                                                                                                                                                                                                          |
| Cullen et al, 2018 (UK Biobank)                                  | UK (England, Scotland and Wales) | Cross-sectional (analysis at baseline) | 2010                 | 86,759 (M+W) (mean 56.86 $\pm$ 8.12 years) | Annual PM <sub>2.5</sub> , PM <sub>2.5-10</sub> , PM <sub>10</sub> , NO <sub>2</sub> and NO <sub>x</sub> were estimated for the years 2005-2007 using a LUR model for Western Europe developed integrating more than 15000 EuroAirnet monitoring sites and satellite-derived air pollution estimates. Air pollution data were mapped to participants' baseline addresses.                                                                                                                                                                                                                                                                                                                             | Reasoning (score 0-13, lower is worse) | <b><math>\beta</math> = 0.0111, (95% CI 0.0054, 0.0169) p=0.0001</b><br>$\beta$ = -0.0103, (95% CI -0.0334, 0.0128) p=0.38<br>$\beta$ = -0.0141, (95% CI -0.0347, 0.0065) p=0.18<br><b><math>\beta</math> = 0.0032, (95% CI 0.0013, 0.0050) p=0.0007</b> | PM <sub>10</sub> increase IQR (4.12 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>10-2.5</sub> increase IQR (0.77 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5</sub> increase IQR (1.08 $\mu\text{g}/\text{m}^3$ )<br>NO <sub>2</sub> increase IQR (13.71 $\mu\text{g}/\text{m}^3$ )<br>NO <sub>x</sub> increase IQR                                                                               | Age, sex, race, Townsend deprivation score, education, smoking, physical activity, time outdoors, proximity to nearest major road, traffic intensity or nearest major road, population density. Further adjustment for noise did not change the results. |

| First author, year (Name of study)                     | Location           | Study design    | Time recruitment/ FU | N cases/cohort size or N Controls (age)  | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Outcome                         | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                   | Exposure                                                                                                                                                                                                                   | Adjustments                                                                                                                                                         |
|--------------------------------------------------------|--------------------|-----------------|----------------------|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                        |                    |                 |                      |                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                 | $\beta = -0.0015$ , (95% CI - 0.0027, -0.00002)<br>p=0.018                                                                                                                                                                     | (14.67 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                          |                                                                                                                                                                     |
| Tonne et al., 2014) Whitehall II                       | Greater London, UK | Cross-sectional | 2007-2009            | 2,867 (M+W) (mean age: 66 $\pm$ 6 years) | Annual average concentration for years 2003-2009 modelled at resolution 20x20 m using the KCLUrban dispersion modelling system which incorporates meteorological data, empirically derived NO-NO <sub>2</sub> -O <sub>3</sub> and PM relationships and emission rates from the London Atmospheric Emission Inventory (agreement between the model and measurements: r=0.78 for PM <sub>10</sub> and 0.74 for PM <sub>2.5</sub> ). Exposure at residence was based on the average concentration at model grid points within 25 m of the residential postcode centre. 1-y average (2007-2009 assessment)<br>1-4 year lag (1-4 years prior to 2007-2009 assessment)<br>3-year average (average concentration of 3 years prior to 2007-2009 assessment)<br>5-y average (year of 2007-2009 measurements plus 4 preceding) | Reasoning (Alice Heim 4-I test) | $\beta = -0.045$ ; (95% CI - 0.09; 0.00)<br><br>$\beta = -0.046$ ; (95% CI - 0.088; -0.005),<br><br>$\beta = -0.043$ ; (95% CI - 0.082; -0.004)<br><br>The values refer to Figure A in Tonne et al (2014) for further details. | PM <sub>2.5</sub> yearly lag 2<br><br>PM <sub>2.5</sub> yearly lag 3<br><br>PM <sub>2.5</sub> yearly lag 4 (1.3 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> exhaust, PM <sub>10</sub> and PM <sub>10</sub> exhaust | Age, sex, race, SES, physical activity, alcohol, age x time interaction and main effect of exposure.                                                                |
| (Zhang et al., 2018) China Family Panel Studies (CFPS) | China              | Cross-sectional | 2010-2014            | 31955 (M+W) (more than 10 years old)     | Air pollution index (API) calculated on daily reading of three air pollutants, namely SO <sub>2</sub> , NO <sub>2</sub> and PM <sub>10</sub> (range 0-500)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Math test score (SD)            | reduction in mean (SD)<br><br><b>0.033 (0.005)</b><br><b>0.064 (0.010)</b><br><b>0.068 (0.023)</b><br><b>0.146 (0.023)</b><br><b>0.146 (0.023)</b><br><b>0.157 (0.025)</b><br><b>0.211 (0.033)</b>                             | Impact of a one SD reduction in mean API<br>1-day<br>7-day<br>30-day<br>90-day<br>1-year<br>2-year<br>3-year                                                                                                               | Year, month, day of the week, post meridiem hour fixed effects, sex, age, income, education, weather variables (temperature, precipitation, wind speed), population |

| First author, year (Name of study) | Location                                                                                    | Study design       | Time recruitment/ FU     | N cases/cohort size or N Controls (age)                                                                                                                                                                                                                                           | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Outcome             | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Exposure                                                                                                                        | Adjustments                         |
|------------------------------------|---------------------------------------------------------------------------------------------|--------------------|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
|                                    |                                                                                             |                    |                          |                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                 | density and industrial value share. |
| Molina-Sotomayor et al., 2019      | Santiago (highly polluted city) and Viña del Mar (city with low levels of pollution), Chile | Quasi-experimental | March 2013-december 2014 | 181 (W): 47 active/polluted air group (AP) (mean age 69.8 $\pm$ 4.3 years); 44 sedentary/polluted air group (SP) (mean age 68.3 $\pm$ 3.5 years); 45 active/clean air group (AC) (mean age 69 $\pm$ 1.2 years); 45 sedentary/clean air group (SC) (mean age 68.5 $\pm$ 2.4 years) | The participants were recruited from women living in a highly polluted city (Santiago) and women living in a city with low levels of pollution (Viña del Mar). They were divided into four groups: AP, SP, AC and SC combining Active (A) and Sedentary (S) Polluted (P) and Clean (C) city groups. The active groups performed a training programme consisting of low/moderate intensity walking on a horizontal plane, with progressive speed increases. The study duration was 24 months, with four training cycles of six months each and three 1-hour sessions per week. | Time orientation    | At the end of the experiment, a statistically significant decreasing rate (p,0.05) was observed in the SC and SP groups (-4% and 9.9% respectively). Results at the end of the experiment:<br>M $\pm$ SD (95% CI)<br>AC: 4.96 $\pm$ 0.21 (4.76-5.15)<br>AP: 4.83 $\pm$ 0.38 (4.64-5.02)<br>SC: 4.80 $\pm$ 0.50 (4.61-4.99)<br>SP: 4.18 $\pm$ 0.71 (3.99-4.37)<br><b>p for intercomparison group=0.000</b><br><br>At the beginning of the experiment no statistically significant difference between groups (p>0.05) | Comparison between four groups: AP, SP, AC and SC combining Active (A) and Sedentary (S) Polluted (P) and Clean (C) city groups | No adjustments                      |
|                                    |                                                                                             |                    |                          |                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Spatial orientation | At the end of the experiment, a statistically significant decreasing rate (p,0.05) was observed in the SC and SP groups (-4% and 9.9% respectively). Results at the end of the experiment:<br>M $\pm$ SD (95% CI)<br>AC: 5 $\pm$ 0.0 (4.87-5.13)                                                                                                                                                                                                                                                                    |                                                                                                                                 |                                     |

| First author, year (Name of study) | Location | Study design | Time recruitment/ FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome     | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Exposure | Adjustments |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|---------------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------|
|                                    |          |              |                      |                                         |                     |             | <p>AP: <math>5 \pm 0.0</math> (4.88-5.12)<br/> SC: <math>4.84 \pm 0.42</math> (4.72-4.97)<br/> SP: <math>4.73 \pm 0.44</math> (4.60-4.86)<br/> <b>p for intercomparison group=0.006</b></p> <p>At the beginning of the experiment no statistically significant difference between groups (<math>p &gt; 0.05</math>)</p>                                                                                                                                                                                                                                                                                                       |          |             |
|                                    |          |              |                      |                                         |                     | Calculation | <p>At the end of the experiment, a statistically significant decreasing rate (<math>p, 0.05</math>) was observed in the SC and SP groups (-4% and 9.9% respectively). Results at the end of the experiment:<br/> M <math>\pm</math> SD (95% CI)<br/> AC: <math>4.58 \pm 0.81</math> (4.23-4.93)<br/> AP: <math>4.17 \pm 1.03</math> (3.83-4.51)<br/> SC: <math>3.84 \pm 1.11</math> (3.50-4.19)<br/> SP: <math>2.68 \pm 1.37</math> (2.33-3.03)<br/> <b>p for intercomparison group=0.000</b></p> <p>At the beginning of the experiment no statistically significant difference between groups (<math>p &gt; 0.05</math>)</p> |          |             |

| First author, year (Name of study)                            | Location | Study design    | Time recruitment/ FU | N cases/cohort size or N Controls (age)          | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Outcome                                                            | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                               | Exposure                                                                                                                                                                                                                                                                           | Adjustments                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------------------------------------------------|----------|-----------------|----------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Shin et al., 2019 (The Korean Frailty and Aging Cohort Study) | Korea    | Cross-sectional | 2016-2017            | 2,896 (M+W) (70-84 years, mean age 76 $\pm$ 3.9) | The level of PM <sub>10</sub> , NO <sub>2</sub> , CO, SO <sub>2</sub> and O <sub>3</sub> were measured hourly at 268 nationwide surveillance stations located in residential areas by the Korean Air Pollutants Emission Service in 2013-2017. As PM <sub>2.5</sub> has only been measured in Korea since 2015, average concentrations of PM <sub>2.5</sub> in the data from 2015 to 2017 were applied. Pollutant levels were matched with the location of the participants' surveillance centres and the average concentrations were calculated. | Frontal Assessment battery score (log-transformed cognitive scale) | $\beta = -0.037$ (95% CI - 0.048, -0.025)<br><br>$\beta = -0.002$ (95% CI - 0.021, 0.017)<br><br>$\beta = -0.006$ (95% CI - 0.019, 0.007)<br><br>$\beta = 0.007$ (95% CI - 0.005, 0.020)<br><br>$\beta = -0.019$ (95% CI - 0.034, -0.005)<br><br>$\beta = 0.011$ (95% CI 0.002, 0.019)<br><br>ORs are reported in the figures in the paper | PM <sub>2.5</sub> increase (1.5 $\mu$ g/m <sup>3</sup> )<br><br>PM <sub>10</sub> increase (4.6 $\mu$ g/m <sup>3</sup> )<br><br>CO increase (0.08 ppm)<br><br>SO <sub>2</sub> increase (0.9 ppb)<br><br>NO <sub>2</sub> increase (7.7 ppb)<br><br>O <sub>3</sub> increase (4.3 ppb) | Age, sex, body mass index, smoking, alcohol intake, physical activity, education, household income, marital status, Carlson's comorbidity index, length of same residence, meteorological data, residence area, PM <sub>2.5</sub> , PM <sub>10</sub> , CO, SO <sub>2</sub> , NO <sub>2</sub> , O <sub>3</sub> were adjusted as fixed effects, and each centre was adjusted as random effects. |
|                                                               |          |                 |                      |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Digit Backward Span (log-transformed cognitive scale)              | $\beta = -0.039$ (95% CI - 0.057, -0.020)<br><br>$\beta = 0.022$ (95% CI - 0.008, 0.053)<br><br>$\beta = -0.022$ (95% CI - 0.046, 0.003)<br><br>$\beta = -0.032$ (95% CI - 0.058, -0.007)<br><br>$\beta = 0.015$ (95% CI - 0.009, 0.040)                                                                                                   | PM <sub>2.5</sub> increase (1.5 $\mu$ g/m <sup>3</sup> )<br><br>PM <sub>10</sub> increase (4.6 $\mu$ g/m <sup>3</sup> )<br><br>CO increase (0.08 ppm)<br><br>SO <sub>2</sub> increase (0.9 ppb)                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                               |

| First author, year (Name of study) | Location     | Study design    | Time recruitment/ FU | N cases/cohort size or N Controls (age) | Exposure assessment            | Outcome                                           | HR, OR, RR, $\beta$ (95% CI)                                                     | Exposure                                                                    | Adjustments                                                                                                                                                                                     |
|------------------------------------|--------------|-----------------|----------------------|-----------------------------------------|--------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |              |                 |                      |                                         |                                |                                                   | $\beta = -0.029$ (95% CI - 0.064, 0.006)                                         | NO <sub>2</sub> increase (7.7 ppb)<br><br>O <sub>3</sub> increase (4.3 ppb) |                                                                                                                                                                                                 |
| Rafie et al., 2019                 | Iran, Tehran | Cross-sectional | April-June 2018      | 200 (M+W) (14-70 years)                 | Self-reported by questionnaire | Executive function (TMT-B score, seconds)         | <b><math>\beta = 0.127</math> (95% CI 0.024, 0.325) <math>p &lt; 0.05</math></b> | Traffic density in area of residence, high vs low                           | Age, sex. Existence of dental amalgam implants, cigarette smoking, water-pipe smoking, insecticide use, metal concentration in hair (Ag, Al, As, B, Ba, Cr, Cu, Fe, Hg, Mn, Ni, Pb, Si, Sn, Zn) |
|                                    |              |                 |                      |                                         |                                | Mental flexibility (TMT-delta score, seconds)     | <b><math>\beta = 0.106</math> (95% CI 0.061, 0.302) <math>p &lt; 0.05</math></b> |                                                                             |                                                                                                                                                                                                 |
|                                    |              |                 |                      |                                         |                                | Cognitive efficiency or dissimulation (TMT ratio) | <b><math>\beta = 0.081</math> (95% CI 0.029, 0.187) <math>p &lt; 0.05</math></b> |                                                                             |                                                                                                                                                                                                 |

### Abbreviations

FU, follow-up; M, men; W, women; SES, socioeconomic status; BC, black carbon, BMI, body mass index; HR, hazard ratio; OR, odds ratio; RR, relative risk; CI, confidence interval; IQR, interquartile range, TMT, The Trailmaking Test; SD, standard deviation



**Table 3.3. Summary of characteristics and outcomes of studies assessing the effect of air pollution on attention included in literature review**

| First author, year (Name of study)                                                                          | Location               | Study design    | Time recruitment/ FU | N cases/cohort size or N Controls (age)                    | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Outcome                                                                                                                                                                                             | HR, OR, RR, $\beta$ (95% CI)                                                                               | Exposure                                                                                                                                                                                                                                                                                                        | Adjustments                                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------|------------------------|-----------------|----------------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ranft et al., 2009 (Study of the influence of Air pollution on Lung function, Inflammation and Aging SALIA) | Ruhr district, Germany | Cross-sectional | 2007-2009            | 399 (W) (68-79 years, Mean age: $74.1 \pm 2.6$ years)      | Individual exposure to PM <sub>10</sub> was estimated from the nearest monitoring station (distributed over the Ruhr district in an 8-km grid) to the participants' residence averaged over the five years before the cohort enrolment (that is, 1980-1993) and over the 5 years from 2002-2006. PM <sub>10</sub> was calculated converting the TSP concentrations into PM <sub>10</sub> using a factor of 0.71. Residential traffic proximity was calculated as the distance of the address to the next busy road with 10,000 cars (traffic counts assessed in the year 2000). All women included lived more than 20 years at the same residential address. | Attention (Stroop test)                                                                                                                                                                             | $\beta = -5.1$ (95% CI -8.2, -2.0)<br>$\beta = 0.0$ (95% CI -0.4, 0.4)<br>$\beta = 0.2$ (95% CI -0.4, 0.7) | Residential Traffic proximity (<50 m)<br><br>5-years average PM <sub>10</sub> background concentration in ambient air at age 55 years<br><br>5-years average PM <sub>10</sub> background concentration in ambient air 2002-2006 (28.3 in Ruhr district and 25 in Rural county Borken $\mu\text{g}/\text{m}^3$ ) | age, education, smoking, environmental tobacco smoking, indoor air pollution, depression, chronic respiratory diseases, diabetes, hypertension, high cholesterol, ever infarction, ever stroke, physical activities, obesity                                                                                   |
| Chen and Schwartz, 2009 (NHANES-III)                                                                        | Nationwide, USA        | Cross-sectional | 1988-1991            | 1764 (M+W) (220-59 years, mean age: $37.4 \pm 10.9$ years) | PM <sub>10</sub> and O <sub>3</sub> concentrations representative of the year prior to cognitive examination were modelled for each geocoded residence address at the centroid of the census-block group using distance weighted averages of all EPA monitors in the residing and adjoining counties.                                                                                                                                                                                                                                                                                                                                                        | Attention (SDLT) (represents the sum of error scores for each trial)<br><br>Attention (SDLT-trial represents total number of trials to reach the criterion of 2 consecutive trials without mistake) | $\beta = 0.57$ (95% CI 0.08; 1.06)<br><br>$\beta = 0.28$ (95% CI 0.06; 0.51)                               | 1-year average O <sub>3</sub> (10 ppb)                                                                                                                                                                                                                                                                          | Age, sex, race, SES, employment status, income, poverty-income ratio poverty, family size, smoking, alcohol, physical activity, urban/rural designation, CVD risk factors (BMI, hypertension, diabetes, HDL level, indoor air pollutant sources (woodstove, environmental tobacco smoke, fireplace, gas stove) |

| First author, year (Name of study)                                                                               | Location                       | Study design                      | Time recruitment/ FU | N cases/cohort size or N Controls (age)  | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Outcome                                                                                                                                                                                             | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                         | Exposure                                                                                                                                                                                                                                                                                                                                                                                                      | Adjustments                                                                  |
|------------------------------------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|----------------------|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
|                                                                                                                  |                                |                                   |                      |                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Attention (SDLT) (represents the sum of error scores for each trial)<br><br>Attention (SDLT-trial represents total number of trials to reach the criterion of 2 consecutive trials without mistake) | $\beta = 0.12$ s; (95% CI -0.07; 0.31)<br><br>$\beta = -0.02$ (95% CI -0.10; 0.07)                                                                                                                                                                                   | 1-year average PM <sub>10</sub> (10 $\mu\text{g}/\text{m}^3$ )<br><br>1-year average PM <sub>10</sub> (10 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                                                                          | Age, sex, race, SES (SDLT trials excludes adjustment for race)               |
| Schikowski et al., 2015 (Study of the influence of Air pollution on Lung function, Inflammation and Aging SALIA) | North Rhine-Westfalia, Germany | Cross-sectional from cohort study | 2007-2009            | 789 (W) (mean age 73.4 $\pm$ 3.05 years) | Exposure to NO <sub>2</sub> , NO <sub>x</sub> , PM <sub>2.5</sub> , PM <sub>2.5abs</sub> and PM <sub>10</sub> was estimated at the participating home addresses by land-use regression (LUR) models. Pollutant levels were measured over a period of one year (2009-2010) and the exposure values to the years 1985-1994 were back-extrapolated by assuming proportional changes over time within city spatial patterns. Daily traffic load within a 100-metre buffer around the home was calculated as the sum of the products of the number of vehicles from all roads with the street section length in the 100m buffer for the year 2000 and from 2007 for the follow-up investigation. Predictor variables on nearby traffic, population/household density and land use were derived from a Geographic Information | Attention (TMT-A)                                                                                                                                                                                   | $\beta = 0.08$ , 95% CI -0.10, 0.26)<br><br>$\beta = -0.06$ , 95% CI -0.19, 0.06)<br><br>$\beta = -0.07$ , 95% CI -0.19, 0.06)<br><br>$\beta = 0.00$ , 95% CI -0.10, 0.10)<br><br>$\beta = -0.05$ , 95% CI -0.19, 0.09)<br><br>$\beta = -0.02$ , 95% CI -0.10, 0.07) | Traffic load ( $\geq 50,000$ cars per day)<br><br>NO <sub>2</sub> IQR increase (9.6 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>x</sub> IQR increase (23.4 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10</sub> IQR increase (2.2 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> IQR increase (1.9 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5abs</sub> IQR increase (0.4 $10^{-3} \times \text{m}^{-1}$ ) | age, urban/rural living, SES, smoking, Environmental Tobacco smoke and APOE. |

| First author, year (Name of study)                           | Location                         | Study design                           | Time recruitment/ FU | N cases/cohort size or N Controls (age)          | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Outcome                                                                 | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                 | Exposure                                                                                                                                                                                                                                                                                                                                                    | Adjustments                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------|----------------------------------|----------------------------------------|----------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                              |                                  |                                        |                      |                                                  | System (GIS) programme and were evaluated to explain spatial variation of annual average concentrations.                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                         |                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                               |
| Cullen et al, 2018 (UK Biobank)                              | UK (England, Scotland and Wales) | Cross-sectional (analysis at baseline) | 2010                 | 86,759 (M+W) (mean age: 56.86 $\pm$ 8.12 years)  | Annual PM <sub>2.5</sub> , PM <sub>2.5-10</sub> , PM <sub>10</sub> , NO <sub>2</sub> and NO <sub>x</sub> were estimated for the years 2005-2007 using a LUR model for Western Europe developed integrating more than 15000 EuroAirnet monitoring sites and satellite-derived air pollution estimates. Air pollution data were mapped to participants' baseline addresses.                                                                                                                                                                         | Reaction time (values above 1 indicate relatively longer reaction time) | Rate ratio = 0.995, (95% CI 0.9986, 1.0004) p=0.2799<br><br>Rate ratio = 1.0019, (95% CI 0.9997, 1.0042) p=0.0887<br><br><b>Rate ratio = 1.0032, (95% CI 1.0012, 1.0053) p=0.0019</b><br><br>Rate ratio = 0.9999, (95% CI 0.9997, 1.0003) p=0.9088<br><br><b>Rate ratio = 1.0002, (95% CI 1.0001, 1.0003) p=0.0037</b>       | PM <sub>10</sub> increase IQR (4.12 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10-2.5</sub> increase IQR (0.77 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> increase IQR (1.08 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>2</sub> increase IQR (13.71 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>x</sub> increase IQR (14.67 $\mu\text{g}/\text{m}^3$ ) | Age, sex, race, Townsend deprivation score, education, smoking, physical activity, time outdoors, proximity to nearest major road, traffic intensity or nearest major road, population density. Further adjustment for noise did not change the results.                                                                                                                                      |
| Shin et al, 2019 (The Korean Frailty and Aging Cohort Study) | Korea                            | Cross-sectional                        | 2016-2017            | 2,896 (M+W) (70-84 years, mean age 76 $\pm$ 3.9) | The level of PM <sub>10</sub> , NO <sub>2</sub> , CO, SO <sub>2</sub> and O <sub>3</sub> were measured hourly at 268 nationwide surveillance stations located in residential areas by the Korean Air Pollutants Emission Service in 2013-2017. As PM <sub>2.5</sub> has only been measured in Korea since 2015, average concentrations of PM <sub>2.5</sub> in the data from 2015 to 2017 were applied. Pollutant levels were matched with the location of the participants' surveillance centres and the average concentrations were calculated. | Digit Forward Span (log-transformed cognitive scale)                    | <b><math>\beta</math> = -0.022 (95% CI -0.040, -0.005)</b><br><br><b><math>\beta</math> = -0.029 (95% CI -0.057, -0.001)</b><br><br><b><math>\beta</math> = 0.052 (95% CI 0.029, 0.075)</b><br><br><b><math>\beta</math> = 0.058 (95% CI 0.035, 0.082)</b><br><br><b><math>\beta</math> = -0.026 (95% CI -0.050, -0.003)</b> | PM <sub>2.5</sub> increase (1.5 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10</sub> increase (4.6 $\mu\text{g}/\text{m}^3$ )<br><br>CO increase (0.08 ppm)<br><br>SO <sub>2</sub> increase (0.9 ppb)<br><br>NO <sub>2</sub> increase (7.7 ppb)                                                                                                               | Age, sex, body mass index, smoking, alcohol intake, physical activity, education, household income, marital status, Carlson's comorbidity index, length of same residence, meteorological data, residence area, PM <sub>2.5</sub> , PM <sub>10</sub> , CO, SO <sub>2</sub> , NO <sub>2</sub> , O <sub>3</sub> were adjusted as fixed effects, and each centre was adjusted as random effects. |

| First author, year (Name of study) | Location     | Study design    | Time recruitment/ FU | N cases/cohort size or N Controls (age) | Exposure assessment            | Outcome                          | HR, OR, RR, $\beta$ (95% CI)                                                                                | Exposure                                          | Adjustments                                                                                                                                                                                     |
|------------------------------------|--------------|-----------------|----------------------|-----------------------------------------|--------------------------------|----------------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |              |                 |                      |                                         |                                |                                  | <b><math>\beta = 0.062</math> (95% CI 0.029, 0.094)</b><br><br>ORs are reported in the figures in the paper | O <sub>3</sub> increase (4.3 ppb)                 |                                                                                                                                                                                                 |
| Rafie et al., 2019                 | Iran, Theran | Cross-sectional | April-June 2018      | 200 (M+W) (14-70 years)                 | Self-reported by questionnaire | Attention (TMT-A score, seconds) | <b><math>\beta = 0.118</math> (95% CI 0.062, 0.238)</b><br><b>p&lt;0.05</b>                                 | Traffic density in area of residence, high vs low | Age, sex. Existence of dental amalgam implants, cigarette smoking, water-pipe smoking, insecticide use, metal concentration in hair (Ag, Al, As, B, Ba, Cr, Cu, Fe, Hg, Mn, Ni, Pb, Si, Sn, Zn) |

### Abbreviations

FU, follow-up, M, men; W, women; SES, socioeconomic status; BC, black carbon, BMI, body mass index; HR, hazard ratio; OR, odds ratio; RR, relative risk; CI, confidence interval; IQR, interquartile range; SDLT, Serial-digit learning test, CVD, cardiovascular; HDL, high density lipoprotein

**Table 3.4. Summary of characteristics and outcomes of studies assessing the effect of air pollution on memory included in literature review**

| First author, year (Name of study)                   | Location    | Study design          | Time recruitment/ FU             | N cases/cohort size or N Controls (age)                | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Outcome                                         | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                    | Exposure                                                                                                                                                                       | Adjustments                                                                                                                                                                                                                                                                                                                               |
|------------------------------------------------------|-------------|-----------------------|----------------------------------|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wellenius et al., 2012 (MOBILIZE Boston Study (MBS)) | Boston, USA | Longitudinal (cohort) | 2005-2008/ 16.8 months (mean FU) | 765 ( $\geq 65$ years, Mean age: $78.1 \pm 5.4$ years) | ArcGIS was used to geocode participant address and calculate the Euclidean distance from residence to the nearest major roadway, defined as roads having US Census Feature Class Code A1 (primary highway with limited access) or A2 (primary road without limited access). Daily outdoor BC levels (a marker of traffic pollution) at participant's address was estimated using a validated spatio-temporal land-use regression model. To create a metric of long-term exposure, modelled residential BC was averaged over the 365 days preceding each cognitive assessment. | Immediate recall (Hopkins verbal Learning test) | $\beta = -1.6$ (95% CI -2.9; -0.3) $p=0.011$<br><br>$\beta = -0.6$ (95% CI -1.1; -0.1) $p=0.015$<br>Significant association among subjects more highly educated and of younger age $\leq 77$ years<br><br>$\beta = -0.36$ (95% CI -0.71; -0.01) $p=0.046$       | Residential distance to major roadway (<100 m vs >1000 m)<br><br>Residential Traffic proximity IQR decrease (851.2 m).<br><br>BC IQR increase (0.11 $\mu\text{g}/\text{m}^3$ ) | Age, sex, race, history of stroke, history of smoking (ever vs never), physical activity, education (three categories), visit number, BMI, household income (below vs above median) season of home interview, percent of neighbourhood population that is non-white and percent of neighbourhood population with college degree or above. |
|                                                      |             |                       |                                  |                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Delayed recall (Hopkins verbal Learning test)   | $\beta = -1.1$ ; (95% CI -1.9; -0.3) $p=0.006$<br><br>$\beta = -0.4$ ; (95% CI -0.7; -0.1) $p=0.011$<br><br>Significant association among subjects more highly educated and of younger age $\leq 77$ years<br><br>$\beta = -0.14$ (95% CI -0.37; 0.09) $p=0.22$ | Residential distance to major roadway (<100 m vs >1000 m)<br><br>Residential Traffic proximity IQR decrease (851.2 m).<br><br>BC IQR increase (0.11 $\mu\text{g}/\text{m}^3$ ) |                                                                                                                                                                                                                                                                                                                                           |

| First author, year (Name of study)                                                                              | Location                       | Study design                      | Time recruitment/ FU | N cases/cohort size or N Controls (age)   | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                         | Outcome                                         | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                 | Exposure                                                                                                                                                                                                                                                                                                                                                                                                         | Adjustments                                                                  |
|-----------------------------------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|----------------------|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
|                                                                                                                 |                                |                                   |                      |                                           |                                                                                                                                                                                                                                                                                                                                                                                                                             | Word recognition (Hopkins verbal Learning test) | $\beta = 0.2$ ; (95% CI -0.3; 0.8)<br>$p = 0.27$<br><br>$\beta = 0.07$ ; (95% CI -0.12; 0.25)<br>$p = 0.47$<br><br>consistent results across strata for age and education<br><br>$\beta = 0.03$ (95% CI -0.12; 0.17)<br>$p = 0.73$                           | Residential distance to major roadway (<100 m vs >1000 m)<br><br>Residential Traffic proximity IQR decrease (851.2 m).<br><br>BC IQR increase (0.11 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                                   |                                                                              |
| Schikowski et al, 2015 (Study of the influence of Air pollution on Lung function, Inflammation and Aging SALIA) | North Rhine-Westfalia, Germany | Cross-sectional from cohort study | 2007-2009            | 789 (W) (mean age: 73.4 $\pm$ 3.05 years) | Exposure to $\text{NO}_2$ , $\text{NO}_x$ , $\text{PM}_{2.5}$ , $\text{PM}_{2.5\text{abs}}$ and $\text{PM}_{10}$ was estimated at the participating home addresses by land-use regression (LUR) models. Pollutant levels were measured over a period of one year (2009-2010) and the exposure values to the years 1985-1994 were back-extrapolated by assuming proportional changes over time within city spatial patterns. | Semantic memory (semantic fluency)              | $\beta = 0.09$ (95% CI -0.08, 0.25)<br><br>$\beta = -0.002$ (95% CI -0.12, 0.12)<br><br>$\beta = 0.01$ (95% CI -0.10, 0.13)<br><br>$\beta = 0.02$ (95% CI -0.07, 0.12)<br><br>$\beta = 0.07$ (95% CI -0.06, 0.20)<br><br>$\beta = 0.01$ (95% CI -0.07, 0.09) | Traffic load ( $\geq 50,000$ cars per day)<br><br>$\text{NO}_2$ IQR increase (9.6 $\mu\text{g}/\text{m}^3$ )<br><br>$\text{NO}_x$ IQR increase (23.4 $\mu\text{g}/\text{m}^3$ )<br><br>$\text{PM}_{10}$ IQR increase (2.2 $\mu\text{g}/\text{m}^3$ )<br><br>$\text{PM}_{2.5}$ IQR increase (1.9 $\mu\text{g}/\text{m}^3$ )<br><br>$\text{PM}_{2.5\text{abs}}$ IQR increase (0.4 $10^{-6} \times \text{m}^{-1}$ ) | age, urban/rural living, SES, smoking, Environmental Tobacco smoke and APOE. |

| First author, year (Name of study) | Location | Study design | Time recruitment/ FU | N cases/cohort size or N Controls (age) | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Outcome                                 | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Adjustments |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                      |                                         | Daily traffic load within a 100-metre buffer around the home was calculated as the sum of the products of the number of vehicles from all roads with the street section length in the 100 m buffer for the year 2000 and from 2007 for the follow-up investigation. Predictor variables on nearby traffic, population/household density and land use were derived from a Geographic Information System (GIS) programme and were evaluated to explain spatial variation of annual average concentrations. | Semantic memory (Boston learning BNT)   | $\beta = -0.03$ (95% CI -0.24, 0.17)<br>$\beta = -0.14$ (95% CI -0.29, 0.01)<br><b><math>\beta = -0.16</math> (95% CI -0.30, -0.01)</b><br>$\beta = -0.05$ (95% CI -0.17, 0.07)<br>$\beta = -0.09$ (95% CI -0.26, 0.07)<br>$\beta = 0.01$ (95% CI -0.09, 0.11)<br>$\beta = -0.07$ (95% CI -0.27, 0.13)<br>$\beta = -0.08$ (95% CI -0.22, 0.06)<br>$\beta = -0.09$ (95% CI -0.23, 0.05)<br>$\beta = 0.01$ (95% CI -0.10, 0.13)<br>$\beta = 0.06$ (95% CI -0.10, 0.22)<br>$\beta = 0.02$ (95% CI -0.08, 0.12) | Traffic load ( $\geq 50,0000$ cars per day)<br>NO <sub>2</sub> IQR increase (9.6 $\mu\text{g}/\text{m}^3$ )<br>NO <sub>x</sub> IQR increase (23.4 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>10</sub> IQR increase (2.2 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5</sub> IQR increase (1.9 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5 abs</sub> IQR increase (0.4 $10^{-6}$ x $\text{m}^{-1}$ )<br>Traffic load ( $\geq 50,0000$ cars per day)<br>NO <sub>2</sub> IQR increase (9.6 $\mu\text{g}/\text{m}^3$ )<br>NO <sub>x</sub> IQR increase (23.4 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>10</sub> IQR increase (2.2 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5</sub> IQR increase (1.9 $\mu\text{g}/\text{m}^3$ ) |             |
|                                    |          |              |                      |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Semantic memory (Phonetic fluency PhFI) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |             |



| First author, year (Name of study) | Location | Study design | Time recruitment/ FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome                              | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                           | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Adjustments |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|---------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                      |                                         |                     | Episodic memory (word list learning) | $\beta = -0.02$ (95% CI -0.22, 0.19)<br>$\beta = -0.01$ (95% CI -0.16, 0.14)<br>$\beta = -0.04$ (95% CI -0.19, 0.10)<br>$\beta = 0.11$ (95% CI -0.01, 0.23)                                                                                                                                                            | PM2.5 abs IQR increase ( $0.4 \cdot 10^{-6} \text{ x m}^{-1}$ )<br><br>Traffic load ( $\geq 50,0000$ cars per day)<br><br>NO <sub>2</sub> IQR increase ( $9.6 \mu\text{g}/\text{m}^3$ )<br>NOx IQR increase ( $23.4 \mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                                                                                                                                          |             |
|                                    |          |              |                      |                                         |                     | Episodic memory (word list recall)   | $\beta = 0.11$ (95% CI -0.06, 0.27)<br>$\beta = 0.05$ (95% CI -0.05, 0.15)<br>$\beta = -0.02$ (95% CI -0.22, 0.17)<br>$\beta = 0.03$ (95% CI -0.12, 0.18)<br>$\beta = -0.01$ (95% CI -0.16, 0.13)<br>$\beta = 0.06$ (95% CI -0.05, 0.18)<br>$\beta = 0.10$ (95% CI -0.07, 0.26)<br>$\beta = 0.11$ (95% CI -0.06, 0.27) | PM10 IQR increase ( $2.2 \mu\text{g}/\text{m}^3$ )<br>PM2.5 IQR increase ( $1.9 \mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5 abs</sub> IQR increase ( $0.4 \cdot 10^{-6} \text{ x m}^{-1}$ )<br><br>Traffic load ( $\geq 50,0000$ cars per day)<br>NO <sub>2</sub> IQR increase ( $9.6 \mu\text{g}/\text{m}^3$ )<br>NOx IQR increase ( $23.4 \mu\text{g}/\text{m}^3$ )<br>PM <sub>10</sub> IQR increase ( $2.2 \mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5</sub> IQR increase ( $1.9 \mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5 abs</sub> IQR increase ( $0.4 \cdot 10^{-6} \text{ x m}^{-1}$ ) |             |

| First author, year (Name of study)             | Location         | Study design                                               | Time recruitment/ FU | N cases/cohort size or N Controls (age)     | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                   | Outcome                                                                                          | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                             | Exposure                                                                                                                                                                                                                                                                           | Adjustments                                                                                  |
|------------------------------------------------|------------------|------------------------------------------------------------|----------------------|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Gatto et al, 2014 (BVAIR, WISH, ELITE studies) | Los Angeles, USA | Cross-sectional analysis of 3 randomised controlled trials | 2000-2006            | 1496 (M+W) (mean age: 60.5 $\pm$ 8.1 years) | Annual average O <sub>3</sub> , PM <sub>2.5</sub> and NO <sub>2</sub> concentrations for 2000-2006 from monitoring stations were spatially interpolated to the subjects' residential addresses using inverse-distance-squared weighting in a GIS programme. Ambient air quality data were extracted from the Air Quality System, maintained by the US Environmental Protection Agency | Logical memory (paragraph recall- Immediate recall (IR) and delayed recall (DR) (WMS-III)        | $\beta$ = 0.24 (95% CI -0.21, 0.68)<br>p for trend 0.15<br><br>$\beta$ = -0.62 (95% CI -1.35, 0.11)<br>p for trend 0.053<br><br>$\beta$ = -0.12 (95% CI -0.40, 0.16)<br>p for trend 0.49 | 8-hour O <sub>3</sub> highest (>49 ppb) vs lowest ( $\leq$ 34 ppb) tertile<br><br>24-hour NO <sub>2</sub> highest (>20 ppb) vs lowest ( $\leq$ 10 ppb) tertile<br><br>24-hour PM <sub>2.5</sub> highest (>17 ug/m <sup>3</sup> ) vs lowest ( $\leq$ 15 ug/m <sup>3</sup> ) tertile | Age, race/ethnicity, sex, highest education level achieved, household income, mood and study |
|                                                |                  |                                                            |                      |                                             |                                                                                                                                                                                                                                                                                                                                                                                       | Visual episodic memory (faces, IR and DR (WMS-III)                                               | $\beta$ = 0.01 (95% CI -0.42, 0.44)<br>p for trend 0.80<br><br>$\beta$ = -0.26 (95% CI -0.97, 0.45)<br>p for trend 0.25<br><br>$\beta$ = -0.19 (95% CI -0.46, 0.08)<br>p for trend 0.16  | 8-hour O <sub>3</sub> highest (>49 ppb) vs lowest ( $\leq$ 34 ppb) tertile<br><br>24-hour NO <sub>2</sub> highest (>20 ppb) vs lowest ( $\leq$ 10 ppb) tertile<br><br>24-hour PM <sub>2.5</sub> highest (>17 ug/m <sup>3</sup> ) vs lowest ( $\leq$ 15 ug/m <sup>3</sup> ) tertile | Age, race/ethnicity, sex, highest education level achieved, household income, mood and study |
|                                                |                  |                                                            |                      |                                             |                                                                                                                                                                                                                                                                                                                                                                                       | Semantic memory (category fluency-animal naming, 60 seconds Boston Naming test, 30-item version) | $\beta$ = -0.12 (95% CI -0.50, 0.26)<br>p for trend 0.75<br><br>$\beta$ = -0.24 (95% CI -0.87, 0.39)<br>p for trend 0.95<br><br>$\beta$ = -0.07 (95% CI -0.31, 0.16)<br>p for trend 0.54 | 8-hour O <sub>3</sub> highest (>49 ppb) vs lowest ( $\leq$ 34 ppb) tertile<br><br>24-hour NO <sub>2</sub> highest (>20 ppb) vs lowest ( $\leq$ 10 ppb) tertile<br><br>24-hour PM <sub>2.5</sub> highest (>17 ug/m <sup>3</sup> ) vs lowest ( $\leq$ 15 ug/m <sup>3</sup> ) tertile | Age, race/ethnicity, sex, highest education level achieved, household income, mood and study |
|                                                |                  |                                                            |                      |                                             |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                  |                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                    |                                                                                              |
|                                                |                  |                                                            |                      |                                             |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                  |                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                    |                                                                                              |
|                                                |                  |                                                            |                      |                                             |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                  |                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                    |                                                                                              |

| First author, year (Name of study)   | Location        | Study design    | Time recruitment/ FU | N cases/cohort size or N Controls (age)                    | Exposure assessment                                                                                                                                                                                                                                                                                   | Outcome                                                                                                          | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                            | Exposure                                                                                                                                                                                                                                                                           | Adjustments                                                                                                                                                                                                                                                                                             |
|--------------------------------------|-----------------|-----------------|----------------------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      |                 |                 |                      |                                                            |                                                                                                                                                                                                                                                                                                       | Verbal learning (California Verbal Learning Test, Immediate recall (IR), and delayed recall (DR))                | $\beta = -0.20$ (95% CI $-0.63, 0.23$ )<br>p for trend 0.33<br><br>$\beta = -0.04$ (95% CI $-0.75, 0.670$ )<br>p for trend 0.59<br><br><b><math>\beta = -0.37</math> (95% CI <math>-0.64, -0.10</math>)</b><br><b>p for trend 0.007</b> | 8-hour O <sub>3</sub> highest (>49 ppb) vs lowest ( $\leq 34$ ppb) tertile<br><br>24-hour NO <sub>2</sub> highest (>20 ppb) vs lowest ( $\leq 10$ ppb) tertile<br><br>24-hour PM <sub>2.5</sub> highest (>17 ug/m <sup>3</sup> ) vs lowest ( $\leq 15$ ug/m <sup>3</sup> ) tertile | Age, race/ethnicity, sex, highest education level achieved, household income, mood and study                                                                                                                                                                                                            |
| Chen and Schwartz, 2009 (NHANES-III) | Nationwide, USA | Cross-sectional | 1988-1991            | 1764 (M+W) (220-59 years, mean age: 37.4 $\pm$ 10.9 years) | PM <sub>10</sub> and O <sub>3</sub> concentrations representative of the year prior to cognitive examination were modelled for each geocoded residence address at the centroid of the census-block group using distance weighted averages of all EPA monitors in the residing and adjoining counties. | Total Serial-digit learning test (SDLT) (represents the sum of error scores for each trial)                      | <b><math>\beta = 0.57</math> (95% CI 0.08; 1.06)</b>                                                                                                                                                                                    | 1-year average O <sub>3</sub> (10ppb)                                                                                                                                                                                                                                              | Age, sex, race, SES, employment status, income, poverty-income ratio, family size, smoking, alcohol, physical activity, urban/rural designation, CVD risk factors (BMI, hypertension, diabetes, HDL level, indoor air pollutant sources (woodstove, environmental tobacco smoke, fireplace, gas stove)) |
|                                      |                 |                 |                      |                                                            |                                                                                                                                                                                                                                                                                                       | SDLT-trials (represents total number of trials to reach the criterion of two consecutive trials without mistake) | <b><math>\beta = 0.28</math> (95% CI 0.06; 0.51)</b>                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                         |
|                                      |                 |                 |                      |                                                            |                                                                                                                                                                                                                                                                                                       | Total Serial-digit learning test (SDLT) (represents the sum of error                                             | $\beta = 0.12$ s; (95% CI $-0.07; 0.31$ )                                                                                                                                                                                               | 1-year average PM <sub>10</sub> (10 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                     | Age, sex, race, SES (SDLT trials excludes adjustment for race)                                                                                                                                                                                                                                          |

| First author, year (Name of study)                        | Location        | Study design    | Time recruitment/ FU | N cases/cohort size or N Controls (age)                 | Exposure assessment                                                                                                                                                                                                         | Outcome                                                                                                                                     | HR, OR, RR, $\beta$ (95% CI)                             | Exposure                                                                                                                     | Adjustments                                                   |
|-----------------------------------------------------------|-----------------|-----------------|----------------------|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
|                                                           |                 |                 |                      |                                                         |                                                                                                                                                                                                                             | scores for each trial)<br><br>SDLT-trials (represents total number of trials to reach the criterion of 2 consecutive trials without mistake | $\beta = -0.02$ (95% CI -0.10; 0.07)                     |                                                                                                                              |                                                               |
| Ailshire and Crimmins, 2014 (Health and Retirement Study) | Nationwide, USA | Cross-sectional | 2004                 | 13,996 (M+W) (>50 age, mean age: $64.0 \pm 10.4$ years) | Annual average PM <sub>2.5</sub> concentration in 2004 was estimated by air monitoring stations within a 60 km radius of each census tract centroid. Values were weighted using the inverse of the distance from the census | Episodic memory                                                                                                                             | <b><math>\beta = -0.17</math>, (95% CI -0.33, -0.01)</b> | PM <sub>2.5</sub> Highest (13.797–20.661 $\mu\text{g}/\text{m}^3$ ) vs lowest quartile (4.5–9.942 $\mu\text{g}/\text{m}^3$ ) | Age, sex, race, education, employment status, income, smoking |

| First author, year (Name of study)                           | Location                         | Study design                           | Time recruitment/ FU | N cases/cohort size or N Controls (age)        | Exposure assessment                                                                                                                                                                                                                                                                                                                                                     | Outcome                                        | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                     | Exposure                                                                                                                                                                                                                                                                                                                                                    | Adjustments                                                                                                                                                                                                                                                                                                  |
|--------------------------------------------------------------|----------------------------------|----------------------------------------|----------------------|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ailshire and Clarke, 2015 (Americans' Changing Lives survey) | Nationwide, USA                  | Cross-sectional                        | 2001-2002            | 780 (M+W) ( $\geq 55$ years)                   | Annual PM <sub>2.5</sub> levels for each respondent were calculated based on EPA air monitoring data from monitoring sites within a 60-km radius of the respondent's tract centroid. Daily monitor values in the year 2000 were aggregated to create a monitor-specific annual average using the inverse distance formula.                                              | tests assessing working memory and orientation | <b>OR= 1.53 (1.02-2.30)</b><br><b>p&lt;0.05</b>                                                                                                                                                                                                                                  | PM <sub>2.5</sub> increase (10 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                                                                                                   | age, sex, race, education, income, marital status, employment status, residential tenure, neighbourhood disadvantage and affluence, BMI, physical activity, smoking, chronic diseases (such as stroke and hypertension), neighbourhood characteristics (including social disorder and older age composition) |
| Cullen et al, 2018 (UK Biobank)                              | UK (England, Scotland and Wales) | Cross-sectional (analysis at baseline) | 2010                 | 86,759 (M+W) (mean age 56.86 $\pm$ 8.12 years) | Annual PM <sub>2.5</sub> , PM <sub>2.5-10</sub> , PM <sub>10</sub> , NO <sub>2</sub> and NO <sub>x</sub> were estimated for the years 2005-2007 using a LUR model for Western Europe developed integrating more than 15000 EuroAirnet monitoring sites and satellite-derived air pollution estimates. Air pollution data were mapped to participants' baseline address. | Numeric memory (score 2-12, lower is worse)    | $\beta$ = -0.0285, (95% CI - 0.0882, 0.0312)<br>p=0.34<br><br><b><math>\beta</math> = -0.2051, (95% CI - 0.3706, - 0.0395)</b><br><b>p=0.015</b><br><br>$\beta$ = -0.0876, (95% CI - 0.1797, 0.0045)<br>p=0.0624<br><br>$\beta$ = -0.0109, (95% CI - 0.0302, 0.0085)<br>p=0.2706 | PM <sub>10</sub> increase IQR (4.12 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10-2.5</sub> increase IQR (0.77 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> increase IQR (1.08 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>2</sub> increase IQR (13.71 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>x</sub> increase IQR (14.67 $\mu\text{g}/\text{m}^3$ ) | Age, sex, race, Townsend deprivation score, education, smoking, physical activity, time outdoors, proximity to nearest major road, traffic intensity or nearest major road, population density. Further adjustment for noise did not change the results.                                                     |

| First author, year (Name of study) | Location | Study design | Time recruitment/ FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome                                                                            | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                       | Exposure                                                                                                                                                                                                                                                                                                                                                    | Adjustments |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|---------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                      |                                         |                     |                                                                                    | <b><math>\beta = -0.0073</math>, (95% CI -0.0135, -0.0012) p=0.02</b>                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                             |             |
|                                    |          |              |                      |                                         |                     | Visuospatial memory (values lower than 1 indicate more errors)                     | Rate ratio = 1.0019, (95% CI 0.9997, 1.0042) p=0.0907<br><br>Rate ratio = 0.9966, (95% CI 0.9874, 1.0059) p=0.47<br><br>Rate ratio = 1.0022, (95% CI 0.9938, 1.0106) p=0.61<br><br>Rate ratio = <b>1.0010, (95% CI 1.0003, 1.0018) p=0.0058</b><br><br>Rate ratio = <b>1.0011, (95% CI 1.0002, 1.0020) p=0.019</b> | PM <sub>10</sub> increase IQR (4.12 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10-2.5</sub> increase IQR (0.77 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> increase IQR (1.08 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>2</sub> increase IQR (13.71 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>x</sub> increase IQR (14.67 $\mu\text{g}/\text{m}^3$ ) |             |
|                                    |          |              |                      |                                         |                     | Prospective memory (values lower than 1 indicate lower odds of a correct response) | OR = 1.0067, (95% CI 0.9994, 1.0141) p=0.073<br><br>OR = 0.9963, (95% CI 0.9674, 1.0261) p=0.6<br><br>OR = 0.9890, (95% CI                                                                                                                                                                                         | PM <sub>10</sub> increase IQR (4.12 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10-2.5</sub> increase IQR (0.77 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> increase IQR (1.08 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>2</sub> increase IQR                                                                                                         |             |

| First author, year (Name of study)                                                   | Location           | Study design    | Time recruitment/ FU | N cases/cohort size or N Controls (age)     | Exposure assessment                                                                                                                                                                                                                                                                             | Outcome                                                                                                                                        | HR, OR, RR, $\beta$ (95% CI)                                                                                                                | Exposure                                                                                                | Adjustments                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------|--------------------|-----------------|----------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                      |                    |                 |                      |                                             |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                | 0.9629, 1.0157)<br>p=0.42<br><br><b>OR = 1.0023, (95% CI 1.0000, 1.0046) p=0.046</b><br><br>OR = 0.9985, (95% CI 0.9970, 1.0000)<br>p=0.052 | (13.71 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>x</sub> increase IQR (14.67 $\mu\text{g}/\text{m}^3$ ) |                                                                                                                                                                                                                                                           |
| Salinas-Rodriguez, 2018 (National Survey of health and Nutrition in Mexico, ENSANUT) | Mexico             | Cross-sectional | 2012                 | 7986 (M+W) (mean age 69.9 $\pm$ 7.63 years) | Annual PM <sub>2.5</sub> levels were estimated considering the average levels for the 5 years preceding the survey using satellite data and simulations with the Goddard Earth Observing system chemical transport model. PM <sub>2.5</sub> data were mapped to participants' baseline address. | Three-word memory test (dichotomous variable, 1 if the subjects did not remember any of the three words, 0 if they recalled at least one word) | <b>OR=1.37 (95%CI 1.08, 1.74)</b>                                                                                                           | PM <sub>2.5</sub> increase (10 $\mu\text{g}/\text{m}^3$ )                                               | Sex, age, paid job, education, alcohol consumption, tobacco, SES, fuel type cooking, ventilation in indoor cooking, dwelling area, disability, depression, diabetes, hypertension, embolism, heart diseases (infarction, angina pectoris, heart failure). |
| Tonne et al., 2014 (Whitehall II)                                                    | Greater London, UK | Cross-sectional | 2007-2009            | 2,867 (M+W) (mean age: 66 $\pm$ 6 years)    | Annual average concentration for years 2003-2009 modelled at resolution 20x20 m using the KCLUrban dispersion modelling system which incorporates meteorological data, empirically derived NO-NO <sub>2</sub> -O <sub>3</sub> and PM relationships and emission rates from the London           | Memory                                                                                                                                         | The values refer to Figure B in Tonne et al (2014) for further details.                                                                     | PM <sub>2.5</sub> exhaust, PM <sub>10</sub> and PM <sub>10</sub> exhaust                                | Age, sex, race, SES, physical activity, alcohol, age x time interaction and main effect of exposure.                                                                                                                                                      |

| First author, year (Name of study) | Location                                                                                    | Study design       | Time recruitment/ FU     | N cases/cohort size or N Controls (age)                                                                                                                                                                                                                       | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Outcome | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                               | Exposure                       | Adjustments    |
|------------------------------------|---------------------------------------------------------------------------------------------|--------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|----------------|
|                                    |                                                                                             |                    |                          |                                                                                                                                                                                                                                                               | Atmospheric Emission Inventory (agreement between the model and measurements: $r=0.78$ for $PM_{10}$ and $0.74$ for $PM_{2.5}$ ). Exposure at residence was based on the average concentration at model grid points within 25 m of the residential postcode centre.<br>1-y average (2007-2009 assessment)<br>1-4 year lag (1-4 years prior to 2007-2009 assessment)<br>3-year average (average concentration of 3 years prior to 2007-2009 assessment)<br>5-y average (year of 2007-2009 measurements plus 4 preceding) |         |                                                                                                                                                                                                                            |                                |                |
| Molina-Sotomayor et al., 2019      | Santiago (highly polluted city) and Viña del Mar (city with low levels of pollution), Chile | Quasi-experimental | March 2013-December 2014 | 181 (W):<br>47 active/polluted air group (AP) (mean age $69.8 \pm 4.3$ years);<br>44 sedentary/polluted air group (SP) (mean age $68.3 \pm 3.5$ years);<br>45 active/clean air group (AC) (mean age $69 \pm 1.2$ years);<br>45 sedentary/clean air group (SC) | The participants were recruited from women living in a highly polluted city (Santiago) and women living in a city with low levels of pollution (Viña del Mar). They were divided into four groups: AP, SP, AC and SC combining Active (A) and Sedentary (S) Polluted (P) and Clean (C) city groups.                                                                                                                                                                                                                     | Recall  | At the end of the experiment, a statistically significant decreasing rate ( $p, 0.05$ ) was observed in the SC and SP groups ( $-4\%$ and $9.9\%$ respectively). Results at the end of the experiment: $M \pm SD$ (95% CI) | Comparison between four groups | No adjustments |



| First author, year (Name of study) | Location | Study design | Time recruitment/ FU | N cases/cohort size or N Controls (age) | Exposure assessment                                                                                                                                                                                                                                                       | Outcome      | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                               | Exposure                       | Adjustments |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|-------------|
|                                    |          |              |                      | (mean age 68.5 $\pm$ 2.4 years)         | The active groups performed a training programme consisting of low/moderate intensity walking on a horizontal plane, with progressive speed increases. The study duration was 24 months, with four training cycles of six months each and three 1-hour sessions per week. |              | AC: 2.96 $\pm$ 0.21 (2.80-3.11)<br>AP: 2.89 $\pm$ 0.31 (2.74-3.04)<br>SC: 2.56 $\pm$ 0.69 (2.40-2.71)<br>SP: 2.59 $\pm$ 0.55 (2.44-2.75)<br><b>p for intercomparison group=0.000</b><br><br>At the beginning of the experiment no statistically significant difference between groups (p>0.05)                                                             |                                |             |
|                                    |          |              |                      |                                         |                                                                                                                                                                                                                                                                           | Registration | At the end of the experiment, a statistically significant decreasing rate (p,0.05) was observed in the SC and SP groups (-4% and 9.9% respectively). Results at the end of the experiment: M $\pm$ SD (95% CI)<br>AC: 2.97 $\pm$ 0.15 (2.87-3.08)<br>AP: 2.98 $\pm$ 0.14 (2.88-3.08)<br>SC: 2.76 $\pm$ 0.57 (2.65-2.86)<br>SP: 2.86 $\pm$ 0.36 (2.76-2.97) | Comparison between four groups |             |

| First author, year (Name of study)                           | Location | Study design    | Time recruitment/ FU | N cases/cohort size or N Controls (age)          | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Outcome                                            | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                             | Exposure                                                                                                                                                                                                                                                                                                     | Adjustments                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------|----------|-----------------|----------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                              |          |                 |                      |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                    | <p><b>p for intercomparison group=0.006</b></p> <p>At the beginning of the experiment no statistically significant difference between groups (<math>p&gt;0.05</math>)</p>                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                               |
| Shin et al, 2019 (The Korean Frailty and Aging Cohort Study) | Korea    | Cross-sectional | 2016-2017            | 2,896 (M+W) (70-84 years, mean age 76 $\pm$ 3.9) | The level of PM <sub>10</sub> , NO <sub>2</sub> , CO, SO <sub>2</sub> and O <sub>3</sub> were measured hourly at 268 nationwide surveillance stations located in residential areas by the Korean Air Pollutants Emission Service in 2013-2017. As PM <sub>2.5</sub> has only been measured in Korea since 2015, average concentrations of PM <sub>2.5</sub> in the data from 2015 to 2017 were applied. Pollutant levels were matched with the location of the participants' surveillance centres and the average concentrations were calculated. | Word List Memory (log-transformed cognitive scale) | <p><b><math>\beta = -0.024</math> (95% CI -0.036, -0.011)</b></p> <p><b><math>\beta = 0.049</math> (95% CI 0.015, 0.083)</b></p> <p><b><math>\beta = -0.035</math> (95% CI -0.063, -0.007)</b></p> <p><math>\beta = -0.010</math> (95% CI -0.039, 0.019)</p> <p><b><math>\beta = 0.034</math> (95% CI 0.006, 0.063)</b></p> <p><math>\beta = 0.009</math> (95% CI -0.031, 0.048)</p> <p>ORs are reported in the figures in the paper</p> | <p>PM<sub>2.5</sub> increase (1.5 <math>\mu\text{g}/\text{m}^3</math>)</p> <p>PM<sub>10</sub> increase (4.6 <math>\mu\text{g}/\text{m}^3</math>)</p> <p>CO increase (0.08 ppm)</p> <p>SO<sub>2</sub> increase (0.9 ppb)</p> <p>NO<sub>2</sub> increase (7.7 ppb)</p> <p>O<sub>3</sub> increase (4.3 ppb)</p> | Age, sex, body mass index, smoking, alcohol intake, physical activity, education, household income, marital status, Carlson's comorbidity index, length of same residence, meteorological data, residence area, PM <sub>2.5</sub> , PM <sub>10</sub> , CO, SO <sub>2</sub> , NO <sub>2</sub> , O <sub>3</sub> were adjusted as fixed effects, and each centre was adjusted as random effects. |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome                                            | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                    | Exposure                                                                                                                                                                                                                                                                               | Adjustments |
|------------------------------------|----------|--------------|---------------------|-----------------------------------------|---------------------|----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                     |                                         |                     | Word List recall (log-transformed cognitive scale) | $\beta = -0.036$<br><b>(95% CI -0.054, -0.018)</b><br><br>$\beta = -0.011$<br>(95% CI -0.033, 0.011)<br><br>$\beta = -0.018$<br><b>(95% CI -0.034, -0.003)</b><br><br>$\beta = -0.038$<br><b>(95% CI -0.060, -0.017)</b><br><br>$\beta = -0.019$<br><b>(95% CI -0.035, -0.003)</b><br><br>$\beta = 0.034$ (95% CI 0.018, 0.049) | PM <sub>2.5</sub> increase (1.5 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10</sub> increase (4.6 $\mu\text{g}/\text{m}^3$ )<br><br>CO increase (0.08 ppm)<br><br>SO <sub>2</sub> increase (0.9 ppb)<br><br>NO <sub>2</sub> increase (7.7 ppb)<br><br>O <sub>3</sub> increase (4.3 ppb) |             |
|                                    |          |              |                     |                                         |                     | Recall storage (log-transformed cognitive scale)   | $\beta = -0.024$<br><b>(95% CI -0.038, -0.010)</b><br><br>$\beta = -0.014$<br>(95% CI -0.031, 0.003)<br><br>$\beta = -0.005$<br>(95% CI -0.017, 0.007)<br><br>$\beta = -0.022$<br><b>(95% CI -0.039, -0.006)</b>                                                                                                                | PM <sub>2.5</sub> increase (1.5 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10</sub> increase (4.6 $\mu\text{g}/\text{m}^3$ )<br><br>CO increase (0.08 ppm)<br><br>SO <sub>2</sub> increase (0.9 ppb)<br><br>NO <sub>2</sub> increase (7.7 ppb)                                          |             |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome                                                 | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                        | Exposure                                                                                                                                                                                                                                                                               | Adjustments |
|------------------------------------|----------|--------------|---------------------|-----------------------------------------|---------------------|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                     |                                         |                     |                                                         | $\beta = -0.007$<br>(95% CI -0.042, 0.015)<br><br><b><math>\beta = 0.013</math> (95% CI 0.001, 0.025)</b>                                                                                                                                                                                           | O <sub>3</sub> increase (4.3 ppb)                                                                                                                                                                                                                                                      |             |
|                                    |          |              |                     |                                         |                     | Word List Recognition (log-transformed cognitive scale) | <b><math>\beta = -0.016</math> (95% CI -0.029, -0.003)</b><br><br>$\beta = 0.001$ (95% CI -0.015, 0.016)<br><br>$\beta = -0.007$ (95% CI -0.018, 0.004)<br><br>$\beta = -0.011$ (95% CI -0.026, 0.004)<br><br>$\beta = -0.003$ (95% CI -0.015, 0.008)<br><br>$\beta = 0.010$ (95% CI -0.001, 0.021) | PM <sub>2.5</sub> increase (1.5 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10</sub> increase (4.6 $\mu\text{g}/\text{m}^3$ )<br><br>CO increase (0.08 ppm)<br><br>SO <sub>2</sub> increase (0.9 ppb)<br><br>NO <sub>2</sub> increase (7.7 ppb)<br><br>O <sub>3</sub> increase (4.3 ppb) |             |

### Abbreviations

M, men; W, women; SES, socioeconomic status; BC, black carbon, BMI, body mass index; HR, hazard ratio; OR, odds ratio; RR, relative risk; CI, confidence interval; FU, follow-up, IQR, interquartile range

**Table 3.5. Summary of characteristics and outcomes of studies assessing the effect of air pollution on constructional praxis and coding ability included in literature review**

| First author, year (Name of study)                                                                               | Location                        | Study design                      | Time recruitment/FU | N cases/cohort size or N Controls (age)  | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Outcome                                | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                       | Exposure                                                                                                                                                                                                                                                                                                                                                                                   | Adjustments                                                                  |
|------------------------------------------------------------------------------------------------------------------|---------------------------------|-----------------------------------|---------------------|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Schikowski et al., 2015 (Study of the influence of Air pollution on Lung function, Inflammation and Aging SALIA) | North Rhine-Westphalia, Germany | Cross-sectional from cohort study | 2007-2009           | 789 (W) (mean age 73.4 $\pm$ 3.05 years) | Exposure to NO <sub>2</sub> , NO <sub>x</sub> , PM <sub>2.5</sub> , PM <sub>2.5abs</sub> and PM <sub>10</sub> was estimated at the participating home addresses by land-use regression (LUR) models. Pollutant levels were measured over a period of one year (2009-2010) and the exposure values to the years 1985-1994 were back-extrapolated by assuming proportional changes over time within city spatial patterns. Daily traffic load within a 100-metre buffer around the home was calculated as the sum of the products of the number of vehicles from all roads with the street section length in the 100m buffer for the year 2000 and from 2007 for the follow-up investigation. Predictor variables on nearby traffic, population/household density and land use were derived from a Geographic Information System (GIS) programme and were evaluated to explain spatial variation of | Constructional praxis (figure copying) | $\beta$ = -0.10 (95% CI -0.35, 0.14)<br><br>$\beta$ = -0.27 (95% CI -0.45, -0.10)<br><br>$\beta$ = -0.25 (95% CI -0.42, -0.08)<br><br>$\beta$ = -0.15 (95% CI -0.29, -0.01)<br><br>$\beta$ = -0.19 (95% CI -0.38, 0.01)<br><br>$\beta$ = -0.12, 95% CI -0.24, 0.01 | Traffic load (26.7 car-km per day)<br><br>NO <sub>2</sub> IQR increase (9.6 $\mu$ g/m <sup>3</sup> )<br><br>NO <sub>x</sub> IQR increase (23.4 $\mu$ g/m <sup>3</sup> )<br><br>PM <sub>10</sub> IQR increase (2.2 $\mu$ g/m <sup>3</sup> )<br><br>PM <sub>2.5</sub> IQR increase (1.9 $\mu$ g/m <sup>3</sup> )<br><br>PM <sub>2.5abs</sub> IQR increase (0.4 $10^{-6}$ x m <sup>-1</sup> ) | Age, urban/rural living, SES, smoking, Environmental Tobacco smoke and APOE. |
|                                                                                                                  |                                 |                                   |                     |                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Constructional praxis (figure recall)  | $\beta$ = 0.03, 95% CI -0.23, 0.17)<br><br>$\beta$ = -0.04, 95% CI -0.18, 0.11)<br><br>$\beta$ = -0.04, 95% CI -0.19, 0.10)<br><br>$\beta$ = 0.02, 95% CI -0.10, 0.13)<br><br>$\beta$ = 0.06, 95% CI -0.10, 0.22)<br><br>$\beta$ = 0.02, 95% CI -0.07, 0.12)       | Traffic load (26.7 car-km per day)<br><br>NO <sub>2</sub> IQR increase (9.6 $\mu$ g/m <sup>3</sup> )<br><br>NO <sub>x</sub> IQR increase (23.4 $\mu$ g/m <sup>3</sup> )<br><br>PM <sub>10</sub> IQR increase (2.2 $\mu$ g/m <sup>3</sup> )<br><br>PM <sub>2.5</sub> IQR increase (1.9 $\mu$ g/m <sup>3</sup> )<br><br>PM <sub>2.5abs</sub> IQR increase (0.4 $10^{-6}$ x m <sup>-1</sup> ) |                                                                              |

| First author, year (Name of study)                                                                        | Location                       | Study design                               | Time recruit ment/F U          | N cases/cohort size or N Controls (age)                                      | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                    | Outcome                                     | HR, OR, RR, $\beta$ (95% CI)                                                                                                                          | Exposure                                                                                                                                                                                                                             | Adjustments                                                                                                                                                                                                                                                                                            |
|-----------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------------------|--------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                           |                                |                                            |                                |                                                                              | annual average concentrations.                                                                                                                                                                                                                                                                                                                                                                                                         |                                             |                                                                                                                                                       |                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                        |
| Chen and Schwartz, 2009 (NHANE S-III)                                                                     | Nationwide, USA                | Cross-sectional                            | 1988-1991                      | 1764 (M+W) (220-59 years, mean age: 37.4 $\pm$ 10.9 years)                   | PM <sub>10</sub> and ozone concentrations representative of the year prior to cognitive examination were modelled for each geocoded residence address at the centroid of the census-block group using distance weighted averages of all EPA monitors in the residing and adjoining counties.                                                                                                                                           | Symbol-digit substitution test (SDST)       | $\beta = 0.12$ (95% CI 0.01, 0.23)                                                                                                                    | 1 year average O <sub>3</sub> (10 ppb)                                                                                                                                                                                               | Age, sex, race, SES, employment status, income, poverty-income ratio, family size, smoking, alcohol, physical activity, urban/rural designation, CVD risk factors (BMI, hypertension, diabetes, HDL level, indoor air pollutant sources (woodstove, environmental tobacco smoke, fireplace, gas stove) |
|                                                                                                           |                                |                                            |                                |                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                             | $\beta = 0.00$ (95% CI -0.04; 0.05)                                                                                                                   | 1-year average PM <sub>10</sub> (10 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                       | Age, sex, SES                                                                                                                                                                                                                                                                                          |
| Huls et al, 2018 (Study of the influence of Air pollution on Lung function, Inflammation and Aging SALIA) | North Rhine-Westfalia, Germany | Cross-sectional analysis from cohort study | 2007-2010 (baseline 1985-1994) | 520 W (mean at baseline 54.3 $\pm$ 0.8 years and at FU 73.3 $\pm$ 3.4 years) | Annual exposure to NO <sub>2</sub> , NO <sub>x</sub> , PM <sub>2.5</sub> , PM <sub>2.5abs</sub> and PM <sub>10</sub> was estimated at the participating home addresses by land-use regression (LUR) models, including information on traffic, industry and population/household density. Pollutant levels were measured over a period of one year (2008-2009) and the exposure values to the years 1985-1994 were back-extrapolated by | Copying geometrical figures (by CERAD-test) | $\beta = -0.25$ (95% CI -0.40; -0.11) $p=0.001$<br>$\beta = -0.21$ (95% CI -0.36; -0.06) $p=0.005$<br>$\beta = -0.26$ (95% CI -0.50; -0.03) $p=0.030$ | PM <sub>10</sub> IQR increase (8.0 $\mu\text{g}/\text{m}^3$ ) at baseline<br>PM <sub>2.5</sub> IQR increase (4.9 $\mu\text{g}/\text{m}^3$ ) at baseline<br>NO <sub>2</sub> IQR increase (13.8 $\mu\text{g}/\text{m}^3$ ) At baseline | Age, height, BMI, SES, smoking status, second-hand smoke, living in an urban area vs a rural area, APO- $\epsilon$ 4, physical activity and depression.                                                                                                                                                |

| First author, year (Name of study) | Location | Study design | Time recruit ment/F U | N cases/cohort size or N Controls (age) | Exposure assessment                                                   | Outcome | HR, OR, RR, $\beta$ (95% CI) | Exposure | Adjustments |
|------------------------------------|----------|--------------|-----------------------|-----------------------------------------|-----------------------------------------------------------------------|---------|------------------------------|----------|-------------|
|                                    |          |              |                       |                                         | assuming proportional changes over time within city spatial patterns. |         |                              |          |             |

### Abbreviations

FU, follow-up; M, men; W, women; SES, socioeconomic status; BC, black carbon, BMI, body mass index; HR, hazard ratio; OR, odds ratio; RR, relative risk; CI, confidence interval; IQR, interquartile range; CVD, cardiovascular disease; CERAD, The Consortium to Establish a Registry for Alzheimer's Disease

**Table 3.6. Summary of characteristics and outcomes of studies assessing the effect of air pollution on language included in literature review**

| First author, year (Name of study)                  | Location    | Study design          | Time recruitment/FU              | N cases/cohort size or N Controls (age)          | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Outcome                        | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                  | Exposure                                                                                                                                                                       | Adjustments                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------|-------------|-----------------------|----------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wellenius et al., 2012 (MOBILIZE Boston Study, MBS) | Boston, USA | Longitudinal (cohort) | 2005-2008/ 16.8 months (mean FU) | 765 ( $\geq 65$ years, Mean age: 78.1 $\pm$ 5.4) | ArcGIS was used to geocode participant address and calculate the Euclidean distance from residence to the nearest major roadway, defined as roads having US Census Feature Class Code A1 (primary highway with limited access) or A2 (primary road without limited access). Daily outdoor BC levels (a marker of traffic pollution) at participant's address was estimated using a validated spatio-temporal land-use regression model. To create a metric of long-term exposure, modelled residential BC was averaged over the 365 days preceding each cognitive assessment. | Language (letter fluency test) | $\beta = -1.5$ (95% CI - 4.7, 1.8) $p=0.053$                                                                                                                                                                                                  | Residential distance to major roadway (<100 m vs >1000 m)                                                                                                                      | Age, sex, race, history of stroke, history of smoking (ever vs never), physical activity, education (3 categories), visit number, BMI, household income (below vs above median) season of home interview, percent of neighbourhood population that is non-white and percent of neighbourhood population with college degree or above. |
|                                                     |             |                       |                                  |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Language (category fluency)    | $\beta = -1.4$ (95% CI - 2.7, -0.2) $p=0.022$<br><br>Significant association among less educated and older subjects<br>$\beta = -0.26$ (95% CI - 1.04; 0.53) $p=0.52$                                                                         | Residential Traffic proximity IQR decrease (851.2 m).<br><br>BC IQR increase (0.11 $\mu\text{g}/\text{m}^3$ )                                                                  |                                                                                                                                                                                                                                                                                                                                       |
|                                                     |             |                       |                                  |                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                | $\beta = -0.8$ (95% CI - 1.9, 0.3) $p=0.016$<br><br>$\beta = -0.7$ (95% CI - 1.1, -0.3) $p=0.002$<br><br>Significant association among younger subjects and for all levels of education<br><br>$\beta = 0.05$ (95% CI - 0.26, -0.3) $p=0.002$ | Residential distance to major roadway (<100 m vs >1000 m)<br><br>Residential Traffic proximity IQR decrease (851.2 m).<br><br>BC IQR increase (0.11 $\mu\text{g}/\text{m}^3$ ) |                                                                                                                                                                                                                                                                                                                                       |



| First author, year (Name of study)                                                   | Location           | Study design    | Time recruitment/FU | N cases/cohort size or N Controls (age)     | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Outcome                               | HR, OR, RR, $\beta$ (95% CI)                                                                                        | Exposure                                                                                       | Adjustments                                                                                                                                                                                             |
|--------------------------------------------------------------------------------------|--------------------|-----------------|---------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zhang et al, 2018 (China Family Panel Studies (CFPS))                                | China              | Cross-sectional | 2010-2014           | 31955 (M+W) (more than 10 years old)        | Air pollution index (API) calculated on daily reading of three air pollutants, namely SO <sub>2</sub> , NO <sub>2</sub> and PM <sub>10</sub> (range 0-500)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Verbal test score (SD)                | 0.131 (0.012)<br>0.278 (0.026)<br>0.599 (0.057)<br>0.712 (0.068)<br>0.895 (0.085)<br>0.942 (0.090)<br>1.132 (0.108) | 1 SD reduction in mean API<br>1-day<br>7-day<br>30-day<br>90-day<br>1-year<br>2-year<br>3-year | Year, month, day of the week, post meridiem hour fixed effects, sex, age, income, education, weather variables (temperature, precipitation, wind speed), population density and industrial value share. |
| Tonne et al., 2014 (Whitehall II)                                                    | Greater London, UK | Cross-sectional | 2007-2009           | 2,867 (M+W) (mean age: 66 $\pm$ 6 years)    | Annual average concentration for years 2003-2009 modelled at resolution 20x20 m using the KCLUrban dispersion modelling system which incorporates meteorological data, empirically derived NO-NO <sub>2</sub> -O <sub>3</sub> and PM relationships and emission rates from the London Atmospheric Emission Inventory (agreement between the model and measurements: r+0.78 for PM <sub>10</sub> and 0.74 for PM <sub>2.5</sub> ). Exposure at residence was based on the average concentration at model grid points within 25 m of the residential postcode centre.<br>1-y average (2007-2009 assessment)<br>1-4 year lag (1-4 years prior to 2007-2009 assessment)<br>3-year average (average concentration of 3 years prior to 2007-2009 assessment)<br>5-y average (year of 2007-2009 measurements plus 4 preceding) | Semantic fluency and phonemic fluency | The results are reported only in the figures (C and D). No association was found.                                   | PM <sub>2.5</sub> , PM <sub>2.5</sub> exhaust, PM <sub>10</sub> and PM <sub>10</sub> exhaust   | Age, sex, race, SES, physical activity, alcohol, age x time interaction and main effect of exposure.                                                                                                    |
| Salinas-Rodriguez, 2018 (National Survey of health and Nutrition in Mexico, ENSANUT) | Mexico             | Cross-sectional | 2012                | 7986 (M+W) (mean age 69.9 $\pm$ 7.63 years) | Annual PM <sub>2.5</sub> levels were estimated considering the average levels for the 5 years preceding the survey using satellite data and simulations with the Goddard Earth Observing system chemical transport model. PM <sub>2.5</sub> data were                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Semantic verbal fluency test          | $\beta$ =-0.72 (95%CI - 1.05, -0.40)                                                                                | PM <sub>2.5</sub> increase (10 $\mu$ g/m <sup>3</sup> )                                        | Sex, age, paid job, education, alcohol consumption, tobacco, SES, fuel type cooking, ventilation in indoor cooking, dwelling area, disability, depression, diabetes, hypertension, embolism, heart      |

| First author, year (Name of study) | Location                                                                                    | Study design       | Time recruitment/FU      | N cases/cohort size or N Controls (age)                                                                                                                                                                                                                                                       | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Outcome  | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Exposure                                                                                                                        | Adjustments                                            |
|------------------------------------|---------------------------------------------------------------------------------------------|--------------------|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
|                                    |                                                                                             |                    |                          |                                                                                                                                                                                                                                                                                               | mapped to participants' baseline addresses.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                 | diseases (infarction, angina pectoris, heart failure). |
| Molina-Sotomayor et al., 2019      | Santiago (highly polluted city) and Viña del Mar (city with low levels of pollution), Chile | Quasi-experimental | March 2013-December 2014 | 181 (W):<br>47 active/polluted air group (AP) (mean age 69.8 $\pm$ 4.3 years);<br>44 sedentary/polluted air group (SP) (mean age 68.3 $\pm$ 3.5 years);<br>45 active/clean air group (AC) (mean age 69 $\pm$ 1.2 years);<br>45 sedentary/clean air group (SC) (mean age 68.5 $\pm$ 2.4 years) | The participants were recruited from women living in a highly polluted city (Santiago) and women living in a city with low levels of pollution (Viña del Mar). They were divided into 4 groups: AP, SP, AC and SC combining Active (A) and Sedentary (S) Polluted (P) and Clean (C) city groups. The active groups performed a training programme consisting of low/moderate intensity walking on a horizontal plane, with progressive speed increases. The study duration was 24 months, with four training cycles of six months each and three 1-hour sessions per week. | Language | At the end of the experiment, a statistically significant decreasing rate (p,0.05) was observed in the SC and SP groups (-4% and 9.9% respectively). Results at the end of the experiment: M $\pm$ SD (95% CI)<br>AC: 8.53 $\pm$ 0.79 (8.22-8.84)<br>AP: 8.49 $\pm$ 0.59 (8.19-8.79)<br>SC: 7.80 $\pm$ 1.20 (7.49-8.11)<br>SP: 7.27 $\pm$ 1.16 (6.96-7.58)<br><b>p for intercomparison group=0.000</b><br><br>At the beginning of the experiment no statistically significant difference between groups (p>0.05) | Comparison between four groups: AP, SP, AC and SC combining Active (A) and Sedentary (S) Polluted (P) and Clean (C) city groups | No adjustments                                         |

### Abbreviations

FU, follow-up; M, men; W, women; SES, socioeconomic status; BC, black carbon, BMI, body mass index; HR, hazard ratio; OR, odds ratio; RR, relative risk; CI, confidence interval; IQR, interquartile range

**Table 3.7. Summary of characteristics and outcomes of studies assessing the effect of air pollution on cognitive decline included in literature review**

| First author, year (Name of study) | Location                         | Study design                          | Time recruitment/FU | N cases/cohort size or N Controls (age)       | Exposure assessment                                                                                                                                                                                                                                                                                                                                                     | Outcome                    | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                              | Exposure                                                                                                                                                                                                                                                                                                                          | Adjustments                                                                                                                                                                                                                                                                            |  |
|------------------------------------|----------------------------------|---------------------------------------|---------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Cullen et al, 2018 (UK Biobank)    | UK (England, Scotland and Wales) | Longitudinal (cohort, analysis at FU) | 2010/2012-2013      | 2,913 (M+W) (mean age 58.30 $\pm$ 7.06 years) | Annual PM <sub>2.5</sub> , PM <sub>2.5-10</sub> , PM <sub>10</sub> , NO <sub>2</sub> and NO <sub>x</sub> were estimated for the years 2005-2007 using a LUR model for Western Europe developed integrating more than 15000 EuroAirnet monitoring sites and satellite-derived air pollution estimates. Air pollution data were mapped to participants' baseline address. | Reasoning change           | $\beta$ = 0.0174, (95% CI -0.0217, 0.0565) p=0.38<br>$\beta$ = -0.0910, (95% CI -0.2019, 0.0199) p=0.11<br>$\beta$ = 0.0013, (95% CI -0.0860, 0.0886) p=0.98<br>$\beta$ = 0.0112, (95% CI -0.0038, 0.0261) p=0.1443<br>$\beta$ = 0.0015, (95% CI -0.0056, 0.0087) p=0.68  | PM <sub>10</sub> increase IQR (4.12 $\mu$ g/m <sup>3</sup> )<br>PM <sub>10-2.5</sub> increase IQR (0.77 $\mu$ g/m <sup>3</sup> )<br>PM <sub>2.5</sub> increase IQR (1.08 $\mu$ g/m <sup>3</sup> )<br>NO <sub>2</sub> increase IQR (13.71 $\mu$ g/m <sup>3</sup> )<br>NO <sub>x</sub> increase IQR (14.67 $\mu$ g/m <sup>3</sup> ) | Age, sex, race, Townsend deprivation score, education, smoking, physical activity, time outdoors, proximity to nearest major road, traffic intensity or nearest major road, population density, time between baseline and FU. Further adjustment for noise did not change the results. |  |
|                                    |                                  |                                       |                     |                                               |                                                                                                                                                                                                                                                                                                                                                                         | Visuospatial memory change | $\beta$ = 0.0324, (95% CI -0.0584, 0.1233) p=0.48<br>$\beta$ = -0.0568, (95% CI -0.3175, 0.2039) p=0.67<br>$\beta$ = -0.0383, (95% CI -0.2428, 0.1663) p=0.71<br>$\beta$ = -0.0252, (95% CI -0.0620, 0.0116) p=0.18<br>$\beta$ = -0.0007, (95% CI -0.0171, 0.0157) p=0.93 | PM <sub>10</sub> increase IQR (4.12 $\mu$ g/m <sup>3</sup> )<br>PM <sub>10-2.5</sub> increase IQR (0.77 $\mu$ g/m <sup>3</sup> )<br>PM <sub>2.5</sub> increase IQR (1.08 $\mu$ g/m <sup>3</sup> )<br>NO <sub>2</sub> increase IQR (13.71 $\mu$ g/m <sup>3</sup> )<br>NO <sub>x</sub> increase IQR (14.67 $\mu$ g/m <sup>3</sup> ) |                                                                                                                                                                                                                                                                                        |  |
|                                    |                                  |                                       |                     |                                               |                                                                                                                                                                                                                                                                                                                                                                         | Prospective memory change  | OR = 1.648, (95% CI 0.9342, 1.2136) p=0.35<br>OR = 0.9940, (95% CI 0.6954, 1.4210) p=0.97<br>OR = 1.0107, (95% CI 0.7685, 1.3293) p=0.94<br>OR = 1.0326, (95% CI 0.9868, 1.0806) p=0.17                                                                                   | PM <sub>10</sub> increase IQR (4.12 $\mu$ g/m <sup>3</sup> )<br>PM <sub>10-2.5</sub> increase IQR (0.77 $\mu$ g/m <sup>3</sup> )<br>PM <sub>2.5</sub> increase IQR (1.08 $\mu$ g/m <sup>3</sup> )<br>NO <sub>2</sub> increase IQR (13.71 $\mu$ g/m <sup>3</sup> )<br>NO <sub>x</sub> increase IQR                                 |                                                                                                                                                                                                                                                                                        |  |
|                                    |                                  |                                       |                     |                                               |                                                                                                                                                                                                                                                                                                                                                                         |                            |                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                        |  |
|                                    |                                  |                                       |                     |                                               |                                                                                                                                                                                                                                                                                                                                                                         |                            |                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                        |  |

| First author, year (Name of study)                           | Location | Study design          | Time recruitment/FU                                                                     | N cases/cohort size or N Controls (age)                                            | Exposure assessment                                                                                                                                                                                                                                             | Outcome                                                                             | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                               | Exposure                                                                                                                                                                                                                                                                                                  | Adjustments                                                                                                                                                                          |
|--------------------------------------------------------------|----------|-----------------------|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                              |          |                       |                                                                                         |                                                                                    |                                                                                                                                                                                                                                                                 |                                                                                     | OR = 1.0098, (95% CI 0.9927, 1.0272) p=0.26                                                                                                                                                                                                                                                | (14.67 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                                                                         |                                                                                                                                                                                      |
| Oudin et al, 2017 (Betula Study)                             | Sweden   | Longitudinal (cohort) | 1988-90/4FU<br>1993-1995, 1998-2000, 2003-2005, 2008-2010 (mean FU 8.6 $\pm$ 4.4 years) | 1,469 (M+W) (60-85 years)                                                          | Land Use Regression model used to estimate the annual mean of NO <sub>x</sub> at each geocoded address, utilising data from 40 monitoring sites that represented a wide range of traffic conditions in residential, industrial, commercial and rural locations. | Episodic memory change                                                              | $\beta$ = -1.45 (95% CI -3.22, 0.31)<br><br>$\beta$ = 0.005 (95% CI -0.018, 0.027)<br>Significant association among older subjects (>70 years vs 60 years)                                                                                                                                 | NO <sub>x</sub> Highest (>24 $\mu\text{g}/\text{m}^3$ ) vs the lowest quartile (<8.4 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>x</sub> increase (1 $\mu\text{g}/\text{m}^3$ )                                                                                                                             | Age, test occasion, number of total tests, cross-product between NO <sub>x</sub> and test occasion, education, sex, smoking, physical activity, living with someone, working status. |
| Wurth et al, 2018 (Boston Puerto Rican health Study (BPRHS)) | USA      | Longitudinal (cohort) | 2004-2008/2008-2012                                                                     | 1255 (M+W) (mean age 57.1 $\pm$ 7.6 years at baseline, 59.3 $\pm$ 7.7 years at FU) | Average daily concentration of PM <sub>2.5</sub> and BC, nickel, sulfur and silicon, measured at the US EPA monitoring site, were used to calculate 1-year and 2-year average exposures ending at the date of each of participants' cognitive exams.            | Verbal memory change (California Verbal List Learning test)                         | $\beta$ = -0.38 (95% CI -0.46; -0.30) p<0.05<br><br>$\beta$ = -0.25 (95% CI -0.40; -0.10) p<0.05<br><br>$\beta$ = 0.09 (95% CI -0.10; 0.27)<br><br>$\beta$ = 0.04 (95% CI -0.05; 0.13)<br><br>$\beta$ = 0.23 (95% CI 0.06; 0.41) p<0.05<br><br>Similar results for the two-pollutant model | 1-year BC increase IQR (53 ng/m <sup>3</sup> )<br><br>1-year Nickel increase IQR (2.00 ng/m <sup>3</sup> )<br><br>1-year Sulfur increase IQR (390 ng/m <sup>3</sup> )<br><br>1-year Silicon increase IQR (11.0 ng/m <sup>3</sup> )<br><br>1-year PM <sub>2.5</sub> increase IQR (1750 ng/m <sup>3</sup> ) | Age, sex, education, season, physical activity, income to poverty ratio. Adjustment for temperature had no effect on the estimates, thus was not included in the model.              |
|                                                              |          |                       |                                                                                         |                                                                                    |                                                                                                                                                                                                                                                                 | Recognition change (List A from California Verbal learning test and 28 distractors) | $\beta$ = -0.35 (95% CI -0.46; -0.25) p<0.05<br><br>$\beta$ = -0.57 (95% CI -0.76; -0.37) p<0.05<br><br>$\beta$ = -0.51 (95% CI -0.75; -0.28) p<0.05                                                                                                                                       | 1-year BC increase IQR (53 ng/m <sup>3</sup> )<br><br>1-year Nickel increase IQR (2.00 ng/m <sup>3</sup> )<br><br>1-year Sulfur increase IQR (390 ng/m <sup>3</sup> )                                                                                                                                     |                                                                                                                                                                                      |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome                                             | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                         | Exposure                                                                                                                                                                                                                                                                                                  | Adjustments |
|------------------------------------|----------|--------------|---------------------|-----------------------------------------|---------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                     |                                         |                     |                                                     | $\beta = -0.25$ (95% CI -0.36; -0.13) $p < 0.05$<br><br>$\beta = -0.35$ (95% CI -0.57; -0.12) $p < 0.05$<br><br>Similar results for the two-pollutant model                                                                                                                                          | 1-year Silicon increase IQR (11.0 ng/m <sup>3</sup> )<br><br>1-year PM <sub>2.5</sub> increase IQR (1750 ng/m <sup>3</sup> )                                                                                                                                                                              |             |
|                                    |          |              |                     |                                         |                     | Mental processing change (Stroop test)              | $\beta = -1.14$ (95% CI -1.55; -0.74) $p < 0.05$<br><br>$\beta = -0.18$ (95% CI -1.91; -0.45) $p < 0.05$<br><br>$\beta = -0.85$ (95% CI -1.72; 0.03)<br><br>$\beta = -0.41$ (95% CI -0.83; 0.01)<br><br>$\beta = -0.18$ (95% CI -1.03; 0.67)<br><br>Similar results for the two-pollutant model      | 1-year BC increase IQR (53 ng/m <sup>3</sup> )<br><br>1-year Nickel increase IQR (2.00 ng/m <sup>3</sup> )<br><br>1-year Sulfur increase IQR (390 ng/m <sup>3</sup> )<br><br>1-year Silicon increase IQR (11.0 ng/m <sup>3</sup> )<br><br>1-year PM <sub>2.5</sub> increase IQR (1750 ng/m <sup>3</sup> ) |             |
|                                    |          |              |                     |                                         |                     | Executive function change (the letter fluency test) | $\beta = -0.94$ (95% CI -1.31; -0.56) $p < 0.05$<br><br>$\beta = -1.94$ (95% CI -2.62; -1.26) $p < 0.05$<br><br>$\beta = -0.14$ (95% CI -0.96; 0.67)<br><br>$\beta = -0.07$ (95% CI -0.46; 0.32)<br><br>$\beta = 0.84$ (95% CI 0.05; 1.62) $p < 0.05$<br>Similar results for the two-pollutant model | 1-year BC increase IQR (53 ng/m <sup>3</sup> )<br><br>1-year Nickel increase IQR (2.00 ng/m <sup>3</sup> )<br><br>1-year Sulfur increase IQR (390 ng/m <sup>3</sup> )<br><br>1-year Silicon increase IQR (11.0 ng/m <sup>3</sup> )<br><br>1-year PM <sub>2.5</sub> increase IQR (1750 ng/m <sup>3</sup> ) |             |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome                                                     | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                     | Exposure                                                                                                                                                                                                                                                                                                  | Adjustments |
|------------------------------------|----------|--------------|---------------------|-----------------------------------------|---------------------|-------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                     |                                         |                     | Visuospatial change (clock drawing and figure copying test) | $\beta$ = -0.03 (95% CI -0.14; 0.07)<br><br>$\beta$ = 0.01 (95% CI -0.18; 0.19)<br><br><b><math>\beta</math> = 0.31 (95% CI 0.08, 0.54) p&lt;0.05</b><br><br><b><math>\beta</math> = 0.15 (95% CI 0.04, 0.26) p&lt;0.05</b><br><br><b><math>\beta</math> = 0.33 (95% CI 0.10, 0.55) p&lt;0.05</b><br>Similar results for the two-pollutant model | 1-year BC increase IQR (53 ng/m <sup>3</sup> )<br><br>1-year Nickel increase IQR (2.00 ng/m <sup>3</sup> )<br><br>1-year Sulfur increase IQR (390 ng/m <sup>3</sup> )<br><br>1-year Silicon increase IQR (11.0 ng/m <sup>3</sup> )<br><br>1-year PM <sub>2.5</sub> increase IQR (1750 ng/m <sup>3</sup> ) |             |

| First author, year (Name of study)                        | Location | Study design          | Time recruitment/FU                                                                                                                            | N cases/cohort size or N Controls (age)                                                                                                                               | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Outcome                                                                                                           | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                             | Exposure                                                                                                                                                                                                                                                                                                                     | Adjustments                                                                                                                                                                                                  |
|-----------------------------------------------------------|----------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cleary et al, 2018                                        | USA      | Longitudinal (cohort) | 2005/2008 (follow-up visit yearly)                                                                                                             | 5,116 (M+W) (3,624 with normal cognition MMSE $\geq 24$ , 1,492 with cognitive impairment, MMSE $\leq 24$ ) (at baseline mean age 76.8 $\pm$ 7.7 years, 60-101 years) | Hierarchical Bayesian Model was used to attribute pollutant exposure at residential address. The HBM combines ground-level monitoring data from the Air Quality System and simulated pollutant data from the Community Multi-scale Air Quality model. Long-term exposure was estimated averaging the daily estimates over each year, starting one year prior to each subject's respective baseline visit. If a subject changed residence during the follow-up period, the ZIP code of the previous visit was used. | Cognitive decline (MMSE and the Cognitive Dementia Rating Sum of Boxes, CDR-SB)<br><br>MMSE<br><br><br>CDR-SB     | $\beta = 0.83$ (95% CI 0.5; 1.2) $p < 0.0001$<br><br>$\beta = 0.35$ (95% CI 0.2; 0.5) $p < 0.0001$<br><br>$\beta = -0.60$ (95% CI -0.8; -0.3) $p < 0.0001$<br><br>$\beta = -0.4$ (95% CI -0.5; -0.3) $p < 0.0001$<br><br>Considering subgroup with MMSE $\geq 24$ , the association of ozone with cognition remained significant on both MMSE and CDR-SB assessment. No significant association in the cognitively impaired subpopulation, MMSE $< 24$ ) | Lowest O <sub>3</sub> (<36.7 ppb) vs the highest (>40 ppb) tertile<br><br>Lowest O <sub>3</sub> (<36.7 ppb) vs the highest (>40 ppb) tertile *time<br><br>Lowest O <sub>3</sub> (<36.7 ppb) vs the highest (>40 ppb) tertile<br><br>Lowest O <sub>3</sub> (<36.7 ppb) vs the highest (>40 ppb) tertile *time                 | Age, sex, education, race, APOE genotype, smoking, B12 deficiency, and population density.                                                                                                                   |
| Weuve et al, 2012 (Nurses' Health Study Cognitive Cohort) | USA      | Longitudinal (cohort) | 1995-2001/1997-2004 (second cognitive assessment mean 1.9 $\pm$ 0.4 years) and 2002-2008 (third cognitive assessment mean 4.3 $\pm$ 0.8 years) | 19,409 (W) ( $\geq 70$ years at enrolment)                                                                                                                            | Averaged month-specific exposures to PM <sub>2.5</sub> , PM <sub>10-2.5</sub> and PM <sub>10</sub> over several intervals preceding the cognitive interview; preceding month, year, 2-year, 5-years and from 1988 through the                                                                                                                                                                                                                                                                                      | Cognitive function change (Telephone Interview for Cognitive Status, difference in 2-y change in cognitive score) | $\beta = -0.006$ (95% CI -0.023; 0.011)<br><br>$\beta = -0.016$ (95% CI -0.036; 0.004)<br><br>$\beta = -0.015$ (95% CI -0.047; 0.017)<br><br>$\beta = -0.049$ (95% CI -0.088; -0.010)                                                                                                                                                                                                                                                                    | Preceding month PM <sub>10-2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Since 1988 PM <sub>10-2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Preceding month PM <sub>2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Since 1988 PM <sub>2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ ) | Age, education, husband's education, long-term physical activity, long-term alcohol consumption. Additional adjustment for BMI, diabetes, smoking, aspirin use and ibuprofen use did not change the results. |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment                                                                                                                                                                                                                                                  | Outcome                                                                                                            | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                           | Exposure                                                                                                                                                                                                                                                                                                                     | Adjustments |
|------------------------------------|----------|--------------|---------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                     |                                         | preceding month. Exposures were estimated using EPA's AQS meteorological data (for PM <sub>10</sub> available from 1988 to 2007; for PM <sub>2.5</sub> not widely available before 1999) and GIS smoothing models for geocoded residential location per participant. | Verbal memory composite change (score change per 2 years)                                                          | $\beta$ = -0.004 (95% CI -0.017; 0.008)<br><br><b><math>\beta</math> = -0.025 (95% CI -0.040; -0.010)</b><br><br>$\beta$ = 0.009 (95% CI -0.008; 0.025)<br><br>$\beta$ = -0.014 (95% CI -0.035; 0.007) | Preceding month PM <sub>10-2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Since 1988 PM <sub>10-2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Preceding month PM <sub>2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Since 1988 PM <sub>2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ ) |             |
|                                    |          |              |                     |                                         |                                                                                                                                                                                                                                                                      | Working memory and attention change (Digit Span Backward, score change per 2 years)                                | $\beta$ = -0.004 (95% CI -0.017; 0.008)<br><br><b><math>\beta</math> = -0.025 (95% CI -0.040; -0.010)</b><br><br>$\beta$ = -0.010 (95% CI -0.031; 0.010)<br><br>$\beta$ = 0.032 (95% CI -0.056; -0.07) | Preceding month PM <sub>10-2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Since 1988 PM <sub>10-2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Preceding month PM <sub>2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Since 1988 PM <sub>2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ ) |             |
|                                    |          |              |                     |                                         |                                                                                                                                                                                                                                                                      | Cognitive function decline (Telephone Interview for Cognitive Status plus other 5 tests, score change per 2 years) | <b><math>\beta</math> = -0.024 (95% CI -0.040, -0.008)</b><br><b>p for trend= 0.01</b><br><br><b><math>\beta</math> = -0.018 (95% CI -0.034; -0.002)</b><br>p for trend= 0.11                          | Highest PM <sub>10-2.5</sub> (11.9-50.2 $\mu\text{g}/\text{m}^3$ ) vs the lowest (1.1-6.6 $\mu\text{g}/\text{m}^3$ ) quintile<br><br>Highest PM <sub>2.5</sub> (11.9-50.2 $\mu\text{g}/\text{m}^3$ ) vs the lowest (1.1-6.6 $\mu\text{g}/\text{m}^3$ ) quintile                                                              |             |
|                                    |          |              |                     |                                         |                                                                                                                                                                                                                                                                      | Verbal fluency change (animal names, score change per 2 years)                                                     | <b><math>\beta</math> = -0.045 (95% CI -0.079; -0.011)</b><br><br>$\beta$ = -0.041 (95% CI -0.084; 0.001)<br><br><b><math>\beta</math> = -0.025 (95% CI -0.045; -0.004)</b>                            | Preceding month PM <sub>10-2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Since 1988 PM <sub>10-2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )<br><br>Preceding month PM <sub>2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )                                                                              |             |



| First author, year (Name of study) | Location           | Study design          | Time recruitment/FU | N cases/cohort size or N Controls (age)  | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Outcome                                                   | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                         | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Adjustments                                                                                          |
|------------------------------------|--------------------|-----------------------|---------------------|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
|                                    |                    |                       |                     |                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                           | $\beta = -0.002$ (95% CI -0.027; 0.023)                                                                                                                                                                                                                                                                                                              | Since 1988 PM <sub>2.5</sub> increment (10 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                      |
| Tonne et al., 2014 (Whitehall II)  | Greater London, UK | Longitudinal (cohort) | 2002-2004/2007-2009 | 2,867 (M+W) (mean age: 66 $\pm$ 6 years) | Annual average concentration for years 2003-2009 modelled at resolution 20x20 m using the KCLUrban dispersion modelling system which incorporates meteorological data, empirically derived NO-NO <sub>2</sub> -O <sub>3</sub> and PM relationships and emission rates from the London Atmospheric Emission Inventory (agreement between the model and measurements: $r=0.78$ for PM <sub>10</sub> and $0.74$ for PM <sub>2.5</sub> ). Exposure at residence was based on the average concentration at model grid points within 25 m of the residential postcode centre. 1-y average (2007-2009 assessment) 1-4 year lag (1-4 years prior to 2007-2009 assessment) 3-year average (average concentration of 3 years prior to 2007-2009 assessment) | Reasoning change (Alice Heim 4-I test) (five year change) | $\beta = -0.011$ (95% CI -0.032; 0.010)<br>$\beta = -0.010$ (95% CI -0.025; 0.006)<br>$\beta = -0.007$ (95% CI -0.025; 0.011)<br>$\beta = -0.003$ (95% CI -0.016; 0.011)<br>$\beta = -0.013$ (95% CI -0.034; 0.007)<br>$\beta = -0.010$ (95% CI -0.024; 0.004)<br>$\beta = -0.007$ (95% CI -0.025; 0.011)<br>$\beta = -0.003$ (95% CI -0.016; 0.011) | PM <sub>10</sub> IQR increase (1.8 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>10</sub> IQR increase (1.8 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)<br>PM <sub>10 exhaust</sub> IQR increase (0.30 $\mu\text{g}/\text{m}^3$ ),<br>PM <sub>10 exhaust</sub> IQR increase (0.30 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)<br>PM <sub>2.5</sub> IQR increase (1.1 $\mu\text{g}/\text{m}^3$ ),<br>PM <sub>2.5</sub> IQR increase (1.1 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)<br>PM <sub>2.5 exhaust</sub> IQR increase (0.27 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>2.5 exhaust</sub> IQR increase (0.27 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination) | Age, sex, race, SES, physical activity, alcohol, age x time interaction and main effect of exposure. |
|                                    |                    |                       |                     |                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Memory change (five year change)                          | $\beta = -0.023$ (95% CI -0.071; 0.025)<br>$\beta = -0.029$ (95% CI -0.065; 0.007)                                                                                                                                                                                                                                                                   | PM <sub>10</sub> IQR increase (1.8 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>10</sub> IQR increase (1.8 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                      |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment                                           | Outcome                 | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Adjustments |
|------------------------------------|----------|--------------|---------------------|-----------------------------------------|---------------------------------------------------------------|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                     |                                         | 5-y average (year of 2007-2009 measurements plus 4 preceding) |                         | $\beta = -0.012$ (95% CI -0.053; 0.029)<br><br>$\beta = -0.010$ (95% CI -0.041; 0.021)<br><br>$\beta = -0.033$ (95% CI -0.080; 0.015)<br><br>$\beta = -0.030$ (95% CI -0.062; 0.002)<br><br>$\beta = -0.012$ (95% CI -0.053; 0.029)<br><br>$\beta = -0.010$ (95% CI -0.041; 0.021)<br><br>Significant association between memory and exposures to PM <sub>10</sub> and PM <sub>2.5</sub> (yearly lag 4) excluding participants who moved out of Greater London between study waves | PM <sub>10</sub> exhaust IQR increase (0.30 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10</sub> exhaust IQR increase (0.30 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)<br><br>PM <sub>2.5</sub> IQR increase (1.1 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> IQR increase (1.1 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)<br><br>PM <sub>2.5</sub> exhaust IQR increase (0.27 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> exhaust IQR increase (0.27 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination) |             |
|                                    |          |              |                     |                                         |                                                               | Semantic fluency change | $\beta = 0.000$ (95% CI -0.035; 0.035)<br><br>$\beta = -0.011$ (95% CI -0.037; 0.016)                                                                                                                                                                                                                                                                                                                                                                                              | PM <sub>10</sub> IQR increase (1.8 $\mu\text{g}/\text{m}^3$ ), 5-year average<br><br>PM <sub>10</sub> IQR increase (1.8 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)                                                                                                                                                                                                                                                                                                                                                                                                                                   |             |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome                 | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                   | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Adjustments |
|------------------------------------|----------|--------------|---------------------|-----------------------------------------|---------------------|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                     |                                         |                     |                         | $\beta = 0.005$ (95% CI -0.025; 0.035)<br><br>$\beta = 0.005$ (95% CI -0.018; 0.027)<br><br>$\beta = -0.006$ (95% CI -0.040; 0.029)<br><br>$\beta = -0.011$ (95% CI -0.035; 0.012)<br><br>$\beta = 0.005$ (95% CI -0.025; 0.035)<br><br>$\beta = 0.005$ (95% CI -0.018; 0.028) | PM <sub>10 exhaust</sub> IQR increase (0.30 $\mu\text{g}/\text{m}^3$ ), 5-year average<br><br>PM <sub>10 exhaust</sub> IQR increase (0.30 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)<br><br>PM <sub>2.5</sub> IQR increase (1.1 $\mu\text{g}/\text{m}^3$ ), 5-year average<br><br>PM <sub>2.5</sub> IQR increase (1.1 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)<br><br>PM <sub>2.5 exhaust</sub> IQR increase (0.27 $\mu\text{g}/\text{m}^3$ ), 5-year average<br><br>PM <sub>2.5 exhaust</sub> IQR increase (0.27 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination) |             |
|                                    |          |              |                     |                                         |                     | Phonemic Fluency change | $\beta = 0.003$ (95% CI -0.032; 0.039)<br><br>$\beta = -0.009$ (95% CI -0.036; 0.018)<br><br>$\beta = 0.004$ (95% CI -0.027; 0.034)<br><br>$\beta = 0.010$ (95% CI -0.013; 0.033)                                                                                              | PM <sub>10</sub> IQR increase (1.8 $\mu\text{g}/\text{m}^3$ ), 5-year average<br><br>PM <sub>10</sub> IQR increase (1.8 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)<br><br>PM <sub>10 exhaust</sub> IQR increase (0.30 $\mu\text{g}/\text{m}^3$ ), 5-year average<br><br>PM <sub>10 exhaust</sub> IQR increase (0.30 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)                                                                                                                                                                                                                                            |             |

| First author, year (Name of study)                                        | Location | Study design       | Time recruitment/FU                             | N cases/cohort size or N Controls (age)                  | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Outcome                                                                                                                       | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                              | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Adjustments                                                                                                                                                                                                                                      |
|---------------------------------------------------------------------------|----------|--------------------|-------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                           |          |                    |                                                 |                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                               | $\beta$ = 0.003 (95% CI -0.038; 0.031)<br><br>$\beta$ = -0.009 (95% CI -0.033; 0.015)<br><br>$\beta$ = 0.004 (95% CI -0.027; 0.034)<br><br>$\beta$ = 0.010 (95% CI -0.013; 0.033)                                                                                                                                                                         | PM <sub>2.5</sub> IQR increase (1.1 $\mu\text{g}/\text{m}^3$ ), 5-year average<br><br>PM <sub>2.5</sub> IQR increase (1.1 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination)<br><br>PM <sub>2.5 exhaust</sub> IQR increase (0.27 $\mu\text{g}/\text{m}^3$ ), 5-year average<br><br>PM <sub>2.5 exhaust</sub> IQR increase (0.27 $\mu\text{g}/\text{m}^3$ ), yearly lag 4 (4 years prior to the 2007-2009 examination) |                                                                                                                                                                                                                                                  |
| Cacciottolo et al., 2017 (Women's Health Initiative Memory Study (WHIMS)) | USA      | Prospective cohort | Enrolment 1995-1999, FU 2010, mean FU 9.9 years | 3647 (W) (65-79 years)<br>173 incident cases of dementia | Yearly time series of PM <sub>2.5</sub> exposure generated from statistically validated Bayesian Model Entropy (BME) estimates applied to geocoded residential location and combined with residential histories to calculate the 3-y moving average exposure. BME method used to construct spatio-temporal models to estimate ambient concentrations of PM <sub>2.5</sub> integrating nationwide monitoring data from the US EPA Air Quality Stations network and output of chemical | Global cognitive decline (defined as having an 8-point (~ 2 standard errors) loss in the MMSE in two consecutive assessments) | <b>HR =1.81 (95% CI 1.42; 2.32) p&lt;0.01</b><br><br><b>HR (by APOE genotype, <math>\epsilon</math>3/3) OR=1.65 (95% CI 1.23; 2.23) p&lt;0.01</b><br><br><b>HR (by APOE genotype, <math>\epsilon</math>3/4) OR=1.93 (95% CI 1.27; 2.90) p&lt;0.01</b><br><br><b>HR (by APOE genotype, <math>\epsilon</math>4/4) OR=3.64 (95% CI 1.36; 9.69) p&lt;0.01</b> | 3-year average PM <sub>2.5</sub> high (>12 $\mu\text{g}/\text{m}^3$ ) vs low ( $\leq$ 12 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                                                                                                                                      | Age, APOE genotype, geographic region, education, income, employment status, smoking, alcohol, physical activity, hormone treatment, prior depression, BMI, hypercholesterolemia, hypertension, diabetes and histories of cardiovascular disease |

| First author, year (Name of study)                                                           | Location        | Study design                      | Time recruitment/FU                                                                                     | N cases/cohort size or N Controls (age) | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                     | Outcome                                                                                 | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                | Exposure                                                                                            | Adjustments                                                                                                                                                                                                                           |
|----------------------------------------------------------------------------------------------|-----------------|-----------------------------------|---------------------------------------------------------------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                              |                 |                                   |                                                                                                         |                                         | transport models to characterise spatio-temporal interdependence of environmental data to estimate mean trends and covariance of the air pollution field over space and time.                                                                                                                                                                                                                           |                                                                                         |                                                                                                                                                                                                                             |                                                                                                     |                                                                                                                                                                                                                                       |
| Xu et al., 2017 (Chinese Longitudinal Healthy Longevity Survey, CLHLS)                       | China           | Longitudinal (5 surveys)          | 2002-2014                                                                                               | 17333 (M+W) ( $\geq 65$ years)          | Residential status: 1) rural, 2) urban, 3) rural-to urban, and 4) urban-to-rural. Persons born in rural areas and are currently living in rural areas are considered "rural;" and persons born in urban areas and are currently living in urban areas are considered "urban." Participants who were born in rural areas and currently living in urban areas were defined as "rural-to-urban" residents. | Cognitive decline (MMSE)                                                                | $\beta = 0.50$ (SE 0.17) $p = <0.01$<br>$\beta = 0.42$ (SE 0.16) $p = <0.01$<br>$\beta = 0.31$ (SE 0.36)<br><br>Rural-to-urban and rural residents demonstrated a faster decline in cognitive function than urban residents | Reference category urban<br>Rural-to-urban residents<br>Rural residents<br>Urban-to-rural residents | Age, sex, race, education, occupation, economic independence, childhood SES, marital status, high proximity to offspring, smoking, physical activity, vegetable and fish consumption, any chronic condition, ADL and IALD disability, |
| Younan et al., 2020 (Women's Health Initiative Study of Cognitive Aging, WHISCA and the WHI) | USA (48 states) | Longitudinal (prospective cohort) | 1999-2010 (WHISCA), annual neurocognitive testing, 2005-2006 (WHIMS-MRI), second MRI between 2009-2010. | 998 (W) (73-87 years)                   | Ambient concentration of $PM_{2.5}$ was estimated using the Bayesian Maximum Entropy (BME)-based spatio-temporal modeling approach, integrating nationwide                                                                                                                                                                                                                                              | Episodic memory/trial 1-3 (CVTL) at MRI-I<br><br>Episodic memory/List B (CVTL) at MRI-I | $\beta = 0.002$ (95% CI -0.052, 0.057)<br><br>$\beta = 0.041$ (95% CI -0.003, 0.084)                                                                                                                                        | 3-year average $PM_{2.5}$ per IQR increase (2.81 $\mu g/m^3$ )                                      | age at MRI-1, race/ethnicity, geographic region of residence, education, household income, employment status, lifestyle factors (smoking, alcohol use, physical activities) and clinical characteristics (use of                      |

| First author, year (Name of study)                     | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Outcome                                                                                                               | HR, OR, RR, $\beta$ (95% CI)                                                                                          | Exposure                                                                           | Adjustments                                                                                              |
|--------------------------------------------------------|----------|--------------|---------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Memory Study of Magnetic Resonance Imaging, WHIMS-MRI) |          |              |                     |                                         | monitoring data from both the US Environmental Protection Agency (EPA) Air Quality System (AQS) and the output of chemical transport models. The BME model was then applied to each geocoded residential location, accounting for residential mobility in 1999-2010, and exposure estimates were then aggregated to represent the average PM <sub>2.5</sub> 3-years preceding the first MRI scan. Residential addresses of WHIMS participants were prospectively collected during each clinic visit and updated at least biannually. | Episodic memory/ short-delay free recall (CVTL) at MRI-I                                                              | $\beta=-0.017$ (95% CI -0.071, 0.038)                                                                                 |                                                                                    | hormone treatment; hypercholesterolemia, hypertension, diabetes, and history of cardiovascular disease). |
|                                                        |          |              |                     |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Episodic memory/ long-delay free recall (CVTL) at MRI-I                                                               | $\beta=-0.026$ (95% CI -0.080, 0.029)                                                                                 |                                                                                    |                                                                                                          |
|                                                        |          |              |                     |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Episodic memory/ Composite score (CVTL) at MRI-I                                                                      | $\beta=-0.017$ (95% CI -0.070, 0.036)                                                                                 |                                                                                    |                                                                                                          |
|                                                        |          |              |                     |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Episodic memory change/trial 1-3 (CVTL) (annual change after MRI-I)                                                   | <b><math>\beta=-0.040</math> (95% CI -0.076, -0.004)</b><br><b>average rate of change= 19.3% (95% CI 1.9%, 36.2%)</b> | 3-year average PM <sub>2.5</sub> per IQR increase (2.81 $\mu\text{g}/\text{m}^3$ ) |                                                                                                          |
|                                                        |          |              |                     |                                         | Episodic memory change/List B (CVTL) (annual change after MRI-I)                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b><math>\beta=-0.057</math> (95% CI -0.096, -0.017)</b><br><b>average rate of change= 14.8% (95% CI 4.4%, 24.9%)</b> |                                                                                                                       |                                                                                    |                                                                                                          |
|                                                        |          |              |                     |                                         | Episodic memory change/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | $\beta=-0.007$ (95% CI -0.045, 0.031)                                                                                 |                                                                                                                       |                                                                                    |                                                                                                          |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome                                                                                                                                                                                                                               | HR, OR, RR, $\beta$ (95% CI)                                                           | Exposure | Adjustments |
|------------------------------------|----------|--------------|---------------------|-----------------------------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------|-------------|
|                                    |          |              |                     |                                         |                     | short-delay free recall (CVTL) (annual change after MRI-I)<br><br>Episodic memory change/ long-delay free recall (CVTL) (annual change after MRI-I)<br><br>Episodic memory change/ Composite score (CVTL) (annual change after MRI-I) | $\beta = -0.002$ (95% CI -0.041, 0.037)<br><br>$\beta = -0.018$ (95% CI -0.051, 0.015) |          |             |

### Abbreviation

FU, follow-up; M, men; W, women; SES, socioeconomic status; MMSE, mini mental status examination; CERAD, The Consortium to Establish a Registry for Alzheimer's Disease; CDR-SB Cognitive Dementia Rating Sum of Boxes; BC, black carbon, BMI, body mass index; HR, hazard ratio; OR, odds ratio; RR, relative risk; CI, confidence interval; SE, standard error.

**Table 3.8. Summary of characteristics and outcomes of studies assessing the effect of air pollution on mild cognitive impairment and incident cognitive impairment included in literature review**

| First author, year (Name of study)                                                  | Location                        | Study design                                                                   | Time recruitment/FU                     | N cases/cohort size or N Controls, Sex (age)                                                  | Exposure Assessment                                                                                                                                                                                                                                                                             | Outcome                                                                                                                                           | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                | Exposure                                                            | Adjustments                                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------|---------------------------------|--------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sanchez-Rodriguez et al, 2006                                                       | Mexico City and Actopan, Mexico | Cross-sectional                                                                | Not reported                            | 189 (M+W) (104 Urban, 85 rural) (mean age Urban: 66.8 $\pm$ 6.4; Rural: 70.8 $\pm$ 8.4 years) | Air pollution exposure by residence in high (urban) and low (rural) polluted areas for 10 years or more.                                                                                                                                                                                        | Cognitive impairment for MMSE $\leq$ 23 vs >23                                                                                                    | Crude OR 1.96 (95% CI: 0.79, 5.21)                                                                                                                                                                                                                          | Rural and urban                                                     | Subjects were not smokers, without acute or chronic diseases and were not receiving prescription medications, physical activity was similar between the two groups                                             |
| Zeng et al., 2010 (Chinese Longitudinal Health Longevity Survey (CLHLS))            | China 866 counties and cities   | Longitudinal (Cross-sectional analysis using data from the two waves of CLHLS) | 2002-2005                               | 15973, 40.9% cognitive impairment ( $\geq$ 65 years, mean age: 86.3 years)                    | Air Pollution Index for 2002                                                                                                                                                                                                                                                                    | Cognitive impairment (MMSE <18)                                                                                                                   | <b>OR = 1.09 (95% CI 1.01, 1.18)</b>                                                                                                                                                                                                                        | Air Pollution Index (API)                                           | NOT CLEAR                                                                                                                                                                                                      |
| Loop et al., 2015 (Reason for geographic And Racial Differences in Stroke, REGARDS) | USA 48 contiguous states        | Longitudinal (prospective cohort)                                              | 2003-2007/4-5 years (annual assessment) | 1633 cognitively impaired subjects / 20,150 M+W (at baseline 64 years)                        | Annual average exposure to PM <sub>2.5</sub> from 2003-2009 was estimated by using an algorithm combining EPA's AQS ground level monitoring data and NASA's MODIS aerosol optical depth satellite data to calculate daily exposure for each participant according to their residential address. | Incident cognitive impairment (by Six-Item Screener 0-6: cognitive intact subjects for scores $\geq$ 5; cognitive impairment for scores $\leq$ 4) | OR=0.98 (95%CI 0.72-1.34)<br>Sensitivity analysis for exposure >12 months<br>OR=0.71 (95%CI 0.38-1.32)<br>Stratified analyses for urbanicity group<br>Rural OR=0.79 (95%CI 0.23-2.69)<br>Mixed OR=0.34 (95%CI 0.11-1.04)<br>Urban OR=1.06 (95%CI 0.77-1.48) | PM <sub>2.5</sub> 10 $\mu$ g/m <sup>3</sup> increase                | Age, sex, race, region, education, income, smoking, alcohol, physical activity, BMI, presence of depression, dyslipidaemia, diabetes, hypertension, incident stroke, temperature, season, length of Follow-up. |
| Tzivian et al., 2016 (Heinz Nixdorf Recall study)                                   | Germany                         | Cross-sectional                                                                | 2006-2008                               | 4,086 (M+W), 592 with cognitive impairment (50–80 years old)                                  | Levels of PM <sub>10</sub> , PM <sub>coarse</sub> , PM <sub>2.5</sub> were measured at 20 sites and NO <sub>x</sub> and NO <sub>2</sub> at 40 sites over 1 year (2009-2009) Long-term exposure                                                                                                  | MCI assessed by a battery of cognitive tests<br>Overall MCI<br>Amnesic MCI<br>Non amnesic MCI                                                     | OR 1.11 (95%CI 0.99-1.23)<br><b>OR 1.17 (95%CI 1.07-1.35)</b><br>OR 1.04 (95%CI 0.90-1.21)                                                                                                                                                                  | PM <sub>10</sub> 1-year IQR increase (2.09 $\mu$ g/m <sup>3</sup> ) | age, sex, socioeconomic status, alcohol consumption, smoking status, self-reported environmental tobacco smoke, any regular physical activity, body mass index.                                                |



| First author, year (Name of study)                    | Location | Study design       | Time recruitment/FU | N cases/cohort size or N Controls, Sex (age)                              | Exposure Assessment                                                                                                 | Outcome                                                                                                                              | HR, OR, RR, $\beta$ (95% CI)                                                               | Exposure                                                                                       | Adjustments                                                                                                                                              |
|-------------------------------------------------------|----------|--------------------|---------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                       |          |                    |                     |                                                                           | was calculated by LUR models.                                                                                       | Overall MCI                                                                                                                          | OR 1.11 (95%CI 0.98-1.26)                                                                  | PM <sub>coarse</sub> 1-year IQR increase (1.00 $\mu\text{g}/\text{m}^3$ )                      |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Amnestic MCI                                                                                                                         | OR 1.26 (95%CI 0.95-1.33)                                                                  |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Non amnestic MCI                                                                                                                     | OR 1.09 (95%CI 0.92-1.29)                                                                  |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Overall MCI                                                                                                                          | <b>OR 1.16 (95%CI 1.05-1.27)</b>                                                           | PM <sub>2.5</sub> 1-year IQR increase (1.44 $\mu\text{g}/\text{m}^3$ )                         |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Amnestic MCI                                                                                                                         | <b>OR 1.22 (95%CI 1.08-1.38)</b>                                                           |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Non amnestic MCI                                                                                                                     | OR 1.10 (95%CI 0.92-1.31)                                                                  |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Overall MCI                                                                                                                          | <b>OR 1.11 (95%CI 1.03-1.19)</b>                                                           | PM <sub>2.5 abs</sub> 1-year IQR increase (0.35x10 <sup>-5</sup> /m $\mu\text{g}/\text{m}^3$ ) |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Amnestic MCI                                                                                                                         | <b>OR 1.17 (95%CI 1.03-1.35)</b>                                                           |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Non amnestic MCI                                                                                                                     | OR 1.03 (95%CI 0.90-1.19)                                                                  |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Overall MCI                                                                                                                          | OR 1.10 (95%CI 0.97-1.25)                                                                  | NO <sub>2</sub> 1-year IQR increase (6.11 $\mu\text{g}/\text{m}^3$ )                           |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Amnestic MCI                                                                                                                         | <b>OR 1.13 (95%CI 1.01-1.38)</b>                                                           |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Non amnestic MCI                                                                                                                     | OR 1.01 (95%CI 0.85-1.20)                                                                  |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Overall MCI                                                                                                                          | OR 1.10 (95%CI 0.96-1.26)                                                                  | NO <sub>x</sub> 1-year IQR increase (15.70 $\mu\text{g}/\text{m}^3$ )                          |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Amnestic MCI                                                                                                                         | OR 1.13 (95%CI 0.96-1.34)                                                                  |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Non amnestic MCI                                                                                                                     | OR 1.05 (95%CI 0.88-1.26)                                                                  |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Overall MCI                                                                                                                          | OR 1.00 (95%CI 0.94-1.07)                                                                  | Traffic load at major roads (vehicles/day)                                                     |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Amnestic MCI                                                                                                                         | OR 1.03 (95%CI 0.96-1.11)                                                                  |                                                                                                |                                                                                                                                                          |
|                                                       |          |                    |                     |                                                                           |                                                                                                                     | Non amnestic MCI                                                                                                                     | OR 0.95 (95%CI 0.85-1.05)                                                                  |                                                                                                |                                                                                                                                                          |
| Chen et al., 2017 c (Women's Health Initiative Memory | USA      | Prospective cohort | 1996-1999/2005-2007 | 7,479 (W), 256 cases with MCI (mean age 71.0 $\pm$ 3.8 years at baseline) | Residence-specific yearly exposures to PM <sub>2.5</sub> were estimated using a BME spatio-temporal model of annual | MCI defined as poor performance (<10 <sup>th</sup> percentile in CERAD norms) on at least one CERAD test, functional impairment, and | HR=0.93 (95% CI 0.79-1.09) p=0.39<br>Significant positive association among obese subjects | PM <sub>2.5</sub> annual IQR increase (3.9 $\mu\text{g}/\text{m}^3$ )                          | Age, race, region, education, income, employment status, smoking, alcohol, exercise, BMI, hormone therapy, presence of depression, hypercholesterolemia. |

| First author, year (Name of study)                                                    | Location    | Study design         | Time recruitment/FU | N cases/cohort size or N Controls, Sex (age)           | Exposure Assessment                                                                                                                                                                                                                                                                                                                                                                                                      | Outcome                                                                                                                                                                                                | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                    | Exposure                                                                                                                                                                 | Adjustments                                                                                                                                                                                                                                                                                                                                                                                                                |
|---------------------------------------------------------------------------------------|-------------|----------------------|---------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study (WHIMS)                                                                         |             |                      |                     |                                                        | monitoring data (1999–2007) recorded in the U.S. EPA Air Quality System (AQS). Annual exposures (1996–2005) to diesel PM (DPM) were assigned to each residential census tract in a nationwide spatio-temporal mapping, based on a generalised additive model (GAM), to conduct census tract specific temporal interpolation of DPM on-road estimates given by the U.S. EPA National-Scale Air Toxics Assessment Program. | absence of psychiatric problems or dementia                                                                                                                                                            | HR=0.96 (95% CI 0.84-1.11) p=0.60<br>HR=0.95 (95% CI 0.82-1.11) p=0.55                                                                                                                                                                                                                                                          | diesel PM annual IQR increase (3.9 $\mu\text{g}/\text{m}^3$ )<br>diesel PM baseline IQR increase (3.9 $\mu\text{g}/\text{m}^3$ )                                         | diabetes, hypertension, CVD histories                                                                                                                                                                                                                                                                                                                                                                                      |
| Lee et al., 2019 (Clinical Research Center for Dementia of South Korea study, CREDOS) | South Korea | Retrospective cohort | 2005-2010           | 645 (M+W), 310 with MCI, (mean age 74 $\pm$ 7.4 years) | Hourly PM <sub>2.5</sub> levels measured in 25 monitoring sites from 2007. Daily exposure was assigned to the subjects' residential address. Measures of NO <sub>2</sub> and SO <sub>2</sub> were constructed based on daily mean concentrations, those of O <sub>3</sub> and CO were calculated using the daily                                                                                                         | MCI assessed by the Korean version of the MMSE. The global severity of disease was assessed using the Clinical Dementia Rating Sum of Box, which measures the global severity of the cognitive domains | <b>Percent change (95%CI) = 40.7(18.3, 67.3) p&lt;0.05 (significant association also considering two-pollutant models including NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>, CO)</b><br>Percent change (95%CI) = 24.9 (-3.1, 61.1) <b>(significant association considering two-pollutant models including NO<sub>2</sub>)</b> | IQR increase of PM <sub>2.5</sub> (8.3 $\mu\text{g}/\text{m}^3$ 1-month average)<br><br>IQR increase of PM <sub>2.5</sub> (7.9 $\mu\text{g}/\text{m}^3$ 2-month average) | Age, sex, visit number, visit year, education, smoking, alcohol consumption, diabetes, hypertension, stroke, cardiovascular diseases, clinical dementia rating-sum of boxes score, deep white matter hyperintensity, periventricular white matter hyperintensity, season, 8-day moving average temperature and rainfall, proportion of medical personnel, proportion of green space and economic environment satisfaction. |

| First author, year (Name of study)                         | Location | Study design             | Time recruitment/FU         | N cases/cohort size or N Controls, Sex (age) | Exposure Assessment                                                                                                                                                                                                                                                                                                                                                                                                                                     | Outcome                                                                                                                                                                   | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                          | Exposure                                                                                                                                                                                                                                                        | Adjustments                                                                                                                                                                  |
|------------------------------------------------------------|----------|--------------------------|-----------------------------|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                            |          |                          |                             |                                              | maximum 8-hour mean concentrations                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                           | Percent change (95%CI) = -2.7 (-27.1, 29.8)<br><br>Percent change (95%CI) = -0.5 (-20.7, 24.9)<br><br>Percent change (95%CI) = 0.2 (-15.7, 19.1)                                                                                                                                                                                                                                      | IQR increase of PM <sub>2.5</sub> (7.4 $\mu\text{g}/\text{m}^3$ 3-month average)<br><br>IQR increase of PM <sub>2.5</sub> (5.9 $\mu\text{g}/\text{m}^3$ 6-month average)<br><br>IQR increase of PM <sub>2.5</sub> (3.9 $\mu\text{g}/\text{m}^3$ 1-year average) |                                                                                                                                                                              |
| Lo et al, 2019 (Taiwan Longitudinal Study on Aging, TLISA) | Taiwan   | Longitudinal (4 surveys) | Four surveys from 1996-2007 | 2241 (M+W), ( $\geq 65$ years)               | Hourly data of PM <sub>10</sub> and O <sub>3</sub> levels were obtained from 75 monitoring stations constructed by the Taiwan Environmental Protection Administration, from 1993 to 2007. The daily average of air pollutants from monitoring stations was assigned to participants. Seven day, 14 day, 21 day, 30 day, 60 day, 90 day, 180 day, 1 year, and 3 year averages prior to each participant's interview date for each survey was calculated. | Moderate-to-severe cognitive impairment (assessed by Short Portable Mental Status Questionnaire (SPMSQ) dichotomised <3 identified individuals with cognitive impairment) | OR=1.030 (95% CI 0.990, 1.083) p=0.218<br><br>OR= 1.000 (95% CI 0.961, 1.062) p=0.731<br><br>OR= 1.010 (95%CI 0.970, 1.062) p=0.526<br><br>OR= 1.020 (95% CI 0.980, 1.073) p=0.337<br><br>OR= 1.020 (95% CI 0.980, 1.073) p=0.331<br><br>OR= 1.030 (95% CI 0.990, 1.073) p=0.218<br><br>OR= 1.041 (95% CI 1.000, 1.083) p=0.063<br><br><b>OR= 1.083 (95% CI 1.000, 1.174) p=0.039</b> | PM <sub>10</sub> increase (10 $\mu\text{g}/\text{m}^3$ )<br>7 days<br><br>14 days<br><br>21 days<br><br>30 days<br><br>60 days<br><br>90 days<br><br>180 days<br><br>1 year                                                                                     | age, sex, personal education, marital status, self-reported financial status, smoking, alcohol consumption, physical activity, IADL, and O <sub>3</sub> and PM <sub>10</sub> |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls, Sex (age) | Exposure Assessment | Outcome | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Exposure                                                                                                                                                                                    | Adjustments |
|------------------------------------|----------|--------------|---------------------|----------------------------------------------|---------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                     |                                              |                     |         | <p>OR= 1.094 (95% CI 1.020, 1.174) p=0.007</p> <p>OR= 0.923 (95% CI 0.787, 1.062) p=0.272</p> <p>OR= 1.000 (95% CI 0.852, 1.197) p=0.926</p> <p>OR= 1.127 (95% CI 0.961, 1.350) p=0.143</p> <p>OR= 1.209 (95% CI 1.020, 1.433) p=0.024</p> <p>OR= 1.405 (95% CI 1.150, 1.716) p&lt;0.001</p> <p>OR= 1.649 (95% CI 1.323, 2.054) p&lt;0.001</p> <p>OR= 1.716 (95% CI 1.323, 2.203) p&lt;0.001</p> <p>OR= 1.954 (95% CI 1.448, 2.664) p&lt;0.001</p> <p>OR= 1.878 (95% CI 1.363, 2.560) p&lt;0.001</p> <p>The joint effect of exposure to PM<sub>10</sub></p> | <p>3 years</p> <p>O<sub>3</sub> increase (10 ppb)</p> <p>7 days</p> <p>14 days</p> <p>21 days</p> <p>30 days</p> <p>60 days</p> <p>90 days</p> <p>180 days</p> <p>1 year</p> <p>3 years</p> |             |

| First author, year (Name of study) | Location | Study design | Time recruitment/FU | N cases/cohort size or N Controls, Sex (age) | Exposure Assessment | Outcome | HR, OR, RR, $\beta$ (95% CI)                                            | Exposure | Adjustments |
|------------------------------------|----------|--------------|---------------------|----------------------------------------------|---------------------|---------|-------------------------------------------------------------------------|----------|-------------|
|                                    |          |              |                     |                                              |                     |         | and O <sub>3</sub> was associated with cognitive impairment (p <0.001). |          |             |

### Abbreviations

FU, follow-up; M, men; W, women; SES, socioeconomic status; BC, black carbon, BMI, body mass index; HR, hazard ratio; OR, odds ratio; RR, relative risk; CI, confidence interval; MMSE, mini mental status examination, IQR, interquartile range; SDLT, Serial-digit learning test; MCI, Mild Cognitive impairment.

**Table 3.9. Summary of characteristics and outcomes of studies assessing the effect of air pollution on dementia and Alzheimer's disease included in literature review**

| First author, year (Name of study)                                           | Location        | Study design          | Time recruitment /FU                    | N cases/cohort size or N Controls (age)                                                                                      | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Outcome                                                                                                                                  | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                     | Exposure                                                                                                                                                                                                                                                                           | Adjustments                                                                                                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------|-----------------|-----------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chen et al, 2017b (Ontario Population Health and Environment Cohort, ONPHEC) | Ontario, Canada | Longitudinal (Cohort) | 2001/2012 or data of dementia diagnosis | 2.2 M (M+W)<br><br>243,611 incident cases of dementia 55-85 (mean age at baseline 66.8 years)                                | Exposure based on residential proximity to a major roadway or highway based on postcode in 1996 (5-y lag). Median distance (continuous) and five categories of distance calculated using ArcGIS: <50 m, 50-100 m, 101-200 m, 201-300 m, >300 m.                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Dementia (all causes) (health administrative databases with a validated algorithm were used to ascertain incident diagnosis of dementia) | <b>HR =1.07 (95% CI 1.06; 1.08)</b><br><b>p=0.039</b><br><br><b>HR = 1.07 (95% CI 1.06-1.08)</b><br><br><b>HR =1.04 (95% CI 1.03-1.05)</b>                       | Residential Traffic proximity <50m vs >300 m (individual's proximity to major roadways based on their residential address in 1996)<br><br>NO <sub>2</sub> IQR increase (11.3 ppb) 4-year average (1998-2001)<br><br>PM <sub>2.5</sub> IQR increase (3.4 $\mu\text{g}/\text{m}^3$ ) | Age, sex, history of diabetes, hypertension, coronary heart disease, stroke, congestive heart failure, arrhythmia, traumatic brain injury, income, urban/rural indicator, census division-level unemployment rate, education, recent immigrations, stratified for living in the greater Toronto area or not. |
| Chen et al, 2017a (Ontario Population Health and Environment Cohort, ONPHEC) | Ontario, Canada | Longitudinal (Cohort) | 2001/2013 or data of dementia diagnosis | 2.2 Million (M+W)<br><br>257,816 incident cases of dementia (55-85 years, mean age at baseline 66.8 years; at FU 73.8 years) | Exposure to PM <sub>2.5</sub> derived from satellite observations in combination with outputs from a global atmospheric chemistry transport model (GEOS-Chem CTM) and calibrated with land cover, elevation, aerosol composition information using geographically weighted regression producing annual mean concentration of PM <sub>2.5</sub> (1x1km) yearly between 1998 and 2012 (annual estimates of PM <sub>2.5</sub> agree with ground-level measurements at fixed sites, R <sup>2</sup> =0.82). Annual measurement of NO <sub>2</sub> in 2006 derived using a national land-use regression model developed using NO <sub>2</sub> observations at fixed-site monitors from Surveillance Network, | Dementia (all causes) (health administrative databases with a validated algorithm was used to ascertain incident diagnosis of dementia)  | <b>HR =1.04 (95% CI 1.03; 1.05)</b><br><br><b>HR =1.10 (95% CI 1.08; 1.12)</b><br><br>HR =0.98 (95% CI 0.96; 1.00)<br>Consistent results across strata of sex, . | PM <sub>2.5</sub> 5-year IQR increase (4.8 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>2</sub> 5-year IQR increase (26.7 $\mu\text{g}/\text{m}^3$ )<br><br>O <sub>3</sub> 5-year IQR increase (12.4 $\mu\text{g}/\text{m}^3$ )                                                       | Age, sex, stratified region, neighbourhood-level income, education, unemployment rate, immigrants, urban residency, north/south indicator, pre-existing brain injury, stroke, diabetes, hypertension, coronary heart disease, heart failure, arrhythmia. Indirect adjustments for smoking, physical          |

| First author, year (Name of study)                                     | Location | Study design                      | Time recruitment /FU                        | N cases/cohort size or N Controls (age)                                               | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Outcome                                                                                                                                                                                                                | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                        | Exposure                                                                                                                                                                                                          | Adjustments                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------|----------|-----------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                        |          |                                   |                                             |                                                                                       | satellite data, industrial land use, distance decay gradient.<br>Long-term exposure to O <sub>3</sub> estimated using optimal interpolation technique combining true observations with benefits of physically based air quality prediction models that account for meteorological and chemical patterns.<br>Annual exposure to these pollutants was assigned to the subjects' residential postal code. Postal code represented centroids or blocks of residence.                                                                                                                                                                                                   |                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                   | activity, obesity and education did not change the magnitude of the association.                                                                                                                                                                 |
| Cacciotto et al, 2017 (Women's Health Initiative Memory Study (WHIMS)) | USA      | Longitudinal (Prospective cohort) | Enrolment 1995-1999/2010, mean FU 9.9 years | 3647 (W) (65-79 years)<br>173 incident cases of dementia                              | Yearly time series of PM <sub>2.5</sub> exposure generated from statistically validated Bayesian Model Entropy (BME) estimates applied to geocoded residential location and combined with residential histories to calculate the 3-y moving average exposure. BME method used to construct spatio-temporal models to estimate ambient concentrations of PM <sub>2.5</sub> integrating nationwide monitoring data from the US EPA Air Quality Stations network and output of chemical transport models to characterise spatio-temporal interdependence of environmental data to estimate mean trends and covariance of the air pollution field over space and time. | Dementia (all causes) (standardised ascertainment, including annual screening of global cognitive function, neuropsychological and functional assessment, and collection of clinical data were used for the diagnosis) | <b>HR =1.92 (95% CI 1.31; 2.80) p&lt;0.01</b><br><br>HR (by APOE genotype, $\epsilon 3/3$ ) OR=1.68 (95% CI 0.97; 2.92) p 0.06<br><br><b>HR (by APOE genotype, <math>\epsilon 3/4</math>) OR=1.91 (95% CI 1.17; 3.14) p 0.01</b><br><br><b>HR (by APOE genotype, <math>\epsilon 3/4</math>) OR=3.95 (95% CI 1.18; 13.19) p 0.03</b> | 3-year average PM <sub>2.5</sub> high (>12 $\mu\text{g}/\text{m}^3$ ) vs low ( $\leq 12 \mu\text{g}/\text{m}^3$ )                                                                                                 | Age, APOE genotype, geographic region, education, income, employment status, smoking, alcohol, physical activity, hormone treatment, prior depression, BMI, hypercholesterolemia, hypertension, diabetes and histories of cardiovascular disease |
| Chen et al, 2017c (Women's Health Initiative Memory Study (WHIMS))     | USA      | Longitudinal (Prospective cohort) |                                             | 7,479 (W), 157 incident cases of dementia (mean age 71.0 $\pm$ 3.8 years at baseline) | Residence-specific yearly exposures to PM <sub>2.5</sub> were estimated using a BME spatio-temporal model of annual monitoring data (1999–2007) recorded in the U.S. EPA Air Quality System (AQS). Annual exposures (1996–2005) to diesel PM (DPM) were assigned to each residential census tract in a nationwide spatio-temporal mapping,                                                                                                                                                                                                                                                                                                                         | Dementia (annual screening of global cognitive function, assessment of behavioural symptoms, detailed clinical neurological examination /neuropsychiatric                                                              | HR=0.99 (95% CI 0.81-1.22) p=0.95<br><br>HR=1.01 (95% CI 0.84-1.2) p=0.95<br><br>HR=1.02 (95% CI 0.83-1.25) p=0.84                                                                                                                                                                                                                  | PM <sub>2.5</sub> annual IQR increase (3.9 $\mu\text{g}/\text{m}^3$ )<br><br>diesel PM annual IQR increase (3.9 $\mu\text{g}/\text{m}^3$ )<br><br>diesel PM baseline IQR increase (3.9 $\mu\text{g}/\text{m}^3$ ) | Age, race, region, education, income, employment status, smoking, alcohol, exercise, BMI, hormone therapy, presence of depression, hypercholesterolemia, diabetes,                                                                               |

| First author, year (Name of study)                                      | Location | Study design          | Time recruitment /FU                    | N cases/cohort size or N Controls (age)                                                                                              | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Outcome                                                                                                                                                                                                                                                    | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                      | Exposure                                                                                                                                                                                                                                                                             | Adjustments                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------------------|----------|-----------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                         |          |                       |                                         |                                                                                                                                      | based on a generalised additive model (GAM), to conduct census tract specific temporal interpolation of DPM on-road estimates given by the U.S. EPA National-Scale Air Toxics Assessment Program.                                                                                                                                                                                                                                                                                           | evaluation, head scan and a series of laboratory tests were used. Dementia was defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition).                                                                                          |                                                                                                                                                                   |                                                                                                                                                                                                                                                                                      | hypertension, CVD histories                                                                                                                                                                                                                                             |
| Jung et al, 2015<br>National Health Insurance Research Database (NHIRD) | Taiwan   | Longitudinal (Cohort) | 2001/2010 or data of dementia diagnosis | 95,690 (M+W) ( $\geq 65$ years), 1,399 incident cases of AD                                                                          | PM <sub>2.5</sub> data were available from 70 monitoring stations in Taiwan after 2006. The mean ratio between PM <sub>2.5</sub> and PM <sub>10</sub> during 2006-2010 was used to estimate the concentrations of PM <sub>2.5</sub> from 2000 to 2006. Annual fourth-highest daily maximum 8-hour average based on 8-h standard of Ozone. The monitoring data of PM <sub>2.5</sub> and O <sub>3</sub> at residential postcode level were interpolated using inverse distance weight method. | AD (AD diagnosis based on longitudinal health insurance database, ICD-9, code 331.0. The coding of AD was assigned by physician based on history, physical examination, laboratory and imaging studies)                                                    | HR = 1.03 (95% CI 0.95, 1.11)<br><br><b>HR = 2.38 (95% CI 2.21, 2.56)</b><br><br><b>HR = 1.06 (95% CI 1.00; 1.12)</b><br><br><b>HR = 3.12 (95% CI 2.92; 3.33)</b> | PM <sub>2.5</sub> increase (13.21 $\mu\text{g}/\text{m}^3$ ) at baseline<br><br>PM <sub>2.5</sub> increase (4.34 $\mu\text{g}/\text{m}^3$ ) at follow up period<br><br>O <sub>3</sub> increase (9.63 ppb) at baseline<br><br>O <sub>3</sub> increase (10.91 ppb) at follow up period | Age, sex, income, diabetes, hypertension, myocardial infarction, asthma and chronic obstructive pulmonary disease.                                                                                                                                                      |
| Wu et al, 2015                                                          | Taiwan   | Case-control          | 2007-2010                               | 249 AD, 125 VaD (M+W) 497 controls ( $\geq 60$ years, mean age AD 79.1 $\pm$ 6.9 years, VaD 79.9 $\pm$ 7.0; controls 72.9 $\pm$ 6.1) | Ambient monitoring data of PM <sub>10</sub> and ozone were obtained from 24 monitoring stations from EPA between 1993 and 2006. BME method was used to estimate the spatio-temporal distribution of PM <sub>10</sub> and O <sub>3</sub> concentration. Exposures of 12-year PM <sub>10</sub> and 14-year O <sub>3</sub> were estimated assuming that elderly tend to live at the same place after they retired.                                                                             | AD (cases recruited from the neurology clinics of three teaching hospitals. MMSE was used to assess cognitive function. Dementia diagnosis was evaluated by Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria. Head magnetic | <b>OR = 4.17 (95% CI 2.31; 7.54) p &lt; 0.0001</b><br><br><b>OR = 2.00 (95% CI 1.14; 3.50) p = 0.03</b>                                                           | PM <sub>10</sub> highest ( $\geq 49.23 \mu\text{g}/\text{m}^3$ ) vs lowest tertile ( $< 44.95 \mu\text{g}/\text{m}^3$ )<br><br>O <sub>3</sub> highest ( $\geq 21.56 \text{ ppb}$ ) vs lowest tertile ( $< 20.20 \text{ ppb}$ )                                                       | age, sex, APOE $\epsilon 4$ status, PM <sub>10</sub> level, ozone level, education, and BMI. AD risk did not show significant heterogeneity across strata of APO $\epsilon 4$ status (carriers and noncarriers) and sex either for PM <sub>10</sub> and ozone exposure. |



| First author, year (Name of study) | Location | Study design | Time recruitment /FU | N cases/cohort size or N Controls (age) | Exposure assessment                                                                         | Outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                   | Exposure                                                                                                                                                                                                                                                                            | Adjustments                                  |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
|                                    |          |              |                      |                                         |                                                                                             | <p>resonance imaging and computed tomography were performed. Diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer's Criteria. Diagnosis of VaD was made according to the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria.</p> <p>VaD</p> | <p><b>OR =3.61 (95% CI 1.67; 7.81) p=0.004</b><br/>No significant heterogeneity across strata of APO <math>\epsilon</math>4 status (carriers and noncarriers) and sex either for PM10 and ozone exposure.</p> <p><b>OR=2.09 (95% CI 1.01; 4.33) p=0.05</b></p> | <p>PM<sub>10</sub> highest (<math>\geq 49.23</math> <math>\mu\text{g}/\text{m}^3</math>) vs lowest tertile (<math>&lt;44.95</math> <math>\text{mg}/\text{m}^3</math>)</p> <p>O<sub>3</sub> highest (<math>\geq 21.56</math> ppb) vs lowest tertile (<math>&lt;20.20</math> ppb)</p> |                                              |
| Chang et al, 2014 National         | Taiwan,  |              | 2000/2010 or data of | 29547 (M+W)                             | Annual pollutant exposure was assigned based on the data obtained from monitoring stations, | Dementia (all-cause)                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>HR = 1.54 (95% CI 1.34; 1.77)</b>                                                                                                                                                                                                                           | NO <sub>2</sub> Fourth ( $>9826$ ppb) vs first quartile ( $<6652$ ppb)                                                                                                                                                                                                              | age, sex, monthly income, Diabetes Mellitus, |

| First author, year (Name of study)         | Location | Study design                        | Time recruitment /FU               | N cases/cohort size or N Controls (age)                           | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                 | Outcome                                                                                                                                                                                                                                                                                                        | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                      | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Adjustments                                                                                                                                      |
|--------------------------------------------|----------|-------------------------------------|------------------------------------|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Health Insurance Research Database (NHIRD) |          | Longitudinal (Retrospective cohort) | dementia diagnosis                 | (mean age 61.4 $\pm$ 8.5 years), 1720 incident cases of dementia  | located across Taiwan, present in the residential district in which the clinic where the people most frequently sought treatment for acute upper respiratory infection was located. Daily NO <sub>2</sub> and CO concentrations were measured at the 74 monitoring stations. Data was available from 1998-2010                                                                                      | (a subset of the NHIRD data containing comprehensive health-care data, including files on ambulatory care claims, inpatient claims, and prescriptions were used. These data files provide a longitudinal medical history of each patient. The health status of each person was identified according to ICD-9). | <b>HR= 1.61 (95% CI 1.39, 1.85)</b><br><br>Consistent results across strata of sex for both exposures.                                                                                                                                                                            | CO fourth (>296.9 ppm) vs first quartile (<196.2 ppm)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Ischaemic Heart Disease, Hypertension, Chronic Obstructive Pulmonary Disease, alcohol and urbanisation.                                          |
| Oudin et al, 2016) (Betula Study)          | Sweden   | Longitudinal (Prospective cohort)   | 1988-1990 and 1993-1995/ 2008-2010 | 1806 (M+W) 191 incident cases of AD, 111 cases of VaD (>55 years) | Mean annual NO <sub>x</sub> concentrations were estimated at the residential address of the participants at baseline (1993-1995) using a land-use regression model derived from 4 weeklong measurements obtained from November 2009 to June 2010 at 36 sites around Umea. Concentration grid of 50x50 m created using geocoded addresses at baseline obtained from the Swedish Population Register. | Dementia (AD and VaD combined)<br><br>AD<br><br>VaD<br><br>(In BETULA cohort neuropsychological testing, structured                                                                                                                                                                                            | <b>HR = 1.60 (95% CI 1.02; 2.10)</b><br><br>HR = 1.05 (95% CI 0.98; 1.12)<br><br>HR = 1.38 (95% CI 0.87; 2.19)<br><br>HR = 1.05 (95% CI 0.97; 1.15)<br><br>HR = 1.47 (95% CI 0.83; 2.61)<br><br>HR = 1.02 (95% CI 0.92; 1.14)<br><br>Excluding sample retested only after 5 years | NO <sub>2</sub> Highest (>26 $\mu\text{g}/\text{m}^3$ ) vs lowest (4.8-9 $\mu\text{g}/\text{m}^3$ ) quartile.<br><br>NO <sub>2</sub> increase (10 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>2</sub> Highest (>26 $\mu\text{g}/\text{m}^3$ ) vs lowest (4.8-9 $\mu\text{g}/\text{m}^3$ ) quartile.<br><br>NO <sub>2</sub> increase (10 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>2</sub> Highest (>26 $\mu\text{g}/\text{m}^3$ ) vs lowest (4.8-9 $\mu\text{g}/\text{m}^3$ ) quartile.<br><br>NO <sub>2</sub> increase (10 $\mu\text{g}/\text{m}^3$ ) | Age, education, physical activity, smoking, sex, BMI, waist-hip ratio, alcohol, ApoE $\epsilon$ 4, history of diabetes, hypertension and stroke. |

| First author, year (Name of study) | Location | Study design | Time recruitment /FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                       | Exposure | Adjustments |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------|
|                                    |          |              |                      |                                         |                     | interviews, and observations made at the health examination and at the cognitive test situation, were done. Participants with suspected dementia were examined by either a specialist in geriatric psychiatry or a specialist in geriatric medicine. Diagnosis was set in accordance with the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, and differentially diagnosed as AD on the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Cognitive and neurological symptoms of vascular complications were taken into account | HR=1.71 (95% CI 1.08-2.73) for the highest vs the lowest NO <sub>2</sub> levels; HR= 1.08 (95% CI 1.00, 1.16) for NO <sub>2</sub> increase (10 µg/m <sup>3</sup> ) |          |             |

| First author, year (Name of study)    | Location | Study design                      | Time recruitment /FU | N cases/cohort size or N Controls (age)                                                       | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                 | Outcome                                                       | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                         | Exposure                                                                                                                                                                                                                                                                                                                                                                      | Adjustments                                                                                                                                                   |
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|                                       |          |                                   |                      |                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                     | for the diagnosis of vascular dementia)                       |                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                               |
| Oudin et al., 2018 (Betula Study)     | Sweden   | Longitudinal (Prospective cohort) | 1993-1995/2008-2010  | 1721 (M+W)<br>191 incident cases of AD, 111 cases of VaD (>55 years, mean age 68.5±9.4 years) | Concentrations of PM <sub>2.5</sub> for 1990, 2000 and 2010 were calculated by the Swedish Meteorological and Hydrological Institute combining emission inventories from traffic and residential heating and meteorology using a wind model and Gaussian air quality model                                                                                                                          | Dementia (AD and VaD combined) (outcome assessment see above) | HR = 1.41 (95% CI 0.97; 2.04)<br><br>HR = 1.14 (95% CI 0.59; 2.23)<br><br>HR = 1.29 (95% CI 0.91; 1.83)<br><br><b>HR = 1.55 (95% CI 1.00; 2.41)</b>                                                                                  | PM <sub>2.5</sub> Highest (>0.24-1.81 µg/m <sup>3</sup> ) vs lowest (0.017-0.086 µg/m <sup>3</sup> ) quartile.<br><br>PM <sub>2.5</sub> increase (1 µg/m <sup>3</sup> )<br><br>Residential wood burning PM <sub>2.5</sub> Highest (>0.91-3.34 µg/m <sup>3</sup> ) vs lowest (0.21-0.54 µg/m <sup>3</sup> ) quartile.<br><br>PM <sub>2.5</sub> increase (1 µg/m <sup>3</sup> ) | Age, physical activity, smoking, sex, BMI, waist-hip ratio, alcohol, PM <sub>2.5</sub> from traffic exhaust, PM <sub>2.5</sub> from residential wood burning. |
| Andersson et al., 2018 (Betula Study) | Sweden   | Longitudinal (Prospective cohort) | 1993-1995/2008-2010  | 1721 (M+W)<br>191 incident cases of AD, 111 cases of VaD (>55 years, mean age 68.5±9.4 years) | Mean annual NO <sub>x</sub> concentrations were estimated at the residential address of the participants at baseline (1993-1995) using a land-use regression model derived from 4 weeklong measurements obtained from November 2009 to June 2010 at 36 sites around Umeå. Concentration grid of 50x50 m created using geocoded addresses at baseline obtained from the Swedish Population Register. | Dementia (AD and VaD combined) (outcome assessment see above) | HR = 1.41 (95% CI 0.97; 2.03)<br><br>HR = 0.95 (95% CI 0.57; 1.57)<br><br>HR = 0.99 (95% CI 0.97; 1.01)<br>No significant association was found when the model considered the interaction between noise and NO <sub>2</sub> exposure | NO <sub>x</sub> Highest (>26 µg/m <sup>3</sup> ) vs lowest (<9 µg/m <sup>3</sup> ) quartile.<br><br>Noise higher (≥55 Leq. 24 h dB) vs lower (<55 Leq. 24 h dB)<br><br>1 dB increase in noise                                                                                                                                                                                 | Age, education, physical activity, smoking, sex, BMI, waist-hip ratio, alcohol, ApoEε4, history of diabetes, hypertension and stroke.                         |

| First author, year (Name of study)              | Location   | Study design                        | Time recruitment /FU          | N cases/cohort size or N Controls (age)                                                                                                                                                              | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                       | Outcome                                                                                                                              | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                          | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Adjustments                                                                                                                 |
|-------------------------------------------------|------------|-------------------------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Carey et al, 2018 (75 Greater London practices) | London, UK | Longitudinal (Retrospective cohort) | 2005/2013 (mean FU 6.9 years) | 130,978 (M+W)<br>2181 incident cases of any dementia (848 AD, 634 VaD, 747 non specific read code) 48 patients received diagnoses for both AD and VaD, they are included in both group (50–79 years) | Average annual concentrations during 2004 of NO <sub>2</sub> , PM <sub>2.5</sub> and O <sub>3</sub> were estimated using the KCLUrban dispersion modelling system at a resolution of 20x20 m incorporating hourly meteorological measurements, empirically derived concentrations of NO-NO <sub>2</sub> -O <sub>3</sub> and PM emissions from the London Atmospheric Emissions Inventory. | All cause dementia (A first recorded diagnosis of dementia and, where specified, subgroups of AD and vascular dementia using ICD-10) | <b>HR= 1.40 (95% CI 1.12-1.74)</b><br><br><b>HR =1.15 ( 95% CI 1.04-1.28)</b><br><br>HR= 1.20 (95% CI 0.97-1.49)<br><br><b>HR =1.06 ( 95% CI 1.01-1.13)</b><br><br><b>HR= 1.26 (95% CI 1.04-1.54)</b><br><br>HR =1.08 ( 95% CI 0.99-1.18)<br><br>HR= 0.72 (95% CI 0.57-0.90)<br><br>HR =0.85 (95% CI 0.76-0.96)<br><br>HR= 1.09 (95% CI 0.94-1.26)<br><br>HR =1.00 (95% CI 0.95-1.05) | NO <sub>2</sub> Highest (>41.5 µg/m <sup>3</sup> ) vs lowest (0-31.9 µg/m <sup>3</sup> ) quintiles<br><br>NO <sub>2</sub> IQR increase (7.47 µg/m <sup>3</sup> )<br><br>PM <sub>2.5</sub> Highest (>16.3 µg/m <sup>3</sup> ) vs lowest (0-15.1 µg/m <sup>3</sup> ) quintiles<br><br>PM <sub>2.5</sub> IQR increase (0.95 µg/m <sup>3</sup> )<br><br>PM <sub>2.5</sub> (traffic) Highest (>1.75 µg/m <sup>3</sup> ) vs lowest (0-1.04 µg/m <sup>3</sup> ) quintiles<br><br>PM <sub>2.5</sub> (traffic) IQR increase (0.58 µg/m <sup>3</sup> )<br><br>O <sub>3</sub> Highest (>41.8 µg/m <sup>3</sup> ) vs lowest (0-34.7 µg/m <sup>3</sup> ) quintiles<br><br>O <sub>3</sub> IQR increase (5.56 µg/m <sup>3</sup> )<br><br>Distance to major road Highest (0-50 m) vs lowest (>250 m)<br><br>Distance to major road IQR increase (310 m) | Age, sex, ethnicity, smoking, BMI, index of Multiple Deprivation, ischaemic heart disease, stroke, diabetes, heart failure. |
|                                                 |            |                                     |                               |                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                           | AD                                                                                                                                   | <b>HR =1.50 (95% CI 1.08-2.08)</b><br><br><b>HR =1.23 (95% CI 1.07-1.43)</b>                                                                                                                                                                                                                                                                                                          | NO <sub>2</sub> Highest (>41.5 µg/m <sup>3</sup> ) vs lowest (0-31.9 µg/m <sup>3</sup> ) quintiles<br><br>NO <sub>2</sub> IQR increase (7.47 µg/m <sup>3</sup> )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                             |

| First author, year (Name of study) | Location | Study design | Time recruitment /FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                              | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Adjustments |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|---------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                      |                                         |                     | VaD     | <p><b>HR =1.42 (95% CI 1.03-1.96)</b></p> <p><b>HR =1.10 (95% CI 1.02-1.18)</b></p> <p><b>HR =1.46 (95% CI 1.08-1.98)</b></p> <p><b>HR =1.13 (95% CI 1.02-1.26)</b></p> <p>HR =0.67 (95% CI 0.48-0.94)</p> <p>HR =0.78 (95% CI 0.66-0.92)</p> <p>HR =1.01 (95% CI 0.66-1.55)</p> <p>HR =1.15 (95% CI 0.96-1.39)</p> <p>HR =0.86 (95% CI 0.57-1.30)</p> <p>HR =1.06 (95% CI 0.97-1.16)</p> | <p>PM<sub>2.5</sub> Highest (&gt;16.3 <math>\mu\text{g}/\text{m}^3</math>) vs lowest (0-15.1 <math>\mu\text{g}/\text{m}^3</math>) quintiles</p> <p>PM<sub>2.5</sub> IQR increase (0.95 <math>\mu\text{g}/\text{m}^3</math>)</p> <p>PM<sub>2.5</sub> (traffic) Highest (&gt;1.75 <math>\mu\text{g}/\text{m}^3</math>) vs lowest (0-1.04 <math>\mu\text{g}/\text{m}^3</math>) quintiles</p> <p>PM<sub>2.5</sub> (traffic) IQR increase (0.58 <math>\mu\text{g}/\text{m}^3</math>)</p> <p>O<sub>3</sub> Highest (&gt;41.8 <math>\mu\text{g}/\text{m}^3</math>) vs lowest (0-34.7 <math>\mu\text{g}/\text{m}^3</math>) quintiles</p> <p>O<sub>3</sub> IQR increase (5.6 <math>\mu\text{g}/\text{m}^3</math>)</p> <p>NO<sub>2</sub> Highest (&gt;41.5 <math>\mu\text{g}/\text{m}^3</math>) vs lowest (0-31.9 <math>\mu\text{g}/\text{m}^3</math>) quintiles</p> <p>NO<sub>2</sub> IQR increase (7.47 <math>\mu\text{g}/\text{m}^3</math>)</p> <p>PM<sub>2.5</sub> Highest (&gt;16.3 <math>\mu\text{g}/\text{m}^3</math>) vs lowest (0-15.1 <math>\mu\text{g}/\text{m}^3</math>) quintiles</p> <p>PM<sub>2.5</sub> IQR increase (0.95 <math>\mu\text{g}/\text{m}^3</math>)</p> |             |

| First author, year (Name of study) | Location | Study design | Time recruitment /FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome               | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                               | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Adjustments |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|---------------------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                      |                                         |                     | Non-specific dementia | HR = 0.99 (95% CI 0.68-1.44)<br><br>HR = 1.08 (95% CI 0.95-1.23)<br><br>HR = 0.92 (95% CI 0.59-1.43)<br><br>HR = 0.88 (95% CI 0.71-1.09)<br><br><b>HR = 1.55 ( 95% CI 1.66-2.07)</b><br><br>HR = 1.13 ( 95% CI 0.99-1.28)<br><br>HR = 1.33 ( 95% CI 0.99-1.77)<br><br>HR = 1.06 ( 95% CI 0.99-1.13)<br><br><b>HR = 1.33 (95% CI 1.00-1.75)</b><br><br>HR = 1.08 (95% CI 0.97-1.19)<br><br>HR = 0.67 (95% CI 0.50-0.90)<br><br>HR = 0.87 (95% CI 0.76-1.01) | PM <sub>2.5</sub> (traffic) Highest (>1.75 $\mu\text{g}/\text{m}^3$ ) vs lowest (0-1.04 $\mu\text{g}/\text{m}^3$ ) quintiles<br><br>PM <sub>2.5</sub> (traffic) IQR increase (0.58 $\mu\text{g}/\text{m}^3$ )<br><br>O <sub>3</sub> Highest (>41.8 $\mu\text{g}/\text{m}^3$ ) vs lowest (0-34.7 $\mu\text{g}/\text{m}^3$ ) quintiles<br><br>O <sub>3</sub> IQR increase (5.6 $\mu\text{g}/\text{m}^3$ )<br><br>NO <sub>2</sub> Highest (>41.5 $\mu\text{g}/\text{m}^3$ ) vs lowest (0-31.9 $\mu\text{g}/\text{m}^3$ ) quintiles<br><br>NO <sub>2</sub> IQR increase (7.47 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> Highest (>16.3 $\mu\text{g}/\text{m}^3$ ) vs lowest (0-15.1 $\mu\text{g}/\text{m}^3$ ) quintiles<br><br>PM <sub>2.5</sub> IQR increase (0.95 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> (traffic) Highest (>1.75 $\mu\text{g}/\text{m}^3$ ) vs lowest (0-1.04 $\mu\text{g}/\text{m}^3$ ) quintiles<br><br>PM <sub>2.5</sub> (traffic) IQR increase (0.58 $\mu\text{g}/\text{m}^3$ )<br><br>O <sub>3</sub> Highest (>41.8 $\mu\text{g}/\text{m}^3$ ) vs lowest (0-34.7 $\mu\text{g}/\text{m}^3$ ) quintiles<br><br>O <sub>3</sub> IQR increase (5.6 $\mu\text{g}/\text{m}^3$ ) |             |

| First author, year (Name of study)                                                    | Location        | Study design                        | Time recruitment /FU                          | N cases/cohort size or N Controls (age)                                                | Exposure assessment                                                                                                                                                                                                                                                                                                                                             | Outcome                                                                                                                                                                                                | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                      | Adjustments                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Lee et al., 2019 (Clinical Research Center for Dementia of South Korea study, CREDOS) | South Korea     | Longitudinal (Retrospective cohort) | 2005-2010                                     | 645 (M+W), 291 with AD, (mean age 74 $\pm$ 7.4 years)                                  | Hourly PM <sub>2.5</sub> concentrations measured in 25 monitoring sites from 2007. Daily exposure was assigned to the subjects' residential address. Measures of NO <sub>2</sub> and SO <sub>2</sub> were constructed based on daily mean concentrations, those of O <sub>3</sub> and CO were calculated using the daily maximum 8-hour mean concentrations     | MCI assessed by the Korean version of the MMSE. The global severity of disease was assessed using the Clinical Dementia Rating Sum of Box, which measures the global severity of the cognitive domains | <b>Percent change (95%CI) = 17.1(2.7, 33.5) p&lt;0.05 (significant association also considering two-pollutant models including NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>, CO)</b><br><b>Percent change (95%CI) = 20.7 (1.8, 43.1) p&lt;0.05 (significant association also considering two-pollutant models including NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>)</b><br>Percent change (95%CI) = 12.3 (-4.7, 32.3)<br><br>Percent change (95%CI) = 4.7 (-8.6, 19.9)<br><br>Percent change (95%CI) = 4.9 (-5.3, 16.3) | IQR increase of PM <sub>2.5</sub> (8.3 $\mu$ g/m <sup>3</sup> 1-month average)<br><br>IQR increase of PM <sub>2.5</sub> (7.9 $\mu$ g/m <sup>3</sup> 2-month average)<br><br>IQR increase of PM <sub>2.5</sub> (7.4 $\mu$ g/m <sup>3</sup> 3-month average)<br>IQR increase of PM <sub>2.5</sub> (5.9 $\mu$ g/m <sup>3</sup> 6-month average)<br>IQR increase of PM <sub>2.5</sub> (3.9 $\mu$ g/m <sup>3</sup> 1-year average) | Age, sex, visit number, visit year, education, smoking, alcohol consumption, diabetes, hypertension, stroke, cardiovascular diseases, clinical dementia rating-sum of boxes score, deep white matter hyperintensity, periventricular white matter hyperintensity, season, 8-day moving average temperature and rainfall, proportion of medical personnel, proportion of green space and economic environment satisfaction. |
| Ilango et al., 2020 (Ontario Population Health and Environment Cohort, ONPHEC)        | Ontario, Canada | Longitudinal (Cohort)               | 1996-2001 (CVD FU)<br>2001/2013 (dementia FU) | 34 391 (M+W) (mean age 60.19 $\pm$ 10.56 years)<br><br>2559 incident cases of dementia | Chronic exposure to ambient NO <sub>2</sub> and PM <sub>2.5</sub> , was estimated by mean measurements of NO <sub>2</sub> and PM <sub>2.5</sub> at a spatial resolution of about 1 x 1km for each year between 1993 and 2013. Running averages of pollutant measurements over the 3 years leading up to the time of baseline survey completion were calculated. | Dementia (all causes)<br><br>(health administrative databases with a validated algorithm was used to ascertain incident diagnosis of dementia)                                                         | HR=1.10 (95% CI 0.99, 1.19)<br><br>HR=1.29 (95% CI 0.99, 1.64)                                                                                                                                                                                                                                                                                                                                                                                                                                                              | NO <sub>2</sub> increase (5 ppb)<br><br>PM <sub>2.5</sub> increase (10 $\mu$ g/m <sup>3</sup> )                                                                                                                                                                                                                                                                                                                               | Age, sex, education, marital status, income quintile, smoking status, body mass index, physical activity, rural residence and northern region; area level: recent immigrants, unemployment and education.                                                                                                                                                                                                                  |



| First author, year (Name of study) | Location | Study design        | Time recruitment /FU | N cases/cohort size or N Controls (age)                                                                            | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Outcome                                                                                                                                                                                                                                                                          | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                         | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Adjustments                                                                                                                                                                                                                                                                                                 |
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| Li et al, 2019                     | Taiwan   | Nested case-control | 2005-2013            | 831 (M+W) incident cases of VaD (mean age 79.08 $\pm$ 7.14 years) and 3324 (M+W) (mean age 79.08 $\pm$ 7.13 years) | Ambient monitoring data of PM <sub>10</sub> , SO <sub>2</sub> , O <sub>3</sub> , CO and NO <sub>2</sub> were obtained from 76 fixed site air quality monitoring stations (AQMSs) supervised by the Taiwan Air Quality Monitoring Network between 1998 and 2013. The measurement of various air pollutants at the monitoring stations was performed as follows: PM <sub>10</sub> through the beta-ray absorption method, SO <sub>2</sub> through ultra-violet fluorescence, O <sub>3</sub> through a combination of microprocessor control with ultra-violet photometry, CO through a nondispersion cross-modulation infrared analysis method and NO <sub>2</sub> through chemiluminescence. Every individual's mean was retrospectively assessed by daily mean exposure to the air pollutants during three periods: 3, 5, and 7 years before VaD diagnosis. | VaD (exposure 5 years before the diagnosis)<br><br>(VaD cases and controls were selected from a cohort of one million beneficiaries of Taiwan's National Health Insurance program, NHIRD. incident VaD according to the ICD, Ninth Revision, Clinical Modification code 290.4x). | OR=0.86 (95% CI 0.61, 1.22)<br><br>OR=0.89 (95% CI 0.72, 1.10)<br><br>OR=0.99 (95% CI 0.98, 1.01)<br><br>OR=0.98 (95% CI 0.67, 1.44)<br><br>OR=0.93 (95% CI 0.79, 1.11)<br><br>OR=0.95 (95% CI 0.83, 1.08)<br><br>OR=0.83 (95% CI 0.60, 1.16)<br><br>OR= 1.02 (95% CI 0.84, 1.24)<br><br>OR=1.01 (95% CI 0.94, 1.08)<br><br><b>OR=2.22 (95% CI 1.35, 3.65)</b><br><br>OR=1.28 (95% CI 0.98, 1.66)<br><br>OR=1.05 (95% CI 0.99, 1.11) | PM <sub>10</sub> ( $\mu\text{g}/\text{m}^3$ ) >75 <sup>th</sup> percentile vs <25 <sup>th</sup> percentile<br><br>PM <sub>10</sub> IQR increase (19.77 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10</sub> increase (10 $\mu\text{g}/\text{m}^3$ )<br><br>SO <sub>2</sub> (ppb) >75 <sup>th</sup> percentile vs <25 <sup>th</sup> percentile<br><br>SO <sub>2</sub> IQR increase (1.26 ppb)<br><br>SO <sub>2</sub> increase (1 ppb)<br><br>O <sub>3</sub> (ppb) >75 <sup>th</sup> percentile vs <25 <sup>th</sup> percentile<br><br>O <sub>3</sub> IQR increase (3.00 ppb)<br><br>O <sub>3</sub> increase (1 ppb)<br><br>NO <sub>2</sub> (ppb) >75 <sup>th</sup> percentile vs <25 <sup>th</sup> percentile<br><br>NO <sub>2</sub> IQR increase (4.64 ppb)<br><br>NO <sub>2</sub> increase (1 ppb) | Age, sex, monthly income, urbanisation, Township-specific median family annual income quartiles, History of comorbidities (Hypertension, Diabetes, Hyperlipidemia, Cerebrovascular disease, COPD), Charlson comorbidity index, PM <sub>10</sub> , SO <sub>2</sub> , O <sub>3</sub> , NO <sub>2</sub> and CO |

| First author, year (Name of study) | Location | Study design                      | Time recruitment /FU | N cases/cohort size or N Controls (age)                                                      | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                  | Outcome                                                        | HR, OR, RR, $\beta$ (95% CI)                                                                            | Exposure                                                                                                                                                                                                                                                         | Adjustments |
|------------------------------------|----------|-----------------------------------|----------------------|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |                                   |                      |                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                | OR=1.17 (95% CI 0.76, 1.79)<br><br>OR=1.12 (95% CI 0.99, 1.28)<br><br>OR=1.78 (95% CI 0.56, 5.61)       | CO (ppm) >75 <sup>th</sup> percentile vs <25 <sup>th</sup> percentile<br><br>CO IQR increase (0.18 ppm)<br><br>CO increase (1 ppm)                                                                                                                               |             |
| (Oudin et al. 2019) (Betula Study) | Sweden   | Longitudinal (Prospective cohort) | 1993-1995/2008-2010  | 1567 (M+W) 173 incident cases of AD, 102 cases of VaD (55-85 years years, mean age 69 years) | Mean annual NO <sub>x</sub> concentrations were estimated at the residential address of the participants at baseline (1993-1995) using a land-use regression model derived from 4 week-long measurements obtained from November 2009 to June 2010 at 36 sites around Umea. Concentration grid of 50x50 m created using geocoded addresses at baseline obtained from the Swedish Population Register. | Dementia (AD and VaD combined) (outcome assessment see above)  | <b>HR = 1.41 (95% CI 1.01; 1.98)</b><br><br>HR = 1.03 (95% CI 0.97; 1.10)                               | NO <sub>x</sub> Highest (>26 µg/m <sup>3</sup> ) vs lowest (4.8-9 µg/m <sup>3</sup> ) quartile.<br><br>NO <sub>x</sub> increase (10 µg/m <sup>3</sup> )                                                                                                          | Age, ApoEε4 |
|                                    |          |                                   |                      |                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                      | AD                                                             | HR = 1.53 (95% CI 0.99; 2.36)<br><br>HR = 1.04 (95% CI 0.96; 1.13)                                      | NO <sub>x</sub> Highest (>26 µg/m <sup>3</sup> ) vs lowest (4.8-9 µg/m <sup>3</sup> ) quartile.<br><br>NO <sub>x</sub> increase (10 µg/m <sup>3</sup> )                                                                                                          |             |
|                                    |          |                                   |                      |                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                      | Dementia (AD and VaD combined) ApoEε4 NO<br><br><br>ApoEε4 YES | HR = 1.40 (95% CI 0.90; 2.17)<br><br>HR = 1.03 (95% CI 0.96; 1.12)<br><br>HR = 1.44 (95% CI 0.84; 2.47) | NO <sub>x</sub> Highest (>26 µg/m <sup>3</sup> ) vs lowest (4.8-9 µg/m <sup>3</sup> ) quartile.<br><br>NO <sub>x</sub> increase (10 µg/m <sup>3</sup> )<br><br>NO <sub>x</sub> Highest (>26 µg/m <sup>3</sup> ) vs lowest (4.8-9 µg/m <sup>3</sup> ) x quartile. | Age         |

| First author, year (Name of study) | Location | Study design                      | Time recruitment /FU                                 | N cases/cohort size or N Controls (age)                                                | Exposure assessment                                                                                                                                                                                                                               | Outcome                                                                                                                                                                         | HR, OR, RR, $\beta$ (95% CI)                                                                                                    | Exposure                                                                                                                                                                                                                      | Adjustments                                                                                                                                                                                                                                                                                                              |
|------------------------------------|----------|-----------------------------------|------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |          |                                   |                                                      |                                                                                        |                                                                                                                                                                                                                                                   |                                                                                                                                                                                 | HR = 1.02 (95% CI 0.92; 1.14)                                                                                                   | NO <sub>x</sub> increase (10 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                          |
|                                    |          |                                   |                                                      |                                                                                        |                                                                                                                                                                                                                                                   | AD<br>ApoE $\epsilon$ 4 NO                                                                                                                                                      | HR = 1.72 (95% CI 0.94; 3.15)<br><br>HR = 1.06 (95% CI 0.96; 1.17)                                                              | NO <sub>x</sub> Highest (>26 $\mu\text{g}/\text{m}^3$ ) vs lowest (4.8-9 $\mu\text{g}/\text{m}^3$ ) quartile.<br><br>NO <sub>x</sub> increase (10 $\mu\text{g}/\text{m}^3$ )                                                  |                                                                                                                                                                                                                                                                                                                          |
|                                    |          |                                   |                                                      |                                                                                        |                                                                                                                                                                                                                                                   | ApoE $\epsilon$ 4 YES                                                                                                                                                           | HR = 1.41 (95% CI 0.75; 2.66)<br><br>HR = 1.01 (95% CI 0.89; 1.14)                                                              | NO <sub>x</sub> Highest (>26 $\mu\text{g}/\text{m}^3$ ) vs lowest (4.8-9 $\mu\text{g}/\text{m}^3$ ) quartile.<br><br>NO <sub>x</sub> increase (10 $\mu\text{g}/\text{m}^3$ )                                                  |                                                                                                                                                                                                                                                                                                                          |
|                                    |          |                                   |                                                      |                                                                                        |                                                                                                                                                                                                                                                   |                                                                                                                                                                                 |                                                                                                                                 |                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                          |
| Bowe et al, 2019                   | USA      | Longitudinal (prospective cohort) | 2006/2016 (median FU 10 years, range 6.8-10.2 years) | 4,522,160 US veterans (M+W) (median [interquartile range] age, 64.1 [55.7-75.5] years) | Modeled PM <sub>2.5</sub> data were obtained from the US Environmental Protection Agency Community Multiscale Air Quality Modeling System. Exposure to PM <sub>2.5</sub> in 2006 was linked with a veteran's county of residence at the baseline. | Burden of death due to dementia (Numbers of death, according to ICD-10 codes, were obtained from the Centers for Disease Control and Prevention WONDER online database in 2017) | Deaths (95% UI)<br>19851.5 (14420.6-31621.4)<br><br><br><br><br><br><br><br><br><br>Incidence rates<br>0.70 (95% CI, 0.68-0.72) | PM <sub>2.5</sub> IQR increase (0.072 $\mu\text{g}/\text{m}^3$ )<br><br><br><br><br><br><br><br><br><br>PM <sub>2.5</sub> Highest (13.9-20.1 $\mu\text{g}/\text{m}^3$ ) vs lowest (4.8-10 $\mu\text{g}/\text{m}^3$ ) quartile | Age, sex, race, smoking, regional characteristics of population density, Area deprivation Index, percentage of population living in a rural area, percentage with limited access to healthy food, with adequate access to exercise opportunities and adults reporting excessive drinking.<br><br>Age, race, sex, smoking |

| First author, year (Name of study) | Location | Study design | Time recruitment /FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome | HR, OR, RR, $\beta$ (95% CI)            | Exposure                                                            | Adjustments |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|---------------------|---------|-----------------------------------------|---------------------------------------------------------------------|-------------|
|                                    |          |              |                      |                                         |                     |         | Hazard Rates<br>1.09 (95% CI 1.06-1.12) | PM <sub>2.5</sub> IQR increase<br>(0.072 $\mu\text{g}/\text{m}^3$ ) |             |

### Abbreviations

FU, follow-up; M, men; W, women, HR, hazard ratio; OR, odds ratio; RR, relative risk, CI, confidence interval; UI, uncertainty interval; MMSE, Mini Mental State Examination; AD: Alzheimer's disease, VaD: Vascular dementia; BMI, body mass index; IQR, interquartile range; APOE, apolipoprotein E; CVD, cardiovascular disease; ICD, International Classification of Disease; COPD, chronic obstructive pulmonary disease.

**Table 3.10. Summary of characteristics and outcomes of studies assessing the effect of air pollution on hospital admissions due to Alzheimer's disease and dementia included in literature review**

| First author, year (Name of study) | Location                 | Time recruitment/FU             | N cases/cohort size or N Controls (age)                                                                      | Exposure assessment                                                                                                                                                                                                                                                                                                            | Outcome                                                                                                             | HR, OR, RR, $\beta$ (95% CI)                                                                                                                      | Exposure                                                                                                                                                                                     | Adjustments                                                                                 |
|------------------------------------|--------------------------|---------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Kioumourtoglou et al., 2016        | USA                      |                                 | 9.8 M ( $\geq 65$ years)                                                                                     | PM <sub>2.5</sub> Levels were obtained from the U.S. Environmental Protection Agency's (EPA) Air Quality System (AQS) database (U.S. EPA 2013), within each city for the period of 1999–2010. Each participant was assigned annual (1 January–31 December) city-average PM <sub>2.5</sub> mass concentrations                  | Dementia admission<br>AD admission<br>Dementia admission<br>AD admission                                            | HR=1.08 (95% CI 1.05; 1.11)<br>HR = 1.15 (95% CI 1.11; 1.19)<br>HR = 2.00 (95% CI 1.70; 2.35)<br>HR = 1.46 (95% CI 1.29; 1.66)                    | PM <sub>2.5</sub> (1 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> (5 $\mu\text{g}/\text{m}^3$ )                                                                                       | /                                                                                           |
| Culqui et al., 2017                | Spain (Madrid)           | 2001–2009                       | 754,005 (M+W) ( $>60$ years), 1183 AD admission                                                              | Daily pollutant levels were obtained from 27 monitoring stations in Madrid                                                                                                                                                                                                                                                     | Daily Alzheimer-related hospital admissions                                                                         | RR = 1.38 (95% CI 1.15; 1.65), lag 2                                                                                                              | PM <sub>2.5</sub> short-term IQR increase (20 $\mu\text{g}/\text{m}^3$ )                                                                                                                     | /                                                                                           |
| Linares et al., 2017               | Spain (Madrid)           | 2001–2009                       | 754,005 (M+W) ( $>60$ years), 1175 admission for dementia ( $\geq 60$ years)                                 | Daily pollutant levels were obtained from 27 monitoring stations in Madrid                                                                                                                                                                                                                                                     | Daily Dementia related Emergency (ICD-9:290-294)                                                                    | RR = 1.19 (95% CI 1.09; 1.30), lag 1<br>RR = 1.15 (95% CI 1.11; 1.20), lag 0<br>RR = 1.09 (95% CI 1.04; 1.15), lag 5                              | O <sub>3</sub> short-term IQR increase (10 $\mu\text{g}/\text{m}^3$ )                                                                                                                        | /                                                                                           |
| Qiu et al., 2019                   | China (Sichuan Province) | 2015–2016                       | 920 (M+W) with dementia (all ages)                                                                           | Hourly PM <sub>2.5</sub> , PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> , CO and O <sub>3</sub> levels obtained from 6 monitoring sites. Daily exposure levels of PM <sub>2.5</sub> , PM <sub>10</sub> , NO <sub>2</sub> , CO and O <sub>3</sub> , as well as 8-hour mean O <sub>3</sub> concentration were calculated | Hospital admissions for Dementia (data obtained from electronic hospitalisation reports, ICD-10, codes F00-F03)     | Percentage change=0.86 (95% CI -1.59, 3.36)<br><br>Percentage change=0.48 (95% CI -1.06, 2.04)<br><br>Percentage change=0.79 (95% CI -2.83, 4.56) | PM <sub>2.5</sub> IQR increase (10 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>10</sub> IQR increase (10 $\mu\text{g}/\text{m}^3$ )<br>PM <sub>c</sub> IQR increase (10 $\mu\text{g}/\text{m}^3$ ) | Time trend, relative humidity, temperature, wind speed, precipitation and sunshine duration |
| Zanobetti et al., 2014             | 121 USA communities      | 1999–2010 Longitudinal (cohort) | $\geq 65$ years (M+W) 2001/2013 or Up to 100 years of age, death, migration or hospitalisation for dementia. | Daily PM <sub>2.5</sub> levels were obtained by US EPA. Community daily mean PM <sub>2.5</sub> were computed using an algorithm that accounts for the different monitor-specific means and variances.                                                                                                                          | Hospitalisation for AD (ICD-9 code 331.0) (Medicare claims records from Medicare Provider Analysis and review file) | Percent increase= 0.20 (95%CI -1.26, 1.69)                                                                                                        | PM <sub>2.5</sub> increase (10 $\mu\text{g}/\text{m}^3$ ) in the 2 days average PM <sub>2.5</sub>                                                                                            | Temperature                                                                                 |

| First author, year (Name of study) | Location     | Time recruitment/FU | N cases/cohort size or N Controls (age)                                                                                                             | Exposure assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Adjustments |
|------------------------------------|--------------|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |              |                     |                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Hospitalisation for dementia (ICD-9 code 290)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Percent increase= 0.92 (95%CI -0.44, 2.30)                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |             |
| Cerza et al., 2019                 | Italy (Rome) | Longitudinal Study  | 350,844 (M+W), 21,548 first hospitalisations for dementia (7497 for VaD, 7669 for AD and 7833 for SD) mean age 74.5 $\pm$ 6.8 years, 65-100 years). | Land Use Regression (LUR) models were used to assess pollutant exposure at the residential address at the time of inclusion. Particulate matter (PM <sub>10</sub> , PM <sub>2.5</sub> and PM <sub>coarse</sub> ) was measured in 20 sites, and nitrogen oxides (NO <sub>x</sub> and NO <sub>2</sub> ) were measured in 40 sites in three two-week periods during 2010. Based on a multilinear regression model, an equation for each pollutant was identified to estimate the pollutant concentration at each individual address. Summer daily O <sub>3</sub> (8 h) exposure was estimated by using a Flexible Air quality Regional Model, a three-dimensional Eulerian model used to simulate the transport and multiphase chemistry of pollutants in the atmosphere. As a proxy measure of exposure to traffic, the distance between residential addresses and the nearest high-traffic road (HTR; roads with >10,000 vehicles per day) was analysed. Distance (m) was measured using ArcGIS software. | Dementia hospitalisations(over all) (dementia hospitalisations were identified from the Hospital Discharge Registry (HDR). From the HDR subjects hospitalised for the first time during the FU with a primary or a secondary diagnosis of Jakob-Creutzfeldt disease (ICD9-CM: 046.1), SD (ICD9-CM: 290.0, 290.2, 290.3), pre-SD (ICD9-CM: 290.1), VaD (ICD9-CM: 290.4), persistent mental disorders due to conditions classified elsewhere (ICD9-CM: 294), AD (ICD9-CM: 331.0), Pick's disease (ICD9-CM: 331.1), or Dementia with Lewy bodies (ICD9-CM: 331.82) | <b>HR=1.00 (95% CI 0.98, 1.03)</b><br><b>HR=0.98 (95% CI 0.96, 1.00)</b><br><b>HR=0.99 (95% CI 0.96, 1.02)</b><br><b>HR= 1.00 (95% CI 0.98, 1.03)</b><br><b>HR= 0.97 (95% CI 0.96, 0.99)</b><br><b>HR= 1.01 (95% CI 1.00, 1.02)</b><br><b>HR= 1.06 (95% CI 1.03, 1.08)</b><br><br><b>HR=1.01 (95% CI 0.97 1.06)</b><br><b>ptrend= 0.827</b> | PM <sub>10</sub> increase (10 $\mu$ g/m <sup>3</sup> )<br>PM <sub>coarse</sub> increase (5 $\mu$ g/m <sup>3</sup> )<br>PM <sub>2.5</sub> increase (5 $\mu$ g/m <sup>3</sup> )<br>PM <sub>2.5abs</sub> increase (10 <sup>-5</sup> /m)<br>NO <sub>2</sub> increase (10 $\mu$ g/m <sup>3</sup> )<br>NO <sub>x</sub> increase (20 $\mu$ g/m <sup>3</sup> )<br>O <sub>3</sub> increase (10 $\mu$ g/m <sup>3</sup> )<br>Distance to high traffic road (fifth quintile<50 m vs first quintile >300 m) | Temperature |
|                                    |              |                     |                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | VaD hospitalisations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>HR=1.06 (95% CI 1.02, 1.10)</b><br><b>HR=1.06 (95% CI 1.03, 1.09)</b><br><b>HR=1.07 (95% CI 1.01, 1.12)</b>                                                                                                                                                                                                                              | PM <sub>10</sub> increase (10 $\mu$ g/m <sup>3</sup> )<br>PM <sub>coarse</sub> increase (5 $\mu$ g/m <sup>3</sup> )<br>PM <sub>2.5</sub> increase (5 $\mu$ g/m <sup>3</sup> )                                                                                                                                                                                                                                                                                                                  | Temperature |
|                                    |              |                     |                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |             |

| First author, year (Name of study) | Location | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome             | HR, OR, RR, $\beta$ (95% CI)                                                                                                                                                                                                                                                                                                                | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Adjustments |
|------------------------------------|----------|---------------------|-----------------------------------------|---------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |                     |                                         |                     |                     | <b>HR=1.15 (95% CI 1.10, 1.19)</b><br><br><b>HR=1.05 (95% CI 1.03, 1.07)</b><br><br><b>HR=1.08 (95% CI 1.06, 1.10)</b><br><br>HR=1.02 (95% CI 0.98, 1.06)<br><br><b>HR=1.17 (95% CI 1.10, 1.24)</b><br><b>p trend=&lt;0.001</b>                                                                                                             | PM <sub>2.5asb</sub> increase (10 <sup>-5</sup> /m)<br><br>NO <sub>2</sub> increase (10 µg/m <sup>3</sup> )<br><br>NO <sub>x</sub> increase (20 µg/m <sup>3</sup> )<br><br>O <sub>3</sub> increase (10 µg/m <sup>3</sup> )<br><br>Distance to high traffic road (fifth quintile<50 m vs first quintile >300 m)                                                                                                                                                        |             |
|                                    |          |                     |                                         |                     | AD hospitalisations | <b>HR=0.95 (95% CI 0.91, 0.99)</b><br><br><b>HR=0.91 (95% CI 0.87, 0.94)</b><br><br><b>HR=0.91 (95% CI 0.85, 0.97)</b><br><br><b>HR=0.91 (95% CI 0.86, 0.96)</b><br><br><b>HR=0.91 (95% CI 0.89, 0.94)</b><br><br><b>HR=0.96 (95% CI 0.94, 0.98)</b><br><br>HR=0.98 (95% CI 0.95, 1.02)<br><br>HR=0.97 (95% CI 0.90, 1.04)<br>p trend=0.206 | PM <sub>10</sub> increase (10 µg/m <sup>3</sup> )<br><br>PM <sub>coarse</sub> increase (5 µg/m <sup>3</sup> )<br><br>PM <sub>2.5</sub> increase (5 µg/m <sup>3</sup> )<br><br>PM <sub>2.5asb</sub> increase (10 <sup>-5</sup> /m)<br><br>NO <sub>2</sub> increase (10 µg/m <sup>3</sup> )<br><br>NO <sub>x</sub> increase (20 µg/m <sup>3</sup> )<br><br>O <sub>3</sub> increase (10 µg/m <sup>3</sup> )<br><br>Distance to high traffic road (fifth quintile<50 m vs | Temperature |

| First author, year (Name of study) | Location | Time recruitment/FU | N cases/cohort size or N Controls (age) | Exposure assessment | Outcome             | HR, OR, RR, $\beta$ (95% CI)                               | Exposure                                                                     | Adjustments |
|------------------------------------|----------|---------------------|-----------------------------------------|---------------------|---------------------|------------------------------------------------------------|------------------------------------------------------------------------------|-------------|
|                                    |          |                     |                                         |                     | SD hospitalisations | HR=0.98 (95% CI 0.94, 1.02)                                | first quintile >300 m)                                                       |             |
|                                    |          |                     |                                         |                     |                     | HR=0.97 (95% CI 0.93, 1.00)                                | PM <sub>10</sub> increase (10 $\mu\text{g}/\text{m}^3$ )                     | Temperature |
|                                    |          |                     |                                         |                     |                     | HR=0.98 (95% CI 0.92, 1.03)                                | PM <sub>coarse</sub> increase (5 $\mu\text{g}/\text{m}^3$ )                  |             |
|                                    |          |                     |                                         |                     |                     | <b>HR=0.93 (95% CI 0.88, 0.98)</b>                         | PM <sub>2.5</sub> increase (5 $\mu\text{g}/\text{m}^3$ )                     |             |
|                                    |          |                     |                                         |                     |                     | <b>HR=0.96 (95% CI 0.94, 0.98)</b>                         | PM <sub>2.5asb</sub> increase (10 <sup>-5</sup> /m)                          |             |
|                                    |          |                     |                                         |                     |                     | HR=0.99 (95% CI 0.97, 1.01)                                | NO <sub>2</sub> increase (10 $\mu\text{g}/\text{m}^3$ )                      |             |
|                                    |          |                     |                                         |                     |                     | <b>HR=1.19 (95% CI 1.15, 1.24)</b>                         | NO <sub>x</sub> increase (20 $\mu\text{g}/\text{m}^3$ )                      |             |
|                                    |          |                     |                                         |                     |                     | <b>HR=0.90 (95% CI 0.83, 0.97)</b><br><b>p trend=0.001</b> | O <sub>3</sub> increase (10 $\mu\text{g}/\text{m}^3$ )                       |             |
|                                    |          |                     |                                         |                     |                     |                                                            | Distance to high traffic road (fifth quintile<50 m vs first quintile >300 m) |             |

### Abbreviations

FU, follow-up; M; men; W, women; HR, hazard ratio; OR, odds ratio; RR, relative risk, CI, confidence interval; AD: Alzheimer's disease; IQR, interquartile range.



**Table 3.11. Summary of characteristics and outcomes of studies assessing the effect of air pollution on neuroimaging included in literature review**

| First author, year (Name of study)               | Location         | Study design    | Time recruitment /FU | N cases/cohort size or N Controls (age)             | Exposure                                                                                                                                                                                                                                                                                                                                             | Outcome                                    | HR, OR, RR, $\beta$ (95% CI), $\beta$ ( $\pm$ standard errors)                                                                       | Exposure                                                                                                         | Adjustments                                                                                                                                                                                                                                                                                                  |
|--------------------------------------------------|------------------|-----------------|----------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wilker et al., 2015 (Framingham Offspring Study) | New England, USA | Cross-sectional | 1998–2001            | 943 (M+W) ( $\geq 60$ years, median 68 IQR 9 years) | Participant primary addresses based on clinical records were geocoded using ArcGIS 10. Distance to the nearest A1, A2, or A3 road (US Census Features Class) was determined for each subject home address at the time of the test. Residential PM <sub>2.5</sub> exposures at home address were calculated using spatio-temporal modelled estimates. | Hippocampal Volume                         | $\beta = 0.005$ (95% CI $-0.004, 0.015$ )<br>$\beta = 0.003$ (95% CI $-0.008, 0.002$ )<br>$\beta = 0.0004$ (95% CI $-0.005, 0.005$ ) | Distance to major road <50 m vs 400 to <1000 m<br>Log (367 m)<br>PM <sub>2.5</sub> (2 $\mu\text{g}/\text{m}^3$ ) | Age, sex, time from exam 7 to MRI, median household income, date of MRI, smoking status, pack-years smoked, education, alcohol, sine and cosine of MRI date to account for seasonal trends, log (homocysteine, systolic blood pressure, diabetes, CVD, history of AF, hypertension medications and obesity). |
|                                                  |                  |                 |                      |                                                     |                                                                                                                                                                                                                                                                                                                                                      | Log (WM Hyperintensities)                  | $\beta = -0.16$ (95% CI $-0.34, 0.02$ )<br>$\beta = 0.09$ (95% CI $-0.0004, 0.18$ )<br>$\beta = -0.08$ (95% CI $-0.17, 0.01$ )       | Distance to major road <50 m vs 400 to <1000 m<br>Log (367 m)<br>PM <sub>2.5</sub> (2 $\mu\text{g}/\text{m}^3$ ) |                                                                                                                                                                                                                                                                                                              |
|                                                  |                  |                 |                      |                                                     |                                                                                                                                                                                                                                                                                                                                                      | Total Cerebral Brain Volume                | $\beta = 0.09$ (95% CI $-0.42, 0.60$ )<br>$\beta = -0.10$ (95% CI $-0.36, 0.16$ )<br>$\beta = -0.26$ (95% CI $-0.53, 0.004$ )        | Distance to major road <50 m vs 400 to <1000 m<br>Log (367 m)<br>PM <sub>2.5</sub> (2 $\mu\text{g}/\text{m}^3$ ) |                                                                                                                                                                                                                                                                                                              |
|                                                  |                  |                 |                      |                                                     |                                                                                                                                                                                                                                                                                                                                                      | Extensive WM Hyperintensity Volume for Age | OR= 0.94 (95% CI 0.53, 1.67)<br>OR= 1.09 (95% CI 0.81, 1.47)<br>OR= 0.94 (95% CI 0.70, 1.26)                                         | Distance to major road <50 m vs 400 to <1000 m<br>Log (367 m)<br>PM <sub>2.5</sub> (2 $\mu\text{g}/\text{m}^3$ ) |                                                                                                                                                                                                                                                                                                              |
|                                                  |                  |                 |                      |                                                     |                                                                                                                                                                                                                                                                                                                                                      | Covert Brain Infarcts                      | OR= 1.29 (95% CI 0.70, 2.36)<br>OR= 1.02 (95% CI 0.75, 1.37)                                                                         | Distance to major road <50 m vs 400 to <1000 m<br>Log (367 m)                                                    |                                                                                                                                                                                                                                                                                                              |

| First author, year (Name of study)                                                                  | Location           | Study design    | Time recruitment /FU | N cases/cohort size or N Controls (age)             | Exposure                                                                                                                                                                                                                                                                                                                                            | Outcome                                                                                                         | HR, OR, RR, $\beta$ (95% CI), $\beta$ ( $\pm$ standard errors)                                                                                                                                | Exposure                                                                                                                                                                                                                                                                        | Adjustments                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------|--------------------|-----------------|----------------------|-----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                     |                    |                 |                      |                                                     |                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                 | <b>OR= 1.37 (95% CI 1.02, 1.85)</b>                                                                                                                                                           | PM <sub>2.5</sub> (2 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                           |
| Wilker et al., 2016 (Massachusetts Alzheimer's Disease Research Centre, MADRC, Longitudinal Cohort) | Massachusetts, USA | Cross-sectional | 2004-2010            | 236 (M+W) (Median 74 years, interquartile 12 years) | Participant primary addresses based on clinical records were geocoded using ArcGIS 10. Distance to the nearest A1, A2, or A3 road (US Census Features Class) was determined for each subject home address at the time of the test. Residential PM <sub>2.5</sub> exposures at home address were calculated using spatio-temporal modelled estimates | Brain Parenchymal fraction (%)                                                                                  | $\beta$ = 0.04 (95% CI -0.46, 0.53)<br><br>$\beta$ = -0.06 (95% CI -0.59, 0.47)                                                                                                               | Distance to major road <50 m vs 400 to <1000 m<br><br>PM <sub>2.5</sub> (2 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                           | Age, age squared, MRI date, sex, education, quartiles of census block group median household income, smoking status, sine and cosine of the day of year, diagnosis (dementia or other), diabetes, statin, hypertension and stroke history |
|                                                                                                     |                    |                 |                      |                                                     |                                                                                                                                                                                                                                                                                                                                                     | Log(WM Hyperintensities (cc))                                                                                   | $\beta$ = -0.13 (95% CI -0.31, 0.04)<br><br><b><math>\beta</math>= -0.19 (95% CI -0.38, -0.01)</b>                                                                                            | Distance to major road <50 m vs 400 to <1000 m<br><br>PM <sub>2.5</sub> (2 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                           |                                                                                                                                                                                                                                           |
|                                                                                                     |                    |                 |                      |                                                     |                                                                                                                                                                                                                                                                                                                                                     | Microbleed presence                                                                                             | OR= 0.89 (95% CI 0.55, 1.43)<br><br>OR= 0.81 (95% CI 0.49, 1.35)                                                                                                                              | Distance to major road <50 m vs 400 to <1000 m<br><br>PM <sub>2.5</sub> (2 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                           |                                                                                                                                                                                                                                           |
| Chen et al., 2017c and Chen, 2015 (Women's Health Initiative Memory Study (WHIMS))                  | USA                | Cross-sectional | 2005-2006            | 1,403 (W) ( $\geq 65$ years)                        | Residence-specific yearly exposures to PM <sub>2.5</sub> were estimated using a BME spatio-temporal model of annual monitoring data (1999–2007) recorded in the U.S. EPA Air Quality System (AQS). Annual exposures (1996–2005) to diesel PM (DPM) were assigned to                                                                                 | Total brain volume<br>Normal brain Volume<br>Association area<br>Frontal lobe<br>Parietal lobe<br>Temporal lobe | <b>P for trend= &lt;0.0001</b><br><b>P for trend= &lt;0.0001</b><br><b>P for trend= &lt;0.0001</b><br><b>P for trend= &lt;0.0001</b><br><b>P for trend= 0.02</b><br><b>P for trend= 0.009</b> | PM <sub>2.5</sub> quartiles:<br>1 <sup>st</sup> : (5.75-10.67 $\mu\text{g}/\text{m}^3$ )<br>2 <sup>nd</sup> : (10.67-12.24 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (12.24-14.16 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (14.16-22.18 $\mu\text{g}/\text{m}^3$ ) | Geographic area, age, race, SES, smoking, alcohol, physical activity, hormone therapy, depressive symptoms, BMI, hypertension, diabetes mellitus, hypercholesterolemia, CVD histories                                                     |
|                                                                                                     |                    |                 |                      |                                                     |                                                                                                                                                                                                                                                                                                                                                     | Ventricle<br>Total GM<br>Association cortex<br>Frontal GM<br>Parietal GM<br>Temporal GM                         | P for trend= 0.16<br>P for trend= 0.19<br>P for trend= 0.24<br>P for trend= 0.30<br>P for trend= 0.25<br>P for trend= 0.28                                                                    | PM <sub>2.5</sub> quartiles:<br>1 <sup>st</sup> : (5.75-10.67 $\mu\text{g}/\text{m}^3$ )<br>2 <sup>nd</sup> : (10.67-12.24 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (12.24-14.16 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (14.16-22.18 $\mu\text{g}/\text{m}^3$ ) |                                                                                                                                                                                                                                           |
|                                                                                                     |                    |                 |                      |                                                     |                                                                                                                                                                                                                                                                                                                                                     | Hippocampus                                                                                                     | P for trend= 0.76                                                                                                                                                                             | PM <sub>2.5</sub> quartiles:<br>1 <sup>st</sup> : (5.75-10.67 $\mu\text{g}/\text{m}^3$ )<br>2 <sup>nd</sup> : (10.67-12.24 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (12.24-14.16 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (14.16-22.18 $\mu\text{g}/\text{m}^3$ ) |                                                                                                                                                                                                                                           |

| First author, year (Name of study) | Location | Study design | Time recruitment /FU | N cases/cohort size or N Controls (age) | Exposure                                                                                                                                                                                                                                                                 | Outcome                                                                                                                      | HR, OR, RR, $\beta$ (95% CI), $\beta$ ( $\pm$ standard errors)                                                                                                                                                                                                                                                                                         | Exposure                                                                                                                                                                                                                                                                        | Adjustments |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|                                    |          |              |                      |                                         | each residential census tract in a nationwide spatio-temporal mapping, based on a generalised additive model (GAM), to conduct census tract specific temporal interpolation of DPM on-road estimates given by the U.S. EPA National-Scale Air Toxics Assessment Program. | Basal ganglia                                                                                                                | P for trend= 0.91                                                                                                                                                                                                                                                                                                                                      | PM <sub>2.5</sub> quartiles:<br>1 <sup>st</sup> : (5.75-10.67 $\mu\text{g}/\text{m}^3$ )<br>2 <sup>nd</sup> : (10.67-12.24 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (12.24-14.16 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (14.16-22.18 $\mu\text{g}/\text{m}^3$ ) |             |
|                                    |          |              |                      |                                         |                                                                                                                                                                                                                                                                          | Small-Vessel Ischaemic Disease (SVID)<br>Total brain SVID volume<br>Association brain GM SVID<br>WM SVID                     | P for trend= 0.06<br>P for trend= 0.22<br>P for trend= 0.18<br>P for trend= 0.14                                                                                                                                                                                                                                                                       | PM <sub>2.5</sub> quartiles:<br>1 <sup>st</sup> : (5.75-10.67 $\mu\text{g}/\text{m}^3$ )<br>2 <sup>nd</sup> : (10.67-12.24 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (12.24-14.16 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (14.16-22.18 $\mu\text{g}/\text{m}^3$ ) |             |
|                                    |          |              |                      |                                         |                                                                                                                                                                                                                                                                          | WM<br>Total WM brain volume association areas WM brain volume<br>frontal WM<br>parietal WM<br>temporal WM<br>corpus callosum | $\beta = -6.23 \pm 1.28 \text{ cm}^3 \text{ p} < 0.01$<br>$\beta = -4.47 \pm 1.12 \text{ cm}^3 \text{ p} < 0.01$<br>$\beta = -2.04 \pm 0.59 \text{ cm}^3 \text{ p} < 0.01$<br>$\beta = -0.73 \pm 0.34 \text{ cm}^3 \text{ p} 0.03$<br>$\beta = -1.70 \pm 0.33 \text{ cm}^3 \text{ p} < 0.01$<br>$\beta = -0.12 \pm 0.04 \text{ cm}^3 \text{ p} < 0.01$ | PM <sub>2.5</sub> annual IQR increment (3.49 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                         |             |
|                                    |          |              |                      |                                         |                                                                                                                                                                                                                                                                          | Total brain volume<br>Normal brain Volume<br>Association area<br>Frontal lobe<br>Parietal lobe<br>Temporal lobe              | P for trend= 0.26<br>P for trend= 0.48<br>P for trend= 0.63<br>P for trend= 0.80<br>P for trend= 0.32<br><b>P for trend= p&lt;0.01</b>                                                                                                                                                                                                                 | Diesel PM quartiles:<br>1 <sup>st</sup> : (0.01-0.24 $\mu\text{g}/\text{m}^3$ )<br>2 <sup>nd</sup> : (0.24 -0.35 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (0.35-0.55 $\mu\text{g}/\text{m}^3$ )<br>3 <sup>rd</sup> : (0.55-3.93 $\mu\text{g}/\text{m}^3$ )               |             |
|                                    |          |              |                      |                                         |                                                                                                                                                                                                                                                                          | Ventricle volume<br>Association areas GM<br>brain volume<br>Frontal GM<br>Parietal GM<br>Temporal GM                         | $\beta = 0.96 \pm 0.43 \text{ cm}^3 \text{ p} 0.03$<br>$\beta = -12.72 \pm 1.88 \text{ cm}^3 \text{ p} < 0.01$<br>$\beta = -6.64 \pm 0.91 \text{ cm}^3 \text{ p} < 0.01$<br>$\beta = -3.85 \pm 0.55 \text{ cm}^3 \text{ p} < 0.01$<br>$\beta = -2.23 \pm 0.63 \text{ cm}^3 \text{ p} < 0.01$                                                           | Diesel PM annual IQR increment (0.31 $\mu\text{g}/\text{m}^3$ )                                                                                                                                                                                                                 |             |

| First author, year (Name of study)                                                               | Location | Study design    | Time recruitment /FU | N cases/cohort size or N Controls (age) | Exposure                                                                                                                                                                                                                                                                   | Outcome                                                                                                                                                                                                                                                        | HR, OR, RR, $\beta$ (95% CI), $\beta$ ( $\pm$ standard errors)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Exposure                                                                                                                                                          | Adjustments                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------|----------|-----------------|----------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                  |          |                 |                      |                                         |                                                                                                                                                                                                                                                                            | Total WM brain volume association areas<br>frontal WM<br>parietal WM<br>temporal WM                                                                                                                                                                            | $\beta = 5.74$ (2.73, 8.75) $\text{cm}^3$ $p < 0.01$<br>$\beta = 3.15$ (1.59, 4.72) $\text{cm}^3$ $p < 0.01$<br>$\beta = 1.78$ (0.86, 2.70) $\text{cm}^3$ $p < 0.01$<br>$\beta = 0.81$ (-0.1, 1.72) $\text{cm}^3$ $p = 0.08$                                                                                                                                                                                                                                                                                                                                    | Diesel PM Fourth quartile (median = 0.78 $\mu\text{g}/\text{m}^3$ )                                                                                               |                                                                                                                                                                                      |
| Casanova et al, 2016 (Women's Health Initiative Memory Study (WHIMS) Magnetic Resonance Imaging) | USA      | Cross-sectional | 2005-2006            | 1,365 (W) (70.5 $\pm$ 3.6 years)        | Residence-specific yearly exposures to $\text{PM}_{2.5}$ were estimated using a BME spatio-temporal model of annual monitoring data (1999–2007) recorded in the U.S. EPA Air Quality System (AQS).                                                                         | GM<br><br>WM<br><br>Hippocampal volumes.                                                                                                                                                                                                                       | Associations clustered in the bilateral superior, middle, and medial frontal gyri.<br><br>Associations clustered in the frontal lobe, with smaller clusters in the temporal, parietal, and occipital lobes.<br><br>No statistically significant association                                                                                                                                                                                                                                                                                                     | $\text{PM}_{2.5}$                                                                                                                                                 | Intracranial volume, age, race, BMI, geographic region, education, family income, employment status, smoking, alcohol, CVD, hypertension treated diabetes and prior hormone therapy. |
| Power et al, 2018 (Atherosclerosis Risk in Communities, ARIC)                                    | USA      | Cross-sectional | 2011-2013            | 1753 (M+W) (53 $\pm$ 5 years)           | $\text{PM}_{10}$ and $\text{PM}_{2.5}$ were estimated for residential address accounting for residential mobility using a spatio-temporal statistical model. The model combines PM monitoring data with geographic, meteorological covariates and were spatially smoothed. | Total brain<br>Frontal lobe<br>Occipital lobe<br>Parietal lobe<br>Temporal Lobe<br>Deep grae<br>Hippocampus<br>AD signature<br><br>Total brain<br>Frontal lobe<br>Occipital lobe<br>Parietal lobe<br>Temporal Lobe<br>Deep grey<br>Hippocampus<br>AD signature | $\beta = -0.02$ (-0.09, 0.04) $p = 0.5$<br>$\beta = -0.02$ (-0.05, 0.01) $p = 0.13$<br>$\beta = -0.01$ (-0.01, 0.08) $p = 0.79$<br>$\beta = -0.02$ (-0.07, 0.03) $p = 0.48$<br>$\beta = 0$ (-0.07, 0.07) $p = 0.99$<br>$\beta = -0.03$ (-0.07, 0) $p = 0.07$<br>$\beta = -0.01$ (-0.05, 0.04) $p = 0.71$<br>$\beta = 0$ (-0.06, 0.05) $p = 0.86$<br><br>$\beta = 0$ (-0.02, 0.01) $p = 0.86$<br>$\beta = 0$ (-0.02, 0.02) $p = 0.86$<br>$\beta = 0$ (-0.03, 0.04) $p = 0.86$<br>$\beta = 0$ (-0.01, 0.02) $p = 0.75$<br>$\beta = 0.01$ (-0.02, 0.05) $p = 0.43$ | 1- $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ increase for exposure 1990-2007<br><br>1- $\mu\text{g}/\text{m}^3$ $\text{PM}_{10}$ increase for exposure 1990-2007 | Age, sex, race, education and estimated intracranial volume                                                                                                                          |

| First author, year (Name of study)                                                                                                                 | Location        | Study design                      | Time recruitment /FU                                                                                    | N cases/cohort size or N Controls (age)               | Exposure                                                                                                                                                                                                                                                                         | Outcome                                                                                                                                                                                                 | HR, OR, RR, $\beta$ (95% CI), $\beta$ ( $\pm$ standard errors)                                                  | Exposure                                                                           | Adjustments                                                                                                                                                                                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                    |                 |                                   |                                                                                                         |                                                       |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                         | $\beta = -0.02$ (-0.04, 0) p 0.02<br>$\beta = -0.01$ (-0.03, 0.02) p 0.7<br>$\beta = 0.01$ (-0.02, 0.04) p 0.54 |                                                                                    |                                                                                                                                                                                                                          |
| Hedges et al, 2019 (UK Biobank)                                                                                                                    | UK              | Cross-sectional                   | 2006-2010 participant enrolment in the UK Biobank study                                                 | 18,278 (M+W) (mean age 62.12 $\pm$ 7.44, 44-80 years) | NO <sub>2</sub> , NO <sub>x</sub> , PM <sub>2.5</sub> , PM <sub>2.5-10</sub> , and PM <sub>10</sub> at the address level for mean annual concentration in 2010 were obtained from ESCAPE LUR models and traffic data for 2008 from land-use regression modeling from Eurostreets | Left Hippocampal Volume (mm <sup>3</sup> )                                                                                                                                                              | $\beta = -10.78$ p<0.01                                                                                         | PM <sub>2.5</sub> 1 $\mu\text{g}/\text{m}^3$                                       | Age, sex, race, SES, overall health, BMI, smoking, Alcohol consumption, inverse distance to major road, total brain volume.                                                                                              |
|                                                                                                                                                    |                 |                                   |                                                                                                         |                                                       |                                                                                                                                                                                                                                                                                  | Right Hippocampal Volume (mm <sup>3</sup> )                                                                                                                                                             | $\beta = -2.28$ p>0.05                                                                                          | PM <sub>2.5</sub> 1 $\mu\text{g}/\text{m}^3$                                       |                                                                                                                                                                                                                          |
|                                                                                                                                                    |                 |                                   |                                                                                                         |                                                       |                                                                                                                                                                                                                                                                                  | Left Hippocampal Volume (mm <sup>3</sup> )                                                                                                                                                              | $\beta = -6.75$ p>0.05                                                                                          | PM <sub>10-2.5</sub> 1 $\mu\text{g}/\text{m}^3$                                    |                                                                                                                                                                                                                          |
|                                                                                                                                                    |                 |                                   |                                                                                                         |                                                       |                                                                                                                                                                                                                                                                                  | Right Hippocampal Volume (mm <sup>3</sup> )                                                                                                                                                             | $\beta = -5.61$ p>0.05                                                                                          | PM <sub>10-2.5</sub> 1 $\mu\text{g}/\text{m}^3$                                    |                                                                                                                                                                                                                          |
|                                                                                                                                                    |                 |                                   |                                                                                                         |                                                       |                                                                                                                                                                                                                                                                                  | Left Hippocampal Volume (mm <sup>3</sup> )                                                                                                                                                              | $\beta = -2.71$ p>0.05                                                                                          | PM <sub>10</sub> 1 $\mu\text{g}/\text{m}^3$                                        |                                                                                                                                                                                                                          |
|                                                                                                                                                    |                 |                                   |                                                                                                         |                                                       |                                                                                                                                                                                                                                                                                  | Right Hippocampal Volume (mm <sup>3</sup> )                                                                                                                                                             | $\beta = -0.82$ p>0.05                                                                                          | PM <sub>10</sub> 1 $\mu\text{g}/\text{m}^3$                                        |                                                                                                                                                                                                                          |
|                                                                                                                                                    |                 |                                   |                                                                                                         |                                                       |                                                                                                                                                                                                                                                                                  | Left Hippocampal Volume (mm <sup>3</sup> )                                                                                                                                                              | $\beta = -0.74$ p>0.05                                                                                          | NO <sub>2</sub> 1 $\mu\text{g}/\text{m}^3$                                         |                                                                                                                                                                                                                          |
|                                                                                                                                                    |                 |                                   |                                                                                                         |                                                       |                                                                                                                                                                                                                                                                                  | Right Hippocampal Volume (mm <sup>3</sup> )                                                                                                                                                             | $\beta = 0.29$ p>0.05                                                                                           | NO <sub>2</sub> 1 $\mu\text{g}/\text{m}^3$                                         |                                                                                                                                                                                                                          |
|                                                                                                                                                    |                 |                                   |                                                                                                         |                                                       |                                                                                                                                                                                                                                                                                  | Left Hippocampal Volume (mm <sup>3</sup> )                                                                                                                                                              | $\beta = -0.45$ p>0.05                                                                                          | NO <sub>x</sub> 1 $\mu\text{g}/\text{m}^3$                                         |                                                                                                                                                                                                                          |
|                                                                                                                                                    |                 |                                   |                                                                                                         |                                                       |                                                                                                                                                                                                                                                                                  | Right Hippocampal Volume (mm <sup>3</sup> )                                                                                                                                                             | $\beta = 0.10$ p>0.05                                                                                           | NO <sub>x</sub> 1 $\mu\text{g}/\text{m}^3$                                         |                                                                                                                                                                                                                          |
| Younan et al., 2020 (Women's Health Initiative Study of Cognitive Aging, WHISCA and the WHI Memory Study of Magnetic Resonance Imaging, WHIMS-MRI) | USA (48 states) | Longitudinal (prospective cohort) | 1999-2010 (WHISCA), annual neurocognitive testing, 2005-2006 (WHIMS-MRI), second MRI between 2009-2010. | 998 (W) (73-87 years)                                 | Ambient concentration of PM <sub>2.5</sub> was estimated using the Bayesian Maximum Entropy (BME)-based spatio-temporal modelling approach, integrating nationwide monitoring data from both the US Environmental Protection Agency (EPA) Air Quality System (AQS) and           | AD pattern similarity scores (a brain-MRI measured neuroanatomical risk for AD), developed by supervised machine learning and validated with data from the Alzheimer's Disease Neuroimaging Initiative. | $\beta = 0.018$ (95% CI 0.001, 0.034)                                                                           | 3-year average PM <sub>2.5</sub> per IQR increase (2.81 $\mu\text{g}/\text{m}^3$ ) | age at MRI-1, race/ethnicity, geographic region of residence, education, household income, employment status, lifestyle factors (smoking, alcohol use, physical activities) and clinical characteristics (use of hormone |

| First author, year (Name of study) | Location | Study design | Time recruitment /FU | N cases/cohort size or N Controls (age) | Exposure                                                                                                                                                                                                                                                                                                                                                                                                                         | Outcome | HR, OR, RR, $\beta$ (95% CI), $\beta$ ( $\pm$ standard errors) | Exposure | Adjustments                                                                                      |
|------------------------------------|----------|--------------|----------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------------------------------------------------------|----------|--------------------------------------------------------------------------------------------------|
|                                    |          |              |                      |                                         | the output of chemical transport models. The BME model was then applied to each geocoded residential location, accounting for residential mobility in 1999-2010, and exposure estimates were then aggregated to represent the average PM <sub>2.5</sub> 3-years preceding the first MRI scan. Residential addresses of WHIMS participants were prospectively collected during each clinic visit and updated at least biannually. |         |                                                                |          | treatment; hypercholesterolemia, hypertension, diabetes, and history of cardiovascular disease). |

### Abbreviations

FU, follow-up; M; men; W, women; HR, hazard ratio; OR, odds ratio; RR, relative risk, CI, confidence interval; WM, white matter; GM, grey matter; HR, hazard ratio; OR, odds ratio; RR, relative risk, CI, confidence interval; IQR, interquartile range; CVD, cardiovascular disease; SES, socioeconomic status; BMI, body mass index

**Table 3.12. Summary of characteristics and outcomes of studies assessing the effect of air pollution on neuroinflammation in humans included in literature review**

| First author, year<br>(Name of study)                        | Location | Study design                                    | Time<br>recruitment/FU | N cases/cohort<br>size or N<br>Controls (age)                                             | Outcome                                                          | HR, OR, RR, $\beta$<br>(95% CI), Mean<br>( $\pm$ SE)                                               | Intervention                                                                                                                                                 | Adjustments |
|--------------------------------------------------------------|----------|-------------------------------------------------|------------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Bos et al 2011,<br>(SHAPES injury<br>surveillance<br>system) | Belgium  | Controlled case-<br>cross-over                  | NR                     | 38 physically fit, non<br>asthmatic<br>volunteers (W+W)<br>(mean age 43<br>years)         | Serum BDNF<br>concentrations (post<br>cycling vs pre<br>cycling) | +14.4% P=0.42<br><b>+0.5% P=0.02</b>                                                               | Participants cycled<br>at 74.0 $\pm$ 8.6% and<br>at 74.1 $\pm$ 8.8% of the<br>maximal heart rate<br>for 30 minutes:<br>In the road test<br>In the clean room | /           |
| Bos et al, 2013                                              | Belgium  | Controlled case-<br>cross-over                  | February-May 2011      | 24 volunteers<br>(M+W) (15 in a rural<br>environment and 9<br>in an urban<br>environment) | Cooper test<br>performance                                       | P values pre and<br>post exercise<br><b>Urban group<br/>p&lt;0.001, Rural<br/>group p&lt;0.001</b> | Aerobic training<br>program of 12<br>weeks, 3<br>sessions/week                                                                                               | /           |
|                                                              |          |                                                 |                        |                                                                                           | Blood Basophil<br>counts, per $\mu$ l                            | Urban group p 0.52,<br>Rural group p 0.08                                                          |                                                                                                                                                              |             |
|                                                              |          |                                                 |                        |                                                                                           | Serum BDNF<br>concentration, ng/ml                               | <b>Urban group p<br/>0.002</b> , Rural group<br>p 0.52                                             |                                                                                                                                                              |             |
|                                                              |          |                                                 |                        |                                                                                           | Exhaled NO, ppb                                                  | <b>Urban group p<br/>0.02</b> , Rural group p<br>0.47                                              |                                                                                                                                                              |             |
|                                                              |          |                                                 |                        |                                                                                           | Blood Leukocyte<br>counts, per $\mu$ l                           | Urban group, p<br>0.04, Rural group p<br>0.65                                                      |                                                                                                                                                              |             |
|                                                              |          |                                                 |                        |                                                                                           | Blood Neutrophil<br>counts, per $\mu$ l                          | <b>Urban group,<br/>p0.08</b> , Rural group,<br>p 0.14                                             |                                                                                                                                                              |             |
|                                                              |          |                                                 |                        |                                                                                           | Blood Lymphocyte<br>counts, per $\mu$ l                          | Urban group, p<br>0.13, Rural group, p<br>0.93                                                     |                                                                                                                                                              |             |
|                                                              |          |                                                 |                        |                                                                                           | Blood Eosinophil<br>counts, per $\mu$ l                          | Urban group, p<br>0.59, Rural group, p<br>0.84                                                     |                                                                                                                                                              |             |
|                                                              |          |                                                 |                        |                                                                                           | Blood Monocyte,<br>per $\mu$ l                                   | Urban group, p<br>0.96, Rural group, p<br>0.75                                                     |                                                                                                                                                              |             |
| Liu et al, 2017                                              | Canada   | Single-blind<br>randomised cross-<br>over trial | Not reported           | 55 non smokers<br>volunteers (M+W)<br>(18-60 years)                                       | Blood markers<br>(change)<br>S1000B                              | $\beta$ = -10.5 (95% CI -<br>21.7; 0.7) p<0.1                                                      | Subjects were<br>exposed to PM <sub>coarse</sub><br>(from 2.5 to 10 $\mu$ m)<br>CAPs for 130                                                                 | /           |
|                                                              |          |                                                 |                        |                                                                                           | NSE                                                              | $\beta$ = -13.2 (95% CI -<br>28; 1.6) p<0.1                                                        |                                                                                                                                                              |             |

| First author, year<br>(Name of study) | Location | Study design | Time<br>recruitment/FU | N cases/cohort<br>size or N<br>Controls (age) | Outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | HR, OR, RR, $\beta$<br>(95% CI), Mean<br>( $\pm$ SE)              | Intervention                                                                                            | Adjustments |
|---------------------------------------|----------|--------------|------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------|
|                                       |          |              |                        |                                               | UCHL1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | $\beta$ = 4.3 (95% CI - 11.3; 19.8)                               | minutes. Time post exposure 21 h.                                                                       |             |
|                                       |          |              |                        |                                               | Cortisol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b><math>\beta</math> = -22.4 (95% CI - 43.7; -1.1) p&lt;0.05</b> |                                                                                                         |             |
|                                       |          |              |                        |                                               | BDNF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | $\beta$ = 1.0 (95% CI - 11.3; 13.3)                               |                                                                                                         |             |
|                                       |          |              |                        |                                               | Urinary markers (change) VMA                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <b><math>\beta</math> = 19.5 (95% CI 1; 37.9) p&lt;0.05</b>       |                                                                                                         |             |
|                                       |          |              |                        |                                               | HVA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | $\beta$ = -1.0 (95% CI - 24.3; 22.3)                              |                                                                                                         |             |
|                                       |          |              |                        |                                               | Cortisol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b><math>\beta</math> = 63.5 (95% CI 0.2; 126.8) p&lt;0.05</b>    |                                                                                                         |             |
|                                       |          |              |                        |                                               | Blood markers (change) S100B                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | $\beta$ = 1.8 (95% CI - 16.8; 20.3)                               | Subjects were exposed to fine (from 0.15 to 2.5 $\mu$ m) CAPs for 130 minutes. Time post exposure 21 h. |             |
|                                       |          |              |                        |                                               | NSE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | $\beta$ = 17.7 (95% CI - 1.7; 37.2) p<0.1                         |                                                                                                         |             |
|                                       |          |              |                        |                                               | UCHL1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | $\beta$ = -15.5 (95% CI - 42.3; 11.2)                             |                                                                                                         |             |
|                                       |          |              |                        |                                               | Cortisol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b><math>\beta</math> = 2.8 (95% CI - 43.7; -1.1) p&lt;0.05</b>   |                                                                                                         |             |
|                                       |          |              |                        |                                               | BDNF                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | $\beta$ = 1.0 (95% CI - 11.3; 13.3)                               |                                                                                                         |             |
|                                       |          |              |                        |                                               | Urinary markers (change) VMA                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <b><math>\beta</math> = 19.5 (95% CI 1; 37.9) p&lt;0.05</b>       |                                                                                                         |             |
|                                       |          |              |                        |                                               | HVA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | $\beta$ = -1.0 (95% CI - 24.3; 22.3)                              |                                                                                                         |             |
|                                       |          |              |                        |                                               | Cortisol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b><math>\beta</math> = 63.5 (95% CI 0.2; 126.8) p&lt;0.05</b>    |                                                                                                         |             |
|                                       |          |              |                        |                                               | Endotoxin content was significantly associated with increased blood ubiquitin C-terminal hydrolase L1 [UCHL1, 11% (5.3%, 16%) per ln(ng/m3+1)] 1-hour post-exposure, while $\beta$ -1,3-d-glucan was significantly associated with increased blood S100B [6.3% (3.2%, 9.4%) per ln(ng/m3+1)], as well as UCHL1 [3.1% (0.4%, 5.9%) per ln(ng/m3+1)], one-hour post-exposure. Ultrafine CAP was not significantly associated with changes in any blood and urinary neural biomarkers examined. |                                                                   |                                                                                                         |             |



| First author, year<br>(Name of study)    | Location                                                                                                                | Study design                | Time<br>recruitment/FU | N cases/cohort<br>size or N<br>Controls (age)                                                                                       | Outcome                                                                                                                                                                                                      | HR, OR, RR, $\beta$<br>(95% CI), Mean<br>( $\pm$ SE)                                                                                                                                                                                                                                                                                          | Intervention                                                                                                                                                                                                                                                                                                       | Adjustments                                                                                                                                                                                   |
|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-----------------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sanchez-Rodriguez<br>et al, 2006         | Mexico City and<br>Actopan, Mexico                                                                                      | Cross-sectional             | Not Reported           | 189 (M+W)<br>(104 urban, 85<br>rural) (mean age<br>urban: 66.8 $\pm$ 6.4<br>years; rural: 70.8 $\pm$<br>8.4 years)                  | Blood<br>Lipoperoxides<br>( $\mu$ mol/L)<br>Blood Total<br>antioxidant status<br>(mmol/L)<br>Blood Superoxide<br>dismutase (SOD)<br>(U/L)<br>Blood Glutathione<br>peroxidase (GPx)<br>(U/L)<br>Blood SOD/GPx | Urban 0.323 $\pm$ 0.012<br><b>p&lt;0.0001</b><br>Rural 0.236 $\pm$ 0.012<br>Urban 1.12 $\pm$ 0.020<br>Rural 1.05 $\pm$ 0.021<br>Urban 1.64 $\pm$ 1.13<br><b>Rural 168<math>\pm</math>0.8</b><br><b>p&lt;0.05</b><br>Urban 6092 $\pm$ 253<br>Rural 7458 $\pm$ 308<br>p=0.001<br>Urban 0.032 $\pm$ 0.001<br>Rural 0.027 $\pm$ 0.001<br>p<0.0001 | Urban and rural                                                                                                                                                                                                                                                                                                    | Subjects were not<br>smokers, without<br>acute or chronic<br>diseases and were<br>not receiving<br>prescription<br>medications,<br>physical activity was<br>similar between the<br>two groups |
| Cliff et al, 2016                        | Canada                                                                                                                  | Double-blinded<br>crossover | Not reported           | 27 healthy adults                                                                                                                   | Blood IL-6, TNF- $\alpha$ ,<br>NSE, S100b, BDNF                                                                                                                                                              | There were no<br>significant time-<br>exposure<br>interactions for IL-6,<br>TNF- $\alpha$ , S100b, NSE<br>or BDNF indication<br>that levels of these<br>markers were not<br>affected by whether<br>subjects were<br>exposed to DE or<br>FA (the results are<br>reported in the<br>figures)                                                    | The subjects were<br>exposed to 2<br>conditions: filtered<br>air (FA) and diesel<br>(DE)exhaust (PM <sub>2.5</sub><br>300 $\mu$ g/m <sup>3</sup> ) for 120<br>minutes. During<br>each exposure the<br>participants cycled<br>on a stationary bike<br>at approximately<br>15L/min/m <sup>2</sup> for 15<br>minutes. | /                                                                                                                                                                                             |
| Calderón-<br>Garcidueñas et al,<br>2008a | Mexico (Mexico<br>City, highly polluted<br>city and Tlaxcala<br>and Veracruz cities<br>with low levels of<br>pollution) | Cross-sectional             | Not reported           | 47 subjects (12<br>from cities with low<br>levels of pollution A,<br>35 from a highly<br>polluted city B)<br>(25.1 $\pm$ 1.5 years) | COX2 lung<br>IL-1 $\beta$ lung<br>COX2 OB<br>IL-1 $\beta$ OB<br>CD14 OB<br>COX2 frontal<br>IL-1 $\beta$ frontal<br>COX2 hippocampus<br>IL-1 $\beta$ hippocampus<br>COX2 substantia<br>nigrae                 | Difference in<br>concentration in<br>tissue between A<br>and B<br><b>p=0.015</b><br>p=0.60<br><b>p=0.0002</b><br><b>p=0.003</b><br><b>p=0.04</b><br><b>p=0.08</b><br><b>p=0.0002</b><br>p=0.1<br>p=0.6<br><b>p=0.03</b><br>p=0.06<br>p=0.7                                                                                                    | Subjects living in a<br>highly polluted city<br>and cities with low<br>levels of pollution                                                                                                                                                                                                                         | /                                                                                                                                                                                             |

| First author, year<br>(Name of study) | Location                                                                                                                      | Study design | Time<br>recruitment/FU | N cases/cohort<br>size or N<br>Controls (age)                                                                                                                                                                                                                                                                                                                                                                  | Outcome                                                                                                                                                                                                                                                                                                                                                                                          | HR, OR, RR, $\beta$<br>(95% CI), Mean<br>( $\pm$ SE)                                                                                                               | Intervention                                                                      | Adjustments                 |
|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|--------------|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------|
|                                       |                                                                                                                               |              |                        |                                                                                                                                                                                                                                                                                                                                                                                                                | IL-1 $\beta$ substantia nigrae<br>CD14 substantia nigrae                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                    |                                                                                   |                             |
|                                       |                                                                                                                               |              |                        |                                                                                                                                                                                                                                                                                                                                                                                                                | COX2 periaqueductal grey<br>IL-1 $\beta$ periaqueductal grey                                                                                                                                                                                                                                                                                                                                     | p=0.12<br>p=0.09                                                                                                                                                   |                                                                                   |                             |
|                                       |                                                                                                                               |              |                        |                                                                                                                                                                                                                                                                                                                                                                                                                | COX2 left vagus<br>COX2 right vagus<br>IL-1 $\beta$ left vagus<br>IL-1 $\beta$ right vagus<br>CD4 left vagus<br>CD4 right vagus                                                                                                                                                                                                                                                                  | <b>p=0.03</b><br><b>p=0.0002</b><br>p=0.06<br>p=0.66<br><b>p=0.01</b><br><b>p=0.02</b>                                                                             |                                                                                   |                             |
|                                       |                                                                                                                               |              |                        |                                                                                                                                                                                                                                                                                                                                                                                                                | Amyloid $\beta$ 42 (A $\beta$ 42) immunoreactivity was observed in 58.8% of apolipoprotein E (APOE) 3/3 <25 y, and 100% of the APOE 4 subjects, whereas $\alpha$ -synuclein was seen in 23.5% of <25 y subjects. Particulate material (PM) was seen in olfactory bulb neurons, and PM <100 nm were observed in intraluminal erythrocytes from lung, frontal, and trigeminal ganglia capillaries. |                                                                                                                                                                    |                                                                                   |                             |
| Calderón-Garcidueñas et al., 2016a    | Mexico, Mexico City and other Mexican cities (with concentration of the 6 criteria air pollutants below the US EPA standards) |              | Not reported           | For oligomeric $\alpha$ -synuclein 92 subjects (M+W) from Mexico City: 78 children mean age (11.4 $\pm$ 5.32 years) and 18 adults mean age 41.05 $\pm$ 22.67 years) and 37 subjects from other cities (M+W): 28 children (and 9 adults (mean age 44.05 $\pm$ 17.8 years). For other markers 50 children (M+W) from Mexico city (11.2 $\pm$ 5.5 years) and 23 children from other cities (12.7 $\pm$ 4.2 years) | In children (cerebrospinal fluid)<br>PrP<br>Total $\alpha$ -synuclein<br>Oligo $\alpha$ -synuclein<br>Amyloid $\beta$ 1-42<br>Total tau<br>H tau<br>THF $\alpha$<br>IL1 $\beta$<br>IL2<br>IL6<br>IL10<br>MCP-1<br>Leptin<br>Insulin<br>BDNF                                                                                                                                                      | P=0.48<br>P=0.98<br>P=0.41<br><b>P=0.005</b><br>P=0.67<br>P=0.80<br>P=0.28<br>P=0.47<br>P=0.053<br>P=0.06<br>P=0.15<br>P=0.22<br>P=0.51<br>P=0.76<br><b>P=0.02</b> | Subjects living in a highly polluted city and cities with low levels of pollution | Matched by age, sex and SES |
|                                       |                                                                                                                               |              |                        |                                                                                                                                                                                                                                                                                                                                                                                                                | In children and adults<br>Total $\alpha$ -synuclein<br>Oligo $\alpha$ -synuclein                                                                                                                                                                                                                                                                                                                 | P=0.47<br>P=0.44                                                                                                                                                   |                                                                                   | Age and sex                 |

| First author, year<br>(Name of study) | Location | Study design    | Time<br>recruitment/FU | N cases/cohort<br>size or N<br>Controls (age)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Outcome                                                | HR, OR, RR, $\beta$<br>(95% CI), Mean<br>( $\pm$ SE)                                                            | Intervention                                                                                                                                               | Adjustments                                                                                                                |
|---------------------------------------|----------|-----------------|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Shaffer et al, 2019                   | USA      | Cross-sectional | 2001-2012              | 73 (M+W)<br>cognitively normal<br>individuals (mean<br>age 71.7 $\pm$ 8 years);<br>60 (M+W)<br>individuals with<br>dementia/MCI<br>(mean age 69.9 $\pm$ 9.7<br>years)<br><br>Short-term (days<br>and months)<br>average PM <sub>2.5</sub><br>exposure was<br>estimated from<br>central monitors.<br>Daily PM <sub>2.5</sub><br>concentration was<br>adjusted for<br>temperature and<br>time.<br><br>Long-term (years)<br>average PM <sub>2.5</sub><br>exposure was<br>estimated at<br>participants'<br>addresses by using a<br>land use regression<br>model and an<br>exponential<br>covariance for the<br>geostatistical<br>smoothing from<br>monitoring stations. | CSF VCAM-1<br>(ng/ml) in<br>cerebrospinal fluid        | Mean (range)<br><b>35.4 (9.7, 61.1)</b><br><b>Consistent effect<br/>for the 2 and 5-day<br/>average periods</b> | 5 $\mu$ g/m <sup>3</sup> increase in<br>7-day average PM <sub>2.5</sub>                                                                                    | Age, sex,<br>education, smoking,<br>ApoE $\epsilon$ 4, BMI,<br>hypertension,<br>coronary heart<br>disease and<br>diabetes. |
|                                       |          |                 |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Among cognitive<br>normal                              | Mean (range)<br><b>51.8 (6.5, 97.1)</b>                                                                         | 5 $\mu$ g/m <sup>3</sup> increase in<br>1-year average<br>PM <sub>2.5</sub>                                                                                |                                                                                                                            |
|                                       |          |                 |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Among the<br>MCI/dementia<br>subgroup                  | Mean (range)<br>16.2 (-8.5, 40.8)<br>Consistent effect for<br>the 2 and 5-day<br>average periods                | 5 $\mu$ g/m <sup>3</sup> increase in<br>7-day average PM <sub>2.5</sub>                                                                                    |                                                                                                                            |
|                                       |          |                 |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                        | Mean (range)<br>17.1 (-33.9, 68.2)<br>Consistent results<br>for 5-year, 10-year<br>and 20-year<br>exposure      | 5 $\mu$ g/m <sup>3</sup> increase in<br>1-year average<br>PM <sub>2.5</sub>                                                                                |                                                                                                                            |
|                                       |          |                 |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | CSF e-selectin<br>(pg/ml) in<br>cerebrospinal<br>fluid | Mean (range)<br>-1.8 (-27.1, 23.4)                                                                              | 5 $\mu$ g/m <sup>3</sup> increase in<br>7-day average PM <sub>2.5</sub>                                                                                    |                                                                                                                            |
|                                       |          |                 |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Among cognitive<br>normal                              | Mean (range)<br><b>53.3 (11, 95.5)</b><br>Consistent results<br>for 5-year, 10-year<br>and 20-year<br>exposure  | 5 $\mu$ g/m <sup>3</sup> increase in<br>1-year average<br>PM <sub>2.5</sub>                                                                                |                                                                                                                            |
|                                       |          |                 |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Among the<br>MCI/dementia<br>subgroup                  | Mean (range)<br>-9.5 (-28.2, 9.1)<br><br>Mean (range)<br>23 (-15.1, 61.2)                                       | 5 $\mu$ g/m <sup>3</sup> increase in<br>7-day average PM <sub>2.5</sub><br><br>5 $\mu$ g/m <sup>3</sup> increase in<br>1-year average<br>PM <sub>2.5</sub> |                                                                                                                            |

### Abbreviations

FU, follow-up; M, men; W, women, CAP, concentrated ambient air, WM, white matter; GM, grey matter; HR, hazard ratio; OR, odds ratio; RR, relative risk, CI, confidence interval; SE, standard error; IQR, interquartile range; CVD, cardiovascular disease; SES, socioeconomic status; BMI, body mass index; BDNF, brain-derived neurotrophic factor; VMA, vanillylmandelic acid; UCHL1, C-terminal hydrolase L1; NSE, neuron-specific enolase; S100B, S100 calcium-binding protein B; HVA, homovanillic acid; COX, cyclooxygenase; IL, interleukine; OB, olfactory bulb; TNF- $\alpha$ , tumour necrosis factor alpha; MCI, mild cognitive impairment; CSF VCAM-1, Cerebrospinal fluid-vascular cell adhesion molecule-1

**Table 3.13. Summary of characteristics and outcomes of studies reporting ageing equivalent to the effect of long-term air pollution on cognition included in literature review**

| Reference / Name of study                                                     | Location        | Sample size               | Age                          | Study design                                                                                                  | Cognitive/ Neurological Outcome | Coefficient <sup>(a)</sup>                                                                                                                                                                                                                                                                                                                                                       | Exposure                                                                                                                                                                                                                                     | Ageing equivalence |
|-------------------------------------------------------------------------------|-----------------|---------------------------|------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| (Power et al, 2011)<br>Normative Aging Study                                  | Boston, USA     | 680 men                   | Range: 51-97<br>Mean: 71 ± 7 | Prospective cohort<br>Cross-sectional analysis of cognitive testing responses obtained between 1996 and 2007. | <b>Global Cognition</b>         | OR (MMSE <25) = 1.3 (95% CI 1.1, 1.6)                                                                                                                                                                                                                                                                                                                                            | Doubling of BC                                                                                                                                                                                                                               | <b>1.9 years</b>   |
| (Tallon et al, 2017)<br>National Social Life, Health and Aging Project cohort | USA             | 3377                      | 57-85                        | Prospective cohort<br>Cross-sectional analysis of 2010-2011 survey                                            | <b>Global Cognition</b>         | $\beta$ (CCFM) = -0.22; (95% CI -0.44; -0.01)                                                                                                                                                                                                                                                                                                                                    | PM <sub>2.5</sub> 1-year IQR increase (4.25 µg/m <sup>3</sup> )                                                                                                                                                                              | <b>1.6 years</b>   |
|                                                                               |                 |                           |                              |                                                                                                               |                                 | $\beta$ (CCFM) = -0.26; (95% CI -0.45, -0.06)                                                                                                                                                                                                                                                                                                                                    | NO <sub>2</sub> 2-year IQR increase (6.66 ppb)                                                                                                                                                                                               | <b>1.9 years</b>   |
| (Chen and Schwartz, 2009)<br>NHANES-III                                       | Nationwide, USA | 1764 (879 men, 885 women) | Mean: 37.4 ± 10.9            | Prospective cohort<br>Cross-sectional analysis (1989-1991)                                                    | <b>Attention &amp; Memory</b>   | $\beta$ (SDLT) = 0.52 s; (95% CI 0.03; 1.01)<br>$\beta$ (No of trials SDLT) = 0.26 s; (95% CI 0.03; 0.48)                                                                                                                                                                                                                                                                        | O <sub>3</sub> (10 ppb)<br>O <sub>3</sub> (10 ppb)                                                                                                                                                                                           | <b>5.3 years</b>   |
| (Wellenius et al, 2012)<br>MOBILIZE Boston Study                              | Boston, USA     | 765 (276 men, 489 women)  | ≥65<br>Mean: 78.1 ± 5.4      | Prospective cohort<br>Longitudinal study (Baseline recruitment 2005-2008; median follow-up of 16.8 months)    | <b>Memory</b>                   | $\beta$ (HVLT-R immediate recall) = -0.6; (95% CI -1.1; -0.1) (subject's age≤77)<br><br>$\beta$ (HVLT-R immediate recall) = -0.66; (95% CI -1.15; -0.17) (subject's education>college)<br><br>$\beta$ (HVLT-R delayed memory) = -0.59; (95% CI -0.87; -0.31) (subject's age≤77)<br><br>$\beta$ (HVLT-R delayed memory) = -0.4; (95% CI -0.7; -0.1) (subject's education>college) | Residential Traffic proximity IQR decrease (851.2 m).<br><br>Residential Traffic proximity IQR decrease (851.2 m).<br><br>Residential Traffic proximity IQR decrease (851.2 m).<br><br>Residential Traffic proximity IQR decrease (851.2 m). | <b>2 years</b>     |

| Reference / Name of study                                                            | Location         | Sample size  | Age                        | Study design                                                                                                          | Cognitive/ Neurological Outcome | Coefficient <sup>(a)</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                          | Exposure                                                                                                           | Ageing equivalence |
|--------------------------------------------------------------------------------------|------------------|--------------|----------------------------|-----------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|--------------------|
|                                                                                      |                  |              |                            |                                                                                                                       | <b>Language</b>                 | $\beta$ (letter fluency) = -1.4; (95% CI -2.7, -0.2)<br><br>$\beta$ (category fluency) = -0.7; (95% CI -1.1, -0.3)                                                                                                                                                                                                                                                                                                                                                  | Residential Traffic proximity IQR decrease (851.2 m).<br><br>Residential Traffic proximity IQR decrease (851.2 m). | <b>4 years</b>     |
| (Weuve et al, 2012) Nurses' Health Study Cognitive Cohort                            | USA              | 19,409 women | $\geq 70$                  | Prospective cohort Longitudinal study (Sub-cohort of NHS: 1995-2001; participants resurveyed in 1997-2004; 2002-2008) | <b>Cognitive decline</b>        | $\beta$ = -0.018; (95% CI -0.035; -0.002)<br><br>$\beta$ = -0.020; (95% CI -0.032; -0.008)                                                                                                                                                                                                                                                                                                                                                                          | PM <sub>2.5</sub> (10 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>10-2.5</sub> (10 $\mu\text{g}/\text{m}^3$ )        | <b>2 years</b>     |
| (Wilker et al, 2015) Framingham Offspring Study                                      | New England, USA | 943          | $\geq 60$                  | Prospective cohort Cross-sectional analysis of responses from the 7 <sup>th</sup> examination (1998–2001)             | <b>Neuroimaging</b>             | $\beta$ (brain volume) = -0.32% (95% CI, -0.59, -0.05)<br><br>$\beta$ (covert brain infarct) = 1.46 (95% CI, 1.10, 1.94)                                                                                                                                                                                                                                                                                                                                            | PM <sub>2.5</sub> (2 $\mu\text{g}/\text{m}^3$ )<br><br>PM <sub>2.5</sub> (2 $\mu\text{g}/\text{m}^3$ )             | <b>1 year</b>      |
| (Chen et al, 2017c; Chen et al, 2015) Women's Health Initiative Memory Study (WHIMS) | USA              | 1,403 women  | 71.0 -89 years at baseline | Prospective cohort Cross-sectional analysis of scans conducted on 2005-2006                                           | <b>Neuroimaging</b>             | $\beta$ (total WM brain volume) = -6.23 $\pm$ 1.28 cm <sup>3</sup> (95% CI 3.72; 8.74)<br><br>$\beta$ (association areas WM brain volume) = -4.47 $\pm$ 1.12 cm <sup>3</sup> (95% CI 2.27; 6.67)<br><br>$\beta$ (frontal WM) = -2.04 $\pm$ 0.59 cm <sup>3</sup><br><br>$\beta$ (parietal WM) = -0.73 $\pm$ 0.34 cm <sup>3</sup><br><br>$\beta$ (temporal WM) = -1.70 $\pm$ 0.33 cm <sup>3</sup><br><br>$\beta$ (corpus callosum) = -0.12 $\pm$ 0.04 cm <sup>3</sup> | PM <sub>2.5</sub> annual IQR increment (3.49 $\mu\text{g}/\text{m}^3$ )                                            | <b>1-2 years</b>   |

**Table 3.14. Summary of consistency of associations between exposure to air pollution or traffic measures and outcomes included in the literature review**

| N   | Reference                        | Cognitive function                                                                                                   |                                                                                                                      |                                                                                                                      |                                                                                                                      |                                                                                                                      |                   | Cognitive Decline                                                                                  | MCI / Incident Cognitive Impairment | Dementia | Hospitalisations | Brain Imaging | Neurological biomarkers | Low Medium Income Country |
|-----|----------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------|-------------------------------------|----------|------------------|---------------|-------------------------|---------------------------|
|     |                                  | Global                                                                                                               | Executive Function                                                                                                   | Attention                                                                                                            | Memory                                                                                                               | Const Prax Coding abil                                                                                               | Language          |                                                                                                    |                                     |          |                  |               |                         |                           |
| 1.  | (Sanchez-Rodriguez et al., 2006) | Urban vs Rural                                                                                                       |                                                                                                                      |                                                                                                                      |                                                                                                                      |                                                                                                                      |                   |                                                                                                    | Urban vs Rural                      |          |                  |               | Urban vs Rural          | Yes                       |
| 2.  | (Sun and Gu, 2008)               | API                                                                                                                  |                                                                                                                      |                                                                                                                      |                                                                                                                      |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | Yes                       |
| 3.  | (Ranft et al., 2009)             | Traffic PM <sub>10</sub>                                                                                             |                                                                                                                      | Traffic PM <sub>10</sub>                                                                                             |                                                                                                                      |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 4.  | (Wellenius et al., 2012)         | Traffic BC                                                                                                           | Traffic BC                                                                                                           |                                                                                                                      | Traffic BC                                                                                                           |                                                                                                                      | Traffic, BC       |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 5.  | (Power et al, 2011)              | BC                                                                                                                   |                                                                                                                      |                                                                                                                      |                                                                                                                      |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 6.  | (Colicino et al, 2016)           | BC                                                                                                                   |                                                                                                                      |                                                                                                                      |                                                                                                                      |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 7.  | (Colicino et al, 2017)           | BC                                                                                                                   |                                                                                                                      |                                                                                                                      |                                                                                                                      |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 8.  | (Gatto et al., 2014)             | PM <sub>2.5</sub><br>O <sub>3</sub><br>NO <sub>2</sub>                                                               | PM <sub>2.5</sub><br>O <sub>3</sub><br>NO <sub>2</sub>                                                               |                                                                                                                      | PM <sub>2.5</sub><br>O <sub>3</sub><br>NO <sub>2</sub>                                                               |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 9.  | (Ailshire and Crimmins, 2014)    | PM <sub>2.5</sub>                                                                                                    |                                                                                                                      |                                                                                                                      | PM <sub>2.5</sub>                                                                                                    |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 10. | (Ailshire et al., 2017)          | PM <sub>2.5</sub>                                                                                                    |                                                                                                                      |                                                                                                                      |                                                                                                                      |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 11. | (Tzivian et al., 2017)           | PM <sub>2.5</sub>                                                                                                    |                                                                                                                      |                                                                                                                      |                                                                                                                      |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 12. | (Tallon et al., 2017)            | PM <sub>2.5</sub><br>NO <sub>2</sub>                                                                                 |                                                                                                                      |                                                                                                                      |                                                                                                                      |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 13. | (Lin et al., 2017a)              | PM <sub>2.5</sub>                                                                                                    |                                                                                                                      |                                                                                                                      |                                                                                                                      |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | Yes                       |
| 14. | (Schikowski et al., 2015)        | NO <sub>x</sub><br>NO <sub>2</sub><br>PM <sub>10</sub><br>PM <sub>2.5</sub><br>PM <sub>2.5</sub> abs<br>traffic load | NO <sub>2</sub><br>NO <sub>x</sub><br>PM <sub>10</sub><br>PM <sub>2.5</sub><br>PM <sub>2.5</sub> abs<br>traffic load | NO <sub>2</sub><br>NO <sub>x</sub><br>PM <sub>10</sub><br>PM <sub>2.5</sub><br>PM <sub>2.5</sub> abs<br>traffic load | NO <sub>2</sub><br>NO <sub>x</sub><br>PM <sub>10</sub><br>PM <sub>2.5</sub><br>PM <sub>2.5</sub> abs<br>traffic load | NO <sub>2</sub><br>NO <sub>x</sub><br>PM <sub>10</sub><br>PM <sub>2.5</sub><br>PM <sub>2.5</sub> abs<br>traffic load |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 15. | (Molina-Sotomayor et al., 2019)  | Clean vs Polluted                                                                                                    | Clean vs Polluted                                                                                                    |                                                                                                                      | Clean vs Polluted                                                                                                    |                                                                                                                      | Clean vs Polluted |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 16. | (Shin et al., 2019)              | PM <sub>2.5</sub><br>PM <sub>10</sub><br>NO <sub>2</sub><br>O <sub>3</sub><br>CO<br>SO <sub>2</sub>                  | PM <sub>2.5</sub><br>PM <sub>10</sub><br>NO <sub>2</sub><br>O <sub>3</sub><br>CO<br>SO <sub>2</sub>                  | PM <sub>2.5</sub><br>PM <sub>10</sub><br>NO <sub>2</sub><br>O <sub>3</sub><br>CO<br>SO <sub>2</sub>                  | PM <sub>2.5</sub><br>PM <sub>10</sub><br>NO <sub>2</sub><br>O <sub>3</sub><br>CO<br>SO <sub>2</sub>                  |                                                                                                                      |                   |                                                                                                    |                                     |          |                  |               |                         | No                        |
| 17. | (Cullen et al., 2018)            |                                                                                                                      | PM <sub>10</sub><br>NO <sub>2</sub><br>PM <sub>2.5</sub><br>PM <sub>coarse</sub><br>NO <sub>x</sub>                  | PM <sub>2.5</sub><br>PM <sub>coarse</sub><br>NO <sub>2</sub><br>NO <sub>x</sub>                                      | NO <sub>2</sub><br>PM <sub>10</sub><br>PM <sub>10</sub><br>PM <sub>coarse</sub><br>NO <sub>x</sub>                   |                                                                                                                      |                   | PM <sub>10</sub> , NO <sub>2</sub><br>PM <sub>2.5</sub><br>PM <sub>10-2.5</sub><br>NO <sub>x</sub> |                                     |          |                  |               |                         | No                        |
| 18. | (Tonne et al., 2014)             |                                                                                                                      | PM <sub>2.5</sub><br>PM <sub>2.5</sub> exhaust<br>PM <sub>10</sub>                                                   |                                                                                                                      | PM <sub>2.5</sub><br>PM <sub>2.5</sub> exhaust<br>PM <sub>10</sub>                                                   |                                                                                                                      | PM <sub>2.5</sub> | PM <sub>2.5</sub><br>PM <sub>2.5</sub> exhaust<br>PM <sub>10</sub>                                 |                                     |          |                  |               |                         | No                        |

## Cognitive decline, dementia and air pollution: a report by the Committee on the Medical Effects of Air Pollutants

| N   | Reference                        | Cognitive function |                     |                     |              |                        |                                     | Cognitive Decline                           | MCI / Incident Cognitive Impairm                                     | Dementia           | Hospitalis ations | Brain Imaging      | Neurologi cal biomarker s | Low Medium Income Country |
|-----|----------------------------------|--------------------|---------------------|---------------------|--------------|------------------------|-------------------------------------|---------------------------------------------|----------------------------------------------------------------------|--------------------|-------------------|--------------------|---------------------------|---------------------------|
|     |                                  | Global             | Executive Function  | Attention           | Memory       | Const Prax Coding abil | Language                            |                                             |                                                                      |                    |                   |                    |                           |                           |
|     |                                  |                    | PM10 exhaust        |                     | PM10 exhaust |                        | PM2.5 exhaust<br>PM10, PM10 exhaust | PM10 exhaust                                |                                                                      |                    |                   |                    |                           |                           |
| 19. | (Zhang et al., 2018)             |                    | API                 |                     |              |                        | API                                 |                                             |                                                                      |                    |                   |                    |                           | Yes                       |
| 20. | (Rafiee et al., 2020)            |                    | Low vs High traffic | Low vs High traffic |              |                        |                                     |                                             |                                                                      |                    |                   |                    |                           | Yes                       |
| 21. | (Chen and Schwartz, 2009)        |                    |                     | PM10 O3             | PM10 O3      | PM10 O3                |                                     |                                             |                                                                      |                    |                   |                    |                           | No                        |
| 22. | (Ailshire and Clarke, 2015)      |                    |                     |                     | PM2.5        |                        |                                     |                                             |                                                                      |                    |                   |                    |                           | No                        |
| 23. | (Salinas-Rodriguez et al., 2018) |                    |                     |                     | PM2.5        |                        | PM2.5                               |                                             |                                                                      |                    |                   |                    |                           | Yes                       |
| 24. | (Huls et al., 2018)              |                    |                     |                     |              | NO2<br>PM10<br>PM2.5   |                                     |                                             |                                                                      |                    |                   |                    |                           | No                        |
| 25. | (Weuve et al., 2012)             |                    |                     |                     |              |                        |                                     | PM2.5<br>PMcoarse                           |                                                                      |                    |                   |                    |                           | No                        |
| 26. | (Cacciottolo et al., 2017)       |                    |                     |                     |              |                        |                                     | PM2.5                                       |                                                                      | PM2.5              |                   |                    |                           | No                        |
| 27. | (Xu et al., 2017)                |                    |                     |                     |              |                        |                                     | Rural vs urban                              |                                                                      |                    |                   |                    |                           | Yes                       |
| 28. | (Oudin et al., 2017)             |                    |                     |                     |              |                        |                                     | NOx                                         |                                                                      |                    |                   |                    |                           | No                        |
| 29. | (Wurth et al., 2018)             |                    |                     |                     |              |                        |                                     | BC<br>Sulphur<br>Silicon<br>Nickel<br>PM2.5 |                                                                      |                    |                   |                    |                           | No                        |
| 30. | (Cleary et al., 2018)            |                    |                     |                     |              |                        |                                     | O3                                          |                                                                      |                    |                   |                    |                           | No                        |
| 31. | (Younan et al. 2020)             |                    |                     |                     |              |                        |                                     | PM2.5                                       |                                                                      |                    |                   | PM2.5              |                           | No                        |
| 32. | (Loop et al., 2015)              |                    |                     |                     |              |                        |                                     |                                             | PM2.5                                                                |                    |                   |                    |                           | No                        |
| 33. | (Zeng et al., 2010)              |                    |                     |                     |              |                        |                                     |                                             | API                                                                  |                    |                   |                    |                           | Yes                       |
| 34. | (Tzivian et al., 2016)           |                    |                     |                     |              |                        |                                     |                                             | PM2.5<br>PM10<br>PMcoarse<br>PM2.5 abs<br>NO2<br>NOx<br>Traffic load |                    |                   |                    |                           | No                        |
| 35. | (Lo et al., 2019)                |                    |                     |                     |              |                        |                                     |                                             | PM10<br>O3                                                           |                    |                   |                    |                           | No                        |
| 36. | (Chen et al., 2017c)             |                    |                     |                     |              |                        |                                     |                                             | PM2.5<br>Diesel PM                                                   | PM2.5<br>Diesel PM |                   | PM2.5<br>Diesel PM |                           | No                        |
| 37. | (Lee et al., 2019)               |                    |                     |                     |              |                        |                                     |                                             | PM2.5                                                                | PM2.5              |                   |                    |                           | No                        |
| 38. | (Chen et al., 2017b)             |                    |                     |                     |              |                        |                                     |                                             |                                                                      | Traffic            |                   |                    |                           | No                        |
| 39. | (Chen et al., 2017a)             |                    |                     |                     |              |                        |                                     |                                             |                                                                      | PM2.5<br>NO2       |                   |                    |                           | No                        |



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| N   | Reference                     | Cognitive function |                    |           |        |                        |          | Cognitive Decline | MCI / Incident Cognitive Impairment | Dementia                                                                               | Hospitalisations                                                                                                                             | Brain Imaging                         | Neurological biomarkers | Low Medium Income Country |
|-----|-------------------------------|--------------------|--------------------|-----------|--------|------------------------|----------|-------------------|-------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------------------------|---------------------------|
|     |                               | Global             | Executive Function | Attention | Memory | Const Prax Coding abil | Language |                   |                                     |                                                                                        |                                                                                                                                              |                                       |                         |                           |
|     |                               |                    |                    |           |        |                        |          |                   |                                     | O <sub>3</sub>                                                                         |                                                                                                                                              |                                       |                         |                           |
| 40. | (Jung et al., 2015)           |                    |                    |           |        |                        |          |                   |                                     | PM <sub>2.5</sub><br>O <sub>3</sub>                                                    |                                                                                                                                              |                                       |                         | No                        |
| 41. | (Wu et al., 2015)             |                    |                    |           |        |                        |          |                   |                                     | PM <sub>10</sub><br>O <sub>3</sub>                                                     |                                                                                                                                              |                                       |                         | No                        |
| 42. | (Chang et al., 2014)          |                    |                    |           |        |                        |          |                   |                                     | NO <sub>2</sub><br>CO                                                                  |                                                                                                                                              |                                       |                         | No                        |
| 43. | (Oudin et al., 2016)          |                    |                    |           |        |                        |          |                   |                                     | NO <sub>x</sub>                                                                        |                                                                                                                                              |                                       |                         | No                        |
| 44. | (Oudin et al., 2018)          |                    |                    |           |        |                        |          |                   |                                     | Wood<br>PM <sub>2.5</sub><br>Traffic<br>PM <sub>2.5</sub>                              |                                                                                                                                              |                                       |                         | No                        |
| 45. | (Oudin et al., 2019)          |                    |                    |           |        |                        |          |                   |                                     | NO <sub>x</sub>                                                                        |                                                                                                                                              |                                       |                         | No                        |
| 46. | (Andersson et al., 2018)      |                    |                    |           |        |                        |          |                   |                                     | NO <sub>x</sub>                                                                        |                                                                                                                                              |                                       |                         | No                        |
| 47. | (Carey et al., 2018)          |                    |                    |           |        |                        |          |                   |                                     | NO <sub>2</sub><br>PM <sub>2.5</sub><br>Traffic<br>PM <sub>2.5</sub><br>O <sub>3</sub> |                                                                                                                                              |                                       |                         | No                        |
| 48. | (Ilango et al., 2020)         |                    |                    |           |        |                        |          |                   |                                     | PM <sub>2.5</sub><br>NO <sub>2</sub>                                                   |                                                                                                                                              |                                       |                         | No                        |
| 49. | (Li et al., 2019)             |                    |                    |           |        |                        |          |                   |                                     | PM <sub>10</sub><br>NO <sub>2</sub><br>O <sub>3</sub><br>CO<br>SO <sub>2</sub>         |                                                                                                                                              |                                       |                         | Yes                       |
| 50. | (Bowe et al., 2019)           |                    |                    |           |        |                        |          |                   |                                     | PM <sub>2.5</sub>                                                                      |                                                                                                                                              |                                       |                         | No                        |
| 51. | (Kioumourtoglou et al., 2016) |                    |                    |           |        |                        |          |                   |                                     |                                                                                        | PM <sub>2.5</sub>                                                                                                                            |                                       |                         | No                        |
| 52. | (Cerza et al., 2019)          |                    |                    |           |        |                        |          |                   |                                     |                                                                                        | PM <sub>2.5</sub><br>PM <sub>10</sub><br>PM <sub>coarse</sub><br>PM <sub>2.5</sub> abs<br>NO <sub>2</sub><br>NO <sub>x</sub><br>Traffic load |                                       |                         | No                        |
| 53. | (Culqui et al., 2017)         |                    |                    |           |        |                        |          |                   |                                     |                                                                                        | PM <sub>2.5</sub>                                                                                                                            |                                       |                         | No                        |
| 54. | (Linares et al., 2017)        |                    |                    |           |        |                        |          |                   |                                     |                                                                                        | O <sub>3</sub>                                                                                                                               |                                       |                         | No                        |
| 55. | (Zanobetti et al., 2014)      |                    |                    |           |        |                        |          |                   |                                     |                                                                                        | PM <sub>2.5</sub>                                                                                                                            |                                       |                         | No                        |
| 56. | (Qiu et al., 2019)            |                    |                    |           |        |                        |          |                   |                                     |                                                                                        | PM <sub>2.5</sub><br>PM <sub>10</sub><br>PM <sub>coarse</sub>                                                                                |                                       |                         | Yes                       |
| 57. | (Wilker et al., 2015)         |                    |                    |           |        |                        |          |                   |                                     |                                                                                        |                                                                                                                                              | PM <sub>2.5</sub><br>Traffic distance |                         | No                        |

| N   | Reference                               | Cognitive function |                    |           |        |                        |          | Cognitive Decline | MCI / Incident Cognitive Impairment | Dementia | Hospitalisations | Brain Imaging                                                                                       | Neurological biomarkers                   | Low Medium Income Country |
|-----|-----------------------------------------|--------------------|--------------------|-----------|--------|------------------------|----------|-------------------|-------------------------------------|----------|------------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------|---------------------------|
|     |                                         | Global             | Executive Function | Attention | Memory | Const Prax Coding abil | Language |                   |                                     |          |                  |                                                                                                     |                                           |                           |
| 58. | (Wilker et al., 2016)                   |                    |                    |           |        |                        |          |                   |                                     |          |                  | PM <sub>2.5</sub><br>Traffic distance                                                               |                                           | No                        |
| 59. | (Chen et al., 2017c; Chen et al., 2015) |                    |                    |           |        |                        |          |                   |                                     |          |                  | PM <sub>2.5</sub><br>Diesel PM                                                                      |                                           | No                        |
| 60. | (Casanova et al., 2016)                 |                    |                    |           |        |                        |          |                   |                                     |          |                  | PM <sub>2.5</sub>                                                                                   |                                           | No                        |
| 61. | (Power et al., 2018)                    |                    |                    |           |        |                        |          |                   |                                     |          |                  | PM <sub>2.5</sub><br>PM <sub>10</sub>                                                               |                                           | No                        |
| 62. | (Hedges et al. 2019)                    |                    |                    |           |        |                        |          |                   |                                     |          |                  | PM <sub>2.5</sub><br>PM <sub>10</sub><br>PM <sub>coarse</sub><br>NO <sub>2</sub><br>NO <sub>x</sub> |                                           | No                        |
| 63. | (Bos et al., 2011)                      |                    |                    |           |        |                        |          |                   |                                     |          |                  |                                                                                                     | Traffic                                   | No                        |
| 64. | (Bos et al, 2013)                       |                    |                    |           |        |                        |          |                   |                                     |          |                  |                                                                                                     | Urban                                     | No                        |
| 65. | (Liu et al., 2017)                      |                    |                    |           |        |                        |          |                   |                                     |          |                  |                                                                                                     | PM <sub>2.5</sub><br>PM <sub>10-2.5</sub> | No                        |
| 66. | (Cliff et al., 2016)                    |                    |                    |           |        |                        |          |                   |                                     |          |                  |                                                                                                     | Diesel exhaust                            | No                        |
| 67. | (Calderon-Garcidueñas et al., 2008a)    |                    |                    |           |        |                        |          |                   |                                     |          |                  |                                                                                                     | Urban                                     | Yes                       |
| 68. | (Calderon-Garcidueñas et al., 2016a)    |                    |                    |           |        |                        |          |                   |                                     |          |                  |                                                                                                     | Urban                                     | Yes                       |
| 69. | (Shaffer et al., 2019)                  |                    |                    |           |        |                        |          |                   |                                     |          |                  |                                                                                                     | PM <sub>2.5</sub>                         | No                        |

A pollutant is displayed in **red** if it shows detrimental statistically significant associations in at least one cognitive test in a specific domain, or in any type of dementia

A pollutant is shown in **black** if the association reported does not reach statistical significance for any of the cognitive tests in the specific domain, or any type of dementia.

A pollutant is shown in **green** if the associations reported reach statistical significance in at least one cognitive tests in a specific domain, or any type of dementia, and shows a counterintuitive beneficial effect (for example, higher exposure related with better cognition). Green takes preference over red or black.

A cell has an **orange background** if a detrimental association reaching statistical significance in at least one cognitive tests in a specific domain, or any type of dementia, is reported for at least one pollutant.

A cell has a **grey background** if the associations reported do not reach statistical significance for any of the cognitive tests in the specific domain, or any type of dementia, for any of the pollutants.

A cell has a **green background** if a counterintuitive beneficial association reaching statistical significance is reported in at least one cognitive test in a specific domain, or any type of dementia, for at least one pollutant. Green takes preference over orange or black.

All studies report the effect of long-term exposure to air pollution with the exception of those reporting associations between short-term exposure to air pollution exposure and risk of hospitalisations.

**Table 3.15. Summary of consistency of associations between exposure to air pollution or traffic measures and brain imaging outcomes included in the literature review**

| References                            | Total Brain                        |                                    | White Matter          |                       |                       |                       |                   | Grey Matter           |                       |                       |                       |                   |                                    |                   | Regions of interest |                                                                                         |                   |                       | Cerebral Vessel Disease            |                                    |                                    |                      |
|---------------------------------------|------------------------------------|------------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-------------------|-----------------------|-----------------------|-----------------------|-----------------------|-------------------|------------------------------------|-------------------|---------------------|-----------------------------------------------------------------------------------------|-------------------|-----------------------|------------------------------------|------------------------------------|------------------------------------|----------------------|
|                                       | Total brain volume                 | brain parenchymal fraction         | WM brain volume       | WM Frontal            | WM Parietal           | WM Temporal           | WM Occipital      | GM brain volume       | GM Frontal            | GM Parietal           | GM Temporal           | GM Occipital      | Deep Grey                          | GM in AD areas    | corpus callosum     | hippocampal                                                                             | Basal ganglia     | Ventricle             | WMH                                | Micro-bleed                        | covert brain infarcts              | Small Vessel Disease |
| (Wilker et al, 2015)                  | PM <sub>2.5</sub> Traffic-Distance |                                    |                       |                       |                       |                       |                   |                       |                       |                       |                       |                   |                                    |                   |                     | PM <sub>2.5</sub> Traffic-Distance                                                      |                   |                       | PM <sub>2.5</sub> Traffic-Distance |                                    | PM <sub>2.5</sub> Traffic-Distance |                      |
| (Wilker et al, 2016)                  |                                    | PM <sub>2.5</sub> Traffic-Distance |                       |                       |                       |                       |                   |                       |                       |                       |                       |                   |                                    |                   |                     |                                                                                         |                   |                       | PM <sub>2.5</sub> Traffic-Distance | PM <sub>2.5</sub> Traffic-Distance |                                    |                      |
| (Chen et al, 2017c; Chen et al, 2015) | PM <sub>2.5</sub> DPM              |                                    | PM <sub>2.5</sub> DPM | PM <sub>2.5</sub> DPM | PM <sub>2.5</sub> DPM | PM <sub>2.5</sub> DPM |                   | PM <sub>2.5</sub> DPM | PM <sub>2.5</sub> DPM | PM <sub>2.5</sub> DPM | PM <sub>2.5</sub> DPM |                   |                                    |                   | PM <sub>2.5</sub>   | PM <sub>2.5</sub>                                                                       | PM <sub>2.5</sub> | PM <sub>2.5</sub> DPM |                                    |                                    |                                    | PM <sub>2.5</sub>    |
| (Casanova et al, 2016)                |                                    |                                    | PM <sub>2.5</sub>     | PM <sub>2.5</sub>     | PM <sub>2.5</sub>     | PM <sub>2.5</sub>     | PM <sub>2.5</sub> |                       | PM <sub>2.5</sub>     | PM <sub>2.5</sub>     | PM <sub>2.5</sub>     | PM <sub>2.5</sub> |                                    |                   | PM <sub>2.5</sub>   | PM <sub>2.5</sub>                                                                       | PM <sub>2.5</sub> |                       |                                    |                                    |                                    |                      |
| (Power et al, 2018)                   | PM <sub>2.5</sub> PM <sub>10</sub> |                                    |                       |                       |                       |                       |                   |                       |                       |                       |                       |                   | PM <sub>2.5</sub> PM <sub>10</sub> |                   |                     | PM <sub>2.5</sub> PM <sub>10</sub>                                                      |                   |                       |                                    |                                    |                                    |                      |
| (Younan et al, 2020)                  |                                    |                                    |                       |                       |                       |                       |                   |                       |                       |                       |                       |                   |                                    | PM <sub>2.5</sub> |                     |                                                                                         |                   |                       |                                    |                                    |                                    |                      |
| (Hedges et al, 2019)                  |                                    |                                    |                       |                       |                       |                       |                   |                       |                       |                       |                       |                   |                                    |                   |                     | PM <sub>2.5</sub> PM <sub>10</sub> PM <sub>coarse</sub> NO <sub>2</sub> NO <sub>x</sub> |                   |                       |                                    |                                    |                                    |                      |

A pollutant is displayed in **red** if it shows detrimental statistically significant associations in at least one cognitive test in a specific domain, or in any type of dementia

A pollutant is shown in **black** if the association reported does not reach statistical significance for any of the cognitive tests in the specific domain, or any type of dementia.

A pollutant is shown in **green** if the associations reported reach statistical significance in at least one cognitive tests in a specific domain, or any type of dementia, and shows a counterintuitive beneficial effect (for example, higher exposure related with better cognition). Green takes preference over red or black.

A cell has an **orange background** if a detrimental association reaching statistical significance in at least one cognitive tests in a specific domain, or any type of dementia, is reported for at least one pollutant.

A cell has a **grey background** if the associations reported do not reach statistical significance for any of the cognitive tests in the specific domain, or any type of dementia, for any of the pollutants.

A cell has a **green background** if a counterintuitive beneficial association reaching statistical significance is reported in at least one cognitive test in a specific domain, or any type of dementia, for at least one pollutant. Green takes preference over orange or black.

All studies report the effect of long-term exposure to air pollution with the exception of those reporting associations between short-term exposure to air pollution exposure and risk of hospitalisations.

DPM is diesel particulate matter.

## 3.4 Confounding factors

Epidemiological analysis aims at establishing whether a specific exposure is a cause of disease, that is, changes the risk of disease. In evaluating the association between exposure and outcome, it is of utmost importance to consider whether the observed effect is truly associated with the exposure or if alternative explanations are possible. Hence, confounding factors (factors that might distort the true association and/or influence its interpretation) need to be carefully considered. Identifying and controlling/adjusting for confounding factors in the assessment of the effects of air pollution on cognitive decline and dementia is as important as in the case of any other health outcome (for example, cardiovascular disease). It is, however, more difficult, as there are many factors which are not well understood that affect cognition and cerebrovascular health. In addition, it is likely that a number of unknown factors may be playing a part. For instance, a recent paper has reported the effect of air pollution on depression and anxiety (Roberts et al, 2019); yet depression (Ownby et al, 2006) and anxiety (Wilson et al, 2011) have also been identified as potential risk factors for cognitive decline and dementia, hence further research is required to understand whether depression and anxiety act as confounders or as mediators.

Factors that should be considered in the analysis of the effects of air pollution on cognitive decline and dementia include age, sex, education, socioeconomic status, ethnic background, smoking, alcohol intake, body mass index, co-morbidities - such as cardiovascular disease, cerebrovascular disease, diabetes and mental health - and sleep deprivation. Other factors related to exposures should include exposure to noise, environmental tobacco smoke, indoor sources (for example, indoor biomass or wood burning), neurotoxins (for example, lead, mercury, pesticides, persistent organic pollutants) from dermal and/or dietary exposure routes.

Most of the studies we have reviewed have adjusted for a number of standard confounding factors such as socioeconomic factors, personal characteristics (for instance age and sex), educational attainment or comorbidities (Killin et al, 2016a; Tzivian et al, 2015a) that might have affected the observed association between air pollution and cognitive performance, cognitive decline, neurological structural changes and dementia incidence. Adjustments for other possible confounding factors were made in some studies, but this has been highly variable (Killin et al, 2016a). Tables 3.1 to 3.12 detail the list of confounding factors that have been considered in the reviewed studies.

Studies have adjusted for individual-level factors whenever available. However, area-level adjustment has been implemented where individual factors were not available (for example, Chen et al 2017b adjusted for area-level socioeconomic factors, but for individual-level co-morbidities diabetes, brain injury). Studies where confounders have individual-level adjustment are likely to have less result bias. Goodman et al (2011) concluded that limited residual socioeconomic confounding existed in epidemiological studies that included comprehensive area-level adjustment. However, this cannot be extrapolated to other confounding factors, such

as smoking, drinking or pre-existence of comorbidities, for which area-level indicators might not adequately control.

Factors indicating social integration and social networks (Zunzunegui et al, 2003), physical activity, contact with nature (access to green and blue spaces) (de Keijzer et al, 2018), sleep quality and quantity (Bliwise, 1993; Ju et al, 2014), depression, anxiety and stress (Wilson et al, 2011) should be also considered in epidemiological analysis, as these have been linked with cognitive performance, cognitive decline and dementia. With the exception of depression, stress and anxiety, these factors have not been accounted for in any of the reviewed studies.

The majority of the studies have controlled for the standard confounding factors. Controlling for other possible confounders has not been consistently implemented in all the studies. Despite all the efforts to account for potential confounding in the reviewed papers, possible residual confounding cannot be completely ruled out. Further research should take account of additional potential confounders (for example, social interactions, sleep, physical activity) and should investigate whether the observed associations with traffic exposure reflects exposure to air pollution, or some other correlated factor such as poorer socioeconomic status, noise, or any of the myriad features of urban living.

The next section details the different confounding factors that have been included in the reviewed studies.

### 3.4.1 Review of evidence on confounding factors

The neurocognitive responses considered in the studies reviewed here might not, of course, be caused by exposure to air pollution. Instead, they might reflect effects on cognition of other factors acting at different ages (Clifford et al, 2016). This section describes several putative causes and confounding factors that should be accounted for when investigating the association between exposure to air pollution and risk of cognitive impairment, cognitive decline and dementia. For a high probability of causality to be inferred, the Bradford Hill characteristics of causal associations should be established in the absence of confounding or upon controlling for any confounding factors that could not be removed in the studies reviewed.

Environmental factors other than air pollutants of current importance might also contribute to the observed association between air pollution and cognitive decline. Past chronic exposures to lead, for example from leaded gasoline, could confound the observed associations, since lead exposure is associated with poor cognitive functioning (Bakulski et al, 2012). In addition, lead exposure could still play a part as lead is a minor constituent of air pollution from sources such as tyre wear and incinerators (Sanderson et al, 2014). Power et al (2012) adjusted for past lead exposures and did not report significant changes in their results. Other environmental neurotoxicants, such as mercury, polychlorinated biphenyls, pesticides and ionising radiation might also play a part or act as confounding factors (Xu et al, 2016). While multiplicative and

additive effects of these neurotoxins with air pollution are possible, none of the reviewed studies has examined such an interaction (Xu et al, 2016).

Smoking and, in non-smokers, Environmental Tobacco Smoke (ETS) have been associated with cognitive impairment (Llewellyn et al, 2009) and with increased risk of dementia and Alzheimer's disease (Chen, 2012; Chen et al, 2013; Ott et al, 2004). Drinking alcohol might be another confounding factor. Some studies reported mixed effects of alcohol intake on cognition (Xu et al, 2016). However, a more recent study found that even moderate alcohol use is a risk factor for dementia (Sabia et al, 2018).

The association between air pollution and Body Mass Index (BMI) is controversial. BMI has been associated with lower cognitive ability (Dahl et al, 2010; Kerwin et al, 2010) and more rapid cognitive decline in later life (Dahl et al, 2010). BMI has also been related to global loss and regional alterations in grey matter volume in healthy adults (Taki et al, 2008). In contrast, a study reported that elderly subjects with a BMI >23 had lower risk of cognitive decline than did elderly subjects with a BMI <23 (Deschamps et al, 2002). Traffic pollution has been associated with increased BMI in children from the Southern California cohort (Jerrett et al, 2014) and with obesity, higher fat content and larger BMI in adults participating in the Framingham Heart Study (Li et al, 2016). Further studies are required to disentangle whether BMI mediates the association between exposure to air pollution and cognitive decline or is a confounder.

Indoor and personal exposures might differ from those estimated by means of geostatistical or proximity models used in most of the reviewed studies (Clifford et al, 2016c; Xu et al, 2016).

It is possible that these factors might confound the relationships observed in some studies. However, studies which adjusted for smoking (Ranft et al, 2009; Sun and Gu, 2008; Wellenius et al, 2012), ETS exposure (Ranft et al, 2009; Schikowski et al, 2015), alcohol consumption (Chen and Schwartz, 2009; Power et al, 2011; Sun and Gu, 2008; Weuve et al, 2012) and for indoor sources (Chen and Schwartz, 2009; Ranft et al, 2009) in their analyses still reported statistically significant associations between ambient air pollution and cognitive performance.

Noise has been suggested as an environmental factor affecting cognitive performance. A study of police officers and office workers showed an effect of noise on arithmetic performance and logical reasoning, as well as on attention (Chiovenda et al, 2007), but authors did not investigate the possible interaction between air pollution and noise. Recent studies conducted in the Heinz Nixdorf Recall study found that noise acts synergistically with air pollution (Tzivian et al, 2017). Air pollution had negative effects on general cognition irrespective of the noise level considered, but the effect was enhanced by higher noise levels. Noise showed a negative trend in relation to cognitive performance in single-agent models, but in 2-pollutant models the negative effect remained only when higher concentrations of pollution were considered (Tzivian et al, 2017). Similar results were found when the effects of air pollution and noise on mild cognitive impairment (MCI) were investigated. Associations between PM<sub>2.5</sub> and MCI were stronger in participants with high noise exposure, whilst the effect of noise was enhanced in

those subjects exposed to higher PM<sub>2.5</sub> concentrations (Tzivian et al, 2016). Carey et al (2018) also found in London that the effect of noise on dementia incidence was no longer statistically significant when adjusted for PM<sub>2.5</sub> or NO<sub>2</sub>. Likewise, no association was found between road traffic noise and risk of developing dementia in the Betula study. In addition, the effect of NO<sub>2</sub> was not modified by adjusting for noise, nor was a significant interaction effect on dementia risk found between noise and NO<sub>2</sub> (Andersson et al, 2018). Additionally, short-term noise exposures have been associated with increased daily dementia-related hospital admissions (Linares et al, 2017). However, few of the epidemiological studies reviewed adjusted for noise levels.

Reduced exposure to green spaces could also be a confounding factor. However, evidence of the effect of 'greenness' on cognition is limited. Studies conducted in children suggest that 'lifelong residential greenness' is associated with increased attention and reduced reaction time (Dadvand et al, 2017), with greater progress in the development of working memory over a calendar year (Dadvand et al, 2015) and with greater cerebral grey and white matter volumes in regions associated with better working memory and reduced inattentiveness (Dadvand et al, 2018). Controlled laboratory studies with adults have indicated that access to green spaces could buffer stress and facilitate cognitive restoration after mental fatigue (Berto, 2005; Mantler and Logan, 2015).

Socioeconomic factors may also play a role. Several potential individual-level and area-level socioeconomic factors could affect the relationship between air pollution exposure and cognitive and neurodegenerative health outcomes. Deprived neighbourhoods are more likely to experience high levels of air pollution (Xu et al, 2016) and lower educational attainment, the latter being associated with an increased risk of dementia later in life (Stern, 2012). Power et al (2016) suggest that sociocultural background may affect the associations between air pollution and cognitive performance, whereas cognitive decline was less susceptible to sociocultural background factors. Socioeconomic factors were also suggested by Xu et al (2017) to explain results of more rapid cognitive decline in residents of rural areas compared with those living in urban areas, which were at odds with the broad conclusions of the reviewed literature. The authors suggested that this effect might have been related to poor access to socioeconomic benefits, such as access to health care and retirement pensions for subjects living in rural areas.

Sex was identified as a confounding factor in a study that showed that women had stronger association between PM<sub>2.5</sub> exposure and cognitive disability in low and middle-income countries, which might be related to inadequate control for indoor air exposure (Lin et al, 2017a).

Poor early cognitive development could also act as a confounder. People with lower cognitive development might have poorer occupational prospects, lower socioeconomic status, be more exposed to pollution and be subject to other risks factors (for example, smoking) later in life. As discussed above, all these have been considered potential confounders of risk estimates.

Pre-existing comorbidities, such as stroke (Bejot et al, 2011; Kalaria et al, 2016) or chronic diseases including hypertension (Faraco and Iadecola, 2013), diabetes mellitus (Biessels et al, 2006), and depression (Byers and Yaffe, 2011; Tallon et al, 2017) could lead to cognitive decline and dementia. Several of the reported studies excluded individuals with history of stroke or chronic disease, which could confound the relationship between air pollution and cognitive decline. On the other hand, such exclusion might have affected the results by over-controlling for mediating factors (Clifford et al, 2016). Some studies which included adjustment for factors related to cardiovascular disease have shown an attenuation of the effect (Chen and Schwartz, 2009; Loop et al, 2013), suggesting that cardiovascular health might be a factor mediating the effect of air pollution on cognitive performance or decline (Tzivian et al, 2015a).

## 3.5 Effect modifiers

A number of factors have been shown to increase the coefficients linking air pollutant concentrations with effects on the brain: these are referred to as effect modifiers. This section reviews the evidence on several putative 'host characteristics' which could potentially influence the risk of deleterious effects of air pollution on cognition and dementia, to determine whether these factors are acting as effect modifiers. The reviewed factors include being an *APOE*  $\epsilon$ 4 allele carrier, the presence of single nucleotide polymorphisms in microRNA-processing genes, telomere length in leukocytes, pre-existent medical conditions (for example, diabetes mellitus, cardiovascular disease, cerebrovascular disease, mental health), body mass index (BMI), smoking, alcohol consumption, sex, education (a surrogate of cognitive reserve) and neighbourhood social stressors.

The existing evidence for each of these factors is detailed below. In general, effect modifiers have been investigated in very few studies, and replication would be required to confirm or exclude any of the factors as effect modifiers. The very few cases where more than one study assessed a specific factor show heterogeneous results. For instance contrasting results have been reported for the following factors as effect modifiers in different studies: being an *APOE*  $\epsilon$ 4 allele carrier (1 of 6 studies); diabetes mellitus (2 of 4); cerebrovascular disease (2 of 3); mental health (1 of 2); body mass index (1 of 2); and sex (1 of 2). Pre-existing cardiovascular disease was rejected as an effect modifier in all studies (3 of 3) and smoking was identified as an effect modifier in all studies (2 of 2).

### 3.5.1 Review of evidence on effect modifiers

The SALIA cohort study reported statistically significant larger concentration-effect functions between traffic ( $p\text{-value}_{\text{interaction}} = 0.0069$ ) and  $\text{PM}_{2.5\text{abs}}$  ( $p\text{-value}_{\text{interaction}} = 0.0380$ ) and reduced constructional praxis in carriers of the *APOE*  $\epsilon$ 4 allele (Schikowski et al, 2015). On the other hand, although Cacciottolo et al (2017) reported higher hazard ratios associated with exposure to  $\text{PM}_{2.5}$  for cognitive decline and dementia amongst *APOE*  $\epsilon$ 4 allele carriers, these interactions were not statistically significant. Likewise, Cleary et al (2018) reported faster cognitive decline rates in subjects harbouring at least one *APOE*  $\epsilon$ 4 allele than in non carriers (but p-



values<sub>interaction</sub> were not reported) (Cleary et al 2018). Wu et al (2015) did not find significant interactions between *APOE*  $\epsilon$ 4 allele genotype and air pollution, for either Alzheimer's disease or vascular dementia. Similarly the Betula study found no evidence for a modifying of *APOE*  $\epsilon$ 4 on the association between NO<sub>x</sub> exposure and all-type dementia or AD (p-value for interaction >0.30 for both) (Oudin et al, 2019).

MicroRNAs (miRNAs) are involved in neuroplasticity, neurodevelopment, synapse formation and maturation, and stress responses (Sharma and Lu, 2018). Alterations in miRNA levels have been reported in a variety of neurological disorders (Femminella et al, 2015; Maes et al, 2009; Miya Shaik et al, 2018; Sharma and Lu, 2018; Swarbrick et al, 2019). miRNAs have also been associated with vascular cognitive impairment in animal models (Ren et al, 2018). Single nucleotide polymorphisms in miRNA processing genes affected the association between BC exposure and global cognition and MMSE scores. The association between BC and MMSE was stronger in heterozygous carriers of the single nucleotide polymorphism rs11077 in gene *XPO5* (OR = 1.99; 95% CI 1.39, 2.85; p-value<sub>interaction</sub> = 0.01; false discovery rate (FDR) = 0.09) and minor variant carriers of polymorphism rs2740348 in gene *GEMIN4* (OR = 1.34; 95% CI 1.05, 1.7; p-value<sub>interaction</sub> = 0.01; FDR = 0.13), compared to their major variant. The association between BC and global-cognition was stronger in heterozygous carriers of polymorphism rs4968104 (-0.10 SD; 95% CI -0.18, -0.02; p-value<sub>interaction</sub> = 0.004; FDR = 0.04), and rs910924 (-0.09 SD; 95% CI -0.17, -0.02; p-value<sub>interaction</sub> = 0.01; FDR = 0.04) in *GEMIN4* relative to the major variant (Colicino et al, 2016). All results are considered relevant provided that FDR <0.15.

Leukocytes with longer telomere length have been shown to be more responsive to inflammatory stimuli. Colicino et al (2017) reported a study of older men which showed that the association between BC concentration and reduced cognitive function was strongest in those with longer leukocyte telomeres (p-value<sub>interaction</sub> = 0.04). A similar increase in effect was seen in those with high C-reactive protein levels (p-value<sub>interaction</sub> = 0.04). This work suggests a link between inflammation and cognitive effects on the brain.

Pre-existing medical conditions have been suggested as effect modifiers, although results are inconclusive. Subjects with diabetes mellitus (DM) or who had suffered a stroke had lower hazard ratios for dementia for PM<sub>2.5</sub> exposure in Canada (p-value<sub>interaction</sub> = 0.003 and 0.030, respectively) (Chen et al, 2017a). The authors suggested that the additional effect from pollution might have been masked by the heightened baseline risk profile of patients with these comorbidities (Chen et al, 2017a). A recent study in London found higher (and statistically significant) adjusted hazard ratios for incidence of dementia due to exposure to NO<sub>2</sub> in subjects without comorbidities (IHD, stroke, DM or heart failure), although the interaction with comorbidities was non-significant (p-value<sub>interaction</sub> = 0.31) (Carey et al, 2018). The associations between exposure to PM<sub>2.5</sub> and diesel PM with white matter or grey matter volumes, mild cognitive impairment or dementia were not significantly modified by existing cardiovascular diseases, or DM, with the exception of diesel PM and grey matter parietal volumes with DM (p-value<sub>interaction</sub> = 0.03) (Chen et al, 2017c). Tallon et al (2017) did not find any interaction between DM or hypertension on the association between air pollution (PM<sub>2.5</sub> and NO<sub>2</sub>) and changes in

cognitive function. However, the effect of PM<sub>2.5</sub> on cognitive decline was more evident in those without pre-existing disease, stroke ( $p = 0.046$ ), anxiety ( $p = 0.03$ ) and stress ( $p = 0.01$ ), all factors with  $p$ -value for interaction  $<0.05$  (Tallon et al, 2017). On the other hand, Tzivian et al (2016) found that whilst associations between PM<sub>2.5</sub> and mild cognitive impairment were stronger in subjects with depressive disorders, the interaction was non-significant ( $p$ -value<sub>interaction</sub> = 0.43). It is of interest to note that the National Social Health and Aging Project (NSHAP) cohort study examined the mediation effect of mood disorders on the association between air pollution and cognitive decline and suggested that the impacts of PM<sub>2.5</sub> and NO<sub>2</sub> on cognitive performance were mediated by depression and stress, respectively (Tallon et al, 2017).

BMI was suggested as an effect modifier of the association between PM<sub>2.5</sub> and white matter volumes in the parietal association region ( $p$ -value<sub>interaction</sub> = 0.03) and the association between diesel PM and grey matter and ventricular volumes ( $p$ -value<sub>interaction</sub> = 0.03) (Chen et al, 2017c). On the contrary, BMI was not found to be an effect modifier of the association between PM<sub>2.5</sub> or NO<sub>2</sub> with changes in cognitive function by (Tallon et al, 2017).

Smoking was suggested as a modifying factor of the effect of air pollution on cognition ( $p$ -value<sub>interaction</sub> = 0.02-0.04) (Ailshire and Crimmins, 2014; Tzivian et al, 2016). Tzivian et al (2016) found that associations of PM<sub>2.5</sub> and mild cognitive impairment were stronger in subjects with no or moderate alcohol consumption ( $p$ -value<sub>interaction</sub> = 0.05) (Tzivian et al, 2016).

Sex may affect the association between exposure to air pollution and decline in cognitive performance (Tzivian et al, 2015a). Elderly men showed a larger detriment of performance on verbal tests associated with air pollution in China for mean air pollution index representative of 30 days ( $p$ -value<sub>interaction</sub>  $<0.01$ ), 1 year and 3-years ( $p$ -value<sub>interaction</sub>  $<0.05$ ) (Zhang et al, 2018) than women. A recent study also suggested a larger effect of air pollution on incidence of dementia in men in London but this interaction was non-significant (Carey et al, 2018).

Education was investigated by Wellenius et al (2012) and shown to modify ( $p$ -value<sub>interaction</sub> = 0.007) the odds ratio of getting a low score ( $<26$ ) in the MMSE global cognition test with an IQR decrease in residential distance to a major roadway (851 metres); the OR was higher for subjects who received college or higher education. A similar modifying effect was suggested for the association between IQR decrease in residential distance to traffic roadside and trail-making test part B scores measuring executive function, but was non-significant ( $p$ -value<sub>interaction</sub> = 0.085) (Wellenius et al, 2012).

Ailshire et al (2017) reported an interaction ( $p$ -value<sub>interaction</sub>  $<0.05$ ) between air pollution and neighbourhood social stressors and reduced cognitive performance. A stronger inverse association between PM<sub>2.5</sub> and cognitive function was found among those subjects exposed to stressful neighbourhood conditions (general lack of upkeep of the neighbourhood, litter in the streets, deteriorating buildings, empty properties) (Ailshire et al, 2017). Their findings remained significant after adjusting for several individual and community-level socioeconomic and

demographic factors. Synergy between air pollution and neighbourhood stress in causing poor cognitive performance is consistent with the neurotoxicity hypothesis suggesting that exposure to stress can increase the rate at which neurons are damaged by toxic challenges (McEwen and Tucker, 2011).

## 3.6 Strengths and limitations of the reviewed literature

The reviewed papers cover a wide range of study designs, including longitudinal, case-control, cross-sectional, and time-series analysis from population-based and prospective cohorts. There have been several large studies, from thousands to millions of subjects. The methodology of the majority of the studies is of very high quality and standard cognitive test and neuroimaging methods have been used.

On the other hand, the limitations include the difficulty in specifying exposure with temporal and spatial misalignment, as well as using surrogate measures of exposure, such as models and a geostatistical interpolation of concentrations measured at the nearest monitors. There is also difficulty in linking some of the endpoints studied (for example, decline in attention) with clinical effects of relevance to this review (for example, mild cognitive impairment, dementia). It is difficult to separate the effects of a mixture of various air pollutants. Despite most of the studies controlling for relevant confounding factors, not all studies have controlled for the same factors, and there is still the possibility of not controlling for unaccounted-for confounding factors. The strengths and limitations of the reviewed studies are discussed in detail below. The quality of most reviewed studies was adequate, after consideration of the exposure and outcome assessment and inclusion of confounding factors.

All the studies used standard cognitive tests to assess cognitive performance. The MMSE has been widely used to assess general cognitive performance as well as cognitive impairment, though it was specifically designed as a screen for early impairment and is relatively poor at assessing general cognitive performance. The threshold used to define impairment in the MMSE test varied among different studies from 18 to 26 out of a maximum score of 30 (Peters et al, 2015). In addition, whilst many studies focused on general cognition, relatively few analysed several cognitive domains at the same time. For instance, Chen and Schwartz (2009) studied the effects of air pollution on attention, short-term memory, constructional praxis and coding ability, whilst Wellenius et al (2012) focused on immediate, delayed and working memory, and language. Many other studies focused only on only one cognitive domain. Some studies assessed the effect of air pollution on dementia using prevalence and incidence of dementia documented in medical records (for example, ICD-9 or ICD-10 codes), which might lead to substantial misclassification. For example, a US-study identified that in only 56% of subjects diagnosed as having a dementia-associated disease could the diagnosis be pathologically confirmed (Taylor et al, 2009). This may be an example of over-diagnosis, though the sensitivity of methods used in studies of pathological changes might be questioned, but

under-diagnosis is also a problem, since only around half of cases in the community are known to clinical services. Under-diagnosis in medical records might not be independent of air pollution exposure since subjects exposed to elevated air pollution are more prone to have cardiorespiratory conditions, leading to frequent interaction with the medical community and an increased chance of diagnosis of dementia. Misdiagnosis of dementia in non-demented people might also influence such studies. Consistent with the advice of Power et al (2016), some caution should be exercised in interpreting the findings of studies relying on ICD codes to evaluate the effect of air pollution on dementia.

Some cohort studies have included representative sex and ethnic strata, whilst others included one sex only (for example, Weuve et al, 2012) or assessed only a selected population group (for example, Wurth et al, 2018). The age of the participants studied has been diverse though most studies have focused on the elderly, who are at greater risk of cognitive decline. However, subjects with the highest exposure and/or poorest levels of cognition are less likely to participate in this type of study (Power et al, 2016) and more likely to discontinue participation in longitudinal studies, leading to selection bias (Killin et al, 2016a). Some studies are clearly not representative of the general population (Peters et al, 2015; Power et al, 2016).

Most of the reviewed articles included versions of logistic and linear regression with adjustment for a range of relevant potential covariates (Peters et al, 2015), although some made very crude adjustments for sociodemographic confounders (Power et al, 2016). Hence, the possibility of residual confounding remains (Killin et al, 2016a). Some studies accounted for repeated measurements and for clustering effects (Peters et al, 2015). Those studies which appropriately adjusted for sociodemographic factors and cardiovascular disease tended to report consistent associations (Power et al, 2016). The magnitude of the risks reported from individual studies will be a function of the health outcomes and exposures to air pollution. Exposures need to be assigned to health outcomes, with both ideally aligned in space and time, the latter allowing for the expected lag between exposures and outcome.

In the case of spatial alignment, assigning exposures to individuals and/or populations in an observational study will, of necessity, often involve a degree of approximation. Exposures are commonly based on measurements from ground monitors that are located in proximity to an individual's place of residence, or the average of measurements made within an administrative area in which a population resides. Alternatively, exposures may be assigned based on modelled concentrations, again often at the place of residence or, in aggregated form, to an administrative area. The use of existing air quality monitors, geo-statistical modelling, or surrogate measures of exposure based on distance to major roads may not adequately reflect individual exposures of subjects participating in the cohort studies (Peters et al, 2015; Xu et al, 2016). None of the studies has characterised individual exposures or adjusted for personal activity patterns (Xu et al, 2016). The approaches used in the reviewed studies might be valid for pollutants that disperse homogeneously over the urban landscape (for example, PM<sub>2.5</sub>), but would be less appropriate for those pollutants with a heterogeneous distribution influenced by local sources (for example, BC, NO<sub>x</sub>) or with shorter residence times (for example, PM<sub>10</sub>).

2.5)(Power et al, 2016). Measurement error may also explain some of the inconsistencies observed in the cognitive effect estimates (Power et al, 2016).

Temporal alignment of health outcomes and exposures over time can often be problematic due to the lack of availability of measurements (and/or modelled estimates) for specific pollutants of interest over the required time period, especially where long-term exposure is of interest. As such, there may be exposure misclassification over both space and time which, in this context, represents a variety of mechanisms that result in differences between assigned exposures and the 'true' exposures of the population at risk at a specified period of time. This includes differences between the 'true' concentrations and measurements and/or modelled values, used when estimating risks, and differences between concentrations and personal exposures.

Examples of temporal misalignment include where exposure data was gathered at different times than when the cognitive tests were performed (generally prior to testing) (Peters et al, 2015). Many of the reviewed studies assessed chronic exposure to air pollution at the current residence of the participants, using a single mean or a composite chronic exposure measure covering less than a 5-year period. Indeed, many studies used shorter periods (such as one to 2 years) (for example, Ailshire and Clarke, 2015, Wilker et al, 2015), whilst newer studies and those assessing incident dementia considered exposures of up to 7 to 14 years (Chen et al, 2017a; Chen et al, 2017c; Jung et al, 2015; Wu et al, 2015). It may be useful to assess the cumulative exposure of a subject given the residential history (Killin et al, 2016a). However, length of residence at the same residential address was not mentioned in most of the studies (Tzivian et al, 2015a). In addition, for those subjects who had changed residence, current residential exposures may not be good surrogates of long-term exposures. The approach might be appropriate if the measured and aetiological windows are close in time but the validity is questionable over longer intervals (Power et al, 2016). This is of special relevance in the current discussion, since the development of dementia involves a long prodromal phase, generally >14 years. Hence recent exposures might not be truly reflective of the window of exposure critical for the health effect under consideration.

If the impact of air pollution on cognition is subtle, multiple testing with detailed neuropsychological tests over time would be required to observe any significant effect (Peters et al, 2015). Hence, longitudinal design including multiple cognitive testing and exposure measurements over a period of time would be very useful to identify critical or sensitive periods within the life course (Killin et al, 2016a).

Studies that included a large variation in estimated exposure were more likely to report significant associations, whereas those with small exposure variability were more likely to report heterogeneous or largely null results (Power et al, 2016). The magnitude and significance of risks may be sensitive to the characterisation of exposures in statistical models that are used to estimate the risks (and associated measures of uncertainty). The relationships between exposures and health outcomes may be non-linear but the use of non-linear models (for the exposure-health relationship) is not common in this setting. If the relationship is non-linear, then

assuming linearity may result in biased estimates of risk. This may be overcome to some extent by categorising exposures but the choice of boundaries for individual categories can itself have an effect on the resulting risk estimates. In addition to the issues associated with the exposure-outcome relationship, the uncertainty associated with estimated exposures when using modelled estimates, or the temporal misalignment between exposures and health outcomes is rarely acknowledged. A complex form of ‘measurement error’ (Gryparis et al, 2009), can result in bias in both estimates and associated uncertainties and thus potentially in subsequent conclusions based on significance.

Bradford Hill wrote his guidelines mainly focused on avoiding making Type I errors: that is, rejecting the null hypothesis (the null hypothesis being that there is not an effect) when in fact it is true. It can be argued that under the precautionary principle, the Type II error, making the opposite mistake and accepting the null hypothesis that there is no effect when in fact there is an effect (when the null hypothesis is actually false) is more important when public health is at risk. The problem in statistical terms is that as the risk of making a Type I error reduces, the risk of making a Type II error increases. The capability of avoiding a Type I error is defined by the p value (commonly 0.05) whereas the capability to avoid Type II error is defined by the power of the statistical test. Increasing the number of subjects studied is the only way of avoiding both error types in well designed epidemiological studies, for example, free from bias and unmeasured confounding. The sample size of some of the cohort studies is large – from thousands to millions of subjects – implying high statistical power and high power to avoid Type I and Type II errors in the reported results. The large sample size also implies that effect sizes rather than statistical significance need to be considered. The effect sizes may be over-estimated by the inability to account for lower cognitive ability selecting into exposure, although this earlier selection would not explain the effects of lifetime exposure. Nonetheless, some of the studies with a lower number of participants (190 to 400) still reported significant associations (for example, Sanchez-Rodriguez et al, 2006). The studies assessing neurological biomarkers examined responses in small numbers of participants (for example, 20 to 60), which might have contributed to the heterogeneity of the results, affecting their validity and making generalisation of their results difficult (Xu et al, 2016).

The majority of the reviewed studies (58 out of 69) were conducted in high-income countries (Killin et al, 2016a). Eleven studies reported associations in low- to middle-income countries and found results consistent with those in developed countries (Calderón-Garcidueñas et al, 2008a; Calderón-Garcidueñas et al, 2016a; Lin et al, 2017a; Qiu et al, 2019; Rafiee et al, 2020, Salinas-Rodriguez et al, 2018; Sanchez-Rodriguez et al, 2006; Sun and Gu 2008; Xu et al, 2017; Zeng et al, 2010; Zhang et al, 2018).

Studies have used a wide variety of cognitive tests to assess outcome, and a diverse range of air pollutants has been considered (Clifford et al, 2016c). Therefore, we do not consider a formal meta-analysis, in which an overall effect would be estimated, to be appropriate in this setting at this time. The wide variety of study designs, health related outcomes, exposure metrics, whilst contributing the overall body of evidence, means that it is not possible to isolate a

single and well-defined relationship that can be represented by a coefficient derived from an adequate meta-analysis. In addition, despite several studies having a large number of participants, the majority of studies have relatively small sample sizes when compared to the few large-scale studies based on electronic medical records in North America (2.2 to 9.8 million). As such, the latter would dominate meta-analysis calculations to an extent that would mean that any overall estimates might not fairly represent the current field of knowledge.

Comparing the effect of different pollutants is also not possible at this stage, and hence the pollutants responsible for the observed outcomes cannot be identified with confidence from the epidemiological literature. Likewise, it is difficult at this stage to evaluate whether air pollution exposure predominantly affects functioning in any particular cognitive domain (Power et al, 2016). In addition, the effect estimates are non-comparable, also precluding evaluation of the likelihood of publication bias (Clifford et al, 2016c; Power et al, 2016).

No study was found which had assessed the association between air pollution and markers of pathological accumulation of A $\beta$  or hyperphosphorylated tau in older adults and elderly participants (Power et al, 2016). Also, whereas some studies assessed within-person change of cognitive function, none has studied within-person brain structural changes related to air pollution (Power et al, 2016). It is also relevant to note that there are usually multiple contributors to dementia in older people (including not only Alzheimer's disease pathology but also Lewy body and vascular pathology, among others), and so a clinical diagnosis of 'Alzheimer's disease', the outcome measure in many of the epidemiological studies considered in this review, is likely to have subsumed a range of different pathological processes. Further studies should consider these research gaps.

## 3.7 Strengths and limitations of this literature review

The current literature review has both strengths and limitations. The strengths include:

1. The number of available studies that have been reviewed and are included in this review is the largest ever reviewed assessing the effects of air pollution on cognitive decline and dementia (69 studies).
2. These studies cover many endpoints, such as global cognition, specific cognitive domains (executive function, attention, memory, constructional praxis and coding ability, language), cognitive function decline, mild cognitive impairment, dementia and Alzheimer's disease, hospital admissions, brain morphology, and neurological biomarkers. A similar approach was conducted by Power et al (2016), but the current review expands the body of evidence from 18 to 69 papers and also includes evidence on neurological biomarkers.
3. Epidemiological studies conducted worldwide have been included, without restricting for study design. These studies are from many different locations in Europe, North America and Asia. Whilst most of the studies originate from developed countries, one study focused on 6 low and middle-income countries, including China, India, Ghana, Mexico, Russia and South

Africa (Lin, 2017), 5 studies studied populations in China (Sun and Gu 2008; Zhang 2018; Xu 2017; Zeng 2010; Qui 2019), 4 in Mexico (Sanchez-Rodriguez 2006; Salina-Rodriguez 2018; Calderón-Garcidueñas 2008a; Calderón-Garcidueñas 2016a) and one in Iran (Rafiee 2020).

4. The Bradford Hill features of causal associations have been applied to assess the likelihood of causality of the association between air pollution exposure and cognitive decline and dementia. Therefore, it expands the analysis conducted by Clifford et al (2016), who used this approach focused only on cognitive performance, and reviewed only 13 papers in this area.
5. This review includes evidence published up to September 2019.

The limitations of the current review include:

1. This is not a systematic review. Despite this, we believe that all epidemiological papers on air pollution and cognitive decline published up to December 2019 have been included as a very comprehensive search was performed.
2. Our literature search was completed in December 2019 and we are aware that additional studies on this topic have been published since this cut-off date. A literature search in ISI Web of Science identified 28 new relevant papers published from December 2019 to December 2020. The findings of these studies are consistent with those of the studies included in this review. All new identified studies report at least one detrimental association with an air pollution metric, these associations were statistically significant in 27 out of the 28 studies. Some studies report associations with several pollutants, not all of which reach statistical significance.<sup>19</sup> Therefore, we are confident that the new available evidence does not alter our overall conclusions. A systematic review of the epidemiological studies on air pollution exposure and late-life cognitive health has been recently published (Weuve et al, 2021). The authors updated the epidemiological evidence previously evaluated (Power et al, 2016) by including studies published from August 2015 to December 2020. Consistent with our interpretation, the authors concluded that: “strong conclusions remain elusive, although the weight of the evidence suggests an adverse association between PM<sub>2.5</sub> and cognitive decline”.
3. A meta-analysis could not be performed due to the heterogeneity of the outcomes and the pollutants considered as well as the study designs used.

## 3.8 Outcomes from existing published epidemiological reviews (2015 to 2016)

Peters et al (2015) reviewed 8 articles reporting the effect of air pollution on cognitive performance and 2 articles related to cognitive decline. Reviewed studies report mixed results,

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<sup>19</sup> This overview is based on information available in the papers' abstracts. More detailed reading of the full papers was not undertaken, as this was outwith the scope of our work.



but overall suggest an association between long-term exposure to air pollution and poorer cognitive function. Mixed results were found for the effect on cognitive decline in the 2 reviewed papers, although some evidence existed for an association between air pollution exposure and risk of cognitive decline.

Tzivian et al (2015) reviewed 15 articles finding that long-term air pollution concentration was associated with one or various measurements of global cognitive function, verbal and non-verbal learning and memory. They concluded that the reviewed evidence generally supports a possible effect of chronic exposure to air pollutants on neurocognitive function. They argued that since reported associations differed in effect size and the cognitive domain showing a positive association, results between studies cannot easily be compared.

Clifford et al (2016) reviewed 13 papers quantifying the relationship between air pollution and cognitive performance and decline. They concluded that the reviewed evidence was coherent in suggesting that exposure to traffic air pollution is associated with quantifiable cognitive decline in the elderly. Due to the different air pollution indices and cognitive end-points measured in the reviewed papers, the limited number of papers and the possibility of publication bias, Clifford et al (2016) argued that insufficient evidence currently exists to allow comment on the consistency of the published findings.

Power et al (2016) reviewed 18 papers and almost all reported an adverse association between at least one air pollutant and one outcome relevant for dementia. They concluded that the epidemiologic evidence is highly suggestive of an association between exposure to air pollution and dementia. They suggested that episodic memory might decline in tandem with other functional domains such as working memory, visuospatial ability, semantic memory and perceptual speed.

Killin et al (2016) reviewed 4 papers and found moderate evidence of an effect of air pollution on dementia.

Xu et al (2016) reviewed 26 articles and concluded that, despite some weaknesses in study designs and mixed findings, there is mounting evidence suggesting adverse effects of ambient or traffic-related air pollution on dementia and neurobehavioural performance in the adult population.

## 3.9 Conclusions

The evidence reviewed is consistent in reporting associations between chronic exposure to air pollution and reduced global cognition. The evidence is also generally consistent in reporting associations between air pollution and visuospatial abilities. Results are heterogeneous as regards executive function, attention, memory, language and mild cognitive impairment.

Cognitive decline and dementia incidence have been almost consistently associated with exposure to air pollution.

The reviewed studies of white matter volume consistently reported associations between exposure to air pollution and reduced white matter volume. Heterogeneous results were found for markers of cerebrovascular health: no association was found with small vessel ischaemic disease or microbleeds, but associations were reported for covert brain infarcts and (counter-intuitively) a lower prevalence of white matter hyperintensities. Associations between air pollution and hippocampal volume were also heterogeneous.

The few studies available on neuro-inflammation tend to report associations with chronic exposure to air pollution.

Several effect modifiers have been suggested in the literature. However, very few studies have analysed whether these factors act as effect modifiers, and the results are heterogeneous. More replication studies are required to evaluate whether these factors are effect modifiers.

The available evidence, which has been reviewed with reference to Bradford Hill's features of causal associations (see [Chapter 5](#)), suggests that long-term exposure to air pollutants is associated with cognitive decline and with the risk of development of dementia. However, the studies are not consistent as to which pollutant is most closely associated with these adverse effects on cognition. In addition, the diversity of study designs and the end-points examined makes meta-analysis inappropriate.

Temporal misalignment (of putative causes and effects) could potentially affect the associations observed between exposure to air pollution and cognitive and neurological changes. Many of the studies considered exposures representative of one to 10 years prior to cognitive testing, dementia incidence or neuroimaging. However, exposures over that period of time are not necessarily representative of exposures over a longer term (for example, 30 years), which might be more relevant to the effect under consideration.

Typical confounding factors have been accounted for in the majority of the reviewed studies. Additional factors have been also controlled for in individual studies, but the adjustment for these factors has not been consistently implemented. A range of possible confounding factors, such as social interactions, physical activity, sleep deprivation and other factors related with urban living and which none of the studies has controlled for, has been identified. Despite all the efforts in controlling for confounding factors in the reviewed studies, a possible effect of the unaccounted-for confounding factors cannot be completely ruled out. Some studies that have included traffic load or distance and components of air pollution have suggested associations with traffic but not with air pollutants (Ranft et al, 2009; Wellenius et al, 2012), whilst other have found associations with air pollutants but not with traffic load or distance (Schikowski et al, 2015; Wilker et al, 2015). It is therefore unclear from the epidemiological evidence whether the factor mainly associated with cognitive decline and dementia is a specific component of air

pollution, the urban air pollution mixture, or factors related to urbanicity and traffic exposure, such as poorer socioeconomic status (that is, poorer people tend to live nearer to major traffic roadsides) or any of the multiple features of urban living such as noise, stress, exposure to artificial light at night, poor access to green spaces, sedentarism, and/or an unbalanced diet.

These various potential confounding factors notwithstanding, in the light of the above discussion it is our view that the epidemiological evidence is suggestive of an association between exposure to a range of air pollutants and a number of effects on the nervous system including the acceleration of cognitive decline and the induction of dementia.

## Chapter 4. Aspects of potential mechanisms

### 4.1 Introduction

It has been suggested that air pollutants could affect cognitive function directly (if they enter the brain) or indirectly (via their effects on other organs and systems). Much of the current interest is the possible role of particulate matter, specifically ultrafine particles (UFP; nano-sized ambient particles). Whether these can reach the brain, and their potential effects if they do, has been a topic of increasing scientific interest and study in recent years.

In contrast to carbon monoxide – which passes into the blood, is carried by haemoglobin and crosses the blood-brain barrier – reactive gaseous pollutants such as NO<sub>2</sub> and O<sub>3</sub> react with components of the lung fluid and nasal mucosa, and so do not enter the circulating blood. It is possible that their reaction by-products may reach the brain, but this would be difficult to study, likely requiring the use of radiolabelled gas. In addition, these pollutants could have indirect effects on the brain, perhaps secondary to inflammatory processes resulting from their reactions in the respiratory tract.

In this Chapter, we consider whether air pollutants enter the brain (Section 4.2, 4.3 and 4.4), and their possible fate and effects (sections 4.5 and 4.6) if they do so. We also consider possible indirect effects of air pollutants on cognitive decline and dementia (Section 4.6. and 4.7).

Sections 4.2, 4.3, 4.4 and 4.5 focus on UFP. Many of the studies in Section 4.6 also examine the potential role of UFP, or pollutant mixtures including UFP. Nonetheless, there is a sizeable literature reporting experimental studies on ozone, which is summarised in this section. Section 4.7 discusses the possible effects of pollutants on cognitive decline and dementia which are secondary to effects on other organs of the body. The literature linking pollution with the intermediate effects is most developed for particulate pollution, but other pollutants may also play a role.

### 4.2 Translocation of inhaled particles to the blood

#### 4.2.1 Summary

It is accepted that small particles which are deposited, after inhalation, in the alveoli of the lung may cross the alveolar walls and enter the blood. The fraction of deposited particles which do so is less than is sometimes thought, of the order of 1%. Of these a small fraction may enter the brain. It is clear that very small particles cross from the lung to blood more easily than do larger particles. Larger particles may enter the lymphatic system of the lung and, again, a fraction of these may find their way into the blood. The extent to which particles found in ambient air, at

ambient concentrations, cross from the lung to the blood is unclear. Some ambient particles occur as aggregates and whether these aggregates break up in the alveoli has been disputed. It is unlikely that aggregates of particles could cross from the lung to the blood. The composition, and surface charge, of particles may also play a part in controlling their passage from the lung to the blood.

## 4.2.2 Introduction

There are 3 routes by which inhaled particulate matter might reach the brain: along cranial nerves (olfactory, trigeminal, vagus, glossopharyngeal); via lymphatic vessels, for example those involved in the drainage of cerebrospinal fluid; and via the blood supply to the brain. As this report deals with the possible effects of air pollution on cognitive decline, the possibility of access of particulate matter to the spinal cord has not been considered; it should, however, be noted that particulate matter reaching the spinal cord, perhaps via sympathetic nerve fibres, might be carried to the brain along ascending neural pathways: as far as is known no work has been done on this. This section deals with translocation of particulate matter from the lung to the blood.

The question of translocation of particles from the lung might be thought to be of recent origin. This is not so. Drinker and Field (1933) noted that:

“Fleiner (1888) recognised the importance of phagocytosis, but also showed that blood corpuscles and ink particles could travel from the alveoli to the bronchial lymph glands in a few minutes and reports that phagocytosis never occurred in his brief experiments”.

And, speaking of their own work:

“Particles are also seen adhering to mononuclear phagocytes but the fact that there are a great number already in the lung substance, and apparently quite unattached to cells of any sort, makes it necessary to believe that the particles coming to rest on the alveolar walls readily drift through the walls into the lung tissue and commence their journey towards the lung lymphatics without the necessity of phagocytosis as the initial step in removal from the alveoli.”

The reader will note that Drinker and Field were concerned with translocation to lung tissue rather than to blood.

The lung is exposed to particulate matter via inspired air. The branching structure of the lung, which provides for a large alveolar surface area for gas exchange, causes the lung to act as a filter for particulate matter. Inhaled particles are deposited within the conducting airways and on the surface of the alveolar epithelium: clearance mechanisms have evolved to remove these particles from the lung. Airborne particles small enough to be inhaled either via the nose or mouth can be divided into those too large to penetrate beyond the larynx, but of which some are deposited in the nasal passages and pharynx, and those small enough to pass the larynx. The

latter are defined as thoracic particles, generally of  $<10\mu\text{m}$  diameter. Of these particles, those of larger size are deposited mainly in the conducting airways; the smaller particles can reach the alveoli and a fraction of those that do are deposited there. Particles deposited in the conducting airways are cleared by the moving sheet of mucus that is propelled towards the larynx by ciliary activity: the mucociliary escalator. It is possible that a small fraction of the particles deposited in the conducting airways pass through the ciliated airway epithelium and into the airway wall. Here they might translocate into lymphatic vessels or, possibly, capillaries or nerve endings. Clearance of particles from the conducting airways is rapid, much more rapid than clearance of particles deposited in the alveoli.

Micron-sized particles which are deposited in the alveoli are removed by macrophages which patrol the alveolar surface and migrate to the junction between the gas exchange zone and the conducting airways and step, so to speak, onto the mucociliary escalator. Some particles either make their own way through the walls of the alveoli and alveolar ducts, or are carried through by macrophages, and enter the interstitium of the lung. From here the particles can enter the lymphatic system of the lung and are carried to pulmonary lymph nodes. The blackened pulmonary lymph nodes of smokers, coal miners and city dwellers testify to the efficacy of this route (Pratt and Kilburn, 1970) although no quantitative data are available. A fraction of the particles that reach lymph nodes pass through those structures and are delivered to the great veins at the root of the neck. Thus, a route from the lung to the blood is established. Once in the blood the particles pass around the body: most are removed by the fixed macrophages of the liver and spleen. Particles of coal dust have been found in both locations in coal miners. In comparison with the amount of particulate matter inhaled by coal miners during a working life the amount reaching the liver and spleen is very small.

What was for long less certain was that particles could cross the alveolar air-blood barrier (ABB) and pass directly to the blood. The alveolar epithelium comprises 2 main cell types; a third and rare cell type, the so-called brush cell, is ignored in this account. Alveolar Type I (ATI) cells cover the vast majority of the alveolar surface (approximately 95%) and are the essential cells of the gas exchange barrier. Alveolar Type II (ATII) cells produce surfactant and, by division, can replace ATI cells. ATII cells take up, as well as secrete, surfactant and some particles are taken up by these cells. Interaction between particles and surfactant leads to wetting of the particles and displacement towards the surface of the epithelial cells (Schürch et al, 1990, Geiser et al, 2003). ATI cells form a thin epithelial layer: the cells are held together at their edges, so to speak, by junctional complexes which include tight junctions. The barrier provided by this attenuated layer of cells is described in functional terms as 'tight'. Some transport across this barrier does occur: ions, proteins and water are cleared from the alveoli to the interstitium (Berthiaume and Matthay, 2007). Endocytotic vesicles within ATI cells can be identified by electron microscopy (EM). Geiser et al (2005) have shown that UFP can cross the epithelial barrier between the air and the pulmonary interstitium by non-phagocytic, non-endocytotic mechanisms. Adhesion of particles to the cell membrane is followed by translocation that seems not to depend on activity of the cells involved: physical processes (interfacial and line tension effects) have been suggested to explain the process. EM studies have not shown the presence

of pores in either the cell membranes of the alveolar epithelium or of the pulmonary capillary endothelium. Thorley et al (2014) have provided a valuable discussion of mechanisms of transport of nanoparticles across the human pulmonary epithelium.

The ABB comprises, in addition to the layer of ATI cells, endothelial cells of the pulmonary capillaries and a joint basement membrane which links the epithelial and endothelial layers. The ABB is of the order of 0.5µm in thickness. What is sometimes forgotten is that the inter-alveolar septa include areas primarily involved in gas exchange, as just described, and areas where the gap between the ATI cells and the endothelial cells is, in comparison, wider and filled by interstitial tissue. Pulmonary capillaries have, so to speak, a gas exchange side and a 'service' side (Nunn, 1993). Weibel and Bachofen (1979) referred to the thin and thick regions of the air blood barrier and described pulmonary capillaries weaving from one side of the interalveolar septum to the other. Particles that cross ATI cells might, therefore, enter either the blood (assuming they could cross the joint basement membrane and the endothelial cells of the capillaries) or the interstitium of the septa (assuming they could cross the single basement membrane of the epithelial cells). Particles entering the septal interstitium are likely to be cleared along with fluid leaking from the service side of the capillaries and absorbed from the alveolar surface, to the intersections of alveolar boundaries (intersections of 3 surfaces, each from an individual alveolus) and onwards to the lymphatic system (Weibel and Bachofen, 1979). Figure 4.1 shows the alveolar unit and illustrates the air-blood barrier (ABB).



**Figure 4.1. Reproduced from Weibel ER Structural design of the alveolar septum and fluid exchange**

(The American Physiological Society grants the Committee on the Medical Effects of Air Pollutants permission to include the following figure from the published Book: Figure 2 from Chapter 1, pages 1 to 20 in Pulmonary Edema eds AP Fishman and EM Renkin American Physiological Society Bethesda Maryland 1979)

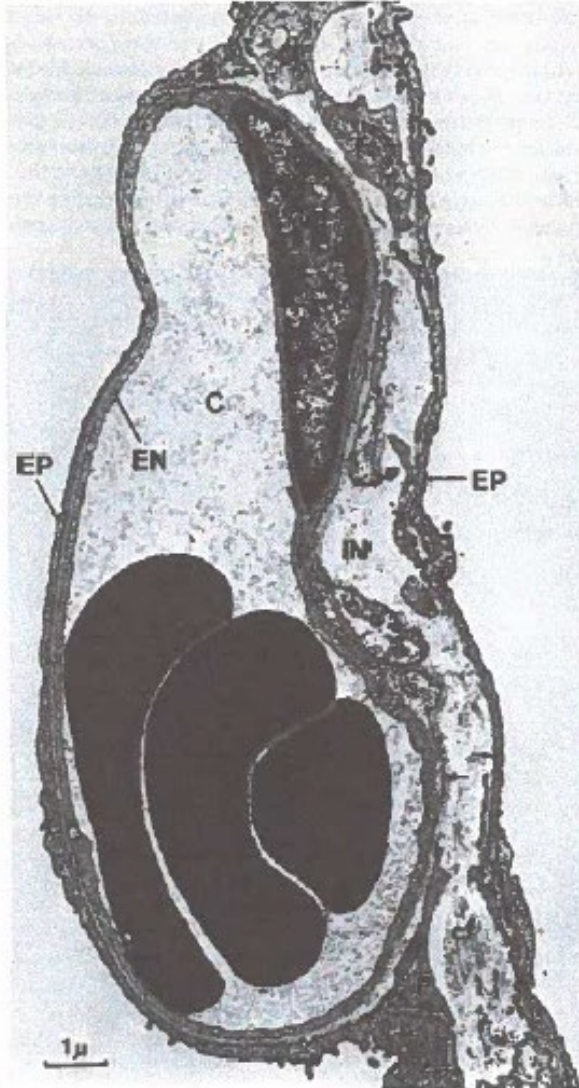


FIG. 2. Transmission electron micrograph of alveolar capillary (C) cross section from human lung. In the upper part of the air-blood barrier the basal laminae of epithelium (EP) and endothelium (EN) are fused, forming a restricted interstitial space; connective tissue fibers (cf) are found in the free interstitial space (IN) in the bottom part of the barrier where the basal laminae (arrows) are separated. Note fibroblast processes (F) associated with fibers.

In recent years, much interest has been shown in ultrafine particles (UFP or nanoparticles, NP) defined as having at least one diameter of  $<100\text{nm}$ . These very small particles deposit with great efficiency in the alveoli; at least this is so unless they are extremely small, of the order of 1 to 5nm in diameter, when the relatively high speed at which they diffuse in air causes them to be deposited, along with large particles, in the nasal passages. Perhaps because of their very small size it has been assumed that UFP might pass readily from the alveoli to the blood. In



fact, this is not generally the case: most studies show that <1% of UFP deposited in the alveoli pass into the blood. That they pass into the interstitium relatively easily is well established: Geiser et al (2005) showed that 24% of inhaled ultrafine TiO<sub>2</sub> particles passed beyond the epithelial barrier of the rat lung within one hour of being inhaled; see also earlier work by Ferin et al (1992). Rather interestingly it has been shown that recycling of particles occurs from the alveoli to the interstitium and back to the airway surface in the smallest of the branches of the conducting airways – in anatomical terms to the boundary between the terminal and respiratory bronchioles (Semmler-Behnke et al, 2007). This recycling pathway plays a part in clearance of particles from the alveoli. There is also evidence to suggest that macrophages that take up particles in the pulmonary interstitium might transport those particles back to the alveolar surface: another recycling process (Lehnert, 1992).

Particle size is of importance: the smallest UFP, <5nm in diameter, are much more likely to translocate to the blood than particles of >20nm diameter (Semmler-Behnke et al, 2008). It is worth noting that some studies have involved the use of aggregates of very small primary particles, produced by spark generation: a high voltage being applied across a pair of electrodes of which one or both comprise the test material (Kreyling et al, 2009). Precisely what happens to aggregates in the lung is not entirely clear. There is some evidence to show that agglomeration of small particles occurs as a result of interaction with the surfactant layer in the alveoli (Kendall et al, 2002); other work suggests disaggregation of particulate material (Maier et al, 2006; McKenzie et al, 2015). Much, no doubt, depends on how firmly the primary particles are attached to one another. The term agglomeration is used to describe weak attachment; the term aggregation implies a firmer attachment. Effective disagglomeration of agglomerates of gold nanoparticles in the lung has been shown by Balasubramanian et al (2013): 45nm agglomerates of 7 and 20nm gold primary particles were studied. Despite similar agglomerate sizes, the uptake of 7nm primary particles exceeded that of 20nm primary particles, suggesting that disagglomeration occurred and that the smaller particles translocated more readily. This is important in the present context because ultrafine particles generated by diesel engines have a primary particle size of about 30nm (Park et al, 2004) but are encountered, in ambient air, as aggregates (for example, Sanderson et al, 2016). The charge on the particles might also be important in attracting or repelling interactions with components of the protein- and phospholipid-containing alveolar lining fluid.

Whether such aggregates break up in the lung is a critical question, as yet unanswered. Uptake of UFP from the gut, to which they have been cleared by swallowing of mucus from the lung, needs to be taken into account in studies of the translocation of UFP from the lung to the blood. Particles reaching the blood may be cleared to the urine (very small particles) or by the fixed macrophages of the liver and spleen. Warner and Brain (1986) have shown, in ruminants, that particles can also be removed from the circulation by pulmonary intravascular macrophages. It is thought that such cells do not occur in man or the rat but that they can be induced, in these species, by disease processes (Schneberger et al, 2012). The development of ideas regarding the clearance and translocation of particles can be found in the work of White (1972), Tucker et al (1973), Berry et al (1977), Oberdörster (1988), Ferin et al (1992), Oberdörster et al (1992),

Oberdörster et al (1994) and Kreyling et al (2002a,b). These important early papers are not discussed here. The general conclusion from this work was that particles of micron size were cleared by macrophages, whilst UFP were cleared much more slowly and translocated to the interstitium of the lung. The more rapid clearance of PM from rat lungs than from human, other primate, and carnivore lungs has been stressed, as has the importance of the rate of deposition of particles in the lung (Ferin et al, 1994).

### 4.2.3 Published reviews

Nakane (2012) published a systematic review of the literature from 1967 up to mid-2011 dealing with the translocation of particles from the respiratory system to the blood. Sixty-one papers were reviewed that provided data on the experimental methods used and on how particles were detected. The studies reviewed included a range of routes or methods of administration of particles: inhalation (nose only, via the trachea, or whole body), intratracheal instillation, pharyngeal aspiration, and intranasal instillation. The review indicated that many studies had shown that particles could be translocated from the lung to the blood. Nakane analysed the results of the studies with a view to identifying explanatory variables that controlled translocation to the blood, brain and other tissues. Particle size was clearly important with a cut off for translocation to the blood of  $\leq 1.0\mu\text{m}$ . This represented the largest size of particle that had been found to be translocated to the blood. The majority of studies suggested that only very much smaller particles could pass from the lung to the blood. No information on the fraction of the deposited dose of particles (expressed either as mass or as number of particles) was provided.

Kermanizadeh et al (2015) have provided a lengthy and systematic review of the literature excluding human studies. The authors pointed out the need to consider the route of exposure and divided their review accordingly. The review is more detailed than that of Nakane (2012), the objective was also different, and individual studies are reported in some detail. Attention was focused on estimates of the percentage of material (deposited in the lung) that translocated to the blood and to secondary organs. It was concluded that inhalation exposure was associated with very limited translocation to blood: 0.00001 – 1% of the applied dose for essentially insoluble material; slightly higher figures for partially soluble material. The authors pointed out that few studies that had looked in detail at translocation had also looked at effects on secondary organs. The authors confirmed that a higher level of translocation, up to 10%, was associated with exposure by intratracheal, intranasal and pharyngeal aspiration.

### 4.2.4 Papers published since 2015

Later work by Pujalté et al (2017), Gaté et al (2017), Creutzenberg et al (2016), Konduru et al (2015), Guttenberg et al (2016) and Buckley et al (2017) has not contradicted the conclusions reached by Kermanizadeh (2015) as regards translocation of particles to the blood.

## 4.2.5 Human studies

Only a few human studies have been reported. Nemmar et al (2002) reported translocation of  $^{99m}\text{Tc}$ -labelled carbon particles (<100nm diameter) to the blood after inhalation of 'Technegas'. This finding was questioned by Mills et al (2006) who showed that separation of the technetium label from the carbon particles might have accounted for the findings of Nemmar et al (2002). Further work with  $^{99m}\text{Tc}$ -labelled carbon particles (35nm diameter and 100nm diameter) by Wiebert et al (2006a, b) showed that little translocation to blood occurred. An important study by Miller et al (2017a and Miller et al 2017b, correction to 2017a) showed that 0.02% of inhaled gold nano-particles (primary particle sizes: 5 and 30nm diameter) translocated to the blood but, very interestingly, a fraction of the translocated particles located to sites of vascular inflammation or atherosclerotic change in both volunteers and *APOE*<sup>-/-</sup>, lipid-fed, mice. The inference was drawn that nanoparticles translocated to sites of arterial disease could play a part in explaining the epidemiological findings linking long-term exposure to particulate matter and an increased risk of mortality from cardiovascular disease.

## 4.2.6 Conclusions

It is clear that only a small fraction, <1%, of inhaled UFP translocate from the lung to the blood. Of these a fraction might gain access to the brain. It is also clear that very small UFP, <5nm diameter, are more likely to translocate to the blood than larger UFP, 30 to 100nm in diameter. Particles in the micron size range are unlikely to translocate to the blood except via the pulmonary lymphatic system and, in this case, the fraction of deposited particles reaching the blood is likely to be very small. In addition, the possibility that materials carried on the surface of UFP could enter the blood and the brain should not be discarded without further study.

# 4.3 Blood-brain barrier

## 4.3.1 Summary

The blood-brain barrier (BBB), formed by the endothelial lining of the capillaries of the brain and dependent on the normal function of ensheathing pericytes and glial cells, presents a selective barrier to the passage of material from the blood to the tissues of the brain. There is much evidence to show that under experimental conditions particles of a wide variety of compositions may cross the BBB and enter the brain. Evidence to show that ambient particles, at ambient concentrations, do so in significant amounts is more limited. The likelihood of particles crossing the BBB may well depend on both the composition of the particles and on their surface charge.

It is accepted that limited areas of the BBB are less competent than the rest of the BBB in preventing entry of materials to the brain and in these areas the passage of particles is likely to be increased. If the BBB is damaged, for example by inflammatory processes, then the passage of particles from the blood to the brain is likely to be increased. Much work is currently being

undertaken to develop pharmaceutical preparations that enhance the passage of drugs from the blood to the brain. Some of this work focuses on the design of particulate materials as carrier systems for drugs. The relevance of the results of this work to thinking about the passage of ambient particles to the brain is, at present, uncertain.

### 4.3.2 Introduction

The literature dealing with the blood-brain barrier (BBB) is vast and expanding rapidly (Weiss et al, 2009, Obermeier et al, 2013, Abbott et al, 2010, Banks, 2016). It has long been recognised that the endothelium of cerebral capillaries presents a barrier to the passage of large molecules into the parenchyma of the brain. This is shown by the exclusion of, for example, dye particles from all parts of the brain except those in which the BBB is known to be functionally weak. The cells of the cerebral endothelium are tightly joined to one another by both tight junctions (zonulae occludentes) and less tight junctions (zonulae adherentes). The latter provide less of a barrier than the tight junctions but are essential for the normal functioning of tight junctions. Much has been learnt about the complexity of these junctions and about the many molecules that contribute to their functional properties: work in genetically modified animal models has shown that the barrier can be weakened by reduced expression of a number of these molecules. But the BBB is much more than just the endothelium: the basal lamina that surrounds the capillaries and the adjacent pericyte cells, the contractile pericyte cells themselves, and the foot processes of astrocytes that sheath the endothelium combine with the endothelial cells to produce a complex micro-anatomical barrier. Two other barriers should also be mentioned: that provided by the choroidal epithelium which interfaces between fenestrated choroidal capillaries and the cerebrospinal fluid (CSF) (Wolburg and Paulus, 2010), and the barrier provided by the arachnoid mater that accompanies arteries, arterioles, venules and veins within the substance of the brain. A fluid-filled space, the Virchow-Robin space, surrounds these blood vessels. This space does not extend to the cerebral capillaries. It is known that astrocyte foot processes are applied to the cells of the arachnoid mater that limits this space. It is thought that CSF, or at least some components of CSF including water, leave the Virchow-Robin space and enter both the intercellular or interstitial space and astrocytes. That there are locations where the BBB is weak has been mentioned above. These areas include the so-called circumventricular organs (Ganong, 2000) where the capillaries are fenestrated. The movement of materials that cross the BBB in these areas to other parts of the brain appears to be controlled by specialised glial cells called tanycytes: these present a further barrier. Figure 4.2 illustrates the blood-brain barrier (BBB).

### Figure 4.2. The blood-brain barrier (BBB)

(Reprinted from *Neurobiology of Disease* 16 (1), Ballabh P, Braun A, Nedergaard M. 'The blood-brain barrier: an overview. Structure, regulation, and clinical implications.' Pages 1 to 13, Copyright (2004) with permission from Elsevier.)

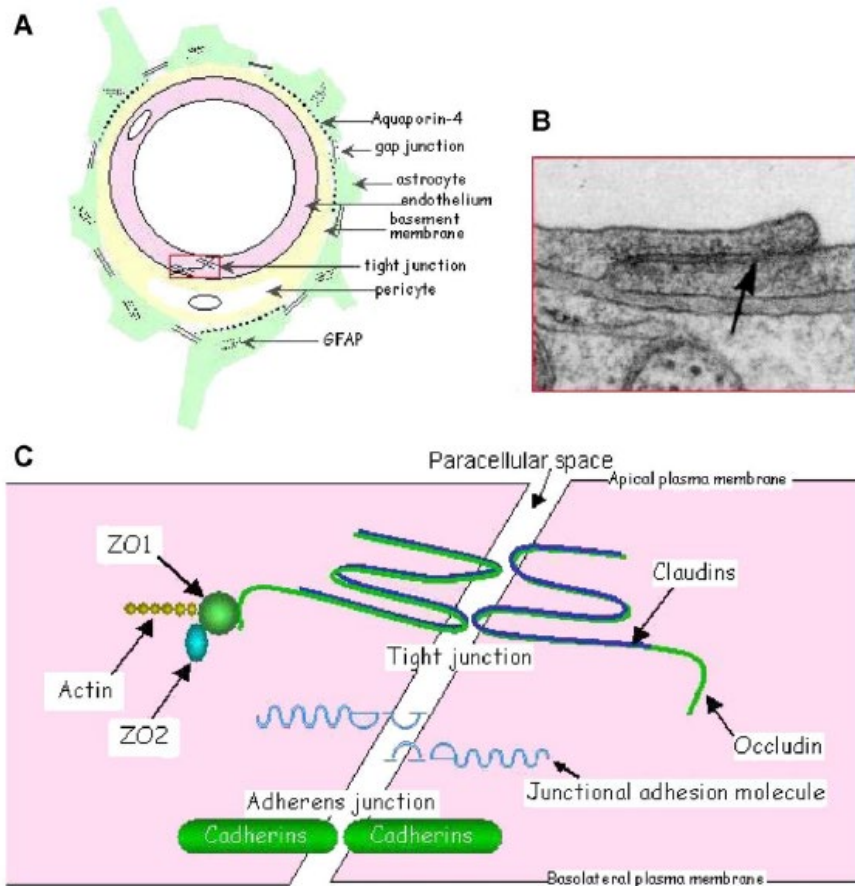


Fig. 1. Blood-brain barrier and the tight junction. (A) Schematic drawing of the blood-brain barrier in transverse section showing endothelium, basement membrane, pericytes, astrocytes, and tight junctions. The localization of gap junction, GFAP, and aquaporin-4 are shown. (B) Electron micrograph of mammalian blood-brain barrier showing endothelial tight junction. [Adapted from: *The Blood-Brain Barrier Cellular and Molecular Biology*. Pardridge, W.M. (Ed.). Raven Press]. (C) Schematic representation of protein interaction associated with tight junctions at the blood-brain barrier. Claudin, occludin, and junction adhesion molecule are the transmembrane proteins, and ZO-1, ZO-2, and ZO-3, cingulin, and others are the cytoplasmic proteins. Claudins are linked to actins through intermediary cytoplasmic proteins.

Despite its tightness, many substances cross the BBB. Gases diffuse across the barrier and substances essential for normal neuronal function, including glucose and amino acids, are transported by special mechanisms. The mechanisms involved in such movements are discussed below. Much work has been done to develop nanomaterials that can cross the BBB and carry drugs into the brain. Albumin, for example, has been used as a carrier for drugs (Zensi et al, 2009). It should also be noted that the functioning of the BBB is affected both by disease and by ageing.

Whether small particles that form part of the ambient aerosol can cross the BBB has been debated at length (Oberdörster et al, 2009).

### 4.3.3 Transport processes

A number of processes have been shown to be involved in the movement of substances across the BBB. Lipid-soluble materials, including the gases oxygen and carbon dioxide, diffuse across the barrier. The energy required is provided by the concentration difference across the barrier. The differing composition of fluids on either side of the barrier suggests that the solubility of gases might vary but the variation is likely to be small and concentration can be substituted for partial pressure. Ionised species, for example the bicarbonate ion ( $\text{HCO}_3^-$ ), are not lipid-soluble and show poor penetration of the barrier. Other compounds including some ions ( $\text{Na}^+$  and  $\text{K}^+$ ), glucose and amino acids, are transported across the barrier by energy-consuming processes linked with the conversion of ATP to ADP. These processes can be described as 'solute carriers' and show directional specificity. The carrier systems are not randomly distributed throughout the endothelial cell membrane: some are found only in the luminal and some only in the abluminal membrane. It is important to note that the tight junctions, the zonulae occludentes, circle the cells and provide a barrier between the luminal and abluminal membranes: materials cannot diffuse within the membrane across this intra-membranous barrier. Water moves through the cell membranes via channels provided by the aquaporin series of molecules. Such movement is osmotically driven. A further and complex series of carriers is provided by ATP-binding cassette (ABC) transporters including the P-glycoprotein transporter, Pgp, of the luminal membrane. These systems are distributed in both the luminal and abluminal membranes of brain capillary endothelial cells and represent an efflux system that removes material from the brain intercellular space. Materials removed include  $\text{A}\beta$ -lipoprotein complexes. The ABC transporters pump lipid-soluble material from the brain into the blood and are energy-consuming. None of the transport processes so far mentioned is likely to be involved in the transport of particulate matter from the blood to the brain.

However, another transport process, that involving the formation of endocytotic vesicles, is involved in such transport. Large molecules, including insulin, leptin, transferrin, growth factors and tumour necrosis factor (TNF), are transported into the brain. Such materials enter the endothelial cells at the luminal membrane by endocytosis and leave, from the abluminal membrane, by exocytosis. Entry may be dependent on receptors on the luminal membrane (receptor-mediated transcytosis, RMT) or, in the case of cationic (positively charged) material by adsorption to the negatively charged glycocalyx of the luminal membrane (adsorption-mediated transcytosis, AMT). The vesicle-mediated transport is highly specialised such that the adsorbed and internalised material evades destruction by the lysosomes of the endothelial cells. These processes are energy-dependent: brain capillary endothelial cells contain 4 times as many mitochondria as do endothelial cells of some other capillaries. The vesicles involved are 50 to 80nm in diameter; presumably the materials transported are limited to about this diameter. Interestingly the number of vesicles increases with inflammation. A non-specific endocytotic process also exists and is thought to be involved in the transport of fluid and small peptides. Nano-sized particulate material has been found in the brains of both humans and experimental animals (Maher et al, 2016; Oberdörster et al, 2009; Elder et al 2006).



In addition to these processes, cells can cross the BBB. Neutrophils, lymphocytes and cells of the monocyte-macrophage series cross from the blood into the brain but to a much lesser extent than they do in other tissues. This is due to the low level of expression of leucocyte adhesion molecules by mature brain capillary endothelial cells. Expression of such molecules is upgraded during inflammatory reactions. In some endothelia, inflammatory cells can pass between normal endothelial cells; this seems unlikely in the brain because of the tightness of the intercellular junctions and it is thought that such cells pass, if they pass, through, rather than between, the normal endothelial cells. Inflammation can loosen the barrier provided by the tight junctions, allowing inflammatory cells to pass between the endothelial cells. Such passage occurs at the venular end of cerebral capillaries and in small veins. This leads to an accumulation of inflammatory cells as cuffs around small vessels. These cuffs are thought to be important in mediating immune responses. It is at least possible that cells of the monocyte series that have taken up particulate matter in the blood stream could carry that material into the brain.

It is important to note that the BBB can be damaged and that damage causes it to become more permeable. Such damage is produced by systemic inflammation, ischaemia and trauma. It is conceivable that particulate matter could damage the BBB and that such damage could allow increased passage of such material into the brain. But it is also possible that damage to the BBB by processes unrelated to the presence of particulate matter could allow increased movement of the particulate material into the brain. This is important in that it is known that, for example, Alzheimer's disease is associated with damage to the BBB (for example, Erickson et al, 2013). Unravelling the directionality of the association between diseases of the brain and the observation of greater numbers of particles in the diseased brain is clearly important but will be difficult.

The functional capacity of the BBB can be modified by other means. Raising the osmotic pressure of the plasma weakens the barrier: this has been used to increase the movement of drugs into the brain (Saraiva et al, 2016; Banks, 2016).

#### 4.3.4 Damage to the blood-brain barrier

BBB damage is demonstrable by neuroimaging in small vessel disease and vascular cognitive impairment (VCI) (Taheri et al, 2011; Topakian et al, 2010; Wardlaw, 2010; Yang and Rosenberg, 2011). Loss of integrity of the BBB has the potential to damage brain tissue by leakage of neurotoxic proteins such as fibrinogen, induction of inflammation, and impaired clearance of toxic brain metabolites including A $\beta$  (Bell et al, 2010; Davalos et al, 2012; Ryu and McLarnon, 2009; Ryu et al, 2015; Schachtrup et al, 2010).

## 4.4 Movement of particles to and through the olfactory bulb

### 4.4.1 Summary

It is accepted that particulate material deposited on the olfactory epithelium of the nasal cavity may enter the olfactory nerves and pass, along the fibres of those nerves, to the olfactory bulbs of the brain. The fraction of deposited particles that make this journey is unclear and it is known that the olfactory epithelium has processes that clear materials deposited on its surface. Soluble particles are likely to dissolve in the surface fluid of the epithelium. Transport processes that may be involved in the movement of particulate material along nerve fibres have been described. It is also possible that particles may enter the terminals of other sensory nerves of the nasal cavity (branches of the maxillary nerve) and make their way to the brain stem. Much work on the uptake of drugs via the olfactory epithelium is currently underway. Specially designed particles are being developed as carrier for drugs administered in this way. The relevance of such work to thinking about the uptake of ambient particles is, at present, unclear.

### 4.4.2 Introduction

The olfactory nerve, which transmits odour signals from the nose to the brain, is a possible route for the transport of inhaled substances directly to the brain. There has been considerable interest in this as a potential route for the delivery of drugs intended to target diseases of the CNS. It is also a possible route by which engineered nanomaterials and ambient ultrafine particulates may reach the brain and cause adverse neurological effects. The available studies of uptake and transport via the olfactory nerve have a number of limitations (use of high doses, bolus-artefacts associated with nasal instillation, and so on) and the extent to which these short-term animal studies are relevant to understanding the health risks to humans exposed, long-term, to low concentrations of ambient ultrafine particles is unclear. Nonetheless, they demonstrate that transport along the nerve fibres leading from the upper respiratory tract to the brain is possible. It is less clear that this direct route of transport is the most important route of delivery to the brain following nasal inhalation.

### 4.4.3 The olfactory system

A main function of the nose is to adjust the temperature and humidity of inhaled air and to filter out airborne particulate matter. These functions are performed by a mucous membrane which lines the nasal cavities. Part of the nasal mucosa contains the receptors for the sense of smell. In some animals, such as rats, this olfactory neuroepithelium is quite extensive. In humans, it covers only a small area in the roof of the nasal cavities. Because of the pattern of flow within the nasal cavities, only a small fraction of inspired air reaches the human olfactory mucosa (Ajmani et al, 2016a; Burkitt et al, 1993; Crowe et al, 2018; Sunderman, 2001).

The olfactory neuroepithelium consists of 3 major cell types: olfactory receptor cells, sustentacular cells and basal cells. The olfactory receptor cells are bipolar neurons with, on one



side, a dendritic knob with cilia that project into the nasal cavity. These cilia display chemoreceptors for odorants. From the other side of the olfactory receptor cell, an axon extends - through holes in the bone plate which covers the roof of the nasal passages - to the olfactory bulb lying beneath the frontal lobe of the brain. In the olfactory bulbs, the olfactory receptor neurons synapse with dendrites of secondary olfactory neurons which project to the olfactory tubercle and other parts of the brain. The axons of the olfactory receptor cells are encompassed by interconnected Schwann-like ensheathing cells which, in turn, are covered by neural fibroblasts. The sustentacular and basal cells are epithelial cells. As well as providing support, the sustentacular cells have microvilli which extend into the nasal cavity, forming a tangled mat with the cilia of the olfactory receptor cells. Basal cells are able to develop into olfactory receptors. Bowman's glands in the underlying tissue produce watery secretions into the nasal cavity, into which odorous substances can dissolve (Ajmani et al, 2016a; Burkitt et al, 1993; Crowe et al, 2018; Sunderman, 2001).

Inhaled substances can cause injury and tissue remodelling in the nose, including to the olfactory neuroepithelium. Loss of (anosmia) or reductions in (hyposmia) the sense of smell can occur following occupational exposures to some metal dusts or aerosols (for example, dusts containing nickel and cadmium). Other effects such as ulceration of the lining of the nasal cavities, perforations in the cartilage wall which divides the 2 nostrils (the nasal septum) and cancers of the epithelium lining of the nose or sinuses have also been reported (Sunderman, 2001). Recent studies have suggested that exposures to ambient air pollution might also affect the ability to detect and identify odours. In a cross-sectional epidemiological study of older adults (aged 57 to 85), Adams et al (2016) found NO<sub>2</sub> concentrations at the monitoring site nearest to the individual's home to be associated with a poorer ability to identify odours. Ajmani et al (2016b) found a relationship between ambient PM<sub>2.5</sub> concentrations and olfactory dysfunction in older adults living in urban areas but not in rural residents. The association was strongest in the youngest group (aged 57 to 64 years). A review of 14 epidemiological studies and 5 pathophysiological studies in humans found evidence of effects of ambient air pollution on olfaction (Ajmani et al, 2016a), although a number of limitations in the studies and evidence base were noted.

#### 4.4.4 Translocation to the brain via the olfactory and other nerves

A 'nose-brain barrier' provides some protection against the translocation of viruses, particles and chemicals to the brain via the olfactory nerve pathway. Nasal mucus provides a physical barrier, and is moved and removed by the mucociliary apparatus. Mucus is turned over once every 20 minutes on average. There are also immunological defences (the underlying lamina layer contains immunocompetent cells) and the sustentacular cells have some ability to metabolise inhaled chemicals. Access to the spaces between olfactory receptor neurons and sustentacular cells is blocked by tight junctions. In addition, epithelial cells which are damaged (for example, by toxic substances) are shed and the tissue regenerated (Crowe et al, 2018; Sunderman, 2001).

Similar impediments apply to the transport of substances via nasal branches of the maxillary branch of the trigeminal nerve, which transmits sensation from areas of the face (including the nose) to the pons (in the brainstem). The pulmonary branch of the vagus nerve (vagal sensory afferents) also provides another potential route for the transport of inhaled pollutants from the respiratory tract to the brain.

Nonetheless, despite these protections, it has been shown that chemicals and particles can be transported from the nose to the brain along these nerve fibres. Studies have been undertaken to investigate the transport of known neurotoxins (such as manganese) or engineered nanoparticles, and to inform the potential development of intranasal delivery of drugs designed to target brain diseases. For example, Dorman and co-workers (Brenneman et al, 2000; Dorman et al, 2002) demonstrated that manganese was transported along the olfactory nerve of rats in experiments in which some animals were able to inhale through both nostrils while others had one nostril occluded. Olfactory neurons are connected to the olfactory bulb on the same side of the head as the nostril from which they originate, and the distribution of radioactive manganese in the olfactory bulbs observed in the animals with an occluded nostril were consistent with a direct olfactory transport route from the nasal cavity to the olfactory bulb.

Kreyling (2016) investigated the differences in distribution of radio-labelled 20nm-sized iridium nanoparticles in rats following either nose-only inhalation (exposure of the whole respiratory tract) or equivalent intratracheal inhalation, for 1 hour (Kreyling, 2016). This showed a 9-fold higher accumulation of nanoparticles in the brain following nose-only inhalation compared with intratracheal inhalation, demonstrating the importance of the olfactory route.

The studies investigating the transport of inhaled materials to the brain have largely been undertaken in laboratory animals. Given the differences between rodents and humans in the structure of the nasal passages, the area covered by olfactory epithelium and the amount of air inhaled per minute (the minute volume) this has raised questions regarding their relevance to human exposure (for example, Kreyling, 2016). Garcia et al (2015) used computational fluid dynamic (CFD) methods to compare estimates of the dose of inhaled nanoparticles that deposit in the olfactory epithelium in the human and the rat. Although the percentage of inhaled particles that deposit in the olfactory region was lower in humans than rats, the dose per unit surface area was estimated to be higher in humans because of their larger minute volume.

#### 4.4.5 Aspects of olfactory nerve transport

Ahmad et al (2017) demonstrated size-dependence of retention of particles (administered as nanoemulsions) in the nasal mucosa. Larger particles (larger than 200nm) were well cleared by the nasal mucociliary clearance mechanisms within 4 hours of administration, while smaller ones (80 or 200nm) were retained in the nasal mucosa for up to 16 or 12 hours, respectively (Ahmad et al, 2017).

Various possible modes of transport of chemicals and particles along olfactory nerve tracts have been proposed. One possibility is uptake into the olfactory receptor cell (by pinocytosis) followed by transport along the nerve axon to the olfactory bulb. Others are that the tight junctions between epithelial cells can be breached, or the sustentacular or basal cells crossed. Once across the epithelium, substances or particles could then be transported within the bundles of nerve fibres, rather than within the fibres themselves.

In an early study, electron microscopy of sections taken following intranasal administration of colloidal gold particles (size 500 Å, 50nm) to squirrel monkeys showed the particles being taken up into the cytoplasm of olfactory receptor cells. The particles travelled along the axon, reaching the olfactory bulb 30 to 60 minutes after administration (de Lorenzo, 1970). A range of different molecules and particles has now been shown to be taken up into olfactory neurons (Crowe et al, 2018). However, the diameter of the axon (approximately 200nm) imposes a size limit on the transport of particles to the olfactory bulb by this route. Kreyling (2016) noted that, although numerous studies have demonstrated the olfactory route for nano-sized particles, no studies have described it for larger (micron or sub-micron) sized particles.

Crowe et al (2018) explain that the tight junctions in nasal epithelia are fairly permeable, allowing the diffusion of smaller hydrophilic molecules. The high turnover rate of the olfactory sensory neurons, which undergo apoptosis after a lifespan of 30 to 60 days, also affects the permeability of the nasal epithelium. Tight junctions become more permeable, or may be absent, during the replacement of the neurons. If a substance passes between the cells of the epithelium, it can then enter the space around the olfactory neuron, between the neuron-ensheathing cells and the neural fibroblasts. From here, it can translocate along the length of the nerve sheath to the subarachnoid space, with the movement likely mediated by bulk flow processes and the perivascular pump (Crowe et al, 2018).

In the olfactory bulbs, the olfactory receptor neurons synapse with mitral and tuft cells. De Lorenzo (1970) observed that colloidal gold particles that had been taken up into olfactory receptor neurons were able to cross the synapse into mitral cell dendrites (de Lorenzo, 1970). This suggests that particles transported within olfactory receptor neurons may be able to cross synapses between neurons, and thereby be distributed into other parts of the brain. However, several authors have suggested that this is unlikely to be the main route of transport of inhaled substances to the brain. Crowe et al (2018) note that many experiments have demonstrated that drugs administered nasally can be distributed to almost every region of the brain, and consider that this makes it unlikely that distribution via the nerve projections from the olfactory bulb is the primary mechanism. The observed speed of distribution also suggests that axonal transport, which is a relatively slow process, is unlikely to be the most important route (Crowe et al, 2018). Crowe et al (2018) therefore consider the extracellular pathway as being a more important target for drug delivery to the brain. Dorman et al (2006) found evidence for olfactory transport of inhaled manganese (administered as soluble manganese (II) sulphate) in Rhesus monkeys (Dorman et al, 2006). However, this did not explain the high concentrations of manganese which accumulated in the globus pallidus, as there are thought to be no significant

neuronal connections between from olfactory bulbs to the globus pallidus. Instead, the authors considered that systemic delivery of manganese was a more likely explanation. In addition, Kreyling (2016) notes that nanoparticles may enter the circulation and cross into the brain via the blood-brain barrier.

Rather than particles themselves entering the wider brain via nerve transport from the nose, it is possible that chemicals carried on particle surfaces may be desorbed and then distributed to the brain. Ahmad et al (2017) investigated the transport to the brain of dyes administered to rats nasally in nanoemulsions. The results demonstrated entry of nano-sized particles via the olfactory and trigeminal nerves, but suggested that only very small particles are translocated into the brain, and only in extremely small amounts. The cargoes (dyes) were transported via the nerves and into the brain in higher concentrations.

## 4.5 The fate of particles which enter the brain

### 4.5.1 Summary

Particles that enter the brain - from the blood, from the cerebrospinal fluid and via nerve fibres - may remain in the tissues of the brain for some time. It is not clear whether such particles are stored, so to speak, mainly in neurons or in glial cells; nor are the effects of such particles upon these cells well understood. Whether particles can move from one neuron to another by crossing synaptic junctions is also unclear, though there is evidence to show that one type of nanoparticle, 50nm gold particles, can do so in the olfactory bulbs. Detection of particles in the brain relies on electron microscopy. The similarity of the appearance of artefacts arising from tissue storage and preparation to that of small particles that have entered the brain make the possibility of misidentification potentially important. A number of mechanisms for clearance of waste materials from the brain exist. Whether particles can be cleared by these processes is, at present, unclear: much further work on the kinetics of particle clearance from the brain is needed. Such work has begun though, to date, the focus has been on materials which can be readily identified in the brain, or which are of possible physiological or pharmacological importance, rather than on ambient particles.

### 4.5.2 The fate of particles which enter the brain

Sections 4.3 and 4.4 show that particulate matter can enter the brain via nerve fibres and also via the blood-brain barrier. As regards the former route most of the evidence relates to movement of particulate matter to the olfactory bulbs via the olfactory nerves but the possibility that particulate matter could reach the brain via the sensory fibres of the trigeminal nerves and also, perhaps, via those of the vagus nerves cannot be excluded.

That a wide range of material presented in particulate form has been found to enter the brain is clear. It is important to distinguish between nanomaterials designed to enter the brain, for example preparations of drugs, and those used to test pathways by which nanomaterials, in

general, might do so. In this report we focus on the latter, in that they are more likely to provide insight into whether ambient particulate matter can enter the brain. That combustion-derived ambient nanoparticles can enter the brain has been suggested by Gonzalez-Maciel et al (2017) although it is our view that the morphology and distribution of at least some of the observed particulates would be in keeping with artefacts arising from tissue storage in phosphate buffered saline (smaller particles) or from deposition of metallic salts used for staining of the ultrathin tissue sections (larger particles). Gonzalez-Maciel et al's (2017) paper also provides an excellent review of, and references to, earlier work undertaken by Calderón-Garcidueñas and her associates which is discussed in Section 4.6.

Kermanizadeh et al (2015) have provided a detailed review of publications reporting the translocation of nanoparticles to secondary organs in laboratory animals; the lung being regarded as the primary or target organ in many studies. The range of materials studied and distribution to secondary organs is well illustrated by the following table (Table 4.1) taken, with permission, from their paper. The reader is directed to this review for the references to the studies included in the table.

**Table 4.1. Showing studies reporting accumulation of nanoparticles in the brain**

(Reproduced from 'Nanomaterial translocation: the biokinetics, tissue accumulation, toxicity and fate of materials in secondary organs - a review.' Kermanizadeh A, Balharry D, Wallin H, Loft S, Moller P. Critical Reviews in Toxicology 2015: volume 45, issue 10, pages 837 to 872. Taylor and Francis, reprinted by permission of the publisher [Taylor and Francis Ltd.](#))

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Crit Rev Toxicol, 2015; 45(10): 837–872

Table 3. Summary of the accumulation and distal effects of nanomaterials on secondary organs following exposure via inhalation, IT, OA, intranasal and dermal routes. In instances where A is shown without T – the physical presence of NMs/ions in secondary organs was not investigated. The NMs are listed according to their solubility (from low to high) in each route of exposure.

| Nanomaterial                       | Route of exposure | Secondary organs (NMs/elemental ions detected = T<br>Adverse effects = A) |         |       |       |        |             |       |       | Reference                                                          |
|------------------------------------|-------------------|---------------------------------------------------------------------------|---------|-------|-------|--------|-------------|-------|-------|--------------------------------------------------------------------|
|                                    |                   | Liver                                                                     | Kidneys | Brain | Heart | Spleen | Bone marrow | Blood | Other |                                                                    |
| Au                                 | Inhalation        |                                                                           | T       | TA    | T     |        |             |       | T     | Balasubramanian et al. 2013                                        |
| Au                                 | Inhalation        | T                                                                         | X       | X     |       | X      |             |       | X     | Braakhuis et al. 2014                                              |
| Au                                 | Inhalation        | T                                                                         |         | T     |       | T      |             | T     | T     | Han et al. 2014                                                    |
| Au                                 | Inhalation        | X                                                                         | T       |       |       |        |             | X     | X     | Sung et al. 2011                                                   |
| Au                                 | Inhalation        |                                                                           | TA      |       | T     | T      |             | T     | T     | Yu et al. 2007                                                     |
| C                                  | Inhalation        | A                                                                         |         |       |       |        |             | X     |       | Khandoga et al. 2010                                               |
| C, Ir                              | Inhalation        | T                                                                         | T       |       | T     | T      |             | T     | T     | Kreyling et al. 2009                                               |
| CB                                 | Inhalation        | X                                                                         |         |       | X     | X      |             | A     |       | Niwa et al. 2008                                                   |
| CB, TiO <sub>2</sub>               | Inhalation        |                                                                           |         |       |       |        |             | A     |       | Saber et al. 2013                                                  |
| Printex 90                         | Inhalation        |                                                                           |         |       |       |        |             | X     |       | Gilmour et al. 2004                                                |
| MWCNT                              | Inhalation        | T                                                                         | T       | T     | T     |        |             |       | T     | Mercer et al. 2013                                                 |
| Ce                                 | Inhalation        | X                                                                         | X       | A     | X     | X      |             | X     | X     | Cassee et al. 2012                                                 |
| MnO                                | Inhalation        |                                                                           |         | TA    |       |        |             |       |       | Elder et al. 2006                                                  |
| Ir                                 | Inhalation        | T                                                                         | T       | T     | T     |        |             |       | T     | Geiser et al. 2014                                                 |
| U                                  | Inhalation        |                                                                           | T       | T     |       |        |             | T     |       | Petitot et al. 2013                                                |
| TiO <sub>2</sub>                   | Inhalation        | X                                                                         | X       | X     |       |        | X           |       | T     | Ravenzwaay et al. 2009                                             |
| Ag                                 | Inhalation        | TA                                                                        |         | T     |       |        |             | X     |       | Ji et al. 2007                                                     |
| Ag                                 | Inhalation        | TA                                                                        | T       | T     |       |        |             | T     |       | Sung et al. 2009                                                   |
| Ag                                 | Inhalation        | T                                                                         | T       |       | T     |        |             | T     | T     | Takenaka et al. 2001                                               |
| CeO <sub>2</sub>                   | Inhalation        | T                                                                         | A       | X     | T     |        |             |       | T     | Aalapati et al. 2014                                               |
| CeO <sub>2</sub>                   | Inhalation        | T                                                                         | T       | T     |       | T      |             |       | T     | Geraets et al. 2012                                                |
| Fe <sub>2</sub> O <sub>3</sub>     | Inhalation        | T                                                                         |         | T     |       | T      |             |       | T     | Kwon et al. 2008                                                   |
| QDs                                | Inhalation        | T                                                                         | T       | X     |       | X      |             | X     | X     | Ma-Hock et al. 2012                                                |
| ZnO                                | Inhalation        | X                                                                         | X       | X     | T     |        |             |       | X     | Adamcakova-Dodd et al. 2014                                        |
| ZnO                                | Inhalation        |                                                                           |         |       | TA    |        |             |       |       | Chuang et al. 2014                                                 |
| Au                                 | IT                | T                                                                         | T       | T     | T     | T      |             | T     | T     | Kreyling et al. 2014                                               |
| Au                                 | IT                | T                                                                         |         |       |       |        |             |       |       | Sadauskas et al. 2009                                              |
| Au                                 | IT                | T                                                                         |         |       |       |        |             | T     | T     | Semmler-Behnke et al. 2008                                         |
| C <sub>60</sub>                    | IT                | T                                                                         |         | T     |       |        |             |       |       | Shinohara et al. 2010                                              |
| Printex 90                         | IT                | A                                                                         |         |       |       |        |             |       |       | Bourdon et al. 2012a                                               |
| Printex 90                         | IT                | A                                                                         |         |       |       |        |             | A     |       | Bourdon et al. 2012b                                               |
| Printex 90                         | IT                | A*                                                                        |         |       |       |        |             |       |       | Jackson et al. 2012                                                |
| MWCNT                              | IT                |                                                                           | T       |       |       |        |             |       | T     | Aiso et al. 2011                                                   |
| MWCNT                              | IT                | A                                                                         |         |       |       |        |             |       |       | Hougaard et al. 2013                                               |
| MWCNT                              | IT                | A                                                                         | A       |       |       |        |             |       |       | Reddy et al. 2010                                                  |
| CB, MWCNT, SWCNT, TiO <sub>2</sub> | IT                | A                                                                         |         |       |       |        |             | A     |       | Saber et al. 2013                                                  |
| Ce                                 | IT                | T                                                                         | T       | T     | T     | T      |             | T     | T     | He et al. 2010                                                     |
| Diamond                            | IT                | TA                                                                        | A       |       | T     | T      | T           | TA    |       | Zhang et al. 2010                                                  |
| Mn                                 | IT                | A                                                                         |         | TA    |       |        |             |       |       | Sárközi et al. 2009                                                |
| Polystyrene                        | IT                | T                                                                         |         |       |       |        |             | T     | T     | Chen, et al. 2006                                                  |
| CeO <sub>2</sub>                   | IT                | A                                                                         | X       |       | X     | X      |             | A     |       | Nalabotu et al. 2012                                               |
| Pb                                 | IT                | TA                                                                        | A       | T     |       |        |             | T     |       | Oszlanczi et al. 2011                                              |
| QD                                 | IT                | X                                                                         | T       | X     | X     |        |             | X     | T     | Roberts et al. 2013                                                |
| Ag, MWCNT, TiO <sub>2</sub> , ZnO  | IT                | TA                                                                        |         |       |       |        |             |       |       | Gosens et al. 2015, Vranic et al. 2015                             |
| ZnO                                | IT                | T                                                                         | T       |       | T     |        |             | TA    |       | Chuang et al. 2014                                                 |
| ZnO                                | IT                | A                                                                         | A       | X     | X     |        |             | A     | X     | Gantedi and Anreddy 2012                                           |
| ZnO                                | IT                | T                                                                         | T       |       | T     |        | T           | T     | T     | Konduru et al. 2014                                                |
| Au                                 | OA                |                                                                           |         |       | T     |        |             |       | T     | Hussain et al. 2013                                                |
| Latex                              | OA                | T                                                                         | T       | X     | X     | X      | T           | TA    | T     | Sarlo et al. 2009                                                  |
| MWCNT                              | OA                | T                                                                         | T       |       |       | T      | T           | X     |       | Czarny et al. 2014                                                 |
| Gd <sub>2</sub> O <sub>3</sub>     | OA                | T                                                                         | T       |       | T     | T      |             |       | T     | Abid et al. 2013                                                   |
| Au                                 | Intranasal        |                                                                           | T       |       |       | T      |             | A     |       | Genter et al. 2012                                                 |
| Polystyrene                        | Intranasal        |                                                                           |         |       |       |        |             |       | TA    | Blank et al. 2013                                                  |
| TiO <sub>2</sub>                   | Intranasal        |                                                                           | A       | TA    |       |        |             | A     |       | Wang et al. 2008                                                   |
| TiO <sub>2</sub>                   | Intranasal        |                                                                           |         | A     |       |        |             |       |       | Zhang et al. 2011                                                  |
| MnO                                | Intranasal        |                                                                           |         | TA    |       |        |             |       |       | Elder et al. 2006                                                  |
| Cu                                 | Intranasal        |                                                                           |         | TA    |       |        |             |       |       | Bai et al. 2014                                                    |
| CB                                 | Oral              | A                                                                         |         |       |       |        |             |       | A     | Danielsen et al. 2010, Folkmann et al. 2012, Vesterdal et al. 2014 |
| C <sub>60</sub> , SWCNT            | Oral              | A                                                                         |         |       |       |        |             |       |       | Folkmann et al. 2009                                               |
| TiO <sub>2</sub>                   | Oral              |                                                                           |         |       |       |        |             |       | TA    | Brun et al. 2014                                                   |
| TiO <sub>2</sub>                   | Oral              | X                                                                         | X       | X     |       | X      |             |       | X     | Cho et al. 2013                                                    |
| TiO <sub>2</sub>                   | Oral              | X                                                                         |         |       |       | X      |             |       | X     | Geraets et al. 2014                                                |
| TiO <sub>2</sub>                   | Oral              | X                                                                         | X       | X     | X     | X      |             | X     | X     | MacNicol et al. 2015                                               |
| TiO <sub>2</sub>                   | Oral              | A                                                                         |         |       |       |        | A           |       | A     | Sycheva et al. 2011                                                |
| TiO <sub>2</sub>                   | Oral              |                                                                           |         |       |       | TX     |             |       | TA    | Tassinari et al. 2014                                              |
| Ag                                 | Oral              | TA                                                                        | TA      | T     |       | T      |             | A     | T     | Lee et al. 2013a                                                   |
| Ag                                 | Oral              |                                                                           |         |       |       |        |             |       | A     | Thakur et al. 2014                                                 |

(Continued)

Table 3. (Continued)

| Nanomaterial                                            | Route of exposure   | Secondary organs (NMs/elemental ions detected = T<br>Adverse effects = A) |         |       |       |        |             |       |       | Reference                 |
|---------------------------------------------------------|---------------------|---------------------------------------------------------------------------|---------|-------|-------|--------|-------------|-------|-------|---------------------------|
|                                                         |                     | Liver                                                                     | Kidneys | Brain | Heart | Spleen | Bone marrow | Blood | Other |                           |
| Ag                                                      | Oral                | T                                                                         | T       | T     |       | T      |             | T     | T     | van der Zande et al. 2012 |
| CeO <sub>2</sub>                                        | Oral                | TA                                                                        | TX      | T     | T     | TA     | A           | TA    | T     | Kumari et al. 2014a       |
| CeO <sub>2</sub>                                        | Oral                | TA                                                                        | TA      | TA    | T     | T      |             |       | A     | Kumari et al. 2014b       |
| SiO <sub>2</sub>                                        | Oral                | T                                                                         |         |       |       |        |             |       |       | Fu et al. 2013            |
| SiO <sub>2</sub>                                        | Oral                |                                                                           | X       |       |       |        |             |       | X     | Kim et al. 2014           |
| SiO <sub>2</sub>                                        | Oral                | TA                                                                        | T       |       |       | T      |             |       |       | van der Zande et al. 2014 |
| SiO <sub>2</sub>                                        | Oral                | X                                                                         | X       |       |       |        |             |       |       | Yoshida et al. 2014       |
| BaSO <sub>4</sub> , SiO <sub>2</sub> , ZnO <sub>2</sub> | Oral                | X                                                                         |         | X     | X     | X      |             | X     | X     | Buesen et al. 2014        |
| Al <sub>2</sub> O <sub>3</sub> , TiO <sub>2</sub> , ZnO | Oral                | A                                                                         |         | A     |       |        |             |       | A     | Shrivastava et al. 2014   |
| ZnO                                                     | Oral                | T                                                                         | T       | T     |       | T      |             |       |       | Cho et al. 2013           |
| ZnO                                                     | Oral                |                                                                           |         |       |       |        | T           | T     | T     | Konduru et al. 2014       |
| ZnO                                                     | Oral                | T                                                                         | T       | X     |       | X      |             |       | T     | Paek et al. 2013          |
| ZnO                                                     | Oral                | T                                                                         | T       |       |       |        |             |       | A     | Park et al. 2014          |
| ZnO                                                     | Oral                | TA                                                                        | A       |       |       |        |             |       |       | Sharma et al. 2012        |
| TiO <sub>2</sub>                                        | Dermal              | X                                                                         |         |       |       |        |             |       | T     | Sadrieh et al. 2010       |
| TiO <sub>2</sub>                                        | Dermal              | T                                                                         |         |       | T     |        |             | X     | T     | Wu et al. 2009a           |
| QD                                                      | Dermal <sup>Φ</sup> | T                                                                         |         |       |       |        |             |       | T     | Gopee et al. 2009         |
| QD                                                      | Dermal <sup>Q</sup> | T                                                                         |         |       |       |        |             |       | T     | Mortensen et al. 2013     |
| SiO <sub>2</sub> , QD                                   | Dermal              | T                                                                         |         | T     |       |        |             |       | T     | Nabeshi et al. 2011       |
| Ag                                                      | Dermal              | A                                                                         |         |       |       | A      |             |       |       | Korani et al. 2011        |
| Ag                                                      | Dermal              | T                                                                         | T       |       | TA    |        | T           |       | T     | Korani et al. 2013        |

\* = Effects in the offspring.

<sup>Q</sup> = Damaged skin.<sup>Φ</sup> = Dermabraded skin.

IT = Intratracheal instillation.

OA = Oropharyngeal aspiration.

A = Adverse effects.

T = NMs/elemental ions detected.

X = No NM-induced effects or translocation to the investigated organ was detected in the investigated organ.

Kermanizadeh et al (2015) also analysed the publications they reviewed in terms of the solubility of the materials studied. Their findings are shown in the following Table 4.2, produced with permission.



**Table 4.2. Showing accumulation of nanoparticles in the brain according to solubility**  
(Reproduced from Nanomaterial translocation--the biokinetics, tissue accumulation, toxicity and fate of materials in secondary organs--a review. Kermanizadeh A, Balharry D, Wallin H, Loft S, Moller P. Critical Reviews in Toxicology 2015: volume 45, issue 10, pages 837 to 872. Taylor and Francis, reprinted by permission of the publisher [Taylor and Francis Ltd.](#))

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Crit Rev Toxicol, 2015; 45(10): 837-872

Table 4. Number of studies with adverse effects or/and accumulation of NMs in secondary organs sub-categorised based on solubility of materials.

| Route of exposure | NM categorisation based on solubility | Number of studies |         |       |       |        |             |       |       |
|-------------------|---------------------------------------|-------------------|---------|-------|-------|--------|-------------|-------|-------|
|                   |                                       | Liver             | Kidneys | Brain | Heart | Spleen | Bone marrow | Blood | Other |
| Inhalation        | Low solubility                        | 6                 | 7       | 7     | 4     | 3      |             | 6     | 7     |
|                   | Slow solubility                       | 7                 | 5       | 4     | 2     | 2      |             | 2     | 4     |
|                   | Fast solubility                       |                   |         |       | 2     |        |             |       |       |
| IT                | Low solubility                        | 14                | 4       | 4     | 3     | 3      | 1           | 7     | 5     |
|                   | Slow solubility                       | 3                 | 2       | 1     | 1     | 1      |             | 2     | 1     |
|                   | Fast solubility                       | 4                 | 3       |       | 2     |        | 1           | 3     | 1     |
| OA                | Low solubility                        | 3                 | 3       |       | 2     | 2      | 2           | 1     | 3     |
|                   | Slow solubility                       |                   |         |       |       |        |             |       |       |
|                   | Fast solubility                       |                   |         |       |       |        |             |       |       |
| Intranasal        | Low solubility                        |                   | 2       | 3     |       | 1      |             | 2     | 1     |
|                   | Slow solubility                       |                   |         |       |       |        |             |       |       |
|                   | Fast solubility                       |                   |         | 1     |       |        |             |       |       |
| Oral              | Low solubility                        | 3                 |         |       |       | 1      | 1           |       | 4     |
|                   | Slow solubility                       | 6                 | 5       | 4     | 3     | 4      | 1           | 3     | 5     |
|                   | Fast solubility                       | 5                 | 4       | 2     |       | 1      | 1           | 1     | 4     |
| Dermal            | Low solubility                        | 1                 |         |       | 1     |        |             |       | 2     |
|                   | Slow solubility                       | 5                 | 1       | 1     | 1     | 1      | 1           |       | 4     |
|                   | Fast solubility                       |                   |         |       |       |        |             |       |       |

NM categorisation.

Low solubility: Au, C, C<sub>60</sub>, CB, Ce, Diamond, Ir, Latex, Mn, MnO, MWCNT, Polystyrene, SWCNT, TiO<sub>2</sub> and U.Slow solubility: Ag, CeO<sub>2</sub>, Fe<sub>2</sub>O<sub>3</sub>, Pb, QD and SiO<sub>2</sub>.

Fast solubility: Cu and ZnO. Note: The table offers a simplified count of the number of studies to date that have demonstrated either translocation or adverse effects in secondary organs. These effects were identified as significant in the individual study. This table is not however, a representative of the frequency of the said observations across the published data.

It is not possible, here, to review these studies in detail. We do, however, point out that in some cases the dose of material administered was large in comparison with that likely to be encountered on exposure to ambient air in the UK today. This is an important point. It is also important to note that particulate material found in ambient air could, in principle, enter the brain via 2 routes: via the olfactory nerves and other nerves supplying the respiratory tract, and via the blood as a result of translocation across the respiratory epithelium or across the epithelium of the gut to which particulate material deposited in the lung and material which has dissolved in lung fluids may be cleared. Of these routes the olfactory route seems likely to be the more efficient as regards a direct link with the brain: see sections 4.2 related to the translocation from lung to blood and Section 4.4 reviewing the olfactory uptake of particulate matter.

What happens to particulate matter that has entered the brain is much less certain. In principle it might move within the brain in nerve fibres, in the fluid compartments of the brain or in microglial cells. Little evidence is available for any of these mechanisms. De Lorenzo (1970) showed by electron microscopy that 50nm gold particles could cross the synaptic gap between primary olfactory fibres and dendrites of mitral cells of the olfactory bulbs of the squirrel monkey. We have been unable to find other work that confirms that this can occur and it is not known whether combustion particles could also cross to the dendrites of mitral cells. Whether they



could, might depend on the size of the particles and also on their composition, charge and protein coating which might, presumably, affect their capacity to interact with cell membranes.

Particulate matter that crosses from primary olfactory fibres to the mitral cells might travel on to the olfactory centres of the cortex; whether they could travel more widely within the brain has not been studied but seems unlikely to us. There is no evidence, as far as we are aware, that particles leave the olfactory bulbs for other parts of the brain. Oberdörster (2004) noted that particles had been identified in many parts of the brain but pointed out that those found, for example, in the cerebellum were more likely to have crossed the blood-brain barrier within the cerebellum than to have travelled from the olfactory bulbs.

The identification of small particles within the brain has relied, inevitably, on electron microscopy. Ultrafine particles, of less than 100nm diameter, cannot be seen with the light microscope unless they are aggregated as clumps of particles. Such particles can, however, be resolved by the electron microscope. A point that has not, in general, been considered in detail is that of artefacts. It is known, for example, that the storage of tissue in phosphate buffered saline can cause artefacts: small particles appear in sections. Such artefacts can also be produced by staining with uranyl acetate and with lead citrate, compounds that are used in preparing tissue for electron microscopy. Distinguishing between artefactual small particles and small particles which have reached the brain from the ambient air is difficult and, in our view, something on which more work is needed.

Another point concerns the similar distribution of pathological changes seen in patients suffering from early onset, autosomal dominant Alzheimer's disease and in those with sporadic late-onset disease. If particulate matter, arriving via the olfactory pathways, was an important cause of sporadic disease one would expect a different distribution of lesions in these patients from those with inherited disease. But this is not the case. This seems to us to weaken the likelihood that direct action of translocated particulate matter plays an important role in the causation of sporadic disease.

Little information is available on the fate of particulate matter that enters the brain. The obvious question is, are such particles cleared from the brain (as indeed they are from the lung) or do they remain, perhaps for the lifetime of the subject? No clear answer is, at present, available. It seems likely that particulate matter might be taken up by microglial cells, but what happens to these cells afterwards is unknown. It may be that they simply remain in the brain and provide a sort of storage or sequestration compartment for particles. It is known that what is generally regarded as 'waste material', lipofuscin, accumulates in the human brain, in neurons, during life (Goyal, 1982). This material, at least, is not cleared from neurons.

The normal functioning of neurons within the brain is dependent on the composition of the intercellular fluid that surrounds these cells. It has recently become clear that the maintenance of the composition of this fluid depends on normal astrocyte functioning. Astrocytes are, for example, known to take up potassium ions released during the passage of action potentials, to

take up transmitter substances and, also, water and other waste products, including neuronally-produced A $\beta$  complexed with lipoproteins and chaperone molecules such as apolipoproteins E and J. Removal of water from the interstitium of the brain is very necessary: neurons produce water as a side product of the metabolism of glucose. That the removal of waste materials is also necessary seems certain. Materials move through the interstitial space of the brain by diffusion and, in the case of water and solutes, by bulk flow of fluid (Abbott, 2004). An additional, and faster, route for fluid transport has been proposed. This is the glymphatic system that depends on the transport of materials, including water, from periarterial spaces, through the parenchyma, to perivenular spaces (Iliff et al 2012, Begley 2012)). Iliff et al (2012) proposed that the aquaporin channels of astrocyte foot processes were key to this system.

Much attention has focused on this proposal: it has been described as a cleansing mechanism of the brain and it has been suggested that it functions most effectively during sleep (Nedergaard, 2016). According to its proponents, this system functions in a way similar to that of the peripheral lymphatic system in other parts of the body, it handles water, solutes and, importantly, lipid soluble materials, but relies on glia cells (astrocytes) rather than lymphatic capillaries: hence the name, glymphatic system (Jessen et al, 2015). Whether such a system exists has been debated. Holter et al (2017) have suggested that bulk flow through the parenchyma is unlikely and that diffusion is the more likely mechanism for the movement of substances in this physiological space. Hladky et al (2014), in a major review, have also criticised the glymphatic hypothesis.

### 4.5.3 The role of neurological fluid systems on particle fate within the brain

An area of special interest regarding the fate of particles within the brain concerns the fluid systems of the brain. Here a good deal is known, especially as regards particulate matter designed for the transport of drugs into the brain. This area has also been studied with regard to the removal of A $\beta$  from the brain.

Toxins and particles in the air may enter the brain transported by the blood vessels, by the fluid that bathes the brain (cerebrospinal fluid, CSF) or by nerve routes. Apart from the blood, there are 2 other major fluids associated with the brain: cerebrospinal fluid and interstitial fluid. The blood circulates within capillaries, arterioles and venules that have unique properties in the brain. As discussed in Section 4.3, one major feature is the presence of the blood-brain barrier that restricts the entry of particles and proteins in the brain (Abbott, 2002). However, the blood-brain barrier allows the transmission of inflammatory signals from the periphery to the brain, worsening the pathological features and clinical symptoms of diseases such as dementia (Holmes et al, 2009).

#### Interstitial fluid

This is produced by local metabolic activity of the cells within the brain and by filtration from the blood (Abbott, 2004). Intramural periarterial drainage (IPAD) of interstitial fluid and soluble

peptides from the brain parenchyma occurs along the basement membranes of cerebral capillaries and arteries, against the direction of blood flow and towards the leptomeningeal arteries (Morris et al, 2016). Failure of IPAD with increasing age is associated with the failure of elimination of fluid and A $\beta$  from the brain, leading to cerebral amyloid angiopathy (CAA) and Alzheimer's disease (Hawkes et al, 2014). Genetic mutations involving amyloidogenic peptides, such as A $\beta$  and cystatin, also result in CAA (Lashley et al, 2006; Snorradottir et al, 2013).

Experimentally, IPAD is impaired in [a] aged mice, [b] in the presence of CAA, [c] in mice with human apolipoprotein E4 (*APOE*  $\epsilon$ 4) genotype, [d] in mice with hyperlipidemia associated with maternal high fat diet during gestation, and [e] in mice associated with the formation of immune complexes in IPAD pathways (Carare et al, 2013; Hawkes et al, 2013; Hawkes et al, 2015; Hawkes et al, 2011; Hawkes et al, 2012; Snorradottir et al, 2013). Changes in the extracellular matrix within artery walls are reflected in the structural, morphological and biochemical modifications of the vascular basement membranes and are associated with CAA (Snorradottir et al, 2017; Wyss-Coray et al, 2000).

### Cerebrospinal fluid (CSF)

Cerebrospinal fluid (CSF) is produced by the choroid plexus in the ventricles and it circulates in the subarachnoid spaces. In humans and large mammals, CSF drains along arachnoid granulations into the venous blood and along subarachnoid channels filled with CSF surrounding olfactory nerves, into the nasal mucosa (Engelhardt et al, 2016; Kida et al, 1995). This pathway is significant in the diagnosis and monitoring progression of Alzheimer's disease, using dynamic positron emission tomography (PET) with 18F-THK5117, a tracer for tau pathology (de Leon et al, 2017). In rodents there are well described routes for the drainage of CSF into the nasal mucosa and then into the cervical lymph nodes (Kida et al, 1993). Recent studies of CSF drainage using novel techniques involved the use of pegylated and small molecular near-infrared tracers and lymphatic specific reporter mice combined with stereo microscopy together with quantitative measurements of tracers in venous blood (Ma et al, 2017). From their studies in mice, the authors suggest that the major route for CSF drainage is by perineural pathways including the olfactory nerves. They found no drainage of tracer along lymphatics in the dura and detected no drainage of CSF directly into venous blood through arachnoid villi. Furthermore, the authors detected reduced clearance of CSF in aged mice which may have relevance for Alzheimer's disease (Ma et al, 2017).

There is experimental evidence that soluble tracers such as [125I]-insulin-like growth factor I (IGF-I, MW=7.65 kDa) in rats and [125I]-interferon- $\beta$ 1B (IFN- $\beta$ 1B, MW = 18.5 kDa) in monkeys enter the olfactory or trigeminal nerve endings in the nasal mucosa and are distributed within 30 minutes into the brain parenchyma (Lochhead et al, 2015). It is possible that solutes and particles from the inspired air may reach the subarachnoid channels surrounding the olfactory nerve, effectively the same channels that drain CSF into the nasal mucosa and cervical lymph nodes. Once they reach the CSF, solutes and particles may access the cerebral parenchyma.

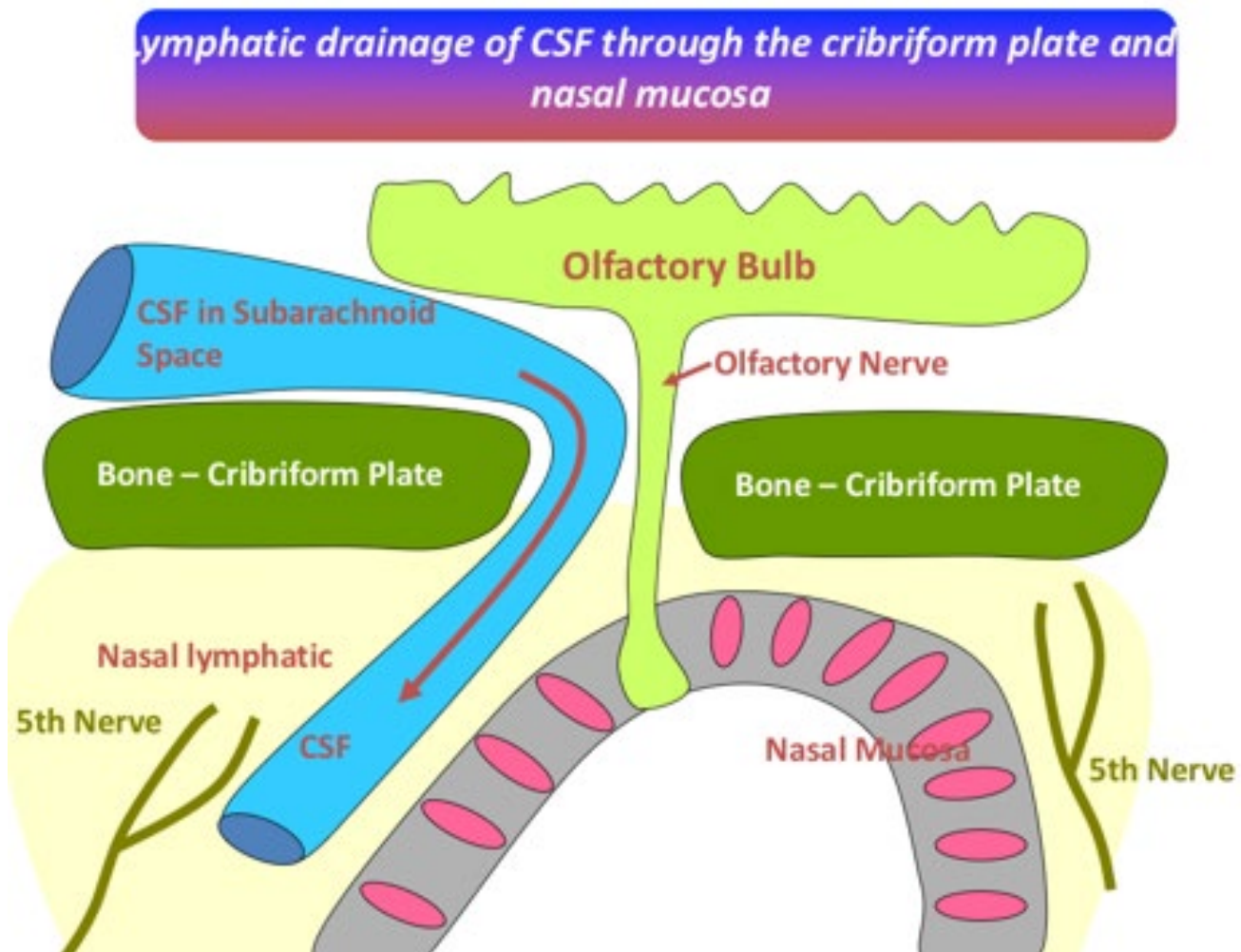
Recent studies demonstrate that 15-nm gold nanoparticles enter the brain parenchyma within 5 minutes of their injection into the CSF, along the glial-pial basement membranes (Morris et al, 2016). The nanoparticles do not move towards the IPAD pathways for drainage of interstitial fluid out of the brain, suggesting that particles remain confined to the parenchyma. Particles from polluted atmosphere may disintegrate and produce toxic soluble material that could generate an inflammatory reaction.

Similar to nanoparticles, recent experiments (Albargothy et al, 2018) show that soluble A $\beta$  injected into the CSF enters the brain along pial glial basement membranes within 5 minutes and by 30 minutes A $\beta$  is found in the IPAD basement membranes surrounding smooth muscle cells. In conclusion, it appears that convective influx of CSF into the brain occurs for both particles and solutes. Particles remain in the parenchyma, whereas solutes enter the normal pathways for the elimination of proteins from the brain, along basement membranes of arteries. It is possible that soluble or particulate material in the air may reach the brain by any of the routes outlined above, in particular along the subarachnoid channels surrounding the olfactory nerves or via the trigeminal nerve endings (see summary Figure 4.3 below), but the effects that they may have upon the normal drainage of soluble A $\beta$  or other metabolites from the brain are not known.

Fluorescent particles of sizes of 20nm to 1 $\mu$ m were injected into the striatum of mice and the brains examined at intervals from 5 minutes to 24 hours. Even when the particles were co-injected with lipopolysaccharide to stimulate inflammatory cells, the particles did not leave the brain (Carare et al, 2008). This is in agreement with earlier studies that suggest that bacillus Calmette Guerin escapes immune recognition and remains in the brain (Matyszak and Perry, 1998). It does appear that particulate matter can enter the brain from the CSF, along the glial pial basement membranes, but will most likely remain sequestered in the brain, after being taken up by macrophages. If there are any soluble compounds generated from the particles, they most probably will drain along the basement membranes surrounding smooth muscle cells (IPAD) and may become toxic to the smooth muscle cells, or impede the drainage of metabolites from the brain. Work for the future should aim to test the hypothesis that inhaled polluted air by rodents results in a failure of IPAD, accelerating the pathogenesis of cerebral amyloid angiopathy and Alzheimer's disease.

**Figure 4.3. Summary figure of the connections between the CSF and the nasal mucosa**

(After Pathophysiology 2010: volume 17, issue 4. Weller RO, Galea I, Carare RO, Minagar A. 'Pathophysiology of the lymphatic drainage of the central nervous system: implications for pathogenesis and therapy of multiple sclerosis.' Pages 295 to 306. Copyright (2010) with permission from Elsevier.)



The olfactory nerve endings and trigeminal nerve endings are present in the nasal mucosa. There is drainage of cerebrospinal fluid (CSF) from the subarachnoid space along channels filled with CSF that are present around the olfactory nerve endings. This is also the route that intranasally delivered tracers take to reach the olfactory bulb in the brain. There is evidence that intranasally delivered tracers enter the nerve endings of the trigeminal nerve and are transported along the nerves into the brainstem where the nuclei of cranial nerve V are located (Oberdörster et al, 2004). The distribution of tracers further than the midbrain has not been shown.

#### 4.5.4 Conclusions

Little is known of the fate of particulate matter that enters the brain. Such evidence as there is does not suggest that particulate matter is rapidly cleared from the brain, indeed there is little

evidence to show that particulate matter is cleared from the brain at all. If such material does enter the brain - and this at least seems probable though the amounts that do so are likely to be small - then it follows that it may accumulate there throughout life. The next and obvious question is, does this material harm the brain? This question is addressed in section 4.6.

## 4.6 Biochemical mechanisms

### 4.6.1 Summary

Much work has been done on the mechanisms by which air pollutants, including particulate material, might damage the brain. Such work began with a focus on ozone and has evolved to include ambient particles and, especially, metal-rich particles. Interest has been focused on the initiation of an inflammatory response in the brain and the role of oxidative stress. Effects on protein homeostasis and disturbances of mitochondrial function and of calcium handling by brain cells may be involved. The extent to which these processes may be the cause or the effect of neurodegenerative disease is not clear. Nor is it clear whether effects of pollutants are locally generated (resulting from a pollutant or reaction by-product which has entered the brain) or are secondary to adverse effects on the lung or in the systemic circulation. It is likely that age may affect the susceptibility to the effects of air pollutants on the brain. However, the evidence on this is not yet clear.

### 4.6.2 Possible mechanisms for the development and progression of neurodegeneration and dementia

#### 4.6.2.1 Oxidative stress and cognitive decline

Numerous studies and reviews have considered the role of free radicals, oxidative stress and inflammation in ageing, neurodegeneration and neurological diseases (for example, reviews by Tuppo and Forman, 2001; Wang and Michaelis, 2010; Guglielmotto et al, 2010). Free radicals, including reactive oxygen and nitrogen species, are generated during the normal functioning of cells, particularly during the consumption of oxygen by mitochondria. As they are very reactive, free radicals can react with cellular molecules such as lipids, proteins and deoxyribonucleic acid (DNA). This means that excessive production of free radicals, or inadequate antioxidant capacity to protect cells against them, can result in deleterious effects.

The brain is understood to be particularly vulnerable to oxidative damage compared with other organs for a number of reasons. These include its high demand for oxygen, high content of easily oxidisable fatty acids and modest antioxidant defence. Oxidative damage occurs as part of the normal ageing process in the brains of non-symptomatic elderly individuals, due to a progressive imbalance between the generation of free radicals in the form of reactive oxygen species (ROS) and available antioxidant defences.

Studies on post-mortem brain tissue from individuals with Alzheimer's disease have demonstrated increased lipid peroxidation and protein oxidation, with some indicating that the



damage is localised in regions of the brain associated with Alzheimer's disease pathology. DNA, particularly mitochondrial DNA, has also been identified as a target of oxidative damage in ageing and in Alzheimer's disease. Mitochondrial mutations that accumulate during brain ageing and neurodegenerative diseases cause respiratory chain dysfunction, which can further increase cellular oxidative stress (Guglielmotto et al, 2010). Some authors, including Swerdlow et al (2014), have proposed that age-related loss of mitochondrial function underpins late-onset sporadic Alzheimer's disease. This 'mitochondrial cascade' hypothesis proposes that effects on amyloid processing and accumulation may be secondary to brain ageing that results from the bioenergetic deficit caused by the declining mitochondrial function within neurons.

Some neuronal cells are more vulnerable to oxidative stress than others. Factors proposed as contributing to the vulnerability of certain neurons include high intrinsic oxidative stress, low adenosine triphosphate (ATP) production, mitochondrial dysfunction and a high inflammatory response (Wang and Michaelis, 2010.) This selective neuronal vulnerability to oxidative stress might explain the patterns of neurodegeneration seen in normal ageing and disease pathology.

Guglielmotto et al (2010) note the complex interaction between oxidative stress and A $\beta$ : A $\beta$  has been demonstrated to induce oxidative stress in-vivo and in-vitro, but evidence has also suggested that oxidative stress may enhance the production and aggregation of A $\beta$  peptides. Evidence supports a role for oxidative stress in mediating the pathogenic effects of risk factors for Alzheimer's disease such as hypoxia and hyperglycaemia. Studies suggest that during ischaemia (for example, during a stroke), production of ROS - due to interruption of the mitochondrial electron-transport chain - activates intracellular signalling which increases A $\beta$  production.

A number of interacting metabolic stress mechanisms have been proposed in Alzheimer's disease (reviewed by De Felice and Lourenco, 2015). These include endoplasmic reticulum stress arising from accumulation of misfolded proteins and/or impaired protein homeostasis.

#### 4.6.2.2 Neuroinflammation and cognitive decline

A neuroinflammatory response of the central nervous system's (CNS) immune system is also understood to play an important role in neurodegenerative diseases, as indicated by the findings of studies in both animals and humans with Alzheimer's disease (for example Amor et al, 2010 and Cunningham, 2013 cited in Perry and Teeling, 2013; Lucin and Wyss-Coray, 2009). Neuroinflammation may be triggered by locally generated damage/effects, or in response to signals from elsewhere in the body, such as during systemic inflammation. Both the brain's innate immune cells (microglial cells, astrocytes) and infiltration of peripheral immune cells have been implicated. Additionally, A $\beta$  oligomers have been shown to activate microglial cells, with evidence suggesting that consequent cytokine release causes injury to synapses.

The response and responsiveness of the immune system changes as the brain ages. Perry and Teeling (2013) suggest that microglia are 'primed' by ageing and neurodegeneration, which

then leads to a maladaptive response and increased susceptibility to future systemic inflammation.

Whilst the innate immune system may respond to damage caused by oxidative stress, it also generates oxidative stress as part of its response. Oxidative stress could, therefore, be either or both a cause and a consequence of inflammation.

### 4.6.3 Linking air pollution exposure with effects in the brain

#### 4.6.3.1 Introduction

Oxidative stress has been suggested as a common mechanism by which air pollutants may cause a wide range of adverse health effects (for example, COMEAP, 2018). In the context of neurological toxicity, there has been a focus on a possible role of oxidative stress initiated locally in the brain, for example by ultrafine particles transported via the olfactory pathway or by compounds adsorbed onto particulate matter (PM). However, indirect effects are also proposed. Circulating cytokines, perhaps produced as a result of systemic inflammation, may impact the CNS - resulting in neuroinflammation, neurotoxicity and damage to the cerebral vasculature (Block and Calderón-Garcidueñas, 2009). Free radicals produced by astroglia and microglia activated during this neuroinflammation have been suggested as playing a role (for example by Jayaraj et al, 2017). Again, activation of microglia could be direct or indirect (Block and Calderón-Garcidueñas, 2009).

A number of reviews are available of studies on the effects of air pollutants or nanoparticles on neurological function and neurodegeneration (eg Genc et al, 2012; Heusinkveld et al, 2016, Jayaraj et al, 2017 Croze and Zimmer, 2018). All these reviews conclude that a causal role is plausible. Some of the relevant studies are summarised below.

#### 4.6.3.2 Observational studies (humans and sentinel animals)

A series of observational studies in Mexico has contributed to the current interest in the possible effect of air pollutants on neurological function and as contributory factors in neurodegenerative diseases. Mexico City, and some other Mexican cities, experience high levels of air pollutants including PM and ozone (O<sub>3</sub>). Calderón-Garcidueñas and colleagues have investigated the potential effects of exposure to these levels of pollution on residents of these cities. Early studies in the 1990s (for example, Calderón-Garcidueñas et al, 1992, 1994), focused on effects in children, adolescents and adults on the internal surface of the nose (the nasal mucosa) and reported changes in the mucosa of new arrivals to Mexico City. Subsequent studies included observations on dogs, as a sentinel species, as well as humans. Most have compared observations (often of post-mortem material) in a relatively small number of humans and/or dogs resident in Mexico City and Monterrey (both cities that have notably high pollution levels) with those resident in Mexican cities with lower levels of pollution. Many of the more recent studies have focused on effects on the olfactory system and the brain. Some of these more recent studies are summarised below. We appreciate the creativity involved in devising and undertaking these studies, and the detailed pathological investigations involved. Nonetheless, these observational studies are weak compared with epidemiological evidence. We also note



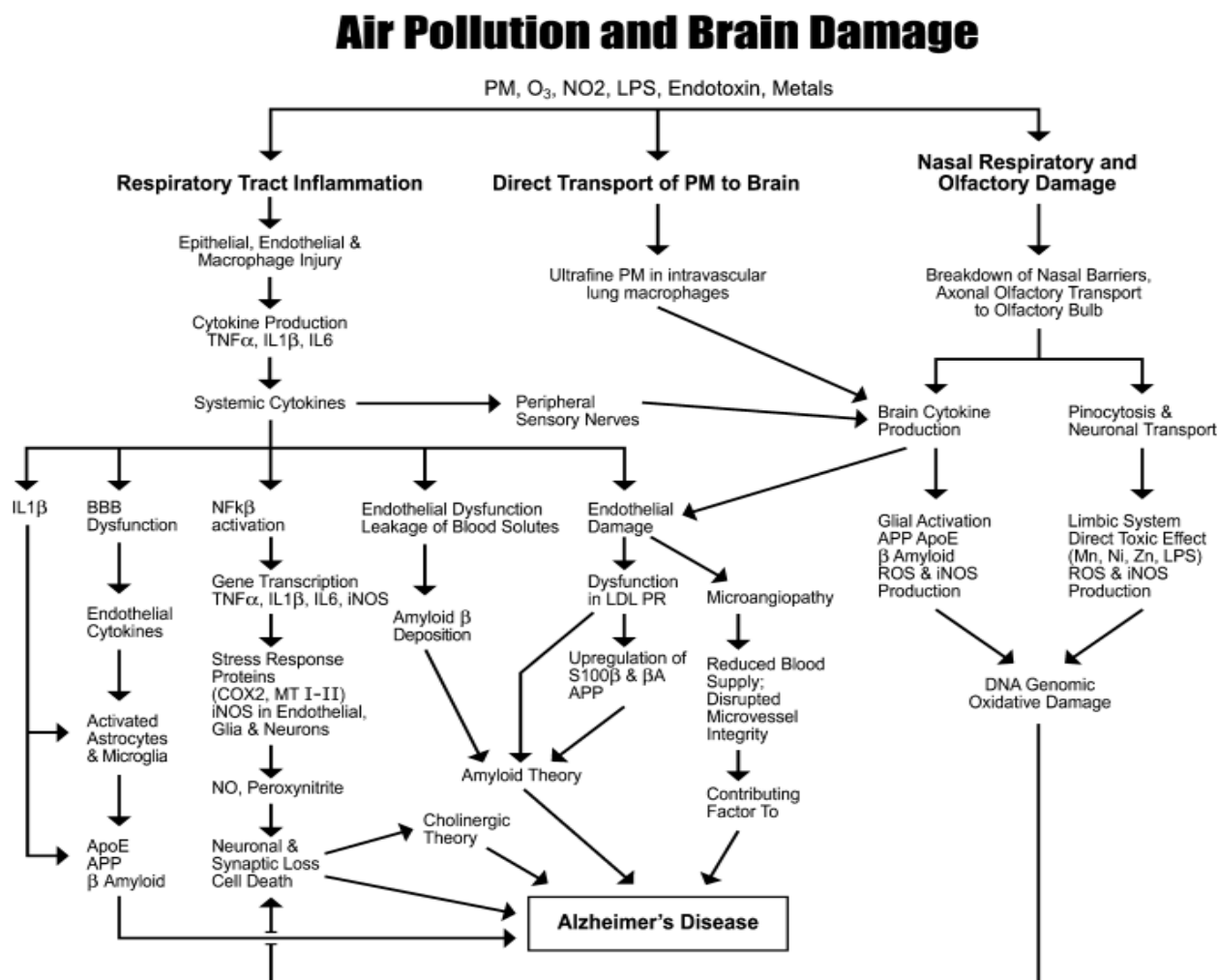
that most of these studies compare subjects in Mexico City with those in other, less polluted, towns. These 'control' towns are smaller than Mexico City and are likely to differ in other aspects as well as levels of air pollution. Therefore, it is possible that the effects seen could be due to another aspect of urbanicity, not necessarily air pollution.

A study in mongrel dogs (Calderón-Garcidueñas et al, 2002) found differences between those which had lived in Mexico City (n = 32) and those living in a less polluted (control) city (n = 8). Those from Mexico City, particularly the older dogs, exhibited signs of damage (for example, hyperplasia) to the epithelia lining the respiratory bronchioles and nose. Damage to the olfactory epithelium of older dogs from Mexico City included degeneration of the sensory and sustentacular (supporting epithelial) cells, and an accompanying loss of nerve bundles in the underlying connective tissue (the lamina propria). Changes in brain tissue also increased with age, including changes to the blood vessels, neuronal damage and loss, and activation of astrocytes. In the younger dogs, effects appeared to be restricted to the areas around blood vessels. The authors noted that capillary pathology was a major finding in the olfactory bulb and frontal cortex, and that observations suggested dysfunction of the blood-brain barrier (BBB) in these areas. They postulated that the effects observed may be secondary to respiratory inflammation caused by air pollutants. Cytokines released into the blood stream could disrupt the blood-brain barrier and activate microglia, causing neuronal and glial cell damage. This could establish a self-perpetuating inflammation in the brain.

A second similar study in dogs (14 controls, 26 from Mexico City) was also reported by Calderón-Garcidueñas et al (2003) and the authors proposed a number of potential pathways by which air pollution could cause brain damage. These included direct transport of PM to the brain via the blood vessels or olfactory nerve and effects secondary to respiratory tract inflammation (see Figure 4.4).

# Figure 4.4. Air pollution and brain damage; potential pathways by which air pollutants may cause brain damage

(Reproduced from Calderón-Garcidueñas L, Maronpot RR, Torres-Jardon R, Henriquez-Roldan C, Schoonhoven R, Acuna-Ayala H, et al. Toxicologic Pathology 2003: volume 31, issue 5. 'DNA damage in nasal and brain tissues of canines exposed to air pollutants is associated with evidence of chronic brain inflammation and neurodegeneration.' pages 524 to 538, copyright © 2003 (SAGE Journals) Reprinted by Permission of SAGE Publications)



The group also undertook studies of human brains. Examination of autopsy brain tissue from adults with no history of cognitive decline or neurological damage revealed that long-term residents ( $n = 10$ ) of cities with high pollution had significantly higher expression of cyclooxygenase-2 (COX2) (a marker of inflammation) in the frontal cortex and hippocampus than did residents ( $n = 9$ ) of a less-polluted city. Greater accumulation of A $\beta$ 42 (the major peptide deposited in Alzheimer's diseased brain) was found in the brains of those who had lived in cities with higher pollution levels. Increased COX2 expression and A $\beta$ 42 were also seen in their olfactory bulbs (Calderón-Garcidueñas et al, 2004).

A study of autopsy tissue from children and young adults (aged 2 - 45 years) also found more indications of neuroinflammation and neurodegeneration in those who had been resident in Mexico City ( $n = 35$ ) compared with those living in less polluted cities ( $n = 12$ ) (Calderón-Garcidueñas et al, 2008a). Particulate matter, COX2, A $\beta$ 42 and reactive gliosis were observed in olfactory bulbs. In cortical sections, vascular and perivascular changes were seen, and inflammatory markers were identified in endothelial cells of cortical capillaries and arterioles and in neurons. Among those with *APOE*  $\epsilon$ 3/3, tight junction abnormalities were detected in a higher proportion of vessels in the frontal cortex of brains from Mexico City residents than those from less polluted cities. These indicate damage to the BBB, although it is not clear whether the observed abnormalities were important in functional terms. The percentage of tight junction abnormalities was even higher in those with *APOE*  $\epsilon$ 3/4. mRNA for inflammatory markers was found in the lungs, olfactory bulbs, hippocampus and substantia nigra. Levels in blood were not measured. Deposition of PM (mainly in macrophages or Kupffer cells) was reported in a range of tissues, including the lung, sub-pleura, peri-bronchial lymph nodes and liver, following examination of stained paraffin sections by light microscopy. The authors proposed 4 potential pathways by which air pollutants might cause the observed effects:

- systemic inflammation (resulting from pulmonary inflammation) leading to disruption of the blood-brain barrier, and resulting in astrocyte activation
- via the olfactory pathway, by damage to the olfactory bulb and subsequent effects on the limbic system
- through the vagus and trigeminal pathways, by upregulation of the CD14 pattern recognition receptor
- direct access of ultrafine PM to the brain, inducing an inflammatory response (such as ROS production by activated microglia and perivascular macrophages), damaging the BBB and potentially enhancing protein fibrillation and A $\beta$  deposition

In a separate study (Calderón-Garcidueñas et al, 2008b), white matter hyperintensities were identified by magnetic resonance imaging (MRI) in the pre-frontal cortex in more than half of children ( $n = 23$ ) and 19 month old dogs (4 of 7) from Mexico City tested, but only 8% (1 of 13) of children from cities with lower pollution. There was upregulation of inflammatory gene mRNA in frontal cortex white matter in Mexico City dogs, and this upregulation was higher in the tissue that contained hyperintensities. Reactive astrogliosis was found in the MRI-hyperintense regions in 3 of the 4 dogs found to have them. Pathological findings from Mexico City dogs

included mild reactive astrocytosis in olfactory bulbs but no PM was found (by light microscopy) in the olfactory bulbs. Widespread vascular pathology was found in frontal sections. In addition, perivascular macrophage-like cells, with abundant lipid vacuoles, were found in contact with walls of frontal white matter vessels. Red blood cells with material described as resembling ultrafine particles were seen, by electron microscopy, in the adjacent endothelial basement membranes.

A number of other studies followed, with similar effects reported. Calderón-Garcidueñas et al (2011) found cognitive deficits and differences in white matter volume in children from Mexico City (n = 20) compared with those from a less polluted city (n = 10). Investigation of exposed children with (n = 10) and without (n = 10) white matter hyperintensities showed different profiles of inflammatory cytokines and markers of other processes (Calderón-Garcidueñas et al, 2012a). Autopsy samples of the frontal cortex from control (n = 8) and exposed (n = 35) children and young adults showed upregulation in genes coding for markers of oxidative stress, DNA damage and inflammation in exposed individuals. Approximately half exhibited tau hyperphosphorylation (40%) and A $\beta$ 42 diffuse plaques (51%), while none was seen in controls (Calderón-Garcidueñas et al 2012b).

Examination of the prefrontal white matter of children and teenagers (n = 34) from Mexico City, by light and electron microscopy, showed changes indicative of leaking capillaries and small arterioles. Other abnormalities of the blood vessels were also seen. Nano-sized particles (20 - 48nm) were reported in the vascular endothelial cells, basement membranes, axons and dendrites. In Mexico City dogs (n = 15) tight junctions were abnormal and white matter perivascular damage was worse than in control dogs (Calderón-Garcidueñas et al, 2016b).

Other studies investigated concentrations of metals and markers of oxidative stress, inflammation and neural and tight-junction antibodies in brains, cerebrospinal fluid or serum of children and young adults from Mexico City (Calderón-Garcidueñas et al, 2013b, 2015). Another investigated the influence of sex, body mass index and *APOE*  $\epsilon$ 4 on cognition in children resident in Mexico City and suggested that *APOE*  $\epsilon$ 4 heterozygous females with higher BMI might be most at risk of severe effects (Calderón-Garcidueñas et al, 2016c).

In a collaboration with UK researchers, (Maher et al, 2016), magnetic analyses and electron microscopy were used to characterise nano-sized particles in human tissue samples taken from the frontal lobes of residents of Mexico City (n = 29) and Manchester, UK (n = 8). Magnetic nanoparticles were found in all samples. Many of the highly magnetic brain samples were from older residents of Manchester (>65 years at death), especially those with moderate to severe Alzheimer's disease. However, the brains of some young (<40 years at death) residents of Mexico City also had high magnetite concentrations. Two types of magnetite nanoparticles were described. Some were angular, cubo-octahedral crystals which were relatively rare and presumed to have been formed endogenously. Others were rounded or spherical particles, some with fused interlocking surface crystallites, with a broad size distribution (median longest diameter 18nm, maximum approx. 150nm). The authors considered these consistent with high-

temperature formation, such as combustion processes. Nano-sized particles consisting of other transition metals (platinum, nickel, cobalt and possibly copper) were also detected, with these metals co-occurring with magnetite. The authors noted that the rounded magnetite particles resembled ubiquitous and prolific nanoparticles found as combustion or high-temperature derived ambient air pollutants. Particles with similar chemical composition and morphology to those described by Maher et al (2016) have been observed in air samples collected from trafficked urban areas in the UK (Sanderson et al, 2016).

Gonzalez-Maciel et al (2017) used transmission electron microscopy to examine nanoparticles in tissue samples from residents of Mexico City (n = 34) and control cities with lower pollution (n = 11) and of dogs housed in Mexico City (n = 15) or control cities (n = 10). Cerebrospinal fluid from the dogs and from residents of Mexico City (n = 80) and control cities (n = 35) was also examined. Most of the nanoparticles found (87% of those in dog tissue, 100% of those in dog CSF) were spherical rather than angular or euhedral, and were present in greater concentrations in CSF or on nasal cilia and cell organelles (mitochondria, Golgi apparatus, nuclei of neurons and glial cells) in those exposed in Mexico City compared with those from control cities. Among other observations, young dogs from Mexico City were reported to have abnormal small blood vessels in grey and white matter, and red blood cells containing nanoparticles. Residents of Mexico City were also reported to have numerous nanoparticles in abnormal mitochondria, while those from control cities had intact mitochondria largely without nanoparticles. The authors reported that nanoparticles were in abnormal mitochondria of every cell type in the brain examined (neurons, astrocytes, olfactory neurons and so on), and also that the endoplasmic reticulum was abnormal in every brain cell of a Mexico City resident examined.

However, they also noted that the autopsy cases were from accidental deaths of individuals presumed to be healthy, so the study did not indicate a direct link between the observed nanoparticles or neuropathology and clinical cognitive effects, although the authors stressed that their earlier and ongoing studies on young Mexico City residents provide some evidence of morphological and functional effects. In addition, it is our view that the morphology and distribution of at least some of the observed particulates would be in keeping with artefacts arising from tissue storage in phosphate buffered saline (smaller particles) or from deposition of metallic salts used for staining of the ultrathin tissue sections (larger particles).

Another study (Calderón-Garcidueñas et al, 2017b) used samples from dogs (Mexico City, n = 6; control n = 4) and autopsy tissues from children and young adults (Mexico City, n = 27; control n = 9) to examine the possibility that swallowed combustion or high-temperature-derived nanoparticles could enter the nervous system. The authors suggested that the particles penetrated and damaged the gastro-intestinal barrier and reached parasympathetic nerve fibres and the vagus nerve. This was based on light and electron microscopy of bowel and vagus samples. Subsequent work by the group has examined tau, A $\beta$  and other markers of neurodegenerative diseases (for example, Calderón-Garcidueñas et al, 2018a, b).

### Summary of observational studies

In summary: Residents of Mexico City are exposed to high ambient concentrations of a number of air pollutants. Ozone concentrations increased after 1986, peaking in 1991 (Calderón-Garcidueñas et al (2008a). Concentrations of PM are also high. Annual average concentrations of PM<sub>2.5</sub> in Southwest Mexico City have been reported to be 25µg/m<sup>3</sup> (Calderón-Garcidueñas et al, 2008a) or 36µg/m<sup>3</sup> (Calderón-Garcidueñas et al, 2011). Lipopolysaccharide concentrations are also high, with concentrations of 15.3 to 20.6 ng/mg PM<sub>10</sub> reported, and endotoxin concentrations of 59 Endotoxin Units (EU)/ mg PM<sub>10</sub><sup>20</sup> (Calderón-Garcidueñas et al, 2008a) reported in Southwest Mexico City.

The majority of the studies available on this population are small, observational studies with geographically distant controls. Many did not report information on inclusion or exclusion criteria and the assessment of possible confounders. Nonetheless, they demonstrate adverse neurological effects apparently associated with air pollutants, including biochemical and structural changes consistent with early indications of neurodegeneration. The extent to which different pollutants, or another urban factor which differs between the 'polluted' and 'control' cities, may contribute to the effects is unclear. Nonetheless, the observations suggest that a role for ultrafine particles is possible.

#### 4.6.3.3 Experimental studies: Introduction

Experimental laboratory studies have been undertaken to investigate whether exposure to air pollutants causes effects consistent with neurodegeneration and, if so, the mechanisms that might be involved. Most in vivo studies have used rodents, with some in transgenic animals which provide a better model of Alzheimer's disease than wild-type animals (for example, Cacciottolo et al, 2017).

Many of the available studies have focused on exposure to particulate air pollution or pollution mixtures (such as diesel engine exhaust) in which particles might be presumed to be the most likely causal agent. As previously discussed, particles, particularly nano-sized ultrafine particles, may cause effects following direct entry into the brain (for instance via the olfactory route, or the circulation). In vitro studies are, therefore, potentially relevant to investigating effects of inhaled particles, particularly ultrafine particles.

A number of studies of exposure to ozone (O<sub>3</sub>) have also been undertaken. O<sub>3</sub> is very reactive and so would not reach brain tissue in the form of ozone itself. Because of this, there has been considerable interest in investigating how inhaling O<sub>3</sub> might cause effects in the brain. As it does not reach the brain, in vitro studies of the impact of O<sub>3</sub> on brain cells are less informative.

While experimental laboratory studies can provide useful information, they have a number of recognised limitations. For example, it is challenging to extrapolate from the results of in vitro

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<sup>20</sup> One EU is equivalent to approximately 0.1 to 0.2 ng endotoxin ([Cell culture FAQs: bacterial endotoxin contamination](#))

studies back to the biology of the intact organism. In addition, the exposure levels used in in vivo experimental laboratory studies are usually much higher than the concentrations that occur in ambient air and, in most, exposures are relatively short. However, some authors (such as Mumaw et al, 2016; Erikson et al, 2017) have noted that, compared with humans, rodents are relatively insensitive to O<sub>3</sub> toxicity. This is because of their complex nasal turbinates, differences in lung morphology and high concentrations of urate and ascorbate (antioxidants) in the airway surfactant. Mumaw et al (2016) suggest that a factor of 3 is accepted in practice for extrapolating concentrations from rodents to primates. They suggest that O<sub>3</sub> concentrations of 0.2 to 0.3 ppm occur frequently in areas of high pollution, and that 1ppm would be considered the equivalent in rodent experiments.

There is interest in the literature in possible links between air pollutants and the development of a range of neurodegenerative diseases, including Parkinson's disease. The text below mainly focuses on studies most relevant to regions of the brain and neuronal systems affected in cognitive decline and dementia.

Most of the available experimental studies on the commonly studied air pollutants have been undertaken using diesel engine exhaust (a complex mixture of pollutants), particles or ozone. Some of this literature is summarised below. A number of pollutants are of interest with respect to neurotoxicity. There is interest in the potential neurotoxicity of polycyclic aromatic hydrocarbons (PAHs) although the USEPA (2017) recently concluded that the available evidence was too limited to allow a conclusion to be drawn regarding the potential neurotoxicity of benzo[a]pyrene following adult exposure.

#### 4.6.3.4 Experimental studies: particles and diesel exhaust

Studies on particles and diesel engine exhaust are discussed together in this section, as diesel exhaust particles (particularly ultrafine particles) are a potential causal agent in diesel exhaust. Nonetheless, diesel engine exhaust includes a range of other potentially active pollutants including volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs) and nitrogen dioxide (NO<sub>2</sub>) which might also play causal roles.

#### **Effects on neurodegenerative disease processes**

Studies have shown increases in levels of proteins involved in the development of Alzheimer's disease (phosphorylated tau and A $\beta$ ), and neurodegenerative effects, following exposure of laboratory animals to air pollutants.

For example, Levesque et al (2011) reported increased phosphorylated tau in the frontal and temporal lobes of male Fischer 344 rats exposed to high levels of diesel engine exhaust (992 $\mu$ g PM/m<sup>3</sup>) for long periods of time (6 hours a day, 7 days per week for 6 months) compared with those exposed to filtered air. Increased phosphorylated tau was also found in the temporal lobe in those exposed to 311 $\mu$ g PM/m<sup>3</sup>, but not in those exposed to 100 or 35 $\mu$ g PM/m<sup>3</sup>.

Cacciottolo et al (2017) used wild-type (C57BL/6) and transgenic (EFAD – carrying human *APOE* alleles and familial Alzheimer's disease genes) female mice to investigate the effects of exposure (5 hours per day, 3 days per week for 10 to 15 weeks) to the nano-scale fraction of urban PM<sub>2.5</sub> (dose not reported). Exposure of both wild-type and transgenic mice to nanoparticles caused selective atrophy of hippocampal CA1 neurites (hippocampal CA1 neurons are involved in memory) and decreased the GluR1 subunit of the glutamate receptor. In the transgenic mice, nanoparticle exposure also increased cerebral fibrillary A $\beta$  and A $\beta$  deposits, exacerbated by *APOE*  $\epsilon$ 4. A $\beta$  oligomers were also increased. In vitro addition of the nanoparticles to neuroblastoma cells increased pro-amyloidogenic processing of the amyloid precursor protein.

Cheng et al (2016) observed degeneration of olfactory neurons in the olfactory epithelium of adult C57BL/6J mice after 20 to 45 hours of cumulative exposure to 343 $\mu$ g/m<sup>3</sup> 'nano-sized' (>0.2 $\mu$ m diameter) particulate matter collected downwind of a freeway in central Los Angeles, but not after 5 hours' exposure. No degeneration was found in the olfactory bulbs.

### **Oxidative stress**

Heusinkveld et al (2016) reviewed the evidence related to small inhaled particles, concluding that evidence from experimental studies has shown that inhalation of PM and nanoparticles is linked to an increase in markers of oxidative stress in the brain.

In an example of a study illustrating this, Guerra et al (2013) exposed male Sprague-Dawley rats to filtered air or coarse (32 $\mu$ g/m<sup>3</sup>), fine (178 $\mu$ g/m<sup>3</sup>) or ultrafine (107 $\mu$ g/m<sup>3</sup>) concentrated ambient particulate matter (CAPs) in Mexico City 5 hours per day, 4 days per week for 8 weeks. Following exposure, the olfactory bulb, frontal cortex, striatum and hippocampus were harvested and markers of oxidative stress, inflammation, apoptosis and unfolded protein response measured. The transcription level of hemoxygenase-1 (HO-1), an indicator of cellular adaptation to oxidative stress, was significantly increased in the olfactory bulb and striatum following exposure to each PM size fraction, compared with exposure to filtered air. The fine and ultrafine fractions also caused increased HO-1 transcription in the frontal cortex and hippocampus. Transcript levels of mitochondrial superoxide dismutase (SOD-2, an antioxidant enzyme involved in the defence system against ROS) and nuclear factor (erythroid-derived 2)-like 2 (Nrf-2, a regulator of antioxidant responses) were also investigated. Exposure to ultrafine PM resulted in activation of Nrf-2 and SOD-2 in striatum and hippocampus, compared with the control group. Significant increases in SOD-2 transcription were also seen in the striatum following exposure to coarse or fine PM. This infers an adaptive response to an oxidative insult.

Cheng et al (2016) reported rapid increases in markers of oxidative stress (4-hydroxy-2-nonenal and 3-nitrotyrosine protein adducts) in the olfactory epithelium and olfactory bulbs of adult C57BL/6J mice exposed to 343 $\mu$ g/m<sup>3</sup> of 'nano-sized' (<0.2 $\mu$ m diameter) particulate matter collected downwind of a freeway in central Los Angeles, but not in the cerebral cortex or cerebellum.



Effects of acute exposure of adult C57BL/6 mice to diesel engine exhaust (PM<sub>2.5</sub> concentration 250 to 300µg/m<sup>3</sup>) or filtered air for 6 hours were investigated by Cole et al (2016). Exposure caused significant increases in both lipid peroxidation and pro-inflammatory cytokines in various brain regions, particularly the olfactory bulb and hippocampus. In some cases, the effects were greater in males than females, which the authors propose may be due to males having lower levels of expression of paraoxonase 2 (PON2), which protects against oxidative stress and inflammation. Exposure to diesel engine exhaust also caused microglia activation. Mice with genetically induced reduced abilities to synthesise glutathione appeared more susceptible than wild-type mice. The authors interpreted their findings as indicating that acute exposure to diesel engine exhaust causes neuroinflammation and oxidative stress in the brain, and suggested that sex and genetic background may modulate susceptibility.

It is possible that nanoparticles, or substances derived from particles, reaching the brain exert a direct oxidative stress on neurons. Another possibility is that nano-particles reach neurons and locate in mitochondria, disrupting mitochondrial function and resulting in intra-cellular oxidative stress. In an early study, of intranasal administration of colloidal gold particles (size 500 Å, 50nm) to squirrel monkeys (de Lorenzo, 1970), particles that had been taken up into olfactory receptor neurons were able to cross the synapse into mitral cells, where they became preferentially located in mitochondria. The reports by Gonzalez-Maciel et al (2017) of combustion-related nanoparticles in mitochondria, and that these mitochondria were abnormal, are relevant to this possibility, although it seems possible that these observations may reflect artefacts arising from the methods used (see discussion above).

### **Neuroinflammation**

Studies have also found that exposure to air pollutants causes neuroinflammation: activation of and response from the brain's immune cells (such as microglia). In their review of the literature linking small inhaled particles with neurodegenerative effects, Heusinkveld et al (2016) noted that a number of studies in rodents have demonstrated neuroinflammatory responses to exposure to concentrated ambient particles, diesel engine exhaust or engineered nanoparticles.

Campbell et al (2005) exposed ovalbumin-sensitised BALB/c mice to CAPs (concentrated x20) or filtered air, 150 metres downwind of heavily trafficked highways in Los Angeles 4 hours per day, 5 days per week for 2 weeks. One and 2 weeks after exposure, mice were challenged with aerosolised ovalbumin. They were sacrificed a day after the second challenge, and brain samples analysed for inflammatory markers. Mice exposed to either the ultrafine (median aerodynamic diameter <0.18µm, mean exposure concentration 282.5µg/m<sup>3</sup>) or PM<sub>2.5</sub> (mean exposure concentration 441.7µg/m<sup>3</sup>) fractions demonstrated significantly increased levels of activated NF-κB (associated with inflammation processes) in the brain nuclear fraction. Inflammatory markers, interleukin-1 alpha (IL-1α) and tumour necrosis factor-alpha (TNF-α) were also measured using real-time polymerase chain reaction (PCR). IL-1α in the brain cytoplasmic fraction increased following exposure to PM<sub>2.5</sub> or ultrafine CAPs, and cytoplasmic TNF-α was increased after exposure to PM<sub>2.5</sub>.

Levesque et al (2011) reported dose-dependent neuroinflammation in male Fischer 344 rats exposed to filtered air or diesel engine exhaust (992, 311, 100, 35 and 0 $\mu\text{g PM}/\text{m}^3$ ) 6 hours per day, 7 days a week for 6 months. Levels of the pro-inflammatory cytokine TNF $\alpha$  in brain homogenate protein from 5 brain regions (olfactory bulb, frontal lobe, temporal lobe, midbrain and cerebellum) were assessed. All regions, with the exception of the cerebellum, expressed elevated TNF $\alpha$  protein following exposure to the highest concentration of exhaust. The midbrain was most sensitive, with elevated levels also occurring following exposures to concentrations of 311 and 100 $\mu\text{g}/\text{m}^3$ .

Guerra et al (2013) exposed male Sprague-Dawley rats to filtered air or coarse (32 $\mu\text{g}/\text{m}^3$ ), fine (178 $\mu\text{g}/\text{m}^3$ ) or ultrafine (107 $\mu\text{g}/\text{m}^3$ ) concentrated ambient PM in Mexico City 5 hours per day, 4 days per week for 8 weeks. Following exposure, olfactory bulb, frontal cortex, striatum and hippocampus were harvested and markers of oxidative stress, inflammation, apoptosis and unfolded protein response measured. Exposure to ultrafine PM caused increased NF- $\kappa$ B activation and transcription of inflammatory cytokines (IL-1 $\beta$  and TNF $\alpha$ ) in the striatum, compared with exposure to filtered air. Antioxidant responses and inflammatory processes are often associated with the presence of misfolded protein aggregation, so 2 markers for an unfolded protein response were also investigated. Increases in both were seen in the striatum following exposure to coarse PM. One of the markers was increased in the hippocampus in the group exposed to ultrafine PM.

Bos et al (2012) exposed C57BL6 mice to traffic-related air pollution (mean PM<sub>2.5</sub> 55.1 $\mu\text{g}/\text{m}^3$ , mean elemental carbon (EC) 13.9 $\mu\text{g}/\text{m}^3$ ) in cages in a busy road tunnel for 5 days. Carbon particles were seen in the macrophages obtained by bronchoalveolar lavage (BAL) from exposed animals, but there were no significant differences in BAL leukocyte counts between animals in the test and control groups. Examination of the lungs, and lung sections, did not indicate any abnormalities or inflammation. Blood leukocyte counts were also not increased. Nonetheless, expression of some genes related to oxidative stress and inflammation (COX2, NOS2 and NOS3) was increased in the hippocampus of exposed animals. Expression of Nrf-2 was also increased compared with one control group. However, in the olfactory bulb, exposure was associated with a downregulation of 2 inflammatory markers (IL-1 $\alpha$  and COX2).

Expression of Nrf-2 and brain-derived neurotrophic factor (BDNF) was also reduced here. The authors concluded that, although this short-term exposure did not induce pulmonary or systemic inflammation, the expression of inflammatory genes was affected in different brain areas. The decreased BDNF expression in the olfactory bulb as a result of exposure to traffic-related air pollution suggests reduced support for survival of the existing neurons. The authors note that they had previously found lower BDNF concentrations in blood in humans exercising near traffic sources (Bos et al, 2011).

Cheng et al (2016) investigated the effects of 'nano-sized' (<0.2 $\mu\text{m}$  diameter) particulate matter collected downwind of a freeway in central Los Angeles in ex vivo and in vitro models as well as

in adult C57BL/6J mice. Increased levels of TNF- $\alpha$  protein were found in the olfactory epithelium, olfactory bulb, cerebral cortex and cerebellum of mice exposed to 343 $\mu\text{g}/\text{m}^3$  for 45 cumulative hours, with induction of TNF- $\alpha$  mRNA occurring earlier in the olfactory epithelium and olfactory bulb. Consistent with this, rapid increases in inducible nitric oxide synthase occurred following in vitro exposure of olfactory epithelium and mixed glial cultures (astrocytes and microglia).

When Cliff et al (2016) exposed healthy human volunteers to diesel engine exhaust (300 $\mu\text{g PM}_{2.5}/\text{m}^3$ ) for 2 hours they found no increase in serum or plasma cytokines, nor in markers of CNS damage or compromised BBB function (the astrocytic protein S100 $\beta$ , the neuronal cytoplasmic enzyme neuron-specific endolase (NSE) and brain-derived neurotrophic factor (BDNF)), either during exposure or in the period up to 24 hours post-exposure.

### **Role of microglia**

It is possible that the neuroinflammation observed following exposure to air pollution occurs in response to cell damage caused by oxidative stress. However, the brain's immune cells produce ROS as part of their armoury, so it is possible that the oxidative stress might be secondary to neuroinflammation, rather than caused directly by the pollutants themselves. A number of studies have been designed to investigate the importance of microglial cells (macrophage-like immune cells within the brain) in eliciting the observed effects.

Block et al (2004) undertook in vitro studies to investigate the role of microglia in the neurotoxicity of diesel exhaust particles. The studies were undertaken in cultures of cells taken from the mid-brain (mesencephalic) of rats. Although they were aimed at understanding effects on dopaminergic cells and possible involvement in Parkinson's disease, the findings are also relevant to consideration of a role of microglia in other neurodegenerative diseases such as dementia. Treatment of neuron-glia cell cultures with diesel exhaust particles (DEP, 5 to 50 $\mu\text{g}/\text{ml}$ ) produced a dose-dependent reduction in dopaminergic neurons and a reduction in uptake of radioactively labelled dopamine. The effect seemed to be dopamine-neuron selective, as uptake of GABA (gamma-aminobutyric acid) was not affected<sup>21</sup>. Cultures containing only neurons were not affected by DEP, but the addition of 10 or 20% microglia reinstated the responsiveness to DEP toxicity, supporting the suggestion that microglia play an important role in the neurotoxicity. The authors also observed that when DEP was added to neuron-glia cultures, glial morphology changed, indicating activation. When DEP was added to cultures enriched with microglia, intracellular ROS and extracellular superoxide increased, suggesting a respiratory burst following phagocytosis of DEP by microglia. Complementary studies using mouse mesencephalic neuron-glia cultures (Block et al, 2004), also found that DEP's toxicity to dopaminergic neurons depended upon microglial activity. The authors suggested that the selective toxicity to dopaminergic neurons was due to a reduced antioxidant capacity compared

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<sup>21</sup> The authors were investigating a suggestion that microglial-derived oxidative stress caused selective damage to dopaminergic neurons, which had been implicated in the pathogenesis of Parkinson's disease. Loss of cholinergic neurons is implicated in dementia, along with imbalances in other neurotransmitters including both dopamine and GABA.

with GABA neurons, due to low intracellular concentrations of glutathione. They postulated that DEP exposure could result in an ongoing and cyclic oxidative insult.

Roque et al (2016) found that diesel exhaust particles (DEP; 0, 25, 50, 100 $\mu\text{g}/2\text{ cm}^2$ ) had no effect on the viability of mouse primary cerebellar granular neurons after 24 hours of treatment *in vitro*. However, when primary cortical microglia were also present, cell death increased 2 to 3-fold after treatment with DEP. DEP (50 $\mu\text{g}/2\text{ cm}^2$ ) treatment of primary microglia for 24 hours induced morphological changes indicating microglia activation, and the medium was toxic to cerebellar granular neurons. DEPs caused a significant increase in ROS in microglia, but antioxidants did not prevent toxicity to neurons. Microglia and neurons from male mice appeared to be somewhat more susceptible than those from female mice.

Campbell (2014) used cultures of normal human brain cells (microglia, neurons and astrocytes) in a pilot study to assess cell-type responses after exposure to ambient ultrafine particles (collected in downtown Los Angeles) *in vitro*. After exposure to  $\mu\text{g}/\text{ml}$ , human neurons exhibited a decrease in formation of ROS and an increase in the proinflammatory cytokine TNF- $\alpha$ . The observed decrease in ROS persisted in the presence of glial cells. The authors note that this contrasted with results from previous studies in rodent cells, which had reported that microglial activation modulated neuronal responses, and suggested that human CNS cells may respond differently to rodent cells.

Woodward et al (2017a) used mixed cell cultures (astrocytes and microglia) to investigate the role of Toll-like receptor 4 (TLR4) activation in the inflammatory response of glial cells to PM *in vitro*. TLR4 is a pattern recognition receptor (PRR) which is important in pathogen recognition and activation of innate immunity. Cells were exposed to 'nanoscale' PM (diameter  $<0.2\mu\text{m}$ ) sub-fraction of traffic related air pollution collected from a freeway, or to the endotoxin lipopolysaccharide. TLR4 and NF- $\kappa\text{B}$  were activated following both exposures. TLR4 siRNA attenuated TNF $\alpha$  and other inflammatory responses following nanoparticle exposure.

Coburn et al (2018) investigated the role of microglia in inhibiting neurogenesis in adult mice in response to acute exposures (6 hours) to diesel exhaust (250 to 300 $\mu\text{g}/\text{m}^3$ ). In male mice, exposure impaired cellular proliferation and reduced the number of new neurons in the hippocampal subgranular zone and the subventricular zone, and in the olfactory bulb. In females, adult neurogenesis was reduced only in the olfactory bulb. When male mice were pre-treated with pioglitazone (which blocks microglial activation) effects of diesel exhaust on microglia, neuroinflammation and oxidative stress were decreased, as was the suppression of neurogenesis in the subgranular zone. The authors interpreted their findings as suggesting that diesel exhaust exposure impairs adult neurogenesis in a sex-dependent manner, by a mechanism likely to involve microglia activation and neuroinflammation.

### **Possible indirect signalling**

In their review, Heusinkveld et al (2016) noted that whether the effects result from the direct action of particles entering the brain, or are secondary to systemic inflammation, remains

unclear. They proposed that peripheral inflammation is likely to be an important connection between inhalable PM and neurodegeneration.

Mohan Kumar et al (2008) examined the effect of CAPs, 500 $\mu\text{g}/\text{m}^3$ , 2.5 $\mu\text{m}$  aerodynamic diameter, 8 hours per day for one or 3 days) on brain neurotransmitters and the activation of the hypothalamus-pituitary-adrenal (HPA) 'stress axis' in normal adult male Brown Norway rats and in animals with pre-existing allergic airway disease (induced by intranasal administration of ovalbumin). Concentrations of noradrenaline in the paraventricular nucleus (PVN) of the hypothalamus were similar in the group exposed to CAPs or ovalbumin, but much higher in the PVN of ovalbumin pre-treated animals exposed to CAPs. Serum corticosterone levels were also highest in this group. The authors interpreted their findings as indicating that allergic airway disease stimulates the stress axis, and that exposure to CAPs aggravates this, suggesting that pre-existing airway disease increases sensitivity to the effects of CAPs. The effects were noted as being specific to the PVN, and not other areas of the hypothalamus, and were time-dependent.

#### **Non-diesel exhaust particles/ PM components**

Few studies have been undertaken on ambient particles from sources other than traffic. Cheng et al (2017) investigated the effects of inhalation (2 hours per day, 7 days a week for 28 days) of ammonium sulphate PM<sub>2.5</sub> (595 $\mu\text{g}/\text{m}^3$ ) on adult neurogenesis in aged (approximately 10 months) male Sprague-Dawley rats. In exposed animals, there was a significant reduction in the maturation of immature neurons in the subgranular zone of the hippocampus, and in their dendritic complexity.

#### **4.6.3.5 Experimental studies: ozone**

At the time of the early work by Calderón-Garcidueñas and colleagues on the olfactory and neurological effects of air pollutants in Mexico City, much of the interest was in a possible role of O<sub>3</sub>. Calderón-Garcidueñas et al (2002) noted that concentrations as high as 0.48 ppm had been reported in Southwest Metropolitan Mexico City during severe pollution episodes, that average maximal daily concentrations were 0.25ppm and that concentrations exceeded 0.08ppm for an average of 4  $\pm$  1 hour per day. (For context, the UK average daily maximum 8 hour mean concentrations at background sites in 2018 were 62.8 $\mu\text{g}/\text{m}^3$  (approximately 0.03ppm) in urban areas and 73.2 $\mu\text{g}/\text{m}^3$  (approximately 0.04ppm) in rural areas, Defra, 2019). Experimental studies on laboratory animals exposed to ozone have been undertaken and suggest neurological effects.

O<sub>3</sub> is a reactive gas with a short half-life, reacting with antioxidants and lipids in airway surfactant (Pryor, 1992, cited in Erickson et al, 2017). The free radicals produced by O<sub>3</sub>'s reactions in the lung are, similarly, reactive. Therefore, neither O<sub>3</sub> nor these radicals are likely to reach the brain themselves. This means that there has been interest in the pathway by which inhaled O<sub>3</sub> could result in effects in the brain. Oxidative by-products (for example, ozonated lipids and proteins), activated monocytes or cytokines from systemic inflammation have been

suggested as possible signals mediating the neuropathological response to O<sub>3</sub> (Block and Calderón-Garcidueñas, 2009).

Croze and Zimmer (2018) reviewed the evidence linking O<sub>3</sub> exposure with a potential role in Alzheimer's disease. Some of the studies are summarised and discussed below.

### **Effects on neurodegenerative disease processes**

Rivas-Arancibia et al (1998) reported that male Wistar rats exposed to ozone (0.2, 0.5 or 1ppm) for 4 hours showed long-term memory deterioration (in a passive avoidance test) and decreased motor activity, which had resolved 24 hours later. These effects were not seen in animals exposed to 0.1ppm ozone. Brain and pulmonary Cu/Zn SOD levels were increased in animals exposed to 0.1, 0.2, 0.5ppm O<sub>3</sub> but decreased after exposure to 1 ppm.

Guerrero et al (1999) reported that acute exposure (4 h) of rats to 0.7ppm ozone reduced long- and short-term memory (evaluated in a passive avoidance test) and increased lipid peroxidation levels in the striatum, hippocampus and frontal cortex. These effects were prevented by administration of the antioxidant vitamin E (50 mg/kg) either before or after exposure to O<sub>3</sub>.

Dorado-Martinez et al (2001) exposed male Wistar rats to ozone (0, 0.1, 0.4, 0.7, 1.1 and 1.5ppm) for 4 hours. O<sub>3</sub> caused memory impairment (evaluated in a passive avoidance test) at doses from 0.7ppm and decreased motor activity at doses from 1.1ppm. Lipid peroxidation was measured in frontal cortex, hippocampus, striatum and cerebellum, and increased at doses from 0.4ppm, increasing with dose. The biggest increases were seen in the hippocampus.

Hernandez-Zimbon and Rivas-Arancibia (2015) exposed male Wistar rats to ozone (0.25ppm, 4 hours per day) for 7, 15, 30, 60 and 90 days and found Aβ<sub>42</sub> accumulation in the mitochondria of hippocampal neurons after exposure for 60 and 90 days.

Akhter et al (2015) investigated the effects of O<sub>3</sub> exposure in an animal model of Alzheimer's disease: double-transgenic mice which over-express Aβ precursor protein (APP) and presenilin (PS-1). Transgenic and non-transgenic mice were exposed to 0.8ppm O<sub>3</sub> 7 hours per day for 5 days, followed by 9 days of filtered air recovery, for 8 cycles. Exposure accelerated learning/memory function loss in male transgenic mice, but not in female or non-transgenic mice. O<sub>3</sub> exposure did not have a significant effect on brain Aβ peptide load in either sex. Male transgenic mice had lower levels of antioxidants than female mice, and experienced more NADPH oxide induction, lipid peroxidation and neuronal apoptosis than females after O<sub>3</sub> exposure. These were not affected in non-transgenic mice. Based on their results, the authors suggest that O<sub>3</sub> may interact with genetic risk factors to accelerate the progression of Alzheimer's disease in genetically predisposed populations.

Pinto-Almazán et al (2018) reported that adult male Wistar rats exposed to ozone (0.25ppm, 4 hours per day) for more than 30 days had an elevated ratio of hyper-phosphorylated to total tau in the hippocampus. This increase was not seen in animals which were also treated with

tibolone, a synthetic hormone used for the treatment of menopausal symptoms, which has antioxidant effects.

### **Oxidative stress**

Martinez-Canabal et al (2008) exposed male Wistar rats to O<sub>3</sub> (0.25 ppm, 4 hours per day) for 7, 15 or 30 days. Lipoperoxidation levels and COX-2 positive cells in the hippocampus were increased in all exposed groups. Fewer COX-2 reactive cells were seen in animals exposed for 15 days that were also treated with growth hormone. The authors suggested that growth hormone might modulate inflammation or the expression of antioxidant systems in the hippocampus. The reduced responses of animals treated with growth hormone and exposed to ozone for 7 or 30 days were not statistically significant.

Rivas-Arancibia et al (2010) reported CNS effects in male Wistar rats exposed to O<sub>3</sub> (0.25 ppm, 4 hours per day for up to 60 days), including lipid peroxidation, changes to neurons, activation of microglia and decreased survival of new neurons.

Rodriguez-Martinez et al (2013) exposed Wistar rats to 0.25ppm O<sub>3</sub> for 7, 15, 30 or 60 days before removing and analysing the hippocampus. Amongst other findings, increased levels of protein carbonyls and Mn-SOD activity (Mn-SOD is located in mitochondria) were seen after 30 days of exposure, along with decreased glutathione peroxidase activity. Succinate dehydrogenase (complex II of the mitochondrial respiratory chain) decreased progressively from day 7 through to 60 days of exposure. After 60 days of exposure, cytochrome c was increased and cellular damage and mitochondrial swelling with a loss of mitochondrial cristae was observed. The authors proposed that chronic exposure to O<sub>3</sub> caused an increase in oxidised proteins, an inhibition of antioxidant systems and subsequent mitochondrial abnormalities that may lead to cell damage.

Farfan-Garcia et al (2014) exposed male Wistar rats to 0.25ppm O<sub>3</sub> 4 hours per day for 7, 15, 30 or 60 days. O<sub>3</sub> exposure increased oxidative stress markers and affected cholinergic neurotransmitters in the hippocampus. Performance in a passive avoidance test for memory was adversely affected. These effects were prevented in animals also treated with tibolone, suggesting tibolone protected against oxidative stress.

Gómez-Crisóstomo et al (2014) assessed activation of forkhead box (Fox) transcription factors (involved in regulating a range of cellular activities), as well as Mn-SOD protein expression, cyclin D2 (involved in cell cycle regulation) and caspase 3 (involved in apoptosis) in the hippocampus of rats exposed to O<sub>3</sub> (0.25ppm 4 hours per day) for 0, 7, 15, 30, 60 or 90 days. The authors suggest that their results indicate that O<sub>3</sub> alters regulatory pathways related to both antioxidant system and the cell cycle, inducing apoptotic death.

### **Neuroinflammation**

Gonzalez-Guevara et al (2014) investigated inflammation in the lungs and cerebral cortex of male Wistar rats exposed to 1ppm O<sub>3</sub> for 1, 3 or 6 hours, or daily for one or 3 hours for 5 days.

Markers of inflammation were elevated in both the lung (increased levels of TNF- $\alpha$  and IL-6) and cerebral cortex (increased levels of TNF- $\alpha$ , IL-6, NF- $\kappa$ B and glial fibrillary acidic protein).

### **Possible indirect signalling**

Gackiere et al (2011) investigated the possible involvement of a neural pathway linking O<sub>3</sub>-induced respiratory tract inflammation to effects on the CNS, by using immunoreactive staining to identify activated neurons. Adult (5 to 6 week old) male Wistar rats were exposed to 0.5 or 2 ppm ozone for 1.5 to 120 hours. Exposure to O<sub>3</sub> caused persistent dose- and time-dependent lung inflammation. The neuronal activation observed indicated the involvement of stress-response regions of the CNS via vagal primary afferents, and that thoracic spinal neurons were not involved.

Drawing on this, and other, research Kodavanti (2016) proposed that a neurohormonal stress response, produced by the sympathetic nervous system and hypothalamus-pituitary-adrenal axis, is involved in mediating the adverse effects of O<sub>3</sub> and, perhaps, other air pollutants. As well as being involved in the CNS effects of air pollutants, Kodavanti suggests that this neurohormonal stress response may mediate other extra-pulmonary effects of air pollutants and, perhaps, the pulmonary effects themselves.

Mumaw et al (2016) found that exposure of Sprague Dawley rats (young adult, 8 week old) to O<sub>3</sub> (1ppm) for 4 hours elicited microglia activation which persisted 24 hours after exposure and which the authors interpreted as suggesting a persistent signal from lung to brain. In order to investigate whether an inflammatory signal was present in the blood after O<sub>3</sub> inhalation, serum collected from the rats 24 hours after exposure was applied ex vivo to rat microglial cultures (of both primary cells and an immortalised cell line). Diluted serum from O<sub>3</sub>-treated rats did not initiate TNF $\alpha$  production and produced only a low-level ROS response.

However, in cells pre-treated with lipopolysaccharide, serum from O<sub>3</sub>-treated animals enhanced TNF $\alpha$  production compared with serum from controls. It also augmented H<sub>2</sub>O<sub>2</sub> production in primary microglia cultures and neurotoxicity in mixed cortical neuron-glia cultures. Analysis of serum for traditional circulating cytokines (CCL2, CCL11, TNF $\alpha$ , IL-6 and IL -1 $\beta$ ) found that these were not modified by O<sub>3</sub> exposure. Further ex vivo assays indicated that the macrophage-1 antigen (MAC1) receptor was important in the microglial response. Taken together, these findings suggest a pro-inflammatory response in the brain and  $\beta$ -amyloid neurotoxicity in response to O<sub>3</sub> exposure, mediated by a blood-borne signal, in the absence of traditional circulating cytokines. It is interesting to note that earlier studies by the same research group also demonstrated that effects of O<sub>3</sub> on the vasculature were mediated by blood-borne factors (Robertson et al, 2013; Paffett et al, 2015).

Erickson et al (2017) undertook experiments in mice to investigate which cytokines, chemokines and acute-phase proteins are up-regulated in the blood after O<sub>3</sub> exposure, to determine whether inflammatory mediators in the blood are associated with pulmonary inflammation, and to determine whether the proinflammatory mediators could reach the CNS by crossing the blood-



brain barrier. Female BALB/c mice (age 12 to 13 weeks) were exposed to air or 3ppm O<sub>3</sub> for 2 hours<sup>22</sup> and responses studied after 6 or 24 h. Of 23 cytokines and chemokines investigated, only one (KC/CXCL1, a neutrophil chemokine) was elevated 6 hours after exposure.

The acute phase protein serum amyloid-A (A-SAA) was significantly increased 24 hours after exposure. As both A-SAA mRNA and protein increased in the liver, this was likely the source of the serum A-SAA.<sup>23</sup> Levels of serum A-SAA 24 hours after exposure correlated with total cells, macrophages and neutrophils in bronchoalveolar lavage fluid. Levels of A-SAA protein in the cortex were elevated in O<sub>3</sub>-treated mice but A-SAA mRNA was not, suggesting that A-SAA enters the brain from the blood after ozone exposure. However, no microgliosis or elevations in proinflammatory cytokines in the cerebral cortex were found, indicating that the expected neuroinflammatory response was not seen. In a follow-up investigation, radiolabelled A-SAA was administered to 8 week old male CD-1 mice by intravenous injection. This was found to enter the brain, in the absence of disruption of the BBB. SAA has also been implicated as a possible mediator of the cardiovascular effects of inhaled particles (Saber et al, 2013).

#### 4.6.3.6 Experimental studies: nitrogen dioxide

Li and Xin (2013) investigated nitrogen dioxide (NO<sub>2</sub>) as a possible risk factor for vascular dementia. Effects of exposure to high concentrations (5 to 20mg/m<sup>3</sup>) 6 hours per day for 7 days were investigated in healthy male Wistar rats and in a rat model of stroke (middle cerebral artery occlusion, MCAO). Results in healthy rats were interpreted as suggesting an excitotoxic response to NO<sub>2</sub> exposure, while a decrease in synaptic plasticity was indicated in the stroke model. The authors suggest that NO<sub>2</sub> exposure could increase the risk of vascular dementia through both of the mechanisms.

#### 4.6.3.7 Experimental studies: effect modification by age

Some studies have indicated that neurological effects of air pollutants may differ depending on the age of the animals exposed.

Rivas-Arancibia et al (2000) investigated the effects of 4 hours of O<sub>3</sub> exposure (0.7 to 0.8ppm) on memory (using a passive avoidance test) in young (47 days), mature (540 days) and old (900 days) male Wistar rats. The potential antioxidant effects of taurine, administered alone or before or after ozone exposure, were also investigated. O<sub>3</sub> exposure reduced both short- and long-term memory in young and old rats, while the effect in mature rats was not significant. Taurine administration, alone, improved performance of old rats only, compared with controls. Whether taurine administration attenuated or enhanced the adverse effects of O<sub>3</sub> exposure on memory depended upon the timing of administration and the age of the rats. The effect of O<sub>3</sub> exposure (4 hours, 1ppm) on lipid peroxidation in the frontal cortex, hippocampus, striatum and cerebellum of young and old rats was also investigated. Peroxidation was found in all brain regions of unexposed (control) old, but not young, rats. The effect of O<sub>3</sub> and taurine exposure or

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<sup>22</sup> This exposure was chosen as being optimal to achieve significant inflammatory and airway obstructive response without respiratory distress.

<sup>23</sup> Erickson and others (2017) explain that A-SAA is an acute phase protein in mice and humans, but not in rats.

co-exposure on lipid peroxidation varied between brain region and age. Nonetheless, ozone exposure (alone) increased lipid peroxidation in the hippocampus and striatum of both age groups.

Woodward et al (2017b) investigated age differences in the effects of exposure (5 hours per day, 3 days per week for 10 weeks) to traffic-derived 'nano-sized' particles (nPM,  $<0.2\mu\text{m}$  diameter,  $342 \pm 49\mu\text{g}/\text{m}^3$ ;  $1.4 \times 10^5 \pm 9.7 \times 10^3$  particles/ $\text{cm}^3$ ) collected 150 metres downwind of a busy freeway on the brains of young (3 months) or middle aged (18 months) female C57BL/6J mice. nPM exposure in young mice caused reductions in neurites and myelin and increased microglial activation in the CA1 region of the hippocampus, with the dentate gyrus relatively unaffected. Older controls had similar changes when compared with young controls, but these effects were not changed by exposure to nPM. These results were interpreted as suggesting an age-ceiling effect.

In contrast, other studies have suggested that the aged brain may be more sensitive than younger brains to adverse CNS effects of exposures to pollutants. Mumaw et al (2016) exposed C57BL/6 mice (6 hours per day for 50 days) to mixed vehicle exhaust ( $300\mu\text{g PM}/\text{m}^3$ , a combination of approx.  $50\mu\text{g PM}/\text{m}^3$  gasoline engine exhaust emissions mixed with  $250\mu\text{g PM}/\text{m}^3$  diesel engine emissions) or filtered air. In order to investigate how ageing might influence effects of exposure, both aged (18 month old) and younger (2 month old) mice were used. Neutrophil counts in BAL fluid and imaging using a radioligand confirmed that young animals exhibited an inflammatory pulmonary response that was absent in aged animals. In contrast, cortical tissue from aged ozone-exposed animals exhibited higher TNF- $\alpha$  mRNA and changed microglia morphology (activation) than in younger mice. Ex-vivo application of serum from O<sub>3</sub>-treated young adult rats to LPS –primed mixed hippocampal glia cultures from young (8 week) or ageing (10 month) mice elicited a much greater increase in TNF- $\alpha$  production in the cell culture from ageing mice than in tissue from young adult mice. This might suggest that microglia cells in ageing animals are more sensitive to the proinflammatory priming effects of ozone than those of younger animals.

Mumaw et al (2016) also suggested that the impaired pulmonary immune response of aged animals following O<sub>3</sub> exposure may contribute to their enhanced neuroinflammatory response. To test this, they compared effects of O<sub>3</sub> (1ppm, 4 hours) in CD36<sup>-/-</sup> mice, which have a minimal pulmonary cellular immune response to O<sub>3</sub>, and wild-type mice. 24 hours after O<sub>3</sub> exposure, TNF- $\alpha$  and IL-1 $\beta$  were increased in the frontal lobes of CD36<sup>-/-</sup> mice and morphological changes reported in cortical microglial morphology. No neural effects were seen in wild-type CD36<sup>+/+</sup> mice. The authors suggested that this supports the suggestion that an impaired pulmonary immune response to airborne pollutants may be linked to augmented neuroinflammation.

Tyler et al (2018) investigated neurological responses of male C57BL/6 mice to an acute O<sub>3</sub> exposure (1.0 ppm for 4 hours). Aged (12 to 18 months) animals demonstrated higher baseline microglial activation than younger ones (8 to 10 weeks). Aged brains also had a greater

response to ozone exposure: microgliosis and  $\beta$ -amyloid protein expression in cortical and limbic regions, and increases in immune cells in the aged cerebellum. This age-related sensitivity appeared to be due to age-related differences in the permeability of the BBB and age-related priming of microglial cells.

#### 4.6.3.8 Experimental studies: summary

In summary: Experimental studies of exposure to particles, engine exhaust or ozone in rodents and cell cultures have reported findings consistent with neurotoxic and neurodegenerative effects. There are some inconsistencies, including negative findings in the few experimental human studies. However, overall, the evidence is supportive of an effect mediated by oxidative stress and neuroinflammation. It is possible that translocated ultrafine PM, or compounds desorbed from particles, may induce direct effects in the brain – either exerting oxidative stress themselves or by disrupting mitochondrial function. However, although it is not entirely clear whether oxidative stress induces a neuroinflammatory response or is a consequence of it, a number of studies appear to suggest that activation of microglial cells is a key step in air pollution eliciting neurological effects. The observation that inhaled ozone (which, because of its high reactivity, will not reach the brain) appears to be neurotoxic raises questions about the mechanism by which this could occur. Suggestions include activation of the hypothalamus-pituitary-adrenal (HPA) ‘stress axis’ or a lung-to-brain signal via a blood-borne messenger. Evidence has been presented in support of both of these possibilities.

Most of the available animal studies have used doses of particles or O<sub>3</sub> which are higher than concentrations experienced in the UK. The results of the few studies which included more UK-relevant exposures are mixed. Levesque et al (2011) and Dorado-Martinez-et al (2001) did not see effects following exposure to lower concentrations of diesel engine exhaust or O<sub>3</sub>, respectively, while Bos et al (2012) observed effects following exposure to ambient traffic-related air pollution. In addition, most experimental studies involved short-term exposures. Therefore, although the available studies indicate biological plausibility of neurotoxic effects, and demonstrate potential mechanisms, their relevance to understanding neurodegeneration following long-term exposure to ambient concentrations is not clear.

It is likely that effects of air pollutants on neurodegeneration are dependent upon genetic background. It is also possible that age modulates effects. Some experimental studies have found differences in sensitivity depending on the age of the animals tested. However, the results are not consistent as to whether older or younger animals are more sensitive.

### 4.6.4 Discussion and overview

#### 4.6.4.1 Discussion

Current understanding is that the changes which lead to cognitive impairment, and the development of dementia, take place over a long period of time. Some may start many years before symptoms occur. Some of the factors that increase the risk of development of these conditions are known, but others remain to be identified. Authors of the Lancet Commission on

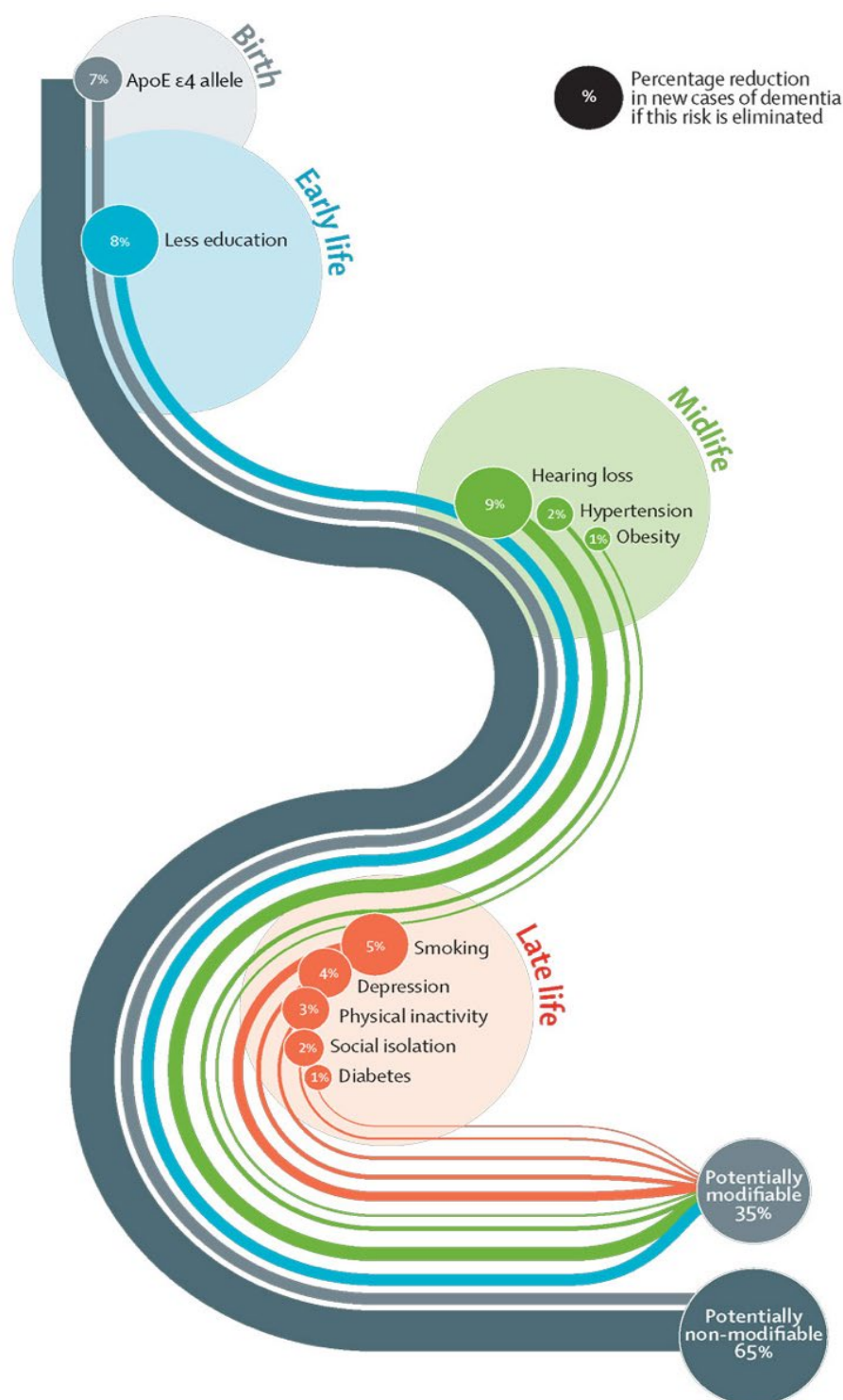
dementia prevention, intervention, and care (Livingston et al, 2017)<sup>24</sup> reviewed various risk factors for dementia and the points over the life-course at which they have been found to be important. This shows that potentially modifiable risk factors have been identified across the whole life course (see Figure 4.5) (Livingston et al, 2017). However, we note that maternal exposures have not been considered in this model; the possible consequences of exposure to air pollutants in utero for health in childhood and later life is a growing area of research.

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<sup>24</sup> We note that the updated 2020 Lancet Commission on dementia (Livingston and others, 2020), of which one of our Sub-Group Members is a co-author, recognises the likely role of air pollution in causing dementia via effects on the vascular system.

# Figure 4.5. Population attributable fraction of potentially modifiable risk factors for dementia

(Reprinted from The Lancet 2017: volume 390. Livingston G, Sommerlad A, Orgeta V, Costafreda S, Huntley J, Ames D, et al. 'Dementia prevention, intervention, and care.' Pages 2,673 to 2,734. Copyright (2017), with permission from Elsevier.)



De Felice and Lourenco (2015) speculated that injuries acquired throughout life (for example, infections, diabetes, obesity) could cause brain metabolic stress and facilitate sporadic

Alzheimer's disease onset in later life. Some recent air pollution studies (for example, Tyler et al, 2017) suggest that the aged brain may have an enhanced vulnerability to the neuropathological effects of air pollutants and, therefore, that exposures in mid or late in life may perhaps be particularly detrimental. However, this is not a consistent finding and it remains possible that exposures earlier in life may also be relevant.

#### 4.6.4.2 Overview

There has been much interest in recent years as to the mechanisms by which UFP that reaches the brain might have adverse effects on neurological disease processes. Oxidative stress and inflammation seem likely to play an important role. Experimental studies suggest that at least some of the effects of air pollution on the brain may be a response to a blood-borne signal, rather than being caused directly by local responses within the brain. This indicates a potential role for a wider range of pollutants which do not reach the brain directly, including O<sub>3</sub>. Indeed, neurological effects of O<sub>3</sub> have been shown in laboratory studies. Cytokines arising from systemic inflammation have been suggested as potential mediators, but some recent studies have suggested that neuroinflammation occurs in the absence of systemic inflammation. Reaction products might be another possibility. The lung-brain signal remains to be elucidated.

## 4.7 Effects on the brain secondary to other health effects

### 4.7.1 Summary

Ischaemic brain damage is an important contributor to dementia; dementia can result from a reduction in the blood supply to the cells of the brain, whether that reduction is caused by disease of small blood vessels within the brain, larger arteries that supply the brain, or disease of the heart itself. The effects on cerebral blood vessels may be subtle and may not, necessarily, include damage to large blood vessels that leads to haemorrhagic or occlusive stroke. It is accepted that long-term exposure to air pollutants, especially to fine particles, causes damage to large and small blood vessels and also the heart. Such damage to the cardiovascular system could lead to dementia. It seems likely that the cardiovascular damage caused by air pollutants would involve both obstruction of small vessels and, importantly, altered responsiveness to local stimuli, which leads to excessive vasoconstriction. The tissues of the brain are particularly sensitive to reductions in their supply of oxygen and nutrients. There is evidence that exposure to ambient particles (PM<sub>2.5</sub>) is associated with acute haemodynamic abnormalities in the human brain. A link between chronic respiratory disease and dementia has also been suggested; the mechanism may be that chronic respiratory disease leads to a reduction in the oxygen supply to the brain.

## 4.7.2 CV effects

### 4.7.2.1 Introduction

The COMEAP report on 'Effects of long-term exposure to ambient air pollution and cardiovascular morbidity: mechanistic evidence' (COMEAP, 2018), summarises a large body of evidence from epidemiological, animal and in vitro studies, and from short-term human experiments, that exposure to air pollutants contributes to the development and severity of cardiovascular disease (CVD). The cerebral vasculature is not spared from the effects of air pollutants on CVD. Exposure to air pollution, including fine particulate matter (PM<sub>2.5</sub>) has been reported in a range of cross-sectional and longitudinal population studies to be associated with an increased risk of stroke and cerebrovascular mortality (Bedada et al, 2012; Beelen et al, 2014; Carugno et al, 2016; Chen et al, 2014; Dabass et al, 2016; Kulick et al, 2017; Leiva et al, 2013; Lin et al, 2017b; Maheswaran et al, 2016; Marabotti et al, 2017; Mate et al, 2010; Samoli et al, 2014; Stafoggia et al, 2014; Wichmann and Voyi, 2012; Wilker et al, 2015; Yorifuji et al, 2016a; Yorifuji et al, 2011; Zanobetti et al, 2014; Zhang et al, 2015; Zhang et al, 2011).

Vascular cognitive impairment (VCI) encompasses a spectrum of disease (O'Brien et al, 2003; Skrobot et al, 2017), ranging from mild, non-progressive cognitive deficits attributable to cerebrovascular disease, to various forms of vascular dementia (VaD), including post-stroke dementia, subcortical ischaemic vascular dementia and multi-infarct dementia, as well as mixed dementias in which neurodegenerative and vascular disease contribute jointly to cognitive impairment. As the risk factors for VCI and VaD overlap those for CVD and include hypertension, myocardial infarction and diabetes mellitus (Duron and Hanon, 2008; Gorelick, 2004; Love and Miners, 2017), all of which have been linked with exposure to air pollution, it is not surprising that air pollution is also associated with VCI and VaD (see COMEAP (2018), and Chapter 3 of this report). Stroke, in particular, greatly increases the risk of VaD, and air pollution (exposure to PM<sub>2.5</sub> in particular) increases the risk of stroke (Scheers et al, 2015; Wang et al, 2014). Some of the risk factors for CVD that may be influenced by air pollution may also be risk factors for Alzheimer's disease (AD). These include diabetes mellitus<sup>25</sup> and hypertension.<sup>26</sup>

### 4.7.2.2 Mechanisms of brain damage in VCI and VaD

The mechanisms of brain damage in VCI and VaD have been considered in detail in several reviews (Esiri, 2000; Love and Miners, 2017; Strozyk et al, 2010). The main substrate of VCI is ischaemic damage to white and grey matter structures within the cerebrum: infarcts and microinfarcts (that is, infarcts that require microscopy or high-resolution imaging for detection), and regions of subtotal ischaemic damage to the white matter (Arvanitakis et al, 2011; Esiri et al, 1997; Fernando et al, 2004; Ince et al, 2017; Roman, 2004; Skrobot et al, 2016; Strozyk et al, 2010; Troncoso et al, 2008; White, 2009; White et al, 2002). There is increasing recognition of the adverse effects on cognition of cortical disconnection resulting from multifocal or diffuse damage to the cerebral white matter (Bennett and Madden, 2014; Filley, 2011; Vasquez and Zakzanis, 2015). The risk of VCI is also increased in people with microbleeds – multiple small

<sup>25</sup> See [Alzrisk Risk Factor Overview](#) for a detailed review of the evidence.

<sup>26</sup> See [Alzrisk Risk Factor Overview](#)



foci of haemorrhage detected using specific magnetic resonance imaging sequences. However, evidence from autopsy studies suggests that ischaemic parenchymal damage is the main cause of cognitive impairment, even in people in whom numerous microbleeds are visible on magnetic resonance imaging (MRI) (Janaway et al, 2014; Lauer et al, 2016), although inflammation and oxidative stress may also contribute. Another probable contributor to brain damage in people with small vessel disease is disruption of the blood-brain barrier (BBB), with leakage of potentially damaging plasma proteins such as fibrinogen into the brain parenchyma (Kisler et al, 2017; Montagne et al, 2015; Taheri et al, 2011) (see Section 4.3).

#### 4.7.3.2 Vessel wall pathology

The main types of sporadic vessel wall pathology in VCI and VaD are atherosclerosis of basal arteries, and cerebral small vessel disease: cerebral arteriolosclerosis, cerebral amyloid angiopathy (CAA) resulting from vascular deposition of A $\beta$  peptide (A $\beta$ ), and degeneration and loss of capillaries (Brown and Thore, 2011; Deramecourt et al, 2012; Fernando et al, 2004; Love and Miners, 2017; Strozyk et al, 2010). Although all of these pathologies have been reported in VCI and VaD, the vessel wall abnormality most closely associated with cognitive impairment is arteriolosclerosis. Atherosclerosis and arteriolosclerosis are strongly associated with hypertension and diabetes mellitus, and both vessel wall pathologies are associated with air pollution (see above, and COMEAP (2018)). There is no direct evidence in the scientific literature that hypertension, diabetes or air pollution is associated with CAA or capillary degeneration (Boulouis et al, 2016). Atherosclerosis and arteriolosclerosis cause narrowing of vessel lumina, reducing vascular conductance as well as increasing turbulence, causing shear stress and endothelial damage (Chiu and Chien, 2011; and see COMEAP, 2018). In addition, collagenous thickening of the vessel wall and loss of smooth muscle cells (or their function) in arteriolosclerosis is likely to contribute to impaired neurovascular coupling (the matching of cerebral blood flow to regional metabolic demand within the brain) in stroke patients and people with hypertension (Girouard and Iadecola, 2006; Lin et al, 2011). However, we are not aware of any studies of the possible effects of air pollution on small vessel disease (arteriolosclerosis) in the brain.

#### 4.7.2.4 Non-structural vascular abnormalities

Ischaemic brain damage in dementia is probably caused not only by vessel wall pathology but also by non-structural vascular abnormalities that result from alterations in the concentrations of several chemical mediators of vascular contractility and dilatation. The level of the vasoconstrictor endothelin-1 (EDN1) is elevated in the cerebral cortex in AD (Miners et al, 2016; Palmer et al, 2009; Palmer et al, 2012; Palmer et al, 2013), and it may also be elevated in the white matter in people with severe arteriolosclerosis (Barker et al, 2014). EDN1 acts on vascular smooth muscle and pericytes to cause vasoconstriction at both arteriolar and capillary level (Dore-Duffy et al, 2011; Ehrenreich and Schilling, 1995; Kawamura et al, 2002). In the frontal cortex there is also upregulation of angiotensin-converting enzyme (ACE)-1 and downregulation of ACE-2, leading to an increase in another vasoconstrictor, angiotensin II (Kehoe et al, 2016; Miners et al, 2010). A $\beta$  peptide also downregulates the production of the vasodilator nitric oxide (NO) (Lamoke et al, 2015; Suhara et al, 2003). All of these biochemical alterations that favour



vasoconstriction and reduced cerebral perfusion have also been reported in association with air pollution (COMEAP, 2018) and may play a role in the detrimental cardiovascular effects of air pollution in other organ systems.

Evidence that exposure to PM<sub>2.5</sub> causes relatively acute haemodynamic abnormalities within the human brain, likely to reflect non-structural vascular changes, comes from a study of Wellenius et al (Wellenius et al, 2013), who used transcranial Doppler ultrasound to measure beat-to-beat blood flow velocity in the middle cerebral artery at rest, in 482 participants from the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) of Boston study. The authors also measured the response to changes in end-tidal CO<sub>2</sub> (to assess cerebral vasoreactivity) and arterial blood pressure (to assess cerebral autoregulation). The association between cerebrovascular haemodynamic parameters and mean PM<sub>2.5</sub> levels 1 to 28 days earlier was analysed, adjusting for age, race, medical history, meteorologic covariates, day of week, temporal trends, and season. An interquartile range increase (3.0µg/m<sup>3</sup>) in mean PM<sub>2.5</sub> levels during the previous 28 days was associated with an 8.6% (95% confidence interval, 3.7% - 13.8%; P<0.001) higher cerebral vascular resistance and a 7.5% (95% confidence interval, 4.2% - 10.6%; P<0.001) lower blood flow velocity at rest. Measures of cerebral vasoreactivity and autoregulation were not associated with PM<sub>2.5</sub> levels.

### 4.7.3 COPD

There is research interest in a possible link between obstructive sleep apnoea and cognitive impairment and dementia (Buratti et al, 2016; Johnson et al, 2017; Osorio et al, 2015; Yun et al, 2017). A possible mechanism for this link is brain hypoxia resulting from breathing difficulties. This raises the possibility of a link between respiratory disease and effects on cognition and dementia. A recent review (Kakkera et al, 2018) found that the available evidence was suggestive of the possibility that chronic obstructive pulmonary disease (COPD) was linked with these effects. A recent cohort study found that poor pulmonary function in early adulthood and midlife was associated with dementia diagnosis in later life (Gilsanz et al, 2018). It could, therefore, be suggested that effects of air pollution on the respiratory system might have a secondary impact on brain function and disease processes. We have not examined this possibility in detail, but note that, although elevated levels of air pollution are acknowledged to exacerbate COPD in those with the condition, the evidence that long-term exposure causes COPD is suggestive, but not conclusive (Schikowski et al, 2014). We think that more work on this possible mechanism is needed.

## 4.8 Possible influence of early life exposures

### 4.8.1 Summary

Early-life exposure to air pollutants has been linked with a range of effects on brain function. These include reduced cognitive performance in childhood, impairment of the development of memory and of IQ, and an increased prevalence of behavioural disorders. It is suggested that

the developing brain is especially susceptible to damage: the blood-brain barrier (BBB) is not fully functional in the fetus and it is known that some air pollutants can cross the placental barrier. It is likely that particulate material could cross the developing BBB more readily than the adult barrier. Development of the BBB requires the interaction of cells of the walls of small blood vessels of the brain, the pericytes associated with these vessels and glial cells. The function and viability of these cells is known to be compromised by inflammatory processes and by local acidosis. In addition, effects when neural pathways are being developed are likely to be of lasting significance. There is some evidence that exposure to air pollutants in utero leads to low birth weight and to a reduction in head circumference at birth. It therefore seems possible that early life exposure to air pollutants could impair brain development.

#### 4.8.2 The developing brain

The developing brain in utero is considered more sensitive to environmental toxicants since it is expanding, creating new cellular networks and is not yet protected by a fully functional BBB (Heusinkveld et al, 2016). Central nervous system (CNS) angiogenesis commences during neural tube development. As the blood vessels mature, they recruit pericytes and astrocytes, which interact with endothelial cells (particularly through TGF $\beta$ 1 signalling) and thereby induce pericytes and endothelial cells to form a perivascular basement membrane, and endothelial cells to form tight junctions (Haddad-Tóvolli et al, 2017; Hagan and Ben-Zvi, 2015). At least in rodents, the formation of the BBB proceeds in a caudo-rostral direction. The BBB is fully functional during late gestation in rodents and by the third trimester in humans (Goasdoue et al, 2017; Haddad-Tóvolli et al, 2017); indeed, immunogold cytochemistry showed serum albumin to be restricted to vessel lumina in the 12th week of gestation and a mature pattern of labelling the glucose transporter GLUT1 in the 18th week (Virgintino et al, 2000). It should be noted, however, that the formation and maintenance of a mature BBB depend on the presence of normally functioning endothelial cells, pericytes and astrocytes. The function and viability of these cells can be disturbed by a range of pathological processes including ischaemia, acidosis and inflammation, and under these conditions there may be breakdown of the BBB.

It is known that some air pollutants can cross the placental barrier. Studies in experimental animals have found nano-sized particles in the placenta, and a recent study (Bove et al, 2019) reported that black carbon (BC) particles accumulate on the fetal side of the human placenta.

Air pollution exposures during infancy and childhood might also affect development of the central nervous system, since brain structures are still developing and neuronal connections continue being created (Heusinkveld et al, 2016). Limited capacity of the nervous system to repair any structural damage might result in permanent and irreversible dysfunction that might affect cognitive functions later in life (Sladek, 2012). In addition, early life exposures in utero or during childhood might produce epigenetic changes that might increase the risk of neurodegenerative diseases later in life (Heusinkveld et al, 2016).

### 4.8.3 Effects of air pollution on fetal organ development

There is increasing evidence that prenatal exposure to air pollution may adversely affect fetal growth. The systematic review and meta-analysis by Li et al (2017) from 23 studies published before July 2016, estimated that the pooled odds ratio (OR) for the association between exposure to PM<sub>2.5</sub> per interquartile range increment, and term low birth weight throughout pregnancy was 1.03 (95% CI: 1.02 to 1.03) (Li et al, 2017). But this review did not address whether reduced birth weight was associated with decreased head circumference, a robust surrogate marker of brain volume. However, Malmqvist et al (2017) used linked registry data for 48,000 pregnancies and exposure data based on residential addresses, and reported a reduction of -0.5mm (-0.7 to -0.2) in head circumference at birth per 10µg/m<sup>3</sup> increment in NO<sub>x</sub>, an effect estimate that remained robust in sensitivity analyses (Malmqvist et al, 2017). Furthermore, in the ESCAPE analysis of pooled data from 14 population-based mother–child cohort studies in 12 European countries, not only was a 5µg/m<sup>3</sup> increase in concentration of PM<sub>2.5</sub> during pregnancy associated with an increased risk of low birth weight at term OR 1.18, (95% CI 1.06 to 1.33), but this increase was also associated with a -0.8 mm (95% CI -1.2 to -0.3) change in head circumference at birth (Pedersen et al, 2013). A recent study reported that in-utero exposure to PM<sub>2.5</sub> was related to structural alterations of the cerebral cortex in the child brain, which partially mediated the association between in-utero exposure to PM<sub>2.5</sub> and impaired child inhibitory control (Guxens et al, 2018). Overall, these data suggest that fetal brain growth may be adversely affected by maternal exposure to air pollution.

Not only may air pollution affect the brain of the fetus, but also there is emerging evidence of a direct link between the adverse effects of air pollution on fetal growth and increased risk of cardiovascular-mediated effects on the adult brain (cardiovascular effects on the brain are discussed in section 4.7.2).

For example, in a recent review Crispi et al (2018), concluded that fetal growth restriction results in: i) metabolic programming that may increase the risk of metabolic syndrome - with its increased cardiovascular morbidity risk in adult life, and ii) fetal cardiac and arterial remodelling resulting in a 'subclinical' state of cardiovascular dysfunction that persists, at the very least, into young adult life (Crispi et al, 2018).

### 4.8.4 Cognitive effects

There is emerging evidence for an association between exposure to air pollution and cognitive effects in early life. For in utero exposure, the systematic review by Clifford et al in 2016 identified 2 interrelated prospective studies which examined the association between exposure to polycyclic aromatic hydrocarbons with neurodevelopment and intelligence, and a single pooled analysis of 6 European prospective studies which looked at the association between in utero exposure to a range of air pollutants and cognitive function in children from one to 6 years of age (Clifford et al, 2016). For postnatal exposure, 8 studies were identified by the systematic review. The review's overall conclusion was that poorer performance was found across several cognitive measures including neurodevelopment, intelligence and memory in

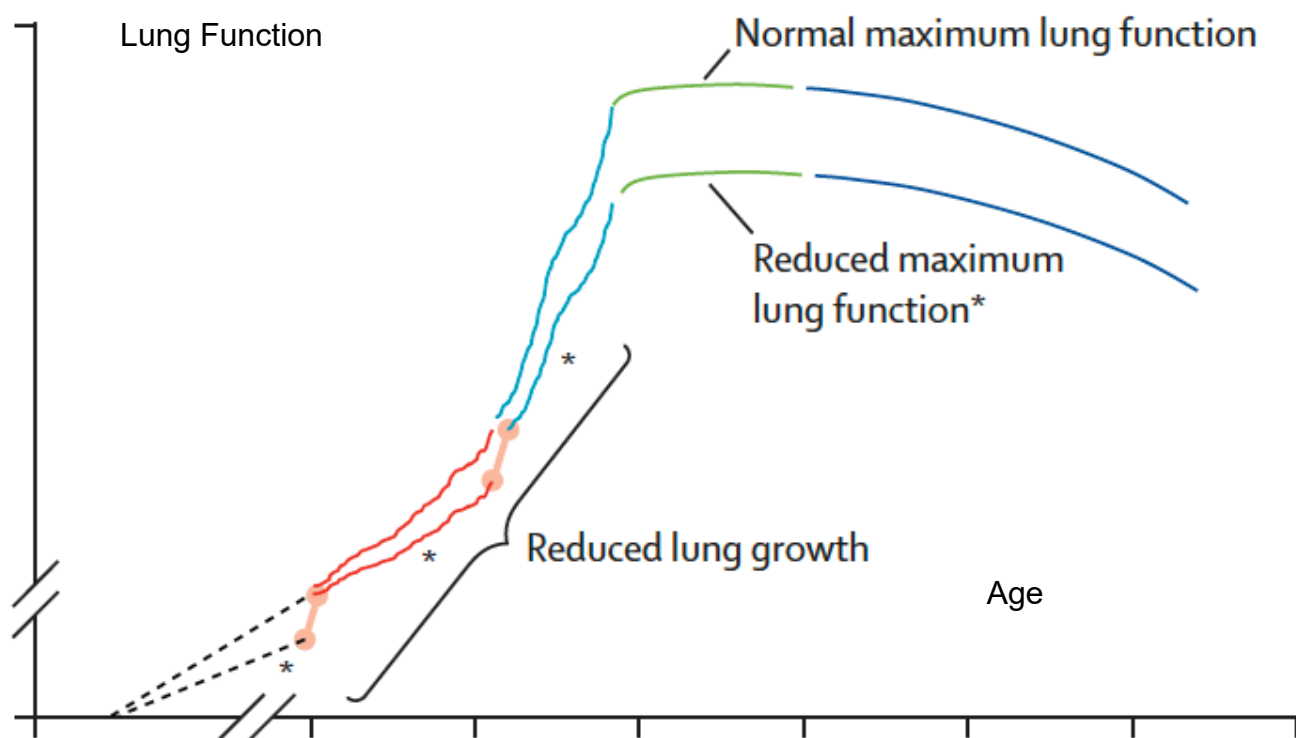
young children exposed to higher levels of air pollution, and that in utero exposures to air pollution were associated with intelligence and neurodevelopment at 3 to 5 years of age (Clifford et al, 2016). Forns et al (2017) measured both indoor and outdoor air pollution at 39 schools across Barcelona, and prospectively assessed the working memory of children attending these schools over a 3.5-year period. Associations were found between all traffic-related air pollutants and annual change in working memory, as assessed by the n-back test. For outdoor NO<sub>2</sub>, the association was equivalent to a -20% (95% CI -30.1, -10.7) change in annual working memory development. A follow up analysis by Alemany et al (2018) on the same cohort of children found that exposure to PAHs, EC, and NO<sub>2</sub> was associated with higher scores in behavioural problem tests, lower reductions in inattentiveness over time, and smaller caudate nucleus volume in children who were APOE ε4 carriers. Weak or null associations were reported for ε4 noncarriers (Alemany et al, 2018). In a separate Spanish study, Sentis et al (2017) studied children who had NO<sub>2</sub> exposure assessed as part of a population-based birth cohort (Sentis et al, 2017). Attention function in 1,298 children in this cohort (aged 4 to 5 years) was done using the Kiddie-Conners Continuous Performance Test. In the fully adjusted model, prenatal exposure to NO<sub>2</sub> was associated with an impaired standard error of the hit reaction time (increase of 1.12ms (95% CI 0.22 to 2.02) per 10µg/m<sup>3</sup> increase in prenatal NO<sub>2</sub>) and increased omission errors (6% (95% CI 1.01 to 1.11) per 10µg/m<sup>3</sup> increase in prenatal modelled exposure to NO<sub>2</sub>). There were no significant associations between these variables and postnatal exposure to NO<sub>2</sub>. The United Nations Children's Fund (UNICEF) recently (Rees/UNICEF, 2017) reviewed the association between air pollution and cognitive function in children. The report identified other studies reporting associations between air pollution exposure and cognitive outcomes, including verbal and nonverbal IQ and memory, reduced test scores, grade-point averages among school children, as well as other neurological behavioural problems (Chiu et al, 2013; Grineski et al, 2016; Newman et al, 2013; Siddique et al, 2011; Suglia et al, 2008; Sunyer et al, 2015; Volk et al, 2013; Wang et al, 2009). Studies identified by the UNICEF report also reported associations between prenatal exposure to air pollution and developmental delay at age 3 years, and psychological and behavioural problems later in childhood (Jedrychowski et al, 2015; Perera et al, 2014; Perera et al, 2009; Perera et al, 2006; Perera et al, 2012; Yorifuji et al, 2016b). The report concluded:

"What research is showing us now is that a variety of other air pollutants may also be harming children's brains. The potential scale and impact are too high for us to ignore. Given all the risks that air pollution poses, the need to act is urgent." (Rees/UNICEF, 2017).

In summary, these emerging data suggest the capacity for air pollution to influence neurocognitive development across the life course. The analogy is with lung function, where it is now generally accepted that clinically small, short-term suppression of lung function growth produces clinically significant effects when suppression persists over long periods (Figure 4.6) (Rennard and Drummond, 2015).

**Figure 4.6. Reduced lung growth due to air pollution reduces maximum lung function, and adults therefore have less 'reserve' to compensate for the normal decline during ageing**

(Reprinted from The Lancet, volume 385, issue 9,979. Rennard SI, Drummond MB. 'Early chronic obstructive pulmonary disease: definition, assessment, and prevention.' Pages 1,778 to 1,188. Copyright (2015) with permission from Elsevier)



## Chapter 5. Discussion

### 5.1 Assessment of the evidence base with regard to the question of causality of the reported associations

In any review of evidence of the health effects of exposure to air pollutants, the first step is to discover whether associations between exposure to air pollutants and changes in health endpoints have been convincingly demonstrated. A number of the epidemiological studies reviewed in Chapter 3 report such associations. It is important to establish whether the majority of the studies report associations. If this is not the case, then it might be concluded that the evidence is simply not persuasive and further discussion is not needed. In the present case the majority of studies do report associations and so we move to the next step.

The second step is to reach a view on whether the reported associations are likely to be causal in nature. It is recognised that certainty about causality is seldom possible in our field but whether causality is more likely than not can be assessed. A well-established approach is to consider the evidence in the light of the features of causal associations outlined by Bradford Hill (Hill, 1965). Bradford Hill set out 9 features: we consider these next.

In addition, the possible effects of publication bias need to be considered: it is possible that studies with negative or null results are less likely to be published, especially as the study of the effects of environmental factors on cognition and dementia is a relatively emerging field (Xu et al, 2016). The following evaluation of the evidence assumes no major publication bias.

#### 5.1.1 Strength of association

Associations reported in epidemiological studies are regarded as strong or weak according to the size of the coefficients linking effects and putative causes. The first test of these associations is of their statistical significance: associations, whether strong or weak, which do not pass this test are regarded as possibly due to chance. It is important to add that examination of a number of associations may reveal a trend indicating likelihood of an effect even if some individual associations do not achieve formal statistical significance: meta-analysis can sometimes be helpful in reaching this interpretation. Strong associations are generally held to be more convincing, as regards the likelihood of their being causal in nature, than weak associations. This is because if strong associations were, in fact, reflecting the effects of confounding factors then those factors should be fairly easy to identify. Such confounding factors are likely to have been controlled for in the study design and it is likely that the reported strong association would reflect the effect of the putative causal agent. In the case of weak associations, it is likely to be more difficult to identify, and thus control for, confounding factors which might be playing a part. The weakness or strength of an association does not, per se,

control the likelihood of causality; it is certainly true that weak associations may be causal in nature. The point is that it is more difficult to be sure that weak associations are causal in nature than is the case for strong associations. It is also true that weak associations, if causal in nature, may reflect major effects on public health. Of course, the size of the possible impact on public health has no effect on the likelihood of causality of an association.

In the air pollution field, it has been found that many associations between exposure to air pollutants and effects on health are reflected by weak but, in general, statistically significant associations. It is important not to confuse strength of association with strength of evidence: it has often been found that there is strong evidence of weak associations. The strength of evidence lies not only in the size and statistical significance of the coefficients but also in the number of studies reporting such coefficients, in the consistency of their findings and in their quality. This takes us to points discussed in the following sections of this chapter.

Our review of epidemiological studies shows that long-term exposure to air pollutants is associated with a small but statistically significant reduction in global cognitive function and visuospatial abilities, with the rate of cognitive decline with age, with morphological changes in the brain and with an increased risk of dementia. The effects on the rate of cognitive decline found in these studies are equivalent to that produced by ageing over a period of one to 5 years. (Chen and Schwartz, 2009; Power et al, 2011; Wellenius et al, 2012; Weuve et al, 2012; Wilker et al, 2015), as summarised in Table 3.13. In that the associations report, in general, small coefficients they are regarded as weak. It should, however, be noted that some studies report strong associations: a recent study in London reports that subjects exposed long-term to the upper quartile of exposure to NO<sub>2</sub> (NO<sub>2</sub> >41.5µg/m<sup>3</sup>) have a 40% greater risk of developing dementia than those less exposed (95% CI: 12% - 74%) (Carey et al, 2018).

### 5.1.2 Consistency of association

The various air pollutants and cognitive endpoints considered, the variations in cognitive tests used, and the diverse range of study designs found in the literature preclude meta-analysis. It also makes it difficult to qualitatively assess the consistency within each study design, for a specific air pollutant and for some cognitive domains.

Nonetheless, studies assessing the effect of air pollution on cognitive performance fairly consistently report associations with exposure to at least one component of air pollution and a decrement in global cognition (13 out of 16 studies) and constructional praxis (3 out of 3).

The findings have been less consistent with respect to executive function (5 out of 9), attention (4 of 6), memory (7 of 11) and language (4 out of 5), as well as in studies reporting associations between air pollution and mild cognitive impairment (4 out of 6) and cognitive decline (5 out of 9).



Proximity to traffic (3 out of 3) and CO (2 of 2) has consistently been associated with increased risk of dementia. NO<sub>2</sub> and NO<sub>x</sub> (7 out of 8) and PM (8 out of 11) have also been associated with dementia in most studies, but O<sub>3</sub> in only 3 out of 5 studies. One study involving a very large number of people (approximately 9 million) reported a statistically significant association between first-time hospital admissions for Alzheimer's disease and other causes of dementia and long-term exposure to PM<sub>2.5</sub> (Kioumourtzoglou et al, 2016). This is consistent with population-based cohort studies showing associations between short-term variations in air pollution and neurological hospital admissions in Madrid (Spain) (Culqui et al, 2017; Linares et al, 2017), Chengdu (China) (Qiu et al, 2019) and USA (in older adults) (Zanobetti et al, 2014). However, a study in Rome did not find consistent associations between air pollutants and first-time hospitalisation for dementia (Cerza et al, 2019). Associations between Alzheimer's disease symptoms and carers' distress with PM<sub>2.5</sub> have been reported in South Korea (Lee et al, 2019).

Evidence of the effects of air pollution on the findings of neuroimaging is limited (only 6 studies in 4 different US cohorts) and consistency of results varies between the outcomes under consideration. Studies from the WHIMS study consistently report associations between exposure to air pollution and reduction of white matter volume (Casanova et al, 2016; Chen et al, 2017c; Chen et al, 2015). In 3 different US cohorts air pollution has not been associated with hippocampal volume (Casanova et al, 2016; Chen et al, 2017c; Chen et al, 2015; Wilker et al, 2015), but left hippocampal volume was associated with air pollution in the UK Biobank cohort (Hedges et al, 2019). Associations between exposures to diesel particulate matter and reduced grey matter volume in the brain were reported in the WHIMS and ARIC cohorts (Casanova et al, 2016; Chen et al, 2017c; Power et al, 2018) and, in the WHISCA and WHIMS-MRI cohorts, with a pattern of atrophy of grey matter structures similar to that in Alzheimer's disease (Younan et al, 2020). Effects of exposure to air pollution on small vessel ischaemic disease and white matter hyperintensities are inconsistent (Chen et al, 2017c; Wilker et al, 2016; Wilker et al, 2015).

Studies on neurological biomarkers measured after chronic exposure to air pollutants are generally consistent, but very limited in number (Calderón-Garcidueñas et al, 2013c; Sanchez-Rodriguez et al, 2006). Results of the very few studies available on short-term exposures are heterogeneous.

On the assumption of no major publication bias we can state that, overall, many of the reviewed studies reported statistically significant associations between concentrations of at least one constituent of air pollution and indices of deleterious effects on the brain. Others reported associations that failed to reach statistical significance also, in general, indicating a deleterious effect. A few studies have found contrary associations: proximity to traffic associated with a lower risk of white matter hyperintensities (Wilker et al, 2016; Wilker et al, 2015), better reasoning and prospective memory (Cullen et al, 2018), better verbal memory and visuospatial skills (Wurth et al, 2018), reduced risk of first time hospitalisation related to dementia (Cerza et al, 2019), better scores on tests of global cognition, executive function, attention and memory



(Shin et al, 2019), reduced cognitive decline (Xu et al, 2017), and a non-significant association between air pollution and improved cognitive performance (Tonne et al, 2014).

In addition, a picture of consistent results from different study designs (cross-sectional, longitudinal, time-series) on the effects of air pollution on cognitive performance, cognitive decline and incidence of dementia and Alzheimer's disease is emerging, even though the results in some studies have failed to reach statistical significance. The review of studies shows that there is considerable, but not complete, consistency across the range of studies reported. Consistency is stronger in the studies linking air pollution with incident dementia, whilst weaker in others (for example, executive function, mild cognitive impairment).

The results in this review are also consistent with observations of structural changes in the brain, neuroinflammation, neurotoxic changes and decreased cognitive performance reported in children from Mexico City. Calderón-Garcidueñas et al (2013a) suggested that these changes may indicate an increased risk of developing Alzheimer's and Parkinson's diseases in later life.

The studies which we have reviewed examine associations with a range of pollutants. Associations suggesting adverse effects have been reported with fractions of PM (including PM<sub>10</sub>, PM<sub>2.5</sub> and BC), NO<sub>x</sub>, NO<sub>2</sub> and metrics related to proximity to or intensity of traffic. A number of studies have examined associations with more than one of these pollutants or with one or more of these pollutants and a traffic metric. These studies are not consistent as regards which of these exposures was found to be associated with adverse effects. However, there is some degree of correlation between these pollutants: especially in urban areas where the concentration gradients often reflect emissions from combustion sources, particularly traffic. Therefore, we can regard associations with these different pollutants as indicating a degree of consistency, even if the studies report associations with different pollutants. Most of the studies that investigated associations with O<sub>3</sub> concentrations, though not all, also reported results consistent with detrimental effects. Associations have also been found with Air Pollution Indices (API).

Moreover, it should be noted that studies have been conducted in a wide range of geographical locations. The air pollution mixture to which participants in different studies have been exposed depends on the specific location. Hence, when assessing the consistency across different studies, the temporal and geographical patterns of the air pollution profile are a consideration: some heterogeneity might not be unexpected.

Table 3.14 summarises the consistency of the reviewed literature in all the different areas, whereas Table 3.15 focuses on consistency on brain imaging evidence.

### 5.1.3 Specificity of association

Bradford Hill (Hill, 1965) described specificity of association as a feature of causal associations. However, he acknowledged that one-to-one relationships are infrequent and that several

causes might lead to the same effect. This might well be the case here, where several putative causes (air pollutants) and, also, confounding factors might lead to cognitive decline. Similarly, one agent, in this case air pollution, might have a variety of health effects, including different types of cancer, cardio-respiratory diseases, reproductive effects, cardio-metabolic disease and increased mortality (Dehbi et al, 2017; Gowers et al, 2012; Pope and Dockery, 2006; Pope et al, 2015; Samoli et al, 2016; Sram et al, 2005). A familiar referent is smoking, where the exposure to tobacco smoke causes a similar range of effects.

Hence, Bradford Hill (Hill, 1965) emphasised the importance of identifying an underlying factor linking cause and effect. It is possible that such an underlying factor could be a unifying biological mechanism, linking exposure to air pollutants with a wide range of effects including cognitive decline or dementia.

### 5.1.4 Temporality

Almost all of the epidemiological studies reviewed have focused on the possible effects of chronic exposure to air pollutants. Such studies imply a sustained exposure to air pollutants prior to the discovery of effects and thus support a temporal relationship between exposure and effect. Only a few studies follow a conventional longitudinal design where cognitive indices are measured at baseline and at follow-up and exposures to air pollutants during the follow-up period are estimated from the subjects' residential addresses. For most of the reviewed studies temporality is supported by the reasonable assumption that spatial variation in recently measured exposures (concentrations) is strongly related to, or is a proxy for, variation in exposure in the past. In other cases, studies have related indices of cognitive function to estimated long-term exposure to air pollutants.

### 5.1.5 Biological gradient

Epidemiological analysis is based on regression analysis. Such analysis yields a mathematical relationship between effect and putative cause and characterises that relationship by a coefficient or gradient. If the coefficient linking exposure and health effect achieves statistical significance, then it is accepted that the regression line suggests a statistically significant association and, if that association is regarded as likely to be causal in nature, that a biological gradient or exposure response relationship has been established.

Statistically significant exposure-response functions (coefficients and 95% confidence intervals) are summarised in Tables 3.1 to 3.12 (Section 3.3.1).

### 5.1.6 Biological plausibility

Experimental studies have demonstrated that inhalation exposure of laboratory animals to particles, diesel engine exhaust and O<sub>3</sub> elicits neurological responses. Effects studied have included functional effects, such as memory impairment. Markers of neuroinflammation and oxidative stress are also increased. In turn, systemic and neuroinflammation are associated with

cognitive decline and dementia (Calderón-Garcidueñas et al, 2011; Calderón-Garcidueñas et al, 2004; Calderón-Garcidueñas et al, 2008a), as described in detail in Section 4.6.

Although most of the experimental studies used high doses and short-term exposure, they demonstrate the biological plausibility of neurological effects of air pollutants. They also provide some information on the potential mechanisms that might be involved. Inflammation could be an underlying factor or specific mechanism linking exposure to air pollution with increased risk of dementia and cognitive decline. Another underlying mechanism might be related to the capacity of air pollution to elicit oxidative stress, overwhelming the cellular antioxidant capacity against free radicals.

Exposure to air pollution adversely affects cardiovascular function, and the cardiovascular effects of air pollutants are likely to be relevant to the development and progression of dementia. Effects on the cerebral blood vessels could be direct (for example, via UFP in the circulating blood) or indirect (for example, secondary to an inflammatory response in the lung). We note that a study of nearly 500 volunteers found effects on cerebral blood flow which were linked to PM<sub>2.5</sub> levels during the previous 28 days (Wellenius et al, 2013).

Experimental evidence, possible mechanisms of action and biological plausibility are discussed in detail in Chapter 4.

### 5.1.7 Coherence of evidence

Statistically significant associations have been reported in studies of chronic exposure to air pollution and a number of endpoints, such as global cognitive performance, memory, attention, constructional praxis, cognitive decline, incidence of dementia, and morphological changes in the brain, especially white matter atrophy. The wide range of endpoints studied allows the establishment of a considerable level of coherence between the findings of the reported studies.

Exposure to air pollution has also been associated with effects on neurological biomarkers, such as increased concentrations of markers of neuroinflammation, oxidative stress (Sanchez-Rodriguez et al, 2006) and damage to the blood-brain barrier (BBB) (for example, blood C-terminal hydrolase L1 and astrocytic calcium-binding protein B) (Liu et al, 2017). Acute exposure to air pollution was associated with reductions of brain-derived neurotrophic factor, which is suggested to promote brain plasticity, cognitive function and memory (Bos et al, 2013). Results from hospitalisation studies also suggest that chronic (Kioumourtzoglou et al, 2016) and acute (Culqui et al, 2017; Linares et al, 2017; Qiu et al, 2019) exposures to air pollution are associated with hospital admissions related to dementia and Alzheimer's disease. Air pollution exposure over 1-month and 2-months was associated with aggravated symptoms related to Alzheimer's disease and mild cognitive impairment and with distress of Alzheimer's disease carers (Lee et al, 2019).

Overall, the reviewed evidence shows coherence across a range of effects linked with cognitive performance, cognitive decline, morphological changes in the brain, alterations of neurological biomarkers, as well as incidence of dementia and aggravation of symptoms and hospitalisations related to dementia associated with exposure to air pollution.

### 5.1.8 The experiment (reversibility)

Bradford Hill (Hill, 1965) made the point that in some cases ‘experimental or semi-experimental’ evidence might aid the discussion of causality. He referred to occasions when action to prevent exposure to some putative cause of disease had been taken and stressed that it would be important to ask whether the action had produced a reduction in disease. In the air pollution field such evidence is sometimes provided by ‘intervention studies’: studies of the effects of a policy intervention designed to reduce exposure to air pollutants. It might also be hoped that such action would reverse or, more likely, slow the rate of progress of disease. For example, if we knew that reducing exposure to air pollutants slowed the rate of progression of dementia or reduced the incidence of dementia, then that would add considerable weight to the conjecture that exposure to air pollutants and effects on the brain were causally associated.

As far as we are aware no studies have looked at the effects of changing individual level exposure to air pollutants on the risk of developing dementia or on the rate of cognitive decline.

Animal studies designed to examine the effects of reducing exposure to air pollutants or the effects of drugs and chemicals which might oppose the effects of air pollutants might be informative. A few experimental studies in laboratory animals are available in which the impact of co-administration of antioxidants were investigated. Some (Guerrero et al, 1999; Pinto-Almazán et al, 2018) reported that effects of O<sub>3</sub> were mitigated in animals which received antioxidants. In contrast, Roque et al (2016) did not find that administration of antioxidants mitigated the effects of exposure to diesel exhaust particles. Rivas-Arancibia et al (2000) reported different impacts of antioxidants on the effects of ozone exposure, depending on the age of the animals.

### 5.1.9 Reasoning by analogy

Although the mixtures of toxicologically active species are likely not identical, we suggest that smoking can be considered as a high-dose parallel of the effects of ambient air pollutants on cognitive decline and dementia. The risk of developing Alzheimer’s disease (as diagnosed clinically) has been found to be significantly higher in active smokers than in former smokers (Durazzo et al, 2014; Merchant et al, 1999; Ott et al, 1998; Peters et al, 2008). The risk of developing dementia and cognitive decline tended also to be greater in smokers than non-smokers or never-smokers, although this association did not reach significance (Peters et al, 2008). In addition, there is evidence that white matter damage associated with smoking declines on cessation of smoking (Gons et al, 2011). If this were true for air pollution, it would have important consequences for public health policies, as reductions on air pollution exposure would be expected to reduce the rate of cognitive decline and the incidence of dementia.

## 5.2 Discussion: overview

Dementia, defined as a level of cognitive decline sufficient to interfere with independence in everyday activities, is one of the most, perhaps the most, serious public health problems of today. This is especially so in countries with an ageing population, such as the UK. In broad terms dementia is defined by its effects: the processes of thought and memory are impaired. All types of dementia are characterised by a loss of connections between neurons or of neurons themselves within the brain. In some types of dementia the underlying mechanism is known or suspected, for example, ischaemia in the case of vascular dementia. In others the disease is defined by its pathological characteristics, for example Alzheimer's disease. There is no doubt that the risk of dementia increases with age - with a doubling of prevalence with every 5 to 6 years of age over the age of 65 years. What, until recently, was less well appreciated was that the changes in brain metabolism and function which, when sufficiently advanced may manifest as dementia, begin in middle age, if not earlier. If exposure to air pollutants increases the risk of development of dementia, and especially if exposure to air pollutants accelerates the development of disease or makes its commencement at an earlier age more likely, then it is possible that, by these effects, exposure to air pollutants poses a major threat to public health. Additionally, it would impose a serious burden on the National Health Service and care services: the care of patients with dementia is costly, and caring for patients over a longer period would greatly add to these costs.

The past 2 decades have seen an increase in the number of epidemiological studies reporting associations between ambient concentrations of air pollutants and accelerated cognitive decline and dementia. These studies now form an impressive body of evidence and have been reviewed several times: the reviews are discussed in this report. The broad conclusion of those reviews, and of our own, is that the evidence suggests an association between ambient concentrations of air pollutants and accelerated cognitive decline and/or dementia.

As in all epidemiological studies in the air pollution field questions relating to case definition, exposure misclassification, the use of current ambient concentrations of air pollutants as indices of long-term exposure and of adjustment for confounding factors must be considered. In addition, and of great importance as regards the current problem, the age structure of the groups studied must be considered. Most studies have focused on older age groups and therefore shed little light on the possible effects of exposure to air pollutants on the time of onset of the disease processes that lead to cognitive decline. Confounding factors are ever a difficulty. With regard to the current problem, authors of published studies have made considerable efforts to deal with known factors. However, few studies have attempted to adjust for noise in their analyses. The possibility that other, unknown, factors might also be playing a part, of course, remains.

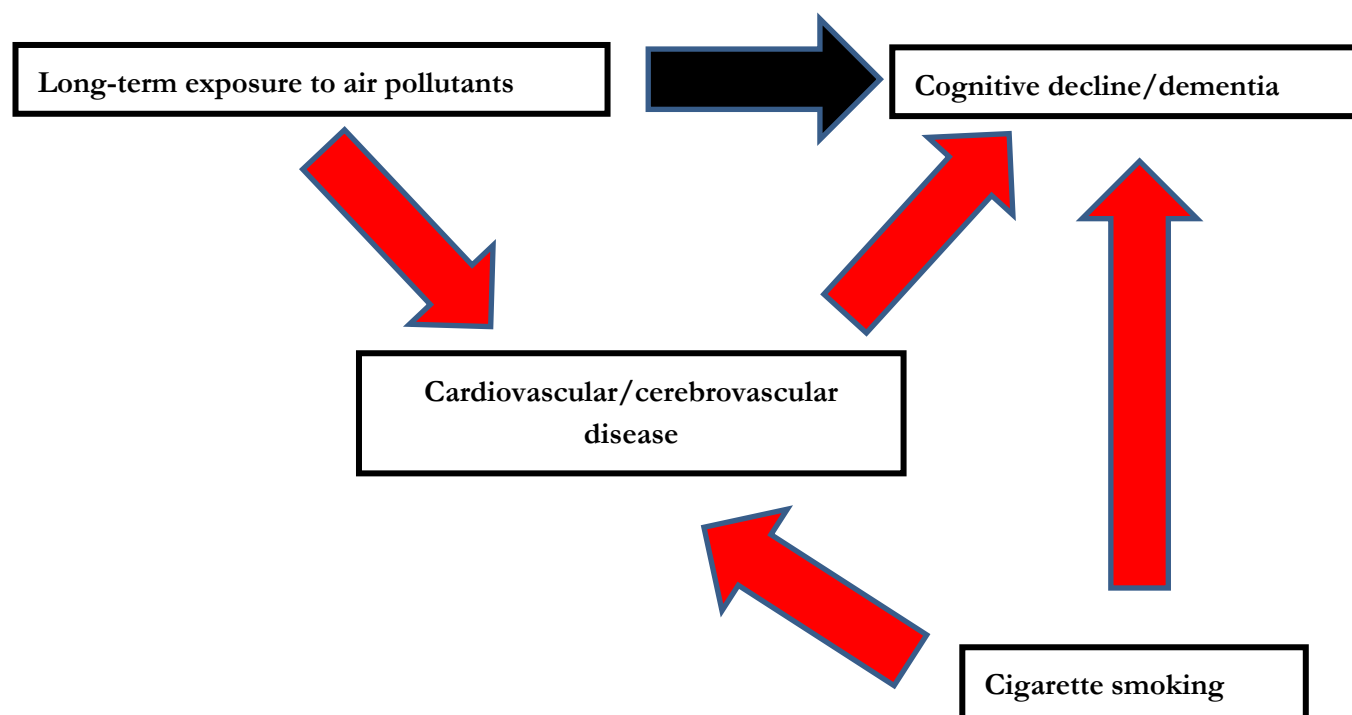
The majority of published studies report statistically significant associations between indices of long-term exposure to air pollutants and accelerated cognitive decline or cognitive

impairment/dementia. Several possible explanations for such findings are discussed in our review. Some studies have reported no effects and, only 2 reported a beneficial effect, that indices of long-term exposure to air pollutants were associated with a reduction in the rate of cognitive decline. However, although the epidemiological evidence is fairly consistent in reporting associations of cognitive decline or dementia with air pollutants, it is less consistent as to which pollutant is associated with these effects.

The demonstration of associations between environmental factors such as air pollutants and effects on health is the first stage of an argument. This argument centres on whether such associations are likely to be causal in nature. Here, as in many other areas of air pollution science and epidemiology in general, we have considered the reported associations in the light of Bradford Hill's features of causal associations. We have noted that of the features of causal associations identified by Bradford Hill only temporality is required, that is it must be met if the case for causality is to be made. In our view this feature has been met as regards associations between ambient concentrations of air pollutants and accelerated cognitive decline/dementia. In addition, the findings are, generally, consistent. In considering the features of coherence and biological plausibility we have noted that a large number of studies have reported associations between long-term exposure to air pollutants and effects on the cardiovascular system and that these associations have been agreed, by others, as likely to be causal in nature. In our view this is a most important point. We have noted that studies of the associations between ambient concentrations of air pollutants and cognitive decline or dementia have, in general, not focused on particular causes of cognitive decline/dementia. We think that the evidence of effects on the cardiovascular system combined with associations between ambient levels of air pollutants and effects on cognitive decline or dementia suggest that effects on the vascular system leading to effects on the brain may be important. We also note that cigarette smoking is associated with cognitive decline or dementia and suggest that the same mechanisms might apply. In the following diagram (see [Figure 5.1](#)) the red arrows indicate what we regard as established causal links. The black arrows indicate associations reported from epidemiological studies.



**Figure 5.1. Illustration of causal links and epidemiological associations**



Cigarette smoking can be regarded as a high-dose parallel to the effects of long-term exposure to air pollutants. Of course, the parallel is imperfect: cigarette smoke contains high concentrations of some substances that are not found, at least not in similar concentrations, in ambient air pollution.

It is not clear, from the epidemiological evidence, which of the common air pollutants are most likely to be associated with cognitive decline or dementia. Many studies have focused on particulate matter, but others have reported associations with common ambient air pollutant gases: sulphur and nitrogen dioxides, carbon monoxide and ozone. We note too, that with regard to the effects of air pollutants on the cardiovascular system, more attention has been given to particulate matter than to gases.

Our discussion of causality led us to consider experimental studies designed to investigate the possible toxicological mechanisms of effects of air pollutants on the brain. The common air pollutant gases, sulphur and nitrogen dioxides and O<sub>3</sub>, are absorbed in the respiratory tract: sulphur dioxide, a very soluble gas, largely in the upper airway, nitrogen dioxide and ozone, less soluble gases, largely in the more distal airways. The gases pass into solution and become available for reaction with components of the lining liquid of the airways. O<sub>3</sub>, a very reactive gas, is unlikely to travel for any distance into the lining liquid or epithelium of the airway without taking part in chemical reactions. These reactive gases are therefore very unlikely to reach the blood stream and, thence, the brain in unchanged form. But this is not to say that they could not have effects on the brain, and there is experimental evidence which indicates effects following exposure to ozone. Such effects could be mediated by reaction products, or be secondary to the inflammatory processes that follow the absorption of reactive gases in the respiratory tract.

This indirect toxicological pathway might also be important in the case of particulate matter. Carbon monoxide is an exception: it passes across the alveolar walls and reacts with haemoglobin in the red cells of the blood. Its toxicological effects at high concentrations are due to its effects of reducing the capacity of the blood to both carry oxygen and to release the oxygen carried to the organs of the body. Carbon monoxide presents very real neurological risks indoors when present in high concentrations. This mechanism is less relevant to the consideration of concentrations of carbon monoxide that occur outdoors. However, carbon monoxide is also now accepted as a chemical messenger or transmitter molecule (Kajimura et al, 2012).

Therefore, much of our discussion of transport and possible mechanisms has focused on the evidence relevant to particulate matter. We began by considering the translocation of inhaled particles from the lung to the bloodstream and continued by looking at penetration of particles into the brain, at what might happen to particles that entered the brain and at what effects they might have. We noted that many publications refer to the capacity of very small particles, especially ultrafine particles, to pass from the air spaces of the lung to the blood. We reviewed the literature on this point and concluded that the percentage of inhaled particles making this journey was likely to be small, probably of the order of 1%. Though this is a small percentage it might, of course, represent a considerable number of particles. Similarly, particles in the blood can penetrate to the brain via the BBB. But here, again, the percentage making the passage is likely to be small. This leads us to doubt that inhaled particulate matter exerts an important toxicological effect on the brain as a direct result of passing from lung to blood and then from blood to brain. We considered the possible fate of particulate matter that does cross the BBB.

The available evidence suggests that such material is likely to remain in close proximity to brain capillaries and not to move about in the parenchyma of the brain. Another route by which very small particles can reach the brain is via the olfactory nerve and other nerves, either transported within the nerve itself or extracellularly between the nerve and its protective sheath. However, there is little evidence to indicate that these particles then reach the areas of the brain affected in dementia.

That particles which reach the brain might be taken up by microglial cells, acting as the 'macrophages of the brain', seems likely but what their subsequent fate might be is much less clear. It may be that the particles simply remain within the brain and thus accumulate over a lifetime. The possibility that such particulate matter could harm the brain cannot be dismissed: in the case of certain materials, including manganese, this seems possible. The central problem, here, is one of dose. It is clear that high doses of reactive particles entering the brain might set up serious inflammatory effects. We are less convinced that this is likely as a result of exposure to ambient concentrations of particulate matter. In general, we were not very impressed by the evidence for this sort of direct effect of particulate matter on the brain.

We have examined the evidence for the transport of particulate matter to the olfactory bulbs via the olfactory nerves. We find this evidence convincing. We note, however, that evidence of



damage to the olfactory bulbs is sparse, if indeed it exists, and that there is little evidence for onward movement of particles along the olfactory pathways to the cerebral cortex. That particles can enter the brain via this route is clear; that such entry underlies effects associated with accelerated cognitive decline/dementia is not clear to us. If particulate matter arriving via the olfactory pathways was an important cause of sporadic disease one would expect a different distribution of lesions in these patients from those with inherited disease. But this is not the case: there is a similar distribution of pathological changes seen in patients suffering from early onset, autosomal dominant Alzheimer's disease and in those with sporadic late-onset disease. This seems to us to reduce the likelihood that direct action of particulate matter translocated via the olfactory nerves plays an important role in the causation of sporadic disease.

Oxidative stress and neuroinflammation seem likely to play an important role in the effects of air pollutants on the brain. Experimental studies have suggested that the oxidative stress is likely to result from activation of microglia, which seems to be required for effects to be observed. They also suggest that effects may be a response to a blood-borne signal or signals. This indicates a potential role for a wider range of pollutants which do not reach the brain directly, including ozone. Indeed, neurological effects of ozone have been shown in laboratory studies. Cytokines arising from systemic inflammation have been suggested as potential mediators, but recent studies have suggested that neuroinflammation occurs in the absence of systemic inflammation. Reaction products might be another possibility, but the lung-brain signal remains to be elucidated. Nonetheless, we note that most experimental studies have used high levels of exposure and short exposure periods. While the mechanistic pathways discussed seem plausible, the evidence base needs to be developed to link the possible short-term actions of air pollutants with possible long-term effects on neurodegeneration.

We were impressed by the idea that the cardiovascular effects of air pollutants are likely to be relevant to the development and progression of dementia. Effects on the cerebral blood vessels could be direct (for example, via UFP in the circulating blood) or indirect (for example, secondary to an inflammatory response in the lung). We note that a study of nearly 500 volunteers found effects on cerebral blood flow which were linked to PM<sub>2.5</sub> levels during the previous 28 days (Wellenius et al, 2013).

It has been suggested that particles might enter the brain of young children by crossing the immature BBB. We think this is possible, but we are not convinced, on the present evidence, that such entry of particles plays an important part in the development of dementia in later life. Experimental studies have suggested that some of the effects of air pollutants on the brain may be age-dependent. However, the current literature is inconsistent as to whether young or aged animals are the more susceptible.

Our consideration of the epidemiological evidence, together with consideration of possible mechanisms, led us to conclude that the reported associations between ambient concentrations of particulate matter and the risk of accelerated cognitive decline or dementia are likely to be causal in nature. This we regard as an important conclusion. Nonetheless, the possibility

remains that part of the association could be explained by confounders such as noise. However, we also concluded that a likely mechanism to explain such effects of air pollutants was a secondary effect of particulate matter on the vascular system of the brain. There is evidence from animal studies of neurological effects of ozone, but the epidemiological evidence for associations of ozone with either neurodegenerative or cardiovascular effects is less strong.

When we turned to the question of quantification of effects we were more cautious. While it might be possible to choose, from the epidemiological evidence base, a coefficient linking ambient concentrations of pollutants with accelerated cognitive decline/dementia and to apply that coefficient to conditions in the UK today, we do not feel that the evidence at present available warrants such a step. In our view, some form of meta-analysis of the epidemiological data would be the best approach to deriving a coefficient suitable for application in the UK before proceeding to quantifying the effects of air pollution on dementia in the UK population.

Such an analysis would currently present significant difficulties due to the heterogeneity of the study designs used and the endpoints studied; the question of transferability of coefficients produced by studies undertaken where levels of air pollutants are quantitatively, and perhaps qualitatively, rather different from those in the UK today would also need to be considered. We think that such work could be done if further studies, as suggested in our recommendations for research, were to be undertaken.

We considered whether the evidence base is sufficiently strong to allow a quantitative estimate in response to the question: **if** there is an effect, and **if** the effect were of a size predicted by the currently available evidence, would quantification of benefits associated with a specified reduction in ambient levels of air pollutants make an important difference to the answer to a question relating to the cost-benefit balance of specified policies designed to reduce levels of air pollutants? We think there is a case for such an approach but point out that further work to identify a suitable coefficient would be necessary before it could be undertaken. Anyone intending to include this quantification as part of an assessment of benefits of policy initiatives should be aware of the uncertainties involved, for example: uncertainties regarding which pollutant is most closely associated with the effects, whether confounding factors such as noise might contribute to the reported associations, and uncertainty as to the extent to which direct effects on the brain contribute to neurodegenerative effects in addition to effects secondary to cardiovascular effects.

We think that consideration could be given to developing an indirect approach to quantification of the effects of particulate air pollution on vascular cognitive impairment or vascular dementia. However, this would require linking the quantification of the cardiovascular effects of particulate pollution with quantitative evidence linking these cardiovascular endpoints to neurological outcomes. We have not reviewed evidence on the quantitative link between cardiovascular effects and dementia; such a review would be needed to establish whether an indirect approach to quantification of the effects of particulate pollution could be developed. We have summarised our conclusions in Chapter 6 and our recommendations for research in [Chapter 7](#).

## Chapter 6. Conclusions

### 6.1 Overview

We conclude that:

- I. The epidemiological evidence is suggestive of an association between exposure to ambient air pollutants and both the risk of developing dementia and acceleration of cognitive decline. The epidemiological literature is inconsistent as to which pollutant is most associated with these effects.
- II. There is evidence that air pollution, particularly particulate air pollution, increases the risk of cardiovascular, including cerebrovascular, disease. These diseases are known to have adverse effects on cognitive function. It is therefore our view that there is likely to be a causal association between particulate air pollution and effects on cognitive function in older people.
- III. The evidence base is currently inadequate to allow direct quantification using a meta-analysis of epidemiological studies linking air pollution with cognitive decline or dementia. Direct quantification of cognitive impairment or dementia associated with air pollution would therefore be subject to unknown uncertainty.
- IV. It may be possible to develop an indirect method of quantification of cognitive effects secondary to the effects of particulate pollution on cardiovascular disease. This would require a review of evidence regarding the quantitative link between cardiovascular endpoints and effects on cognition.

These views are based on the following considerations:

### 6.2 Epidemiological evidence

- i). Associations between long-term average concentrations of air pollutants and increased cognitive decline and dementia have been reported in epidemiological studies.
- ii). The epidemiological evidence for such associations is fairly consistent.
- iii). The epidemiological evidence is less consistent as to which pollutant is most closely associated with these effects.

### 6.3 Mechanistic evidence

- iv). Reactive gaseous air pollutants such as sulphur dioxide, nitrogen dioxide and ozone are unlikely to reach the brain

- v). Very small particles have been found in the brains of people and experimental animals. The type of particles and their source require further investigation
- vi). Only a very small fraction of inhaled ultrafine particles reaches the bloodstream
- vii). Ultrafine particles in the blood may be able to cross the blood-brain barrier, although it is likely that only a small proportion of those deposited in the lung do so
- viii). Ultrafine particles can be transported, directly, to the part of the brain (the olfactory bulb) which transmits information on smell from the nose to the olfactory cortex
- ix). The brain does not appear to have well-developed processes for clearing particles: particles reaching the brain may remain there for some time, perhaps for a lifetime
- x). Particles translocated to the brain could cause damage via oxidative stress and inflammation
- xi). We consider the plausibility of, and evidence for, a mechanism involving direct toxicity to the brain from translocated particles contributing to effects on cognition and dementia to be, at present, unconvincing. This view is informed, in part, by the similar pathology in both hereditary and sporadic dementia
- xii). Experimental evidence suggests that activation of microglial cells and neurological effects occur in response to either particle or ozone exposure, and that indirect pathways seem to be involved. However, most of the available studies have used high doses and short-term exposures and their relevance to understanding neurodegeneration following long-term exposure to ambient concentrations is not clear
- xiii). It is accepted that exposure to particulate air pollutants is causally associated with cardiovascular, including cerebrovascular, disease. We think that associations between exposure to particulate matter and the onset and progression of cognitive decline and dementia are likely to be, at least in part, secondary to such effects

## 6.4 Possible influence of early life exposures

- xiv). There is some evidence to suggest that early life exposure to air pollutants leads to impairment of development of the blood-brain barrier and to the development of the interconnections between neurons that are necessary for normal development of cognitive functioning
- xv). Whether this leads to an increased risk of dementia in later life is not currently known. Further work in this area is needed

## Chapter 7. Research recommendations

We recommend that research be undertaken to further develop the evidence on this important topic. We recommend work in the following areas:

### Epidemiological studies on cognitive decline and dementia

1. Determining changes in health effects linked to changes, over time, in the pollution mixture.
2. Using existing UK cohorts (including the Lothian birth cohorts, the 1946 cohort and UK Biobank) to look, over a longer period than has been done previously, at the relationship between exposure to air pollution and cognition.
3. Implementing longitudinal studies including multiple cognitive testing and exposure measurements over a period of time to identify critical or sensitive periods within the life course.
4. Studying the effects of large variations in exposure to air pollutants to maximise statistical power in epidemiological analysis.
5. Determining associations between exposure to non-particulate pollutants and cognitive decline and dementia (for example, build the evidence base for nitrogen dioxide, and ozone exposure).
6. Undertaking epidemiological studies using similar designs (including similar methods of assessing exposure and outcome) to facilitate meta-analysis.
7. Investigating genetic susceptibilities to neurological effects of air pollutants.
8. Using mediation analysis to appraise possible mechanistic pathways.

### Imaging and pathological studies

1. Investigating the possible influence of air pollution on small vessel cerebrovascular disease (encompassing arterioles, through capillaries to venules), probably by a combination of imaging and pathological studies.
2. Assessing the contribution of different cardiovascular mechanisms, such as changes in cerebral vascular resistance, atherosclerosis, increased blood pressure, increased blood clotting on the risk of developing dementia and cognitive decline.
3. Assessing the association between air pollution and markers of pathological accumulation of A $\beta$  or hyperphosphorylated tau in older adults.

### Research on how the brain handles particulate matter

1. Examining the effects of air pollution upon the clearance of interstitial and cerebrospinal fluids from the brain, including the profile of inflammatory cells.
2. Determining how the brain handles external particles once these enter the brain, how these might be cleared from the brain, including the rate at which particles might be cleared from the brain.

3. Testing the hypothesis that inhalation of polluted air by rodents results in a failure of intramural periarterial drainage, accelerating the pathogenesis of cerebral amyloid angiopathy and Alzheimer's disease.
4. Using labelled or model particles to ascertain the route of entry of particles into the brain, and if this entry directly contributes to pathological effects and functional changes.

## Mechanistic research

1. Determining whether reaction products of gaseous pollutants are able to access and enter the brain.
2. Investigating possible indirect pathways by which exposure to air pollutants may elicit neurological responses.
3. Assessing the effects of realistic doses of, and longer exposures to, air pollutants.

## Neurological effects of fetal exposure to pollutants

1. Exploring associations between maternal exposure to air pollution and direct measures of fetal brain growth, including the potential mechanisms.
2. Exploring the effects of maternal exposure to PM on the presence of PM in either the fetus or the placenta in animal models.

## Quantification

1. Exploring methods for indirect quantification of effects of particulate air pollution on vascular cognitive impairment and vascular dementia via effects on the cardiovascular system. Such work should include a review of evidence providing a quantitative link between effects on the cardiovascular system and dementia.

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# Appendix 1. Terms of reference for the COMEAP sub-group on the effects of exposure to air pollutants on cognitive decline and dementia

## A1.1 Aims

To develop a draft report on the evidence linking exposure to air pollution with effects on cognitive decline and dementia, for consideration by COMEAP. The report should discuss:

- the strength of evidence of associations from epidemiological studies
- possible biological mechanisms
- evidence that air pollution elicits these effects via these mechanisms
- members' views on whether air pollutants are likely to play a contributory role in accelerating cognitive decline in adults and causing dementia

## A1.2 Background

The relationship between exposure to air pollution and effects on cognitive function, cognitive decline and dementia has gathered increasing scientific interest in the past few years. Five review papers assessing the relationship between air pollution and cognitive function and decline have been published in the past 2 years (Clifford et al, 2016b; Killin et al, 2016b; Peters et al, 2015; Power et al, 2016; Tzivian et al, 2015b), with 2 focusing specifically on dementia (Killin et al, 2016b; Power et al, 2016).

All the reviews agree that, although insufficient evidence is available to make robust conclusions, the existing evidence supports an association between air pollution and cognitive impairment as well as a relationship between air pollution exposure and dementia. In addition, 2 recently published large population-based cohort studies, which were not included in the previous literature reviews, have identified effects of air pollution on cognitive decline and dementia. A study in Canada has reported an increased risk of dementia for people living in close proximity (<200 metres) to a major road, with risk decreasing with increasing distance (Chen et al, 2017b). A study on the Heinz Nixdorf Recall Study cohort found amnesic and overall mild cognitive impairment were associated with increased PM<sub>2.5</sub> and PM<sub>2.5</sub> absorbance (equivalent to black carbon, a diesel tracer)(Tzivian et al, 2016).

The scientific literature suggests possible toxicological mechanisms which could be responsible for the decline of the cognition function and incidence of dementia observed in people exposed to air pollution. These include neuroinflammation (Brockmeyer and D'Angiulli, 2016), accumulation of amyloid  $\beta$ 42(Calderón-Garcidueñas et al, 2012), stimulation of apoptosis

(Sama et al, 2007), reduced brain volume (Wilker et al, 2015), and white matter lesions (Guxens and Sunyer, 2012) among others.

## A1.3 Proposed terms of reference and questions to be addressed

The Committee is asked to assess the strength of evidence for hazard. Based on the available epidemiological and mechanistic evidence, what is the Committee's view on:

- i). The strength and consistency of the epidemiological evidence for associations of air pollutants with cognitive decline and dementia?
- ii). Are there biologically plausible mechanisms by which air pollutants could contribute causally to cognitive decline and dementia?
- iii). How strong is the evidence that air pollutants act via these mechanisms to cause these effects?
- iv). Based on the available evidence, which pollutants are most likely to be causally related to these effects?
- v). Does the evidence indicate at which points in the life-course exposure might be most relevant?
- vi). What future research work would the Committee recommended to increase the understanding of this topic?

The Committee is also invited to consider whether the evidence is sufficient to propose that a QUARK working group be established to consider quantification of cognitive decline and dementia associated with air pollution in the UK. In coming to this view, it may wish to consider:

- vii). For which pollutants and endpoints?
- viii). Any existing approaches which have been used, by others, to quantify these effects.

## A1.4 Scope of the work

It is suggested that consideration of the epidemiological evidence is largely based on recent published reviews (Clifford et al, 2016b; Killin et al, 2016b; Peters et al, 2015; Power et al, 2016; Tzivian et al, 2015b), supplemented by recent large population-based cohort studies (Chen et al, 2017b; Tzivian et al, 2016), which were not included in previous reviews.

The mechanistic evidence has not been reviewed thoroughly in the published literature, but will be important in reaching a view on the effects of air pollution on cognitive decline and dementia.



The working group will take a systematic approach to identifying the relevant literature, but a full systematic review is likely beyond its resources.

The sub-group's discussion should present the available evidence in the context of current UK pollution mixture, including consideration of recent and likely future changes in that mixture.

## A1.5 Resources

A COMEAP Sub-group will be formed to review the current evidence linking air pollutants with effects on cognitive decline and dementia. This will largely comprise current COMEAP Members, but a need to co-opt additional specialist expertise (for example, in relevant biological mechanisms and dementia or geriatric medicine) has been identified.

Dr Juana Maria Delgado-Saborit (University of Birmingham) will lead this work on behalf of the Secretariat, with support from Alison Gowers (COMEAP Secretariat).

## A1.6 Timescales

The COMEAP Sub-group on the Effects of Air Pollutants on Cognitive Decline and Dementia will be established during June 2017. Regular follow-up meetings of the group will be organised (the frequency of meetings will be decided at the first sub-group meeting).

The sub-group should aim to bring an initial view on the evidence, and a draft statement, for discussion at the COMEAP meeting in late February/early March 2018. Following further refinement by the Sub-group (if necessary), it is expected that a final statement will be agreed for publication at the COMEAP meeting to be held in June 2018.

## A1.7 Proposed outputs

A COMEAP statement on hazard is anticipated to be ready for publication by August 2018. This should include discussion of the epidemiological evidence and also the evidence on biological mechanisms.

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## Appendix 2. Glossary of terms and abbreviations

This report contains a large number of technical terms. A number of terms are defined, on first usage, in the text and have not been included here. Terms that are in everyday use, for example diabetes and hypertension, have also not been included.

| Term                                | Meaning                                                                                                                                                                                                                                       |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ABB                                 | Air-blood barrier                                                                                                                                                                                                                             |
| Abluminal (cell) membrane           | The surface of an endothelial (qv) cell not in contact with the blood                                                                                                                                                                         |
| ACE                                 | Angiotensin-converting enzyme                                                                                                                                                                                                                 |
| AD                                  | Alzheimer's disease                                                                                                                                                                                                                           |
| Air-blood barrier (ABB)             | Comprises a thin layer of epithelial Alveolar Type 1 cells and endothelial cells of the pulmonary capillaries and a joint basement membrane which links the epithelial and endothelial layers. The ABB is of the order of 0.5µm in thickness. |
| Air Pollution Index (API)           | Composite index accounting for sulphur dioxide, nitrogen dioxide, particulate matter of <10µm in diameter (PM <sub>10</sub> ), carbon monoxide, and ozone concentrations.                                                                     |
| Alveolar Type I (ATI) cells         | ATI cover the vast majority of the alveolar surface (approximately 95%) and are the essential cells of the gas exchange barrier.                                                                                                              |
| Alveoli                             | Small terminal air spaces of the lung                                                                                                                                                                                                         |
| Alzheimer's disease                 | A form of dementia, see <a href="#">Chapter 2</a>                                                                                                                                                                                             |
| Amyloid                             | Aggregation of protein molecules forming a dense material which surrounds cells and stains, histologically, in the same way as starch: for example, with iodine.                                                                              |
| Amyloid-β peptide (Aβ)              | Peptides of 36 to 43 amino acids involved in the formation of plaques in the brain in Alzheimer's disease.                                                                                                                                    |
| Angiogenesis                        | The development of blood vessels                                                                                                                                                                                                              |
| Angiotensin Converting Enzyme (ACE) | An enzyme which converts angiotensin I to angiotensin II. Involved in the control of blood pressure.                                                                                                                                          |
| ApoE ε4 allele                      | The Apo (apolipoprotein) gene occurs in a variety of forms. The ε4 variant occurs more frequently in patients with Alzheimer's disease.                                                                                                       |

| Term                                   | Meaning                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Arteriosclerosis                       | Disease characterised by hardening of the walls of arterioles (small branches of arteries), commonly found in hypertension and diabetes mellitus.                                                                                                                                                                                                                                |
| Astrocyte                              | A cell type found in the brain. Astrocytes are one of the 3 types of glial cells. Astrocytes are found in close association with neurons and capillaries. Among other functions, they provide biochemical support to endothelial cells that form the blood-brain-barrier and neurons, regulate extracellular ion balance and modulate synaptic transmission.                     |
| Atheroma                               | Degeneration of the walls of arteries and arterioles involving the deposit of fatty material in the walls of the vessels.                                                                                                                                                                                                                                                        |
| Atheromatous plaques                   | Areas of fatty material found in the walls of blood vessels (see Atheroma)                                                                                                                                                                                                                                                                                                       |
| Atherosclerosis                        | Disease characterised by the accumulation of atheroma (qv) in the walls of arteries.                                                                                                                                                                                                                                                                                             |
| ATI                                    | Alveolar Type I cells                                                                                                                                                                                                                                                                                                                                                            |
| ATP                                    | Adenosine triphosphate                                                                                                                                                                                                                                                                                                                                                           |
| ATP-binding cassette (ABC) transporter | A protein molecule that controls the movement of lipids (cholesterol and phospholipids) in the brain.                                                                                                                                                                                                                                                                            |
| BAL                                    | Bronchoalveolar lavage                                                                                                                                                                                                                                                                                                                                                           |
| Basal ganglia                          | Collections of neurons (nuclei) found deep in the forebrain: including the caudate nucleus and the putamen, the globus pallidus, the ventral striatum (nucleus accumbens and olfactory tubercle), the subthalamic nuclei and the substantia nigra (qv). Involved in the control of movement. Parkinson's disease is characterised by a loss of dopamine in the substantia nigra. |
| Black Carbon (BC)                      | Particulate matter found in ambient air which contains a high percentage of inorganic carbon; produced during incomplete combustion of fossil fuels, for example, by diesel engines. Measured by techniques based on colour, for example by reflectance.                                                                                                                         |
| Black Smoke (BS)                       | Non-reflective (dark) particulate matter, measured by the smoke stain method.                                                                                                                                                                                                                                                                                                    |
| BDNF                                   | Brain-derived neurotrophic factor                                                                                                                                                                                                                                                                                                                                                |

| Term                                         | Meaning                                                                                                                                                                                                                                 |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Blood-brain barrier (BBB)                    | The functional barrier which separates the cells of the brain from the blood.                                                                                                                                                           |
| BMI                                          | Body mass index                                                                                                                                                                                                                         |
| Brain-derived neurotrophic factor (BDNF)     | BDNF increases brain plasticity and is thought to be linked to enhanced cognition and improved memory function.                                                                                                                         |
| BS                                           | Black Smoke                                                                                                                                                                                                                             |
| CAA                                          | Cerebral amyloid angiopathy                                                                                                                                                                                                             |
| CAP/ CAPs                                    | Concentrated ambient particulate matter                                                                                                                                                                                                 |
| C-reactive protein                           | A marker of inflammation, produced by the liver and found in the blood.                                                                                                                                                                 |
| Cardiovascular disease                       | Disorders of the heart and secretory system. Ischaemic heart disease (IHD) and cerebro-vascular disease (CBD) are 2 of its major subdivisions.                                                                                          |
| Caudo-rostral                                | Term used to indicate direction within the central nervous system: from the spinal cord and brain stem to the frontal parts of the brain.                                                                                               |
| Chaperone molecules                          | Proteins that assist in the assembly of other macromolecules                                                                                                                                                                            |
| Chronic Obstructive Pulmonary Disease (COPD) | Group of lung conditions in which there is limitation to the flow of air along the airways of the lungs because of airways narrowing, often a combination of chronic bronchitis and emphysema.                                          |
| CI                                           | Confidence interval                                                                                                                                                                                                                     |
| Circumventricular organs                     | A series of structures found in association with the ventricular system of the brain, including the area postrema of the fourth ventricle and the vascular organ of the lamina terminalis. Characterised by a weak blood-brain barrier. |
| Coding ability                               | The skill of finding appropriate rules for converting a piece of information into another form or representation, for example, symbols or letters.                                                                                      |
| Cognitive function                           | The capacity for logical thought                                                                                                                                                                                                        |
| Cohort study                                 | An epidemiological technique involving the study of a defined group, cohort, of subjects over time.                                                                                                                                     |
| CNS                                          | Central nervous system                                                                                                                                                                                                                  |
| COMEAP                                       | Committee on the Medical Effects of Air Pollutants                                                                                                                                                                                      |

| Term                     | Meaning                                                                                                                                                                                                                                          |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Conducting airways       | The airways of the lung which conduct air to and from the gas exchange region of the lung.                                                                                                                                                       |
| Confidence interval (CI) | A measure of the precision with which a result is known. It provides the range of values within which the true population result is likely to lie (usually with 95% probability) assuming no bias in the studies used to determine the estimate. |
| Constructional praxis    | To assemble, join, or articulate independent parts to form a single unitary structure. For example, building a tower out of blocks.                                                                                                              |
| COPD                     | Chronic Obstructive Pulmonary Disease: Group of lung conditions in which there is limitation to the flow of air along the airways of the lungs because of airways narrowing; often a combination of chronic bronchitis and emphysema.            |
| Cortex                   | The outer layers of the brain which contain masses of neuron cell bodies.                                                                                                                                                                        |
| COX                      | Cyclooxygenase (marker of inflammation).                                                                                                                                                                                                         |
| Cranial nerve V          | The trigeminal nerve. A cranial nerve which supplies the muscles involved in mastication as well as providing sensory innervation to much of the head.                                                                                           |
| CSF                      | Cerebrospinal fluid                                                                                                                                                                                                                              |
| CVD                      | Cardiovascular disease                                                                                                                                                                                                                           |
| Cystatin                 | A marker of neurodegeneration                                                                                                                                                                                                                    |
| DEP                      | Diesel exhaust particles                                                                                                                                                                                                                         |
| Diabetes Mellitus (DM)   | Disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood.                                                     |
| DLB                      | Dementia with Lewy bodies                                                                                                                                                                                                                        |
| DM                       | Diabetes Mellitus                                                                                                                                                                                                                                |
| DNA                      | Deoxyribonucleic acid                                                                                                                                                                                                                            |
| Dopaminegic              | A term used to describe neurons that release dopamine at their axon terminals                                                                                                                                                                    |
| EC                       | Elemental carbon                                                                                                                                                                                                                                 |
| EM                       | Electron microscopy                                                                                                                                                                                                                              |
| Endothelium              | The thin layer of cells that line blood vessels                                                                                                                                                                                                  |

| Term                                          | Meaning                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epithelium                                    | A histological term used to describe single and multiple layers of cells, for example the lining of the airways and gut.                                                                                                                                                                                         |
| ETS                                           | Environmental tobacco smoke                                                                                                                                                                                                                                                                                      |
| FDR                                           | False discovery rate                                                                                                                                                                                                                                                                                             |
| Fenestrated endothelium                       | The cells of the endothelium of some capillaries are characterised by small holes which allow the passage of fluid: for example, in the glomeruli of the kidney. The capillaries of the brain are not fenestrated.                                                                                               |
| Fine motor skills                             | The control of the small muscles in the fingers for grasping and manipulation.                                                                                                                                                                                                                                   |
| Fronto-temporal cortex                        | That part of the cerebral cortex covering the frontal and temporal lobes of the brain.                                                                                                                                                                                                                           |
| GABA                                          | Gamma-Aminobutyric acid                                                                                                                                                                                                                                                                                          |
| Glia                                          | The supporting cells of the central nervous system including astrocytes (qv), microglia (qv) and oligodendrocytes which produce myelin. The word glia means glue: early workers thought the cells provided the glue that held neural tissue together; it is now known that their functions are many and various. |
| Greenness                                     | A term used to describe an environment characterised by grassy spaces and trees: for example, parks.                                                                                                                                                                                                             |
| Grey matter (GM)                              | The parts of the brain and spinal cord characterised by a high density of neuron cell bodies.                                                                                                                                                                                                                    |
| GM                                            | Grey matter                                                                                                                                                                                                                                                                                                      |
| Hazard Ratio (HR)                             | A ratio defined as the observed risk divided by the expected risk. For example, long term exposure to fine particulate air pollution increases the risk of cardiovascular disease: the hazard ratio for heart attacks is increased.                                                                              |
| HDL                                           | High density lipoprotein                                                                                                                                                                                                                                                                                         |
| Hippocampus                                   | A part of the brain involved in memory function. Named for the similarity between its curled structure and the tail of the sea horse: the hippocampus.                                                                                                                                                           |
| Hopkins Verbal Learning Test-Revised (HVLT-R) | Used to test for immediate recall, short-term memory and working memory.                                                                                                                                                                                                                                         |
| HVA                                           | Homovanillic acid                                                                                                                                                                                                                                                                                                |
| HVLT-R                                        | Hopkins Verbal Learning Test-Revised                                                                                                                                                                                                                                                                             |

| <b>Term</b>                     | <b>Meaning</b>                                                                                                                                                                                                                                                                  |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hypoxia                         | A pathological state characterised by a reduced level of oxygen                                                                                                                                                                                                                 |
| ICD-9 codes                     | The Ninth revision of the International Classification of Disease                                                                                                                                                                                                               |
| ICD-10 codes                    | The Tenth revision of the International Classification of Disease                                                                                                                                                                                                               |
| IHD                             | Ischaemic heart disease                                                                                                                                                                                                                                                         |
| IL                              | Interleukine                                                                                                                                                                                                                                                                    |
| Infarction                      | Death of an area of tissue caused, for example, by interruption of its blood supply                                                                                                                                                                                             |
| IPAD                            | Intramural periarterial drainage                                                                                                                                                                                                                                                |
| IQR                             | Interquartile range                                                                                                                                                                                                                                                             |
| Ischaemia                       | A pathological state in which tissue is totally or partially deprived of its blood supply                                                                                                                                                                                       |
| Kriging                         | A statistical method of interpolation based primarily on empirical observations                                                                                                                                                                                                 |
| Land use regression model (LUR) | The land use regression model is an exposure assessment tool frequently used in air pollution epidemiological studies to estimate the concentration of air pollution at unmonitored locations.                                                                                  |
| Longitudinal studies            | A longitudinal study is a research design that involves repeated observations of the same variables over time.                                                                                                                                                                  |
| LUR                             | Land use regression model.                                                                                                                                                                                                                                                      |
| Lymph node                      | A small organ, organelle, found along the path of lymphatic vessels. Contains lymphocytes and macrophages and is involved both in the filtration of lymph and in the mounting of an immune response. The lymph nodes of, for example, the groin swell when the leg is infected. |
| Macrophage                      | A cell type found in the blood and in other tissues: involved in the removal of bacteria and particulate matter.                                                                                                                                                                |
| MCI (Mild cognitive impairment) | Refers to cognitive decline that is not sufficient for a diagnosis of dementia – the boundary between these 2 definitions is often unclear.                                                                                                                                     |
| Meninges                        | The fibrous coverings of the brain and spinal cord including the outer dura mater, the intermediate                                                                                                                                                                             |



| Term                                                         | Meaning                                                                                                                                                                                                                                                                                                  |
|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                              | arachnoid mater and the pia mater which is closely applied to the surface of the neural tissue.                                                                                                                                                                                                          |
| Meta-analysis                                                | Statistical technique used to summarise the results of multiple studies of a given exposure-outcome relationship.                                                                                                                                                                                        |
| Microglia                                                    | A type of glial cell similar in function and origin to the macrophage                                                                                                                                                                                                                                    |
| Micro RNAs                                                   | A type of single-stranded ribonucleic acid (RNA), typically 20 to 25 nucleotides long, which is believed to downregulate the expression of genes.                                                                                                                                                        |
| Mitral cells                                                 | Cells found in the olfactory bulb, nerve fibres from the olfactory epithelium contact these cells. Named for similarity of appearance, in histological sections, to a bishop's mitre.                                                                                                                    |
| MMSE (Mini-Mental State Examination)                         | Global cognition test                                                                                                                                                                                                                                                                                    |
| MRI                                                          | Magnetic resonance imaging                                                                                                                                                                                                                                                                               |
| Mucociliary escalator                                        | The surface cells of the conducting airways carry cilia. These propel a sheet of mucus from deep within the lung to the larynx from whence it is expectorated or swallowed. Dust particles are removed from the lung by the moving layer of mucus: hence escalator.                                      |
| NATA (U.S. EPA National-Scale Air Toxics Assessment Program) | Estimates ambient concentrations of around 50 of the more prevalent and higher risk hazardous air pollutants from emission inventories using a blend of chemical transport models with a dispersion model (AERMOD).                                                                                      |
| Neocortex                                                    | The most recently evolved part of the cerebral cortex, reaches its largest size in man. The phylogenetically older parts of the cortex are the archicortex (hippocampus and associated structures) and the paleocortex (that part of the cortex (pyriform lobe in lower mammals) involved in olfaction). |
| NHIRD                                                        | National Health Insurance Research Database (NHIRD) of Taiwan                                                                                                                                                                                                                                            |
| Nitrogen dioxide (NO <sub>2</sub> )                          | Gas produced during combustion by the oxidation of atmospheric nitrogen.                                                                                                                                                                                                                                 |
| NSE                                                          | Neuron-specific enolase                                                                                                                                                                                                                                                                                  |
| Odds Ratio (OR)                                              | A measure of association between an exposure (for example, air pollution) and disease outcome which                                                                                                                                                                                                      |

| Term                    | Meaning                                                                                                                                                                                                                                  |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                         | compares the odds of disease of those exposed to the odds of disease those unexposed. Often approximates the ratio of rates of disease in exposed to unexposed.                                                                          |
| Olfaction               | The sense of smell                                                                                                                                                                                                                       |
| Olfactory cortex        | That part of the cerebral cortex involved in the appreciation of odour. Includes the well developed pyriform lobe in rodents and is represented by the uncus, limen insulae and parahippocampal gyrus in man.                            |
| Olfactory epithelium    | The sensory epithelium lying high in the nasal cavity. It contains the primary sensory neurons of the olfactory system.                                                                                                                  |
| Olfactory nerves        | The olfactory nerves are bundles of axons running from the primary sensory neurons of the olfactory epithelium to the olfactory bulbs.                                                                                                   |
| Olfactory bulbs (OB)    | Small oval bodies lying beneath the frontal lobes of the brain and above the nasal cavity, attached to the brain by the olfactory tracts which run to the parts of the cerebral cortex involved in the appreciation of odours.           |
| Olfactory pathway       | The neuronal pathway taken by impulses generated, first, in the primary olfactory neurons. The pathway contains a number of synapses including those which occur in the olfactory bulbs.                                                 |
| OR                      | Odds Ratio                                                                                                                                                                                                                               |
| Ozone (O <sub>3</sub> ) | Tri-atomic form of oxygen. An oxidant gas produced by the photochemical breakdown of nitrogen dioxide (NO <sub>2</sub> ) to nitric oxide (NO) and an activated oxygen atom (O•) that reacts with oxygen to form ozone (O <sub>3</sub> ). |
| PAHs                    | Polycyclic aromatic hydrocarbons                                                                                                                                                                                                         |
| Parkinson's disease     | A degenerative disease of the substantia nigra (qv) characterised by a loss of dopamine producing neurons. Symptoms and signs of the disease include tremor, muscular rigidity, lack of facial expression and, in some cases, dementia.  |
| Particulate matter      | A collective term of (usually) very small solid or liquid particles of micrometre or nanometre dimensions.                                                                                                                               |
| PRR                     | Pattern recognition receptor                                                                                                                                                                                                             |
| PCR                     | Polymerase chain reaction                                                                                                                                                                                                                |
| Pia                     | The innermost layer of the meninges (qv)                                                                                                                                                                                                 |

| Term                                                    | Meaning                                                                                                                                                                                                                                                                          |
|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PM                                                      | Particulate matter                                                                                                                                                                                                                                                               |
| PM <sub>2.5</sub>                                       | Particulate matter of <2.5µm aerodynamic diameter                                                                                                                                                                                                                                |
| PM <sub>10</sub>                                        | Particulate matter of <10µm aerodynamic diameter                                                                                                                                                                                                                                 |
| Polychlorinated biphenyls                               | Chlorine containing organic compounds known to produce a range of toxicological effects and suspected of causing impairment of cognitive functioning in children.                                                                                                                |
| PET                                                     | Positron emission tomography                                                                                                                                                                                                                                                     |
| PVN                                                     | Paraventricular nucleus                                                                                                                                                                                                                                                          |
| Pyramidal cells                                         | Cells of the grey matter of the brain, prominent in the cerebral cortex including the hippocampus.                                                                                                                                                                               |
| QUARK (Quantification of Air Pollution Risks in the UK) | A subgroup of COMEAP                                                                                                                                                                                                                                                             |
| Random Effects (model)                                  | In epidemiology and statistics, a random effects model is a statistical model where the model parameters are random variables. RE models are used to determine summary estimates in meta-analyses, especially where there is heterogeneity in the results of individual studies. |
| Relative risk (RR)                                      | In epidemiology, the relative risk is the ratio of the probability of a health outcome in an exposed group to the probability of an outcome in an unexposed group. It is a rate multiplier.                                                                                      |
| ROS                                                     | Reactive oxygen species                                                                                                                                                                                                                                                          |
| RR                                                      | Relative risk                                                                                                                                                                                                                                                                    |
| Serial-digit learning test (SDLT)                       | Test (measuring attention and short-term memory)                                                                                                                                                                                                                                 |
| SD                                                      | Standard deviation                                                                                                                                                                                                                                                               |
| SEM                                                     | Scanning electron microscopy                                                                                                                                                                                                                                                     |
| SES                                                     | Socioeconomic status                                                                                                                                                                                                                                                             |
| SDLT                                                    | Serial digit learning test                                                                                                                                                                                                                                                       |
| Striatum                                                | Part of the basal ganglia (qv) including the caudate nucleus and the putamen (the globus pallidus is sometimes included), named for their striated appearance caused by nerve fibres running through the tissue.                                                                 |
| Stroke                                                  | A clinical event characterised by haemorrhage from, or blockage of, arteries of the brain. Damage to local neural tissue characteristically leads to paralysis. Dementia may occur after a stroke.                                                                               |

| Term                                       | Meaning                                                                                                                                                                                                                                                                |
|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Subcortical                                | The neural tissue lying deep to the cerebral cortex                                                                                                                                                                                                                    |
| Substantia nigra                           | A part of the basal ganglia characterised by the presence of neuromelanin (a pigment) which gives the tissue a dark appearance in histological sections. Dopamine is an important transmitter in the substantia nigra.                                                 |
| Synapse                                    | The point of contact between nerve fibres and the cell bodies or processes of neurons. Chemical transmitters are released from the terminals of the fibre running to the synapse, and either stimulate or inhibit the activity of the neuron contacted at the synapse. |
| Tau (tau protein)                          | A protein involved in the stabilisation of microtubules within neurons, known to be defective in Alzheimer's and Parkinson's diseases.                                                                                                                                 |
| Telomere                                   | A specific sequence of nucleotides at the end of chromosomes, known to decrease in length with age.                                                                                                                                                                    |
| Tight junctions                            | Intercellular junctions where the opposed cell membranes are brought into close contact with one another.                                                                                                                                                              |
| Time-series study                          | An epidemiological technique involving the correlation of events that occur in time: for example, the number of cases of admission to hospital and the levels of air pollutants over a series of days.                                                                 |
| TMT                                        | Trailmaking test                                                                                                                                                                                                                                                       |
| TNF- $\alpha$                              | Tumour necrosis factor alpha                                                                                                                                                                                                                                           |
| Trailmaking Test (TMT)                     | Test used to measure executive function                                                                                                                                                                                                                                |
| TSP                                        | Total suspended particulate matter                                                                                                                                                                                                                                     |
| Translocation                              | The movement of material from one location to another.                                                                                                                                                                                                                 |
| UCHL1                                      | C-terminal hydrolase L1                                                                                                                                                                                                                                                |
| UFP                                        | Ultrafine particles                                                                                                                                                                                                                                                    |
| Ultrafine particles (UFP)                  | Particles <100nm diameter                                                                                                                                                                                                                                              |
| UNICEF                                     | United Nations Children's Fund                                                                                                                                                                                                                                         |
| Vascular cell adhesion molecule-1 (VCAM-1) | VCAM-1 is expressed on cytokine-activated endothelium and helps regulate vascular adhesion and transendothelial migration of leukocytes (for instance, macrophages and T cells) during inflammatory processes.                                                         |
| VaD                                        | Vascular dementia                                                                                                                                                                                                                                                      |

| Term                                | Meaning                                                                                                                   |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Vascular dementia (VaD)             | A form of dementia caused by impairment of the blood supply to parts of the brain.                                        |
| VCAM-1                              | Vascular cell adhesion molecule-1                                                                                         |
| VCI                                 | Vascular cognitive impairment                                                                                             |
| Visuo-motor skills                  | The coordination of visual input and fine motor skills (qv) to produce actions.                                           |
| VMA                                 | vanillylmandelic acid                                                                                                     |
| VOCs                                | volatile organic compounds                                                                                                |
| White matter (WM)                   | That part of the brain and spinal cord which contains masses of nerve fibres but few neuron cell bodies.                  |
| White matter hyperintensities (WMH) | Lesions in periventricular and deep white matter, which have been associated with demyelination, gliosis and axonal loss. |
| WHO                                 | World Health Organization                                                                                                 |
| WM                                  | White matter                                                                                                              |
| µm                                  | Abbreviation for micrometre or micron (a unit of length).<br>1µm = one thousandth of a millimetre                         |
| µg/m <sup>3</sup>                   | Micrograms per cubic metre. 1µg = 1 millionth of a gram                                                                   |

## Appendix 3. Membership lists

### Membership of the Committee on the Medical Effects of Air Pollutants

**Chair** Professor Frank Kelly BSc PhD FRSB FKC

**Members** Dr Richard Atkinson BSc MSc PhD PG Cert HE  
Professor Anna Hansell BA Hons (Cantab), MB BChir, MRCP, MPH, PhD, FFPH  
Professor Alan R Boobis OBE PhD CBiol FSB FBTS  
Dr Nicola Carslaw BSc MSc PhD  
Ms Ruth Chambers MA MSc, OBE  
Dr Beth Conlan BSc MSc PhD  
Professor Jonathan Grigg BSc MBBS MRCP MD FRCPCH  
Professor Roy Harrison OBE PhD DSc CChem FRSC FRMetS HonFFOM  
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Dr Mike Holland BSc PhD  
Mr J Fintan Hurley MA  
Professor Debbie Jarvis MBBS MRCP MD FFPH  
Professor Robert L Maynard CBE FRCP FRCPPath FFOM (co-opted)  
Dr Mark Miller BSc PhD  
Professor Gavin Shaddick BSc MSc PhD (co-opted)  
Mr John Stedman BA  
Dr Heather Walton BSc DPhil  
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**Secretariat** Ms Alison Gowers BSc MSc (Scientific)

Dr Artemis Doutsis PhD, MEnvSc (Scientific)  
Dr Karen Exley BSc MSc PhD (Scientific)  
Dr Naomi Earl BSc PhD, MCIWEM, CEnv (Scientific)  
Dr Philippa Douglas BSc PhD (Scientific)  
Dr Christina Mitsakou BSc MSc PhD (Scientific)  
Dr Sarah Robertson BSc MSc PhD (Scientific)

Note that the lists above reflect those who were members of the Committee and the Secretariat at any point during the active period of the preparation of the report for discussion. This has been taken to be from the presentation of the proposed terms of reference in June 2017 until the last active discussion of the report in November 2019. In addition, members of the Secretariat who were actively involved in the finalisation of the report for publication have also been included.

## Membership of the Committee on the Medical Effects of Air Pollutants Sub-group on the Effects of Exposure to Air Pollutants on Cognitive Decline and Dementia

**Chair** Professor Robert L Maynard CBE FRCP FRCPATH FFOM

**Members** Professor Roxana Carare MD PhD (co-opted to sub-group)  
Professor Jonathan Grigg BSc MBBS MRCP MD FRCPCH  
Professor Nick Fox MD FRCP FMedSci (co-opted to sub-group)  
Professor Seth Love MBBCh PhD FRCP FRCPATH (co-opted to sub-group)  
Dr Ian Mudway BSc PhD (co-opted to sub-group)  
Professor Gavin Shaddick BScMSc PhD

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Ms Alison Gowers BSc MSc (Scientific)