World Health Organization

European Region

Health risks of air pollution in Europe: HRAPIE-2 project

Updated guidance on concentration–response functions for health risk assessment of air pollution in the WHO European Region

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Abstract

Air pollution remains the leading environmental health risk both regionally and globally, contributing to reduced life expectancy and a wide range of noncommunicable diseases. Health risk assessment is a critical tool for quantifying the effects of air pollution and informing evidence-informed clean air and climate change mitigation policies. This document updates the 2013 *Health risks of air pollution in Europe* report and provides up-to-date guidance on concentration–response functions and associated information for key pollutants (particulate matter, ozone and nitrogen dioxide) and health outcomes to support the assessments of effects from different exposure durations. Based on comprehensive systematic reviews and other evidence syntheses, it includes guidance for a large number of mortality and morbidity outcomes, thus enabling more comprehensive assessments. Although this guidance is intended for the WHO European Region, its evidence base and suggestions can be considered broadly relevant to other WHO regions. This work supports WHO regional and global policy frameworks, including the Budapest Declaration on Environment and Health, by enhancing Member States' capacity to assess the health effects and economic costs of air pollution and take action.

Keywords

AIR POLLUTANTS, ENVIRONMENTAL HEALTH, EVIDENCE-BASED PRACTICE, HEALTH POLICY, NITROGEN DIOXIDE, OZONE, PARTICULATE MATTER

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Abbreviations

ALRI	acute lower respiratory infection
AQG	air quality guideline (level)
CI	confidence interval
COMEAP	Committee on the Medical Effects of Air Pollutants (United Kingdom)
COPD	chronic obstructive pulmonary disease
CRF	concentration–response function
EEA	European Environment Agency
ELAPSE	Effects of Low-Level Air Pollution: a Study in Europe
EMAPEC	Estimating the Morbidity from Air Pollution and its Economic Costs (project)
GAINS	Greenhouse Gas – Air Pollution Interactions and Synergies (model)
GBD	Global Burden of Disease
HRA	health risk assessment
HRAPIE	Health risks of air pollution in Europe (project)
HRAPIE-2	update of Health risks of air pollution in Europe (project)
IARC	International Agency for Research on Cancer
ICD-10	10th revision of the International Classification of Diseases
IHD	ischaemic heart disease
IIASA	International Institute for Applied Systems Analysis
ISA	Integrated Science Assessment (United States Environmental Protection Agency)
MCC	Multi-Country Multi-City (Collaborative Research Network)
O_3	ozone
NO_2	nitrogen dioxide
PAF	population attributable fraction
PI	prediction interval
$PM_{2.5}$	particulate matter, where particles have an aerodynamic diameter equal to or less than 2.5 µm
PM_{10}	particulate matter, where particles have an aerodynamic diameter equal to or less than 10 µm
RAD	restricted activity day
RR	relative risk
SOMO35	sum of ozone daily maximum 8-hour moving means over 35 parts per billion
US EPA	United States Environmental Protection Agency

1. Introduction

1.1 Health risk assessment of air pollution

Air pollution is the largest environmental risk factor for health and contributes to a wide range of health problems. Globally, household and outdoor air pollution are estimated to be responsible for approximately 6.7 million attributable deaths and 180 million disability-adjusted life-years each year (according to 2019 data) and, thus, rank among the leading causes of morbidity and mortality. The adverse health effects include reduced life expectancy and cardiovascular and respiratory diseases, as well as lung cancer. Additionally, emerging evidence suggests links to conditions such as type 2 diabetes and neurological disorders (WHO, 2024).

Within the WHO European Region, air pollution also remains the most significant environmental health risk, mainly contributing to the burden of noncommunicable diseases. In 2019 alone, ambient air pollution was responsible for an estimated 569 000 deaths, while household air pollution from solid fuel or kerosene combustion contributed to an additional 182 000 lives lost. Further insights into the health burden reveal that of the 10 million disability adjusted life-years attributed to ambient air pollution in 2019, ischaemic heart disease (IHD) accounted for a substantial proportion (62%), followed by stroke (18%), with lower respiratory infections, chronic obstructive pulmonary disease (COPD), and trachea, bronchus and lung cancer collectively contributing to an additional 20% (WHO, 2024). Moreover, ambient air pollution, primarily particulate matter with an aerodynamic diameter of $\leqslant$ 2.5 μm ($PM_{2.5}$), has been designated as carcinogenic by the International Agency for Research on Cancer (IARC) (Straif et al., 2013). The accumulated evidence clearly demonstrates the serious health risks of air pollution and supports calls for immediate action through policies that are based on the best available, up-to-date research.

One of the key approaches to translate research findings into practical information for policy formulation is the use of health risk assessments (HRAs) of air pollution. Quantitative estimation of the health effects of air pollution has become an increasingly important tool that allows technical experts and policy-makers to design and implement more effective and efficient policies to mitigate air pollution. An HRA of air pollution aims to "estimate the risks of past, current or future exposure to air pollution and of changes in exposure that may result from planned policies or other modifications of air quality" (WHO Regional Office for Europe, 2016). In other words, an HRA can provide "information about the usefulness of policy measures to reduce air pollution (the 'impact' of policies) [and] the scale of the problem (the 'burden' imposed on public health)" (COMEAP, 2010). Even in the absence of reliable data on incidence of a disease in a population, an HRA can be used to estimate the health burden in terms of the population attributable risk, that is, the proportion (or percentage) of cases that can be attributed to exposure in the population. Some assessments are also followed by calculation of the economic value of the health benefits that result from a policy change. It is important to recognize that an HRA typically estimates those health effects that can be quantified with a certain level of certainty, provided that a reliable concentration–response function (CRF) is available

(WHO Regional Office for Europe, 2016). A CRF can be defined as a statistical function or model based on the results of epidemiological studies to estimate the relative risk (RR) from air pollution for a health outcome in a population for a given increment in concentration. The RR is used as an equivalent measure of association to a hazard ratio or odds ratio that may have informed the systematic reviews and meta-analyses. The WHO Regional Office has published several relevant documents that provide more in-depth information on the principles and methods of HRAs (WHO Regional Office for Europe, 2000a, 2000b, 2014, 2016). Regarding health burden calculations, WHO has published key reports on the standard methodology and regularly updates global, regional and country estimates (WHO, 2024 and references therein).

In addition to well-established methodological approaches, the past 15 years have seen an increased demand for guidance on the selection and application of parameters and inputs to inform these assessments (Forastiere et al., 2024a). In response, in 2013 the WHO Regional Office for Europe published the *Health risks of air pollution in Europe: HRAPIE project* (WHO Regional Office for Europe, 2013a). The guidance was supported by the *Review of evidence on health aspects of air pollution: REVIHAAP project* and provided CRFs for mortality and a limited number of morbidity outcomes, along with associated information to facilitate their use. In total, approximately 20 CRFs for different pollutant–outcome pairs and exposure durations were provided. The air pollutants addressed were $PM_{2.5}$, particulate matter with an aerodynamic diameter of ⩽ 10 µm (PM_{10}), ozone (O_3) and nitrogen dioxide (NO_2). Health experts involved in the project suggested several sensitivity analysis options to reflect the uncertainties of risk assessment (WHO Regional Office for Europe, 2013a, 2013b; Héroux et al., 2015).

This effort was followed by the updated *WHO global air quality guidelines*, which recommended the concentrations of air pollutants to be achieved to reduce health risk of air pollution, as well as CRFs and suggestions on the shape of these functions (WHO, 2021). The air pollutants covered were $PM_{2.5}$, PM_{10}, O_3, NO_2, sulfur dioxide and carbon monoxide.

Since completion of these projects, a large body of new evidence has emerged on the association of key air pollutants with both mortality and morbidity outcomes. The inclusion of a wider range of morbidity outcomes was recently identified as an enabler in the communication of risks and benefits in different types of assessments related to air pollution. In particular, the inclusion of morbidity outcomes in economic evaluations of air quality policies may enhance the communication of clean air benefits to decision-makers by paving the way for a direct comparison between the economic gains from reduced morbidity in market costs and investments into actions.

To support this approach, the Estimating the Morbidity from Air Pollution and its Economic Costs (EMAPEC) project –coordinated by WHO headquarters – was launched in October 2021 (WHO, 2025a). The project aims to "establish a methodology to estimate economic costs of selected morbidity outcomes of exposure to air pollution within a population [and test its application at] various geographical scales (national, regional and global)". Its main objectives are (i) the prioritization and review of the epidemiological literature on morbidity outcomes of air pollution and (ii) selection of CRFs for economically important diseases. The pollutants under review include $PM_{2.5}$, NO_2 and O_3.

Shortly after, an update of the Health risks of air pollution in Europe (HRAPIE) project (WHO Regional Office for Europe, 2013a), known as HRAPIE-2, was initiated in March 2022 with the aim to cover mortality-related CRFs and the relevant information needed to support their application in the WHO European Region.

Guidance from the HRAPIE-2 project aligns with the latest regional and global policy frameworks. At the Seventh Ministerial Conference on Environment and Health (in Hungary, July 2023), Member States in the WHO European Region endorsed the Budapest Declaration (WHO Regional Office for Europe, 2023). The Declaration and its roadmap emphasized the need for comprehensive action on environmental health challenges, including air pollution. It also highlighted the need for advancing knowledge to enable effective action. Countries made a commitment to update policies, including air quality standards, using WHO guidelines and tools. In support of the WHO fourteenth General Programme of Work (WHO, 2025b), the *Updated road map for an enhanced global response to the adverse health effects of air pollution* (2025–2030) also identified four key areas of action: knowledge and evidence, measuring progress, institutional capacity strengthening, and global leadership and coordination (WHO, 2025c). Each key area is accompanied by a sequence of actions, outputs and outcomes to guide governments that give a central role to HRA.

Therefore, this guidance document is essential to advance existing WHO priorities. The guidance also support the broader United Nations agenda, particularly the revision of the Gothenburg Protocol (UNECE, 2012), through their incorporation into the 2022–2023 workplan of the Joint WHO/Convention Task Force on the Health Aspects of Air Pollution under the United Nations Economic Commission for Europe's Convention on Long-range Transboundary Air Pollution (UNECE, 2021). HRA guidance from HRAPIE (WHO Regional Office for Europe, 2013a) and the 2021 *WHO global air quality guidelines* (WHO, 2021) is extensively used by other international institutions. This includes its application by the European Environment Agency in its annual *Air quality status report* (European Environment Agency, 2025), by the International Institute for Applied Systems Analysis (IIASA) for modelling under the UNECE Convention on Long-range Transboundary Air Pollution (UNECE, 1979) and by the IIASA on behalf of the European Commission (e.g. in the EU Thematic Strategy on Air Pollution and revision of the air quality directives) (European Commission, 2005, 2025; Klimont, 2025; IIASA, 2024). IIASA's Greenhouse Gas – Air Pollution Interactions and Synergies model has also been used for wider modelling efforts related to climate action, energy policy and the European Green Deal (European Commission, 2024). These CRFs are also included as the baseline options in the WHO AirQ+ software tool, which is recognized as one of the most used tools for estimating the health effects of air pollution (WHO Regional Office for Europe, 2025a). AirQ+ extends the impact of the guidance globally owing to its use in many assessments at the national and subnational levels (Amini et al., 2024). It also informs the Climate Change Mitigation, Air Quality and Health tool, known as CLIMAQ-H, which allows for estimations of the health and related economic gains achieved by implementing actions aimed at mitigating climate change by reducing domestic carbon emissions (WHO Regional Office for Europe, 2025b). Overall, the HRAPIE-2 guidance document is expected to provide HRA practitioners, technical experts and researchers with updated and much-needed guidance and, ultimately, to empower policy-makers by enabling them to make well-informed decisions regarding the formulation and implementation of clean air and climate change mitigation policies.

1.2 Development process for the HRAPIE-2 project

The development of the current guidance document, based on the HRAPIE-2 project, followed a rigorous process and involved several groups of individuals with well-defined roles, responsibilities and tasks. The process consisted of the following main steps: planning and formulation of the scope; a systematic review of the relevant evidence; assessment of the certainty level of the body of evidence; evaluation of the

epidemiological associations supporting the CRFs for risk quantification, as well as the functional shape of the CRFs; and determination of the exposure range applicable to each relevant CRF. Adherence to the principles guiding the development of WHO normative products was maintained at all stages.

The WHO Secretariat at the European Centre for Environment and Health was primarily involved in initiating, scoping, structuring, guiding and executing the process according to the principles and methods for the development of normative products. The document development group (comprising experts in environmental epidemiology and HRA working in different parts of Europe) was responsible for supporting the Secretariat in determining the scope of the document, selecting the pollutant–outcome pairs for consideration, developing the review questions; providing inputs to the systematic review team as needed; and appraising the evidence and formulating the guidance. In addition, the systematic review team conducted systematic reviews of evidence and the external review group provided input and review when needed.

Throughout the project, meetings were held: two in-person meetings in Bonn (Germany) on 15–16 April and 3–5 December 2024 and several online meetings when needed during the document development process. In addition, intensive exchanges took place via email and online collaborative tools.

All experts who participated in the process were asked to complete declaration of interest forms. None of the experts declared relevant or significant conflicts that required them to be excluded from their roles. The document development group reached decisions through consensus, facilitated by discussions led by the designated chair or co-chairs. The systematic review team conducted their reviews independently but maintained regular communication with the WHO Secretariat and the document development group to ensure that key issues were properly addressed. One member of the review team supported methodological aspects of the process and preparation of the final document. External review was conducted at different stages of the process. The external reviewers provided information on specific topics, peer-reviewed the protocol of the commissioned systematic reviews and the subsequent journal manuscripts, and/or commented on the draft guidance document. In particular, external review of the draft guidance document was managed through an online survey. In accordance with the established procedure, the review focused on identifying missing data, ambiguous content, factual errors and implementation-related issues, but not on changing the guidance. All comments received during the external review of the draft guidance document were thoroughly considered by the document development group and the WHO Secretariat, and the guidance document was revised where deemed appropriate.

A comprehensive list of pollutant–outcome pairs was selected for inclusion in two systematic reviews commissioned to the systematic review team. The list included long-term exposure and mortality pairs addressed in HRAPIE (WHO Regional Office for Europe, 2013a; Héroux et al., 2015), supplemented by those examined in the systematic reviews on long-term air pollution exposure and mortality that informed the *WHO global air quality guidelines* (WHO, 2021). Additionally, for long-term NO_2 exposure, the list was expanded to include mortality from all circulatory diseases and, separately, from IHD, cerebrovascular disease and lung cancer to reflect emerging evidence suggesting that the associations had increased since the most recent causality assessment published in 2016 (US EPA, 2016; Schneider et al., 2018; IRAS, 2022). Although HRAs typically focus on the long-term effects of air pollution, it was agreed to also update the CRFs for the short-term exposures and mortality associations included in HRAPIE by leveraging the comprehensive data from the Multi-Country Multi-City (MCC) Collaborative Research Network (coordinated by the London School of Hygiene and Tropical Medicine), where available (MCC Collaborative Research Network, 2025). These

extended meta-analytic models were chosen because they involve standardized analyses of local datasets and provide more granular information on segments of air pollutant concentrations than those obtainable from a standard systematic review of the published literature. The provision of some CRFs for short-term exposures was retained because they were included in HRAPIE and estimating their effects remained useful for specific purposes (e.g. assessing the effect of a certain number of days above an air pollutant level such as an air quality standard).

Overall, the metrics for short-term exposures were harmonized to an exposure time window of 24 hours (or 8 hours in the case of O_3) to align with the best available evidence and enhance the applicability of the guidance. Box 1 shows the mortality outcomes that were considered for each air pollutant.

Box 1. Longlist of pollutant–mortality pairs considered

Long-term exposure

$PM_{2.5}$, PM_{10} or NO_2 was paired with:

- natural mortality[1]
- circulatory disease
- IHD
- cerebrovascular disease
- respiratory disease
- COPD
- ALRI
- lung cancer.

O_3 was paired with:

- natural mortality
- respiratory disease
- COPD
- ALRI.

PM_{10} (additional) was paired with:

- post-neonatal mortality (age 1–12 months).

Short-term exposure

$PM_{2.5}$, NO_2 or O_3 was paired with:

- natural mortality.

O_3 (additional) was paired with:

- circulatory disease
- respiratory disease.

ALRI: acute lower respiratory infection.

For long-term exposures, the evaluation was based on results from commissioned systematic reviews that updated those informing the *WHO global air quality guidelines* (WHO, 2021), following identical procedures and including further harmonization and updates where necessary. A unified protocol for both systematic reviews was registered in PROSPERO in May 2023 (CRD42023425327) (PROSPERO, 2023). The systematic reviews included detailed descriptions of the methodology for $PM_{2.5}$ and PM_{10} (Orellano et al., 2024) and for

1 Natural mortality refers to deaths from all causes, excluding external or accidental causes such as injury, suicide or homicide.

NO_2 and O_3 (Kasdagli et al., 2024). They also provided assessments of the certainty level of evidence for each pollutant–mortality outcome pair and an evaluation of the shape of the associated CRFs. Regarding short-term exposures, the evaluation used the available results from relevant studies from the MCC Collaborative Research Network (2025).

Because the EMAPEC and HRAPIE-2 projects complement each other, the document development group decided to use the methods of the former for the following steps. To determine the confidence level of associations for each pollutant–outcome pair for risk quantification, consolidated and emerging causality considerations were used (Straif et al., 2013; US EPA, 2016, 2019, 2020, 2022; Schneider et al., 2018; IRAS, 2022), together with several criteria for assessing the confidence in the results of systematic reviews and meta-analyses (Table 1), according to a general procedure (Forastiere et al., 2024b). Based on this approach, CRFs were classified into three lists: core List A, where a reliable quantification of health effects is possible in an HRA; non-core List B+, where an HRA is possible, but there is greater uncertainty around the reliability of the CRF compared with the pollutant–outcome pairs on List A; and List B-, for those that cannot be advised at the time of the evaluation for application in an HRA because the strength of evidence is insufficient. To prevent the mechanistic application of these criteria, an integrative approach that considered all relevant dimensions of the selection process was employed. Box 2 provides a short overview of the structure and process of the EMAPEC project.

In addition to the evaluation of the confidence level in associations for risk quantification, the range of (in principle, annual) mean exposures (or median, as available in the primary studies) to which the CRFs would apply was evaluated. These ranges of me(di)an exposures represent concentrations where the CRFs are considered reliable, as the populations in the underlying epidemiological studies were exposed to similar levels. Ranges of me(di)an exposures were proposed only for List A and List B+ associations, and concentrations were rounded to the closest multiple of 10 or 5. Outside the proposed range, the same RR could be used for HRA but with a greater level of uncertainty because there is less evidence. Where an HRA is applied outside the proposed range, it is advised that it should be regarded as a sensitivity analysis (see section 1.3.3).

Part of the evidence analysis was an exploration of the heterogeneity of effects between WHO regions to check whether a region-specific CRF would be a more appropriate parameter for an HRA than the global one.

Lastly, it is important to note that the report provides guidance on the use of CRFs derived from total ambient concentrations of a given air pollutant rather than source-specific CRFs, since the former are supported by a much more extensive evidence base and have broader applicability, particularly where source apportionment data are limited or uncertain.

The report is organized into four chapters and two annexes. Following this Introduction, Chapter 2 focuses on CRFs and associated information for mortality outcomes. Drawn from the EMAPEC project, Chapters 3 and 4 summarize CRFs and other relevant information for morbidity outcomes and present key considerations for conducting an economic assessment, respectively. Annex 1 contains additional methodological details and Annex 2 contains supplementary tables and figures that support the main text.

Table 1. EMAPEC criteria for confidence in the results of systematic reviews and meta-analyses

Criterion		Comment
No.	Description	
Key criteria		
1i	Number of studies	For mortality, generally > 5
1ii	Statistical significance	Statistical significance ($P < 0.05$) of the meta-analysis result
Important criteria		
2i	Geographical coverage	Studies in the meta-analysis should be distributed across various continents/countries
2ii	Weight distribution in meta-analysis	The meta-analytic weights should be distributed across the studies to avoid to possibility that only a few (e.g. one third or less of the studies) contribute over two thirds of the overall sum of weights
2iii	Precision of the RR (CI/RR%)	The width of the 95% CI as a proportion of the central effect estimate should be < 100%
2iv	Heterogeneity (I^2)	I^2 should be < 75% or the lower bound of the 80% PI should not include the null hypothesis (PI > 1)
2v	Consistency of more recent studies	Recently published results (not in the systematic review) should be consistent with the systematic review/meta-analysis results. Divergent results should be discussed

CI: confidence interval; PI: prediction interval.
Source: data are taken from Forastiere et al. (2024b).

Box 2. Description of the EMAPEC project structure and process

The EMAPEC project involved two in-person meetings held on 23–25 April 2022 in Geneva (Switzerland) and 29–31 March 2023 in London (United Kingdom), as well as a number of online meetings and exchanges. The project was organized into five work packages: one focused on coordination led by WHO headquarters, while the other four were assigned to different academic and government institutions from Europe and beyond, with input from WHO. A detailed explanation of the selection of long-term exposure and morbidity outcome pairs considered in EMAPEC and the criteria for evaluating and classifying the associations and for determining their ranges of exposure can be found in Forastiere et al. (2024b). An additional number of short-term exposure and morbidity outcomes (including those related to restricted activity days (RADs)) were also selected. For outcomes related to RADs, a systematic review by Orellano et al. (2023) informed the selection of CRFs; for other short-term exposures, the project drew on a limited number of systematic reviews that had previously been considered by the Committee on the Medical Effects of Air Pollutants (COMEAP).

1.3 HRA: methodological considerations

HRAs incorporate uncertainties corresponding to choices relevant to the input parameters and beyond those associated with the choice of the RR. These uncertainties relate to the choice of baseline health data, exposure data, air pollutant metrics, counterfactuals and risk of double counting of health effects when assessing multiple exposures that share common health outcomes. This section provides some guidance on commonly encountered considerations related to HRA for air pollution health effects and explains the rationale for choices made in determining the proposed CRFs.

1.3.1 Background health data

The document development group noted the importance of using both mortality and morbidity health outcomes for HRAs of air pollution exposure. The quality of databases of the baseline health statistics that inform an HRA is crucial to the validity of the output estimates. Mortality data are based on national databases for vital statistics that are routinely collected and, hence, more widely available than morbidity data. Nevertheless, even the quality of mortality data may still pose issues when assessing spatial levels, such as in small city areas. In such cases, the group suggested to use baseline data for larger areas (e.g. at regional scale). In certain parts of the world where mortality registries may have quality issues, assessors should consider the uncertainties and refrain from basing effect calculations on inaccurate data.

The evidence base supporting this guidance consists of studies that primarily address all-cause mortality, and the RRs obtained were derived for this outcome. For HRAs, background data on natural mortality should be applied. If only all-cause mortality baseline data are available, it is proposed to estimate natural mortality as 95% of these. This estimate is based on data from European and North American countries that provide the most evidence in the proposed RRs in Chapter 2. Nevertheless, it is recognized that, in some cases, the population structure and background health may differ from those informing the RRs. It is clear that in these areas more research is needed, but until then the proposed RRs and approaches should be applied (and also for comparability with other regions).

Annex 1, Table A1.1 presents the proportion of natural mortality over all-cause mortality in several regions based on WHO 2019 health data (WHO, 2025d). The impact of using all-cause versus natural mortality baseline data for the HRA estimates is minimal compared with the impact of the other uncertainties underlying the HRA, including the quality of health and exposure data, uncertainty in the RR, and the potential of double counting of health effects from co-exposure to multiple air pollutants.

The availability and quality of morbidity (incidence) data vary by country. For most outcomes of interest, incidence data are lacking, except possibly for limited information on hospital admissions, but the available data are often incomplete and potentially inaccurate. Estimating approaches for incidence data have been proposed, for example in the 2015 and 2019 Global Burden of Disease (GBD) studies that developed methods for synthesizing epidemiological data to produce estimates of the global incidence and prevalence of disease (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016; GBD 2019 Diseases and Injuries Collaborators, 2020). In the case of a large uncertainty in the background morbidity data, the burden assessment should be restricted to calculating the population attributable fraction (PAF) (Forastiere et al., 2024b; WHO, 2025a).

This guidance does not aim to address all potential HRA applications; nevertheless, as there is growing concern about socioeconomic-specific analyses, it proposes that such applications should use group-specific exposures and baseline health data, if available, and, since there are no group-specific RRs, the advised global RR. However, it must be recognized that such an approach may ignore potential differences in the susceptibility of various socioeconomic groups to air pollution exposure. Nevertheless, any group-specific RR should be based on studies that address such groups in a consistent way (i.e. using a harmonized definition of the subgroups, which for socioeconomic status is a challenge). This would constitute a separate project and the feasibility of such a project would depend on the availability of relevant studies. Furthermore, any group-specific HRA would need to use group-specific background mortality data – which would be a challenge in most settings.

1.3.2 Exposure data

The considered studies examined associations between the risk of various health outcomes and ambient concentrations of air pollutants over specific time periods. It is important to clarify that in this context, the term **exposure** refers to these ambient (modelled or measured) concentrations of air pollutants (i.e. overall mass and not source-specific), which serve as a proxy for personal exposure from ambient sources. Ambient concentrations are more commonly used in epidemiological studies than metrics of personal exposure due to their availability and consistency. These studies capture the effects not only of outdoor exposure but also of indoor exposure to pollutants that infiltrate from outdoors. Additionally, studies of short-term exposure (such as time-series or case-crossover designs) focus on temporal variations in air pollutant levels, whereas studies of long-term exposure examine spatial variations, thus reflecting differences in pollution levels across geographical areas.

Common choices related to the exposure data used to inform an HRA include decisions on the metric of the pollutants (e.g. daily mean or daily maximum concentration), size of ambient particles and counterfactual scenarios associated with the pollutant of concern. These issues are addressed in the following subsections.

1.3.2.1 $PM_{2.5}$ and PM_{10}

While the document development group agreed to provide guidance for mortality outcomes resulting from long-term exposure to both $PM_{2.5}$ and PM_{10}, it proposed not to assess the effects of both particle fractions ($PM_{2.5}$ and PM_{10}) in a single HRA, and to use the proposed association for PM_{10} only $PM_{2.5}$ concentration data are unavailable. This is based on the United States Environmental Protection Agency (US EPA) (certain or likely) causality assessment for $PM_{2.5}$ (US EPA, 2019, 2022), which was stronger than the suggestive causality for the coarse fraction of PM_{10}, that is $PM_{10-2.5}$. Nevertheless, if data on $PM_{2.5}$ level are not available, then use of PM_{10} is proposed, based on the rationale that $PM_{2.5}$ is part of PM_{10} and, hence, the toxicity of the former will be reflected in the effects of the latter. This proposal entails fewer assumptions than the possibility to transform PM_{10} levels into $PM_{2.5}$ levels based on location-specific factors. Although ambient particles of varying sizes originate from different sources, $PM_{2.5}$ is considered a good indicator of a wide range of sources.

1.3.2.2 Choice of O_3 metric

Various metrics for O_3 have previously been used, including the daily maximum 1-hour mean, daily maximum of the 8-hour means, and sum of O_3 daily maximum 8-hour moving means over 35 parts per billion, or 70 µg/m^3 (SOMO35). For an HRA of short-term exposures, the document development group suggests using the daily maximum of the 8-hour mean because this metric was mostly used in the analysis that informed the proposed RR.

For an HRA long-term exposure to O_3, the group suggests using the annual mean of the daily maximum 8-hour means, since this was the most-used metric in the original studies that informed the RR.

1.3.3 Choice of counterfactual scenario and range of me(di)an exposure levels

In this report, the term **counterfactual scenario** refers to the assessed specific policy scenario, such as zero pollution, compliance with the air quality guideline (AQG) level or no anthropogenic pollution. The counterfactual scenario depends on the policy assessment being made, but the document development group instead proposes to calculate the benefits of reductions in air pollutant levels from existing levels down to the relevant WHO long-term AQG level and not to assess the current burden attributable to concentrations below the long-term WHO AQG level. Hence, the guidance is to use the relevant long-term AQG level for the pollutant of interest for a burden assessment and to use the policy target or long-term AQG level, whichever is larger, for an impact analysis. The rationale for using the AQG level in the proposed counterfactual approach is the larger degree of uncertainty below that level. Hence, it is the assessor's responsibility when applying HRAPIE-2-suggested RRs below the long-term AQG level to consider the exposure–outcome pairs, linearity of the association, etc. (see section 1.3.2). The proposed counterfactual approach of using the long-term AQG level recognizes the limits of the current knowledge and best evidence, and does not indicate that there are no health effects below the long-term AQG level.

Conducting the HRA for concentrations above the proposed upper limit of the indicated range is also associated with substantial uncertainty, since it is not well supported by epidemiological evidence. If such an analysis is conducted, it should be accompanied by a sensitivity analysis to evaluate the effect of including exposures that exceed the upper limit.

1.3.4 Avoiding double counting of the effects

There is concern that HRA estimates may be overestimated due to double counting in cases where HRA applications involve multiple air pollutants or multiple related health outcomes.

1.3.4.1 Between air pollutants

As the proposed RRs for an HRA are based on single pollutant models, the document development group agrees with the general practice of not adding pollutant-specific attributed estimated cases. Some general guidance is provided below for the potential combination of effects of the main pollutants (i.e. $PM_{2.5}$, NO_2 and O_3) in burden estimates. The same approach can be used to avoid double counting in impact assessments.

As noted in section 1.3.2.1, if data on both $PM_{2.5}$ and PM_{10} concentrations are available, the group favours the use of $PM_{2.5}$ in the HRA, although the choice between the two fractions may depend on the policy to be assessed and the exposure assessment method applied.

For assessment of the joint effects of $PM_{2.5}$ and NO_2, correlations between the concentrations of both pollutants are a concern. The group suggests using the approach proposed by Chen et al. (2024) to account for the effect of both pollutants, but only for calculating the pollution-attributable natural mortality. Detailed descriptions of the approach for deriving the revised RRs are provided in sections 2.1.1 and 2.2.1 and Annex 2. The revised RRs can then be applied to estimate the PAFs for each pollutant in the mixture, and then these PAFs may be summed to estimate the combined effect of $PM_{2.5}$ and NO_2 on natural mortality. The PAF estimate accounts for overlap and avoids the risk of double counting. To refine these estimates, simulations could be conducted to derive revised 95% confidence intervals (CIs) for the adjusted RRs. This approach ensures a robust assessment of uncertainty and provides more reliable evidence for policy-making.[2]

There is less concern about summing the estimates of effect on mortality outcomes following long-term exposure to O_3 and $PM_{2.5}/NO_2$ because only the association between annual exposure to O_3 and respiratory mortality was assigned to List B+. This summation should be considered a sensitivity analysis owing to the differential classification of the associations (List B+ for respiratory mortality and O_3 versus List A for natural and respiratory mortality and $PM_{2.5}$ and NO_2). Considering the low correlation between O_3 and $PM_{2.5}$, the group proposes that the output of the HRA for long-term O_3 exposure is added to the results for $PM_{2.5}$ exposure and natural or respiratory mortality. Similarly, if the policy addresses O_3 and NO_2, then the output of the HRA for O_3 exposure could also be added to the results of the HRA for NO_2 exposure and natural or respiratory mortality.

On the choice between assessing long-term or short-term exposure, the group agrees with the general practice of selecting long-term exposure for HRA. The situation is more complicated for O_3, where the evidence for short-term exposure is stronger than for long-term exposure and different health outcomes are proposed in each case: the guidance for short-term exposure relates to natural mortality and for long-term exposure relates to respiratory mortality. In all cases, specific policy questions may need to address the short-term effects, such as addressing health effects for days with air quality standard or daily AQG level exceedances.

1.3.4.2 On related health outcomes

If assessing multiple mortality outcomes in an HRA, the group suggests conducting a primary analysis for natural mortality and to consider cause-specific analysis as a secondary analysis. It should be noted that in the latter case, combining cause-specific outcomes is not advised when one outcome is part of another (of a larger category), for example, COPD and respiratory mortality outcomes because the former is part of the latter. The identification of such overlaps may be guided by the 10th revision of the International Classification of Diseases (ICD-10) codes. It is important to note also that the sum of cause-specific effects is not expected to add up to the overarching greater cluster. The misclassification issue may be a reason to choose the greater category.

2 Note that GBD uses a multiplicative approach for combining population-attributable fractions across multiple risk factors for the same outcome. This method operates under the assumption that risk factors are independent: it does not account for correlation between exposures and effect size modification or mediation that may occur between risk factors in a cluster (Lim et al., 2012).

1.3.5 Cessation lags

Regarding long-term health effects, since these arise from cumulative processes that affect health status, the reduction in the rate of health deterioration is not immediate once exposure ceases. Cessation lag refers to the period between the reduction or cessation of exposure to a harmful agent and the onset of measurable health benefits (such as reduced disease incidence or mortality). This is the reason why life-table methods are used for health impact assessments of interventions. Users can refer to Walton (2010), Chanel and Cucchi (2024) and US EPA (2025) for detailed discussions about cessation lags.

1.3.6 Preference for global RRs

The document development group prefers the use of global estimates because they are robust as a consequence of being derived from a broader and more diverse body of evidence.

1.3.7 Shape of the CRF

The systematic reviews of long-term exposure to air pollutants and mortality outcomes concluded that there is insufficient evidence for a departure from linearity within the applicable exposure ranges. Similar conclusions were reached for morbidity outcomes in the EMAPEC project (WHO, 2025a). In the case of CRFs for short-term exposures to air pollutants and mortality, Annex 2 provides graphical representations of CRF curves from the MCC Collaborative Research Network.

For detailed information on available subgroup analyses by WHO region and on the shapes of CRFs for mortality, see Liu et al. (2019), Vicedo-Cabrera et al. (2020), Meng et al. (2021), Kasdagli et al. (2024) and Orellano et al. (2024).

2. Mortality outcomes

All mortality outcomes, except for post-neonatal mortality (death in infants aged between 1 and 12 months) and long-term exposure to PM_{10}, were assessed among adults (mostly those aged 25 years and over) (Kasdagli et al., 2024; Orellano et al., 2024). For applications in HRAs, the lowest age of the (adult) target population will depend on the available population and mortality data, and the estimates (as number of attributable cases) will be determined by the background mortality. It is acknowledged that although in the WHO European Region and WHO Region of the Americas mortality rates in adults aged 18 years and over are the same as in those aged 25 years and over, this may not be the case in other parts of the world.

2.1 PM

2.1.1 Effects of long-term $PM_{2.5}$ exposure

Table 2 presents the proposed RRs and 95% CIs for mortality outcomes associated with long-term exposure to $PM_{2.5}$, along with the range of me(di)an exposure levels, within which the application of these RRs is advised. The range of median exposures in the studies that informed the natural mortality meta-analysis was 5–72 µg/m^3 (Orellano et al., 2024). Based on this, and using the mean and median indistinguishably, the proposed range of me(di)an exposures for the application of the RRs in HRA for all associations with $PM_{2.5}$ is from the AQG level (5 µg/m^3) to the maximum me(di)an in the studies included in the natural (all-cause) mortality meta-analysis, rounded to the nearest multiple of 5, i.e. 70 µg/m^3 (Annex 2, Fig. A2.1; based on Orellano et al. (2024), Table 1). The document development group proposes to use the same range for all other cause-specific RRs based on the concrete evidence on natural mortality and the fact that cause-specific analyses included, in most cases, subsamples from the studies that informed the natural mortality meta-analysis.

In Table 2, all $PM_{2.5}$–outcome pairs were assigned to List A (Annex 2, Table A2.1) based on previous support for causality and because they fulfilled the EMAPEC criteria. Specifically, associations of $PM_{2.5}$ with natural or cardiovascular mortality outcomes were considered causal based on the 2019 US EPA Integrated Science Assessment (ISA) (US EPA, 2019, 2022), with lung cancer were considered causal according to the 2013 IARC assessment for carcinogenic to humans (Group 1) categorization, and with respiratory non-malignant outcomes were considered likely causal (US EPA, 2019, 2022).

Annex 2, Table A2.1 presents a detailed assessment using the EMAPEC criteria. In short, CRFs for all pollutant–outcome pairs were informed by a sufficient number of studies (ranging from 12 for acute lower respiratory infection (ALRI) to 53 for natural mortality; criterion 1i; Fig. 1) (also see Orellano et al., 2024, Supplemental Data Sheet 1, Figs S3–S9). The RRs were statistically significant (criterion 1ii), the studies covered various continents (criterion 2i) and the meta-analysis weights were evenly distributed (criterion 2ii). Newer results from papers (available for all outcomes except for ALRI and COPD mortality (Orellano et al., 2024)) published after the meta-analysis were consistent with the reported pooled effect estimates (criterion 2v).

Table 2. Proposed RRs (95% CIs) for mortality outcomes from long-term exposure (annual mean) to $PM_{2.5}$ and to inform an HRA

Mortality outcome	ICD-10	List	RR (95% CI) per 10 µg/m³	Range of me(di)an exposure (µg/m³)
Natural	A00–R99	A	1.10 (1.06–1.13)	5–70
Circulatory	I00–I99	A	1.13 (1.10–1.15)	5–70
Cerebrovascular	I60–I69	A	1.15 (1.10–1.19)	5–70
IHD	I20–I25	A	1.14 (1.10–1.19)	5–70
Respiratory (non-malignant)	J00–J99	A	1.14 (1.08–1.20)	5–70
COPD	J40–J44, J47	A	1.14 (1.08–1.20)	5–70
ALRI	J12–J18, J20–J22	A	1.20 (1.10–1.33)	5–70
Trachea, bronchus and lung cancer	C33–C34	A	1.09 (1.05–1.14)	5–70

Source: data are taken from Orellano et al. (2024).

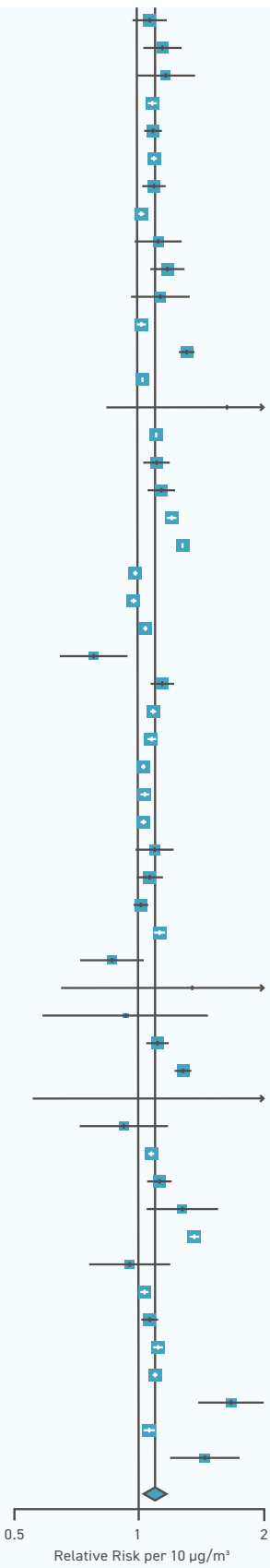
The meta-analytic estimates were considered precise (criterion 2iii) for all pairs (range: 39% for circulatory mortality to 88% for lung cancer) except for ALRI, where the width of the 95% CI as a proportion of the central estimate was < 100% at 112%. However, the classification for ALRI was not downgraded from List A because of the small exceedance of the proposed 100% limit, causality, and fulfilment of the remaining criteria.

All associations presented high heterogeneity (criterion 2iv), as indicated by I^2 values of > 75% (range: 82% for ALRI mortality to 100% for natural mortality). Heterogeneity may be introduced by differences in $PM_{2.5}$ composition, the risk profile of the population, exposure assessment methods, or other reasons. However, based on the strong prior determination of causality, heterogeneity was not deemed sufficient to downgrade confidence in the proposed RRs. This decision was supported by the overlap of regional CIs (for all-cause and respiratory mortality) and the non-inclusion of 1 in prediction intervals (PIs; for the other mortality outcomes). Heterogeneity in lung cancer mortality estimates was partly driven by inconsistent evidence from the WHO Region of the Americas compared with the WHO European and Western Pacific regions (Orellano et al., 2024, Table 2 and Supplemental Data Sheet 1, Fig. S37). This discrepancy may be attributed to regional differences, mainly between the WHO European Region and the WHO Region of the Americas, including the fleet penetration of diesel vehicles and interactions between air pollution exposure and smoking. In addition, some studies from the WHO Region of the Americas were older and used earlier exposure assessment methods, thereby adding to the heterogeneity. The high effect of estimates from the WHO European Region in the meta-analyses was largely driven by Dutch cohort studies. The $PM_{2.5}$–lung cancer mortality association pair is a good example of the usefulness of applying the global RR (compared with a regional one) in HRAs because it is more stable and accounts for various potential sources of heterogeneity between studies and across WHO regions. Hence, although subgroup analyses were applied to investigate heterogeneity between regions in meta-analyses of mortality outcomes that informed this guidance (Kasdagli et al., 2024; Orellano et al., 2024), it is proposed to use the global RRs in an HRA.

Fig. 1. Forest plot for the association between long-term exposure to $PM_{2.5}$ and all-cause mortality

Author Year	Cohort	RR	95%-CI	Weight
Beelen 2008	NLCS-AIR	1.060	[0.969; 1.159]	1.9%
Beelen 2014	ESCAPE	1.140	[1.027; 1.266]	1.8%
Bentayeb 2015	Gazel cohort	1.160	[0.985; 1.367]	1.3%
Bouma 2023	Dutch administrative	1.077	[1.056; 1.099]	2.3%
Bowe 2018	American veterans	1.080	[1.031; 1.131]	2.2%
Brauer 2022	MAPLE (CanCHEC)	1.084	[1.073; 1.096]	2.4%
Brauer 2022	MAPLE (CCHS)	1.086	[1.021; 1.155]	2.1%
Brown 2022	MDS	1.010	[0.995; 1.025]	2.3%
Carey 2013		1.110	[0.979; 1.259]	1.6%
Chen 2021	RDCS	1.170	[1.070; 1.280]	1.9%
Dirgawati 2019	HIMS	1.124	[0.958; 1.319]	1.4%
Enstrom 2005	CA CPS I	1.010	[0.990; 1.030]	2.3%
Guo 2022	MJ	1.300	[1.246; 1.356]	2.2%
Hales 2021	New Zealand Statistics	1.018	[1.015; 1.021]	2.4%
Hanigan 2019	45 and Up Study	1.629	[0.835; 3.176]	0.2%
Hao 2023	Medicare	1.101	[1.099; 1.104]	2.4%
Hart 2011	Trucking industry cohort	1.100	[1.023; 1.183]	2.1%
Hart 2015	NHS	1.130	[1.048; 1.218]	2.0%
Huang 2023	Four Northern Chinese cities	1.200	[1.170; 1.230]	2.3%
Hwang 2020	National Health Insurance	1.274	[1.270; 1.278]	2.4%
Hystad 2020	PURE	0.980	[0.965; 0.995]	2.3%
Jalali 2021	ICS	0.974	[0.960; 0.988]	2.3%
Kim 2020	NHIS-NSC	1.034	[1.027; 1.041]	2.4%
Klompmaker 2020	Dutch administrative	0.784	[0.653; 0.942]	1.2%
Lepeule 2012	Harvard Six Cities	1.140	[1.068; 1.217]	2.1%
Li 2018	CLHLS	1.080	[1.065; 1.095]	2.3%
Li 2023	DHS	1.070	[1.050; 1.090]	2.3%
Liao 2022	DHS/NFHS-4	1.025	[1.017; 1.034]	2.4%
Lim 2019	NIH-AARP Diet and Health	1.030	[1.005; 1.055]	2.3%
Lim 2021	NHID	1.024	[1.009; 1.039]	2.3%
Mcdonnell 2000	AHSMOG	1.090	[0.981; 1.211]	1.8%
Nieuwenhuijsen 2018	SIDIAP Barcelona	1.061	[0.991; 1.136]	2.1%
Ostro 2015	California Teachers Study	1.010	[0.971; 1.051]	2.3%
Pope 2019	NHIS	1.120	[1.085; 1.156]	2.3%
Puett 2011	Health Professionals Follow-Up Study	0.860	[0.723; 1.024]	1.3%
Sawada 2022	JPHC	1.344	[0.650; 2.777]	0.1%
Sommar 2021	Umea-VIP	0.927	[0.588; 1.463]	0.3%
Stafoggia 2022	ELAPSE administrative	1.109	[1.043; 1.178]	2.1%
Strak 2021	ELAPSE pooled	1.277	[1.223; 1.333]	2.2%
Traini 2022	LIFEWORK	3.679	[0.556; 24.361]	0.0%
Tseng 2015		0.920	[0.722; 1.173]	0.9%
Turner 2016	ACS-CPS II	1.070	[1.055; 1.085]	2.3%
Villeneuve 2015	CNBSS	1.120	[1.048; 1.197]	2.1%
Wang 2022	UK Biobank	1.270	[1.045; 1.543]	1.1%
Wang 2023		1.357	[1.324; 1.390]	2.3%
Weichenthal 2014	AHS	0.950	[0.759; 1.189]	1.0%
Xia 2023	PURE-China	1.030	[1.010; 1.050]	2.3%
Yang 2018	EHS	1.060	[1.016; 1.106]	2.2%
Yang 2020	China-PAR	1.110	[1.080; 1.140]	2.3%
Yin 2017	Chinese men	1.090	[1.080; 1.100]	2.4%
Yorifuji 2019		1.664	[1.393; 1.988]	1.2%
Zhang 2021	CFPS	1.055	[1.023; 1.089]	2.3%
Zhang 2021	OHS	1.438	[1.192; 1.735]	1.2%
Random effects pooled estimate		**1.095**	**[1.064; 1.127]** [0.966; 1.241]	**100.0%**

80% Prediction Interval
Heterogeneity:
$I^2 = 100\%$, $\tau^2 = 0.0091$, $p = 0$



ACS-CPS II: American Cancer Society Cancer Prevention Study II; AHS: Agricultural Health Study; AHSMOG: Adventist Health and Smog Study; CA CPS I: California Cancer Prevention Study I; CanCHEC: Canadian Census Health and Environment Cohorts; CCHS: Canadian Community Health Surveys; CFPS: China Family Panel Studies; China-PAR: Prediction for Atherosclerotic cardiovascular disease Risk in China (project); CLHLS: Chinese Longitudinal Healthy Longevity Survey; CNBSS: Canadian National Breast Screening Study; DHS: Demographic and Health Surveys (programme); DHS/NFHS-4: Demographic and Health Survey/National Family Health Survey 2015–2016; EHS: Elderly Health Service; ELAPSE: Effects of Low-Level Air Pollution: a Study in Europe; ESCAPE: European Study of Cohorts for Air Pollution Effects; HIMS: Health in Men Study; ICS: Isfahan Cohort Study; JPHC: Japan Public Health Centre-based (prospective study); MAPLE: Mortality due to Air Pollution at Low levels of Exposure; MDS: Million Death Study; NHID: National Health Information Database; NHIS: National Health Interview Surveys; NHIS-NSC: National Health Insurance Service – National Sample Cohort; NHS: Nurses' Health Study; NIH-AARP: National Institutes of Health – American Association of Retired Persons; NLCS-AIR: Netherlands Cohort Study on air pollution; OHS: Ontario Health Study; PURE: Prospective Urban and Rural Epidemiology (study); RDCS: Rural Deqing Cohort Study; SIDIAP: *Sistema d'Informació pel Desenvolupament de la Investigació en Atenció Primària* [Information System for the Development of Research in Primary Care]; UK Biobank: United Kingdom Biobank; Umea-VIP: Västerbotten Intervention Program (Umeå residents). All references can be found in the Supplementary Material for the source document.
Source: Orellano et al. (2024). Reproduced under the CC-BY 4.0 licence (https://creativecommons.org/licenses/by/4.0/).

2.1.2 Effects of short-term $PM_{2.5}$ exposure

The use of natural mortality is proposed as the health outcome for HRAs associated with short-term exposure to $PM_{2.5}$ because the association is assigned to List A. Based on the global harmonized analysis of the MCC collaborative study (Liu et al., 2019), the proposed RR is 1.0068 per 10 µg/m³ (95% CI: 1.0059–1.0077) in daily mean $PM_{2.5}$ levels. Due to the considerably smaller RRs associated with short-term exposures than with long-term exposures, the RR values are given to more decimal places in order to more accurately present the magnitude of the effect estimate and associated 95% CIs (Table 3). The proposed range of daily exposure is 5–100 µg/m³ based on the $PM_{2.5}$ levels in contributing cities (Annex 2, Fig. A2.4; reproduced from Liu et al. (2019), Fig. 3) and the range within which the association is linear. Regarding the population age range, in short-term exposure analyses the general population, which includes all ages, should be used.

Table 3. Proposed RR (95% CI) for a mortality outcome from short-term exposure (24-hour mean) to $PM_{2.5}$ to inform an HRA

Mortality outcome	ICD-10	List	RR (95% CI) per 10 µg/m³	Range of me(di)an exposures µg/m³)
Natural	A00–R99	A	1.0068 (1.0059–1.0077)	5–100

Source: data are taken from Liu et al., 2019.

2.1.3 Effects of long-term PM_{10} exposure

Table 4 shows the proposed mortality outcomes (assigned to List A or List B+) and corresponding RRs associated with long-term exposure to PM_{10}, along with the range of me(di)an exposure levels. Me(di)an exposures in studies that informed the natural mortality meta-analysis ranged from 4 µg/m³ to 112 µg/m³ (Orellano et al., 2024). Based on this, the proposed range of me(di)an exposures for the application of the proposed RRs in HRAs for all associations with PM_{10} is from the AQG level (15 µg/m³) to the maximum me(di)an in the studies included in the natural mortality meta-analysis, rounded to the nearest multiple of 5, i.e. 110 µg/m³ (Annex 2, Fig. A2.1; based on Orellano et al., 2024, Table 1). According to the chosen methods, the same range is also proposed for cause-specific analyses. In contrast to the mortality outcomes assessed for $PM_{2.5}$ exposure, ALRI mortality was not considered for PM_{10} exposure because only one study was identified in the systematic review (Orellano et al., 2024). As previously indicated, all mortality outcomes, except for

post-neonatal mortality (death in in infants aged between 1 and 12 months) and long-term exposure to PM_{10}, were assessed in adults (mostly those aged over 25 years) (Orellano et al., 2024).

The causality assessment for PM_{10} followed that for $PM_{2.5}$ for natural, circulatory and respiratory non-malignant mortality (US EPA, 2019, 2022) and the IARC assessment as carcinogenic to humans (Group 1) categorization for lung cancer mortality (Straif et al., 2013).

Table 4. Proposed RRs (95% CIs) for mortality outcomes from long-term exposure (annual mean) to PM_{10} to inform an HRA

Mortality outcomes	ICD-10	List	RR (95% CI) per 10 µg/m³	Range of me(di)an exposures (µg/m³)
Natural	A00–R99	A	1.08 (1.05–1.11)	15–110
Circulatory	I00–I99	A	1.08 (1.04–1.12)	15–110
Respiratory (non-malignant)	J00–J99	A	1.12 (1.08–1.17)	15–110
Trachea, bronchus and lung cancer	C33–C34	A	1.10 (1.05–1.15)	15–110
IHD	I20–I25	B+	1.06 (1.02–1.09)	15–110
COPD	J40–J44, J47	B+	1.22 (1.03–1.44)	15–110

Note: these proposals are to be used only when $PM_{2.5}$ data are unavailable. Restricted range, with most evidence: 15–60 µg/m³.
Source: data are taken from Orellano et al. (2024).

Specifically, PM_{10} was considered to have a causal effect on natural mortality based on the US EPA ISA for $PM_{2.5}$ (Annex 2, Table A2.2) (US EPA, 2019, 2022). The PM_{10}–natural mortality pair was assigned to List A because 28 studies informed the meta-analysis (criterion 1i) (Orellano et al., 2024, Supplemental Data Sheet 1, Fig. S2), the RR was statistically significant (criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii) and the estimate was precise (72%; criterion 2iii), and there were no published results after the systematic review (criterion 2v). Heterogeneity was high (I^2 = 98%; 80% PI: 0.99–1.18; criterion 2iv), but the classification was not downgraded based on the strong causality assumption and the borderline inclusion of unity in the PI. Moreover, heterogeneity was partly attributed to differences between WHO regions (Orellano et al., 2024, Table 2 and Supplemental Data Sheet 1, Fig. S32). Specifically, the studies from the WHO Region of the Americas (all of which were from the United States of America) reported lower RRs than those observed in other regions. Since the United States studies were older than those from other regions, the difference may be partly driven by use of an older methodology for exposure assessment based on monitoring data.

PM_{10} was considered to have a causal effect on circulatory mortality based on the US EPA ISA for $PM_{2.5}$ (US EPA, 2019, 2022). The association was assigned to List A because 26 studies informed the meta-analysis (criterion 1i) (Orellano et al., 2024, Supplemental Data Sheet 1, Fig. S10), the RR was statistically significant (criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii) and the estimate was precise (98%; criterion 2iii); newer results were not available (criterion 2v). Although the heterogeneity was high (I^2 = 98%; 80% PI: 0.97–1.20; criterion 2iv), the classification was not downgraded based on the strong causality determination.

Classification of the association between long-term PM_{10} exposure and diagnosis-specific cardiovascular mortality was downgraded to List B+ for IHD and to List B- for cerebrovascular mortality (hence, the latter is not included in the proposed CRFs shown in Table 4), although both were considered causal following the US EPA ISA for $PM_{2.5}$ (US EPA, 2019, 2022). The List B+ classification for IHD mortality (Orellano et al., 2024, Supplemental Data Sheet 1, Fig. S11) was mainly driven by the imprecise pooled effect estimate (133%; criterion 2iii) and also by the unexplained heterogeneity (I^2 = 88%; 80% PI: 0.99–1.13; criterion 2iv). The remaining criteria were fulfilled: 16 studies informed the meta-analysis (criterion 1i), the RR was statistically significant (criterion 1ii), the review covered various continents (criterion 2i) and the meta-analysis weights were evenly distributed (criterion 2ii), and there were no newer results (criterion 2v).

The association between long-term PM_{10} exposure and cerebrovascular mortality was downgraded onto List B- because the association was not statistically significant (RR: 1.05; 95% CI: 0.97–1.13; criterion 1ii) (Orellano et al., 2024, Supplemental Data Sheet 1, Fig. S12), as informed by 15 studies (criterion 1i). Furthermore, the RR was highly imprecise (322%; criterion 2iii) and there was a large degree of heterogeneity, as indicated by the PI interval including unity (I^2 = 99%; 80% PI: 0.88–1.25; criterion 2iv).

PM_{10} was considered to have a causal effect on respiratory non-malignant mortality following the US EPA ISA for $PM_{2.5}$ (US EPA, 2019, 2022). The association was assigned to List A since 21 studies informed the meta-analysis (criterion 1i) (Orellano et al., 2024, Supplemental Data Sheet 1, Fig. S14), the RR was statistically significant (1.12; 95% CI: 1.08–1.17; criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii) and the estimate was precise (76%; criterion 2iii); there were no newer studies (criterion 2v). Heterogeneity was high (I^2 = 92%; 80% PI: 1.02–1.24; criterion 2iv) but the classification was not downgraded since the 80% PI did not include unity and there was a strong assumption of causality.

The association between long-term PM_{10} exposure and COPD mortality, assuming causality for respiratory outcomes (US EPA, 2019, 2022), was downgraded onto List B+ because the RR was highly imprecise (191%; criterion 2iii) and there was an unexplained high level of heterogeneity (I^2 = 83%; 80% PI: 0.89–1.67; criterion 2iv). The other criteria were fulfilled: the RR was informed by seven studies (criterion 1i) (Orellano et al., 2024, Supplemental Data Sheet 1, Fig. S15) and was statistically significant (1.22; 95% CI: 1.03–1.44; criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii) and there were no newer results (criterion 2v).

Long-term exposure to PM_{10} was considered to have a causal effect on lung cancer mortality following its classification as a Group 1 carcinogen in the 2013 IARC assessment. The association was assigned to List A since 17 studies had informed the meta-analysis (criterion 1i) (Orellano et al., 2024, Supplemental Data Sheet 1, Fig. S13), the RR was statistically significant (1.10; 95% CI: 1.05–1.15; criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii) and the estimate was precise (99%; criterion 2iii). The high heterogeneity (I^2 = 94%; 80% PI: 1.00–1.22; criterion 2iv) was driven by the larger RRs in the WHO European Region compared with studies from elsewhere, as was the case for the $PM_{2.5}$–lung cancer mortality association.

The proposed range of exposures for PM_{10}–outcome pairs is 15–110 μg/m^3 (Table 4), representing the range of me(di)an exposures of studies included in the meta-analysis (Orellano et al., 2024). Nevertheless, a restricted range of me(di)an exposures is also proposed, within which there is greater confidence in

applying the proposed CRFs. The restricted range is not provided as advice but rather as an option because of limited evidence at the upper end of the distribution. The restricted range extends from the same low level as the proposed range (based on the AQG level) of 15 μg/m^3 up to 60 μg/m^3. The upper limit is the me(di)an exposure among the studies included in the original review (Orellano et al., 2024) after excluding three with the highest me(di)an PM_{10} levels from the natural mortality analysis because they were evaluated as outliers (Annex 2, Fig. A2.1).

HRAPIE considered the effects of long-term exposure to PM_{10} on post-neonatal mortality based on one study that reported a RR of 1.04 per 10 μg/m^3 (95% CI: 1.02–1.06) (WHO Regional Office for Europe, 2013a). The original systematic review did not conduct a meta-analysis for this pollutant–outcome pair because only one study was identified that fulfilled the eligibility criteria (Orellano et al., 2024). Nevertheless, a recent meta-analysis using expanded eligibility criteria and combining results from four cohort and case–control studies reported a pooled odds ratio for post-neonatal mortality of 1.04 per 10 μg/m^3 increase in PM_{10} (95% CI: 1.02–1.06) (Wilkie et al., 2025). The association would be assigned to List B+ due to the small number of studies (criterion 1i), although most of the remaining key and important criteria were fulfilled: the RR was statistically significant (criterion 1ii) and precise (criterion 2i), the meta-analysis included studies from two WHO regions (criterion 2i), but heterogeneity was low (meeting criteria 2iii and 2iv). Three of the four studies that informed this meta-analysis reported a me(di)an PM_{10} level of between 5 μg/m^3 and 30 μg/m^3, so the applicability of the RR for higher concentrations is more uncertain.

As previously stated, no CRF for short-term PM_{10} exposure and mortality is proposed, in line with HRAPIE (WHO Regional Office for Europe, 2013a).

2.2 NO_2

2.2.1. Effects of long-term NO_2 exposure

Table 5 shows the proposed mortality outcomes assigned to List A or List B+, with the corresponding RRs associated with long-term exposure to NO_2, along with the range of me(di)an exposure levels. The range of me(di)an exposures in the studies that informed the natural mortality meta-analysis was between 7 μg/m^3 and 130 μg/m^3 (Kasdagli et al., 2024). Based on this, the proposed range of me(di)an exposures for the application of the proposed CRFs in HRAs for all associations with NO_2 is from the AQG level (10 μg/m^3) to the maximum me(di)an in the studies included in the natural (all-cause) mortality meta-analysis, rounded to the nearest multiple of 5, i.e. 130 μg/m^3 (Annex 2, Fig. A2.2) (Kasdagli et al., 2024, Table 1). All mortality outcomes were assessed in adults (aged 18 years and over). The great majority of outcomes were assessed in people aged 25 years and over, although the age range varied between studies and varied slightly by the outcome assessed.

According to the US EPA ISA, there is a likely causal association for NO_2 and respiratory outcomes (US EPA, 2016), and this is also expected to be reflected in all-cause mortality. Following this rationale, NO_2 was considered to have a likely causal effect on natural, respiratory (non-malignant), COPD and ALRI mortality (Annex 2, Table A2.3). Causality was assessed as suggestive for circulatory and lung cancer mortality, but relevant RRs are proposed based on the increasing evidence for an association and the 2016 US EPA evaluation.

Table 5. Proposed RRs (95% CIs) for mortality outcomes from long-term exposure (annual mean) to NO_2 to inform an HRA

Mortality outcome	ICD-10	List	RR (95% CI) per 10 µg/m³	Range of me(di)an exposures (µg/m³)
Natural	A00–R99	A	1.05 (1.03–1.07)	10–130
Respiratory (non-malignant)	J00–J99	A	1.05 (1.03–1.07)	10–130
COPD	J40–J44, J47	A	1.04 (1.02–1.06)	10–130
ALRI	J12–J18, J20–J22	A	1.08 (1.04–1.12)	10–130
Circulatory	I00–I99	B+	1.05 (1.03–1.08)	10–130
IHD	I20–I25	B+	1.05 (1.03–1.08)	10–130
Trachea, bronchus and lung cancer	C33–C34	B+	1.07 (1.04–1.10)	10–130

Note: restricted range, with most evidence: 10–40 µg/m³.
Source: data are taken from Kasdagli et al. (2024).

The association of NO_2 exposure with natural mortality was assigned to List A and considered likely causal based on the rationale stated in the previous paragraph: 34 studies informed the meta-analysis (criterion 1i) (Kasdagli et al., 2024, Fig. 2), the RR was statistically significant (criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii) and the estimate was precise (80%; criterion 2iii). Newer results following the meta-analysis literature review were consistent with the reported pooled effect estimates (criterion 2v) (Kasdagli et al., 2024). Heterogeneity was high (I^2 = 95%; 80% PI: 0.98–1.12; criterion 2iv), but the classification was not downgraded due to the borderline inclusion of unity in the PI and the complete overlap of 95% CIs between the WHO European Region and WHO Region of the Americas (Fig. 2) (Kasdagli et al., 2024, Supplemental Fig. S2). Studies in the WHO Western Pacific Region consistently reported higher RRs than those in the other two WHO regions.

Since NO_2 was considered to have a suggestive causal relationship with circulatory-related mortality outcomes, the association was assigned to List B+. This decision was made despite rather strong supporting evidence: the CRF was based on 28 studies (criterion 1i), the RR was statistically significant (criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii), the estimate was precise (100%; criterion 2iii), and newer results were consistent (criterion 2v) (Kasdagli et al., 2024, Supplemental Fig. S5). Heterogeneity was high (I^2 = 97%; 80% PI: 0.97–1.15; criterion 2iv) but the association was not further downgraded due to the borderline inclusion of unity in the PI and the borderline overlap of WHO regional estimates (Kasdagli et al., 2024, Supplemental Fig. S7).

Similar to circulatory mortality, the association between long-term NO_2 exposure and IHD mortality was assigned to List B+ because the CRF was based on 20 studies (criterion 1i) (Kasdagli et al., 2024, Supplemental Fig. S9), the estimate was statistically significant (criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii) and the estimate was sufficiently precise (100%; criterion 2iii). Newer results were not available (criterion 2v) (Kasdagli et al.,

2024). Heterogeneity was high (I^2 = 95%; 80% PI: 0.99–1.12; criterion 2iv) but the association was not further downgraded due to the borderline inclusion of unity in the PI.

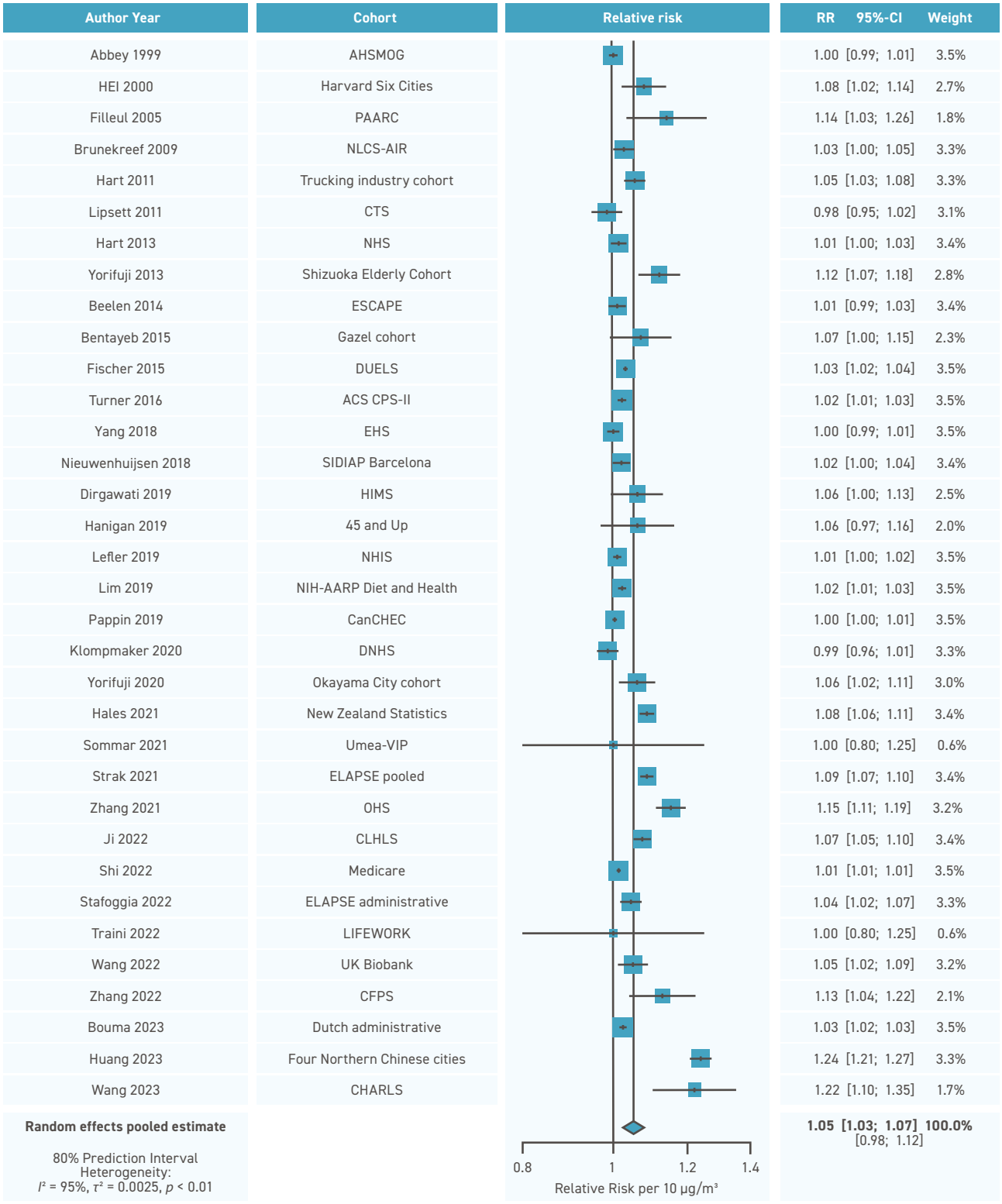
The association between long-term NO_2 exposure and cerebrovascular mortality was downgraded onto List B- and, hence, is not presented in Table 5. Reasons for downgrading were that the association was not statistically significant (RR: 1.08; 95% CI: 0.99–1.19; criterion 1ii), although it was informed by 20 studies (criterion 1i) (Kasdagli et al., 2024, Supplemental Fig. S14), the RR was highly imprecise (250%; criterion 2iii) and there was large heterogeneity, with the PI interval including unity (I^2 = 98%; 80% PI: 0.82–1.43).

US EPA considers NO_2 to have a likely causal effect on respiratory non-malignant mortality (US EPA, 2016). The association was assigned to List A, since 25 studies informed the meta-analysis (criterion 1i) (Kasdagli et al., 2024, Supplemental Fig. S16), the RR was statistically significant (1.05; 95% CI: 1.03–1.07; criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii) and the estimate was precise (80%; criterion 2iii). Newer findings following the systematic review were consistent with the pooled effect estimate (criterion 2v) (Kasdagli et al., 2024). Heterogeneity was high (I^2 = 90%; 80% PI: 0.99–1.11; criterion 2iv) but smaller than for natural mortality; the classification was not downgraded because the 80% PI only marginally included unity.

As for respiratory non-malignant mortality, long-term NO_2 exposure was considered likely causal for both COPD mortality and ALRI mortality (US EPA, 2016) and fulfilled the assessment criteria. Hence, the classification for both associations was List A. Specifically, the CRF for COPD mortality was informed by 15 studies (criterion 1i) (Kasdagli et al., 2024, Supplemental Fig. S20), the RR was statistically significant (1.04; 95% CI: 1.02–1.06; criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii), the estimate was sufficiently precise (100%; criterion 2iii) and there were no newer studies following the systematic review (criterion 2v) (Kasdagli et al., 2024). Heterogeneity was moderate (I^2 = 62%; 80% PI: 0.99–1.09; criterion 2iv).

The CRF for ALRI mortality was informed by nine studies (criterion 1i) (Kasdagli et al., 2024, Supplemental Fig. S24), the RR was statistically significant (1.08; 95% CI: 1.04–1.12; criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii), the estimate was precise (100%; criterion 2iii), and there were no newer studies following the systematic review (criterion 2v) (Kasdagli et al., 2024). Heterogeneity was high but the PI did not include unity (I^2 = 92%; 80% PI: 1.00–1.16; criterion 2iv).

Fig. 2. Forest plot for the RR of all-cause mortality associated with a 10 μg/m³ increase in long-term exposure to NO_2



ACS-CPS II: American Cancer Society Cancer Prevention Study II; AHSMOG: Adventist Health and Smog Study; CanCHEC: Canadian Census Health and Environment Cohorts; CFPS: China Family Panel Studies; CHARLS: China Health and Retirement Longitudinal Study; CLHLS: Chinese Longitudinal Healthy Longevity Survey; CTS: California Teachers Study; DNHS: Dutch National Health Survey; DUELS: Dutch Environmental Longitudinal Study; EHS: Elderly Health Service; ELAPSE: Effects of Low-Level Air Pollution: a Study in Europe; ESCAPE: European Study of Cohorts for Air Pollution Effects; HIMS: Health in Men Study; NHIS: National Health Interview Surveys; NIH-AARP: National Institutes of Health – American Association of Retired Persons; NHS: Nurses' Health Study; NLCS-AIR: Netherlands Cohort Study on air pollution; OHS: Ontario Health Study; PAARC: *Pollution Atmosphérique et Affections Respiratoires Chroniques* [Air Pollution and Chronic Respiratory Diseases] (survey); SIDIAP: *Sistema d'Informació pel Desenvolupament de la Investigació en Atenció Primària* [Information System for the Development of Research in Primary Care]; UK Biobank: United Kingdom Biobank; Umea-VIP: Västerbotten Intervention Program (Umeå residents). All references cited in the figure can be found in the source document.

Source: Kasdagli et al. (2024). Reproduced under the CC-BY 4.0 licence (https://creativecommons.org/licenses/by/4.0/).

The relationship between long-term exposure to NO_2 and lung cancer mortality was considered to be suggestive causal due to increased evidence and the 2016 US EPA assessment (US EPA, 2016). This was supported by the use of NO_2 as a traffic indicator in many studies, following the same rationale as adopted by IARC to classify the mixture of outdoor air pollution as carcinogen to humans (Group 1). In this context, NO_2 itself may not necessarily be the causal agent, but could act as a marker for other carcinogenic components of the traffic pollution mixture such as volatile organic compounds and polycyclic aromatic hydrocarbons emitted from traffic. Additionally, the Health Effects Institute considered the evidence for an association between traffic-related air pollution and lung cancer as moderate to high, which also accounted for an association with traffic-related NO_2 of 1.04 per 10 μg/m^3 (95% CI: 1.01–1.07) based on five studies (Health Effects Institute, 2022). Hence, the association between long-term NO_2 exposure and lung cancer mortality was assigned to List B+ due to suggestive causality as all the remaining criteria were fulfilled. Specifically, 20 studies informed the meta-analysis (criterion 1i) (Kasdagli et al., 2024, Supplemental Fig. S28), the RR was statistically significant (1.07; 95% CI: 1.04–1.10; criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were evenly distributed (criterion 2ii) and the estimate was precise (86%; criterion 2iii). There was high heterogeneity (I^2 = 92%; 80% PI: 0.99–1.14; criterion 2iv) but the evidence was not downgraded because the 80% PI only marginally included unity. A Chinese study published after the systematic review estimated a much higher RR: 1.66 (95% CI: 1.49–1.84; criterion 2v) (Guo et al., 2024).

The proposed range of exposures for NO_2–outcome pairs is 10–130 μg/m^3 (Table 5), which represents the range of me(di)an exposures of studies included in the meta-analysis (Kasdagli et al., 2024). However, this guidance also proposes a restricted range of me(di)an exposures within which there is greater confidence for applying the proposed CRFs. The restricted range is only presented as an option for consideration based on limited evidence at the upper end of the distribution. The restricted range extends from the same low level as the proposed range (based on the AQG level) of 10 μg/m^3 up to 40 μg/m^3. The upper limit is the me(di)an exposure among studies included in the Kasdagli et al. (2024) review after excluding the four studies with the highest me(di)an NO_2 levels in the natural mortality analysis because they were evaluated as outliers (Annex 2, Fig. A2.2).

2.2.2 Effects of short-term NO_2 exposure

Natural mortality is proposed as the health outcome for HRAs targeting short-term exposure to NO_2 (Table 6). The association is assigned to List A. Based on the global harmonized analysis of the MCC collaborative study (Meng et al., 2021), the proposed RR is 1.0046 per 10 μg/m^3 (95% CI: 1.0036–1.0057) in daily (24-hour) mean NO_2 levels. The proposed applicable range of 24-hour mean exposure is 10–80 μg/m^3, based on the levels in contributing cities (Annex 2, Fig. A2.5; reproduced from Meng et al. (2021), Fig. 2) and accounts for

the range within which the association is linear. Regarding the underlying population age range, in short-term exposure analyses is the general population, which includes all ages, should be used.

Table 6. Proposed RR (95% CI) for a mortality outcome from short-term exposure (24-hour mean) to NO_2 to inform an HRA

Mortality outcome	ICD-10	List	RR (95% CI) per 10 µg/m³	Range of me(di)an exposures (µg/m³)
Natural	A00–R99	A	1.0046 (1.0036–1.0057)	10–80

Source: data are taken from Meng et al. (2021).

2.3 O_3

2.3.1 Effects of long-term O_3 exposure

The only association between long-term O_3 exposure and mortality proposed for the use in HRAs is between the annual mean O_3 and respiratory mortality (Table 7 and Annex 2, Table A2.4). The RR for this association (assigned to List B+) was the only one among those assessed for O_3 (annual or warm/peak season[3] and with more than two contributing studies) that reached statistical significance following the meta-analyses (Fig. 3) (Kasdagli et al., 2024).

Table 7. Proposed RR (95% CI) for a mortality outcome from long-term O_3 exposure (annual mean of daily maximum 8-hour means) to inform an HRA

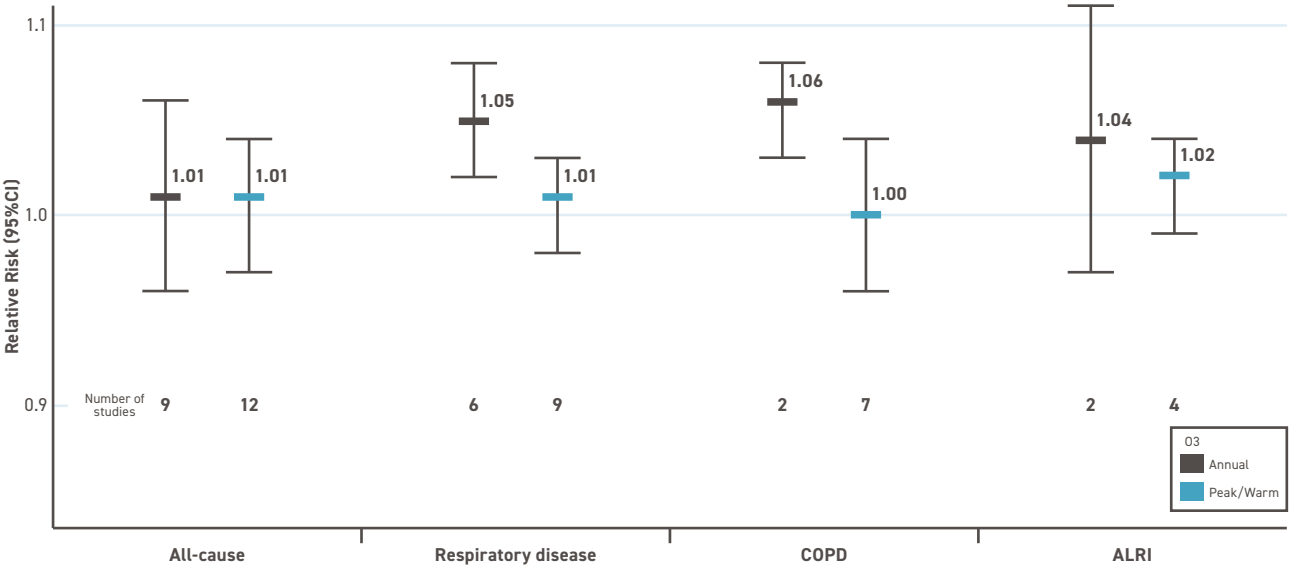
Mortality outcome	ICD-10	List	RR (95% CI) per 10 µg/m³	Range of me(di)an exposures (µg/m³)
Respiratory (non-malignant)	J00–J99	B+	1.05 (1.02–1.08)	60–95

Source: data are taken from Kasdagli et al. (2024).

US EPA has classified the association between long-term O_3 exposure and respiratory mortality as likely causal (US EPA, 2020). The association was downgraded from List A to List B+ because the pooled effect estimate was imprecise (120%; criterion 2iii) and based on only six studies that informed the meta-analysis (criterion 1i; Fig. 4) (Kasdagli et al., 2024, Supplemental Fig. S35). Regarding the other criteria, the RR was statistically significant (1.05; 95% CI: 1.02–1.08; criterion 1ii), the review covered various continents (criterion 2i), the meta-analysis weights were rather evenly distributed (criterion 2ii) and there was moderate heterogeneity (I^2 = 65%; 80% PI: 1.00–1.09; criterion 2iv). No new studies had been published following the systematic review (criterion 2v) (Kasdagli et al., 2024).

3 Peak season is defined as the 6 consecutive months of the year with the highest 6-month running-average O_3 concentration. In regions at a distance from the equator, this period will typically be in the warm season within a single calendar year (northern hemisphere) or spanning 2 calendar years (southern hemisphere). Close to the equator, such clear seasonal patterns may not be obvious, but a running-average 6-month peak season will usually be identifiable from existing monitoring or modelling data (WHO, 2021).

Fig. 3. RRs for associations between a 10 μg/m^3 increase in long-term exposure to annual or warm/peak season O_3 and mortality outcomes

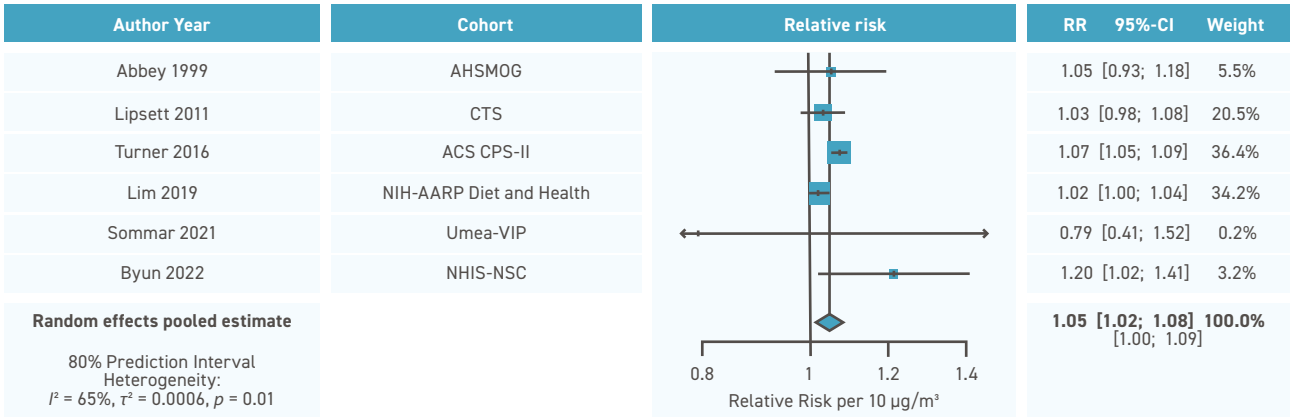


Source: Kasdagli et al. (2024). Reproduced under the CC-BY 4.0 licence (https://creativecommons.org/licenses/by/4.0/).

It should be emphasized that while a study reported an association between annual O_3 and respiratory mortality in the WHO European Region, the RR was < 1 (Fig. 4) (Sommar et al., 2021) . Hence, any assessment for the Region would largely rely on the results from other WHO regions. As with other mortality outcomes, the adult population should be considered when conducting an HRA, and the proposed range reflects the range of the me(di)an levels from studies included in the meta-analysis (full range: 51–94 μg/m^3; Annex 2, Fig. A2.3; based on Kasdagli et al., 2024, Table 2) and the general approach for setting the range of exposure levels presented in section 1.3.3.

For the remaining mortality outcomes, only natural mortality (Kasdagli et al., 2024, Supplemental Fig. S32) was considered for an association with long-term exposure to annual O_3 because only two studies on COPD or ALRI mortality had previously been identified (Kasdagli et al., 2024, Table 2A). The association between annual O_3 and all-cause mortality was assigned to List B- because the RR was not statistically significant (1.01; 95% CI: 0.96–1.06; criterion 1ii) and was informed by nine studies (criterion 1i) that covered various locations (criterion 2i), the RR was extremely imprecise (1000%; criterion 2iii), meta-analysis weights were equally distributed (criterion 2ii) and heterogeneity was high (I^2 = 92%; 80% PI: 0.91–1.11; criterion 2iv).

Fig. 4. Forest plot for respiratory disease mortality associated with a 10 μg/m³ increase in annual O_3 levels



ACS-CPS II: American Cancer Society Cancer Prevention Study II; AHSMOG: Adventist Health and Smog Study; CTS: California Teachers Study; NHIS-NSC: National Health Interview Surveys – National Sample Cohort; NIH-AARP: National Institutes of Health – American Association of Retired Persons; Umea-VIP: Västerbotten Intervention Program (Umeå residents). All references cited in the figure can be found in the source document.
Source: Kasdagli et al. (2024). Reproduced under the CC-BY 4.0 licence (https://creativecommons.org/licenses/by/4.0/).

All assessed associations between long-term exposure to warm/peak season O_3 and mortality outcomes (natural, respiratory, COPD and ALRI) were assigned to List B- (Annex 2, Table A2.4). Although there is suggestive causality evidence for an association with natural mortality and a likely association with respiratory mortality (Health Canada, 2013; US EPA, 2020), criteria on statistical significance (criterion 1ii), imprecision (criterion 2iii) and heterogeneity (criterion 2iv) were not fulfilled.

Specifically, for natural mortality the RR was not statistically significant (1.01; 95% CI: 0.97–1.04; criterion 1ii; Annex 2, Table 2.4; reproduced from Kasdagli et al. (2024), Table 2) and was highly imprecise (700%; criterion 2iii), and the meta-analyses revealed high heterogeneity (I^2 = 98%; 80% PI: 0.92–1.10; criterion 2iv) (Kasdagli et al., 2024, Supplemental Figs S41 and S45). Similarly, for respiratory mortality, the pooled effect estimate was not statistically significant (RR: 1.01; 95% CI: 0.98–1.03; criterion 1ii; Annex 2 Table A2.4) (based on Kasdagli et al. (2024), Table 2) and was highly imprecise (500%; criterion 2iii), and the meta-analyses revealed high heterogeneity (I^2 = 95%; 80% PI: 0.95–1.06, criterion 2iv) (Kasdagli et al., 2024, Supplemental Figs S41 and S45). However, for both associations, the criteria for geographical coverage (criterion 2i) and the equal distribution of meta-analytic weights (criterion 2i) were met.

For both natural mortality and respiratory mortality, the pooled effect estimate was driven by negative findings in the only European study included in the meta-analysis: the Effects of Low-Level Air Pollution: a Study in Europe (ELAPSE) (Kasdagli et al., 2024; Figs S43 and S47). The ELAPSE results may be attributed to residual confounding, especially considering that a high negative correlation between O_3 and NO_2 is frequently observed (Strak et al., 2021; Stafoggia et al., 2022). The opposite pattern has been reported in studies from the United States (Kazemiparkouhi et al., 2020), and ELAPSE also noted the smaller exposure contrasts in O_3 compared with the United States studies. Lastly, the differences may also relate to the differential exposure windows and different health outcomes assessed by the studies. Additionally, there is limited confidence in deriving conclusions for Europe from a single study on the effects of warm/peak O_3 exposure (ELAPSE), and this topic was identified as a future research need.

Although meta-analysis of the results from studies conducted in the United States (the large majority of which were included in the subgroup analysis for the WHO Region of the Americas) yield a significant RR of 1.03 per 10 µg/m³ (95% CI: 1.01–1.04), with a range of median values of 75–110 µg/m³ (Kasdagli et al., 2024, Table 2 and Supplemental Figs S43 and S47, Table S2), a global RR for warm/peak O_3 and respiratory mortality is not proposed, especially in the light of the likely causal association. It is important to note that the solid evidence for the effects of short-term O_3 exposure is not reflected for the effects of long-term exposure. This may be partly attributed to difficulties associated with exposure assessment methods to capture the highly oxidative nature of O_3 and its diverse spatial patterns (de Hoogh et al., 2018) because air pollution epidemiological studies have shown that errors in exposure measurement drive associations towards the null (Butland et al., 2020).

As for warm/peak season O_3 and respiratory mortality, the same approach is proposed for studying the association between warm/peak O_3 and COPD mortality, which is the main illness contributing to respiratory mortality (Kasdagli et al., 2024, Supplemental Fig. S50). The global association between warm/peak O_3 and COPD mortality was rated as List B-, mainly due to the null non-statistically significant RR (1.00 per 10 µg/m³; 95% CI: 0.96–1.04; criterion 1ii; Annex 2 Table A2.4) (based on Kasdagli et al. (2024), Table 2). The RR was informed by seven studies in multiple locations (criterion 1i) and was highly imprecise (> 1000% as a consequence of RR = 1; criterion 2iii). Additionally, there was high heterogeneity (I^2 = 95%; 80% PI: 0.92–1.09; criterion 2iv). Nevertheless, considering the consistent evidence for the United States (Kasdagli et al., 2024, Supplemental Fig. S52) and in accordance with the proposal above on HRA for warm/peak O_3 and respiratory mortality, an HRA for COPD mortality may be restricted to the United States, with a RR of 1.04 per 10 µg/m³ (95% CI: 1.02–1.07) based on United States studies.

Lastly, the association between warm/peak O_3 and ALRI mortality was assigned to List B- because there is considerably less evidence for this outcome compared with the other respiratory outcomes (Kasdagli et al., 2024, Supplemental Fig. S54). Specifically, only four studies (three from the United States and one from the WHO European Region) informed the RR, which was not statistically significant (1.02; 95% CI: 0.99–1.04; criterion 1ii) and highly imprecise (250%; criterion 2iii). There was also high heterogeneity (I^2 = 80%; 80% PI: 0.97–1.07; criterion 2iv).

2.3.2 Effects of short-term O_3 exposure

This guidance proposes the use of natural mortality as the health outcome for an HRA targeting short-term exposure to O_3 (Table 8). The association is assigned to List A. Based on a global harmonized analysis of the MCC collaborative study (Vicedo-Cabrera et al., 2020), the proposed RR is 1.0018 per 10 µg/m³ (95% CI: 1.0012–1.0034) for the daily maximum 8-hour mean O_3 levels. The proposed range of exposure is 60–150 µg/m³ based on the levels in contributing cities (Annex 2, Fig. A2.6; reproduced from Vicedo-Cabrera et al. (2020), eFig. 2) and starting from the 5th percentile of the distribution, that is, 60 µg/m³. Within this range, the association is linear. Regarding the population age range, in short-term exposures analyses the general population, which includes all ages, should be used.

Results for circulatory and respiratory mortality were not available in the MCC Collaborative Research Network, and natural mortality was considered sufficient for the HRA of short-term effects.

Table 8. Proposed RR (95% CI) for a mortality outcome from short-term exposure (daily maximum of the 8-hour mean) to O_3 to inform an HRA

Mortality outcome	ICD-10	List	RR (95% CI) per 10 µg/m³	Range of me(di)an exposures (µg/m³)
Natural	A00–R99	A	1.0018 (1.0012–1.0024)	60–150

Source: data are taken from Vicedo-Cabrera et al. (2020).

3. Morbidity outcomes

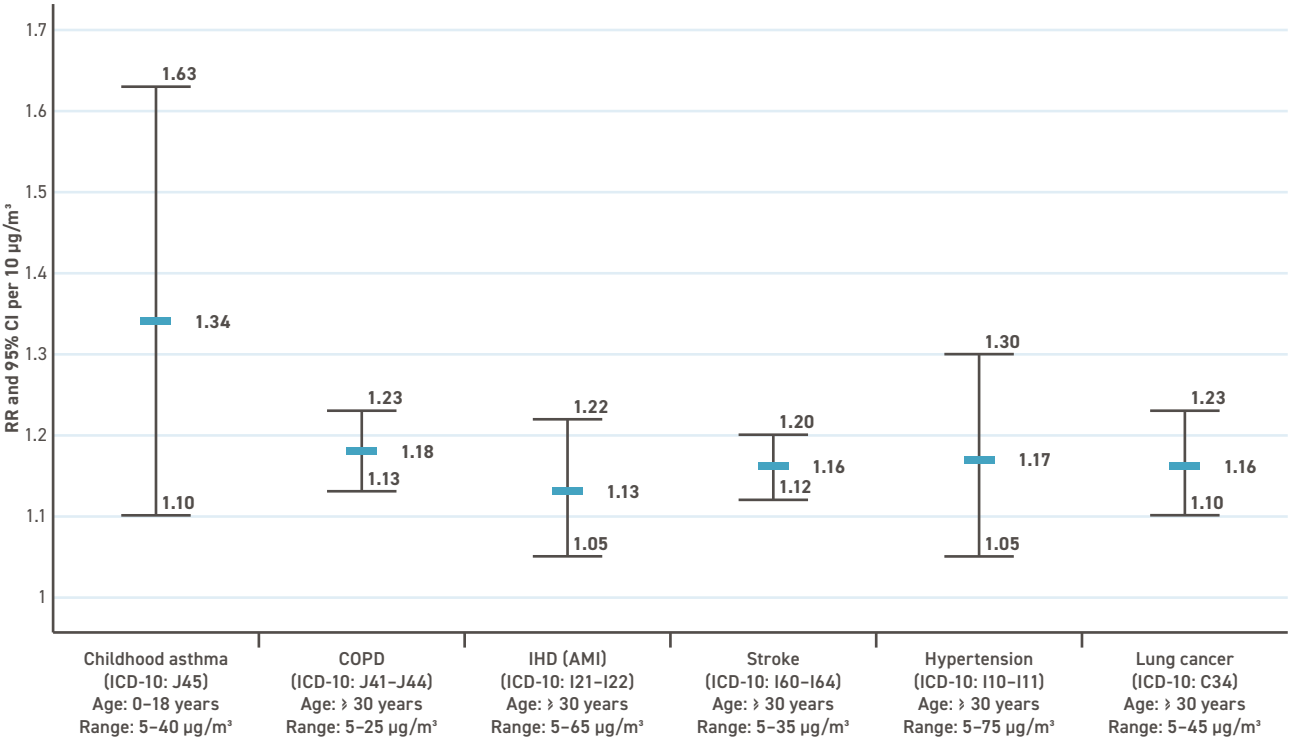
Chapters 3 and 4 are taken from the EMAPEC project, which was coordinated by WHO headquarters. For further details, users may refer to Orellano et al. (2023), Forastiere et al. (2024b) and WHO (2025a).

3.1 Long-term exposure to $PM_{2.5}$ and NO_2

The RRs linking the incidence of selected diseases with long-term exposure to $PM_{2.5}$, NO_2 and O_3 were identified within the framework of the EMAPEC project (Forastiere et al., 2024b; WHO, 2025a). In summary, the diseases considered in the analysis belonged to the group of outcomes for which the available US EPA causality determination indicated a "causal" or "likely to be causal" relationship with the exposure (including respiratory, cardiovascular and neurological effects, as well as lung cancer). Additionally, for type 2 diabetes, the relationship was classified as "suggestive" but there is growing epidemiological evidence for the association with $PM_{2.5}$ exposure. A total of 44 relevant systematic reviews were identified through a structured search of the literature, and the most recent reviews were evaluated to identify the most reliable sources of RRs. After verification of the quality of the systematic reviews and evaluation of the epidemiological evidence of the RR coefficients, nine outcomes related to long-term exposure to $PM_{2.5}$ and three outcomes for long-term exposure to NO_2 were advised for use in an HRA. No reliable CRFs were identified for long-term exposure to O_3. Depending on the outcome, between five and 21 original studies provided the basis for the pooled RRs. For most outcomes, the total number of subjects included in the meta-analyses ranged between 1.1 million and 5.7 million individuals, with the total pool of participants exceeding 40 million for studies related to dementia. The smallest number of study subjects was for the association between ALRI and NO_2 exposure: the meta-analysis was based on results from 11 cohorts with 107 000 participants. A reliable HRA (List A) is possible for six health outcomes related to $PM_{2.5}$ exposure (childhood asthma, COPD, IHD (acute myocardial infarction events), stroke, hypertension and lung cancer) (Fig. 5a), and for three outcomes related to NO_2 exposure (asthma and ALRI in children, and asthma in adults) (Fig. 5b). Three additional $PM_{2.5}$–outcome pairs were identified (type 2 diabetes, dementia and autism spectrum disorders (Fig. 5c) that could be used in an HRA, but results should be regarded as more uncertain (List B+). Other associations (e.g. between $PM_{2.5}$ and atrial fibrillation and Parkinson disease, and between NO_2 and COPD) were noted, but the current epidemiological evidence was graded as insufficient for use in an HRA (List B-).

Fig. 5. Proposed RRs from the meta-analyses of studies on the incidence of the selected diseases and long-term exposure (annual mean) to $PM_{2.5}$ assigned to List A (a), NO_2 assigned to List A (b), and $PM_{2.5}$ assigned to List B+ (c)

(a) Long-term exposure (annual mean) to $PM_{2.5}$ assigned to List A



(b) Long-term exposure (annual mean) to NO_2 assigned to List A

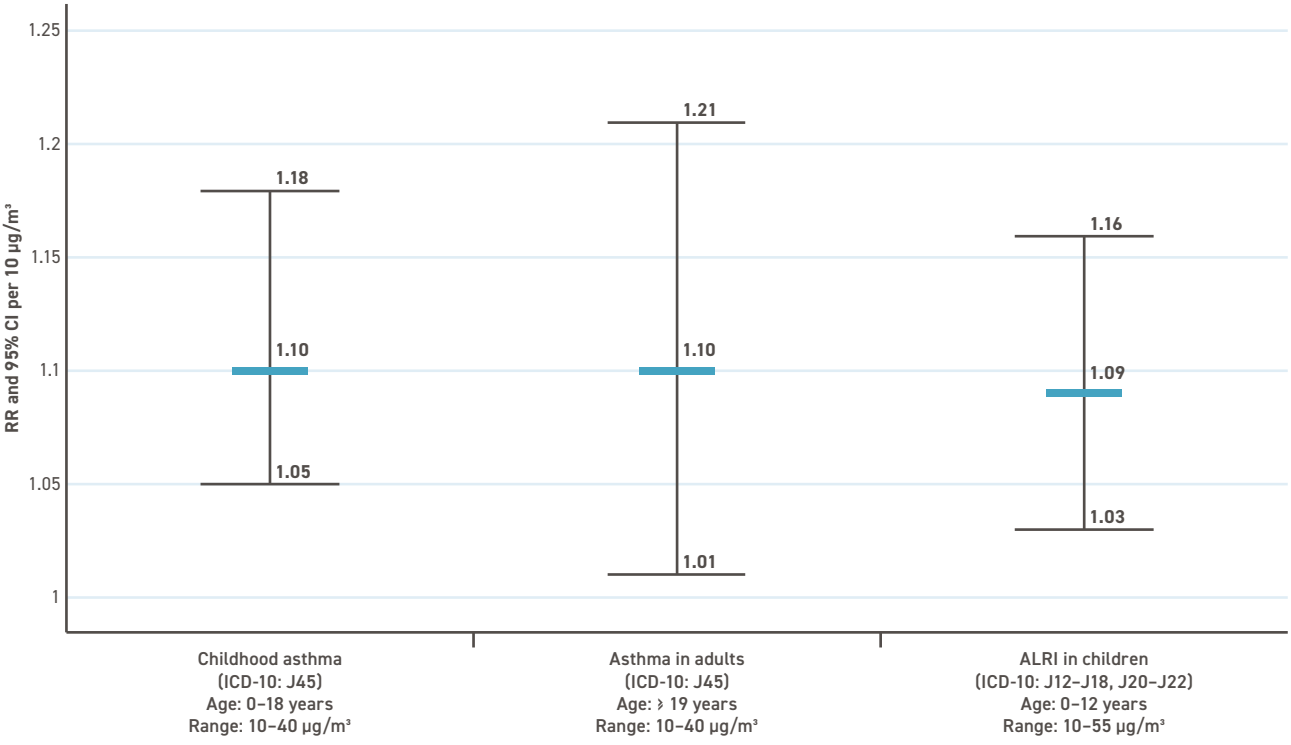
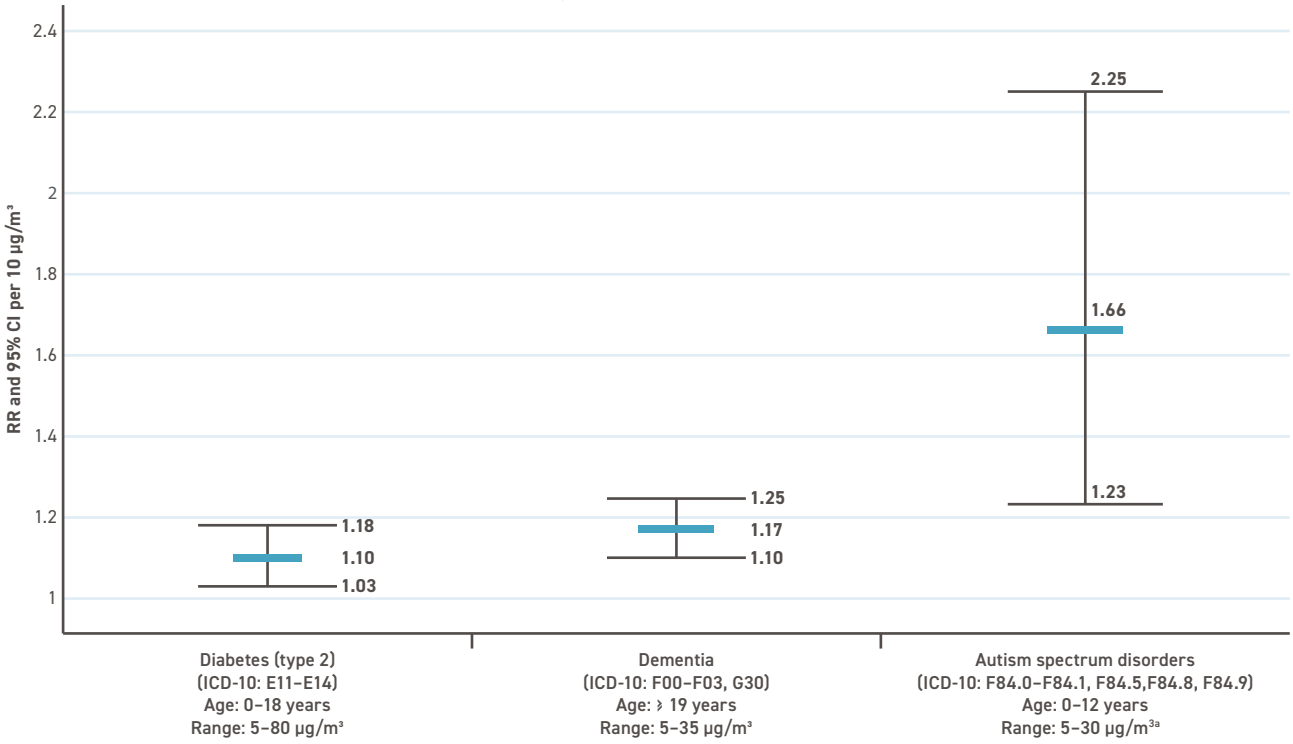


Fig. 5 contd

(c) Long-term exposure (annual mean) to $PM_{2.5}$ assigned to List B+



AMI: acute myocardial infarction

[a] For autism, restrict applicability of the CRF to exposure differences not larger than 10 µg/m³ within the indicated concentration range.

Source: data are taken from Forastiere et al. (2024b) and the updated RR for dementia is based on data from Best Rogowski et al. (2025).

Based on the accumulated evidence, the age ranges of the population at risk and the concentration ranges for the applicability were determined. As already noted for the RRs on mortality, the lower limit of the applicable exposure range was set at the WHO AQG level (5 µg/m³ for $PM_{2.5}$ and 10 µg/m³ for NO_2) for all the outcomes. There is good evidence in the original studies to support this decision. However, there was a greater variability between outcomes in evidence on the upper limit of the range: this varied from 25 µg/m³ to 75 µg/m³ for $PM_{2.5}$ and from 40 µg/m³ to 55 µg/m³ for NO_2. (Note that for consistency with the mortality analysis, the values of limits of the exposure range were rounded to the nearest 5 in this report.)

Since the $PM_{2.5}$ exposure contrasts in the original studies on autism spectrum disorders did not exceed 10 µg/m³, it is proposed to restrict the applicability of the RRs in an HRA to exposure differences of not larger than 10 µg/m³.

Wherever the original studies provided relevant information, the shape of the association was evaluated. It was concluded that there is insufficient evidence for a departure from linearity within the applicable concentration range.

The incidence of dementia and its impact on the economic evaluation of morbidity associated with pollution has notable public health significance. However, an evaluation identified several methodological and applicability concerns (Forastiere et al., 2024b). Recently, several new studies on dementia and $PM_{2.5}$ have been published, and an updated evaluation has been conducted. A recent systematic review and meta-analysis included 21 studies that considered over 17 million participants (Best Rogowski et al., 2025): the

revised RR was 1.17 per 10 μg/m^3 increase in $PM_{2.5}$ (95% CI: 1.10–1.25). This updated value is significantly lower than the previous estimate (Forastiere et al., 2024b). One meta-analysis excluded studies where dementia diagnosis was based on administrative data on hospital admissions (Best Rogowski et al., 2025); the inclusion of these studies markedly increased the RR. However, several methodological concerns about the evidence base remain, so the RR is still assigned to List B+.

3.2 Short-term exposure to $PM_{2.5}$, NO_2 and O_3

3.2.1 Hospital admissions

For short-term exposure, the determinations of "causal" or "likely to be causal" were taken from the US EPA ISA for $PM_{2.5}$ and respiratory and cardiovascular effects (US EPA, 2019, 2022), NO_2 and respiratory effects (US EPA, 2016), and O_3 respiratory and metabolic effects (US EPA, 2020). Therefore, EMAPEC considered as health outcomes hospital admissions/emergency room visits in the total population (all ages) and hospital admissions for cardiovascular and respiratory diseases (Table 9).

Table 9. Proposed RRs (95% CIs) for hospital admissions following short-term exposure to $PM_{2.5}$, NO_2 (24-hour mean) and O_3 (daily maximum of the 8-hour mean) to inform an HRA

Hospital admissions	ICD-10	List	RR (95% CI) per 10 μg/m^3	Range of me(di)an exposures (μg/m^3)
$PM_{2.5}$				
All cardiovascular	I00–I99	A	1.009 (1.0026–1.0153)	5–25
NO_2				
All respiratory	J00–J99	A	1.0057 (1.0033–1.0082)	10–65
O_3				
All respiratory	J00–J99	B+	1.0075 (1.003–1.012)	60–110

Source: data are taken from COMEAP (2022).

This guidance relied on the recent work completed by COMEAP in the United Kingdom (COMEAP, 2022). The three meta-analyses that COMEAP identified as being important for selecting RRs to quantify the effects of short-term exposure to air pollution on hospital admissions provided sufficient information to perform a quality assessment.

3.2.2 RADs

A RAD occurs when a person reduces his/her normal activities for the whole day because of illness or injury, with bed days, school-loss days (school absenteeism) and work-loss days (work absenteeism) included in the total number of RADs (Wilder, 1972). There is no determination of causality for the relationship of RADs to air pollution exposure; however, a suggestion of causality is assumed here on the basis of the link between RADs and diseases for which such a determination exists. This calls for additional caution regarding HRAs based on RAD indicators. A review commissioned by WHO headquarters for the EMAPEC

project investigated the associations between air pollutants and RADs in time-series studies of short-term exposures, measured as work-loss days or school-loss days (Orellano et al., 2023). Both were statistically significant associations for PM_{10} and $PM_{2.5}$, but not for NO_2 or O_3. The strongest evidence (List B+) was for the relationship with school-loss days (Table 10), which provided a statistically significant RR based on five studies from various regions, with a good distribution of study weights and acceptable heterogeneity (I^2 = 69%). However, the RR was rather imprecise (CI = 180% of the effect size). The results of this review were robust to sensitivity analyses based on the risk of bias in different domains. Confidence in the remaining associations that were evaluated was either unspecified (PM_{10}–RADs, $PM_{2.5}$–school-loss days) or assigned to List B- ($PM_{2.5}$–RADs, $PM_{2.5}$–respiratory RADs). The term unspecified was employed to indicate that insufficient data were available to assess the reliability of the CRF, and that an HRA should be done with caution.

Table 10. Proposed RR (95% CI) for school-loss days from short-term exposure (24-hour mean) to PM_{10} to inform an HRA

Outcome	Age (years)	List	RR (95% CI) per 10 µg/m³	Range of me(di)an exposures (µg/m³)
School-loss days	5–14	B+	1.0149 (1.0017–1.0283)	10–75

Source: data are taken from Orellano et al. (2023).

4. Economic assessment

The economic valuation of mortality effects generally relies on the metric value of a statistical life when considering the number of premature deaths avoided (Lindhjem et al., 2011) or of the value of a statistical life-year when considering the overall number of lost life-years avoided (Hammitt and Tunçel, 2023). Both metrics express a society's willingness to pay to reduce the probability of death among its population. Recent developments propose correcting the value of a statistical life and value of a statistical life-year to take account of an individual's life expectancy, quality of life and wealth status (Yin et al., 2021).

The economic evaluation of morbidity effects can involve three types of costs (Hunt and Ferguson, 2020; Dajnak et al., 2022): direct health costs include the resources consumed (e.g. charges arising from primary care, use of medication, screening and diagnostic testing, curative expenses, and rehabilitation costs), indirect costs include resources lost (e.g. loss of production or productivity by the patient or relatives), and welfare loss (changes in quality of life due to pain and suffering).

Economic assessment for a given country ideally requires data collection and studies specific to the country and to each health indicator. Since this is often incompatible with time and budget constraints, it is possible to rely on monetary values that already exist in the literature. In such a case, care must be taken to ensure that the transferred values are consistent with the country's health system and income level. Regarding the mortality effect, the broader group including a specific cause of death is advised. Regarding morbidity, the economic evaluation is more complex, especially for long-term effects, and follows the EMAPEC decisions (WHO, 2025a).

Losses of well-being associated with illness can be based directly on willingness to pay to avoid hospitalization or illness (chronic or acute) or on an evaluation of disability-adjusted life-years (GBD 2021 Risk Factors Collaborators, 2024). Lastly, the economic costs should be expressed at the national price level for the year/period studied and based on the inflation and exchange rates, as provided, for example, by local agencies or the World Bank (World Bank, 2025).

Three points deserve particular attention in economic assessments: double counting of economic effects, temporal issues and economic uncertainties.

Double counting of mortality and long-term morbidity economic effects can occur for several reasons. First, it is proposed to avoid double counting of effects among cause-specific mortality outcomes by using the broader mortality outcome (section 1.3.4.2). Secondly, when summing morbidity health effects (i.e. the effects of diseases associated with a given pollutant, for a given scenario), a (small) part of the cost may represent both the principal cost of one disease and the complication cost of another. Thirdly, for diseases that have a significant effect on survival, the effect on mortality is measured in terms of delayed death or changes in the number of years of life lived. The loss of well-being associated with long-term morbidity for patients or their relatives may be partially included in

the valuation of mortality effects. Lastly, the most accurate economic effect should be based on net effects over the long term from a societal perspective. The point at stake is the comparison of the joint morbidity and mortality effects due to a change in air pollution exposure: the economic valuation of an attributable death (mortality) on the one hand, and the avoided morbidity costs (counterfactual scenario) over the expected lifetime on the other.

Temporal issues matter when economic results are intended to support decision-making (e.g. in cost–benefit analyses). For short- and long-term effects, the change in population exposure will (generally) not be immediate but instead will be gradual due to political/technical implementation timescales. This affects the flows of both morbidity and mortality effects and, as these flows occur at different times, expressing them in current economic value (i.e. discounting) and the future adjustments due to growth in economic output and health system running costs will affect the differences in the total health and economic valuation.

Economic uncertainties are based on an assessment that is, for some components, more subjective than scientific, involving the assessment method and the unit monetary values used for mortality, as well as technical parameters such as discount rates or the valuation of welfare loss. Given that long-term effects involve higher unit economic values (cost per case of illness or attributable mortality), the economic uncertainty should be greater for these than for short-term effects. Accounting for epidemiological and economic uncertainties can be further addressed using a sensitivity study or, more formally, by considering a statistical uncertainty analysis based, for example, on simplified methods (as described in Rabl et al., 2014) or using Monte Carlo or Bayesian approaches in which parameters are replaced with probability distributions that describe the confidence range of the input data.

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Annex 1. Additional materials for methodological considerations

Combining the effects of long-term exposure to $PM_{2.5}$ and NO_2 on natural mortality

A systematic search identified 17 cohort studies that used both single- and two-pollutant models to assess long-term exposure to particulate matter, where particles have an aerodynamic diameter equal to or less than 2.5 µm ($PM_{2.5}$) and nitrogen dioxide (NO_2) and their association with all-cause mortality (Chen et al., 2024). The pooled relative risks (RRs) for mortality from single-pollutant (RR1) and two-pollutant (RR2) models were 1.053 (95% confidence interval (CI): 1.034–1.071) and 1.035 (95% CI: 1.014–1.057), respectively, for a 5 µg/m³ increase in $PM_{2.5}$. The RRs for a 10 µg/m³ increase in NO_2 were 1.032 (95% CI: 1.014–1.049) for the RR1 model and 1.024 (95% CI: 1.000–1.049) for the RR2 model. The absolute coefficient differences between models RR1 and RR2 (ln(RR1)-ln(RR2)) were 0.017 for $PM_{2.5}$ and 0.008 for NO_2. The calculated percentage coefficient differences ((ln(RR1)-ln(RR2))/ln(RR1)) from the RR1 to the RR2 model were 33.4% for $PM_{2.5}$ and 24.7% for NO_2. It is clear from simple calculations that the use of only $PM_{2.5}$ to represent the mixture of both pollutants would not be appropriate because the results vary according to the $NO_2/PM_{2.5}$ ratio (the ratio of the increments of NO_2 and $PM_{2.5}$, i.e. 10 µg/m³ for NO_2 and 5 µg/m³ for $PM_{2.5}$) (Chen et al., 2024), with larger ratios leading to greater underestimation.

The combined impact of $PM_{2.5}$ and NO_2 on mortality can be estimated using methods derived from Chen et al. (2024), as follows.

The new systematic reviews and meta-analyses provide updated RRs:

$PM_{2.5}$: RR = 1.046 per 5 µg/m³ increase (Orellano et al., 2024)
NO_2: RR = 1.05 per 10 µg/m³ increase (Kasdagli et al., 2024).

Using the calculated percentage coefficient differences from Chen et al. (2024), the revised RRs become:

$PM_{2.5}$: RR = 1.0304 [or, Exp((ln(1.046)) × (1–0.334))] per 5 µg/m³
NO_2: RR = 1.0374 [or, Exp((ln(1.05)) × (1–0.247))] per 10 µg/m³.

These revised RRs can be applied in PAF calculations to estimate the combined impact of $PM_{2.5}$ and NO_2.

For example, to calculate the combined PAF for natural mortality with exposure changes of a 5 μg/m³ increase in $PM_{2.5}$ and a 20 μg/m³ increase in NO_2 using the revised RRs:

$PM_{2.5}$: RR = 1.0304 (for 5 μg/m³)
NO_2: RR = 1.0762 (for 20 μg/m³).

The $RR_{combined}$ = $RR(PM_{2.5})$ × $RR(NO_2)$ = 1.032×1.076 = 1.11

Assuming an exposure prevalence (p) of 100% (i.e. p = 1):

Population attributable fraction = (p × (RR-1)) / (1+p × (RR-1)) = (1 × (1.11–1)) / (1+1 × (1.11–1)) = 0.11/1.11 = 0.099 or 9.9%

Natural mortality estimates

Table A1.1 shows the natural mortality estimates for 2019.

Table A1.1. Share of all-cause deaths due to natural mortality estimates for 2019, by WHO region

WHO regions	Value	Minimum	Maximum
African Region	91%	88%	97%
Region of the Americas	92%	85%	96%
South-East Asia Region	93%	83%	97%
European Region	95%	93%	98%
Eastern Mediterranean Region	92%	91%	96%
Western Pacific Region	94%	91%	97%

Note: for the WHO African Region, the 95% CI is 88–92%; for the WHO European Region, the 95% CI is 94–97%.
Source: based on WHO (2025d).

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5 All references were accessed on 8 September 2025.

Annex 2. Additional tables and figures

Tables A2.1–A2.4 provide the Estimating the Morbidity from Air Pollution and its Economic Costs (EMAPEC) classification criteria for pollutant exposure–mortality outcome pairs: particulate matter, where particles have an aerodynamic diameter equal to or less than 2.5 µm ($PM_{2.5}$) or less than 10 µm (PM_{10}), nitrogen dioxide (NO_2) and ozone (O_3). Figs A2.1–A2.6 show ranges for short-term exposures informed by the Multi-Country Multi-City studies. Table and figures are based on levels reported in Kasdagli et al. (2024) and Orellano et al. (2024), or reproduced from Liu et al. (2019), Vicedo-Cabrera et al. (2020) or Meng et al. (2021).

Table A2.1. Detailed EMAPEC classification criteria for long-term exposure to $PM_{2.5}$ with mortality outcomes

Outcome	Causality	List	RR (95% CI) per 10 µg/m³	Criterion						
				1i	1ii	2i	2ii	2iii	2iv, I^2, 80% PI	2v
Natural	Causal	A	1.10 (1.06–1.13)	53	✓	✓	✓	66%	100%, 0.97–1.24	✓
Circulatory	Causal	A	1.13 (1.10–1.15)	42	✓	✓	✓	39%	95%, 1.05–1.21	✓
Cerebrovascular (including stroke)	Causal	A	1.15 (1.10–1.19)	28	✓	✓	✓	62%	92%, 1.04–1.27	✓
Ischaemic heart disease	Causal	A	1.14 (1.10–1.19)	34	✓	✓	✓	59%	94%, 1.03–1.27	✓
Respiratory (non-malignant)	Likely	A	1.14 (1.08–1.20)	28	✓	✓	✓	87%	89%, 0.99–1.31	✓
Chronic obstructive pulmonary disease	Likely	A	1.14 (1.08–1.20)	19	✓	✓	✓	86%	84%, 1.02–1.27	NA
Acute lower respiratory infection	Likely	A	1.20 (1.10–1.33)	12	✓	✓	✓	113%	82%, 1.01–1.44	NA
Trachea, bronchus and lung cancer	Causal (IARC)	A	1.09 (1.05–1.14)	26	✓	✓	✓	88%	84%, 1.00–1.20	✓

✓: fulfilled; X; not fulfilled; CI: confidence interval; IARC: International Agency for Research on Cancer; PI: prediction interval; RR: relative risk; NA: not assessed or not applicable.
Sources: data are taken from US EPA (2019, 2022), Forastiere et al. (2024) and Orellano et al. (2024).

Table A2.2. Detailed EMAPEC classification criteria for long-term exposure to PM_{10} with mortality outcomes

Outcome	Causality	List	RR (95% CI) per 10 µg/m³	Criterion						
				1i	1ii	2i	2ii	2iii	2iv, I^2, 80% PI	2v
Natural	Causal (because of $PM_{2.5}$)	A	1.08 (1.05–1.11)	28	✓	✓	✓	72%	98%, 0.99–1.18	NA
Circulatory	Causal (because of $PM_{2.5}$)	A	1.08 (1.04–1.12)	26	✓	✓	✓	98%	98%, 0.97–1.20	NA
Cerebrovascular	Causal (because of $PM_{2.5}$)	B-	1.05 (0.97–1.13)	15	X	✓	✓	322%	99%, 0.88–1.25	NA
Ischaemic heart disease	Causal	B+	1.06 (1.02–1.09)	16	✓	✓	✓	133%	88%, 0.99–1.13	NA
Respiratory (non-malignant)	Likely (because of $PM_{2.5}$)	A	1.12 (1.08–1.17)	21	✓	✓	✓	76%	92%, 1.02–1.24	NA
Chronic obstructive pulmonary disease	Likely (because of $PM_{2.5}$)	B+	1.22 (1.03–1.44)	7	✓	✓	✓	192%	83%, 0.89–1.67	NA
Acute lower respiratory infection	Likely	NA	NA	1	NA	NA	NA	NA	NA	NA
Trachea, bronchus and lung cancer	Causal (IARC)	A	1.10 (1.05–1.15)	17	✓	✓	✓	99%	94%, 1.00–1.22	NA

✓: fulfilled; X; not fulfilled; CI: confidence interval; IARC: International Agency for Research on Cancer; PI: prediction interval; RR: relative risk; NA: not assessed or not applicable.
Sources: data are taken from US EPA (2019, 2022), Forastiere et al. (2024) and Orellano et al. (2024).

Table A2.3. Detailed EMAPEC classification criteria for long-term exposure to NO_2 with mortality outcomes

Outcome	Causality	List	RR (95% CI) per 10 µg/m³	Criterion						
				1i	1ii	2i	2ii	2iii	2iv, I^2, 80% PI	2v
Natural	Likely	A	1.05 (1.03–1.07)	34	✓	✓	✓	80%	95%, 0.98–1.12	✓
Circulatory	Suggestive	B+	1.05 (1.03–1.08)	28	✓	✓	✓	100%	97%, 0.97–1.15	✓
Cerebrovascular	Suggestive	B-	1.08 (0.99–1.19)	20	X	✓	✓	250%	98%, 0.82–1.43	NA

Table A2.3 contd

Outcome	Causality	List	RR (95% CI) per 10 µg/m³	Criterion						
				1i	1ii	2i	2ii	2iii	2iv, I^2, 80% PI	2v
Ischaemic heart disease	Suggestive	B+	1.05 (1.03–1.08)	20	✓	✓	✓	100%	95%, 0.99–1.12	NA
Respiratory (non-malignant)	Likely	A	1.05 (1.03–1.07)	25	✓	✓	✓	80%	90%, 0.99–1.11	✓
Chronic obstructive pulmonary disease	Likely	A	1.04 (1.02–1.06)	15	✓	✓	✓	100%	62%, 0.99–1.09	NA
Acute lower respiratory infection	Likely	A	1.08 (1.04–1.12)	9	✓	✓	✓	100%	92%, 1.00–1.16	NA
Trachea, bronchus and lung cancer	Suggestive	B+	1.07 (1.04–1.10)	20	✓	✓	✓	86%	92%, 0.99–1.14	✓

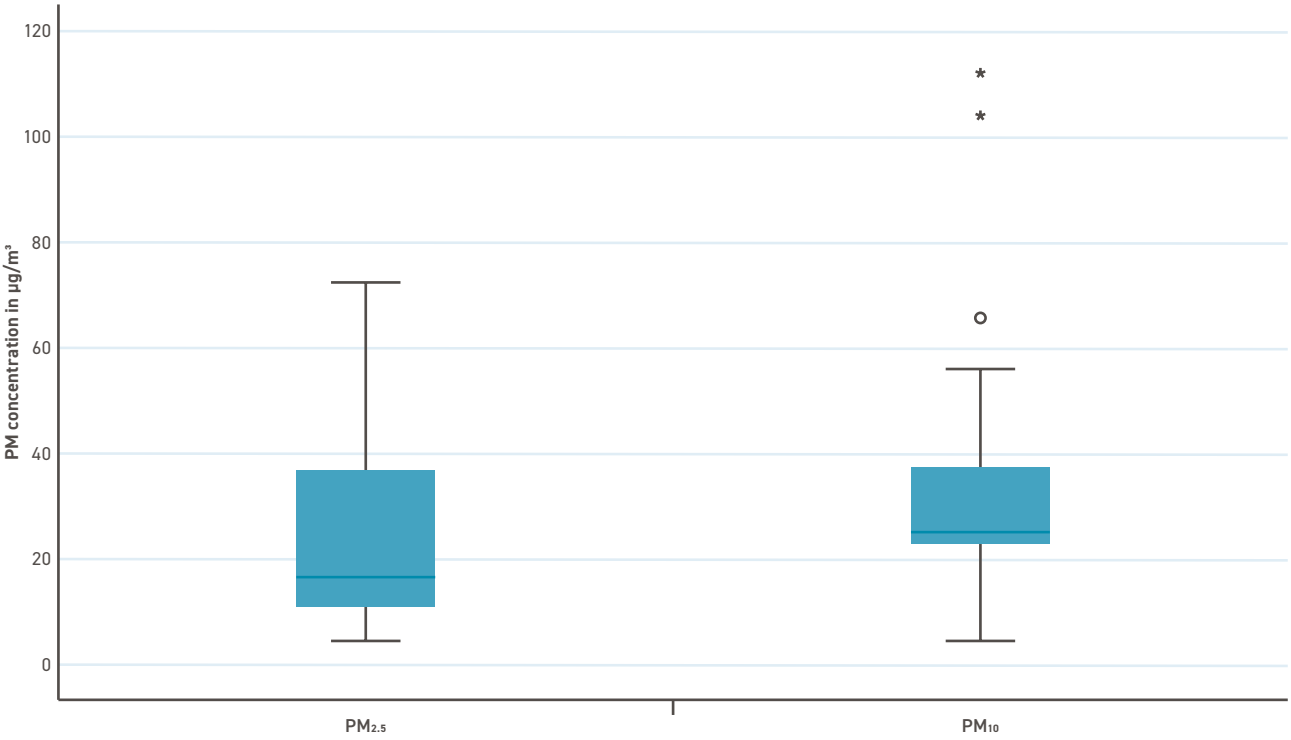
✓: fulfilled; X; not fulfilled; CI: confidence interval; PI: prediction interval; RR: relative risk; NA: not assessed or not applicable.
Sources: data are taken from US EPA (2016), Forastiere et al. (2024) and Orellano et al. (2024).

Table A2.4. Detailed EMAPEC classification criteria for long-term exposure to O_3 with mortality outcomes

Pollutant	Outcome	Causality	List	RR (95% CI) per 10 µg/m³	Criterion						
					1i	1ii	2i	2ii	2iii	2iv, I^2, 80% PI	2v
O_3 annual	Natural	Suggestive	B-	1.01 (0.96–1.06)	9	X	✓	✓	1000%	92%, 0.91–1.11	✓
	Respiratory (non-malignant)	Likely	B+	1.05 (1.02–1.08)	6	✓	✓	X	120%	65%, 1.00–1.09	NA
	COPD[a]	NA	NA	NA	2	NA	NA	NA	NA	NA	NA
	ALRI[a]	NA	NA	NA	2	NA	NA	NA	NA	NA	NA
O_3 warm/peak season	Natural	Suggestive	B-	1.01 (0.97–1.04)	12	X	✓	✓	700%	98%, 0.92–1.10	✓
	Respiratory (non-malignant)	Likely	B-	1.01 (0.98–1.03)	9	X	✓	✓	500%	92%, 0.95–1.06	NA
	COPD	NA	B-	1.00 (0.96–1.04)	7	X	✓	✓	> 1000%	95%, 0.92–1.09	NA
	ALRI	NA	B-	1.02 (0.99–1.04)	4	X	✓	✓	250%	80%, 0.97–1.07	NA

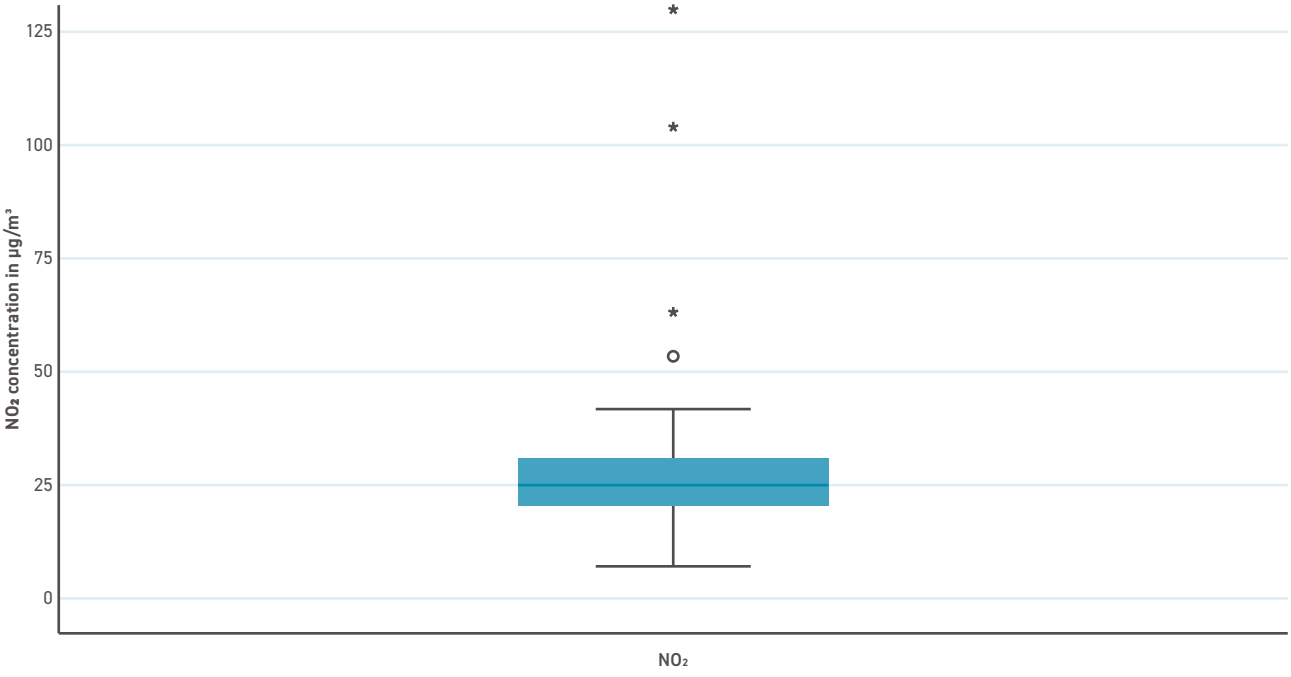
✓: fulfilled; X; not fulfilled; ALRI: acute lower respiratory infection; CI: confidence interval; COPD: chronic obstructive pulmonary disease; PI: prediction interval; RR: relative risk; NA: not assessed or not applicable.
[a] Outcome omitted because of inadequate number of studies.
Source: data are taken from Forastiere et al. (2024), Kasdagli et al. (2024) and US EPA (2020).

Fig. A2.1. Box plots for the ranges of me(di)an ambient $PM_{2.5}$ and PM_{10} concentrations for studies used in all-cause mortality analyses



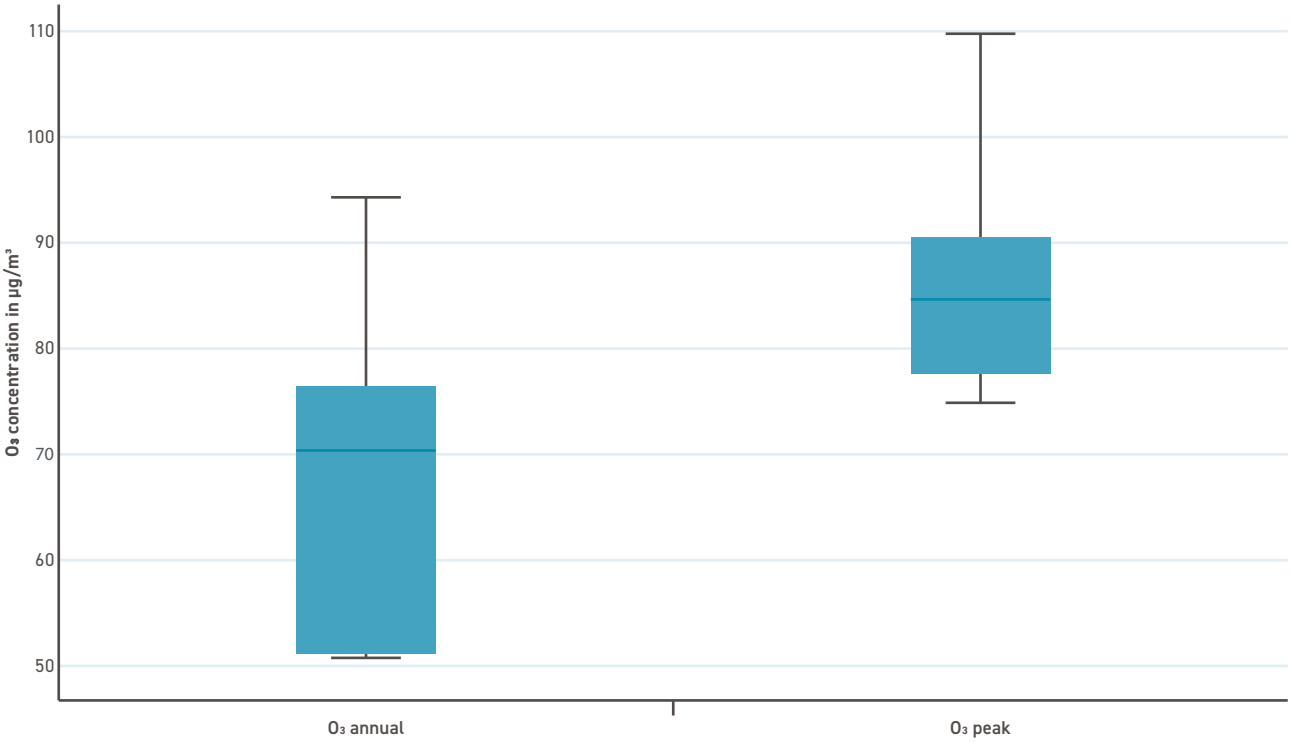
Source: data are taken from Orellano et al. (2024).

Fig. A2.2. Box plots for the ranges of me(di)an ambient NO_2 for studies in all-cause mortality analyses



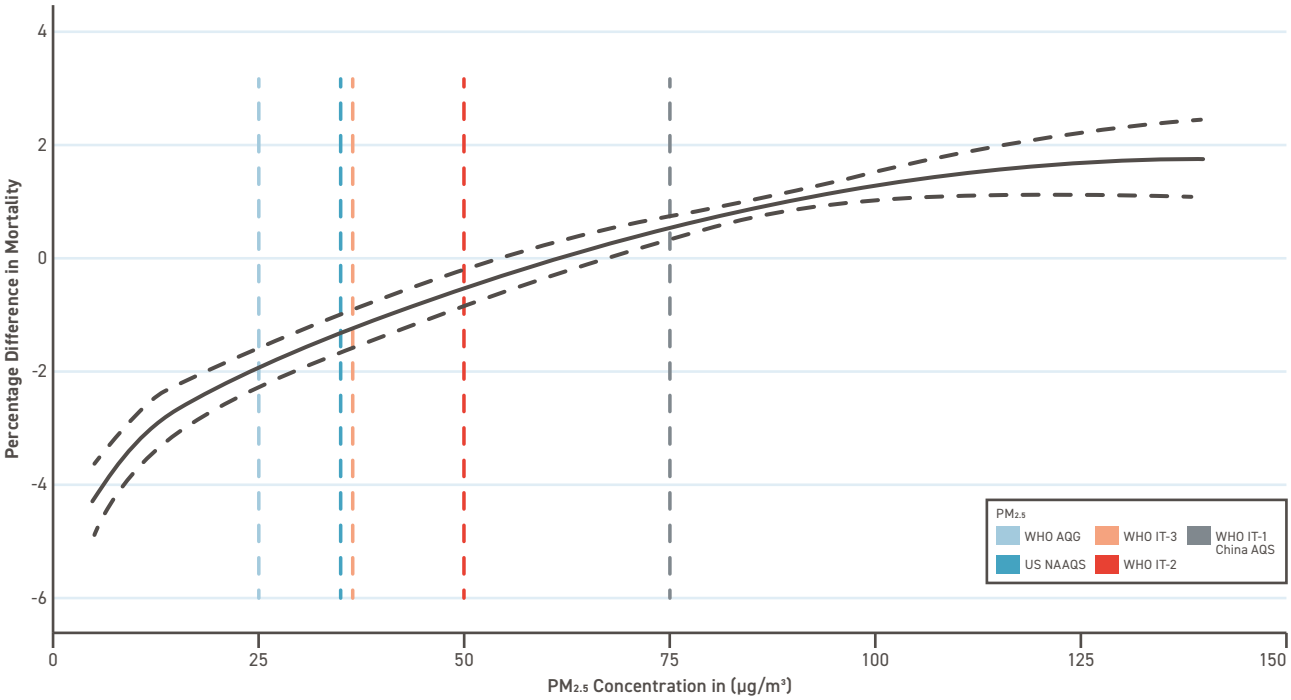
Source: data are taken from Kasdagli et al. (2024).

Fig. A2.3. Box plots for the ranges of me(di)an annual or warm/peak season O_3 for studies in respiratory mortality analyses



Source: data are taken from Kasdagli et al. (2024).

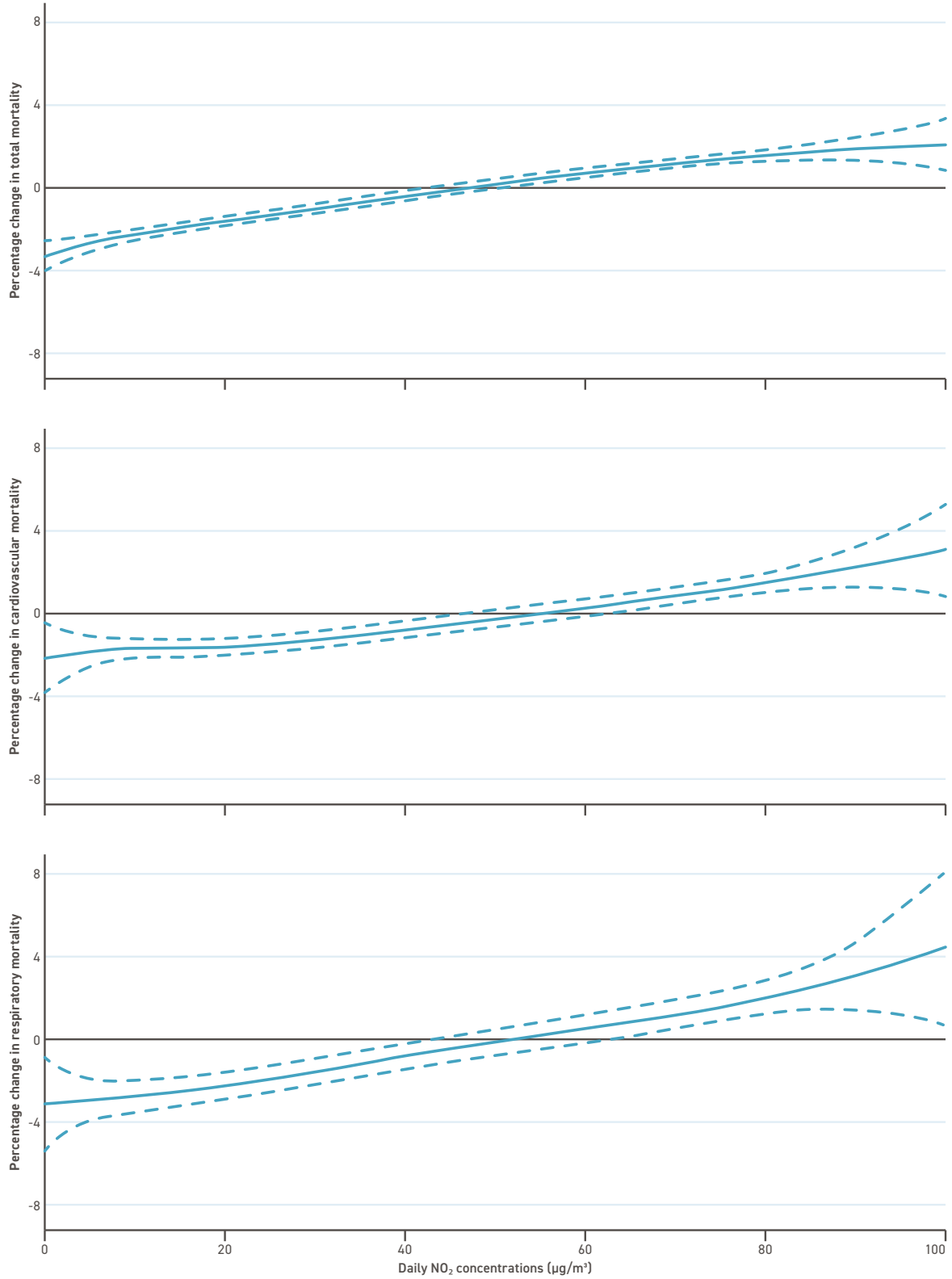
Fig. A2.4. Association between short-term exposure to $PM_{2.5}$ and all-cause mortality



China AQS: China Air Quality Standard; WHO AQG: WHO Air Quality Guidelines; WHO IT-1: Interim Target 1; WHO IT-2: Interim Target 2; WHO IT-3: Interim Target 3; US NAAQS: United States National Ambient Air Quality Standard.

Source: reproduced from Liu et al. (2019), Fig. 3, panel B. Copyright© 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

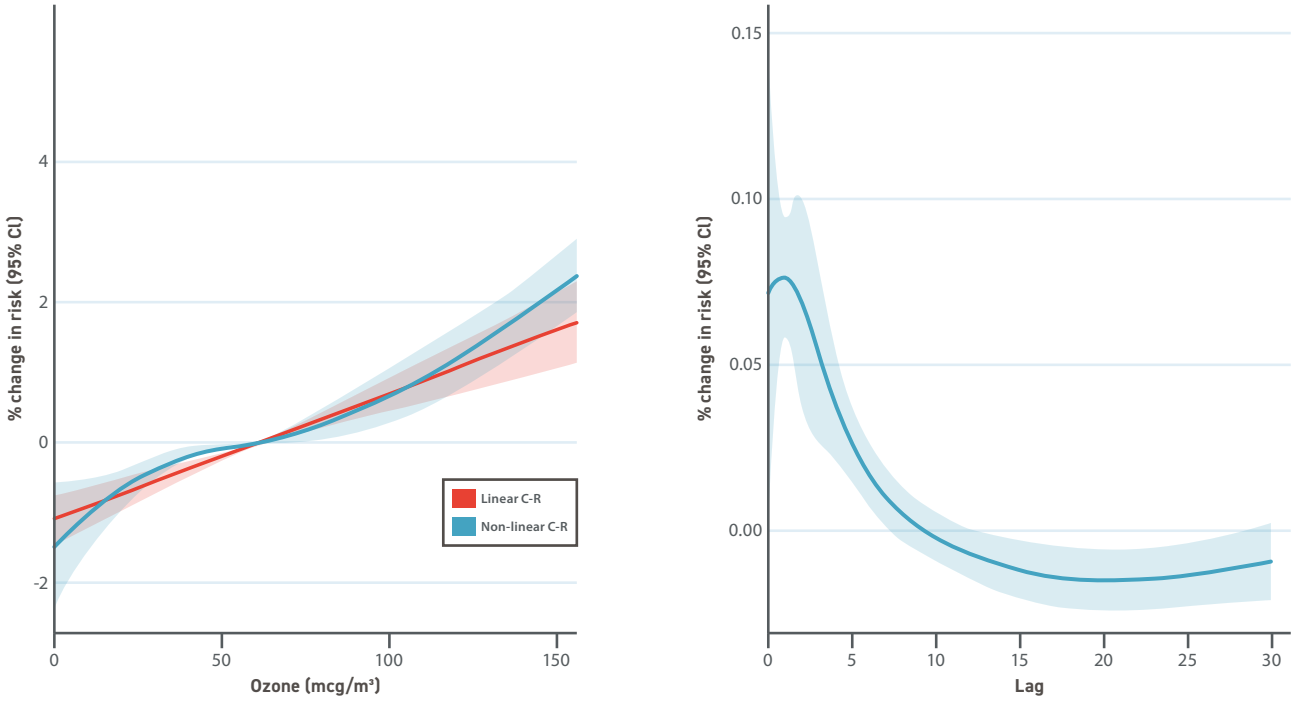
Fig. A2.5. Concentration–response curve between NO_2 concentration (lag 1) and total, cardiovascular and respiratory mortality



Note: The vertical scale can be interpreted as the relative change of the mean effect of NO_2 on mortality; the fraction of the curve below zero denotes a smaller estimate than the mean effect.

Source: Meng et al. (2021), Fig. 2. Reproduced under the CC-BY-NC-ND 4.0 licence.

Fig. A2.6. Association between short-term exposure to O_3 and all-cause mortality



Notes: Comparison of the average concentration–response (C–R) shapes using linear and non-linear functions (left) and lag–response associations up to 30 days (right) per 10-unit increase in ozone. q-AIC linear: 10376950, Q-AIC non-linear: 10379020.
Source: Vicedo-Cabrera et al. (2020), eFig. 2. Reproduced under the CC-BY 4.0 licence (https://creativecommons.org/licenses/by/4.0/).

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