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REVIEW

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The last decade of air pollution epidemiology and the challenges of quantitative risk assessment

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Abstract

Epidemiologic research and quantitative risk assessment play a crucial role in transferring fundamental scientific knowledge to policymakers so they can take action to reduce the burden of ambient air pollution. This commentary addresses several challenges in quantitative risk assessment of air pollution that require close attention. The background to this discussion provides a summary of and conclusions from the epidemiological evidence on ambient air pollution and health outcomes accumulated since the 1990s. We focus on identifying relevant exposure-health outcome pairs, the associated concentration-response functions to be applied in a risk assessment, and several caveats in their application. We propose a structured and comprehensive framework for assessing the evidence levels associated with each exposure-health outcome pair within a health impact assessment context. Specific issues regarding the use of global or regional concentration-response functions, their shape, and the range of applicability are discussed.

Keywords Air pollution, Chemicals, Concentration-response function, Health Impact Assessment, Mortality, Morbidity, Nitrogen Dioxide, Risk assessment, Particles, $PM_{2.5}$

Introduction

It is widely acknowledged that air pollution is one of the most significant environmental risks to health globally [76]. The updated World Health Organization (WHO) air quality guidelines (AQGs), published in September 2021, underscore the urgent need for immediate action to combat the adverse effects of pollutants such as fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) on public health and the environment [85]. Modern quantitative health risk assessment (HRA) plays a crucial role in transferring fundamental scientific knowledge to policymakers, empowering them to take action to reduce the burden of air pollution, and evaluating the health benefits of interventions. Rigaud et al.'s recent contribution to this Journal (2024) provides an extensive overview of HRA methods and offers excellent examples. This commentary addresses some of the challenges in quantitative risk assessment of ambient air pollution that require close attention, especially considering the lessons learnt from the recently completed WHO project Estimating the Morbidity from Air Pollution and its Economic Costs (EMAPEC) [26]. A summary of the epidemiological evidence on air pollution and health

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outcomes accumulated over the last decades provides a background to this discussion.

Early epidemiological studies on short and long-term exposure

During the early stages of research in environmental epidemiology, the identification of an association between short (on the scale of hours to days) and long-term exposure to air pollution (on the scale of months to years) and various adverse health outcomes, particularly the impact on mortality, laid the foundation for quantifying the attributable burden of pollution. Short-term observational studies began gaining prominence in the late 1980s and early 1990s [6, 67, 68]. These studies were driven by growing concerns about air quality and its impact on public health, particularly in urban areas with significant air pollution levels. Throughout the 1990s, these short-term studies expanded, particularly with the use of time-series analyses, which examined daily fluctuations in air pollution levels and corresponding health outcomes, such as hospital admissions and mortality, in several cities [39]. These studies provided compelling evidence of the acute health effects of air pollution. Regarding long-term exposure, a seminal air pollution research paper published in 1993, the 'Six Cities' cohort study in the United States [21], demonstrated a link between mortality and long-term exposure to $PM_{2.5}$. This discovery gained further support in 1995 after the analysis of the health data from the American Cancer Society (ACS), a cohort of approximately half a million residents from across the United States [61], which revealed an almost linear increase in mortality risk across the entire range of observed $PM_{2.5}$ annual mean concentrations (from 10 to 30 $\mu g/m^3$) in urban background areas. A subsequent 2002 analysis of cardiovascular and lung cancer mortality with exposure to $PM_{2.5}$ [61] of the same ACS cohort triggered research into the biological mechanisms responsible for these effects. Note that the statistical methodology used in the ACS study was advanced and considered several individual potential confounders. The potential spatial autocorrelation due to missing or mismeasured risk factors spatially correlated with air pollution was addressed in the statistical model by incorporating a spatially-varying random-effects component to correct for autocorrelation, a practice that has been in common use in subsequent years. This overall evidence led to the formulation of the first global air quality guidelines by WHO in 2005 [84].

The first decade of the 21st century witnessed a convergence of epidemiological studies, controlled human exposure trials, and animal experiments. Epidemiological studies in humans (both on short- and long-term exposures) have provided refined estimates of environmental risks, with evidence suggesting that associations between PM and health outcomes are present even at ambient concentrations below the WHO air quality guideline levels. Mechanistic studies in animals and humans have provided a framework for understanding the pathways by which air pollution exposure may predispose individuals to health effects. This interdisciplinary approach deepened the understanding of the cardiovascular effects of PM exposure and confirmed the causality of $PM_{2.5}$ effects [5]. Results from cohort studies during this period further strengthened the epidemiological evidence of the effects of $PM_{2.5}$ and NO_2 on all-cause (in many cases non-accidental or natural mortality) and cause-specific mortality, and the development (incidence) of selected cardiovascular and respiratory diseases. Evidence from European cohorts, such as the collaborative ESCAPE study [1], confirmed earlier findings reported in North American studies. In addition, epidemiological studies began using administrative databases, including census and mortality registries, which enabled large-scale data pooling of millions of individuals for a period extending a decade or longer, as exemplified by the observational study of the 2.1 million people from Canada [16] and 1.3 million residents of Rome [10]. Exposure to ultrafine particles has been gaining attention because of the potential translocation from the lungs to the circulatory system and the possible effects on the heart [35, 55].

The last decade of air pollution epidemiology

Several studies based on "administrative cohorts" have been published in the last decade [7, 11, 17, 19, 25]. Cohorts based on administrative data have several advantages over "traditional cohorts" in investigating air pollution risks, namely their size, including millions of people, their representativeness of the general population, including different demographic and socioeconomic groups, enhancing the generalizability of findings, data collected over many years that allow for an extended follow-up. These advantages make administrative cohorts a valuable resource for large-scale, population-based research. However, the lack of detailed individual-level data on lifestyle factors is a drawback. This limitation has been partially overcome using area-based indicators to represent individual data, for example, area-based socioeconomic status (SES) as a surrogate for individual SES. In addition, several cohorts have used "indirect adjustment" for individual confounders that employs an ancillary database that matches the demographic characteristics of the original cohort and contains information

on both the individual factors (that are missing in the original cohort) and air pollution exposure data [24, 73].

While most initial cohort studies were conducted in North America and Europe, areas in which populations were exposed to low or medium levels of $PM_{2.5}$ concentration (< 30 μg/m^3), the last decade has seen a notable expansion of epidemiological studies in regions with higher ambient air pollution levels, particularly in China and Korea [43, 46], where observed PM exposures were typically 2 to 4 times higher than in previous studies. The newer studies accounted for various confounders that may influence mortality, such as diet, lifestyle, and climate. A meta-analysis published in 2020, specifically designed to support the work in updating the WHO AQGs, considered the findings from over 100 cohort studies that examined the link between PM_{10} or $PM_{2.5}$ and all-cause and cause-specific premature mortality [12]. This latter meta-analysis has been recently updated to consider several studies published in the last few years [57].

The literature on air pollution and its impact on health has witnessed significant methodological advancements over the past decade. Firstly, the modelling of air pollution exposure has undergone substantial enhancements. Early evaluations at the population level relied primarily on fixed monitors, which, while providing benchmark standards, were limited in assessing small-scale exposure variability due to geographical constraints. To address this issue, recent air pollution exposure assessments have incorporated various indicator variables to measure fine-scale exposures, including land-use regression variables to better capture a subject's proximity to roads and industrial facilities, as well as using remote sensed satellite measurements with appropriate downscaling, and results of chemical transport model (CTM) estimates of $PM_{2.5}$ and NO_2 concentrations [18, 20, 30, 80]. These enhancements have broadened the geographical coverage of exposures, especially in areas lacking physical monitoring stations, to provide highly spatially resolved concentration maps in both urban and rural settings, with a typical resolution scale of one kilometre, or less (100 m) in some cases. This spatial precision allows for addressing issues related to community exposure disparities and pinpointing local pollution hotspots. A recent application of these models in the US over the past decade revealed an increase in racial and ethnic relative disparities in $PM_{2.5}$-related mortality and NO_2-related pediatric asthma despite overall declines in public health effects associated with these pollutants [40].

Secondly, notable systemic consequences of air pollution have been identified, leading to additional adverse health outcomes. While respiratory and cardiovascular conditions have traditionally been linked to air pollution, recent studies suggest potential associations with neurological conditions (such as Parkinson's and Alzheimer's disease), diabetes, various types of cancer (in addition to lung cancer, which was studied long before), neurobehavioral development issues in children, mental disorders, and perinatal health [75]. Ongoing research explores the mechanistic pathways connecting environmental exposure to these health outcomes, highlighting the potential role of air pollution-induced inflammatory responses and the persistent generation of reactive oxygen radicals [53]. Moreover, investigations into the intake of ultrafine particles and their passage across biological barriers, including the circulatory system, blood-brain barrier, and placental barrier, have spurred additional insights. Ultrafine particles can reach all organs of the body, and potentially accumulate at sites of disease [66]. Epidemiological research on ultrafine particles is complicated because of the difficulties in exposure assessment, but increasing evidence in both North America and Europe suggests important health impacts [56].

Most recently, three large-scale studies funded by the Health Effects Institute (HEI) have investigated the health effects of low-level air pollution exposure in Canada, the United States, and Europe. These studies are the "Mortality Air Pollution Associations in Low Exposure Environments" (MAPLE) Canadian study by Brauer et al. [3], the USA Medicare study by Dominici et al. [23], and the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) by Brunekreef et al. [7]. These studies included millions of participants, employed advanced exposure assessment techniques, and used comprehensive statistical analyses with innovative approaches. All three studies reported statistically significant positive associations between long-term $PM_{2.5}$ exposure and mortality risks in nationally representative administrative cohorts. The hazard ratios (HR) and 95% confidence intervals (CI) associated with an increase in $PM_{2.5}$ exposure of 5 μg/m^3 and mortality from natural causes were as follows: 1.041 (95%CI 1.036, 1.047) in the Canadian Census Health and Environment Cohorts (CanCHEC) in MAPLE; 1.032 (95%CI 1.029, 1.036) in the USA Medicare cohort; and 1.053 (95%CI 1.021, 1.085) in the six ELAPSE administrative cohorts. Note that the USA Medicare cohort used the all-cause mortality (i.e. including accidental deaths) in the cohort older than 65 years old. The pooled analysis of the three studies provided by Chen et al. [11] suggests an increasing risk starting from the lowest observed exposure level (3.7 μg/m^3). The ELAPSE study in Europe, using pooled data from several traditional cohorts [74], also explored several morbidity outcomes, including myocardial infarction and stroke [88], asthma in adults [51], COPD [50], and lung cancer [37].

The insights derived from these "low-level studies" [2] have informed the WHO in its work on the 2021 AQGs and played a crucial role in shaping recent regulations on $PM_{2.5}$ in both the USA and Europe. Notably, the US Environmental Protection Agency's decision to lower the National Ambient Air Quality Standards (NAAQS) for fine particulate matter air pollution ($PM_{2.5}$) in urban background areas from 12 to 9 μg/m^3 in 2024[1], and the European Parliament's decision to approve the revision of the Ambient Air Quality Directive to reduce the annual limit value for $PM_{2.5}$ from 25 μg/m^3 to 10 μg/m^3 in 2030 [2] are outcomes directly influenced by the information provided by these studies.

Global burden of Disease (GBD) studies

The first in a series of GBD studies was published in 1993, and detailed the state of global health for eight world regions as of 1990 [54]. The comparative risk assessment covered 106 illnesses and ten risk factors. The study of morbidity and mortality was an effort to characterise the burden of disease using a standardised approach. The risk factors included behavioural, occupational, metabolic, and environmental factors, including air pollution.

In 2007, a new study (GBD 2010) was funded by the Bill & Melinda Gates Foundation (BMGF) [48]. An important innovation of the air pollution health impact assessment methodology in GBD 2010 was the introduction of the integrated exposure-response functions (IERs) for cause-specific mortality. Since $PM_{2.5}$ levels in many regions of the world exceed the levels observed in epidemiological studies, the IERs combined population exposure to various sources of combustion particulates, such as outdoor and indoor air pollution, environmental tobacco smoke (second-hand smoke), and active smoking. The health outcomes included diseases of the cardiovascular and respiratory systems, and lung cancer. The IERs, which have changed considerably over the years [58], have a non-linear shape, and they increase monotonically with concentration, starting from a "counterfactual concentration", also known as the theoretical minimum risk exposure level (TMREL), which represents the lowest exposure across the available epidemiological studies with the lowest credible level for the existence of a health burden. In principle, the TMREL is uncertain, and might vary by location and demographic characteristics. Since 2015, the GBD study has used a TMREL for $PM_{2.5}$ based on a uniform distribution over the range of 2.4 to 5.9 μg/m^3.

Since GBD 2010, several revisions of the GBD have been published, with the most recent update in 2024 and identified as GBD 2021 [27]. Each iteration has contributed to methodological innovations and the development of more robust techniques for exposure assessment, data synthesis, analysis, and interpretation. Furthermore, with each iteration of GBD, the level of detail of the results has improved, including added diseases and risk factors, geographical stratification, and specification of health effects by age. The latest GBD 2021 study provides results (e.g. attributable deaths and disability-adjusted life years (DALYs)) for 88 risk factors across 204 countries and 811 subnational areas for the historical period between 1990 and 2021. Forecasted estimates for 2050 are also available [28]. The current calculations for PM are based on an updated risk function, estimated in an analysis of epidemiological studies of the effect of particulate air pollution from outdoor and indoor sources, with no inputs from studies on environmental tobacco smoke or active smoking. According to the GBD 2021 study, the global mortality attributed to $PM_{2.5}$ ambient air pollution in 2021 was 4.7 2 (95% Uncertainty Interval: 3.48; 5.80) million deaths, including 4.51 million deaths among the population over 25 years (97 deaths per 100,000 in the population 25+, or 7.9% of natural deaths). Air pollution has increased its importance compared to other leading risk factors like high systolic blood pressure, smoking, and high fasting plasma glucose. Among all risk factors, particulate matter pollution (indoor plus outdoor exposure) contributed the largest share of global DALYs (approx. 8%), and the second largest share of global deaths (approx. 12%) in 2021. (https://vizhub.healthdata.org/gbd-compare/)

The benefits of quantitative risk assessment

Briggs [4] focused on the evolution from risk assessment of single exposures to the more complex need to predict "the health-related impacts of policies and other interventions that affect the environment in ways that take account of the complexities, interdependencies and uncertainties of the real world" in an integrated Health Impact Assessment (HIA). Therefore, risk assessment is traditionally focused on single exposures or events while HIA takes a broad concept of both the environment and health [86]. Rigaud et al. [64] emphasize that there is a terminology issue, and the term "quantitative risk assessment" represents a systematic approach that uses the same methodology to evaluate and present the potential health impacts of single exposures, projects, policies, or programs with the aim of protecting public health. For this reason, we will use the term quantitative risk assessment or health impact assessment interchangeably. Quantitative risk assessment has been crucial in formulating air pollution guidelines and regulatory criteria to

[1] https://www.epa.gov/pm-pollution/national-ambient-air-quality-standards-naaqs-pm.

[2] https://www.europarl.europa.eu/legislative-train/theme-a-european-green-deal/file-revision-of-eu-ambient-air-quality-legislation.

safeguard human health. Recent initiatives by regulatory bodies like the US Environmental Protection Agency and the European Parliament indicated above have underscored the significance of quantitative risk assessment in shaping appropriate regulatory measures. In both the USA and EU, the CRFs derived from large epidemiological studies are used to estimate the health impacts of air pollution. In setting air quality standards, a cost-benefit analysis is conducted where benefits (e.g. lives saved) are monetized using value of statistical life (VSL) and compared to the costs of achieving lower air pollution levels through regulations. Undoubtedly, the total number of deaths attributable to exposure in a population speaks more clearly than relative risks or hazard ratios, providing an indication of the actual number of cases that a population has to deal with because of the exposure. The number of cases/deaths serves as a cornerstone for understanding the risks associated with exposure to major air pollutants. It is the basis for an economic assessment to identify the cost efficiency of the proposed interventions, and to guide the implementation of measures to safeguard public well-being. Rigaud et al. [64] provide valuable references for historical context and methodological insights, drawing from works such as those by Harris-Roxas et al. [32] and Briggs [4], as well as resources like the WHO document "Health risk assessment of air pollution – general principles" [86].

Approaches like the Global Burden of Disease (GBD) [27] and those adopted by the European Environment Agency (EEA) [71] have contributed significantly to this field. For the specific situation of Europe, Khomenko et al. [41, 42] conducted studies estimating the proportion of annual deaths due to air pollution in numerous cities across Europe. Their work also evaluates spatial and sector-specific emission contributions to ambient air pollution, and assesses the effects of source-specific reductions in pollutants on mortality in European cities.

Navigating new challenges in quantitative risk assessment

The basic approach in a Health Impact Assessment (HIA) is well-established [87]. It uses exposure data (either measured or modelled pollutant concentrations), baseline health data (e.g. mortality/morbidity data from registers), and concentration-response functions (CRF) from epidemiological studies to quantify the health effects in terms of premature death and/or morbidity. Rigaud et al. [64] have underscored several important challenges that we will specifically address in this discussion, e.g., issues about identifying pollution/health outcome pairs, the associated concentration-response functions, and their application in an HIA. Other pertinent issues will be reserved for future deliberations, such as estimates of vulnerable populations, exposure data, baseline morbidity and mortality data, methodological uncertainties, and counterfactual values.

Traditionally, air pollution HIA have focused on all-cause (non-accidental or natural mortality) and cause-specific mortality based on CRFs derived from systematic literature reviews and meta-analyses, which synthesize the epidemiological evidence on the health effects of air pollution. While the most appropriate CRFs for the relationship between long-term exposure to $PM_{2.5}$/NO_2 and mortality are currently under discussion [36], the ongoing work in the revision of the WHO-HRAPIE project (Health risks of air pollution in Europe) [34] is actively addressing this aspect by carrying out updated meta-analyses on CRFs [56]. Earlier, morbidity outcomes reflecting the multiplicity of air pollutant effects on various organs have often been overlooked [75], leading to an underestimation of the full burden of air pollution. When considering societal costs, chronic conditions such as chronic obstructive pulmonary disease (COPD) or dementia place a significant burden on social welfare and healthcare systems. The EMAPEC project coordinated by WHO has proposed CRFs for the incidence of various diseases related to long-term exposure to $PM_{2.5}$ and NO_2 [26]. The selection was made after reviewing the empirical epidemiological evidence and screening for acceptable systematic review/meta-analysis quality to propose appropriate CRFs.

The most recent studies, based on very large populations and advanced air pollution modelling methods, go beyond using a mass concentration of $PM_{2.5}$ as a health risk determinant and explore the associations of selected $PM_{2.5}$ chemical components with mortality [31, 83]. Confirmation of these associations, including the relevant CRFs, in further studies, especially from regions with different pollution levels and sources, would create new opportunities for risk assessment, allowing better impact assessment of source- (and component-) specific $PM_{2.5}$ reduction.

Ongoing research is anticipated to yield further proposals for pollutant/outcome pairs in the future. This multiplicity of potential CRFs makes Rigaud's open question regarding "*proposing a formal approach to the quantitative handling of the level of evidence regarding each exposure-health outcome pair*" very relevant and timely. Based on insights gained in EMAPEC, we address it in a proposed framework illustrated in Fig. 1. This framework aims to provide a structured and comprehensive approach to assessing the evidence levels associated with each exposure-health outcome pair in an HIA or cost-benefit analysis (CBA) context.

1. Is causality a necessary condition*?*

Conducting an HIA requires a causality determination of the health effects associated with the specific exposure. It would be difficult to recommend a particular risk assessment function if the qualitative relationship between exposure and disease has not passed the hazard identification steps, which consider the entirety of human, toxicological and mechanistic evidence. In other words, we must be certain that a specific exposure is causally related to a particular outcome before quantifying the impact. In the EMAPEC project, the decision on hazard identification was taken based on the determination from the US Environmental Protection Agency's Integrated Science Assessment (EPA ISA) for NO_2 [77] and $PM_{2.5}$ [78]. Only pollutant/outcome pairs categorised as "*Causal" or "Likely to be causal*" according to the US EPA ISA methodology [59] were considered (this is schematically summarised in the left part of Fig. 1. The sole exception was for the relationship between $PM_{2.5}$ and type II diabetes, which was not considered as "*Causal" or "Likely to be causal*" in the US EPA ISA 2019, but its inclusion in the list of relevant health outcomes was supported, in our view, by independent new epidemiological and toxicological evidence [46, 47].

It should be acknowledged that relying solely on the US EPA ISA is a conservative approach, especially if the assessment is outdated (as in the case of $NO_{2,}$ which was last reviewed in 2016; in this specific case, insufficient adjustment for other pollutants was a major reason for giving a low causality rating for this pollutant). Choosing causality as a prerequisite, especially when a causality assessment has not already been done, might lead to a potential underestimation of the health burden or impact. We aim to avoid neglecting emerging hazards due to insufficient data for a comprehensive impact assessment, as Rigaud et al. [63, 64] highlighted, we do not want to "*leave emerging hazards by the roadside*".

A possible solution is to compile two lists of CRFs to be used in an HIA, one that contains the CRFs for which the causality link has been well established (Core list) and one that includes CRFs for which the causality assessment has yet to be established, but the emerging evidence of an association is reasonably strong to consider the exposure-outcome pair in a sensitivity analyses (Non-Core list) (Fig. 1). The right part of Fig. 1 illustrates the situation when there is a causality evaluation less than "Likely to be causal" (e.g. "Suggestive"), including situations where the causality evaluation has not been done. In such cases, the decision to proceed is influenced by the information gathered from epidemiological studies, and the supporting evidence from toxicological and mechanistic studies. While the relationship between $PM_{2.5}$ and diabetes is well-supported in the published literature [62, 63], for other illnesses reaching a decision could be more challenging as it would require careful consideration and justification for inclusion by experts using multiple sources of information. A guiding principle in this respect is a critical evaluation of the quality of the available epidemiologic studies and the information they provide. Following the general framework for the design and analysis of aetiologic studies [52], the likelihood of

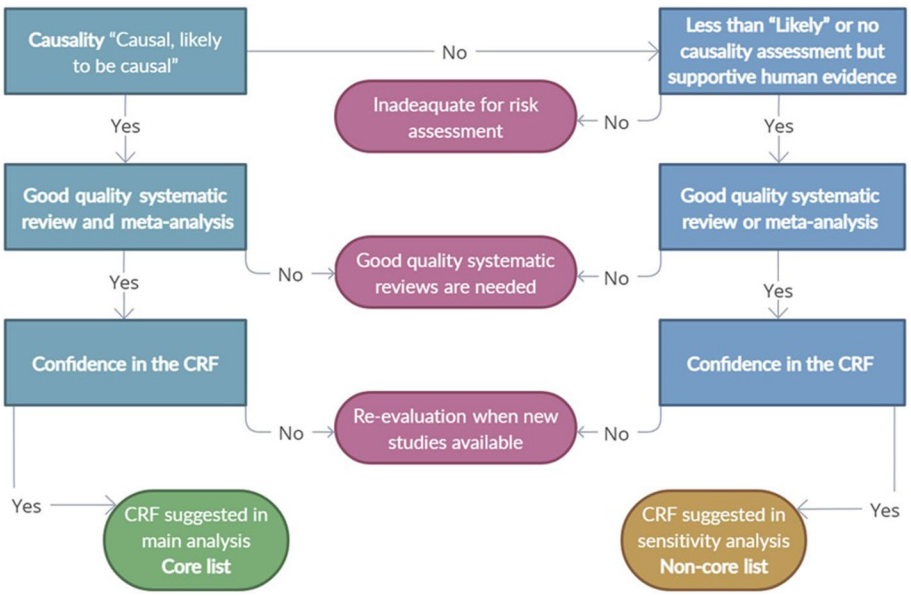

Fig. 1 Schematic representation of the steps in choosing the appropriate concentration-response function (CRF)

finding evidence of causality in air pollution research is higher when more scientifically rigorous decisions are taken [22]. An in-depth evaluation of design choices, such as the exposure levels being compared, appropriate comparison group, and care to control confounding, should be used to determine the evidence of causation. Triangulation can be useful as it involves considering different studies that reach or do not reach the same conclusion about the risk association, but that are potentially affected by different biases (or the same bias to different extents). In other words, we can justify the need to proceed with the assessment if the epidemiological studies are of good design, are robust to covariate adjustment, and the cross-study results are consistent. The presence of information from toxicology and the mechanism of action is important, but it should not be a prerequisite. For instance, in the IARC strategy [65], "sufficient" evidence from human observational investigations (e.g. epidemiological studies) is enough in categorising a substance as being carcinogenic to humans (Group 1).

Pollutant/outcome pairs from this part of the evaluation enter the "Non-Core" list rather than the "Core" list and might be applied in a sensitivity analysis. The "Non-Core" category may include pollutant/outcome pairs with varying levels of evidence supporting causality, allowing for a nuanced approach to assessing health effects. Further, a pollutant/outcome pair could migrate from the "Non-Core" list to the "Core" list once a formal level of evidence of causality has been established based, for example, on the US EPA or other authoritative agencies evaluation. In the EMAPEC work, a Core CRF list (list A) and a Non-Core CRF list (List B+) were suggested. For $PM_{2.5,}$ the Core list (List A) included incidence of asthma in children, COPD, ischemic heart disease events, stroke, hypertension, and lung cancer. For NO_2, a Core list (list A) was provided for the incidence of asthma in children, asthma in adults, and acute respiratory infections in children. Three outcomes (diabetes, dementia, and autism spectrum disorders) in relation to $PM_{2.5}$ were added to the list for sensitivity analysis (Non-Core, list B+).

2. Quality of Systematic Reviews and Meta-analyses providing CRF

To provide a reliable CRF, it is imperative to gather evidence from human studies, which is typically achieved through systematic reviews (SRs) and meta-analyses. Situations may arise where no SRs exist or existing reviews on a given health effect are outdated. In such cases, the only viable solution is to initiate a new SR, carefully considering the required human and time resources to do the work. Luckily, recent SRs are often readily available, and two primary options exist:

- *New SR based on a comprehensive selection of individual studies from all available SRs.* One option is to select all individual studies from all available SRs and then use this collective experience to perform a new SR. This approach leverages the groundwork laid by previous SRs, streamlining the search, scrutiny, and selection of primary studies. However, the subsequent work would involve conducting a new SR to synthesise the entirety of the collected information.
- *Quality evaluation and selection of SRs*. Alternatively, as undertaken in the EMAPEC project, one can assess the quality of all recently available SRs, and then choose those with the highest quality for further consideration. A meticulous evaluation of systematic reviews is crucial for extracting reliable CRFs. Based on the EMAPEC experience, this was achieved by considering various aspects, including literature search, inclusion criteria, data extraction, statistical analysis, and bias assessment [26, 69]).

In both options, verifying the evidence included in the SRs based on original papers is advisable. The experience from EMAPEC shows that mistakes (e.g. the inclusion of studies that do not fit the review scope, or the use of incorrect risk estimates in the meta-analysis) or simply selective choices (e.g. a fully co-pollutant adjusted estimate versus a non-co-pollutant adjusted estimate, or an estimate in a subgroup versus an estimate in the full population) may occur even in SRs that are deemed to be of overall good quality.

Drawing lessons from previous experiences, such as the need to consider new outcomes in the HEI traffic review [33] or the approach taken in EMAPEC when multiple SRs were available, can significantly improve the assessment process.

3. Confidence in the CRF

To ascertain confidence in the findings derived from selected systematic reviews and meta-analyses, which serve as sources for the recommended CRFs, a comprehensive evaluation of various aspects concerning the robustness of the results should be taken into consideration [26]:

- Number of studies and size of the cohorts: Evaluate the number of studies (and their size, e.g. the size of the various cohort studies) used in the systematic reviews and meta-analyses. A larger database often contributes to more robust and reliable findings, providing a broader foundation for drawing meaningful conclusions.

- Geographic coverage: Assess the geographic diversity of the studies included in the systematic reviews. A wide-ranging representation of diverse populations and regions enhances the generalisability and applicability of the CRFs, contributing to their reliability across different geographical settings.
- Weight of studies: Consider the relative weight of individual studies within the systematic reviews. Higher-quality studies with robust methodologies and larger sample sizes should have more influence in the selection of the CRFs, ensuring that the recommendations are anchored in strong evidence. At the same time, it is desirable that the evidence should come from various studies and regions, rather than a limited number of studies.
- Precision of effect estimates: Scrutinise the precision of effect estimates provided by the systematic reviews. Precise estimates, indicated by narrow confidence intervals, signify a higher degree of certainty in the observed relationships and contribute to increased confidence in the recommended CRFs.
- Unexplained heterogeneity: Evaluate the level of heterogenicity across the studies, as lower unexplained heterogenicity provides greater confidence in the results. The presence of factors that could explain heterogeneity among the included studies should be considered. A practical approach is to evaluate whether there is heterogenicity across regions [12]. Heterogeneity in the direction of associations (both positive and negative associations) across studies should be considered a factor limiting the confidence in the CRF more than when heterogeneity is in the magnitude of the effects (different effect estimates but in the same direction). Addressing and understanding sources of heterogeneity contribute to the robustness of the CRFs, ensuring that the recommended functions are not unduly influenced by the variability of external factors.

By systematically evaluating these aspects, one can gain valuable insights into the reliability and robustness of the concentration-response functions derived from the systematic reviews and meta-analyses.

A different approach to assess the quality of the epidemiological evidence has been applied in GBD 2021, namely, based on Zheng et al. [90]; a "Burden of proof risk function (BPRF)" method was developed to understand, evaluate and summarise evidence of risk across different risk-outcome pairs. Five outcomes associated with particulate air pollution (Ischemic Heart Disease, Diabetes, Stroke, Lung cancer, Lower Respiratory Infection) were assigned 3 stars (indicating moderate evidence of association), while COPD was rated 4 stars (indicating strong evidence of association).

4. Global versus regional CRF

The choice between using a global (based on the ensemble of studies from across the world) or regional CRF (based on studies in a particular continent, country, or location) to estimate the effects of air pollution will depend on several factors, including the nature of the assessment, the specific policy questions, and the intended application. There are various advantages to using global CRFs. (1) they are derived from pooled data covering multiple regions and populations, thus providing a broader perspective of the overall relationship by integrating susceptibility across world populations. (2) The uncertainty around the global estimate could be narrower than the one based on fewer regional studies. (3) A single global CRF can be applied to estimate health impacts in various locations without requiring region-specific CRFs (although region-specific baseline health data would still be necessary). (4) It is suitable for generating overarching policies and general recommendations for widespread application. The last reason is the most compelling because policies for large areas are not intended to account for local specificity. For instance, the Global monitoring of the Sustainable Development Goal (SDG) indicator 3.9.1 (mortality attributed to air pollution) that was established by the United Nations deliberation [79] applies global functions to estimate the attributable proportions [84]. Overall, the inclusive nature of global CRF assumes consistent biological linkages between exposure and health effects across different populations and locations and may facilitate a more comprehensive integration of the available evidence.

On the other hand, regional CRFs could better reflect such factors as population demographics (age distribution, disease profile, health status and access to health care coverage), socioeconomic status, personal behavioural risk factors, and local environmental conditions (source contribution and pollution composition) that may influence the relationship between pollutant exposure and health outcomes. For instance, using specific European CRFs for EU regulations could be suggested as it would increase confidence in the calculated disease burden. Regional CRFs are valuable for conducting HIAs tailored to specific communities or regions, providing confidence to local communities in the estimates of the health effects of air pollution [60]. The argument for using location-specific CRFs is strongest if there is a dominant local source (e.g. a local refinery, or power plant), a particular local PM composition, and also specific population characteristics (for example, the ageing

European population compared to much younger populations in other regions of the world).

The regional CRF could be used in an ad hoc analysis to show the particularities of the impact under specific conditions. Another possibility is to construct a CRF that combines the information from the global evidence with that coming from regional studies, such as a weighted mean of the regional value and the pooled estimate e.g. the shrunken estimate approach proposed in Le Tertre et al. [44]. Of course, the use of a regional CRF is possible only if studies covering a relevant population exists. For many regions, this is still not the case, so the use of the evidence gathered in other parts of the world remains the only choice for the HIA.

5. Shape of the CRF

The shape of the CRF should be carefully considered. Understanding how the health risk changes with varying levels of exposure (especially in the low and high concentration range) is crucial in a health impact assessment. Most health impact assessments have employed linear concentration-response functions. These relationships assign the same percentage increase in health risk for the same change in $PM_{2.5}$ over the entire ambient air pollution concentration range observed in the epidemiological studies. For example, the assessment conducted by the European Environment Agency [71] assumed a linear concentration-response function for $PM_{2.5}$ and natural mortality. However, recent epidemiologic evidence has suggested that the CRF shape at low $PM_{2.5}$ concentrations may be supralinear, meaning the change in health risk per unit change in concentration is larger at lower exposures.

In a close examination of the available studies on $PM_{2.5}$ and mortality, Vodonos et al. [81] showed that the CRF slope decreased at higher concentrations. Worth noting that the $PM_{2.5}$ contrast range was limited to <30 μg/m^3, except for three studies in Asia. The maximum average $PM_{2.5}$ concentration was 43.7 μg/m^3 (a study in China). They found that a specific non-linear function approximated the data well, with a larger slope at lower concentration levels, and provided a parametric estimate that fit better than a linear or logarithmic term for average $PM_{2.5}$. In the Global Exposure Mortality Model (GEMM) developed by Burnett et al. [9], the authors proposed a non-linear CRF for $PM_{2.5}$ and mortality (calculated as the sum of noncommunicable diseases and lower respiratory infections in the adult population), based on published health risk data from 41 cohorts in 16 countries. They observed that the hazard ratio predictions increased at low $PM_{2.5}$ concentrations, indicating a supralinear association at lower exposures, meanwhile, a gradually decreasing health risk was predicted at higher concentrations [8, 9]. The estimated European burden of mortality attributable to $PM_{2.5}$ has increased considerably because of the use of this new model in a health impact assessment [45]. Sigsgaard and Hoffmann [70] have underlined that the use of the global linear CRF underlying the 2021 WHO Air Quality Guidelines [12] resulted in a disease burden of 275,000 premature deaths attributable to $PM_{2.5}$ exposure in Europe in 2020 (Soares et al. [71]), but when applying estimates from the supralinear concentration-response functions the resulting disease burden in Europe from $PM_{2.5}$ and NO_2 would be much larger (i.e., by ~40% for $PM_{2.5}$ and ~110% for NO_2). Weichenthal et al. [82] indicated that considering a supralinear CRF for outdoor $PM_{2.5}$ and mortality at the low end of the exposure distribution results in more than 1.5 million additional attributable deaths each year globally.

The most recent evidence from the combined analysis of the "low-level" studies supported by the Health Effects Institute (HEI) should be considered. Chen et al. [11] reported that the shape of the CRFs differed substantially across the various cohorts. For the ELAPSE study in Europe [72], only two cohorts (Norway and Denmark) contributed to the shape of the CRF at $PM_{2.5}$ levels below 10 μg/m^3, and only Norway for levels below 7 μg/m^3. The cohorts from Norway and Canada [3] reported a supralinear shape up to 7 μg/m^3. Such a supra-linear pattern has not been observed in the USA Medicare study [23], which reported a sub-linear pattern below 7 μg/m^3, and then a steep slope from 7 to 9 μg/m^3. Overall, the preliminary conclusion is that the evidence regarding the shape of the CRF at low concentrations is not clear and regional considerations could greatly affect the results.

Since there are uncertainties on the form of the relationship and how to accurately quantify the disease burden from air pollution in areas with low (or high) exposure, it is preferable to consider, as COMEAP indicated in 2022 [15], that the evidence is not sufficient to recommend any change from the assumption of a linear CRF for long-term exposure to $PM_{2.5}$, at least for concentration levels observed in Europe and North America. With (expected) growth of the epidemiological evidence on the shape of the CRFs at various exposure levels (in particular, in the higher concentrations), better supported decisions on the selection of CRF shape for HIA in a particular population should be possible.

The different shapes of the CRFs and the non-linearities could depend on several factors, including population characteristics, exposure assessment, spatial variation in the composition of total $PM_{2.5}$ mass, and measured and unmeasured confounders. For instance, Boogaard et al. [2] indicated that different population characteristics in rural areas of Canada with lower levels of air pollution

might have contributed to the results for that country. In a simulation study, Glasgow et al. [29] found that the relationship between $PM_{2.5}$ and mortality could falsely appear to be supralinear when the fraction of the mass that is toxic is higher in areas with lower total $PM_{2.5}$ mass as compared to areas with higher total $PM_{2.5}$ mass. Despite the intensive research already conducted, the scientific question of whether some PM mixture components are more toxic than others is still a priority in research [2].

6. Applicability of the CRF

Several key assumptions are inherent in all the applications of health impact assessment of air pollution, including two important aspects, namely the generalisability of the CRFs to different age ranges and their applicability to various concentration levels. It is usually assumed that the CRF derived in epidemiology studies conducted in a few countries applies globally despite differences in pollution mix, ethnicity, lifestyle factors, socioeconomic status, temperature, health status, and access to medical care. However, as different populations' susceptibility to the effects of air pollution is possible, it is at least important to restrict the age range of application of the CRFs to the same age range considered in the specific epidemiologic studies that have generated the CRF. This is why EMAPEC [26] provided specific age ranges for applying the CRFs in an HIA.

Another important consideration is the concentration range pertinent to the selected CRF. It is advisable to check the range of pollutant concentrations investigated in the original epidemiological studies and apply the CRF only over that range [26]. The range of mean concentrations in source studies indicates the range of mean exposures for which the uncertainty of the risk assessment is minimised. Figure 2 shows the risk coefficients of the association between $PM_{2.5}$ and the incidence of dementia (upper panel) and autism spectrum disorder (ASD) (lower panel) by ranges of concentrations in the various studies that have been evaluated in EMAPEC. For dementia, the bulk of the studies considered in the systematic review by Cheng et al. [13] cover the range from less than 5 $\mu g/m^3$ to 17 $\mu g/m^3$, with two studies extending the range to 25 $\mu g/m^3$, while only one study has been conducted for larger concentrations. For ASD, the bulk of the studies reviewed by Lin et al. [48] lie in the 5–30 $\mu g/m^3$ concentration range, with only one study exceeding this interval. Furthermore, the $PM_{2.5}$ contrast intervals (range of concentrations being compared) in most of the individual studies for both diseases was around 10 $\mu g/m^3$. Therefore, in EMAPEC, it was recommended to apply these CRFs in an HIA within the concentration ranges 5–25 $\mu g/m^3$ for dementia and 5–30 $\mu g/m^3$ for ASD, but for changes in $PM_{2.5}$ concentration less than 10 $\mu g/m^3$.

7. Risk of Double Counting

Understanding the interplay between various CRFs and their respective health predictions is necessary to ensure accurate risk assessments. There are two possible reasons for double counting: when different pollutants cause the same health outcome (as in the well-known case of $PM_{2.5}$ and NO_2) and across different CRFs when one outcome predicts another outcome.

Note that an attempt to separate the effects of individual pollutants would be pertinent information in assessing the cost of mitigation, as the level of emissions of different pollutants is source-dependent (although interventions that mitigate NOx emission, also affect PM emissions, and vice versa). A potential resolution to the double counting dilemma concerning $PM_{2.5}$ and NO_2 in relation to mortality has been thoroughly deliberated by the UK Committee on the Medical Effects of Air Pollutants [14]. A majority of the Committee agreed that when adding the health effects of NO_2 to the unadjusted $PM_{2.5}$ "*it was plausible that the effects on mortality attributable to NO_2 itself lay within the range of 25–55% of the unadjusted coefficient; and that, with suitable strong caveats, this could be used as a guide for policy assessment*".

An alternative approach is to consider the Cumulative Risk framework, initially introduced by Crouse et al. [17], which expanded previous work published by Jerrett et al. [38]. This approach considers the cumulative effects of exposure to various pollutants in the same model in a specific epidemiological study, providing a more comprehensive understanding of the overall health risks associated with air pollution exposure. The cumulative risk estimate assumes additive effects of combined pollutant exposures on the outcome and represents the relative hazard for 1-unit increases in each of the pollutants in the mix compared with no increase in any of the exposures. In the Crouse et al. [17] analysis of the CanCHEC study in Canada, for example, the single pollutant effect on mortality for $PM_{2.5}$ was 1.035 (95%CI 1.029, 1.041) for 5.0 $\mu g/m^3$, the single pollutant effect for NO_2 was 1.052 (1.045, 1.059) for 8.1 ppb (i.e. 15.2 $\mu g/m^3$), and the cumulative risk estimate (for the same increments of the pollutants, i.e. 5 $\mu g/m^3$ for $PM_{2.5}$ and 8.1 ppb for NO_2) was 1.070 (1.062, 1.078). This example shows that there is only a small overlap of the effects as the cumulative effect (1.070) is only slightly smaller than the sum of the single pollutant effects (1.035 and 1.052). A systematic review and meta-analysis of several epidemiological studies that provide results from single pollutant models as well as from two-pollutant models could better inform the

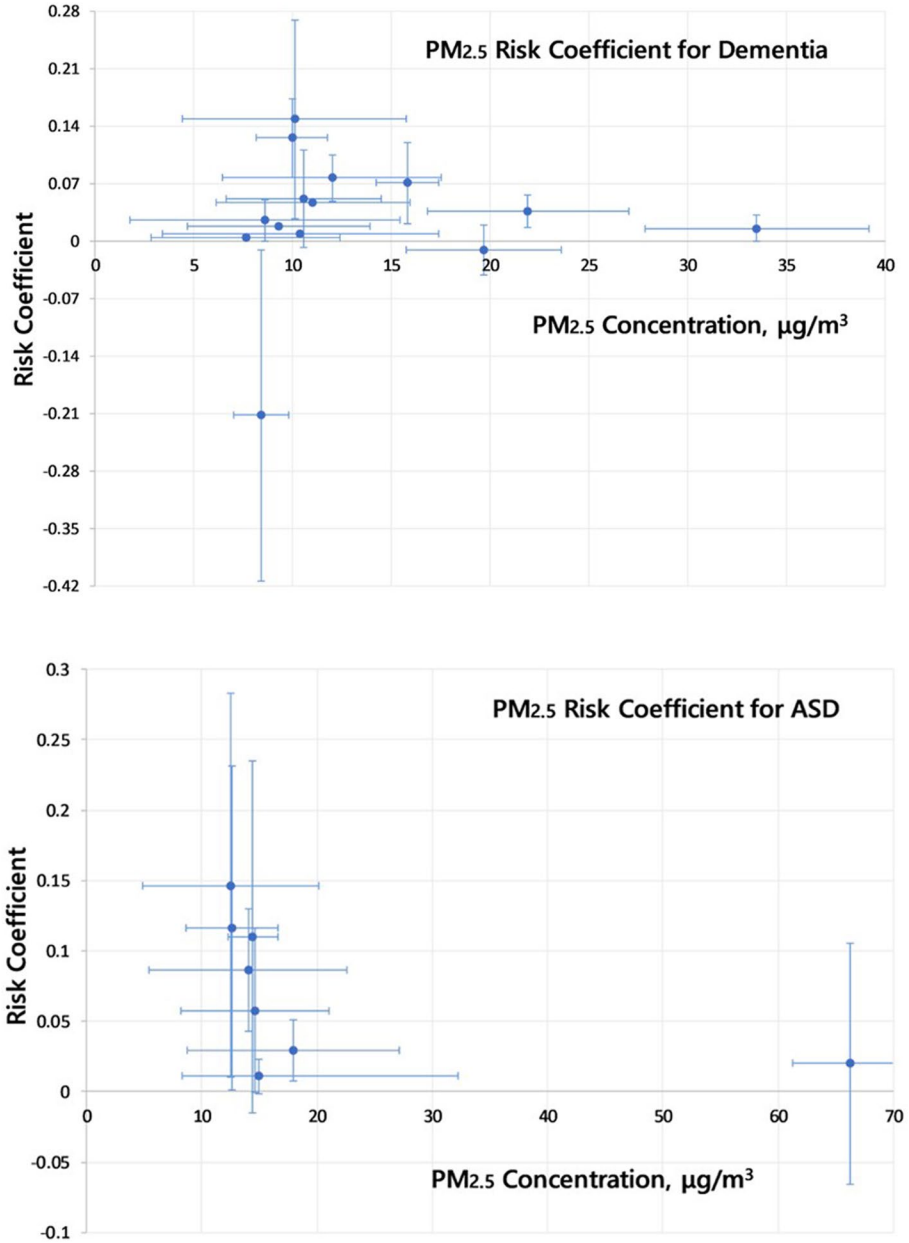

Fig. 2 Risk coefficients of the association between $PM_{2.5}$ exposure and risk of dementia incidence (upper panel) and Autism Spectrum Disorder (ASD) incidence (lower panel) by ranges of concentrations in the various studies included in the systematic reviews by Cheng et al. [13] and Lin et al. [49]

debate about the overlap, double counting, and decision-making process.

There are numerous scenarios in which a particular disease or disorder acts as an antecedent, or risk factor, for another health condition. Figure 3 illustrates the interconnection between various health outcomes commonly suggested for health impact assessments, drawing from robust evidence in established medical literature. However, a crucial question arises regarding whether these associations might lead to double counting of the health impact. For instance, when predicting the influence of air pollution on the incidence of specific disorders like diabetes and stroke, the independent counting of diseases is generally not problematic. However, if we shift our focus to prevalence instead of incidence, considering that an individual can simultaneously have diabetes and be a survivor of a stroke episode, or if we aim to evaluate the economic costs associated with these health outcomes, a

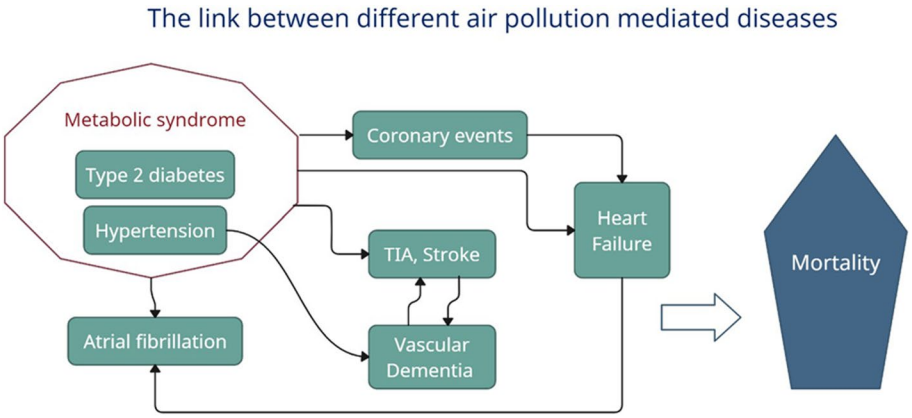

Fig. 3 Schematic representation of the links between various air pollution-related outcomes (TIA, transient ischaemic attack)

more cautious approach is warranted. This necessitates careful consideration of the interplay between different health conditions and their implications for health impact assessment and economic evaluation. Emerging studies on the role of air pollution in the transition between various stages of the same disease or related diseases include, for example, Zhang et al. [89] and Zou et al. [91].

Conclusion

Quantitative risk assessment requires a robust framework for choosing the relevant CRFs and their application to the population at risk. The evolving landscape of air pollution epidemiology underscores the urgency of science-based support to actions addressing global risks of air pollution through robust research, advanced modelling, and comprehensive risk assessments. Rigaud et al.'s [64] contribution and the studies discussed in this review collectively contribute to the evolving risk assessment methodology. Addressing challenges requires a comprehensive and adaptive approach, drawing on lessons from past experiences, incorporating the latest research findings, and fostering collaboration between different disciplines involved in the health impact assessment. Finally, a robust and reliable quantitative risk assessment is critical in supporting a cost-benefit analysis of measures to mitigate air pollution.

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Authors' contributions
FF wrote the first draft of the main text, while HO, MK, and JVS provided noteworthy comments and substantial editing of the manuscript. All authors reviewed and approved the last version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
There was no need to consent as there are no individual data.

Consent for publication
There was no need of consent.

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