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Systematic Review

Long-term exposure to traffic-related air pollution and non-accidental mortality: A systematic review and meta-analysis

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ABSTRACT

Background: The health effects of traffic-related air pollution (TRAP) continue to be of important public health interest across the globe. Following its 2010 review, the Health Effects Institute appointed a new expert Panel to systematically evaluate the epidemiological evidence regarding the associations between long-term exposure to TRAP and selected health outcomes. This paper describes the main findings of the systematic review on non-accidental mortality.

Methods: The Panel used a systematic approach to conduct the review. An extensive search was conducted of literature published between 1980 and 2019. A new exposure framework was developed to determine whether a study was sufficiently specific to TRAP, which included studies beyond the near-roadway environment. We performed random-effects meta-analysis when at least three estimates were available of an association between a

Abbreviations: ACS-CPS II, American Cancer Society—Cancer Prevention Study II; ALRI, acute lower respiratory infection; BC, black carbon; BMI, body mass index; BS, black smoke; CanCHEC, Canadian Census Health and Environment Cohort; CI, confidence interval; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CTM, chemical transport model; Cu, Copper; DDCH, Danish Diet, Cancer and Health; EC, elemental carbon; ELAPSE, Effects of Low-Level Air Pollution: A Study in Europe; ERF, exposure–response function; ESCAPE, European Study of Cohorts for Air Pollution Effects; Fe, Iron; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HIMS, Health in Men Study; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; IHD, ischemic heart disease; ISA, Integrated Science Assessment; LUR, land use regression; MINAP, Myocardial Ischaemia National Audit Project; NO, nitric oxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; NLCS-AIR, Netherlands Cohort Study on Diet and Cancer; OHAT, Office of Health Assessment and Translation; ONS-Longitudinal, Office for National Statistics Longitudinal Study; OR, odds ratio; PECOS, population, exposure, comparator, outcome and study; PPS, Primary Prevention Study; PM, particulate matter; $PM_{2.5}$, particulate matter $\leq$2.5 μm in aerodynamic diameter; $PM_{2.5\ abs}$, $PM_{2.5}$ absorbance; PM_{coarse}, PM with aerodynamic diameter between 10 μm and 2.5 μm; PM_{10}, PM $\leq$10 μm in aerodynamic diameter; PAHs, polycyclic aromatic hydrocarbons; RoB, Risk of bias; RR, relative risk; SALIA, Study on the Influence of Air Pollution on Lung Function, Inflammation and Ageing; SES, socioeconomic status; TRAP, traffic-related air pollution; UFP, ultrafine particles; U.S. EPA, U.S. Environmental Protection Agency; Veh, Vehicle; WHO, World Health Organization; Zn, Zinc.

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specific exposure and outcome. We evaluated confidence in the evidence using a modified Office of Health Assessment and Translation (OHAT) approach, supplemented with a broader narrative synthesis.
Results: Thirty-six cohort studies were included. Virtually all studies adjusted for a large number of individual and area-level covariates—including smoking, body mass index, and individual and area-level socioeconomic status—and were judged at a low or moderate risk for bias. Most studies were conducted in North America and Europe, and a few were based in Asia and Australia. The meta-analytic summary estimates for nitrogen dioxide, elemental carbon and fine particulate matter—pollutants with more than 10 studies—were 1.04 (95% CI 1.01, 1.06), 1.02 (1.00, 1.04) and 1.03 (1.01, 1.05) per 10, 1 and 5 μg/m^3, respectively. Effect estimates are interpreted as the relative risk of mortality when the exposure differs with the selected increment. The confidence in the evidence for these pollutants was judged as high, because of upgrades for monotonic exposure–response and consistency across populations. The consistent findings across geographical regions, exposure assessment methods and confounder adjustment resulted in a high confidence rating using a narrative approach as well.
Conclusions: The overall confidence in the evidence for a positive association between long-term exposure to TRAP and non-accidental mortality was high.

1. Introduction

The health effects of traffic-related air pollution (TRAP) continue to be of important public health interest across the globe, with the highest exposures in urban settings and residences in proximity to busy roadways. TRAP is a complex mixture of gases and particles resulting from the use of motor vehicles. Motor vehicles emit a variety of pollutants including nitrogen dioxide (NO_2), elemental carbon (EC), and particulate matter $\leq$ 2.5 μm in aerodynamic diameter ($PM_{2.5}$). When emitted through vehicle exhaust, these pollutants are called tailpipe emissions. When emitted by other means, such as evaporative emissions of fuel, the resuspension of dust, the wear of brakes and tires, and the abrasion of road surfaces, they are called non-tailpipe emissions (Frey 2018; Harrison et al. 2021; HEI 2010).

In 2010, the Health Effects Institute (HEI) published a comprehensive review that drew conclusions about whether the associations between exposure to TRAP and health outcomes were causal, evaluating both toxicological and epidemiological evidence. At that time, it was concluded that the evidence was "sufficient" to support a causal relationship between short and long-term exposure to TRAP and exacerbation of asthma in children. Furthermore, the 2010 review documented evidence deemed "suggestive" of a causal relationship between exposure to TRAP and other outcomes, including all-cause and cardiovascular mortality (HEI 2010).

Since the 2010 HEI review, many additional studies investigating the health effects of exposure to TRAP have been published, exposure assessment has been enhanced and regulations and vehicular technology have advanced significantly. Therefore, HEI formed a new Panel, consisting of 13 experts in epidemiology, exposure assessment, and statistics, to conduct a new review. The objective of this review was to systematically evaluate the epidemiological evidence regarding the associations between long-term exposure to ambient TRAP and selected health outcomes. The resulting HEI Special Report was recently published (HEI 2022), along with a short communication paper on the main findings (Boogaard et al. 2022).

Mortality effects of major air pollutants including NO_2 and $PM_{2.5}$ have recently been systematically reviewed in the context of the revisions to the World Health Organization (WHO) global air quality guidelines (Chen and Hoek 2020; Huangfu and Atkinson 2020). These reviews did not specifically consider the sources of the pollutants. Ultimately, pollutant sources comprise a primary target for intervention, and traffic has been and remains a major pollutant source. Nonetheless, assessing TRAP-specific mortality effects is challenging as no specific pollutant fully distinguishes traffic from other sources.

This paper aims to describe the main findings of the systematic review on associations between TRAP and non-accidental mortality. A specific aim was to illustrate the challenges encountered during confidence assessment. The paper builds on the HEI report chapter on mortality (HEI 2022), but new analyses, clarifications and discussions have been added responding to peer review comments.

2. Methods

The Panel used a systematic approach to search the literature, select studies for inclusion in the review, assess study quality, summarize results, and reach conclusions about the confidence in the association between TRAP and mortality. Results were quantitatively combined using meta-analyses techniques, where appropriate. To this end, a review protocol was published in 2019 (HEI 2019) and registered in Prospero.

The following PECOS (Population, Exposure, Comparator, Outcome and Study) question was developed: "In the general population, including subgroups of adults and children, what is the increase in risk of non-accidental mortality for a change in long-term exposure to traffic-related air pollution, observed in studies relevant for the health outcome and exposure duration of interest?" We included more than a dozen exposure metrics, since motorized traffic emits multiple pollutants, which are not specific to traffic as they are also emitted by other combustion sources. The individual pollutants are considered indicators of the TRAP mixture, and there is no aggregated measure of TRAP available (See Section 2.1.2).

2.1. Eligibility criteria

We applied the following eligibility (inclusion and exclusion) criteria structured by PECOS items:

2.1.1. Population

Studies reporting on the general population, of all ages, with no geographical restrictions were included. Studies that relied primarily on indoor and occupational exposure were excluded because they would be difficult to combine with general population exposures and were not found to be useful in the 2010 HEI Traffic Review (HEI 2010).

The Panel additionally evaluated whether associations between TRAP and non-accidental mortality were more pronounced for selected populations with specific health conditions than in the general population. The selected populations were persons with ischemic heart disease, stroke, diabetes, heart failure, and hypertension—conditions that are relatively common in the general population.

2.1.2. Exposure

Studies assessing long-term exposure (months to years) to TRAP were included. To determine whether a study was sufficiently specific to TRAP, we developed a new exposure framework, which includes studies beyond the near-roadway environment. The framework was deemed necessary as the pollutants emitted by motorized traffic, are also emitted by other (combustion) sources. Therefore, a transparent method for selecting studies in which traffic was a major determinant of exposure contrast was needed. The exposure framework included three strategies: the selection of traffic-related pollutants, the exposure assessment method, and the spatial resolution. Eligible pollutants included NO_2,

NO_x, NO, carbon monoxide (CO), EC (including related metrics such as black carbon, black smoke, and PM absorbance), ultrafine particles (UFP), non-tailpipe PM trace metals (e.g., copper (Cu), iron (Fe) and Zinc (Zn)), polycyclic aromatic hydrocarbons (PAHs), benzene, PM_{10}, $PM_{2.5}$ and PM_{coarse}. We included $PM_{2.5}$, PM_{10} and PM_{coarse} because in specific settings (especially urban areas), the contrast in PM exposure may be driven primarily by traffic emissions. Studies that evaluated exposure to PM, however, had to meet even more stringent exposure assessment and study setting requirements for inclusion, to better ensure that the exposure contrasts were likely due to variation in traffic emissions. For example, the Panel excluded PM studies where the exposure assessment was solely derived from monitoring data. We additionally included studies of indirect traffic measures, such as distance to major roads and traffic density. Studies were also subject to spatial resolution criteria (e.g., resolution of both pollution surface and address < 5 km). This resolution threshold stemmed from the *a priori* decision to include studies that assessed traffic emissions in the near-roadway environment and the neighborhood scale (defined as areas of a scale of 5 km or less). While traffic emissions affect air pollution concentrations at larger scales as well, the Panel judged that at these larger scales separation of traffic and other sources would be very difficult. Because of the focus on local and neighborhood scale exposure contrasts, studies that exclusively used between-city contrasts, such as the American Cancer Society study (Pope et al. 2002), were not included. Studies that used both between- and within-city contrasts were included only if they adjusted for differences between the urban areas in the epidemiological analyses. Hence, most nationwide studies (e.g., Crouse et al. 2012; Di et al. 2017) were not included because across these large geographic areas it is very difficult to disentangle TRAP from other sources. Appendix Table 1 provides the specific criteria.

Furthermore, the Panel developed a "traffic specificity" indicator (high or moderate) based on even stricter criteria. This additional classification would further differentiate studies according to whether they exhibited moderate or high traffic specificity, given that low traffic specificity studies were already excluded from consideration under the exposure framework. For example, all PM studies were considered as having moderate (as opposed to high) traffic specificity. Furthermore, the spatial scale of the pollution surface needed to be within 1 km for high traffic specificity as opposed to only 5 km for the study to be included in the review. The traffic specificity indicator was used in a sensitivity analysis to inform the confidence assessment—not as an eligibility criterion.

2.1.3. Comparator

Each selected study evaluated the association between a continuous or categorical TRAP exposure and mortality, comparing mortality among participants with relatively high versus relatively low exposure. The reference comparator in each individual study was exposure to relatively low levels of TRAP in the population. We refer to Section 2.6 for the increments used to present relative risks in meta-analyses.

2.1.4. Outcomes

Health outcomes selected in relation to long-term exposure to TRAP included: non-accidental mortality (10th revision of the International Classification of Diseases [ICD-10] codes A00–R99) or all–cause mortality (ICD-10 A00–Z99). Equivalent definitions using ICD-9 or other versions were included. There were no restrictions regarding the outcome ascertainment, though all included studies used death certificates or other registry data.

Preference was given to non-accidental (natural) mortality; all-cause mortality was only used if non-accidental mortality was unavailable. Non-accidental mortality is mortality from all causes except external causes such as accidents, suicide, and homicide. We considered effect estimates from studies of non-accidental mortality equivalent to all-cause mortality, as natural-cause mortality accounts for the majority of all-cause mortality and there is no clear evidence that air pollution is associated with accidental mortality (Chen and Hoek 2020). We performed a sensitivity analysis to test the equivalence of effect estimates for both outcomes. Throughout the paper, we refer to non-accidental mortality (which also includes studies on all-cause mortality), unless specifically stated otherwise.

2.1.5. Study

Epidemiological studies with individual-level data and adopting a cohort, case-cohort, case-control, cross-sectional, or intervention design were selected. Studies exclusively analysing area-level data were excluded. The studies were required to be published or accepted for publication in a peer-reviewed journal, to be written in English, and to report a quantitative estimate of association and corresponding measure of precision.

Studies reporting only unadjusted results (e.g., results had to be adjusted for at least age and sex) and clear evidence of an analytical error were excluded. Studies where no original data were analysed, reviews, or methodological papers were excluded. Studies in very selective subgroups were excluded, such as patients with lung transplantations, or patients with active tuberculosis.

2.2. Search strategy

HEI hired a contractor team at the Swiss Tropical and Public Health Institute, Switzerland, to execute certain parts of the review, particularly bibliographic searches and data extraction, in close collaboration with HEI staff and Panel members.

An extensive search was conducted of literature published between January 1980 and July 2019 in PubMed. Initial literature searches revealed that the addition of a second electronic database, Web of Science, added very few relevant papers to the PubMed search but added a large number of hits to screen. The search strategy is included in Appendix Table 2. In addition to PubMed, the LUDOK database was checked for potentially relevant studies. The LUDOK database is developed and maintained by the Swiss Tropical and Public Health Institute and provides a rich compilation of air pollution and health studies since 1985. LUDOK stems from monthly searches in PubMed and hand-searches in selected relevant journals not listed in PubMed, such as Atmospheric Environment and Air Quality and Atmosphere & Health. The search strategy was supplemented with hand-searches of references in reviews identified by the search, and other reviews. The search strategy is described in full in the HEI Special Report, chapter 5 (HEI 2022).

2.3. Study selection

Two reviewers from the contractor team experienced in evaluating environmental epidemiology studies screened independently all titles and abstracts of the search results for relevance. Two reviewers from the contractor team and HEI staff further independently assessed the full text of the articles yielded from abstract screening for compliance with eligibility criteria. The reasons for excluding studies at the full-text review stage were documented (Appendix Table 3). Any disagreement on inclusion was resolved by discussion. Appendix Table 1 provides the specific criteria that were checked in each paper to test whether the study fulfilled the exposure framework requirements.

2.4. Data extraction

First, minimal data extraction was performed by one reviewer from the contractor team, including key information for meta-analysis. Second, full data extraction was conducted by another person from the contractor team or HEI staff, which entailed evaluating the data extracted in the minimal data extraction phase and adding relevant additional information, such as details on the study population, study design, and analysis.

To represent the associations specific to the TRAP mixture, effect estimates from single-pollutant models (as opposed to multi-pollutant models) were selected for the meta-analysis. In this review we consider the pollutants as indicators of TRAP and do not attempt to assess which pollutant in the complex mixture is most health relevant. Additionally, effect estimates were extracted adjusted for traffic noise, where available.

In case multiple effect estimates were reported with different sets of confounders, the Panel extracted the effect estimates from the main model (defined as the one in the abstract and otherwise preferred by the authors) except when the inclusion criteria for the review were only met for models other than the main analyses. Adjusted models without potential mediators, such as pre-existing comorbidities, were preferred. In most cases, the main model was also the most adjusted model. In Appendix Table 4 we evaluated the potential bias of selecting author-favored effect estimates.

No attempts were made to contact the authors of included studies to obtain missing data.

DistillerSR, a web–based, systematic review software program, was used for study selection and data collection to ensure standardization of the process.

2.5. Risk of bias

We assessed risk of bias using a modified version of the tool developed for the risk of bias assessment in the systematic reviews underpinning the WHO Global Air Quality Guidelines (WHO 2020; WHO 2021). Similar to the WHO systematic reviews (Chen and Hoek 2020; Huangfu and Atkinson 2020), the risk of bias assessment was only conducted for exposure–outcome associations included in the meta-–analyses. In brief, the risk of bias tool guides the assessment of each study across 6 domains: (1) confounding; (2) selection bias; (3) exposure assessment; (4) outcome measurement; (5) missing data; and (6) selective reporting. Most domains have subdomains. The risk of bias for each subdomain and for each domain overall was given a rating of low, moderate or high. No summary classification was derived across the domains (WHO 2020).

The Panel condensed the large WHO list of confounders (10 in total in the original tool). Confounding is not easy to recognize and differs widely between study populations and settings. Typically, risk factors of health outcomes are generalizable, but the relationship between exposure and the potential confounder differs across populations. *A priori,* and partly based on subject matter-informed directed acyclic graphs, the Panel developed a condensed list of important potential confounders, which included age, sex, individual-level or neighborhood socioeconomic status (SES), body mass index (BMI) and individual smoking. These confounders are the largest risk factors for mortality and therefore have the highest potential to be a confounder, if they are related to the exposure of interest. A study could only be classified as low risk of bias if all potential confounders were adjusted for; if not all confounders were adjusted for and without support (e.g., exploratory analysis) of minimal risk due to residual confounding, the study was classified as high risk of bias; otherwise, a moderate risk of bias was assigned.

Moreover, the Panel disregarded the risk of bias item in the WHO tool on exposure contrast (e.g., low risk of bias if exposure contrast was large compared with the precision of exposure assessment) because a small exposure contrast results primarily in a large confidence interval and those studies received a low weight in the meta-analysis, information was typically not reported, and has led to a classification of low risk of bias in almost all long-term studies in the systematic reviews underpinning the WHO Global Air Quality Guidelines (Chen and Hoek 2020; Huangfu and Atkinson 2020).

The Panel modified the missing data items and some other items for clarity and provided additional guidance to distinguish between aspects more explicitly in the different domains. Specifically, in the item selection bias, the Panel considered potential bias when selecting participants for the study. In the item missing outcome data, it was clarified that bias due to loss-to-follow-up (attrition bias) was considered.

For further elaborations on the risk of bias, we refer readers to HEI's Special report, Additional Materials 5.2 (HEI 2022).

We reported the risk of bias per domain per study but indicated if it differs across exposure-outcome associations within a study. One member of the Panel or HEI staff assessed the risk of bias in each study. The assessments were checked by HEI staff and other Panel members for completeness, accuracy, and consistency. Disagreements were resolved through discussions with additional members of the Panel and HEI staff. In addition, detailed quality checks were conducted by HEI staff to ensure comparability and subsequently discussed by the Panel.

2.6. Data-analysis

We performed random-effects meta-analysis when at least three estimates were available of an association between a specific exposure and outcome. The restricted maximum likelihood method was used to estimate the between studies' variance (DerSimonian and Laird 1986; Veroniki et al. 2016). Random-effects models were chosen *a priori* because of the expected differences in populations and pollution mixtures.

For each pollutant, we established a contrast that was uniformly applied to all contributing estimates and the resulting meta-analytic summary estimate for presentation purposes (e.g., RR per 10 $\mu g/m^3$ increment in NO_2), which necessitated converting some contributing estimates. We chose the contrast of a given pollutant to reflect a realistic range of exposure contrasts in most studies, by using the pollutant concentration increments from a large European ESCAPE study (Beelen et al. 2014; 2015).

Effect estimates for pollutants expressed as ppb or ppm were converted to $\mu g/m^3$, or mg/m^3 (CO) using standard WHO scaling factors (standardization of units). For example, 1 ppb NO_2 = 1.88 $\mu g/m^3$, assuming an ambient pressure of 1 atmosphere and a temperature of 25 °C (DEFRA 2005). Differences in actual atmospheric conditions in studies were not accounted for and may have contributed to some likely minor heterogeneity in effect estimates. The Panel converted black carbon (BC), black smoke (BS), and PM absorption (soot), into EC-equivalent estimates for use in meta-analysis (Babich et al. 2000; Cyrys et al. 2003; Janssen et al. 2011; Watson and Chow 2002).

An estimate from a given cohort was not automatically excluded from meta-analysis if the same cohort was also analyzed in a multicohort analysis (e.g., in ESCAPE) unless these studies used the same population and exposure assessment. The primary meta-analyses excluded *a priori* patient populations (as the main question was on the general population), studies in the same population for which a more informative study was available and studies not using linear exposure metrics.

We assessed statistical heterogeneity using I^2, where values of $< 50\%$ were interpreted as low; between 50% and 75% as moderate; and $> 75\%$ as high degree of heterogeneity, respectively (Woodward 2013). In the confidence assessment we distinguished whether heterogeneity was derived from differences in effect estimates in direction or magnitude.

If a sufficient number of studies was available, we performed additional meta-analyses chosen *a priori* to assess consistency of the association. Specifically, we conducted meta-analyses across geographic regions (North America, Western Europe, Asia and Australia-New Zealand), by level of risk of bias per domain (low and moderate versus high), and traffic specificity (high versus moderate). Also in a sensitivity analysis, the Panel added the results from the selected patient populations. We additionally explored the outcome definition (all-cause versus non-accidental).

When a meta-analysis was not possible, we used the method of vote counting, taking into account only the direction of effect, irrespective of the statistical significance, a method considered acceptable in the Cochrane Handbook (McKenzie and Brennan 2022).

To assess publication bias, we used funnel plots (Light and Pillemer 1984) and Egger tests (Egger et al. 1997) on asymmetry, if there were 10 or more studies available for meta-analysis. We additionally performed doi plots and calculated LFK indices (Furuya-Kanamori et al. 2018), which may have greater sensitivity for detection of asymmetry.

We conducted these analyses using R (version 3.6.0), and the libraries "metafor" (v.2.4-0),"meta", (v. 4.16-2), "forestplot" (v.1.10.1),"ggplot" (v. 3.3.3) for the analyses and plots.

2.7. Confidence assessment

Conclusions regarding the confidence in the association between TRAP and non-accidental mortality were based on two complementary approaches, fully described in the HEI Special Report, Additional Materials 5.3 (HEI 2022). We also reflect on the confidence assessments in Boogaard et al. 2023.

2.7.1. Modified OHAT assessment

An adapted GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment was performed of the confidence in the quality of the body of evidence using the Office of Health Assessment and Translation (OHAT) method as a guide (OHAT 2019). In short, available studies are initially grouped by key study design features (i.e., controlled exposure, exposure prior to outcome, individual outcome data and a comparison group). Each grouping of studies is given an initial confidence rating by those features. This initial confidence rating for the body of evidence from each group of studies is then downgraded for factors that decrease confidence in the body of evidence (risk of bias, unexplained inconsistency, indirectness, imprecision, and publication bias) and upgraded for factors that increase confidence in the body of evidence (large magnitude of effect, exposure–response, consistency, and consideration of residual confounding or other factors).

OHAT directly translates confidence ratings in the quality of the body of evidence into level of evidence in support of the presence versus the absence of an adverse health effect. The Panel determined that, before drawing conclusions about an effect based on a confidence rating, additional relevant factors should be scrutinized, such as the number and size of the studies, direction and magnitude of the association, the consistency of the results from the meta-analyses and the studies not meta-analyzed, and the generalizability of the findings. In addition, it is conceptually problematic to evaluate an evidence base for support of no adverse health effect. Hence, the Panel restricted the formal confidence assessment to a rating of the quality of the body of evidence and added a separate complementary and broader narrative assessment of the confidence in the presence of an association (See Section 2.7.2).

The Panel also slightly modified the OHAT approach. In contrast to OHAT guidance, the Panel gave all types of cohort studies (not only prospective) an initial rating of moderate because three key study design features were often present (exposure precedes the outcome, individual-level data, and comparison group). Furthermore, we did not apply two grading factors—indirectness and large magnitude of effect—in the process of downgrading and upgrading of confidence in the body of evidence. The factor indirectness was not applicable because we included only studies of human exposure to TRAP in direct association with mortality. Large magnitude of effect was unlikely to be meaningful, based on experiences in the WHO systematic reviews of air pollution, where large or very large effect sizes (i.e., large RR $>$ 2 or very large RR $>$ 5 as defined in OHAT) never occurred (Chen and Hoek 2020; Huangfu and Atkinson 2020). Large RRs were not observed in our review either.

The Panel first evaluated the body of evidence separately for each exposure metric (e.g., NO_2, EC) included in meta-analysis. The Panel then evaluated the body of evidence across all included traffic-related air pollutants to obtain an assessment of the confidence in the quality of the evidence for TRAP. The rationale for combination of pollutant-specific confidence assessments was that each pollutant is considered as an indicator of the complex traffic pollution mixture. Concentrations of multiple traffic-related pollutants are often highly correlated because they originate from the same source. The methodology for combining confidence assessments across pollutants is less established. We gave more weight to pollutants with more studies in the combined assessment. In this combined assessment, the Panel also used evidence from studies of indirect traffic measures, such as distance to major roadways and traffic density, and other results that did not enter a meta-analysis, such as those involving categorized or log-transformed exposures or involving traffic-related air pollutants with fewer than three studies. The Panel also used the traffic specificity indicator in this TRAP assessment.

2.7.2. Narrative assessment

The narrative assessment accompanied and complemented the modified OHAT assessment in evaluating the level of confidence in the presence of an association of TRAP with mortality. The narrative confidence assessment was also performed on the body of evidence and based on the systematic review and meta-analysis. We then evaluated many of the same factors related to the internal validity of the studies addressed in the OHAT approach, but there was inspection of additional factors too. Importantly, the narrative approach did not use the "formulaic" rating scheme of OHAT with up- and downgrades and treating every factor as equally important and was less geared towards studies entering a meta-analysis. The narrative approach included the following factors: evaluation of the number of studies, the variability of their locations, and sample size; risk of bias of the individual studies, including traffic noise for some outcomes; the variability in magnitude and direction of the association; a monotonic exposure–response function; consistency of study findings across populations, age groups, time periods, study designs, and pollutants, and the generalizability of study results. For example, associations that were replicated in several studies across different populations, across several pollutants or that used different epidemiological approaches were more likely to represent a true association than isolated observations from small, single studies.

In summary, in evaluating the level of confidence that TRAP is associated with mortality, the broader, narrative assessment considered all evidence in the systematic review, from both the meta-analytic results and the results of single studies not entering a meta-analysis, without using a formal rating scheme. We acknowledge that the narrative assessment is less structured. We note, however, that all frameworks, including the OHAT framework require expert judgement. Furthermore, we note that authoritative organizations including International Agency for Research on Cancer (IARC) and the US Environmental Protection Agency (U.S. EPA) in its Integrated Science Assessments perform confidence assessments without a "formulaic" approach, but with a detailed narrative framework of which factors to assess (Samet et al. 2020; U.S. EPA 2015).

2.7.3. Overall confidence

Both approaches (modified OHAT and narrative assessment) could yield confidence ratings of high, moderate, low or very low. Subsequently, we combined the findings from both assessments into an overall confidence assessment (Table 1). In case of agreement, the overall assessment was the same as the individual assessments (e.g., two assessments of high resulted in high overall); if not in agreement we have indicated both (e.g., moderate to high, since the Panel considered both assessments complementary, reflecting the complex issues in determining the level of confidence.

2.8. Deviations from the review protocol

As anticipated in the review protocol, the Panel elaborated on some methods when the review was already underway: (1) the Panel further elaborated on the overall evaluation of the epidemiological evidence, including the narrative assessment; (2) additional considerations were added related to how well exposure contrast in the included studies represents participants' exposure to TRAP (the traffic specificity

Table 1
Overall assessment - Description of the level of confidence in the evidence for an association[a].

High	Evidence is sufficient to conclude that the strength of the evidence for an association is high, that is, the exposure has been shown to be associated with health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. The determination is based on multiple high-quality studies conducted in different populations and geographical areas with consistent results for multiple exposure indicators. High confidence in the association between exposure and the outcome
Moderate	Evidence is sufficient to conclude that an association is likely to exist, that is, the exposure has been shown to be associated with health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. The determination is based on some high-quality studies in different populations and geographical areas but the results are not entirely consistent across areas and for multiple exposure indicators. Moderate confidence in the association between exposure and the outcome
Low	Evidence is suggestive but limited, and chance, confounding, and other biases cannot be ruled out. Generally, the body of evidence is relatively small, with few high-quality studies available and at least one high-quality epidemiologic study shows an association with a given health outcome and/or when the body of evidence is relatively large but the evidence from studies of varying quality and across multiple exposure indicators is generally supportive but not entirely consistent. Low confidence in the association between exposure and the outcome
Very Low	Evidence is inadequate to determine if an association exists with the relevant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect. Very low confidence in the association between exposure and the outcome.

[a] The overall assessment of the association of each health outcome with long-term exposure to TRAP is a combination of the narrative assessment and the formal confidence assessment using the modified OHAT framework. The descriptors are modified from U.S. EPA 2015 and OHAT 2019.

variable). All elaborations were based solely on methodological considerations and independent of study results.

3. Results

3.1. Study selection

We identified 167 studies on mortality for full text review (Fig. 1). Of those, 36 studies fulfilled our inclusion criteria and were included in the systematic review. The most common reason for exclusion was not meeting the exposure framework, such as that the study did not include a necessary area adjustment in nation-wide studies (N = 26 studies), there was insufficient spatial resolution (N = 22 studies), or studies were solely based on PM monitoring or satellite data (N = 20). The list of excluded mortality studies, with their corresponding reason for exclusion, can be found in Appendix Table 2.

Studies not meeting the criteria of the exposure framework included the Harvard Six City Study, most American Cancer Society studies, the US-wide Medicare cohort study and the Canadian-wide CanCHEC study (e.g., Crouse et al. 2012; Di et al. 2017; Dockery et al. 1993; Pope et al. 1995; 2002). From CanCHEC, only the distance to roadway estimate was selected and an NO_2 estimate from a subset of the Canadian 1991 CanCHEC cohort based on the Canadian census was considered to sufficiently reflect a traffic impact (Cakmak et al. 2019; Crouse et al. 2015).

3.2. Study description

Most selected studies were conducted in Europe (N = 20) and North America (N = 11), and a few were based in Asia and Australia (N = 5) (Table 2). Most studies (N = 31) have been published after 2008 – the end of the search date for the 2010 HEI Traffic Review. All studies used a cohort study design. The studies differed substantially in sample size, ranging from several thousands to several million participants. Virtually all studies (N = 35) adjusted for a large number of individual and area-level covariates—including smoking, body mass index, and individual and area-level socioeconomic status. Exposure assessment was based on land use regression models or dispersion/chemical transport models. Exposures reflected annual average or longer. None of the selected studies used monitoring data alone. Start and follow-up periods differed across studies. Start of the study mostly ranged from about 1990 to 2005, and 13 studies had follow-up extending until 2010–2015. Mean TRAP exposures were mostly moderate (e.g., annual average $PM_{2.5}$ exposure < 30 μg/m^3 and NO_2 < 40 μg/m^3) but differed widely across studies. Most studies (N = 26) were performed in general population samples of adults; the remaining in populations of patients suffering from specific conditions, such as ischemic heart disease (N = 10). A few studies were conducted only with older adults (65 +) (N = 3) or only in men or in women (N = 3 in each category). About half of the studies (N = 17) investigated non-accidental (natural) mortality as opposed to all-cause mortality.

Studies were conducted in different populations, locations and settings. Studies adjusting for individual lifestyle factors, included the Danish DCH study in Copenhagen and Aarhus, Denmark (Hvidtfeldt et al. 2019; Raaschou-Nielsen et al. 2012); female teachers across California of the California Teachers study (Ostro et al. 2015); participants from ACS-CPS II in New York and Los Angeles with $PM_{2.5}$ estimated by city-specific land use regression models (Krewski et al. 2009); participants 65 years and older in Hong Kong (Yang et al. 2018) and in the Shizuoka region in Japan (Yorifuji et al. 2010, 2013); and two Australian adult cohorts at low pollution levels in Perth and Sydney (Dirgawati et al. 2019; Hanigan et al. 2019).

Moreover, we included several cohorts using administrative data, covering very large populations, such as all residents of the city of Rome (Badaloni et al. 2017; Cesaroni et al. 2013); all residents of the city of Barcelona (Nieuwenhuijsen et al. 2018); 840,000 adults selected from a General Practitioners network from multiple cities across England (Carey et al. 2013); and a 1% random sample (370,000 individuals) of the 1971 English census (Hansell et al. 2016). Administrative cohort studies often lack data on individual lifestyle factors, though these studies typically included detailed data on individual- and area-level SES.

The cohort studies in patient populations were typically smaller than the general population studies (Table 2), with the exception of the myocardial infarction survivor study in England and Wales (Tonne and Wilkinson 2013). All but one (Jerrett et al. 2009) patient study investigated all-cause mortality, thus including accidental deaths.

In total 7.1 million participants were included in the studies making up the body of evidence (not counting overlapping study populations). The number of participants added in the meta-analysis differed per pollutant. For example, in the NO_2 meta-analysis 4.4 million participants were included.

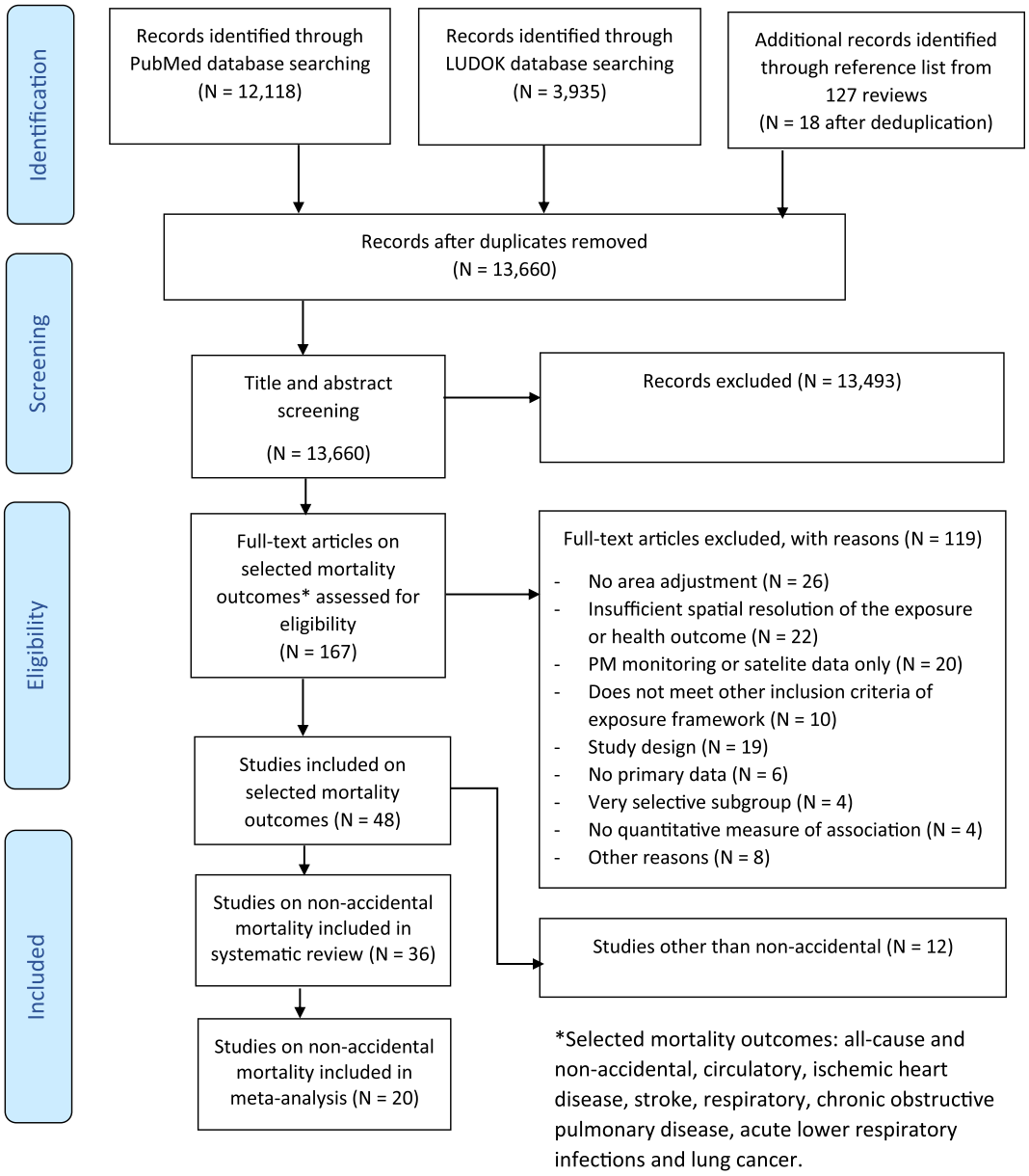

Fig. 1. Study selection flow chart.

3.3. Primary meta-analyses

Fig. 2 shows the meta-analytical summary effect estimates for all pollutants based on the general population studies. We included 20 studies in the meta-analyses, which was fewer than the 36 selected studies, due to exclusion of studies in patient populations (e.g., Tonne and Wilkinson 2013, N = 10), studies that used log-transformed exposures (Raaschou-Nielsen et al. 2012), studies that reported only on indirect traffic measures (Cakmak et al. 2019; Gehring et al. 2006; Heinrich et al. 2013), studies in the same population for which a more informative study has been published (Yorifuji et al. 2013 instead of Yorifuji et al. 2010), and estimated effects for pollutants for which there were fewer than 3 studies (Villeneuve et al. 2013). The number of individual study estimates contributing to a pollutant's summary effect estimate ranged from three (Cu and Fe) to twelve ($PM_{2.5}$). Appendix Table 4 documents that we extracted the full adjusted effect estimates and hence no bias occurred because of selecting author-favored effect estimates.

The summary effect estimates for all pollutants documented positive associations with non-accidental mortality, with relative risks ranging from 1.01 to 1.06 (Fig. 2). The summary estimates for the most studied pollutants NO_2, EC, and $PM_{2.5}$ were statistically significant. The summary effect estimate for the eleven studies of NO_2 was 1.04 (95% CI: 1.01–1.06) per 10-μg/m^3; for the eleven studies of EC, the summary estimate was 1.02 (1.00–1.04) per 1-μg/m^3; and for the twelve studies of $PM_{2.5}$, it was 1.03 (1.01–1.05) per 5-μg/m^3. Most studies contributed information on multiple pollutants; therefore, summary estimates for the different pollutants were not completely independent.

Fig. 3 shows the forest plots for NO_2, EC, and $PM_{2.5}$. For all three pollutants, most studies reported positive associations with non-accidental mortality, with varying degrees of magnitude and precision. The summary estimate was not influenced heavily by an individual study, as indicated by the weights in the forest plots. Heterogeneity gauged by the I^2 statistic was high for NO_2 and EC and moderate for $PM_{2.5}$.

The summary estimate for the five studies of NO_x was 1.05 (95% CI: 0.97–1.14) per 20-μg/m^3, with all but one study (Bauleo et al. 2019) showing positive associations (Fig. 4). The summary estimate for the six

Table 2
Key study characteristics of adult cohort studies included in the systematic review for non-accidental mortality.

Reference	Study Name	Location	Study period	Sample size	Population	Mortality definition	Exposure assessment	Confounders adjusted for[a]				Mean exposure[b]	Pollutants	Effect estimate (95% CI) per increment[c]
								SES	Ind. smoking	BMI	Indirect smoking			
Badaloni et al. 2017	Rome Longitudinal	Rome, Italy	2001–2010	1,249,108	General	Non-accidental	LUR	Y	N	N	Y	3	$PM_{2.5\ abs}$	**1.05 (1.03, 1.06) per 1.5 1 × 10^{-5}/m**
												37	PM_{10}	**1.03 (1.01, 1.04) per 17.2 μg/m^3**
												20	$PM_{2.5}$	**1.03 (1.01, 1.05) per 6.6 μg/m^3**
												15	Cu	**1.06 (1.04, 1.08) per 15.4 ng/m^3**
												260	Fe	**1.05 (1.03, 1.07) per 275.5 ng/m^3**
												24	Zn	1.06 (1.04, 1.08) per 16.3 ng/m^3
Bauleo et al. 2019	Civitavecchia Study	Civitavecchia, Italy	1996–2013	71,362	General	Non-accidental	Dispersion / CTM	Y	N	N	N	5.8	NO_x	**0.98 (0.91, 1.05) per 12.8 μg/m^3**
Beelen et al. 2008	NLCS-AIR	The Netherlands	1987–1996	117,528	General	Non-accidental	LUR	Y	Y	N	N	36.9	NO_2	**1.08 (1.00, 1.16) per 30 μg/m^3**
												16.5	BC	**1.05 (1.00, 1.11) per 10 μg/m^3**
												28.3	$PM_{2.5}$	**1.06 (0.97, 1.16) per 10 μg/m^3**
												NA	Density	1.05 (0.97, 1.12) per 335,000 veh/day
												NA	Distance	1.02 (0.97, 1.07) <100m to highway or <50m to major road vs. higher
Beelen et al. 2014	ESCAPE	Multiple cities, multiple countries	1985–2008	315,615	General	Non-accidental	LUR	Y	Y	Y	N	5.2–59.8	NO_2	**1.01 (0.99, 1.03) per 10 μg/m^3**
												8.7–107.3	NO_x	**1.02 (1.00, 1.04) per 20 μg/m^3**
												0.5–3.2	$PM_{2.5\ abs}$	**1.02 (0.97, 1.07) per 1 1 × 10^{-5}/m**
												13.5–48.1	PM_{10}	**1.04 (1.00, 1.09) per 10 μg/m^3**
												4.0–20.7	PM_{coarse}	1.04 (0.98, 1.1) per 5 μg/m^3
												6.6–31.0	$PM_{2.5}$	**1.07 (1.02, 1.13) per 5 μg/m^3**
												NA	Density	1.01 (0.98, 1.05) per 4,000 veh-km/day
Beelen et al. 2015	ESCAPE	Multiple cities, multiple countries	1985–2008	291,816	General	Non-accidental	LUR	Y	Y	Y	N	1–12	Cu	**0.98 (0.92, 1.04) per 5 ng/m^3**
												40–320	Fe	**1.03 (0.98, 1.09) per 100 ng/m^3**
												16–41	Zn	1.03 (0.99, 1.08) per 20 ng/m^3
Cakmak et al. 2019	1991 CanCHEC	Canada	1991–2011	2,644,370	General	Non-accidental	NA	Y	N	N	Y	NA	Distance	1.57 (1.44, 1.72) <475 vs. >1,583m 1.10 (1.07, 1.13) 475–1,152 vs. >1,583m 1.04 (1.03, 1.05) 1,152–1,583 vs. >1,583m
Carey et al. 2013	English National Cohort	England	2003–2007	830,842	General	All-cause	Dispersion / CTM	Y	Y	Y	N	22.5	NO_2	**1.02 (1.00, 1.04) per 10.7 μg/m^3**
												19.7	PM_{10}	**1.00 (0.98, 1.02) per 3.0 μg/m^3**
												12.9	$PM_{2.5}$	**1.00 (0.98, 1.02) per 1.9 μg/m^3**
Cesaroni et al. 2013	Rome Longitudinal	Rome, Italy	2001–2010	1,265,058	General	Non-accidental	LUR	Y	N	N	Y	43.6	NO_2	**1.03 (1.02, 1.03) per 10 μg/m^3**
												23.0	$PM_{2.5}$	1.04 (1.03, 1.05) per 10 μg/m^3
												NA	Density	1.01 (0.99, 1.03) >6,650 vs. <250 vehicle-km/day 1.01 (0.99, 1.02) 3,230–6,650 vs. <250 veh-km/day 0.99 (0.98, 1.01) 1,630–3,220 vs. <250 veh-km/day 1.04 (1.03, 1.06) 250–1,620 vs. <250 veh-km/day

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Table 2 (*continued*)

Reference	Study Name	Location	Study period	Sample size	Population	Mortality definition	Exposure assessment	Confounders adjusted for[a]				Mean exposure[b]	Pollutants	Effect estimate (95% CI) per increment[c]
								SES	Ind. smoking	BMI	Indirect smoking			
												NA	Distance	1.03 (1.01, 1.05) 50–100 vs. >250m 1.03 (1.01, 1.05) 100–150 vs. >250m 1.02 (1.00, 1.04) 150–250 vs. >250m
Cohen et al. 2019	Israel Coronary Intervention	Petah Tikva, Israel	2004–2017	10,627	Patient	All-cause	LUR	Y	Y	N	N	24.5	NO_x	1.07 (0.98, 1.18) <25 vs. >25 ppb
Crouse et al. 2015	1991 CanCHEC	Multiple cities, Canada	1991–2006	735,590	General	Non-accidental	LUR	Y	N	N	Y	25.2	NO_2	**1.05 (1.04, 1.07) per 5 ppb**
Desikan et al. 2016	South London Stroke Register	London, United Kingdom	2005–2012	1,800	Patient	All-cause	Dispersion / CTM	Y	N	N	N	44.59	NO_2	0.97 (0.87, 1.08) per 5.0 μg/m^3
												34.39	NO	0.96 (0.85, 1.08) per 8.86 μg/m^3
												78.98	NO_x	0.96 (0.85, 1.08) per 14.0 μg/m^3
												28.84	PM_{10}	1.12 (0.98, 1.29) per 2.2 μg/m^3
												15.35	$PM_{2.5}$	1.28 (1.08, 1.53) per 1.9 μg/m^3
												0.8	$PM_{2.5}$ exhaust	0.98 (0.84, 1.14) per 0.3 μg/m^3
												0.92	Non-tailpipe $PM_{2.5}$	0.94 (0.85, 1.03) per 0.2 μg/m^3
Dirgawati et al. 2019	HIMS	Perth, Australia	1996–2012	11,627 Male[d]	General	All-cause	LUR	Y	Y	Y	N	13.4	NO_2	**1.06 (1.00, 1.13) per 10 μg/m^3**
												32.3	NO_x	**1.02 (1.00, 1.04) per 10 μg/m^3**
												0.9	$PM_{2.5\ abs}$	**1.12 (1.02, 1.22) per 1 1 × 10^{-5}/m**
												5.1	$PM_{2.5}$	**1.07 (0.98, 1.16) per 5 μg/m^3**
Finkelstein et al. 2005	Hamilton Pulmonary Cohort	Hamilton, Ontario, Canada	1985–2001	5,228	Patient	All-cause	NA	Y	N	Y	N	NA	Distance	1.18 (1.02, 1.38) <50 m from major road or <100m from highway vs. higher
Gehring et al. 2006	SALIA	North Rhine-Westphalia, Germany	1985–2003	4,230 Female	General	All-cause	NA	Y	Y	N	N	NA	Distance	1.29 (0.93, 1.78) <50 vs. >50m
Hanigan et al. 2019	45 and Up Study	Sydney, Australia	2006–2015	75,148	General	All-cause	LUR	Y	Y	Y	N	17.75	NO_2	**1.03 (0.98, 1.07) per 5 μg/m^3**
												4.49	$PM_{2.5}$	**1.05 (0.98, 1.12) per 1 μg/m^3**
Hansell et al. 2016	ONS-Longitudinal	England and Wales, United Kingdom	1971–2009	367,658	General	Non-accidental	LUR	Y	N	N	Y	42.7	BS	**1.02 (1.01, 1.04)[e] per 10 μg/m^3**
												20.7	PM_{10}	**1.24 (1.16, 1.34)[e] per 10 μg/m^3**
Heinrich et al. 2013	SALIA	North Rhine-Westphalia, Germany	1985–2008	4,615 Female	General	All-cause	NA	Y	Y	Y	N	NA	Distance	1.42 (1.12, 1.79) <50 vs. >50m
Hvidtfeldt et al. 2019	DDCH	Copenhagen and Aarhus, Denmark	1993–2015	49,564	General	Non-accidental	Dispersion / CTM	Y	Y	Y	N	25.0	NO_2	**1.07 (1.04, 1.10) per 10 μg/m^3**
												0.92	BC	**1.09 (1.04, 1.15) per 1 μg/m^3**
												25.1	PM_{10}	**1.12 (1.03, 1.22) per 10 μg/m^3**
												18.0	$PM_{2.5}$	**1.13 (1.05, 1.21) per 5 μg/m^3**
Jerrett et al. 2009	Toronto Respiratory Cohort	Toronto, Canada	1992–2002	2,360	Patient	Non-accidental	LUR	Y	Y	Y	N	22.9	NO_2	1.17 (1.00, 1.36) per 4 ppb

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Table 2 (*continued*)

Reference	Study Name	Location	Study period	Sample size	Population	Mortality definition	Exposure assessment	Confounders adjusted for[a]				Mean exposure[b]	Pollutants	Effect estimate (95% CI) per increment[c]
								SES	Ind. smoking	BMI	Indirect smoking			
												NA	Distance	1.19 (0.92, 1.53) <50m from major road or <100m from highway vs. higher
Krewski et al. 2009	ACS-CPS II LA	Los Angeles, California, United States	1982–2000	22,905	General	All-cause	LUR	Y	Y	Y	N	20	$PM_{2.5}$	**1.14 (1.03, 1.27) per 10 μg/m^3**
Krewski et al. 2009	ACS-CPS II NYC	New York City, New York, United States	1982–2000	44,056	General	All-cause	LUR	Y	Y	Y	N	14.3	$PM_{2.5}$	**0.98 (0.95, 1.02) per 1.5 μg/m^3**
Maheswaran et al. 2010	South London Stroke Register	London, United Kingdom	1995–2006	3,320	Patient	All-cause	Dispersion / CTM	Y	Y	N	N	41	NO_2	1.28 (1.11, 1.48) per 10 μg/m^3
												25	PM_{10}	1.52 (1.06, 2.18) per 10 μg/m^3
Medina-Ramón et al. 2008	Worcester Heart Failure	Worcester, Massachusetts, United States	2000–2005	1,389[d]	Patient	All-cause	NA	Y	N	N	Y	NA	Density	1.15 (1.05, 1.25)[f] per 1,379 veh-km/day
												NA	Distance	0.98 (0.91, 1.05)[f] per 2,008m
Nafstad et al. 2004	Oslo men's cohort	Oslo, Norway	1972–1998	16,209 Male	General	All-cause	Dispersion / CTM	Y	Y	Y	N	10.7	NO_x	**1.08 (1.06, 1.11) per 10 μg/m^3**
Nieuwenhuijsen et al. 2018	Barcelona Mega Cohort	Barcelona, Spain	2010–2014	792,649	General	All-cause	LUR	Y	Y	N	N	53.42	NO_2	**1.01 (1.00, 1.02) per 5 μg/m^3**
												2.64	$PM_{2.5\ abs}$	**1.02 (1.00, 1.05) per 1 1 × 10^{-5}/m**
												38.29	PM_{10}	**1.00 (0.97, 1.03) per 10 μg/m^3**
												16.08	$PM_{2.5}$	**1.03 (0.99, 1.06) per 5 μg/m^3**
Ostro et al. 2015	California Teachers Study	California, United States	1995–2007	101,884 Female	General	Non-accidental	Dispersion / CTM	Y	Y	Y	N	1.1	EC	**1.00 (0.97, 1.04) per 0.8 μg/m^3**
												17.9	$PM_{2.5}$	**1.01 (0.98, 1.05) per 9.6 μg/m^3**
												0.5	Cu	**1.00 (0.98, 1.03) per 0.4 ng/m^3**
												0.4	Fe	**1.00 (0.97, 1.04) per 0.2 μg/m^3**
												1,293	UFP	1.01 (0.98, 1.05) per 969 ng/m^3
												0.4	On-road diesel	1.00 (0.97, 1.04) per 0.4 μg/m^3
												0.3	On-road gasoline	0.99 (0.95, 1.02) per 0.3 μg/m^3
Raaschou-Nielsen et al. 2012	DDCH	Copenhagen and Aarhus, Denmark	1993–2009	52,061	General	Non-accidental	Dispersion / CTM	Y	Y	Y	N	16.9	NO_2	1.08 (0.98, 1.18)[f] per 1 μg/m^3
												NA	Density	1.01 (0.99, 1.03)[f] per 1 veh-km/day
												NA	Distance	0.94 (0.85, 1.05) <50 vs. >50m
Stockfelt et al. 2015	PPS	Gothenburg, Sweden	1970–2007	6,557 Male	General	Non-accidental	Dispersion / CTM	Y	Y	Y	N	42	NO_x	**1.02 (1.01, 1.04) per 10 μg/m^3**
Tonne and Wilkinson 2013	MINAP	England and Wales, United Kingdom	2004–2010	154,204	Patient	All-cause	Dispersion / CTM	Y	Y	N	N	18.8	NO_2	1.01 (0.98, 1.04) per 10 μg/m^3
												28.3	NO_x	1.00 (0.99, 1.02) per 10 μg/m^3
												17	PM_{10}	1.01 (0.92, 1.10) per 10 μg/m^3
												11	$PM_{2.5}$	1.20 (1.04, 1.38) per 10 μg/m^3

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Table 2 (*continued*)

Reference	Study Name	Location	Study period	Sample size	Population	Mortality definition	Exposure assessment	Confounders adjusted for[a]				Mean exposure[b]	Pollutants	Effect estimate (95% CI) per increment[c]
								SES	Ind. smoking	BMI	Indirect smoking			
Tonne et al. 2016	London MI Cohort	London, United Kingdom	2003–2010	18,138	Patient	All-cause	Dispersion / CTM	Y	N	N	Y	37.1	NO_2	1.04 (0.99, 1.10) per 8 μg/m^3
												61.8	NO_x	1.03 (0.98, 1.08) per 19.2 μg/m^3
												0.7	Non-tailpipe $PM_{2.5}$	1.04 (1.00, 1.09) per 0.3 μg/m^3
												0.6	Traffic $PM_{2.5}$	1.02 (0.98, 1.07) per 0.3 μg/m^3
Villeneuve et al. 2013	Ontario Tax Cohort	Toronto, Canada	1982–2004	58,760	General	Non-accidental	LUR	Y	N	N	Y	0.64	Benzene	1.05 (1.03, 1.08) per 0.1 μg/m^3
von Klot et al. 2009	Worcester Heart Attack	Worcester, Massachusetts, United States	1995–2005	3,895	Patient	All-cause	LUR	N	N	N	Y	0.45	EC	1.15 (1.03, 1.29) per 0.2 μg/m^3 (after 2nd year of survival) 1.02 (0.93, 1.11) per 0.2 μg/m^3 (in first two years of survival)
Wilker et al. 2013	Boston Stroke Patients	Boston, Massachusetts, United States	1999–2012	1,683	Patient	All-cause	NA	Y	Y	N	N	NA	Distance	1.20 (1.01, 1.43)[f] <100 vs. >400m 1.08 (0.88, 1.31)[f] 100–200 vs. >400m 0.99 (0.82, 1.20)[f] 200–400 vs. >400m
Yang et al. 2018	Hong Kong Elderly	Hong Kong, China	1998–2011	61,386[d]	General	Non-accidental	LUR	Y	Y	Y	N	104	NO_2	**1.00 (0.97, 1.03) per 25.6 μg/m^3**
												147	NO	0.99 (0.97, 1.02) per 167 μg/m^3
												12.1	BC	**1.03 (1.00, 1.05) per 9.6 μg/m^3**
												42.2	$PM_{2.5}$	**1.03 (1.01, 1.06) per 5.5 μg/m^3**
Yap et al. 2012	Renfrew/Paisley	Glasgow, Scotland	1972–1998	15,188	General	All-cause	LUR	Y	Y	Y	N	19.3	BS	**1.08 (1.02, 1.15) per 10 μg/m^3**
Yap et al. 2012	Collaborative cohorts	Glasgow, Scotland	1972–1998	6,255	General	All-cause	LUR	Y	Y	Y	N	23.2	BS	**1.01 (0.95, 1.06) per 10 μg/m^3**
Yorifuji et al. 2010	Shizuoka Elderly	Shizuoka, Japan	1999–2006	12,029[d]	General	All-cause	LUR	Y	Y	Y	N	25	NO_2	1.02 (0.96, 1.08) per 10 μg/m^3
Yorifuji et al. 2013	Shizuoka Elderly	Shizuoka, Japan	1999–2009	13,412[d]	General	All-cause	LUR	Y	Y	Y	N	22	NO_2	**1.12 (1.07, 1.18) per 10 μg/m^3**

CTM = Chemical transport model. LUR = land use regression. NA = not applicable.

[a] All studies adjusted for age and sex in the design or analysis.

[b] Mean or median exposure. Units are in the last column.

[c] Effect estimates are expressed as relative risk or hazard ratio. Bold indicates the effect estimate was included in the meta-analysis.

[d] In older adults (65+).

[e] Odds Ratio.

[f] Log transformed.

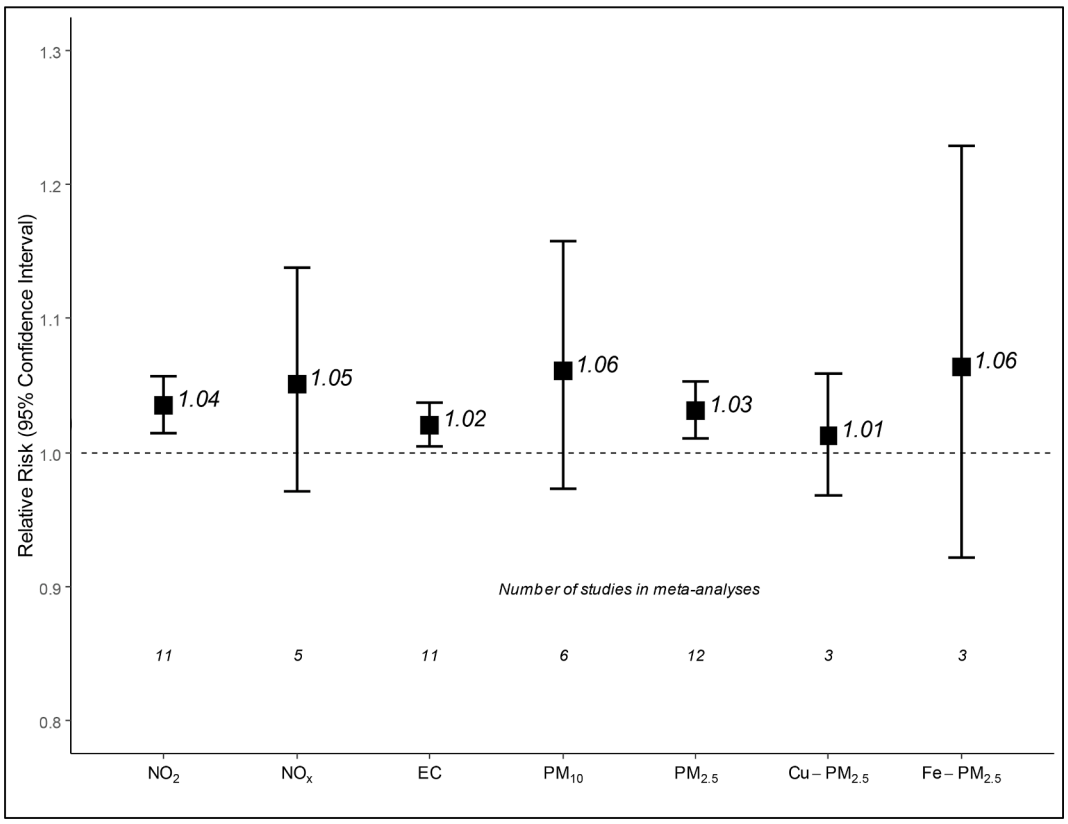

Fig. 2. Meta-analysis of associations between traffic-related air pollutants and non-accidental mortality.

studies of PM_{10} mortality was 1.06 (0.97–1.16) per 10-μg/m^3, with four studies showing RRs above unity and two studies where the RR equalled unity (Carey et al. 2013; Nieuwenhuijsen et al. 2018). For both Cu and Fe in $PM_{2.5}$ three studies were available, of which the Rome Longitudinal study showed a positive association and had high weight in the meta-analysis (Badaloni et al. 2017), the California Teachers study a null finding (Ostro et al. 2015) and the ESCAPE study a positive association for Fe and an inverse association for Cu, both with wide CIs (Beelen et al. 2015).

For NO, PM_{coarse}, UFP, Zinc (Zn) and benzene only one or two studies were available. The two NO studies showed no associations, with RRs below unity. The few studies on PM_{coarse}, UFP, Zn and benzene showed positive associations with mortality (Table 2).

3.4. Associations with indirect traffic measures

The studies on indirect traffic measures provide further support for a positive association of TRAP with non-accidental mortality (Table 2 and Appendix Fig. 1). The indirect traffic measures were too heterogeneously defined across studies to allow meta-analysis. Eight of the ten studies comparing a short distance to major road category (e.g., <50 m) with the largest distance category, reported higher non-accidental mortality for participants living at short distances from major roads. The magnitude of the associations varied substantially between studies. The traffic density measures showed effect estimates slightly above unity in three general population cohort studies (Beelen et al. 2008; 2014; Cesaroni et al. 2013).

3.5. Additional meta-analyses and co-exposure with traffic noise

Appendix Fig. 2 shows that positive associations were reported in studies irrespective of outcome definition (all-cause versus non-accidental mortality). The summary estimates for studies of all-cause and non-accidental mortality were similar and did not differ significantly from each other. We only included pollutants with at least three studies per outcome in this analysis (NO_2, EC and $PM_{2.5}$).

Appendix Fig. 3 illustrates that the cohort studies conducted in patient populations, which were excluded in the primary meta-analysis, also showed predominantly positive associations between NO_2, EC, and $PM_{2.5}$ and non-accidental mortality. There were five, one, and two studies available for NO_2, EC, and $PM_{2.5}$, respectively. Patient cohorts tended to be small, providing less precise, more variable effect estimates than estimates from the general population studies. For NO_2, the meta-analytical summary estimate of the five studies in patients was 1.09 (95% CI: 0.93–1.26). This summary estimate is larger but less precise and not statistically significantly different from the summary estimate for the general population studies.

Fig. 5 shows that the majority of studies for NO_2 and EC were rated as having high traffic specificity. For each pollutant, only two studies were rated as having moderate traffic specificity (Carey et al. 2013; Hanigan et al. 2019; Hansell et al. 2016; Ostro et al. 2015). *A priori* all $PM_{2.5}$ studies included in this review were rated as moderate traffic specificity. The meta-analytic summary estimates of the high traffic specificity studies were positive for both NO_2 and EC, and somewhat larger than the estimates from the two moderate traffic specificity studies.

Appendix Fig. 4 illustrates that positive associations between NO_2, EC, and $PM_{2.5}$ and non-accidental mortality were found in different geographic regions of the world. The Panel found positive associations for NO_2 in the four identified geographical areas (Western Europe, Asia, North America, and Australia–New Zealand). The number of studies outside Europe was modest, limiting the comparison.

Four TRAP studies reported associations adjusted for road traffic noise (Appendix Table 5). In three of these studies, traffic-related air pollutants associations were not or very mildly attenuated (Nieuwenhuijsen et al. 2018; Raaschou-Nielsen et al. 2012; Tonne et al. 2016). In the most recent DDCH study (Hvidtfeldt et al. 2019), effect

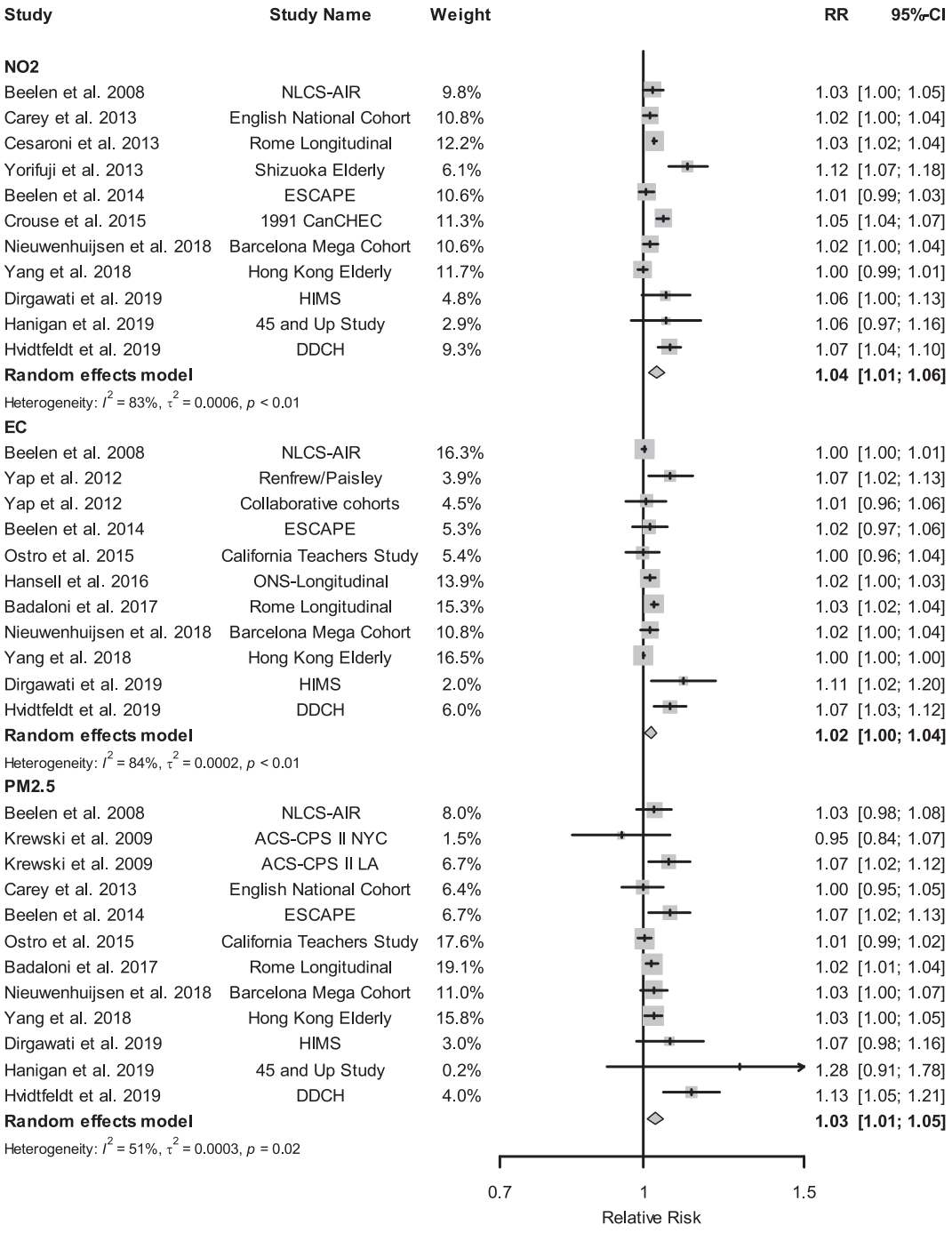

Fig. 3. Association between NO_2 (per 10 μg/m^3), EC (per 1 μg/m^3), and $PM_{2.5}$ (per 5 μg/m^3) and non-accidental mortality: meta-analysis.

estimates were substantially attenuated but still indicative of an association with non-accidental mortality. The correlation between air pollutants and noise in these studies was generally low to moderate (~0.2. to 0.6). The generally modest attenuation in the non-accidental mortality estimates with adjustment for traffic noise is consistent with traffic noise being a relatively weak risk factor for non-accidental mortality. Traffic noise is a risk factor for only a selection of (cardiometabolic) diseases (WHO 2018).

3.6. Risk of bias

Risk of bias did not differ for the different exposure metrics within a study; hence results were presented by study. Most studies were rated as low to moderate risk of bias in most domains. The exception was the confounding domain where about 25% of the studies were rated as high risk of bias (Appendix Tables 6 and 7). In particular, erring on the side of caution with respect to confounding, the Panel applied a strict assessment of the adjustment for important potential important confounders. The administrative cohorts tended to lack data on and adjustment for individual-level smoking or BMI were thus rated high risk of bias. The administrative studies have used a range of methods to assess potential confounding by missing lifestyle factors, including indirect adjustment approaches (e.g., Crouse et al. 2015), assessment of an association between exposure and smoking in a subgroup (e.g., Badaloni et al. 2017), adjustment for pre-existing disease as proxies of smoking and BMI (e.g., Cesaroni et al. 2013), and area-level rates of lung cancer as a proxy for

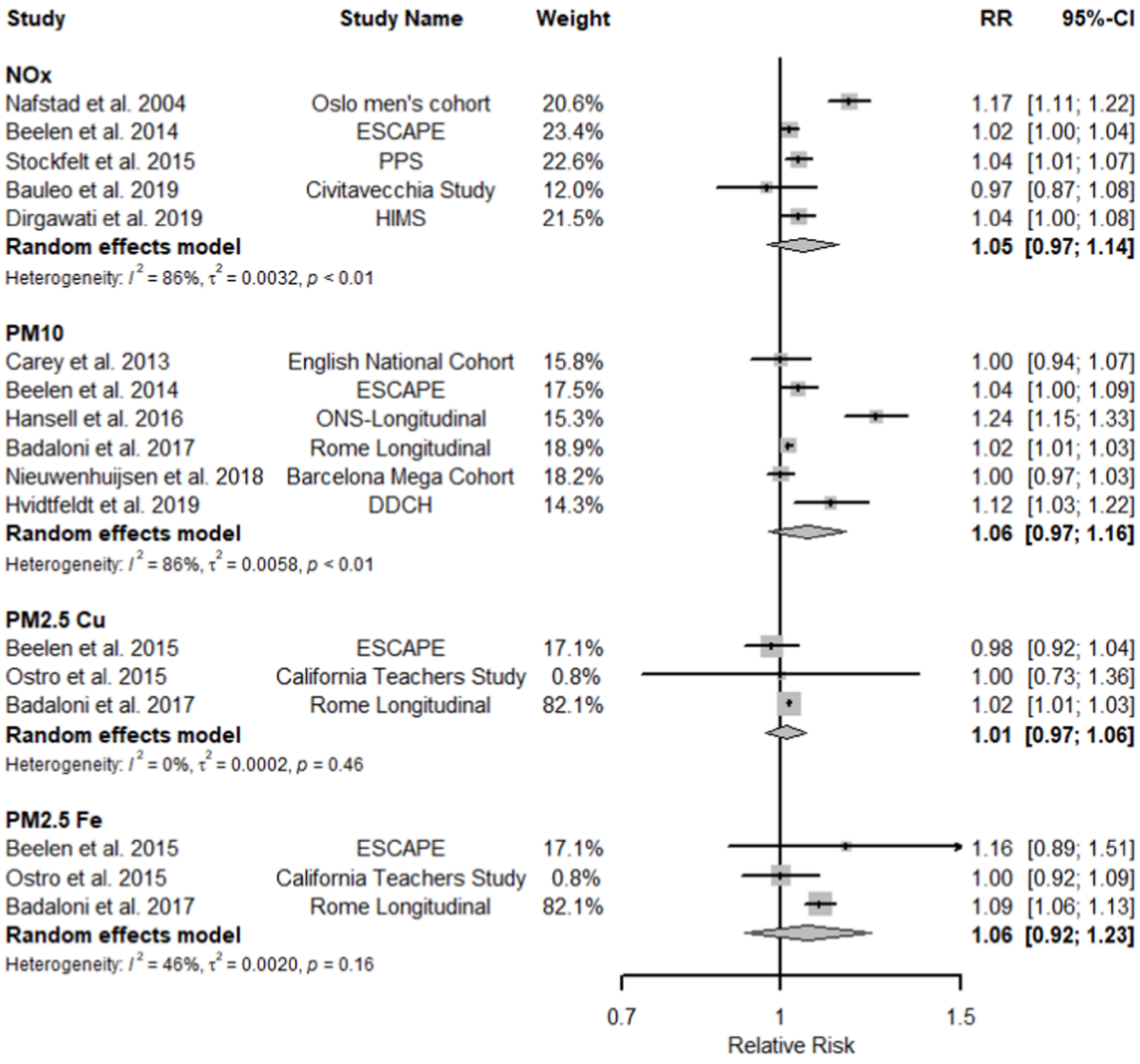

Fig. 4. Association between NO_x (per 20 μg/m^3), PM_{10} (per 10 μg/m^3), Cu (per 5 ng/m^3), and Fe (per 500 ng/m^3) and non-accidental mortality: meta-analysis.

smoking (e.g., Hansell et al. 2016). In most instances, however, this did not result in a lower risk rating (e.g., to moderate risk of bias).

When we compared the effect estimates from the studies of NO_2, EC and $PM_{2.5}$ that were rated at low or moderate risk of confounding bias with the corresponding estimates from the studies rated at high risk, we found no marked differences (Fig. 6). The estimates from the low and moderate risk of bias groups were slightly larger than those in the high risk of bias groups. Nonetheless, these comparisons were limited: only two studies each of NO_2 and $PM_{2.5}$ and three studies of EC were rated as high risk of bias (Badaloni et al. 2017; Cesaroni et al. 2013; Hansell et al. 2016; Nieuwenhuijsen et al. 2018). The difference in effect estimates between high and moderate risk of bias studies of EC was highly non-significant. We did not test differences for NO_2 and $PM_{2.5}$.

For PM_{10}, three of the six studies in the meta-analysis were rated as high risk of bias due to missing important confounders in the analysis (Badaloni et al. 2017; Hansell et al. 2016; Nieuwenhuijsen et al. 2018). The effect estimates in the low and moderate risk of bias group were positive (RR 1.05; 95% CI: 0.92–1.19) and only slightly smaller than in the high risk of bias group (RR 1.08; 0.80–1.44).

For Cu and Fe in $PM_{2.5}$ there were just three studies, making the comparison difficult. For both components, the study carrying most of the weight was rated as high risk of bias (Badaloni et al. 2017). For Cu, this was the only study with a positive association. For Fe, the high risk of bias study effect estimate did not differ substantially from those of the other two studies.

3.7. Confidence assessment

3.7.1. Modified OHAT assessment

Table 3 provides the Panel's confidence assessment in the quality of the body of evidence for traffic-related air pollutants and non-accidental mortality. The table includes only the pollutants for which there were sufficient studies to conduct meta-analyses. As all studies followed a cohort study design, the Panel's initial confidence rating was moderate.

The judgements for each pollutant were derived from a combination of downgrades because of imprecision (NO_x, PM_{10} and Fe) and risk of bias (Cu), and upgrades because of monotonic exposure–response patterns (all pollutants except Cu and Fe) and consistency across regions (NO_2).

We downgraded for imprecision because although the criterion for study power was met, the effect estimates for NO_x, PM_{10} and Fe were imprecise with a wide 95% confidence interval and the confidence interval clearly included unity.

Risk of bias resulted in a downgrade only for Cu. For the other pollutants, few studies were rated as high risk of bias, and summary estimates in the low-moderate risk of bias studies group tended to be higher than in the high risk of bias group except for PM_{10}. For PM_{10}, fairly robust effect estimates were reported in low and moderate risk of bias studies, that were only slightly smaller than in the high risk of bias group (See Section 3.6). Hence, the Panel did not think a downgrade was needed.

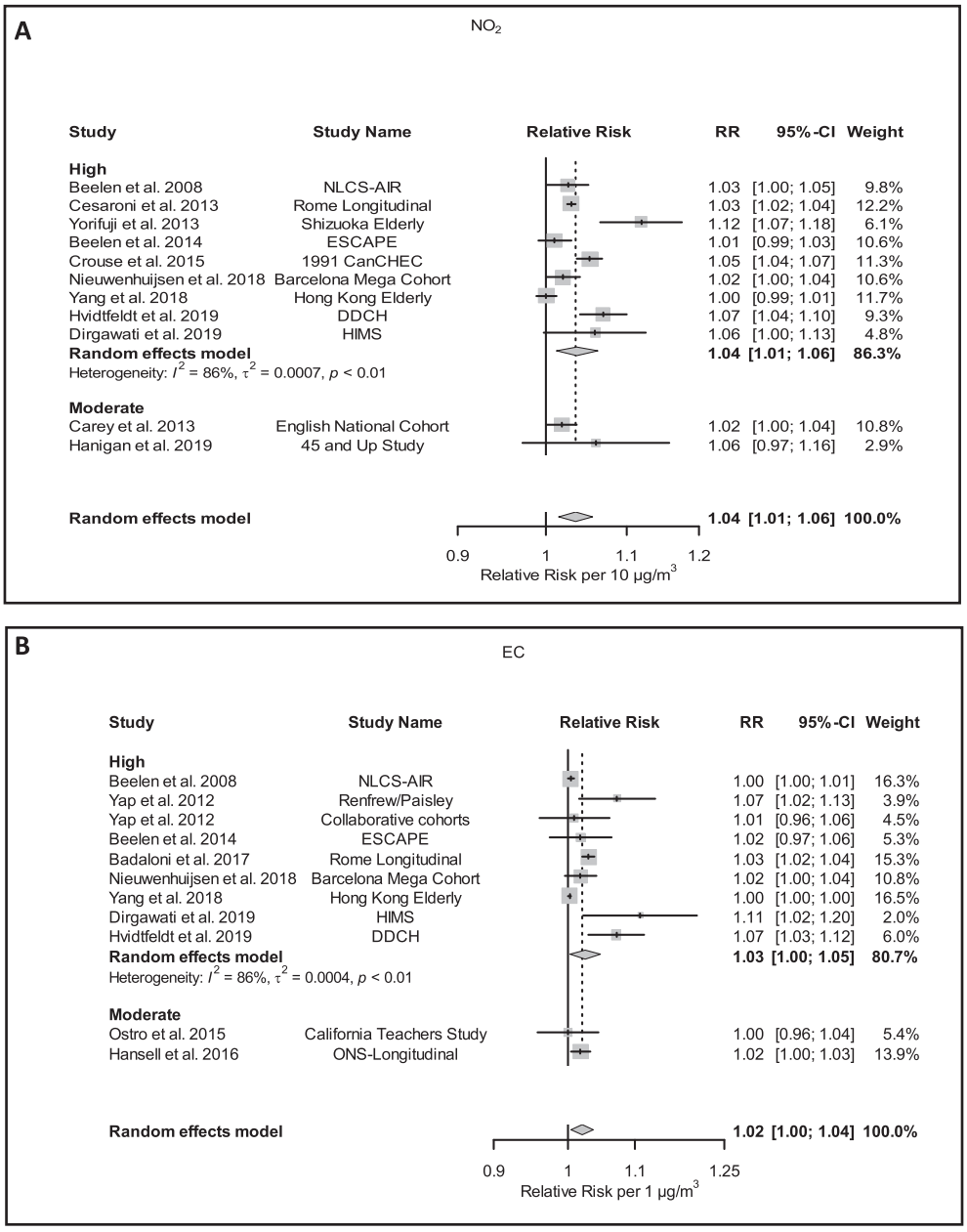

Fig. 5. Association between NO_2 (A) and EC (B) and non-accidental mortality: meta-analysis by traffic specificity.

We did not downgrade for inconsistency despite high heterogeneity for some pollutants (NO_2, NO_x, EC and PM_{10}) based on I^2. The heterogeneity was due to differences in magnitude and not direction of the association. In this review we assess the confidence in presence of an association, not a specific value of the effect estimate. Furthermore I^2 gauges dispersion on a relative rather than an absolute scale, a quality that can exaggerate differences in small yet consistent estimates, such as those reported by many of the studies in this review. Finally, for some pollutants (specifically NO_2), part of the heterogeneity measured by I^2 was explained by the *a priori* chosen stratification variables, such as geographical region. Changes in the composition of TRAP over time or country likely have contributed to heterogeneity in observed health effects.

The Panel decided not to downgrade for publication bias despite a highly significant Egger test for EC (Fig. 7), and evidence for asymmetry from Doi plots and LFK indices for NO_2, EC and $PM_{2.5}$ (Appendix Fig. 5). A small Egger test p-value and high LFK values can be due to heterogeneity and publication bias, and the Panel judged that the observed asymmetry was more likely due to the former than to the latter based on a comparison of various pollutants. The Panel noted that seven of the eleven EC studies also reported estimates for NO_2, for which the Egger test p-value was large (0.5). It is difficult to imagine a scenario in which the publication bias mechanism is stronger for EC than for NO_2 and $PM_{2.5}$ studies. The Panel did not expect that publication bias would be a major issue in cohort studies, given the effort required to conduct cohort studies on outdoor air pollution, which often entails collaboration between different institutions and across multiple disciplines, an argument made in a recent WHO systematic review as well (Chen and Hoek 2020). Most cohort studies included in this review were set up for reasons other than studying air pollution (e.g., diet and cancer). Hence air pollution epidemiologists needed to reach out to cohort owners to perform the included studies. In this setting not publishing negative studies is less likely. Finally, we note that a fairly large number of individual studies (especially on $PM_{2.5}$) yielded statistically non-significant results, further supporting the idea that publication bias is not a major issue in this review.

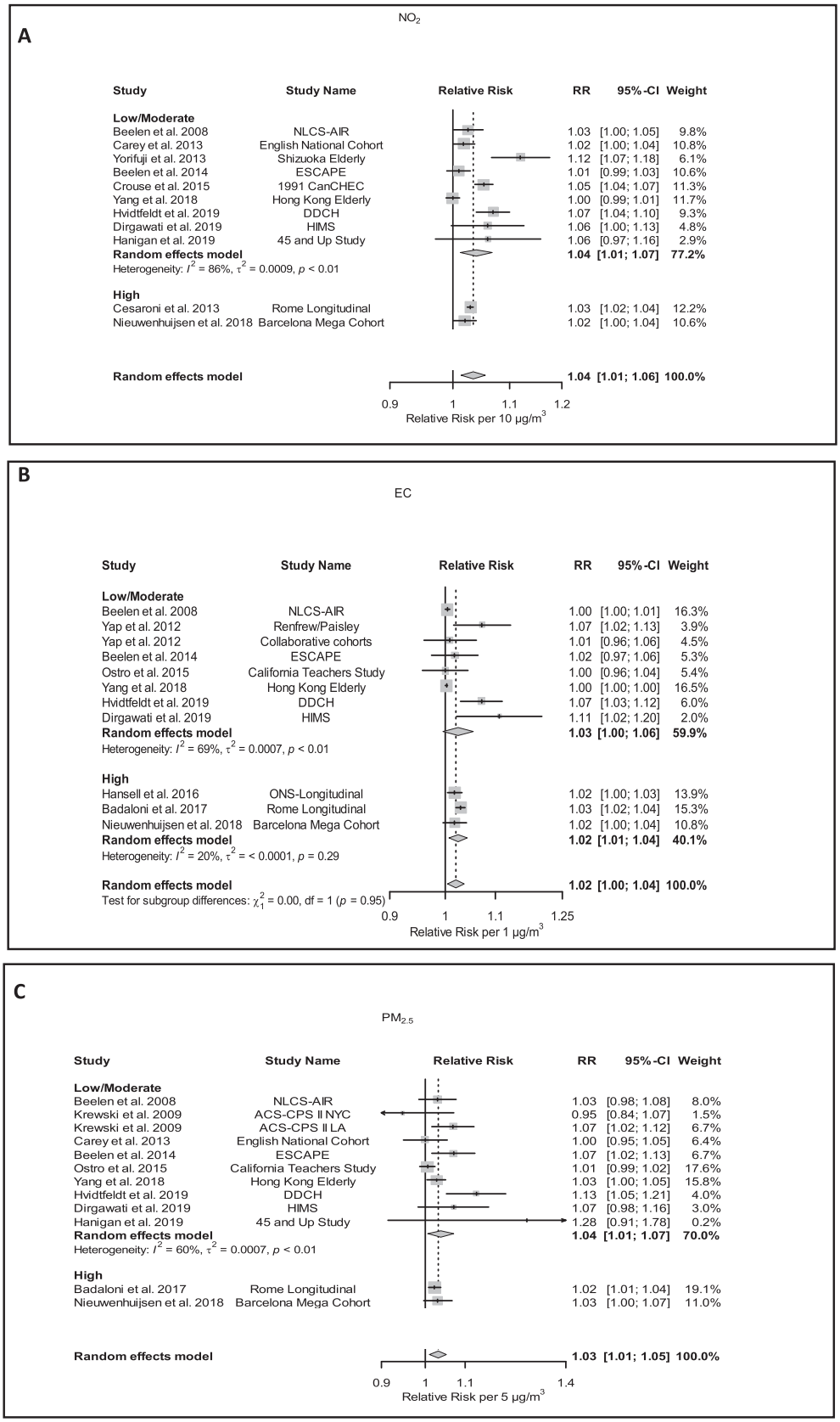

Fig. 6. Association between NO_2 (A), EC (B), and $PM_{2.5}$ (C) and non-accidental mortality: meta-analysis by risk of bias due to confounding.

Table 3
Confidence rating for traffic-related air pollutants and non-accidental mortality using modified OHAT.

	Factors decreasing confidence 0 if no concern; −1 if serious concern to downgrade confidence						Factors increasing confidence 0 if not present; +1 if sufficient to upgrade confidence			
Pollutant	**Study design**	**Initial confidence rating** (# studies)	Risk of bias	Unexplained inconsistency	Imprecision	Publication bias	Monotonic exposure–response	Consideration of residual confounding	Consistency across populations	**Final confidence rating**
NO_2	Cohort	Moderate ($N = 11$)	0	0	0	0	+1	0	+1	High
	Rationale	Cohort design initially rated as moderate	Few studies high RoB and robust effect estimates in low and moderate RoB studies.	High heterogeneity ($I^2 = 83\%$) due to magnitude not direction.	Sample size met, and confidence interval does not include unity.	Limited evidence found in plots and tests.	Clear evidence of plausible shape of ERF (Cesaroni et al. 2013; Crouse et al. 2015; Dirgawati et al. 2019; Hvidtfeldt et al. 2019; Raaschou-Nielsen et al. 2012).	Confounding in both directions possible.	Across geographic regions robust effect estimates.	
NO_x	Cohort	Moderate ($N = 5$)	0	0	–1	0	+1	0	0	Moderate
	Rationale	Cohort design initially rated as moderate	Few studies serious RoB and robust effect estimates in low and moderate RoB studies	High heterogeneity ($I^2 = 86\%$) mostly due to magnitude not direction	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	Clear evidence of plausible shape of ERF (Beelen et al. 2014; Dirgawati et al. 2019; Nafstad et al. 2004; Stockfelt et al. 2015).	Confounding in both directions possible.	Too few studies to assess robustness across geographic regions.	
EC	Cohort	Moderate ($N = 11$)	0	0	0	0	+1	0	0	High
	Rationale	Cohort design initially rated as moderate	Few studies serious RoB and robust effect estimates in low and moderate RoB studies.	High heterogeneity ($I^2 = 84\%$) due to magnitude not direction.	Sample size met and estimate consistent with an association.	Asymmetry in plots and tests, unlikely due to publication bias.	Clear evidence of plausible shape of ERF (Dirgawati et al. 2019; Hansell et al. 2016; Hvidtfeldt et al. 2019).	Confounding in both directions possible.	Across geographic regions insufficient evidence for robust effect estimates.	
PM_{10}	Cohort	Moderate ($N = 6$)	0	0	–1	0	+1	0	0	Moderate
	Rationale	Cohort design initially rated as moderate	Three of six studies high RoB. Fairly robust effect estimates in low and moderate RoB studies.	High heterogeneity ($I^2 = 86\%$) due to magnitude not direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible..	Clear evidence of plausible shape of ERF (Beelen et al. 2014; Hvidtfeldt et al. 2019).	Confounding in both directions possible.	All studies European, no consistency check possible.	
$PM_{2.5}$	Cohort	Moderate ($N = 12$)	0	0	0	0	+1	0	0	High
	Rationale	Cohort design initially rated as moderate	Few studies serious RoB and robust effect estimates	Moderate heterogeneity ($I^2 = 51\%$) due to magnitude not direction.	Sample size met, and confidence interval does not include unity.	Limited evidence found in plots and only borderline significant Egger test,	Clear evidence of plausible shape of ERF (Beelen et al. 2014; Cesaroni	Confounding in both directions possible.	Insufficient evidence for robustness across geographic regions.	

(*continued on next page*)

Table 3 (*continued*)

Pollutant	Factors decreasing confidence 0 if no concern; −1 if serious concern to downgrade confidence						Factors increasing confidence 0 if not present; +1 if sufficient to upgrade confidence			Final confidence rating
	Study design	**Initial confidence rating** (# studies)	Risk of bias	Unexplained inconsistency	Imprecision	Publication bias	Monotonic exposure–response	Consideration of residual confounding	Consistency across populations	
			in low and moderate RoB studies.			unlikely due to publication bias.	et al. 2013; Dirgawati et al. 2019; Hvidtfeldt et al. 2019).			
Cu	Cohort	Moderate ($N = 3$)	–1	0	0	0	0	0	0	Low
	Rationale	Cohort design initially rated as moderate	One study with high RoB which is the only study with an effect estimate above unity.	Low heterogeneity ($I^2 = 0\%$) mostly due to magnitude not direction.	Sample size met and confidence interval includes unity, but confidence interval precise.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	All studies European, no consistency check possible.	
Fe	Cohort	Moderate ($N = 3$)	0	0	–1	0	0	0	0	Low
	Rationale	Cohort design initially rated as moderate	One study with high RoB with similar effect estimates as the two low - moderate RoB studies.	Low heterogeneity ($I^2 = 46\%$) due to magnitude not direction.	Sample size met but confidence interval wide and clearly includes unity.	No formal evaluation possible.	No evidence of plausible shape of ERF.	Confounding in both directions possible.	All studies European, no consistency check possible.	

Upgrades were made for a monotonic exposure–response pattern for pollutants with evidence from at least two influential studies (Appendix Table 8). For this upgrade, we additionally required a (borderline) significant summary effect estimate to avoid upgrading essentially null findings. Studies not included in the meta-analysis were also used for this judgment; specifically, for the Rome Longitudinal cohort studies, an analysis of the shape of the exposure–response function was evaluated for $PM_{2.5}$ by Cesaroni and colleagues (Cesaroni et al. 2013), but not in Badaloni et al. (2017) in the same study population.

For NO_2 an upgrade was made for consistency across geographical regions, even though the number of studies outside Europe was modest. For the final confidence assessment for NO_2, this upgrade did not make a difference, because the evidence was already given a high confidence rating because of an upgrade for a monotonic-exposure response.

The Panel conferred a rating of high confidence in the quality of the body of evidence between TRAP and non-accidental mortality. This assessment is supported by high confidence judgements for the evidence on NO_2, EC and $PM_{2.5}$, pollutants with the largest number of studies. We note lower confidence ratings for the evidence on pollutants with substantially<10 studies (moderate for NO_x and PM_{10}; low for Cu and Fe). The meta-analytic summary estimates of these pollutants were positive, but less precise than the estimates for NO_2, EC and $PM_{2.5}$. These other pollutants, as well as the indirect traffic measure studies, thus provided some additional support for the high confidence rating for the totality of evidence on TRAP and non-accidental mortality.

3.7.2. *Narrative assessment*

The primary meta-analysis supplemented with additional analyses, and findings from studies that could not be meta-analyzed provided clear evidence of the presence of an association between TRAP and non-accidental mortality. All studies used the cohort study design, used registries to assess mortality, and virtually all of them directly or indirectly adjusted for major potential confounders, such as smoking, body mass index and socio-economic status. In total 36 studies in different regions conducted by multiple research groups formed the evidence base. Some large administrative cohort studies were included limiting potential selection bias. The total sample size was 7.1 million participants.

Particularly important was the careful adjustment in most studies of both individual- and area-level SES covariates, following the strategy developed in the early American Cancer Society study (Pope et al. 2002). A risk factor for mortality (e.g., smoking) confounds associations of air pollution with mortality, if there is a correlation with air pollution exposure, and if air pollution is not a determinant of that risk factor. Correlations between air pollution and lifestyle factors can be mediated by SES. A key observation is that the direction of the association between SES and air pollution differs substantially across studies (both positive and negative). Hence, insufficient adjustment for SES and lifestyle factors can bias the effect estimates both up and downwards. The finding of consistent positive associations in different geographical settings is therefore reassuring and increases the confidence in an association between TRAP and non-accidental mortality. For traffic noise as a source of confounding, this argument does not hold, because the correlation between TRAP and traffic noise is positive in all locations since they share the same source. The four studies that assessed potential confounding by traffic noise found that TRAP remained associated with non-accidental mortality after adjustment for traffic noise, typically with only small changes in effect estimates.

Furthermore, the large majority of NO_2 and EC studies were rated as high traffic specificity studies. RRs were elevated for both the high and

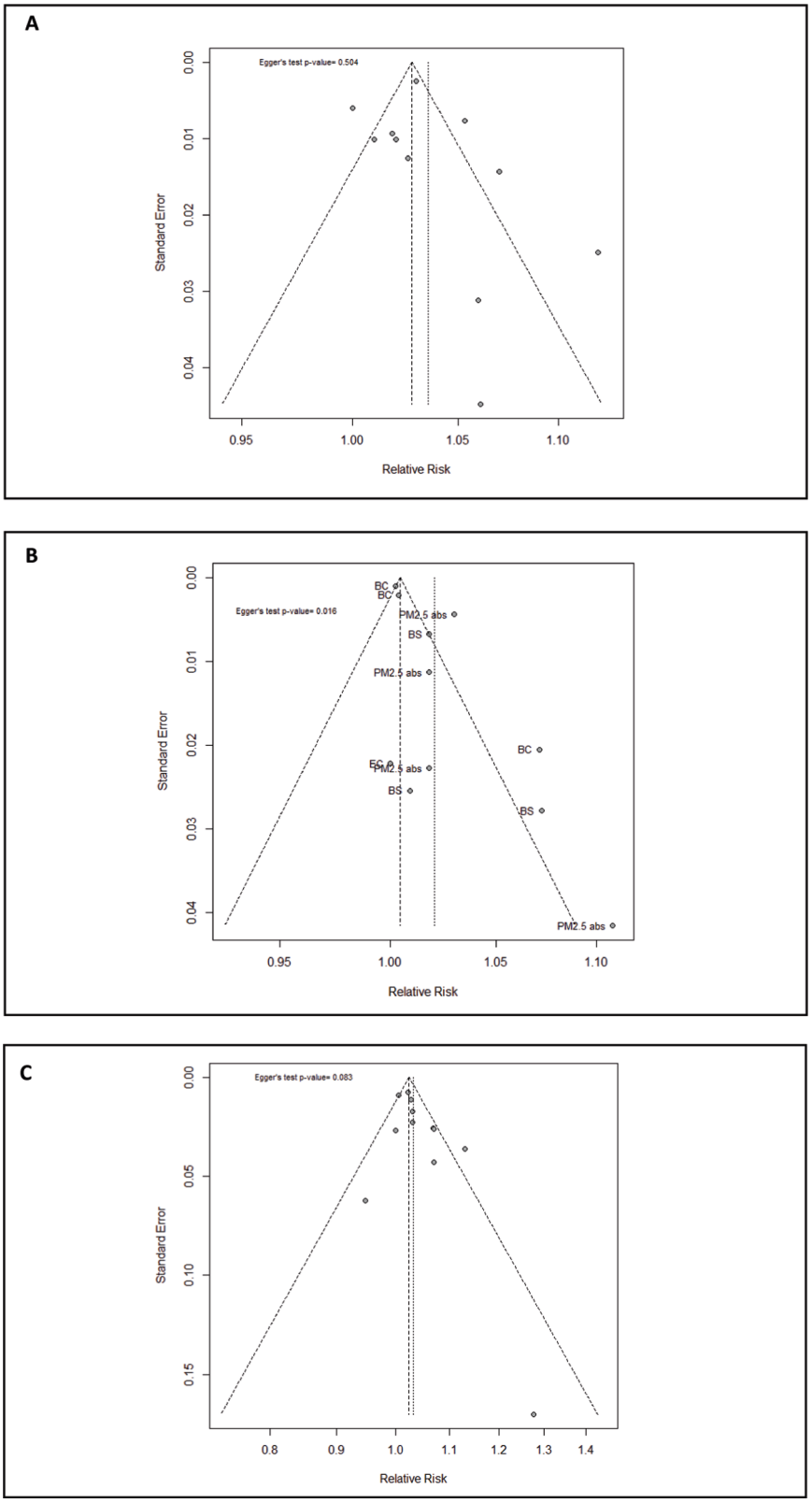

Fig. 7. Funnel plots and Egger's tests for NO_2 (A), EC (B), and $PM_{2.5}$ (C) and non-accidental mortality.

moderate traffic specificity studies. Moreover, the studies on pollutants not included in the meta-analyses and the studies with indirect traffic measures (distance and density measures) provided further support for an association of TRAP with non-accidental mortality. Likewise, generally positive associations were found in five patient populations representing a potentially sensitive subgroup, but they had wider CIs compared with the general population studies related to the smaller sample size.

In sum, the finding of associations between TRAP and non-accidental mortality in substantially different populations, across different geographical regions, exposure assessment methods and confounder control lends further support to the presence of an association. If different approaches—with different types of biases—all point to the same conclusion, the confidence is strengthened, which is defined as triangulation in epidemiology (Pearce et al. 2019).

4. Discussion

The overall confidence in the evidence for a positive association between long-term exposure to TRAP and non-accidental mortality was high. This judgement was based on positive associations in meta-analyses for all pollutants with non-accidental mortality, and consistent findings across different populations, geographical regions, exposure assessment methods and confounder adjustment.

The high confidence judgement in an association between TRAP and non-accidental mortality marks a notable increase in confidence compared with the judgement of the 2010 HEI Traffic Review, in which the evidence on this association was deemed "suggestive" (HEI 2010). The increased confidence stems primarily from the emergence of a large number of new studies published since the 2010 review. The current review furthermore also included studies that considered TRAP exposure beyond the near-roadway environment (neighbourhood). This likely does not explain differences with the 2010 review, because we found that estimates from studies that were highly traffic-specific (including a near-roadway component) were similar to the overall effect estimates.

4.1. Findings in relation to other assessments and studies

The Panel's judgement generally agrees with other recent evidence assessments for two main pollutants included in this review (NO_2 and $PM_{2.5}$). In these other assessments, the pollutant was evaluated irrespective of the source, and based on different evidence synthesis methods. In the 2019 integrated science assessment (ISA) for PM from the U.S. EPA, the association between $PM_{2.5}$ and all-cause mortality was rated as "causal", based on assessment of different scientific disciplines beyond the epidemiological mortality studies (U.S. EPA 2019). We rendered a judgment of lower confidence in an association of PM_{10} (sum of $PM_{2.5}$ and PM_{coarse}) than of $PM_{2.5}$ with mortality, consistent with the "suggestive" rating of the ISA assessment for PM_{coarse} (the ISA does not include a rating for PM_{10}). The ISA for PM included substantially more studies than the current review, primarily because the Panel did not include $PM_{2.5}$ studies based on monitoring alone and most nationwide studies, because these studies were thought to be insufficiently specific for evaluating health effects of TRAP. In the 2016 ISA for NO_2, associations with all-cause mortality were judged as "suggestive" (U.S. EPA 2016), in particular because of uncertainty about the independent effect of NO_2. Because NO_2 is spatially correlated with other pollutants from traffic combustion sources, including EC and UFP, some of the effects attributed to NO_2 may actually be due to other pollutants. Health Canada judged the evidence for a causal association between NO_2 and all-cause mortality as "suggestive", with a very similar rationale as provided by the U.S. EPA (Health Canada 2016). In our review, the issue of independent effects for NO_2 is less of an issue as we assess evidence for TRAP as a mixture and are not evaluating which pollutant in the mixture is responsible for health effects.

The systematic reviews of the association between long-term exposure to $PM_{2.5}$ and NO_2 and mortality, conducted for the 2021 WHO Global Air Quality Guidelines revision found strong evidence of an association (Chen and Hoek 2020; Huangfu and Atkinson 2020). The systematic review on $PM_{2.5}$ and all-cause mortality documented a meta-analytic summary estimate 1.08 per 10 $\mu g/m^3$ with a confidence interval of (1.06, 1.09), based on 25 studies (Chen and Hoek 2020). The systematic review on NO_2 and all-cause mortality reported a summary estimate of 1.02 per 10 $\mu g/m^3$ with a confidence interval of (1.01, 1.04), based on 24 studies (Huangfu and Atkinson 2020). The number of studies was again larger than in the current review because studies were included irrespective of the air pollution source. Furthermore, application of adapted GRADE methods resulted in an assessment of high ($PM_{2.5}$) and moderate (NO_2) certainty of evidence with all-cause mortality.

In another recent systematic review, significant associations between NO_2 and all-cause mortality were reported, and the quality of the evidence rated as moderate (Stieb et al. 2021). In a systematic review by Huang and colleagues, also robust epidemiological evidence was found for an association of NO_2 with all-cause mortality (Huang et al. 2021).

Some large new studies have been identified after the completion of the search for this review. The ELAPSE study documented consistent positive associations between $PM_{2.5}$, NO_2, BC, and non-accidental mortality in a large pooled European cohort with detailed lifestyle covariates (Brunekreef et al. 2021; Strak et al. 2021). The study was based on fine resolution (100 m × 100 m) Europewide hybrid LUR models, using statistical procedures as in the included ESCAPE studies, exploiting only within-cohort exposure contrasts (Beelen et al. 2014). Within ELAPSE, consistent associations for these pollutants were also found in large administrative cohorts, but six of them would likely not have been included as they were national cohorts (Stafoggia et al., 2022). Analyses within the Rome Longitudinal cohort confirmed associations included in the current review (Badaloni et al. 2017; Cesaroni et al. 2013). In a large Dutch national cohort, PM from traffic sources—assessed with a dispersion model assessing specific sources—was associated with non-accidental mortality, adjusting for particles from other sources (Fischer et al. 2020). The new studies support the overall findings of the current review.

4.2. Challenges in application of modified OHAT and risk of bias

Regarding the formal risk of bias assessment, it is important to stress that risk of bias assessment is an assessment of the potential risk of bias, not a determination of actual bias in an individual study. Risk of bias assessment for confounders furthermore does not specify in which direction the estimates may be biased, nor how large the bias might be, if it exists at all. Bias assessments should focus more on identifying the most likely influential sources of bias, classifying each specific study on the basis of how effectively it has addressed each potential bias and determining whether results differ across studies in relation to each hypothesized source of bias, as described in Savitz et al. 2019.

It was challenging to evaluate the downgrading factor unexplained inconsistency. Following the *a priori* defined study protocol, the Panel primarily downgraded the evidence if there was heterogeneity due to difference in direction, but also discussed the degree of unexplained heterogeneity in magnitude. The Panel furthermore noted that if the degree of heterogeneity was so large that the meta-analytical CIs clearly included unity and was wide, a downgrade was applied for imprecision. The meta-analytical summary CIs generally were wider than those of some individual studies, related to substantial heterogeneity. The Panel preferred this approach compared to downgrading due to heterogeneity based on the difficult-to-interpret I^2 statistics or the statistical significance of other heterogeneity tests. The I^2 statistic is expressed on a relative scale and may be interpreted as high, even if all effect estimates can be considered as small (e.g., for NO_2 all RRs were between 1.00 and 1.12 with an I^2 of 83%).

Downgrading based upon risk of bias was not straightforward either. We evaluated differences in effect estimates between studies with low and moderate versus high risk of bias to decide upon downgrades in combination with the distribution of risk of bias judgements. Distinguishing heterogeneity from publication bias remained another challenge. Finally, the application of a "formulaic" approach, giving equal weight to the different down- and upgrading factors is a strong assumption, though transparent. In the narrative assessment, we were less bound by these assumptions, at the expense of a less transparent approach. Readers can however judge the reasoning qualitatively. A more detailed discussion on the confidence assessments can be found in Boogaard et al. 2023.

Despite the difficulties of applying the modified OHAT assessment, the Panel noted that the conclusions from the narrative evaluation and the OHAT assessment were identical: high confidence.

4.3. Strengths and limitations

Our review advances the synthesis of evidence on TRAP and non-accidental mortality in its approach for identifying, selecting, and evaluating epidemiologic studies using transparent frameworks for exposure and confidence assessment. The application of both a narrative assessment and a modified OHAT assessment is another strength, given the discussions about evidence synthesis and risk of bias assessment of observational studies in environmental health (e.g., Savitz et al. 2019; Steenland et al. 2020).

The main limitations in the review include: (a) difficulties in the judgment of which studies involved exposure contrasts that were primarily traffic-related and (b) difficulties in applying the formal risk of bias and confidence assessment methods (Section 4.2). Additional limitations included that no independent, dual risk of bias assessment was conducted, and risk of bias was conducted on meta-analyzed studies only.

In the exposure framework, the Panel excluded studies at the urban and regional scale because of difficulties in separating exposure contrasts related to traffic sources from other sources. The implication is that the Panel did not assess the full impact of traffic sources, as traffic emissions affect urban and regional background as well.

The meta-analytical summary estimates of the review may be useful in future health impact assessments of TRAP. Especially health impact assessments using $PM_{2.5}$ in locations where traffic is a major determinant of $PM_{2.5}$ exposure contrasts, such as in major cities, may benefit from the selection of $PM_{2.5}$ studies in our review.

4.4. Future directions for research

The Panel considered pollutants to be indicators of TRAP and did not address the question of which components of TRAP may be most toxic, a key question that remains largely unresolved.

More long-term studies on non-tailpipe PM indicators and UFP are warranted; there are reasons to suspect they both might be health relevant beyond what is already known (e.g., Harrison et al. 2021; HEI 2013; Ohlwein et al. 2019). More TRAP studies in low- and middle-income countries are needed.

The review was limited to TRAP, although consideration was given to other factors of traffic, most notably noise. There is a clear need to evaluate TRAP in the broader context of transportation and mobility impacts on public health. Emerging knowledge suggests that transportation can affect health through many intertwined pathways such as traffic accidents, noise, climate change, temperature, stress, and the lack of physical activity and green space (Glazener et al. 2021). Studies on the interactions and effect modifications of air pollution effects through other exposures such as green space, heat, noise, and physical activity are relatively scarce, but are needed as they reflect real-world conditions and may further advance our understanding of the implications of transportation activities on TRAP and health (Khreis et al. 2020).

5. Conclusion

The overall confidence in the evidence for a positive association between long-term exposure to TRAP and non-accidental mortality was high, both in a formal OHAT approach and in a more narrative assessment. This judgement was based on positive associations in meta-analyses for all pollutants with non-accidental mortality, and consistent findings across different populations, geographical regions, exposure assessment methods and confounder adjustment.

The implication is that policies reducing TRAP will result in public health gains. Health gains may be substantial given the ubiquitous nature of exposure to TRAP. The quantitative effect estimates in our study may be useful to assess the health benefits of policies directed towards reducing TRAP, instead of the currently used effect estimates for pollutants, often $PM_{2.5}$ and sometimes NO_2, irrespective of the source.

6. Source of funding

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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References

Babich, P., Davey, M., Allen, G., Koutrakis, P., 2000. Method comparisons for particulate nitrate, elemental carbon, and $PM_{2.5}$ mass in seven U.S. cities. J Air Waste Manag Assoc. 50, 1095–1105. https://doi.org/10.1080/10473289.2000.10464152.

Badaloni, C., Cesaroni, G., Cerza, F., Davoli, M., Brunekreef, B., Forastiere, F., 2017. Effects of long-term exposure to particulate matter and metal components on mortality in the Rome Longitudinal Study. Environ. Int. 109, 146–154. https://doi.org/10.1016/j.envint.2017.09.005.

Bauleo, L., Bucci, S., Antonucci, C., Sozzi, R., Davoli, M., Forastiere, F., et al., 2019. Long-term exposure to air pollutants from multiple sources and mortality in an industrial area: A cohort study. Occup. Environ. Med. 76, 48–57. https://doi.org/10.1136/oemed-2018-105059.

Beelen, R., Hoek, G., van den Brandt, P.A., Goldbohm, R.A., Fischer, P., Schouten, L.J., et al., 2008. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). Environ. Health Perspect. 116, 196–202. https://doi.org/10.1289/ehp.10767.

Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J., Weinmayr, G., Hoffmann, B., et al., 2014. Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383, 785–795. https://doi.org/10.1016/S0140-6736(13)62158-3.

Beelen, R., Hoek, G., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J., Weinmayr, G., et al., 2015. Natural-cause mortality and long-term exposure to particle components: An analysis of 19 European cohorts within the multi-center ESCAPE project. Environ. Health Perspect. 123, 525–533. https://doi.org/10.1289/ehp.1408095.

Boogaard, H., Atkinson, R.W., Brook, J.R., Chang, H.H., Hoek, G., Hoffmann, B., et al., 2023. Evidence synthesis of observational studies in environmental health: Lessons learned from a systematic review on traffic-related air pollution (under review).

Boogaard, H., Patton, A.P., Atkinson, R.W., Brook, J.R., Chang, H.H., Crouse, D.L., et al., 2022. Long-term exposure to traffic-related air pollution and selected health outcomes: A systematic review and meta-analysis. Environ. Int. 164, 107262. https://doi.org/10.1016/j.envint.2022.107262.

Brunekreef, B., Strak, M., Chen, J., Andersen, Z., Atkinson, R., Bauwelinck, M., 2021. Mortality and morbidity effects of long-term exposure to low-level $PM_{2.5}$, black carbon, NO_2, and O_3: An analysis of European cohorts in the ELAPSE Project. Health Effects Institute Research Report 208. Boston, MA: Health Effects Institute.

Cakmak, S., Hebbern, C., Vanos, J., Crouse, D.L., Tjepkema, M., 2019. Exposure to traffic and mortality risk in the 1991–2011 Canadian Census Health and Environment Cohort (CanCHEC). Environ. Int. 124, 16–24. https://doi.org/10.1016/j.envint.2018.12.045.

Carey, I.M., Atkinson, R.W., Kent, A.J., van Staa, T., Cook, D.G., Anderson, H.R., 2013. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am. J. Respir. Crit. Care Med. 187, 1226–1233. https://doi.org/10.1164/rccm.201210-1758OC.

Cesaroni, G., Badaloni, C., Gariazzo, C., Stafoggia, M., Sozzi, R., Davoli, M., et al., 2013. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ. Health Perspect. 121, 324–331. https://doi.org/10.1289/ehp.1205862.

Chen, J., Hoek, G., 2020. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. Environ. Int. 143, 105974. https://doi.org/10.1016/j.envint.2020.105974.

Cohen, G., Steinberg, D.M., Yuval, Levy, I., Chen, S., Kark, J.D., et al., 2019. Cancer and mortality in relation to traffic-related air pollution among coronary patients: Using an ensemble of exposure estimates to identify high-risk individuals. Environ. Res. 176, 108560. https://doi.org/10.1016/j.envres.2019.108560.

Crouse, D.L., Peters, P.A., van Donkelaar, A., Goldberg, M.S., Villeneuve, P.J., Brion, O., et al., 2012. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: A Canadian national-level cohort study. Environ. Health Perspect. 120, 708–714. https://doi.org/10.1289/ehp.1104049.

Crouse, D.L., Peters, P.A., Villeneuve, P.J., Proux, M.O., Shin, H.H., Goldberg, M.S., et al., 2015. Within- and between-city contrasts in nitrogen dioxide and mortality in 10 Canadian cities: A subset of the Canadian Census Health and Environment Cohort (CanCHEC). J. Eposure Sci. Environ. Epidemiol. 25, 482–489. https://doi.org/10.1038/jes.2014.89.

Cyrys, J., Heinrich, J., Hoek, G., Meliefste, K., Lewné, M., Gehring, U., et al., 2003. Comparison between different traffic-related particle indicators: Elemental carbon (EC), $PM_{2.5}$ mass, and absorbance. J. Expo. Anal. Environ. Epidemiol. 13, 134–143. https://doi.org/10.1038/sj.jea.7500262.

DEFRA (Department for Environment, Food and Rural Affairs). 2005. Air Quality Library-Defra, UK. Available: https://uk-air.defra.gov.uk/library/reports?report_id=306 [accessed 13 December 2022].

DerSimonian, R., Laird, N., 1986. Meta-analysis in controlled trials. Control. Clin. Trials. 7, 177–188. https://doi.org/10.1016/0197-2456(86)90046–2.

Desikan, A., Crichton, S., Hoang, U., Barratt, B., Beevers, S.D., Kelly, F.J., et al., 2016. Effect of exhaust- and nonexhaust-related components of particulate matter on long-term survival after stroke. Stroke 47, 2916–2922. https://doi.org/10.1161/STROKEAHA.116.014242.

Di, Q., Wang, Y., Zanobetti, A., Wang, Y., Koutrakis, P., Choirat, C., et al., 2017. Air pollution and mortality in the Medicare population. N. Engl. J. Med. 376, 2513–2522. https://doi.org/10.1056/NEJMoa1702747.

Dirgawati, M., Hinwood, A., Nedkoff, L., Hankey, G.J., Yeap, B.B., Flicker, L., et al., 2019. Long-term exposure to low air pollutant concentrations and the relationship with all-cause mortality and stroke in older men. Epidemiology 30, S82–S89. https://doi.org/10.1097/EDE.0000000000001034.

Dockery, D.W., Pope, C.A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., et al., 1993. An association between air pollution and mortality in six U.S. cities. N. Engl. J. Med. 329, 1753–1759. https://doi.org/10.1056/NEJM199312093292401.

Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634. https://doi.org/10.1136/bmj.315.7109.629.

Finkelstein, M.M., Jerrett, M., Sears, M.R., 2005. Environmental inequality and circulatory disease mortality gradients. J. Epidemiol. Community Health 59, 481–487. https://doi.org/10.1136/jech.2004.026203.

Fischer, P.H., Marra, M., Ameling, C.B., Velders, G.J.M., Hoogerbrugge, R., de Vries, W., et al., 2020. Particulate air pollution from different sources and mortality in 7.5 million adults - The Dutch Environmental Longitudinal Study (DUELS). Sci. Total Environ. 705, 135778. https://doi.org/10.1016/j.scitotenv.2019.135778.

Frey, H.C., 2018. Trends in onroad transportation energy and emissions. J. Air Waste Manag. Assoc. 68, 514–563. https://doi.org/10.1080/10962247.2018.1454357.

Furuya-Kanamori, L., Barendregt, J.J., Doi, S.A.R., 2018. A new improved graphical and quantitative method for detecting bias in meta-analysis. Int. J. Evid. Based Healthc. 16, 195–203. https://doi.org/10.1097/XEB.0000000000000141.

Gehring, U., Heinrich, J., Krämer, U., Grote, V., Hochadel, M., Sugiri, D., et al., 2006. Long-term exposure to ambient air pollution and cardiopulmonary mortality in women. Epidemiology 17, 545–551. https://doi.org/10.1097/01.ede.0000224541.38258.87.

Glazener, A., Sanchez, K., Ramani, T., Zietsman, J., Nieuwenhuijsen, M.J., Mindell, J.S., et al., 2021. Fourteen pathways between urban transportation and health: A conceptual model and literature review. J. Transp. Health 21, 101070. https://doi.org/10.1016/j.jth.2021.101070.

Hanigan, I.C., Rolfe, M.I., Knibbs, L.D., Salimi, F., Cowie, C.T., Heyworth, J., et al., 2019. All-cause mortality and long-term exposure to low level air pollution in the '45 and Up Study' cohort, Sydney, Australia, 2006–2015. Environ. Int. 126, 762–770. https://doi.org/10.1016/j.envint.2019.02.044.

Hansell, A., Ghosh, R.E., Blangiardo, M., Perkins, C., Vienneau, D., Goffe, K., et al., 2016. Historic air pollution exposure and long-term mortality risks in England and Wales: Prospective longitudinal cohort study. Thorax 71, 330–338. https://doi.org/10.1136/thoraxjnl-2015-207111.

Harrison, R.M., Allan, J., Carruthers, D., Heal, M.R., Lewis, A.C., Marner, B., et al., 2021. Non-exhaust vehicle emissions of particulate matter and VOC from road traffic: A review. Atmos. Environ. 262, 118592. https://doi.org/10.1016/j.atmosenv.2021.118592.

Health Canada. 2016. Human health risk assessment for ambient nitrogen dioxide. Ottawa, Canada: Health Canada.

HEI (Health Effects Institute). 2010. Traffic-related air pollution: A critical review of the literature on emissions, exposure, and health effects. Special Report 17. Boston, MA: Health Effects Institute.

HEI (Health Effects Institute). 2013. Understanding the health effects of ambient ultrafine particles. HEI review panel on ultrafine particles. HEI Perspectives 3. Boston, MA: Health Effects Institute.

HEI (Health Effects Institute). 2019. Protocol for a systematic review and meta-analysis of selected health effects of long-term exposure to traffic-related air pollution. Boston, MA: Health Effects Institute. Available: https://www.healtheffects.org/system/files/TrafficReviewProtocol.pdf.

HEI (Health Effects Institute). 2022. Systematic review and meta-analysis of selected health effects of long-term exposure to traffic-related air pollution. Special Report 23. Boston, MA: Health Effects Institute.

Heinrich, J., Thiering, E., Rzehak, P., Krämer, U., Hochadel, M., Rauchfuss, K.M., et al., 2013. Long-term exposure to NO_2 and PM_{10} and all-cause and cause-specific mortality in a prospective cohort of women. Occup. Environ. Med. 70, 179–186. https://doi.org/10.1136/oemed-2012-100876.

Huang, S., Li, H., Wang, M., Qian, Y., Steenland, K., Caudle, W., et al., 2021. Long-term exposure to nitrogen dioxide and mortality: A systematic review and meta-analysis. Sci. Tot. Environ. 776, 145968. https://doi.org/10.1016/j.scitotenv.2021.145968.

Huangfu, P., Atkinson, R., 2020. Long-term exposure to NO_2 and O_3 and all-cause and respiratory mortality: A systematic review and meta-analysis. Environ. Int. 144, 105998. https://doi.org/10.1016/j.envint.2020.105998.

Hvidtfeldt, U.A., Sørensen, M., Geels, C., Ketzel, M., Khan, J., Tjønneland, A., et al., 2019. Long-term residential exposure to $PM_{2.5}$, PM_{10}, black carbon, NO_2, and ozone and mortality in a Danish cohort. Environ. Int. 123, 265–272. https://doi.org/10.1016/j.envint.2018.12.010.

Janssen, N.A., Hoek, G., Simic-Lawson, M., Fischer, P., van Bree, L., ten Brink, H., 2011. Black carbon as an additional indicator of the adverse health effects of airborne particles compared with PM_{10} and $PM_{2.5}$. Environ. Health Perspect. 119, 1691–1699. https://doi.org/10.1289/ehp.1003369.

Jerrett, M., Finkelstein, M.M., Brook, J.R., Arain, M.A., Kanaroglou, P., Stieb, D.M., et al., 2009. A cohort study of traffic-related air pollution and mortality in Toronto, Ontario, Canada. Environ. Health Perspect. 117, 772–777. https://doi.org/10.1289/ehp.11533.

Khreis, H., Nieuwenhuijsen, M., Zietsman, J., Ramani, T. (Eds.), 2020. Traffic-Related Air Pollution, 1st ed. Elsevier, Waltham, MA.

Krewski, D., Jerrett, M., Burnett, R.T., Ma, R., Hughes, E., Shi, Y., et al., 2009. Extended follow-up and spatial analysis of the American Cancer Society study linking

particulate air pollution and mortality. Research Report 140. Boston, MA: Health Effects Institute.
Light, R.J., Pillemer, D.B., 1984. Summing up: The science of reviewing research. Harvard University Press: Cambridge, MA. https://doi.org/10.2307/j.ctvk12px9.
Maheswaran, R., Pearson, T., Smeeton, N.C., Beevers, S.D., Campbell, M.J., Wolfe, C.D., 2010. Impact of outdoor air pollution on survival after stroke: population-based cohort study. Stroke 41, 869–877. https://doi.org/10.1161/STROKEAHA.109.567743.
McKenzie, J.E., Brennan, S.E., 2022. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Available from www.training.cochrane.org/handbook.
Medina-Ramón, M., Goldberg, R., Melly, S., Mittleman, M.A., Schwartz, J., 2008. Residential exposure to traffic-related air pollution and survival after heart failure. Environ. Health Perspect. 116, 481–485. https://doi.org/10.1289/ehp.10918.
Nafstad, P., Håheim, L.L., Wisløff, T., Gram, F., Oftedal, B., Holme, I., et al., 2004. Urban air pollution and mortality in a cohort of Norwegian men. Environ. Health Perspect. 112, 610–615. https://doi.org/10.1289/ehp.6684.
Nieuwenhuijsen, M.J., Gascon, M., Martinez, D., Ponjoan, A., Blanch, J., Garcia-Gil, M.D. M., et al., 2018. Air pollution, noise, blue space, and green space and premature mortality in Barcelona: A mega cohort. Int. J. Environ. Res. Public Health 15, 2405. https://doi.org/10.3390/ijerph15112405.
OHAT (Office of Health Assessment and Translation). 2019. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Durham, NC: National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services.
Ohlwein, S., Kappeler, R., Kutlar Joss, M., Künzli, N., Hoffmann, B., 2019. Health effects of ultrafine particles: A systematic literature review update of epidemiological evidence. Int. J. Public Health 64, 547–559. https://doi.org/10.1007/s00038-019-01202-7.
Ostro, B., Hu, J., Goldberg, D., Reynolds, P., Hertz, A., Bernstein, L., et al., 2015. Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: Results from the California Teachers Study Cohort. Environ. Health Perspect. 123, 549–556. https://doi.org/10.1289/ehp.1408565.
Pearce, N., Vandenbroucke, J.P., Lawlor, D.A., 2019. Causal inference in environmental epidemiology: Old and new approaches. Epidemiology 30, 311–316. https://doi.org/10.1097/EDE.0000000000000987.
Pope, C.A., Thun, M.J., Namboodiri, M.M., Dockery, D.W., Evans, J.S., Speizer, F.E., et al., 1995. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am. J. Respir. Crit. Care Med. 151, 669–674. https://doi.org/10.1164/ajrccm/151.3_Pt_1.669.
Pope, C.A., Burnett, R.T., Thun, M.J., Calle, E.E., Krewski, D., Ito, K., et al., 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. J. Am. Med. Assoc. 287, 1132–1141. https://doi.org/10.1001/jama.287.9.1132.
Raaschou-Nielsen, O., Andersen, Z.J., Jensen, S.S., Ketzel, M., Sørensen, M., Hansen, J., et al., 2012. Traffic air pollution and mortality from cardiovascular disease and all causes: A Danish cohort study. Environ. Health 11, 60. https://doi.org/10.1186/1476-069X-11-60.
Samet, J.M., Chiu, W.A., Cogliano, V., Jinot, J., Kriebel, D., Lunn, R.M., et al., 2020. The IARC Monographs: updated procedures for modern and transparent evidence synthesis in cancer hazard identification. J. Natl Cancer Inst. 112, 30–37. https://doi.org/10.1093/jnci/djz169.
Savitz, D.A., Wellenius, G.A., Trikalinos, T.A., 2019. The problem with mechanistic risk of bias assessments in evidence synthesis of observational studies and a practical alternative: Assessing the impact of specific sources of potential bias. Am. J. Epidemiol. 188, 1581–1585. https://doi.org/10.1093/aje/kwz131.
Stafoggia, S., Oftedal, B., Chen, J., Rodopoulou, S., Renzi, S., Atkinson, R., et al., 2022. Long-term exposure to low ambient air pollution concentrations and mortality among 28 million subjects: Results from seven European large cohorts within the ELAPSE Project. Lancet Planet Health 6, e9–e18. https://doi.org/10.1016/S2542-5196(21)00277-1.
Steenland, K., Schubauer-Berigan, M.K., Vermeulen, R., Lunn, R.M., Straif, K., Zahm, S., et al., 2020. Risk of bias assessments and evidence syntheses for observational epidemiologic studies of environmental and occupational exposures: Strengths and limitations. Environ. Health Perspect. 128, 95002. https://doi.org/10.1289/EHP6980.
Stieb, D.M., Berjawi, R., Emode, M., Zheng, C., Salama, D., Hocking, R., et al., 2021. Systematic review and meta-analysis of cohort studies of long-term outdoor nitrogen dioxide exposure and mortality. PLoS One 16, e0246451. https://doi.org/10.1371/journal.pone.0246451.
Stockfelt, L., Andersson, E.M., Molnár, P., Rosengren, A., Wilhelmsen, L., Sallsten, G., et al., 2015. Long term effects of residential NO_x exposure on total and cause-specific mortality and incidence of myocardial infarction in a Swedish cohort. Environ. Res. 142, 197–206. https://doi.org/10.1016/j.envres.2015.06.045.
Strak, M., Weinmayr, G., Rodopoulou, S., Chen, J., de Hoogh, K., Andersen, Z.J., et al., 2021. Long-term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: Pooled analysis. BMJ 374 (1904). https://doi.org/10.1136/bmj.n1904.
Tonne, C., Halonen, J.I., Beevers, S.D., Dajnak, D., Gulliver, J., Kelly, F.J., et al., 2016. Long-term traffic air and noise pollution in relation to mortality and hospital readmission among myocardial infarction survivors. Int. J. Hyg. Environ. Health 219, 72–78. https://doi.org/10.1016/j.ijheh.2015.09.003.
Tonne, C., Wilkinson, P., 2013. Long-term exposure to air pollution is associated with survival following acute coronary syndrome. Eur. Heart J. 34, 1306–1311. https://doi.org/10.1093/eurheartj/ehs480.
U.S. EPA (U.S. Environmental Protection Agency). 2015. Preamble to the Integrated Science Assessments. EPA/600/R-15/067. Research Triangle Park, NC: U.S. Environmental Protection Agency.
U.S. EPA (U.S. Environmental Protection Agency). 2016. Integrated Science Assessment for Oxides of Nitrogen–Health Criteria. EPA/600/R-15/068. Research Triangle Park, NC: U.S. Environmental Protection Agency.
U.S. EPA (U.S. Environmental Protection Agency). 2019. Integrated Science Assessment for Particulate Matter. EPA/600/R-19/188. Research Triangle Park, NC: U.S. Environmental Protection Agency.
Veroniki, A.A., Jackson, D., Viechtbauer, W., Bender, R., Bowden, J., Knapp, G., et al., 2016. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res. Synth. Methods 7, 55–79. https://doi.org/10.1002/jrsm.1164.
Villeneuve, P.J., Jerrett, M., Su, J., Burnett, R.T., Chen, H., Brook, J., et al., 2013. A cohort study of intra-urban variations in volatile organic compounds and mortality, Toronto, Canada. Environ. Pollut. 183, 30–39. https://doi.org/10.1016/j.envpol.2012.12.022.
von Klot, S., Gryparis, A., Tonne, C., Yanosky, J., Coull, B.A., Goldberg, R.J., et al., 2009. Elemental carbon exposure at residence and survival after acute myocardial infarction. Epidemiology 20, 547–554. https://doi.org/10.1097/EDE.0b013e31819d9501.
Watson, J.G., Chow, J.C., 2002. Comparison and evaluation of in situ and filter carbon measurements at the Fresno Supersite. J. Geophys. Res. 107, 8341. https://doi.org/10.1029/2001JD000573.
WHO (World Health Organization), 2018. Environmental Noise Guidelines for the European Region. WHO Regional Office for Europe. World Health Organization, Geneva.
WHO (World Health Organization), 2020. Risk of bias assessment instrument for systematic reviews informing WHO Global Air Quality Guidelines. WHO Regional Office for Europe. World Health Organization, Geneva.
WHO (World Health Organization), 2021. WHO Global Air Quality Guidelines: Particulate matter ($PM_{2.5}$ and PM_{10}), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. World Health Organization, Geneva.
Wilker, E.H., Mostofsky, E., Lue, S.H., Gold, D., Schwartz, J., Wellenius, G.A., et al., 2013. Residential proximity to high-traffic roadways and poststroke mortality. J. Stroke Cerebrovasc. Dis. 22, e366–e372. https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.03.034.
Woodward, M., 2013. Epidemiology: Study Design and Data Analysis, Third Edition. Chapman and Hall/CRC, New York. https://doi.org/10.1201/b16343.
Yang, Y., Tang, R., Qiu, H., Lai, P.C., Wong, P., Thach, T.Q., et al., 2018. Long term exposure to air pollution and mortality in an elderly cohort in Hong Kong. Environ. Int. 117, 99–106. https://doi.org/10.1016/j.envint.2018.04.034.
Yap, C., Beverland, I.J., Heal, M.R., Cohen, G.R., Robertson, C., Henderson, D.E., et al., 2012. Association between long-term exposure to air pollution and specific causes of mortality in Scotland. Occup. Environ. Med. 69, 916–924. https://doi.org/10.1136/oemed-2011-100600.
Yorifuji, T., Kashima, S., Tsuda, T., Takao, S., Suzuki, E., Doi, H., et al., 2010. Long-term exposure to traffic-related air pollution and mortality in Shizuoka, Japan. Occup. Environ. Med. 67, 111–117. https://doi.org/10.1136/oem.2008.045542.
Yorifuji, T., Kashima, S., Tsuda, T., Ishikawa-Takata, K., Ohta, T., Tsuruta, K., et al., 2013. Long-term exposure to traffic-related air pollution and the risk of death from hemorrhagic stroke and lung cancer in Shizuoka, Japan. Sci. Total Environ. 443, 397–402. https://doi.org/10.1016/j.scitotenv.2012.10.088.