



TRAFFIC-RELATED AIR POLLUTION:

A Systematic Review-Based
Human Health Risk
Assessment of Mortality



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To obtain additional information, please contact:

Health Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications-publications@hc-sc.gc.ca

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Dan Crouse, M.Sc., Ph.D. (Health Effects Institute)

Stéphane Buteau, Ph.D. (Université de Montréal)

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LIST OF ABBREVIATIONS

ACE	acute coronary event
ACS-CPSII	American Cancer Society—Cancer Prevention Survey II
BC	black carbon
BS	black smoke
CAD	Canadian dollar
CanCHEC	Canadian Census Health and Environment Cohort
CBVD	cerebrovascular disease
CCME	Canadian Council of Ministers of the Environment
CHD	coronary heart disease
CI	confidence interval
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CPD	cardiopulmonary disease
CSD	circulatory system disease
DE	diesel exhaust
EC	elemental carbon
ESCAPE	European Study of Cohorts for Air Pollution Effects
GIS	geographic information system
HEI	Health Effects Institute
HF	heart failure
HR	hazard ratio
HRV	heart rate variability
ICD	International Classification of Disease
IHD	ischemic heart disease
LUR	land-use regression
MI	myocardial infarction
NA	not available
NHS	Nurses' Health Study
NLCS	Netherlands Cohort Study on Diet and Cancer
NO	nitric oxide
NO₂	nitrogen dioxide
NO_x	nitrogen oxide

O₃	ozone
OR(s)	odds ratio(s)
PAH	polycyclic aromatic hydrocarbon
PM	particulate matter
PM_{2.5}	particulate matter with a diameter less than 2.5 micrometres
PM_{2.5 abs}	PM _{2.5} absorbance
PM₁₀	particulate matter with a diameter less than 10 micrometres
RE	risk estimate
REVEAL-HBV	Risk Evaluation of Viral Load Elevation and Associated Liver Disease / Cancer Hepatitis B Virus
RoB	risk of bias
ROS	reactive oxygen species
RR(s)	relative risk(s)
SALIA	Study on the influence of air pollution on lung function, inflammation and ageing
SES	socio-economic status
SIDIAP	Sistema d'Informació pel Desenvolupament de la Investigació en Atenció Primària
SR-MA	systematic review—meta-analysis
TRAP	traffic-related air pollution
UFPs	ultrafine particles
UK	United Kingdom
USA	United States of America
US EPA	United States Environmental Protection Agency
VOC	volatile organic compound
WHO	World Health Organization

EXECUTIVE SUMMARY

Traffic-related air pollution (TRAP) is the contribution of on-road vehicles to air pollution. It is a mixture of vehicle exhausts, secondary air pollutants formed in the atmosphere from vehicle emissions, evaporative emissions from vehicles, and other non-combustion emissions (e.g., road dust, brake wear, and tire wear). TRAP is of particular concern in urban areas and near highways, where concentrations are the most elevated. Health Canada has estimated that approximately 4 out of 10 Canadians live within 250 m of a high-traffic roadway and that TRAP is responsible for 1,200 premature deaths per year in Canada, which has an estimated annual monetized value of \$9 billion (CAD 2015) for this health outcome alone (Health Canada, 2022a, b).

Health Canada has previously evaluated the association between exposure to TRAP and asthma, allergy, lung function, and selected cancer types (Health Canada, 2020, 2022c). The objective of this risk assessment is to evaluate the association of mortality with TRAP exposure. This will inform and support programs and policies designed to mitigate exposure to, and the health impacts of, TRAP in Canada.

For this risk assessment, the epidemiological literature (from January 1, 2000 to July 11, 2022) regarding the associations between TRAP exposure and mortality was evaluated using systematic review techniques, including meta-analysis. Sixty-four primary articles were included in the risk assessment following a librarian-assisted search and screening process. From this evaluation, a weight of evidence approach was used to determine the causal role of TRAP exposure in mortality from all causes, circulatory mortality and some subtypes, as well as respiratory mortality and some subtypes. This weight of evidence included 1) the quantitative analysis of TRAP pollutant concentrations, 2) the qualitative analysis of TRAP pollutants for which meta-analysis could not be conducted, and 3) the qualitative evidence based on various metrics of proximity to traffic and road networks. In addition, mechanistic evidence gathered from risk assessments of TRAP and relevant primary literature was considered to assess the biological plausibility of these associations and to support the determinations of causality. The biological evidence supports a role for TRAP exposure in cellular and tissue dysfunction, including oxidative stress and inflammation, and enhancement of disease progression, which can ultimately lead to mortality.

Based on the overall weight of evidence, **it is concluded that:**

- i. there is **sufficient evidence of a causal relationship** between long-term exposure to TRAP and all-cause mortality;
- ii. there is **sufficient evidence** that the relationship between long-term TRAP exposure and mortality from circulatory system disease (CSD) **is likely to be causal**;
- iii. there is **sufficient evidence** that the relationship between long-term TRAP exposure and mortality from coronary heart disease (CHD) **is likely to be causal**;
- iv. the evidence is **suggestive of, but not sufficient to infer, a causal relationship** between long-term TRAP exposure and mortality from respiratory disease;

-
- v. the evidence is **suggestive of, but not sufficient to infer, a causal relationship** between long-term TRAP exposure and mortality from chronic obstructive pulmonary disease;
 - vi. there is **inadequate evidence to infer a causal relationship** between long-term TRAP exposure and mortality from cerebrovascular disease (CBVD).

The size of the evidence base varied considerably depending on the specific cause of mortality evaluated and this is reflected in the causality conclusions. The causality conclusions for all-cause mortality, CSD mortality, and CHD mortality were each founded on a large evidence base and consistency in the meta-analyses. In contrast, a causal relationship could not be determined for CBVD mortality as a result of the limited evidence base and the lack of consistency in the meta-analyses. Additionally, only a limited number of studies were conducted on other causes of mortality such as heart failure and myocardial infarction, and on populations that may be disproportionately impacted, including patient populations.

Additional research and analyses to address the identified data gaps would be useful to further characterize and understand the role of TRAP exposure in mortality. Identification of populations that may be disproportionately impacted by TRAP exposure could also be used to develop targeted policies or programs that would reduce or mitigate their risks. As such, these conclusions may be updated and expanded in the future to include other specific causes of mortality and/or sub-populations.

CHAPTER 1: INTRODUCTION

1.1. BACKGROUND

As a source of air pollution, traffic-related air pollution (TRAP) is ubiquitous and predominates in urban areas. TRAP refers to the mixture of vehicle exhausts, secondary air pollutants formed in the atmosphere from vehicle emissions, evaporative emissions from vehicles, and other non-combustion emissions (e.g., road dust, brake wear, and tire wear). Approximately 4 out of 10 Canadians live within 250 m of a high-traffic roadway (e.g., expressways, highways, arterial roads, and major roads), an area that is associated with a higher risk of exposure to TRAP (Health Canada, 2022a). Health Canada has also estimated that 1,200 premature deaths per year are attributable to TRAP based on contributions from on-road vehicle emissions to particulate matter with a median mass aerodynamic diameter less than 2.5 micrometres ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) ambient concentrations in Canada (Health Canada, 2022b). This analysis also estimated that TRAP contributed to 2.7 million acute respiratory symptom days, 1.1 million restricted activity days, and 210,000 asthma symptom days per year in Canada. The total annual monetized¹ value of this health burden was estimated at \$9.5 billion (CAD 2015), with \$9 billion associated with premature deaths. As such, the study of the health effects and health burden of TRAP is an active field of research in Canada and around the world.

Exposure to TRAP is particularly challenging to study because of its high spatial and temporal variability, the lack of a unique marker for this source, and differences in vehicle fleet composition over space and time (Khreis and Nieuwenhuijsen, 2017). Two broad categories of surrogates have been widely used in the TRAP literature to assess the contribution of traffic emissions to ambient air pollution: (1) concentrations of individual traffic-related pollutants such as NO_2 , nitrogen oxide (NO_x), $PM_{2.5}$, PM with a median mass aerodynamic diameter less than 10 micrometres (PM_{10}), and elemental carbon (EC); and (2) measures based on traffic and road network infrastructure such as distance to the nearest road and traffic density (Health Effects Institute [HEI] Panel on the Health Effects of Traffic-Related Air Pollution, 2010, 2022). A brief summary of how these surrogates specifically relate to TRAP follows:

- NO_x is primarily emitted from combustion sources and is made up of nitric oxide (NO) and NO_2 . Vehicle emissions are predominantly NO which is rapidly converted to NO_2 (HEI, 2010; Health Canada, 2016a). In urban areas, traffic is often the primary source of NO_x in the atmosphere and the main contributor to the variability in NO_x levels (Hamra et al., 2015). NO_2 is considered to be the most direct measure of TRAP exposure as local traffic sources contribute up to 80% of the ambient NO_2 in urban settings (Khreis and Nieuwenhuijsen, 2017). Given the availability of ambient NO_2 measurements, it is the most commonly used surrogate to estimate TRAP exposure.

¹ The monetized values represent economic welfare values that consider the potential impacts associated with treatment costs, lost productivity, pain and suffering, and the impacts of changes in mortality risk (Judek et al., 2019).

- Particulate matter (PM) is a complex mixture of small liquid and solid particles and is associated with many sources, including vehicle emissions and traffic. PM is categorized based on size: PM_{10} ; PM_{coarse} (PM > 2.5 μm and < 10 μm in aerodynamic diameter); $PM_{2.5}$; and ultrafine particles (UFPs) (PM \leq 0.1 μm in aerodynamic diameter). PM_{10} , PM_{coarse} , and $PM_{2.5}$ are typically measured based on mass concentration (i.e., $\mu g/m^3$) while UFPs are commonly reported as a number concentration. With respect to TRAP, PM is an important pollutant in the mixture as local traffic is responsible for 9% to 53% of urban PM_{10} , and 9% to 66% of urban $PM_{2.5}$ (Khreis and Nieuwenhuijsen, 2017). Additionally, some components of PM are commonly used as surrogates of TRAP, including EC, black carbon (BC), black smoke (BS), and $PM_{2.5}$ absorbance ($PM_{2.5\ abs}$). These carbonaceous pollutants are indicators of diesel exhaust (DE) emissions, especially in cities, and are defined by the techniques used for measurement rather than fundamental differences in chemical properties (HEI, 2022).
- Anthropogenic carbon monoxide (CO) is primarily formed by the incomplete combustion of carbon-containing fuels. On-road vehicles are a notable contributor to total emissions of CO in Canada with contributions of 28% according to the 2015 Canadian emissions inventory (Health Canada, 2022b).
- Benzene is a naturally occurring constituent of crude oil and is formed through the incomplete combustion of organic materials (Canada, 1993). Concentrations of benzene tend to be higher in vehicles and at urban roadsides, with levels decreasing as distance from the source increases (e.g., levels decreasing from roadside to urban areas to rural areas) (CCME, 2012; HEI, 2010).
- Compared with the use of specific air pollutants, measures based on traffic and road network parameters such as distance to roadway and traffic density, are specific to traffic sources and are simple and cost-effective to obtain (Khreis and Nieuwenhuijsen, 2017). However, these metrics may not account for the volume of traffic or the types of vehicles (e.g., proportion of cars and trucks) making up the traffic, which are key determinants for the relative concentrations of pollutants in the TRAP mixture. These metrics may also represent more than air pollution (e.g., noise) and can vary substantially between studies (e.g., differing distances to roadways; different road classifications), limiting the ability to readily compare and contrast the results.

In 2010, the HEI published a critical review of the literature on emissions, exposure, and health effects of TRAP (HEI, 2010). With respect to health effects, the epidemiological literature was evaluated to infer the presence of causal associations between TRAP exposure and health outcomes. In support of that evaluation, the toxicological literature was reviewed to identify any biological mechanism(s) for the purposes of understanding the role of traffic emissions in the effects observed in the epidemiological studies. The HEI review classified the causal associations between exposure to TRAP and a number of health outcomes. As the result of the growing database on the health effects related to TRAP exposure and the significant advances in regulations and vehicular technology, HEI published a Special Report in 2022 focusing on the systematic review of the epidemiological evidence regarding the associations between long-term exposure to TRAP and selected adverse health outcomes (HEI, 2022). The Panel evaluated the confidence in the quality of the body of evidence and assessed the level of confidence in the presence of an association between long-term TRAP exposure and selected outcomes, rather than assessing causality. A summary of the mortality outcomes evaluated as well as the conclusions from the two HEI reports (2010, 2022) is provided in **Table 1.1**.

TABLE 1.1: Summary of mortality outcomes associated with TRAP exposure and conclusions from HEI (2010, 2022)^a

Mortality outcome	Classification of causal association (HEI, 2010)	Overall confidence in the evidence (HEI, 2022)
All-cause mortality	Suggestive but not sufficient	High
Cardiovascular mortality Circulatory mortality	Suggestive but not sufficient —	— High
IHD mortality	NA	High
Stroke mortality	NA	Low to moderate
Respiratory mortality	NA	Moderate
COPD mortality	NA	Low

COPD: chronic obstructive pulmonary disease; IHD: ischemic heart disease; NA: not available

^a Adapted from Table 7.3 of HEI (2010) and from the executive summary table of HEI (2022)

Using an umbrella review-based approach, Health Canada has evaluated the association between TRAP and asthma, allergy, and lung function (Health Canada, 2020), and the association between TRAP and selected cancer types (Health Canada, 2022c). The conclusions of these assessments are provided in **Table 1.2**. This current report focuses on TRAP exposure and the risk of mortality.

TABLE 1.2: Summary of health outcomes and classification of causal associations from Health Canada (2020; 2022c)

Health outcome	Classification of causal association
Asthma incidence (children)	Causal relationship
Asthma prevalence (children)	Causal relationship
Asthma incidence (adults)	Inadequate to infer a causal relationship
Asthma prevalence (adults)	Suggestive of, but not sufficient to infer, a causal relationship
Lung function	Likely to be a causal relationship
Allergic sensitization and allergic responses	Suggestive of, but not sufficient to infer, a causal relationship
Lung cancer (adults)	Causal relationship
Breast cancer (adults)	Suggestive of, but not sufficient to infer, a causal relationship
Childhood leukemia	Likely to be a causal relationship

1.2. OBJECTIVES AND APPROACH

The objective of this risk assessment is to use systematic review techniques, including meta-analysis, in the evaluation of the epidemiological literature regarding the associations between exposure to TRAP and mortality. A weight of evidence approach was used to determine the causal role of TRAP in mortality, including mortality from all causes, circulatory mortality and some subtypes, and respiratory mortality and some subtypes. Additionally, mechanistic evidence gathered from recent risk assessments of TRAP and recent primary literature was considered to assess the biological plausibility of the associations identified in the review of the epidemiological evidence and to support the determinations of causality.

This risk assessment document is organized as follows:

- Chapter 1 provides background information and describes the objectives and approach;
- Chapter 2 describes the methodology undertaken for this risk assessment in detail;
- Chapter 3 presents the evidence from the included epidemiological primary articles and data analysis;
- Chapter 4 critically evaluates the evidence from Chapter 3 and presents biological evidence to support the findings from the epidemiological studies for determination of causality;
- Chapter 5 presents the conclusions and identifies key uncertainties and gaps.

A supporting document is also available upon request. This document includes the refined search strategy for the literature update, the Risk of Bias (RoB) guidelines used for the assessment of cohort studies, additional quantitative analyses of the epidemiological studies, and tabular summaries of the biological evidence.

CHAPTER 2: METHODOLOGY

In this chapter, the methodology for this risk assessment is described in detail. Section 2.1 summarizes the process used to identify the relevant epidemiological literature relating to TRAP exposure and adverse health outcomes, including the scoping review, the TRAP and traffic exposure framework, and the subsequent literature search updates specific to mortality endpoints considered in this risk assessment. Section 2.2 details the screening, data extraction, RoB assessment, and data analysis. Section 2.3 describes how the biological evidence related to TRAP and the health endpoints of interest were used to assess biological plausibility. Lastly, section 2.4 presents the criteria used to determine the level of causality in the weight of evidence approach.

2.1. IDENTIFICATION OF RELEVANT LITERATURE

2.1.1. Scoping review

As a first step, a scoping review² of the epidemiological literature on the human health effects of TRAP was conducted (Matz et al., 2019). The primary research question for this scoping review was as follows: “What is the current body of scientific literature regarding the association between TRAP exposure and adverse human health endpoints, including effects on various systems (respiratory, circulatory, immunological, reproductive/developmental, and nervous), as well as other health endpoints such as cancer and mortality?”. The scoping review included primary epidemiological research articles and some review types (as described below) that were published in peer-reviewed journals and address the scoping review objectives. The observational study designs that were included were case-control, cohort, cross-sectional, panel, ecological, time-series, and case-crossover designs. Biological studies were included only if human subjects were involved in the study (i.e., controlled human exposure studies). Review types included in the scoping review were systematic reviews, meta-analyses, scoping reviews, and critical reviews that included an evaluation of causal association. With respect to TRAP and traffic exposure metrics, the inclusion criteria were adapted from the critical review of TRAP by the HEI (2010). These criteria allowed the reviewers to identify the studies that were TRAP- or traffic-centric from a larger body of general air pollution studies. Exposure metrics meeting the inclusion criteria were distance to roadways; measures of traffic density; modelling (e.g., land-use regression [LUR] and dispersion) that estimated traffic-specific exposure; traffic-based source apportionment; occupations characterized by traffic exposure (e.g., taxi drivers and truckers); subjects in locations characterized by level of traffic exposure (e.g., high- vs. low-exposure sites); and monitoring of TRAP-related pollutants (e.g., NO₂ and BC) when the measurements could be reasonably related to traffic sources (e.g., roadway-specific monitoring). To target TRAP-related exposures, studies that characterized exposure based on proximity to gas stations or service stations were excluded from the scoping review.

² A scoping review systematically maps the available literature on a broad topic, identifying key concepts, types and sources of information, and gaps in the research.

The literature searches were conducted by a Health Canada librarian in two databases, Ovid Embase and Ovid MEDLINE, and covered the period from January 1, 2000, to April 4, 2018. The detailed search strategy and inclusion criteria are described in Matz et al. (2019). The references identified from the literature search were screened independently by two reviewers for eligibility, first by title and abstract and then by full text; disagreements were resolved by consensus. To generate the evidence map, data extraction included study design parameters and human health outcomes. Descriptive summary tables were developed to provide a high-level summary of the number and types of articles evaluating the different types of health effects and cross-tabulations by study design parameters. The entire review process was managed using DistillerSR (DistillerSR Inc., Ottawa, ON).

From the scoping review, the association between TRAP exposure and mortality was identified as a candidate for a human health risk assessment, as a relatively large body of primary literature was identified in the evidence map. In addition, mortality is the most severe health outcome, so it is important to understand the causes and associated risks for the population.

2.1.2. Framework for traffic and TRAP exposure assessment

HEI published a protocol for a systematic review and meta-analysis of the selected health effects of long-term exposure to TRAP (HEI, 2019) to support its updated assessment of TRAP (2022). This protocol included an updated exposure framework for the evaluation of the health effects of TRAP in epidemiological studies. This framework retained the fundamental concepts of the 2010 HEI report while refining the criteria for identifying studies in which the exposure contrast(s) of TRAP pollutant(s) were primarily due to traffic sources. This refinement aided in the identification and selection of TRAP-specific studies from the larger body of air pollution research (i.e., studies of ambient air pollution considering all sources). Additionally, the HEI protocol indicated that studies of occupational exposure to TRAP (e.g., in taxi drivers and truckers) had not been considered useful in HEI's 2010 report and that these studies would be difficult to combine with ambient exposure studies; and that, as a result, occupational exposures were not considered in scope for HEI's updated report on TRAP (HEI, 2019, 2022).

For the present risk assessment of TRAP exposure and mortality, the primary studies identified from the scoping review and literature search updates were also assessed for inclusion or exclusion based on the updated HEI exposure framework. The details of the exposure assessment framework developed by HEI are described in detail in their TRAP review documents (HEI, 2010, 2019, 2022) and the key concepts are summarized in this section.

For any urban area, the overall air quality is a composition of:

- the regional background air pollutants entering the city;
- the urban background air pollutants dispersed from primary emissions sources, which includes traffic and other sources, and associated secondary air pollutants of these sources; and
- the direct contribution from local traffic sources (e.g., hot spots).

In urban areas, TRAP emissions are greater in areas with higher levels of traffic, and the increased levels of TRAP pollutants in these areas are readily attributed to the roadway network and traffic volumes. For this near-roadway environment, factors such as traffic volume, fleet composition,

fuel source, and driving behaviour are the main determinants of traffic emissions. Diurnal patterns of pollutant concentrations are observable corresponding with traffic volumes (e.g., morning and evening peaks associated with rush-hour traffic). Additionally, as the distance from roadways increases, concentrations of the primary TRAP pollutants (e.g., CO, NO, EC, UFPs) decrease. As the primary traffic emissions are dispersed from the near-road environment, they mix with other pollutants and are subject to the same chemical and physical processes as pollutants from other sources, and eventually become a part of the overall urban background.

Given this complexity of urban air quality, three strategies were considered in combination to identify studies in which the exposure contrast(s) of TRAP pollutant(s) were primarily due to traffic sources:

- the pollutant(s) or traffic metric(s);
- the spatial scale; and
- the exposure assessment method and its spatial resolution.

First, as there is no pollutant unique to TRAP, certain pollutants were considered to represent traffic sources better than others (e.g., NO₂ vs. polycyclic aromatic hydrocarbons [PAHs]). For pollutants with regional contributions from other sources (e.g., PM_{2.5}, PM_{coarse}, and PM₁₀), the exposure contrasts within an urban setting (i.e., within-city contrasts) were considered to be largely attributable to traffic sources, as the regional component is largely constant across large areas. Additionally, if the evidence for an association with a health endpoint was for PM but not for other pollutants with greater TRAP specificity, such as NO₂ or EC, the confidence in the association with TRAP was lowered. Measures of traffic based on road network infrastructure (e.g., distance to roadway or traffic density) were considered to be highly specific markers of variations in traffic exposure, though indirect measures of TRAP exposure.

Second, the spatial scale of a study is an important element of evaluating the specificity of the exposure contrast(s) for TRAP. Spatial scales were defined as regional (>50 km), urban (5 km to 50 km), neighbourhood (1 km to 5 km), and local (<1 km). At the regional and urban scales, it is difficult to isolate the contrasts in TRAP compared with the contrasts due to all sources. In comparison, exposure contrasts at the neighbourhood and local scales were considered relevant to TRAP. As such, studies that used within-city comparisons were included. However, studies that relied on between-city comparisons and studies that considered very large geographical areas (e.g., nationwide or statewide studies) were excluded due to lack of specificity for TRAP compared with other sources—the exposure contrast being considered mostly attributable to regional differences in all sources, and not attributable to differences in traffic.

Third, the spatial resolution of the exposure assessment method was evaluated to select the studies in which the exposure contrasts were due to within-city variations in traffic at the local to neighbourhood scale. Thus, the required resolution of the air pollutant exposure surface was ≤5 km (i.e., 5 x 5 km grid or smaller) corresponding to the upper range of the neighbourhood scale. For indirect measures of TRAP, based on road network infrastructure, the required resolution was ≤1 km (i.e., ≤1 km from a major roadway or highway), corresponding to the upper range of the local scale. Additionally, the required spatial resolution of the address data (e.g., exact address, detailed postal code, census blocks) of the study participants was determined to be 5 km for air pollutants and 100 m for indirect exposure metrics.

2.1.3. Literature search update and handsearching

For this risk assessment, literature search updates using a refined search strategy with the scope limited to studies of mortality, were conducted by a Health Canada librarian using two databases, Ovid Embase and Ovid Medline, on October 16, 2020 and July 11, 2022. This refined search strategy is provided in section 1 of the supporting documentation. The primary studies identified through the literature search updates were assessed for inclusion using the same criteria and method as employed in the scoping review (Matz et al., 2019) and with the updated HEI exposure framework (HEI, 2019). The screening and selection of relevant primary studies from the literature search updates were managed using DistillerSR (DistillerSR Inc., Ottawa, ON).

To supplement the literature searches, the references from two recent systematic review—meta-analyses (SR-MAs) of long-term exposure to NO₂ and mortality (Huangfu and Atkinson, 2020; Stieb et al., 2021) and one recent SR-MA of long-term exposure to PM_{2.5} (Chen and Hoek, 2020) were handsearched. Two of these three SR-MAs (Huanfu and Atkinson, 2020; Chen and Hoek, 2020) had been conducted to inform air quality guidelines developed by the World Health Organization (WHO, 2021).

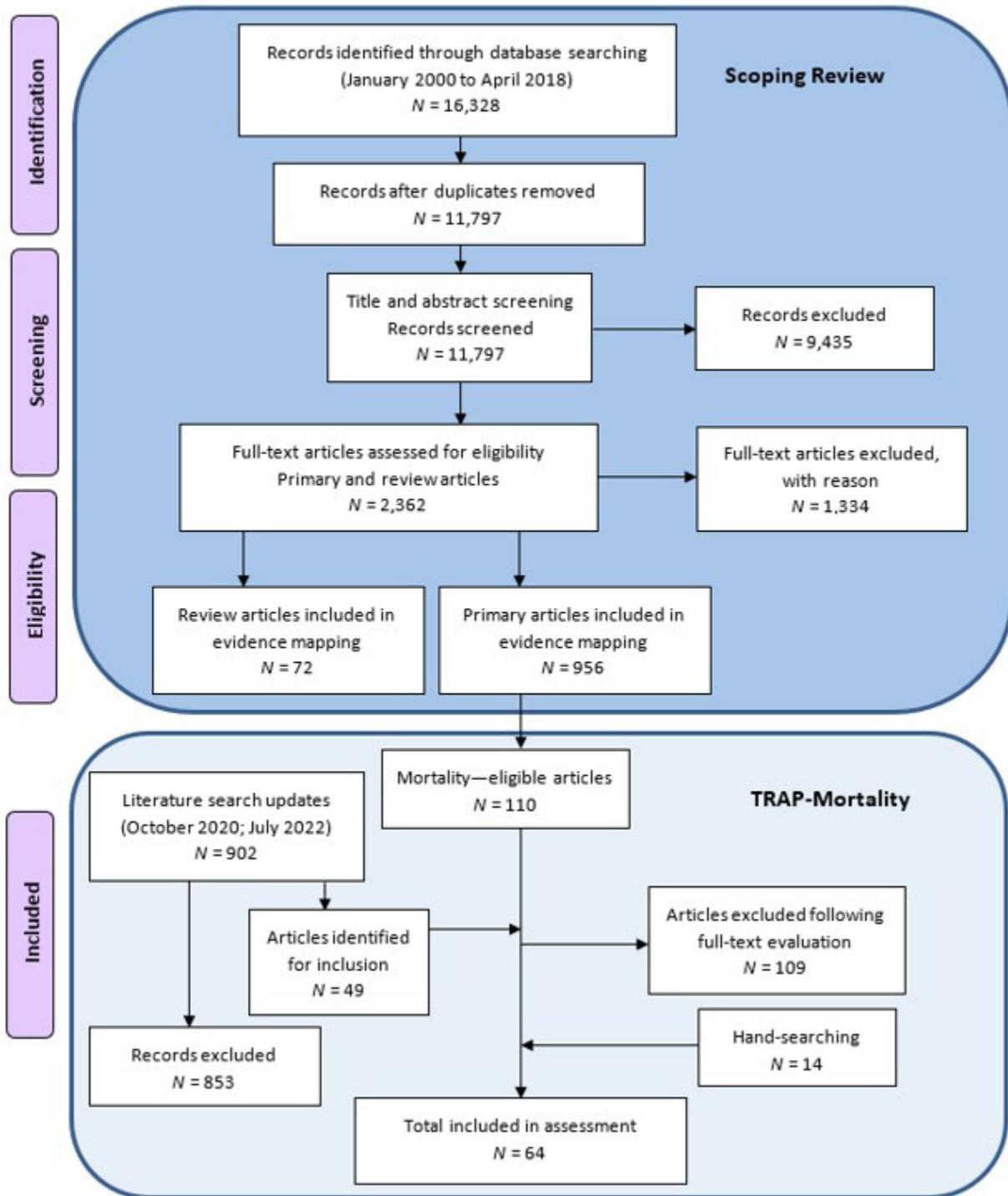
2.2. SCREENING, DATA EXTRACTION, RISK OF BIAS ASSESSMENT, AND DATA ANALYSIS

2.2.1. Screening and data extraction

All studies identified from the scoping review (n = 110), literature search updates (n = 902), and handsearching (n = 14) were screened based on the exposure assessment framework identified in section 2.1.2 and for evaluation of mortality as a health endpoint. For mortality, both all-cause and cause-specific mortality were considered. For this assessment, all-cause mortality referred to the total number of deaths (i.e., death from all causes) as well as deaths that were not the result of an accident or suicide (i.e., non-accidental or natural). Lung cancer mortality was excluded as the association between TRAP exposure and lung cancer in adults was previously assessed by Health Canada (2022c) and determined to have a causal relationship. Title and abstract screening and full-text screening were performed in duplicate; any discrepancies were resolved by consensus and/or consultation with a third reviewer. As a result, 64 primary articles were included in the risk assessment. None of the studies evaluating short-term exposure to TRAP pollutants met the criteria for traffic specificity as per the exposure framework described in section 2.1.2 (e.g., exposures were assigned at the city level).

The study selection process is depicted in **Figure 2.1**.

FIGURE 2.1: Study selection process for the scoping review and the systematic review–based assessment on mortality



For each study, several domains of data were extracted: bibliographic information; study period and location; study size and demographics; pollutant or exposure metric, exposure assessment method, spatial scale, and exposure distribution; cause of death and International Classification of Disease (ICD) codes (if available); model covariates (including potential confounders); and risk estimates (REs) including 95% confidence intervals (CIs) and pollutant increments. Full cohort analyses were selected over case-cohort analyses. Data extraction was completed by two reviewers with partial duplication of approximately 30% of the included studies; any discrepancies were resolved by consensus and/or consultation with a third reviewer.

2.2.2. Risk of bias assessment

As an important element of the systematic review process, a RoB assessment was conducted to assess the validity of included studies and to establish transparency in the evidence synthesis of results (Higgins et al., 2011). The RoB assessment tool employed for this risk assessment was based on the criteria proposed by Lam et al. (2016) in a systematic review and meta-analysis on air pollution and autism spectrum disorder, and was utilized in Stieb et al. (2021) and Health Canada (2022d) with minor modifications. The definitions and guidelines for the RoB tool for the assessment of cohort studies are presented in section 2 of the supporting documentation. The RoB at the study level was evaluated for the following domains: selection bias and generalizability, exposure assessment with regards to modelling and monitoring, confounding, outcome assessment, completeness of outcome data, selective outcome reporting, conflict of interest, and other sources of bias. With respect to the confounding domain, age, sex, smoking, and individual- or area-level socio-economic status (SES) were chosen a priori as critical potential confounders. The same RoB guidelines were used to evaluate case-control studies, with the exception of the selection bias domain, where professional judgment was used. Two reviewers assessed the RoB for each study and discrepancies between the assessments of the two reviewers were resolved by consensus and consultation with a third reviewer when necessary.

2.2.3. Data analysis

Data analysis was performed separately for each individual exposure-outcome pair (e.g., NO₂—all-cause mortality). The exposure candidates included NO₂, NO_x, NO, PM_{2.5}, PM₁₀, EC, benzene, CO, traffic proximity, and traffic density. The outcome candidates consisted of all-cause mortality, circulatory mortality and its specific causes, and respiratory mortality and its specific causes. For each exposure-outcome pair, the most appropriate RE (i.e., derived using the most appropriate statistical model and/or identified as the primary findings by the study authors) was selected from each study, and if two or more studies provided REs for the same cohort, only one study from the same cohort was selected for the analysis. The term risk estimate (RE) is used in this report to encompass each risk ratio measure identified by individual studies when referring to them collectively in the meta-analysis.

Statistical significance of the REs was assessed based on the 95% CI. A RE was considered significant if the CI did not include 1.0 (i.e., the null association) and borderline significant if, for REs greater than 1, the lower 95% confidence limit was 0.9 to 1.0, inclusively, or, for REs less than 1, the upper confidence limit was 1.0 to 1.1, inclusively.

Data analysis was undertaken quantitatively where possible, or qualitatively when quantitative analysis could not be performed. Pollutant-outcome pairs with a minimum number of REs ($n = 4$) were quantitatively analyzed, and pollutant-outcome pairs that did not meet the minimum number of REs were described qualitatively. Traffic and roadway infrastructure metrics (i.e., traffic proximity and traffic density) were analyzed qualitatively, as there is insufficient consistency and standardization in these metrics to allow for quantitative synthesis.

Quantitative analysis: meta-analysis

Meta-analysis was performed for traffic pollutant–outcome pairs that had a minimum of four REs available, similar to other published systematic reviews with meta-analysis in the field (Khreis et al., 2017). Only REs based on single-pollutant models that could be recalculated on a standardized scale (i.e., continuous, but not dichotomous or log-transformed results) were eligible to be included in the meta-analysis. REs from multipollutant models were not retained as the focus was on the TRAP mixture and not its individual components. Of note, for most of the studies, the analyses were conducted using single-pollutant models. Like HEI (2022), Health Canada determined that due to a high degree of heterogeneity between the general population and patient populations, studies from these two population groups would not be pooled together and are presented separately.

Meta-analysis was conducted in R version 4.1.2 (R Core Team, 2021) using the metafor package (Viechtbauer, 2010). For each exposure-outcome pair, the study-specific REs were pooled using the random-effects modelling approach. The random-effects approach was chosen over the fixed-effects approach as it allows generalization of the conclusions beyond the particular set of studies included in the analysis. The models were fitted using Restricted Maximum Likelihood. Hazard ratios (HRs), relative risks (RRs), and odds ratios (ORs) were all eligible for pooling in the same meta-analysis, given that the outcome of interest is common but the effect size is relatively small (Davies et al., 1998), in line with what has been done in previous meta-analyses (Khreis et al., 2017; HEI, 2022). Conversion factors for pollutants to be converted to $\mu\text{g}/\text{m}^3$ were based on those presented in HEI (2022) and are outlined in **Table 2.1**. For all pollutants except EC, the pooled REs were converted to an increment of $10 \mu\text{g}/\text{m}^3$ of pollutant. The pooled REs for EC were converted to an increment of $1 \mu\text{g}/\text{m}^3$ of pollutant. Heterogeneity was evaluated using the I^2 statistic, which represents the percent of total variance attributable to heterogeneity. Values of 0%–40%, 30%–60%, 50%–90%, and 75%–100% correspond to the following categories: might not be important, may represent moderate heterogeneity, may represent substantial heterogeneity, and may represent considerable heterogeneity, respectively (Higgins et al., 2022).

TABLE 2.1: Conversion factors for units in meta-analysis

Pollutant	Conversion	Factor ^a
NO ₂	ppb to µg/m ³	1.88
NO	ppb to µg/m ³	1.23
NO _x	ppb to µg/m ³	1.55
CO	ppm to mg/m ³	1.15
BC	µg/m ³ to µg/m ³ EC	1.25
BS	µg/m ³ to µg/m ³ EC	0.11
PM _{2.5 abs}	10 ⁻⁵ /m to µg/m ³ EC	1.1

^a Based on HEI 2022 Report Appendix 5C. Scaling and conversion factors for use in meta-analysis

Meta-analysis can only be performed on unique cohorts (Higgins et al., 2022). Therefore, the rationales for selecting the most appropriate RE for inclusion into the meta-analysis were as follows:

- If two or more studies provided REs on the same cohort, the study with the cohort that had the longest length of follow-up, largest sample size, and greater overall completeness of data necessary to perform a meta-analysis (e.g., RE, 95% CI) was selected for inclusion in the meta-analysis.
- If one study presented REs based on multiple exposure assignments (e.g., at baseline, average, last year in study), the RE calculated using a moving average, with longer ranging averages preferred, was selected. Moving averages are often chosen to stabilize REs (van Donkelaar et al., 2015).
- If one study presented REs based on multiple methods of exposure measurement (e.g., LUR model, dispersion model), REs based on LUR models were chosen over dispersion models for better representation of TRAP (de Hoogh et al., 2014).

Additional analyses were conducted to ascertain the robustness of results of the main meta-analysis, specifically subgroup analyses, sensitivity analyses, and tests for influence and publication bias. First, subgroup analysis was conducted based on exposure assessment methodology (e.g., LUR or dispersion modelling). The LUR model subgroup analysis also included an exposure assessment using hybrid models (i.e., assessment methods that combined more than one modelling technique such as a dispersion model with a chemical transport model) as they were deemed sufficiently similar for the purposes of meta-analysis. Subgroup analysis by geographical region was not conducted due to an insufficient number of Canadian or North American studies. Second, sensitivity analyses were performed to identify whether studies with high RoB were influencing the results; only studies with low or probably low ratings for RoB in the exposure assessment and confounding domains were included. Finally, the influence of individual studies on the overall pooled RE was examined using leave-one-out analysis. Evidence of the potential effect of publication bias was investigated by identifying asymmetry in funnel plots, performing Begg's rank correlation and Egger's regression tests, and using the trim-and-fill method.

2.3. BIOLOGICAL EVIDENCE

An evaluation of biological evidence was conducted to assess the biological plausibility of the associations between TRAP exposure and mortality. The studies included in the evaluation of the biological evidence typically consider short-term exposures and are designed to detect subtle changes in biomarkers which are relatable to long-term health effects observed in the epidemiological literature. For efficiency, this evaluation was non-exhaustive and built on existing reviews of TRAP by Health Canada (2020, 2022c) and HEI (2010, 2022). In addition, a search of the primary literature from the past 10 years (i.e., 2013–2022) was conducted to identify the most relevant recent studies. This literature search focused on human and experimental animal studies that evaluated real-world TRAP exposures, as these provide the most direct evidence of the associated biological effects. Controlled exposure studies of vehicle exhaust (i.e., DE) were also included as they were considered to represent an important component of the total TRAP mixture and the study design addressed some of the confounding associated with panel study design (e.g., differences in noise between exposure locations). The literature review centred on health effects associated with the circulatory and respiratory systems, as these were determined to be the most relevant for this risk assessment, and they comprised a majority of the biological evidence literature.

2.4. DETERMINATION OF CAUSALITY

The quantitative estimates of TRAP pollutant concentrations were considered to provide the highest level of evidence, while the qualitative analysis of the metrics of traffic and the road network infrastructure and of TRAP pollutants for which quantitative analysis was not undertaken provided support in the evidence base for the determination of causality. The biological evidence was used to support the associations observed in the epidemiological literature as well as to support a determination of causality.

In the weight of evidence approach used in this assessment to determine the causal role of TRAP in the development of specific health effects, consideration is given to a number of criteria, including those of causal inference developed by Bradford Hill (1965). The criteria, widely used in reviews of epidemiological literature and considered collectively in the weight of evidence evaluation, are as follows:

- Biological plausibility: there is a plausible mechanism between the exposure and the effect;
- Temporal sequence: the exposure precedes the health outcome;
- Consistency of the association: the association is reported by different researchers, for different study designs, in different populations, etc.;
- Coherence: evidence from toxicological studies, controlled human exposure studies, and epidemiological studies of various types provides support for the effects observed and potential modes of action;
- Biological gradient: there is evidence of an exposure-response relationship;

- Strength of the association: the greater the magnitude of the RE, the less likely that the relationship is due to uncontrolled residual confounding; and
- Robustness of the association: the associations are robust to model specifications and adjustment for potential confounders such as weather, temporal trends, and co-occurring pollutants.

These criteria are used to inform a conclusion as to whether the relationship between TRAP exposure and a health effect is causal, likely to be causal, suggestive of a causal relationship, inadequate to infer a causal relationship, or not likely to be causal. The definitions of each of these determinations of causality are derived from the United States Environmental Protection Agency (US EPA, 2015) and are provided in **Table 2.2**. Health Canada has previously used this causality framework in the risk assessments of DE (2016b); NO₂ (2016b); gasoline exhaust (2017); TRAP and asthma, allergy, and lung function (Health Canada, 2020); and TRAP and selected cancer types (Health Canada, 2022c).

TABLE 2.2: Weight of evidence for determination of causality (derived from US EPA 2015)

Relationship	Description
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (e.g., doses or exposures generally within one to two orders of magnitude of recent concentrations). That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects, or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence (e.g., animal studies or mode of action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) observational studies show association, but co-pollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or (2) animal toxicological evidence from multiple studies from different laboratories demonstrates effects, but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.
Suggestive of, but not sufficient to infer, a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures but is limited because chance, confounding, and other biases cannot be ruled out. For example: (1) when the body of evidence is relatively small, at least one high-quality epidemiologic study shows an association with a given health outcome and/or at least one high-quality toxicological study shows effects relevant to humans in animal species; or (2) when the body of evidence is relatively large, evidence from studies of varying quality is generally supportive but not entirely consistent, and there may be coherence across lines of evidence (e.g., animal studies or mode of action information) to support the determination.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant 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.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and life stages, are mutually consistent in not showing an effect at any level of exposure.

CHAPTER 3: LITERATURE REVIEW AND EVALUATION

3.1. CHARACTERISTICS OF THE INCLUDED ARTICLES

Overall, 64 primary articles were included in the risk assessment (details are provided in section 2.2.1); all were long-term exposure studies. Most of these articles used a cohort study design (n = 62); the remaining two articles were case-control studies (Rosenlund et al., 2006, 2009).

The most frequently examined cause of death was all-cause (including natural and non-accidental) followed by circulatory and respiratory (**Table 3.1**). Other causes of mortality evaluated in more than one article included various types of cancer other than lung cancer (n = 6), a proportion of overall mortality (i.e., overall mortality not including certain specific causes of mortality; n = 6), diabetes (n = 3), digestive system diseases (n = 3), and endocrine disorders (n = 2). **Table 3.1** provides a breakdown of the 64 articles included in the analysis with the type of exposure metric measured for each of the causes of mortality reported.

TABLE 3.1: Number of articles^a included in the risk assessment per publication date and exposure metric for each cause of mortality

Cause of mortality	Number of primary articles	Publication date from 2013–2022	TRAP pollutant	Traffic and road network infrastructure
All-cause	47	29	31	20
Circulatory	41	22	27	19
Respiratory	20	13	15	7
Other	14	6	7	8

^a Numbers reported do not add up to the total number of articles included in this risk assessment as some articles reported more than one cause of mortality and/or used more than one exposure metric.

For all-cause, circulatory, and respiratory mortality, the majority of the articles identified were relatively recent with a publication date after 2012. TRAP pollutants were more commonly used than traffic and the road network infrastructure to assess TRAP exposure in articles investigating all-cause, circulatory, and respiratory mortality.

General study characteristics of the 64 primary articles are provided in **Table 3.2**. An overall synthesis of these articles is presented in this section followed by a more in-depth evaluation by cause of mortality in the subsequent sections of this chapter. Overall, the cohort studies were conducted in Canada (n = 10), the United States of America (USA) (n = 12), Europe (n = 30), Asia (n = 8), and Australia (n = 2), while the case-control studies were conducted in Europe (n = 2). The studies were mostly based on the general population, with the exception of 16 articles that pertained to studies

with various patient populations, a combination of general and patient populations, or patient populations for only certain mortality outcomes. Diverse exposure assessment methods were used to assess long-term exposure to TRAP and mortality, including modelling such as LUR (n = 22), dispersion (n = 13), and hybrid or other models (n = 7), as well as traffic and road network infrastructure metrics (n = 32). The most frequently assessed TRAP pollutants were NO₂ (n = 28), PM_{2.5} (n = 20), PM₁₀ (n = 13), and NO_x (n = 13). A number of other pollutants attributed to TRAP were also used to evaluate exposure in a limited number of articles; they include BC (n = 6), NO (n = 5), PM_{2.5 abs} (n = 6), PM_{coarse} (n = 4), CO (n = 2), EC (n = 1), and benzene (n = 1). Although UFPs are a key marker for TRAP, no studies were identified for this pollutant. With regards to traffic and the road network infrastructure, traffic proximity (n = 26) was the most commonly used metric, followed by traffic density (n = 13).

TABLE 3.2: General study characteristics by geographical location and year of publication for long-term exposure to TRAP

First author and year	Cohort ^a (Study period)	Study location	Study population	TRAP pollutant/metric	Exposure assessment method	Cause of death ^b
Canada						
Finkelstein 2004	(1992–2001)	Hamilton, ON	Patient	Traffic proximity	Traffic and road network infrastructure	A
Finkelstein 2005	(1985–1999)	Hamilton, ON	Patient	Traffic proximity	Traffic and road network infrastructure	C, R
Jerrett 2009	(1992–2002)	Toronto, ON	Patient	NO ₂ (all), traffic proximity (A, C, O)	LUR model, traffic and road network infrastructure	A, C, R, O
Gan 2010	(1994–2002)	Vancouver, BC	General	Traffic proximity	Traffic and road network infrastructure	C
Gan 2011	(1994–2002)	Vancouver, BC	General	NO, NO ₂ , PM _{2.5} , BC	LUR model	C
Chen 2013	Ontario Tax Cohort (1982–2004)	Toronto, Hamilton, Windsor, ON	General	NO ₂ , traffic proximity	LUR model, traffic and road network infrastructure	C
Gan 2013	(1999–2002)	Metropolitan Vancouver, BC	General	NO, NO ₂ , PM _{2.5} , BC	LUR model	R
Villeneuve 2013	Ontario Tax Cohort (1982–2004)	Toronto, ON	General	NO ₂ , benzene	LUR model	A, C, R, O
Crouse 2015	Canadian Census Health and Environment Cohort (CanCHEC) 1991 (1991–2006)	10 cities (Edmonton, Hamilton, London, Montreal, Sarnia, Toronto, Vancouver, Victoria, Windsor, Winnipeg)	General	NO ₂	LUR model	A, C, R

First author and year	Cohort ^a (Study period)	Study location	Study population	TRAP pollutant/metric	Exposure assessment method	Cause of death ^b
Cakmak 2019	CanCHEC 1991 (1991–2011)	Canada	General	Traffic proximity	Traffic and road network infrastructure	A, C, R, O
USA						
Jerrett 2005	American Cancer Society—Cancer Prevention Survey II (ACS-CPSII) (1982–2002)	Los Angeles, CA	General	PM _{2.5}	Hybrid or other models	A, C, O
Medina-Ramón 2008	Worcester Heart Failure Study (2000–2005)	Worcester, MA	Patient	Traffic proximity, traffic density	Traffic and road network infrastructure	A
Krewski 2009	ACS-CPSII (1982–2000)	New York City, NY Los Angeles, CA	General	PM _{2.5}	LUR model	A, C, O
von Klot 2009	Worcester Heart Attack Study (1995–2005)	Worcester metropolitan area, MA	Patient	EC	LUR model	A
Hart 2013	Nurses' Health Study (NHS) (1990–2008)	All 50 states	General	Traffic proximity	Traffic and road network infrastructure	A
Wilker 2013	(1999–2012)	Boston, MA	Patient	Traffic proximity	Traffic and road network infrastructure	A
Hart 2014	NHS (1986–2012)	All 50 states	General	Traffic proximity	Traffic and road network infrastructure	C
Blount 2017	(2000–2012)	California	Patient	Traffic density	Traffic and road network infrastructure	A
Alexeeff 2018	Kaiser Permanente Northern California (2010–2015)	Oakland, CA	General	NO, NO ₂ , BC	Hybrid or other models	C
Kulick 2018	The Northern Manhattan Study (1993–2016)	Northern Manhattan, NY	General	Traffic proximity	Traffic and road network infrastructure	A, C
DuPré 2019	NHS and NHS II (1988–2008)	NHS: 11 states NHSII: 14 states	General	Traffic proximity	Traffic and road network infrastructure	O
Villanueva 2021	(1996–2016)	California	General	Traffic proximity	Traffic and road network infrastructure	O
Europe						
Hoek 2002	Netherlands Cohort Study on Diet and Cancer (NLCS) (1986–1994)	Netherlands	General	Traffic proximity	Traffic and road network infrastructure	A, C, O
Nafstad 2004	(1972–1998)	Oslo, Norway	General	NO _x	Dispersion model	A, C, R

First author and year	Cohort ^a (Study period)	Study location	Study population	TRAP pollutant/metric	Exposure assessment method	Cause of death ^b
Gehring 2006	Study on the influence of air pollution on lung function, inflammation and ageing (SALIA) (1985–2003)	North Rhine–Westphalia, Germany	General	Traffic proximity	Traffic and road network infrastructure	A, C, O
Rosenlund 2006	Case-control (1992–1994)	Stockholm, Sweden	General	NO ₂ , PM ₁₀ , CO	Dispersion model	C
Naess 2007	(1992–1998)	Oslo, Norway	General	NO ₂ (C, R), PM ₁₀ (C, R), PM _{2.5} (all)	Dispersion model	A, C, R
Rosenlund 2008	(1998–2005 [A]; 1998–2000 [C])	Rome, Italy	Patient (A), General (C)	NO ₂	LUR model	A, C
Beelen 2008	NLCS-AIR Study (1987–1996)	Netherlands	General	Traffic proximity, traffic density	Traffic and road network infrastructure	A, C, R, O
Beelen 2009	NLCS (1987–1996)	Netherlands	General	Traffic proximity, traffic density	Traffic and road network infrastructure	C
Brunekreef 2009	NLCS-AIR Study (1986–1996; followed from 1987–1996)	Netherlands	General	Traffic proximity, traffic density	Traffic and road network infrastructure	A, C, R, O
Rosenlund 2009	Case-control (1985–1996)	Stockholm, Sweden	General	NO ₂ , PM ₁₀ , CO	Dispersion model	C
Huss 2010	Swiss National Cohort (2000–2005)	Switzerland	General	Traffic proximity	Traffic and road network infrastructure	C
Maheswaran 2010	(1995–2006)	London, United Kingdom (UK)	Patient	NO ₂ , PM ₁₀	Hybrid or other models	A
Nawrot 2011	(1997–2009)	Leuven, Belgium	Patient	Traffic proximity	Traffic and road network infrastructure	A
Cesaroni 2012	Rome Longitudinal Study (2001–2006)	Rome, Italy	General	NO ₂	LUR model	A
Raaschou-Nielsen 2012	Diet, Cancer and Health cohort study (1993–2009)	Copenhagen and Aarhus, Denmark	General	NO ₂ , traffic proximity, traffic density	Hybrid or other models, traffic and road network infrastructure	A, C
Carey 2013	Clinical Practice Research Datalink (2003–2007)	England	General	NO ₂ , PM _{2.5} , PM ₁₀	Dispersion Model	A, C, R
Cesaroni 2013	Rome Longitudinal Study (2001–2010)	Rome, Italy	General	NO ₂ , PM _{2.5} , traffic proximity, traffic density	LUR model, dispersion model, traffic and road network infrastructure	A, C, R
Heinrich 2013	SALIA (1985–2008)	North Rhine-Westphalia, Germany	General	Traffic proximity	Traffic and road network infrastructure	A, C, R

First author and year	Cohort ^a (Study period)	Study location	Study population	TRAP pollutant/metric	Exposure assessment method	Cause of death ^b
Beelen 2014a	European Study of Cohorts for Air Pollution Effects (ESCAPE) (earliest 1985; follow-up range from 6.3 to 18.6 y)	13 countries	General	NO ₂ , NO _x , PM _{2.5} , PM _{2.5 abs} , PM ₁₀ , PM _{coarse} , traffic density	LUR model, traffic and road network infrastructure	A
Beelen 2014b	ESCAPE (earliest 1985; follow-up range from 6.3 to 18.6 y)	13 countries	General	NO ₂ , NO _x , PM _{2.5} , PM _{2.5 abs} , PM ₁₀ , PM _{coarse} , traffic density	LUR model, traffic and road network infrastructure	C
Dimakopoulou 2014	ESCAPE (earliest 1985; follow-up range from 6.3 to 18.6 y)	11 countries	General	NO ₂ , NO _x , PM _{2.5} , PM _{2.5 abs} , PM ₁₀ , PM _{coarse} , traffic density	LUR model, traffic and road network infrastructure	R
Goeminne 2014	(2006–2013)	Leuven, Belgium	Patient	Traffic proximity, traffic density	Traffic and road network infrastructure	A
Stockfelt 2015	Multifactor Primary Prevention Study (1973–2007)	Gothenburg, Sweden	General	NO _x	Dispersion model	A, C, R
Desikan 2016	(2005–2012)	London, UK	Patient	NO, NO ₂ , NO _x , PM _{2.5} , PM ₁₀ , PM _{coarse}	Dispersion model	A
Tonne 2016	(2003–2010)	Greater London, UK	Patient	NO ₂ , NO _x , PM _{2.5} (exhaust and non exhaust), PM ₁₀ (exhaust and non exhaust), traffic density	Dispersion model, traffic and road network infrastructure	A
Badaloni 2017	Rome Longitudinal Study (2001–2010)	Rome, Italy	General	PM _{2.5} , PM _{2.5 abs} , PM ₁₀	LUR model	A, C
Ruttens 2017	(1987–2013)	10 countries	Patient	Traffic proximity	Traffic and road network infrastructure	A
Nieuwenhuijsen 2018	Sistema d'Informació pel Desenvolupament de la Investigació en Atenció Primària (SIDIAP) (2010–2014)	Barcelona, Spain	General	NO ₂ , PM _{2.5} , PM _{2.5 abs} , PM ₁₀	LUR model	A
Bauleo 2019	(1996–2013)	Civitavecchia, Italy	General	NO _x	Dispersion model	A, C, R, O
Andersson 2020	Primary Prevention Study cohort (1970–2011)	Gothenburg, Sweden	General	NO _x	Dispersion model	A, C
So 2020	Danish Nurse Cohort (1993–2013)	Denmark (capital region only)	General	PM _{2.5}	Hybrid or other models	A
Carlsen 2022	Malmo Diet and Cancer cohort (1991–1996)	Malmo, Sweden	General	NO _x , PM _{2.5} , PM ₁₀ , BC	Dispersion model	C

First author and year	Cohort ^a (Study period)	Study location	Study population	TRAP pollutant/metric	Exposure assessment method	Cause of death ^b
Asia						
Yorifuji 2010	Shizuoka elderly cohort (1999–2006)	Shizuoka, Japan	General	NO ₂	LUR model	A, C, R, O
Yorifuji 2013	Shizuoka elderly cohort (1999–2009)	Shizuoka, Japan	General	NO ₂	LUR model	A, C, R
Barratt 2018	Hong Kong Elderly Health Services (1998–2011)	Hong Kong, China	General	NO, NO ₂ , PM _{2.5} , BC	LUR model	A, C, R
Yang 2018	Hong Kong Elderly Health Services (2001–2011)	Hong Kong, China	General	NO ₂ , PM _{2.5} , BC	LUR model	A, C, R
Cohen 2019	(2004–2017)	Israel	Patient	NO _x	LUR model, hybrid or other models, dispersion model	A, O
Cohen 2021	(1992–2018)	Israel	General and patient	NO _x	LUR model	A
Pan 2021	Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer Hepatitis B Virus (REVEAL-HBV) (2000–2014)	Taipei and Pingtung, Taiwan	General	Traffic density	Traffic and road network infrastructure	C
Hadley 2022	Golestan Cohort Study (2004–2008)	Golestan province, Iran	General	Traffic proximity	Traffic and road network infrastructure	A, C
Australia						
Dirgawati 2019	Health in Men Study (1996–2012)	Perth, Western Australia	General	NO ₂ , NO _x , PM _{2.5} , PM _{2.5 abs}	LUR model	A, C
Hanigan 2019	45 and Up Study (2006–2015)	Sydney	General	NO ₂ , PM _{2.5}	Hybrid or other models	A

Abbreviations: LUR: land-use regression

^a Cohort or study name when specified in the article

^b Causes of death were divided into the following categories: all-cause (A), circulatory (C), respiratory (R), and other (O)

As indicated in section 2.2.2 of this risk assessment, an RoB assessment was conducted to evaluate the validity of the included studies and establish transparency in the evidence synthesis of the results. The RoB ratings (where a higher rating signifies a greater risk of a bias in that domain) for the individual studies are summarized in **Table 3.3**. Outcome assessment and selective outcome reporting were the most uniformly low RoB domains. Risk of conflict of interest was rated low or probably low for all studies. Completeness of outcome data was also rated low or probably low with the exception of three studies with a probably high rating, which was largely attributed to shorter lengths of follow-up (< 4 years or median follow-up of 5.5 years). Similarly, risk of selection bias was mostly rated low or probably low with the exception of four studies that had a probably high rating. This probably high rating was attributed to a low response rate, recruitment, and retention of selective participants (i.e., self-selection for enrolment of a preventive service), loss to follow-up specific to certain demographics (e.g., older, current smokers, diabetes, financially non-capable, and more polluted area), or inconsistencies in the selection process across the cohorts. RoB from exposure assessment was rated probably low for most studies, but four studies rated probably high or high in this domain. The latter was largely attributable to a lack of data on residential mobility or time-activity patterns and issues with spatial and/or temporal accuracy of exposure estimates. Among the domains evaluated, the confounding domain showed the most variability between low, probably low, and probably high RoB. For the confounding domain, a probably high RoB rating was mostly from lack of account for smoking, and one study did not account for SES. One study was rated high for RoB in the confounding domain as it provided only unadjusted REs.

TABLE 3.3: RoB assessment

Reference	Selection bias	Exposure assessment	Confounding	Outcome assessment	Completeness of outcome data	Selective outcome reporting	Conflict of interest	Other
Hoek et al., 2002	2	3	1	1	2	1	1	1
Finkelstein et al., 2004	2	2	3	1	2	1	2	1
Nafstad et al., 2004	2	1	1	1	1	1	1	1
Finkelstein et al., 2005	2	4	3	1	2	1	1	1
Jerrett et al., 2005	2	2	1	2	1	1	2	1
Gehring et al., 2006	2	2	1	1	1	1	2	1
Rosenlund et al., 2006 ^a	2	2	1	1	1	1	2	1
Naess et al., 2007	1	2	3	1	1	1	1	1
Beelen et al., 2008	1	2	2 for full cohort 1 for case-cohort	1	1	1	1	1
Medina-Ramón et al., 2008	1	2	1	1	1	1	1	1
Rosenlund et al., 2008	1	2	3	1	1	1	2	1
Beelen et al., 2009	2	3	1	1	1	1	1	1
Brunekreef et al., 2009	2	1	1	1	1	1	1	1
Jerrett et al., 2009	1	1	1	1	2	1	1	1
Krewski et al., 2009 (LA and NYC)	2	2	1	1	2	1	1	1
Rosenlund et al., 2009 ^a	2	2	3	1	1	1	2	1
von Klot et al., 2009	1	2	2	1	1	1	2	1
Gan et al., 2010	1	1	3	1	1	1	2	1
Huss et al., 2010	1	2	3	1	1	1	1	1
Maheswaran et al., 2010	2	1	1	1	1	1	1	1
Yorifuji et al., 2010	3	2	1	1	1	1	1	1
Gan et al., 2011	1	1	3	1	3	1	1	1
Nawrot et al., 2011	2	2	1	2	2	1	1	1
Cesaroni et al., 2012	1	2	3	1	1	1	1	1
Raaschou-Nielsen et al., 2012	2	1	1	1	1	1	1	1
Carey et al., 2013	1	2	1	1	1	1	1	1
Cesaroni et al., 2013	1	1	3	1	1	1	1	1
Chen et al., 2013	1	1	1	1	1	1	1	1
Gan et al., 2013	1	1	3	1	2	1	2	1
Hart et al., 2013	2	2	1	1	1	1	1	1
Heinrich et al., 2013	2	2	1	1	1	1	1	1
Villeneuve et al., 2013	1	2	3 for NO ₂ 1 for benzene	1	1	1	1	1

Reference	Selection bias	Exposure assessment	Confounding	Outcome assessment	Completeness of outcome data	Selective outcome reporting	Conflict of interest	Other
Wilker et al., 2013	1	2	1	1	1	1	1	1
Yorifuji et al., 2013	3	1	1	1	1	1	1	1
Beelen et al., 2014a	2	2	1	1	2	1	1	1
Beelen et al., 2014b	2	2	1	1	2	1	1	1
Dimakopoulou et al., 2014	2	2	1	1	1	1	1	1
Goeminne et al., 2014	1	2	1	1	3	1	1	1
Hart et al., 2014	2	1	1	1	1	1	1	1
Crouse et al., 2015	1	1	1	1	1	1	1	1
Stockfelt et al., 2015	1	1	1	1	1	1	1	1
Desikan et al., 2016	1	2	3	1	1	1	1	1
Tonne et al., 2016	2	2	1	1	1	1	2	1
Badaloni et al., 2017	1	2	1	1	1	1	2	1
Blount et al., 2017	1	2	3	1	1	1	1	1
Ruttens et al., 2017	1	2	2	2	3	1	1	2
Alexeeff et al., 2018	1	2	1	1	2	1	2	1
Barratt et al., 2018	3	2	1	1	1	1	1	1
Kulick et al., 2018	1	2	1	2	1	1	1	1
Nieuwenhuisjen et al., 2018	1	1	2	1	1	1	1	1
Yang et al., 2018	2	1	1	1	1	1	1	1
Bauleo et al., 2019	1	3	3	1	1	1	1	1
Cakmak et al., 2019	1	2	1	1	1	1	2	1
Cohen et al., 2019	2	2	1	1	2	1	1	1
Dirgawati et al., 2019	1	1	1	1	1	1	1	1
DuPré et al., 2019	2	1	1	2	1	1	1	1
Hanigan et al., 2019	2	2	1	1	1	1	1	1
Andersson et al., 2020	2	2	1	1	1	1	1	1
Cohen et al., 2021	3	2	1	1	1	1	1	1
Pan et al., 2021	2	2	3	1	1	1	1	1
So et al., 2020 (capital region only)	2	1	1	1	1	1	1	1
Villanueva et al., 2021	1	2	4	1	1	1	1	1
Carlsen et al., 2022	1	1	1	1	1	1	1	1
Hadley et al., 2022	2	2	1	1	1	1	1	1

^a Case-control study design; all other studies are cohorts.
Legend: 1: low RoB; 2: probably low RoB; 3: probably high RoB; 4: high RoB

A literature review and evaluation of the studies are presented in the sections below for all-cause mortality, circulatory mortality, and respiratory mortality. The study details, organized by exposure metric, are provided in Appendix A. Additional analyses, including subgroup, sensitivity, leave-one-out, and publication bias analyses, are provided in section 3 of the supporting documentation. Other causes of mortality were not further considered in this risk assessment due to the limited number of studies identified.

3.2. ALL-CAUSE MORTALITY

All-cause mortality (also referred to as natural cause, non-accidental cause, and total mortality) was evaluated in 47 of the 64 articles evaluating the association between long-term exposure to TRAP and mortality.

3.2.1. Nitrogen oxides (NO, NO₂, and NO_x)

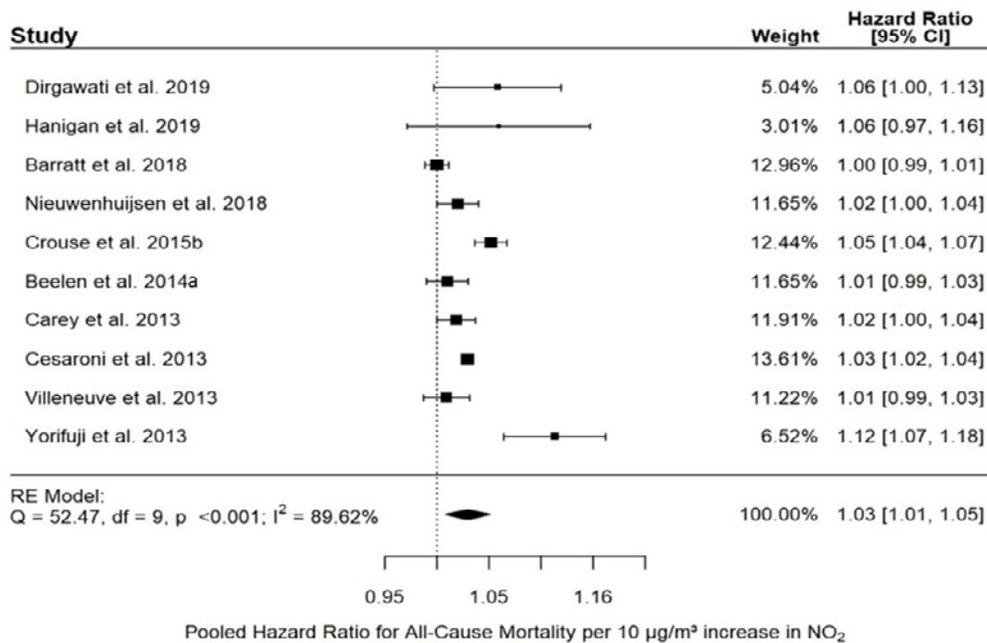
NO₂ is the most frequently measured TRAP pollutant for all-cause mortality with 19 studies while NO was among the least measured TRAP pollutants with only 2 studies. Ten studies used NO_x to assess TRAP exposure.

NO₂

For studies of NO₂, the study details regarding study population, exposure assessment, confounders, and REs are provided in Appendix A.1. Most of the studies were conducted in Europe (n = 10); for North America, 3 studies were conducted in Canada while no studies conducted in the USA were identified in the literature searches. The majority of the studies (n = 14) were drawn from the general population with a cohort size ranging from 11,627 (Dirgawati et al., 2019) to 1,265,058 (Cesaroni et al., 2013). For exposure assessment of the general population cohorts, LUR modelling (n = 11) was the most common method used, followed by hybrid modelling (n = 2) and dispersion modelling (n = 1). Exposures were assigned based on the residential address, postal code, or census tract and the mean (or median) exposures ranged from 5.2 to 104 µg/m³. The lowest exposures were assigned to one of the Swedish cohorts included in the ESCAPE study (Beelen et al., 2014a) while the highest exposures were noted in a study conducted in Hong Kong, China (Yang et al., 2018). All 14 studies accounted for age and sex, as well as individual SES and/or area-level SES; 2 studies did not adjust for smoking (Cesaroni et al., 2012, 2013). Many studies also considered additional confounders, which are listed in Appendix A.1.

The most appropriately adjusted RE identified from each study pertaining to all-cause mortality is also specified in Appendix A.1. For the general population, 12 of the 14 REs were positive, of which 4 were statistically significant and 3 were borderline significant. The forest plot and results of the random-effects meta-analysis for all-cause mortality and NO₂ in the general population are presented in **Figure 3.1**. Ten studies were included in the meta-analysis with REs ranging from 1.00 to 1.12. The pooled RE for the association between NO₂ and all-cause mortality was significantly positive with a HR of 1.03 (95% CI: 1.01–1.05) and heterogeneity was substantial (I² = 89.62%).

FIGURE 3.1: Association between all-cause mortality and long-term exposure to NO₂ in the general population



Heterogeneity remained substantial ($I^2 = 91.63\%$) in subgroup analysis based on the exposure assessment method when it was limited to studies that used LUR / hybrid models (RE: 1.03; 95% CI: 1.01–1.06), which included all but one study from the main analysis. Sensitivity analysis based on RoB was not done for the exposure domain as all the studies included in the meta-analysis scored low or probably low in this domain. When the analysis was limited to only studies that were low and probably low RoB for the confounder domain, the pooled estimate was robust with a RE of 1.04 (95% CI: 1.01–1.07; $I^2 = 88.60\%$). Similarly, leave-one-out analysis indicated the results were robust with pooled RE ranging from 1.02 to 1.03. There was evidence of publication bias as demonstrated by the asymmetric distribution of the funnel plot but this was not supported by either Egger's ($p = 0.0898$) or Begg's test ($p = 0.7275$). Additionally, the trim-and-fill method suggested that two hypothetical studies are needed to make the funnel plot symmetrical.

As indicated in Appendix A.1, five studies examining the association between all-cause mortality and NO₂ focused exclusively on various patient populations, including patients from a respiratory disease clinic in Toronto, Ontario (Jerrett et al., 2009); patients surviving a coronary event in Rome, Italy (Rosenlund et al., 2008); and stroke (Maheswaran et al., 2010; Desikan et al., 2016) and myocardial infarction (MI) (Tonne et al., 2016) patients in London, United Kingdom. The cohort size of these studies ranged from 1,800 (Desikan et al., 2016) to 18,138 (Tonne et al., 2016). The studies used LUR models ($n = 2$), dispersion modelling ($n = 2$), and hybrid models ($n = 1$) to assess exposure

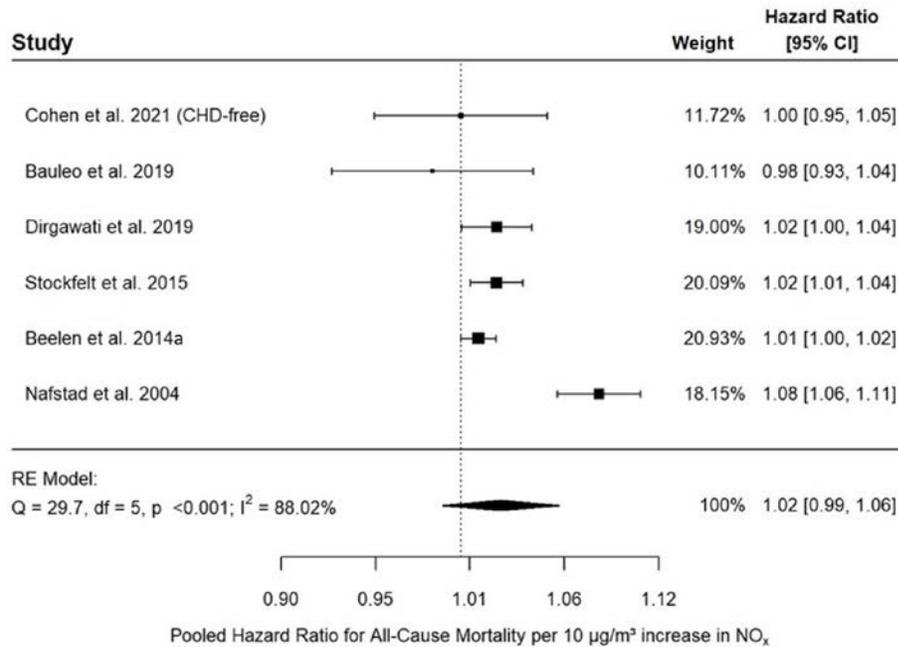
and the majority ($n = 3$) accounted for the key confounders of age, sex, SES, and smoking. As summarized in Appendix A.1, three of the five REs were positive, of which one was statistically significant and one was borderline significant. The REs from the four studies in patients with a cardiovascular etiology (Rosenlund et al., 2008; Maheswaran et al., 2010; Desikan et al., 2016; Tonne et al., 2016) were pooled using a random-effects meta-analysis; the forest plot and results of this meta-analysis are presented in the supporting document. The pooled RE was 1.05 (95% CI: 0.84–1.30) per $10 \mu\text{g}/\text{m}^3$ NO_2 exposure and heterogeneity was considered substantial ($I^2 = 85.17\%$).

NO_x

For NO_x , 10 studies conducted in Europe ($n = 7$), Israel ($n = 2$), and Australia ($n = 1$) examined the association between long-term exposure to NO_x and all-cause mortality; the study details are depicted in Appendix A.2. Six of these studies were drawn from the general population and these cohorts ranged in size from 6,304 (Andersson et al., 2020) to 367,251 (Beelen et al., 2014a). An additional study with both population-based and patient-based cohorts of CHD also reported a RE for the general population ($n = 2,393$) (Cohen et al., 2021). For the general population cohorts, the majority of the studies used dispersion modelling ($n = 4$) followed by LUR modelling ($n = 3$) to assess NO_x exposure and all studies assigned NO_x exposure at the residential address; the mean (or median) exposures ranged from 5.80 to $107.3 \mu\text{g}/\text{m}^3$. The lowest exposures were estimated in a study conducted in Civitavecchia, Italy (Bauleo et al., 2019) while the highest exposures were modelled in one of the Italian cohorts included in the ESCAPE study (Beelen et al., 2014a). All studies accounted for the key confounders of age, sex, and SES (individual and/or area-level) and all but one study (Bauleo et al., 2019) also adjusted for smoking. Additional confounders were also considered in these studies.

The most appropriately adjusted RE for NO_x and all-cause mortality from each study is summarized in Appendix A.2. Six of the 10 REs were positive, of which 2 were statistically significant and 2 were borderline significant. The forest plot and results of the random-effects meta-analysis for all-cause mortality and NO_x in the general population are presented in **Figure 3.2**. For the general population, six studies, with the exception of Andersson et al. (2020) which provided HRs by exposure quintile, were included in the meta-analysis with REs ranging from 0.98 to 1.08 per $10 \mu\text{g}/\text{m}^3$ NO_x . The pooled RE for the association between NO_x and all-cause mortality in the general population was positive and borderline significant with a HR of 1.02 (95% CI: 0.99–1.06; $I^2 = 88.02\%$). Heterogeneity was substantial and was largely attributed to Nafstad et al. (2004) as no heterogeneity ($I^2 = 0.00\%$) was observed when this study was removed from the meta-analysis in the leave-one-out analysis.

FIGURE 3.2: Association between all-cause mortality and long-term exposure to NO_x in the general population



Subgroup analysis based on exposure assessment methodology indicated associations similar to the main analysis when the analysis was limited to studies using LUR modelling and dispersion modelling with pooled REs of 1.01 (95% CI: 1.00–1.03; I² = 0.00%) and 1.03 (95% CI: 0.92–1.16; I² = 91.34%), respectively. No heterogeneity was observed for pooled studies using LUR modelling to assess NO_x exposure; in contrast, heterogeneity was greater than the main analysis when limited to studies using dispersion modelling. Sensitivity analysis with respect to RoB showed robust associations between NO_x and all-cause mortality when only studies with low or probably low RoB for the exposure domain or confounder domain were included; the same study (Bauleo et al., 2019) was excluded for each of these analyses, resulting in a pooled RE of 1.03 (95% CI: 0.99–1.07; I² = 89.75%). Leave-one-out analysis indicated that the main analysis was robust as the pooled RE ranged from 1.01 to 1.03 and that Nafstad et al. (2004) was the main source of heterogeneity as omitting this study removed heterogeneity from the main analysis (I² = 0.00%). Publication bias was assessed but may be of limited use as fewer than 10 studies were included in the meta-analysis. The asymmetric distribution of the funnel plot indicated some evidence of a publication bias but this was not supported by either Egger’s (p = 0.4660) or Begg’s (p = 1.0000) tests. Additionally, the trim-and-fill method suggested that two hypothetical studies are needed to make the funnel plot symmetrical.

Four studies examined the association between long-term exposure to NO_x and all-cause mortality in patient populations (Appendix A.2). Two of these studies were conducted in stroke (Desikan et al., 2016) and MI (Tonne et al., 2016) patients in London, United Kingdom. The other two studies were conducted in Israel in patients undergoing percutaneous coronary interventions (Cohen et al., 2019) and in CHD patient cohorts that were matched to population-based cohorts (Cohen et al., 2021).

The cohort size of these studies ranged from 1,800 (Desikan et al., 2016) to 18,138 (Tonne et al., 2016). For the exposure assessment, Desikan et al. (2016) and Tonne et al. (2016) used dispersion modelling and Cohen et al. (2021) used LUR modelling, while Cohen et al. (2019) used three different methods (i.e., dispersion modelling, LUR modelling, and hybrid modelling) to estimate exposure to NO_x . All studies accounted for the key confounders of age, sex, SES, and smoking, with the exception of Desikan et al. (2016) whose study did not adjust for smoking. As summarized in Appendix A.2, four of the six REs pertaining to patient populations were positive of which one was statistically significant. As only three of these REs could be pooled, meta-analysis was not conducted.

NO

The literature searches identified two studies evaluating the association between all-cause mortality and NO; both were based on the general population. The study details are depicted in Appendix A.3. One study was conducted on a cohort of 1,800 participants in London, United Kingdom (Desikan et al., 2016) and the other on a cohort of 60,548 participants residing in Hong Kong, China (Barratt et al., 2018). Both studies estimated exposure at the residential address; one used dispersion modelling (mean NO = 34.39 $\mu\text{g}/\text{m}^3$; Desikan et al., 2016) while the other used an LUR model (mean NO = 489 $\mu\text{g}/\text{m}^3$; Barratt et al., 2018). Both studies also included adjustments for the key confounders of age, sex, and SES, as well as additional confounders, but Desikan et al. (2016) did not adjust for smoking. As indicated in Appendix A.3, neither RE indicated an association.

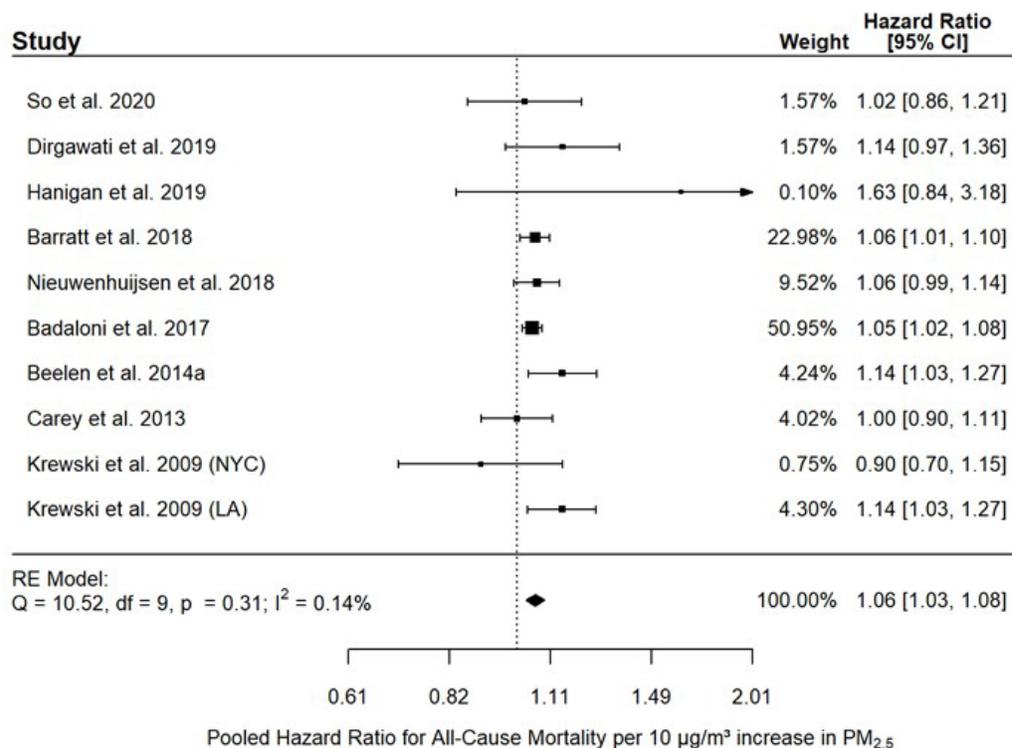
3.2.2. PM

PM_{2.5}

The literature searches identified 15 studies evaluating the association between all-cause mortality and PM_{2.5} that was indicative of TRAP exposure (section 2.1.2). Study details including study population, exposure assessment, confounders, and REs are provided in Appendix A.4. A majority of the studies were conducted in Europe (n = 9); no studies conducted in Canada were identified in the literature searches. Most of the studies were conducted in general population cohorts (n = 13) and these cohorts ranged in size from 11,627 (Dirgawati et al., 2019) to 1,265,058 (Cesaroni et al., 2013). For exposure assessment, the most common methods were LUR (n = 7) and dispersion modelling (n = 6), and exposures were assigned based on the residential address, postal code, or census tract. The lowest mean or median exposures were estimated for a study conducted in Australia (4.49 $\mu\text{g}/\text{m}^3$; Hanigan et al., 2019) and the highest exposure was estimated for a study conducted in Hong Kong, China (42.4 $\mu\text{g}/\text{m}^3$; Barratt et al., 2018). Each of the studies included adjustments for the key confounders of age, sex, and SES, and typically included additional confounders. With respect to smoking, three studies did not include adjustment, either direct or indirect, for individual-level smoking (Naess et al., 2007; Cesaroni et al., 2013; Desikan et al., 2016).

Summarized in Appendix A.4 is the most appropriately adjusted RE identified from each study. For the general population-based studies, 11 of 13 REs were positive, and 7 were statistically significant and 4 were borderline significant. The forest plot and random-effects meta-analysis for all-cause mortality and PM_{2.5} are presented in **Figure 3.3**. Ten studies were included in the meta-analysis with standardized REs ranging from 0.90 to 1.63. The pooled RE for the association between PM_{2.5} and all-cause mortality was significant at 1.06 (95% CI: 1.03–1.08) and the heterogeneity was minimal and likely not of importance ($I^2 = 0.14\%$).

FIGURE 3.3: Association between all-cause mortality and long-term exposure to PM_{2.5} in the general population



As the primary studies were evaluated as low or probably low RoB for the exposure and confounding domains, a sensitivity analysis based on RoB was not performed. Subgroup analysis based on the exposure assessment method (i.e., LUR modelling or dispersion modelling) did not indicate a difference from the main analysis. Leave-one-out analysis indicated that the main analysis was robust (pooled RE varied between 1.05 and 1.07) and no one study distorted the overall results. Neither test for publication bias indicated the presence of a bias (Egger’s test $p = 0.359$; Begg’s test $p = 1.000$). Also, trim-and-fill analysis indicated that one hypothetical study would be required to make the funnel plot symmetrical.

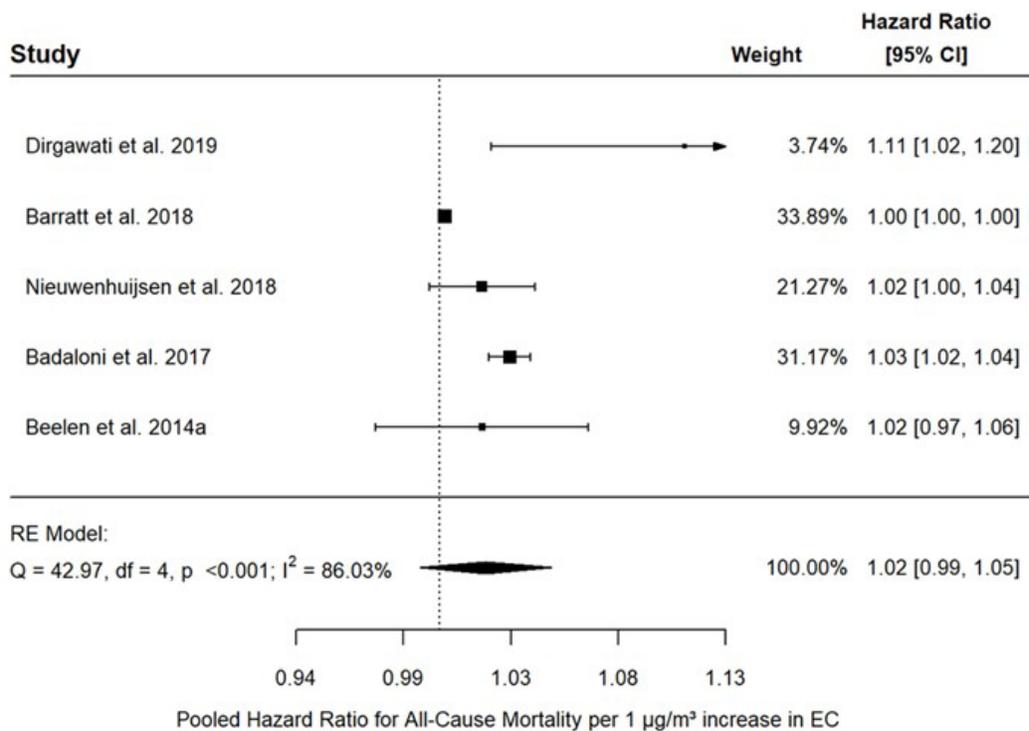
Two studies based on patient populations were identified in the literature search. Both studies were conducted in London, United Kingdom; one was based on stroke patients (N = 1800) (Desikan et al., 2016) and one on MI patients (N = 18,138) (Tonne et al., 2016). Both studies used dispersion modelling to estimate PM_{2.5} exposure. Tonne et al. (2016) considered PM_{2.5} from traffic exhaust sources and PM_{2.5} from traffic non-exhaust sources (i.e., brake dust, tire wear, and dust resuspension). Each of the three REs were positive and significant or borderline significant (Appendix A.4), and the REs were similar for both the traffic and non-traffic exhaust sources. Desikan et al. (2016) reported a stronger, though less precise, association for the stroke patients (HR = 1.28, 95% CI: 1.08–1.52, per 1.86 µg/m³) compared with the associations reported in the general population studies.

EC, PM_{2.5 abs'} and BC

Seven studies that evaluated exposure to EC, PM_{2.5 abs'} or BC and the risk of mortality were identified; study details are provided in Appendix A.5. Given the similar interpretation of the TRAP-surrogates, BC and PM_{2.5 abs} were converted to EC-equivalent estimates to support pooling of the studies in a meta-analysis (as described in section 2.2.3). The studies were conducted in Europe (n = 3), Asia (n = 2), the USA (n = 1), and Australia (n = 1); the literature searches did not identify any studies conducted in Canada. Six of the studies considered the general population while one considered a patient population. For the general population studies, study size ranged from 11,627 (Dirgawati et al., 2019) to 1,249,108 (Badaloni et al., 2017). Each of these studies utilized LUR modelling to estimate exposure at residential address, and, based on EC-equivalents, the mean or median exposures ranged from 0.55 (Beelen et al., 2014a) to 16.4 µg/m³ (Barratt et al., 2018). Adjustments for the key confounders of age, sex, and SES were accounted for in each of the studies; a direct or indirect adjustment for smoking was accounted for in each study, except for Badaloni et al. (2017).

Summarized in Appendix A.5 is the most appropriately adjusted RE identified from each study. For the general population, all six REs were positive; two were significant and the other four were borderline significant. The forest plot and random-effects meta-analysis for all-cause mortality and EC are presented in **Figure 3.4**. Five studies were included in the meta-analysis with standardized REs ranging from 1.00 to 1.11. The pooled RE for the association between EC exposure and all-cause mortality was 1.02 (95% CI: 0.99–1.05) with substantial heterogeneity ($I^2 = 86.03\%$).

FIGURE 3.4: Association between all-cause mortality and long-term exposure to EC in the general population



As the primary studies were evaluated as low or probably low RoB for the exposure and confounding domains, a sensitivity analysis based on RoB was not performed. Similarly, as each of the studies used LUR models, no subgroup analysis based on exposure assessment was performed. Leave-one-out analysis indicated the results were robust as the pooled RE ranged from 1.01 to 1.03. There was no indication of publication bias, as trim-and-fill analysis did not identify any missing studies and the tests did not indicate a bias (Egger's test $p = 0.1895$; Begg's test $p = 0.8167$).

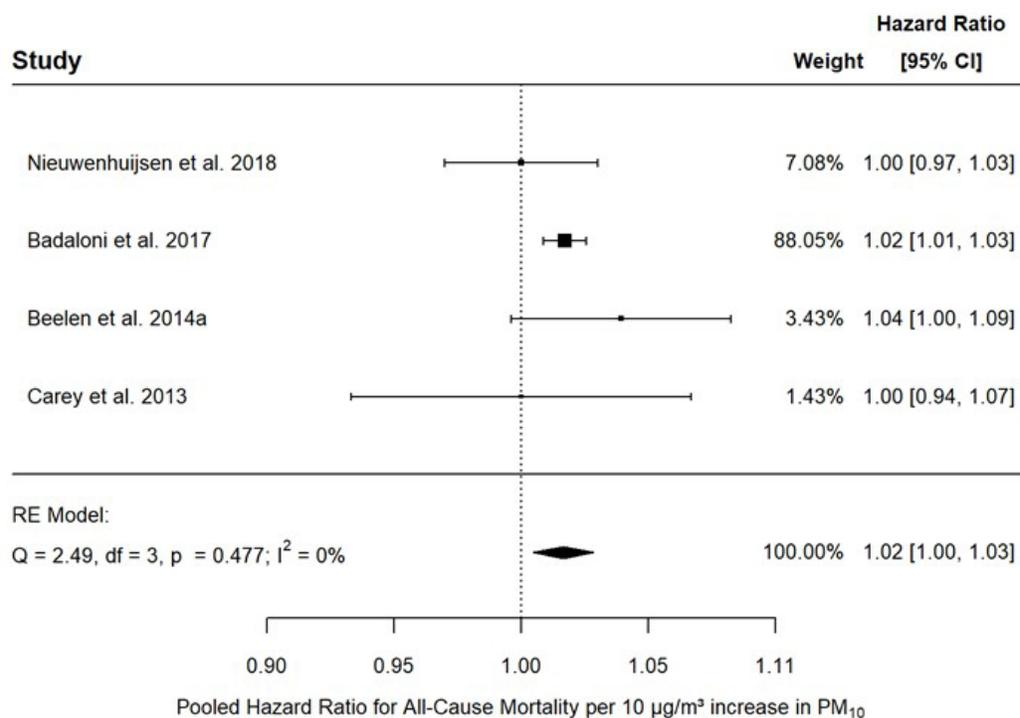
The one patient population study was conducted in the USA based on adults hospitalized with acute MI (von Klot et al., 2009; summarized in Appendix A.5). The study identified a significant positive association between all-cause mortality and EC exposure, and included adjustments for age, sex, SES, and smoking. As only the single study was identified, a meta-analysis was not conducted.

PM₁₀ and PM_{coarse}

The literature searches identified seven studies of PM₁₀ and two studies of PM_{coarse} that evaluated an association with all-cause mortality. As the literature available for PM_{coarse} is limited, this assessment will focus on the PM₁₀ literature. Study details including study population, exposure assessment, confounders, and REs are provided in Appendix A.6. Each of the studies was conducted in Europe, with four based on the general population and three based on patient populations. No studies conducted in Canada were identified in the literature searches. For the general population studies, the sample sizes were large, ranging from 322,159 (Beelen et al., 2014a) to 1,249,108 (Badaloni et al., 2017). For the exposure assessment, three of the studies employed LUR models and one utilized dispersion modelling, and exposures were assigned based on the residential address, postal code, or census tract. For PM₁₀, the mean exposures ranged from 13.5 to 48.1 $\mu\text{g}/\text{m}^3$ (Beelen et al., 2014a). Each of the studies adjusted for the key confounders of age, sex, SES, and directly or indirectly adjusted for smoking, except for Badaloni et al. (2017), which did not account for smoking.

Summarized in Appendix A.6 is the most appropriately adjusted RE identified from each study. For the general population, two of four REs for PM₁₀ were positive and significant or borderline significant, and two indicated a null effect. The forest plot and random-effects meta-analysis for all-cause mortality and PM₁₀ are presented in **Figure 3.5**. All of the general population studies were included in the meta-analysis; the standardized REs ranged from 1.00 to 1.04 and the pooled RE was 1.02 (95% CI: 1.00–1.03). No heterogeneity ($I^2 = 0.00\%$) was noted for this main analysis.

FIGURE 3.5: Association between all-cause mortality and long-term exposure to PM₁₀ in the general population



As each of the primary studies in the main analysis was evaluated as low or probably low RoB for the exposure and confounding domains, a sensitivity analysis based on RoB was not performed. Subgroup analysis based on the exposure assessment method (i.e., LUR modelling or dispersion modelling) did not indicate a difference from the main analysis. Leave-one-out analysis did not indicate that any one study was influencing the main analysis (pooled RE = 1.01–1.02). There was no indication of publication bias, as trim-and-fill analysis did not identify any missing studies and the tests did not indicate a bias (Egger’s test $p = 0.8851$; Begg’s test $p = 1.000$).

Three studies based on patient populations were identified. Each of the studies was conducted in London, United Kingdom. Two considered stroke patients and one considered MI patients (summarized in Appendix A.6). The cohorts ranged in size from 1,800 (Desikan et al., 2016) to 18,128 (Tonne et al., 2016). Two of the studies used dispersion modelling and one used hybrid modelling. For PM₁₀, both REs were positive and significant or borderline significant. Tonne et al. (2016) evaluated the association of PM₁₀ from exhaust and non-exhaust sources separately, and both REs were positive and borderline significant. The mean exposures were an order of magnitude smaller in Tonne et al. (2016) compared with the other patient population studies. Due to the small number of studies, a meta-analysis was not conducted.

3.2.3. Other TRAP pollutants: benzene

Only one study that examined the association between long-term exposure to benzene, as a marker of TRAP, and all-cause mortality was identified in the literature searches. This Canadian study by Villeneuve et al. (2013) was conducted in the general population of Ontario, accounted for the key confounders including indirect adjustment for smoking, and reported a significant, positive association (summarized in Appendix A.7).

3.2.4. Traffic and the road network infrastructure

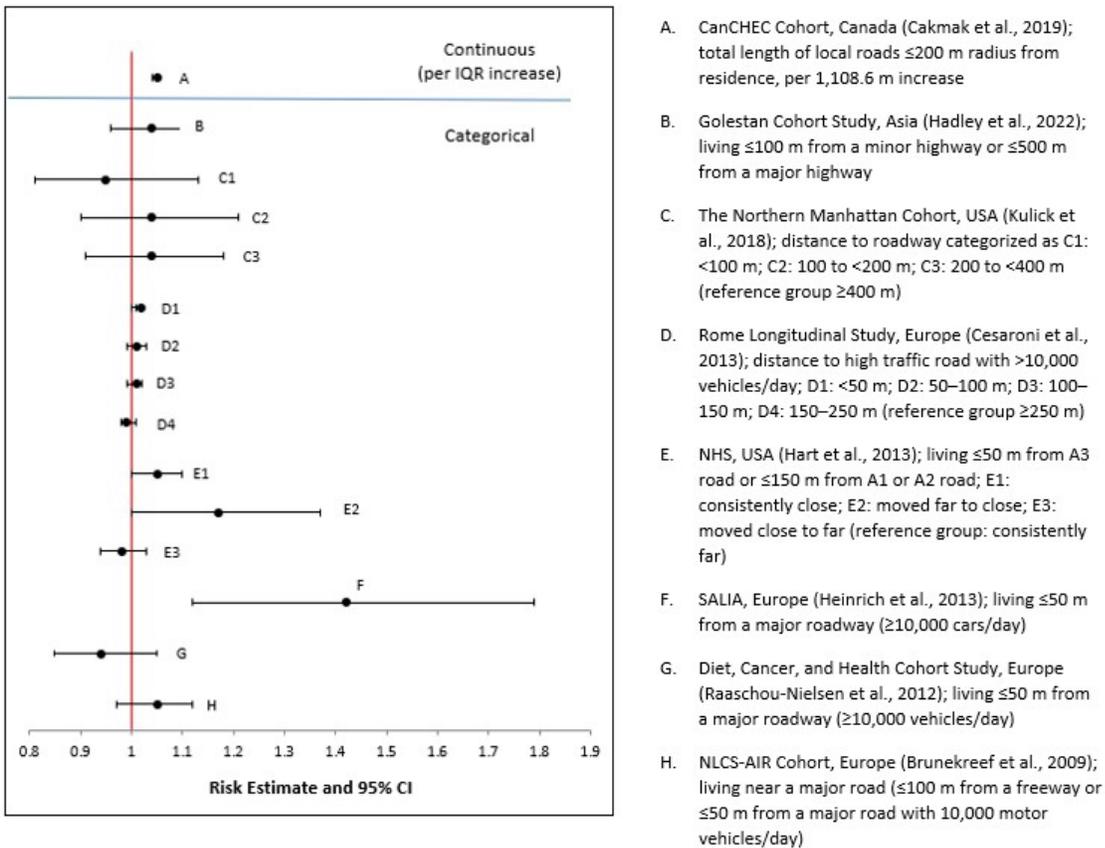
Traffic proximity

Traffic proximity or distance to roadway was the most commonly used metric of traffic and the road network infrastructure that examined the association between traffic and all-cause mortality with 18 studies, of which 11 were conducted on the general population and 7 on various patient populations. The study details regarding study population, exposure assessment, confounders, and REs are provided in Appendix A.9.

For the general population, the majority of the studies were conducted in Europe ($n = 7$) followed by the USA ($n = 2$), Canada ($n = 1$), and Asia ($n = 1$). They ranged in size from 3,287 (Kulick et al., 2018) to 2,644,370 (Cakmak et al., 2019). All the studies conducted in the USA, Canada, and Asia were based on unique cohorts while those conducted in Europe were based on four cohorts: NLCS-AIR (Hoek et al., 2002; Beelen et al., 2008; Brunekreef et al., 2009); SALIA (Gehring et al., 2006); the Diet, Cancer, and Health Cohort Study (Raaschou-Nielsen et al., 2012); and the Rome Longitudinal Study (Cesaroni et al., 2013). All studies accounted for the key confounders of age, sex, and SES (individual- and/or area-level) and all but two studies (Cesaroni et al., 2013; Cakmak et al., 2019) also adjusted for smoking. Many studies also considered additional confounders. Proximity to traffic was directly measured in a geographic information system (GIS) and was based on the exact residential address for all but two studies. The Canadian study used the residential postal code centroid (Cakmak et al., 2019) while the study conducted in Iran used the geographic centre of each village for rural residents and the location of the primary health centre for urban residents (Hadley et al., 2022). No consistent definitions or categories were used to assess traffic proximity across the studies.

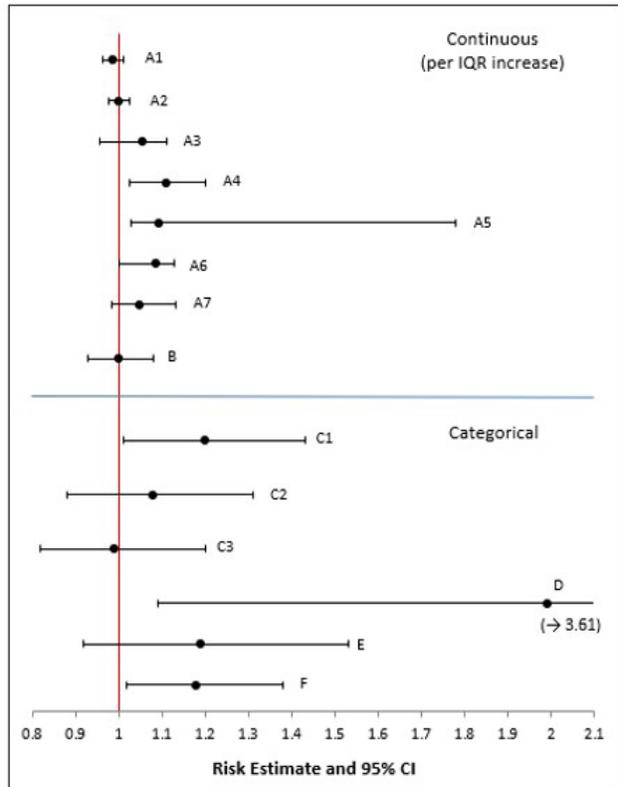
The associations between traffic proximity and risk of all-cause mortality in the general population are summarized in **Figure 3.6**; only unique cohorts and non-transformed data are included in the forest plot. Two studies considered traffic proximity as a continuous variable. In a Canada-wide study, Cakmak et al. (2019) reported a positive and significant association. In comparison, Kulick et al. (2018) did not observe any association based on log-transformed proximity. When traffic proximity was evaluated as a categorical variable, 10 of the 14 REs were positive, of which one was significant and the remainder were borderline significant. Of the three studies that examined exposure-response relationships, Cesaroni et al. (2013) and Hart et al. (2013) identified an increased risk with increased exposure while Kulick et al. (2018) did not.

FIGURE 3.6: Forest plot of risk estimates for long-term exposure to traffic proximity and all-cause mortality in the general population



Traffic proximity and risk of all-cause mortality were also examined in a diverse group of patient populations (summarized in Appendix A.9 and **Figure 3.7**). These studies were conducted in Canada ($n = 2$), the USA ($n = 2$), and Europe ($n = 3$). With the exception of one study that did not account for any confounders (Finkelstein et al., 2004), all accounted for age and sex, five accounted for SES, and three accounted for smoking; many studies also accounted for additional confounders. For the majority of the studies, exposure was based on the exact residential address while two studies used postal or ZIP code to assign exposure (Finkelstein et al., 2004; Medina-Ramón et al., 2008). For the two studies that assessed exposure as a continuous variable (Medina-Ramón et al., 2008; Ruttens et al., 2017), no association was observed based on distance to a major road or freeway. Ruttens et al. (2017) identified positive associations that were significant or borderline significant when considering the total length of roads in buffer zones, with the greatest risk for a 100-m buffer zone. Goeminne et al. (2014) reported that each 10-fold increase in the distance to a major road resulted in a significant lower risk of dying (HR = 0.28; 95% CI: 0.10–0.77). When traffic proximity was evaluated as a categorical variable, positive associations that were significant or borderline significant were observed, and Wilker et al. (2013) observed an exposure-response relationship.

FIGURE 3.7: Forest plot of risk estimates for long-term exposure to traffic proximity and all-cause mortality in patient populations



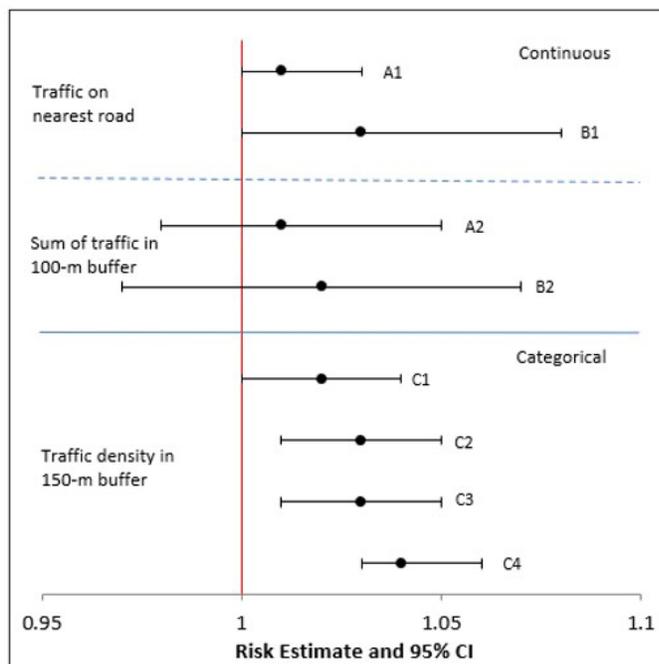
- A. Lung transplant patients across 10 European countries (Ruttens et al., 2017); A1: distance to freeway, per 1,233 m; A2: distance to major road, per 241 m; total road length within different buffers: A3: 50 m, per 108 m; A4: 100 m, per 279 m; A5: 200 m, per 756 m; A6: 500 m, per 4,092 m; A7: 1000 m, per 15,403 m
- B. Worcester Heart Failure Study, USA (Medina-Ramón et al., 2008); distance to major roadway, per 2,008 m
- C. Ischemic stroke patients, USA (Wilker et al., 2013); distance to roadway with >10,000 vehicles/day; C1: ≤100 m; C2: >100 to 200 m; C3: >200 to 400 m (reference >400 m)
- D. Lung transplant patients with long-term follow-up at UZ Leuven, Belgium (Nawrot et al., 2011); living ≤171 m from a major road
- E. Patients from a respiratory disease clinic, Canada (Jerrett et al., 2009); living ≤50 m from a major road or ≤100 m from a highway
- F. Pulmonary function testing at clinic, Canada (Finkelstein et al., 2004); living ≤50 m from a major road or ≤100 m from a highway

Traffic density

The literature search identified nine studies that evaluated the association between traffic density and all-cause mortality; five studies were conducted in the general population and four considered patient populations. Study details including study population, exposure assessment, confounders, and REs are provided in Appendix A.10. For the general population studies, each was conducted in Europe and considered risks in the general population. They ranged in size from 52,061 (Raaschou-Nielsen et al., 2012) to 1,265,058 (Cesaroni et al., 2013). Beelen et al. (2008) and Brunekreef et al. (2009) were conducted with the same cohort and had identical results. Each of the studies accounted for the key confounders of age, sex, and SES, and smoking was accounted for in each of the studies, except for Cesaroni et al. (2013).

The REs for traffic density and all-cause mortality in the general population are summarized in a forest plot (**Figure 3.8**). Both the ESCAPE study (Beelen et al., 2014a) and NLCS-AIR Cohort (Brunekreef et al., 2009) considered traffic as a continuous variable. For both these studies, positive, borderline-significant associations were observed when evaluated based on traffic on the nearest road to the residence and sum of traffic in a 100-m buffer around the residence. Cesaroni et al. (2013) evaluated quintiles of traffic density in a 150-m buffer around the residence and identified a positive association for each quintile and a significant trend increasing risk ($p < 0.001$).

FIGURE 3.8: Forest plot of risk estimates for long-term exposure to traffic density and all-cause mortality in the general population



- A. ESCAPE, Europe (Beelen et al., 2014a); A1: traffic on nearest road (per 5,000 vehicles/day); A2: sum of traffic intensity in 100-m buffer (per 4×10^6 vehicle-m/day)
- B. NLCS-AIR Cohort, Europe (Brunekreef et al., 2009); B1: traffic on nearest road (per 10,000 vehicles/day); B2: sum of traffic intensity in 100-m buffer (per 335,000 vehicles/day)
- C. Rome Longitudinal Study, Europe (Cesaroni et al., 2013); traffic density in 150-m buffer (vehicle-m/day); C1: $(0.25-1.63) \times 10^6$; C2: $(1.63-3.23) \times 10^6$; C3: $(3.23-6.66) \times 10^6$; C4: $\geq 6.66 \times 10^6$ (reference: $< 0.25 \times 10^6$)

Four studies conducted in patient populations were identified in the literature search (summarized in Appendix A.10). These studies, representing a diverse group of patient populations, were conducted in the USA ($n = 2$) and Europe ($n = 2$), and had a wide range of study sizes (183 [Goeminne et al., 2014] to 32,875 [Blount et al., 2017]). Each of the studies accounted for key confounders of age, sex, and SES, while smoking was only accounted for in Goeminne et al. (2014) and Tonne et al. (2016). A positive, borderline significant or significant association between traffic density and all-cause mortality was observed in each study.

3.2.5. Summary

The association between TRAP and all-cause mortality has been investigated in 47 cohort studies. The majority of these studies were based on a general population and were conducted in Europe. Over 60% of the studies assessed exposure to TRAP by modelling individual pollutants, while the remainder used metrics of traffic and the road network infrastructure as indirect measures of exposure. Nearly all the studies accounted for the key confounders of age, sex, SES, and smoking and many considered additional confounders. For the pooled analyses based on the general population, a positive association was determined for each of the pollutants evaluated (i.e., NO_2 , NO_x , $\text{PM}_{2.5}$, EC, and PM_{10}), and these associations with pooled REs ranging from 1.02 to 1.06 were significant for NO_2 and $\text{PM}_{2.5}$ and borderline significant for NO_x , EC, and PM_{10} . While there was no or little heterogeneity for $\text{PM}_{2.5}$ and PM_{10} , heterogeneity was substantial for NO_2 , NO_x , and EC.

The results from the pooled analyses was supported by the qualitative analysis of the different metrics for traffic and the road network infrastructure, which also provided some indication of an exposure-response relationship. For patient populations, pooled analysis could only be conducted for NO₂, where a positive non-significant association was observed for patients with a cardiovascular etiology. For NO and benzene, the evidence was limited and did not support conducting a pooled analysis.

3.3. CIRCULATORY MORTALITY

Circulatory mortality (also referred to as cardiovascular mortality) was evaluated in 41 of the 64 articles evaluating the association between long-term exposure to TRAP and mortality. An evaluation of the studies examining the effects of long-term exposure to TRAP and circulatory mortality are presented below by TRAP pollutant or metric. These studies evaluated mortality from circulatory system diseases (CSD) as a group, as well as from more specific causes (e.g., CHD [also referred to as IHD], MI, heart failure [HF], and cerebrovascular disease [CBVD], including stroke). In the few instances that studies reported cardiopulmonary or cardiorespiratory mortality without presenting the results for circulatory and respiratory mortality separately, the studies were considered a measure of circulatory mortality, as these causes dominate the combined category (HEI, 2022). Similarly, as stroke is the most common cause of CBVD, and consistent with the approach taken by HEI (2022), CBVD mortality and stroke mortality were pooled for meta-analysis or qualitatively evaluated together in the absence of a quantitative analysis.

3.3.1. Nitrogen oxides (NO, NO₂, and NO_x)

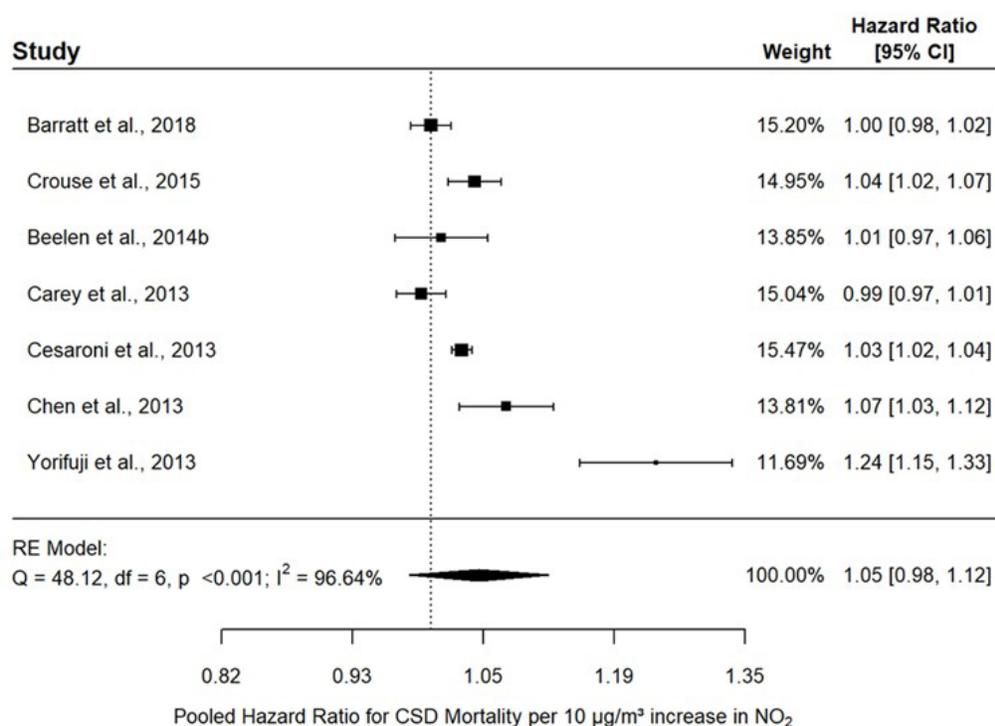
NO₂

For NO₂ studies (n = 19), details including study population, exposure assessment, confounders, and REs are provided in Appendix A.1. Most of the studies were conducted in Europe (n = 8), Canada (n = 5), and Asia (n = 4). Two of the studies had a case-control study design (Rosenlund et al., 2006, 2009), and the rest were cohort studies. All but one Canadian study (Jerrett et al., 2009) were drawn from the general population with a study size ranging from 3,210 (Rosenlund et al., 2006) to 1,265,058 (Cesaroni et al., 2013). For exposure assessment of the studies conducted in the general population, LUR modelling (n = 12) was the most common method used, followed by dispersion modelling (n = 4) and hybrid modelling (n = 2). Exposures were assigned based on the residential address, postal code, census block, or at the neighborhood level, with the mean (or median) exposures ranging from 5.2 to 107 µg/m³. The lowest exposures were assigned to one of the Swedish cohorts included in the ESCAPE study (Beelen et al., 2014a) while the highest exposures were noted in a study conducted in Hong Kong, China (Barratt et al., 2018). Studies conducted in the general population each examined one or more endpoints pertaining to circulatory mortality, including mortality from CSD (n = 12), CHD (n = 12), CBVD (n = 10) and stroke (n = 1), MI (n = 3), and dysrhythmias, HF, and cardiac arrest (n = 2). All 18 studies accounted for age and sex, as well as individual SES and/or area-level SES; 5 studies did not adjust for smoking (Naess et al., 2007; Rosenlund et al., 2008, 2009; Gan et al., 2011; Cesaroni et al., 2013). Many studies also considered additional confounders.

The most appropriately adjusted RE identified from each study for each relevant outcome pertaining to circulatory mortality is also specified in Appendix A.1.

For the general population, 12 of the 15 REs pertaining to CSD mortality were positive, of which 7 were statistically significant and 5 were borderline significant. Four of these REs were derived from the same study (Naess et al., 2007) and correspond to different age groups and sex. The forest plot and results of the random-effects meta-analysis for CSD mortality and NO₂ are presented in **Figure 3.9**. Seven studies were included in the meta-analysis for the general population with REs ranging from 0.99 to 1.24. The pooled RE for the association between NO₂ and CSD mortality was borderline significant at 1.05 (95% CI: 0.98–1.12) with considerable heterogeneity ($I^2 = 96.64\%$).

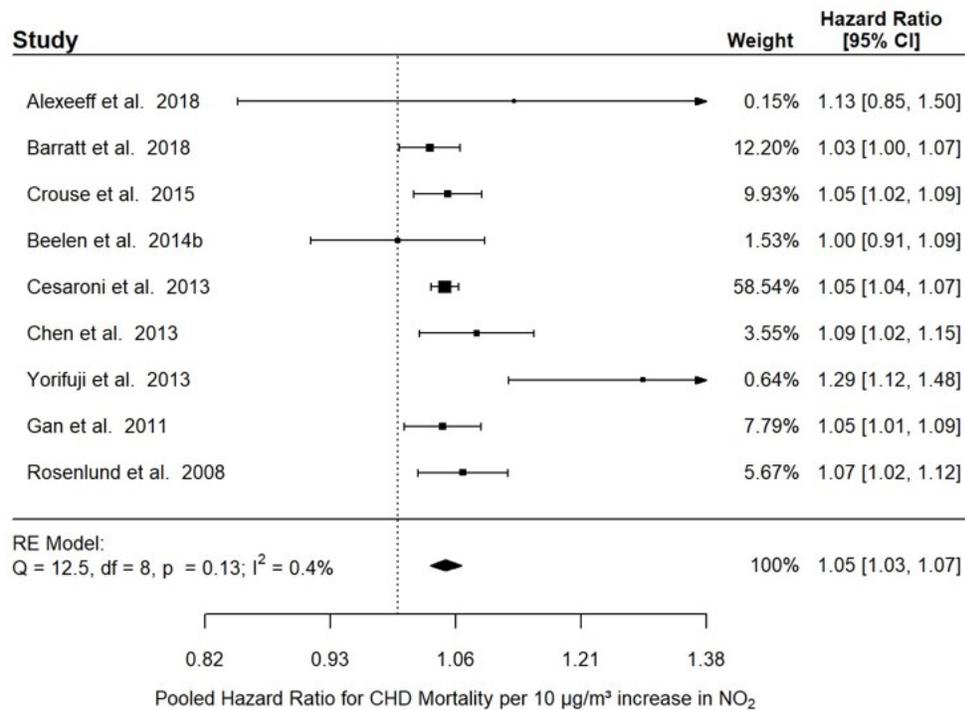
FIGURE 3.9: Association between CSD mortality and long-term exposure to NO₂ in the general population



Heterogeneity remained considerable ($I^2 = 96.68\%$) when the analysis was limited to studies that used LUR models (RE: 1.06; 95% CI: 0.98–1.14), which included all but one study from the main analysis. Sensitivity analysis based on RoB was not done for the exposure domain as all the studies included in the meta-analysis scored low or probably low for this domain, but when the analysis was limited to studies with low and probably low RoB for the confounder domain, the pooled RE was robust (RE: 1.05; 95% CI: 0.97–1.14) and heterogeneity was unchanged ($I^2 = 95.7\%$). Leave-one-out analysis indicated that the results were robust for all studies with the exception of Yorifuji et al. (2013); removing the latter resulted in a lower pooled RE of 1.02 and reduced heterogeneity ($I^2 = 80.96\%$). Although the Egger’s test indicated evidence of a publication bias ($p = 0.04067$), this was not supported by the Begg’s test ($p = 0.2389$) or the trim-and-fill analysis, which did not identify any missing studies.

For CHD mortality in the general population, 11 of the 12 REs were positive, of which 7 were statistically significant and 2 were borderline significant. The forest plot and results of the random-effects meta-analysis for CHD mortality and NO₂ are presented in **Figure 3.10**. Nine studies were included in the meta-analysis for the general population with REs ranging from 1.00 to 1.29. The pooled RE for the association between NO₂ and CHD mortality was significant at 1.05 (1.03–1.07) and the heterogeneity was minimal and likely not of importance (*I*² = 0.4%).

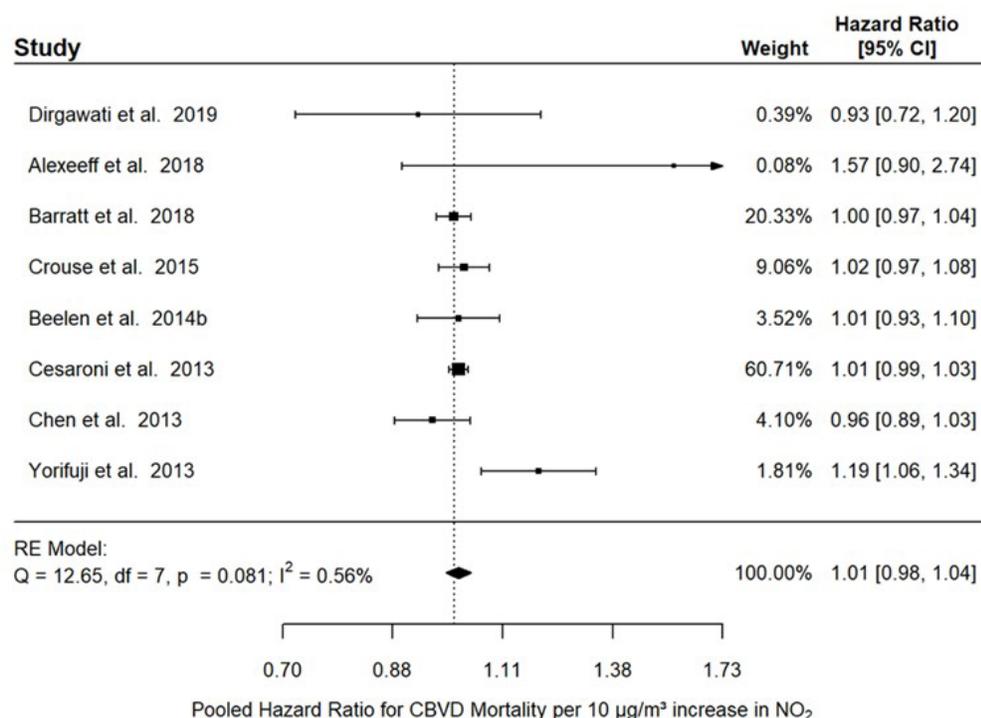
FIGURE 3.10: Association between CHD and long-term exposure to NO₂ in the general population



As all the primary studies included in the meta-analysis used LUR models to assess exposure and were evaluated as low or probably low RoB for the exposure domain, subgroup analysis by exposure assessment and sensitivity analysis based on RoB for the exposure domain were not performed. When analysis was limited to studies with low and probably low RoB for the confounder domain, which excluded three studies (i.e., Rosenlund et al., 2008, Gan et al., 2011, and Cesaroni et al., 2013), the pooled RE was robust (RE: 1.06) but there was increased uncertainty around the RE (95% CI: 0.99–1.14) and heterogeneity became substantial (*I*² = 61.9%). Leave-one-out analysis did not indicate that any one study was influencing the main analysis; the association remained significant with a pooled RE = 1.05. Neither test for publication bias suggested the presence of a bias (Egger’s test *p* = 0.2371; Begg’s test *p* = 0.1194) while trim-and-fill analysis indicated that two hypothetical studies would be required to make the funnel plot symmetrical.

For CBVD mortality (including stroke mortality) in the general population, 7 of the 11 REs were positive, of which 1 was statistically significant and 5 were borderline significant. The forest plot and results of the random-effects meta-analysis for CBVD mortality and NO₂ are presented in Figure 3.11. Eight studies were included in the meta-analysis for the general population with REs ranging from 0.93 to 1.57. The pooled estimate for the association between NO₂ and CBVD mortality was borderline significant at 1.01 (95% CI: 0.98–1.04) and the heterogeneity was minimal and likely not of importance ($I^2 = 0.56\%$).

FIGURE 3.11: Association between CBVD mortality and long-term exposure to NO₂ in the general population



Subgroup analysis by exposure assessment and sensitivity analysis based on RoB for the exposure domain were not performed as all the primary studies included in the meta-analysis used LUR modelling or hybrid modelling to assess exposure and were evaluated as low or probably low RoB for the exposure domain. When analysis was limited to studies with low and probably low RoB for the confounder domain, which included all but Cesaroni et al. (2013), the pooled estimate was robust (RE: 1.02) but heterogeneity became moderate ($I^2 = 50.81\%$). Limiting the analysis to studies exclusively evaluating CBVD mortality (i.e., excluding stroke mortality) did not change the pooled estimate (RE: 1.01) or the heterogeneity ($I^2 = 0.54\%$). Similarly, leave-one-out analysis did not indicate that any one study was influencing the main analysis (pooled RE = 1.01–1.02). Neither test for publication bias indicated the presence of a bias (Egger’s test $p = 0.4139$; Begg’s test $p = 0.7195$) while trim-and-fill analysis indicated that one hypothetical study would be required to make the funnel plot symmetrical.

A limited number of studies (three or less) were identified in the literature searches pertaining to NO₂ exposure and MI mortality, dysrhythmias, HF, and cardiac arrest mortality in the general population; these studies reported mostly positive associations that were borderline significant or significant.

The only study to examine the association between long-term exposure to NO₂ and circulatory mortality in a patient population was conducted in adult patients from a respiratory disease clinic in Toronto, Ontario, (Jerrett et al., 2009). This Canadian study accounted for the key confounders including smoking, and reported a significant, positive association between NO₂ and CSD mortality (summarized in Appendix A.1).

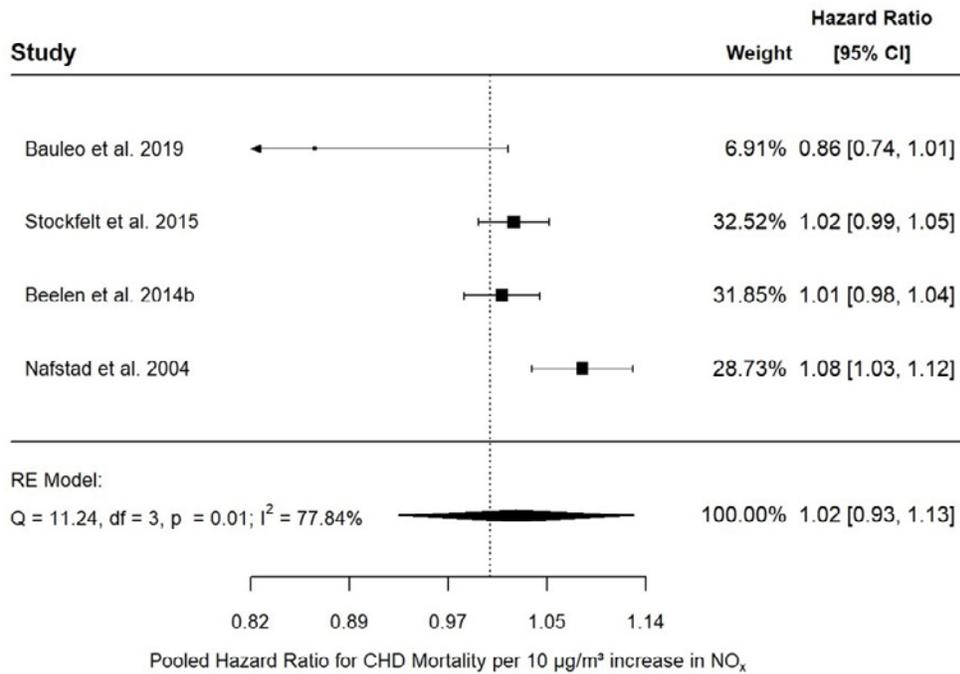
NO_x

For NO_x, seven studies examined the association between long-term exposure to NO_x and circulatory causes of mortality; the study details are depicted in Appendix A.2. They were conducted in Europe (n = 6) and Australia (n = 1) and all were drawn from the general population with cohorts ranging in size from 6,304 (Andersson et al., 2020) to 367,383 (Beelen et al., 2014a). The majority of the studies used dispersion modelling (n = 5) followed by LUR modelling (n = 2) to assess NO_x exposure and all studies assigned NO_x exposure at the residential address; the mean (or median) exposures ranged from 5.80 to 107.3 µg/m³. The lowest exposures were estimated in a study conducted in Civitavecchia, Italy (Bauleo et al., 2019) while the highest exposures were modelled in one of the Italian cohorts included in the ESCAPE study (Beelen et al., 2014a). The studies each examined one or more endpoints pertaining to circulatory mortality, including mortality from CSD (n = 4), CHD (n = 4), CBVD (n = 4) and stroke (n = 1), MI (n = 3), cardiac diseases (n = 1), and acute coronary events (ACE; n = 1). All studies accounted for the key confounders of age, sex, and SES (individual- and/or area-level) and all but one study (Bauleo et al., 2019) also adjusted for smoking. Additional confounders were also considered in these studies.

The most appropriately adjusted RE from each study for each relevant outcome pertaining to circulatory mortality is summarized in Appendix A.2.

For CHD mortality, three of the four REs were positive of which two were borderline significant and one was statistically significant. The forest plot and results of the random-effects meta-analysis for CHD mortality and NO_x in the general population are presented in **Figure 3.12**. Four studies were included in the meta-analysis with REs ranging from 0.86 to 1.08. The pooled RE for the association between NO_x and CHD mortality was borderline significant at 1.02 (95% CI: 0.93–1.13) and the heterogeneity was substantial (I² = 77.84%).

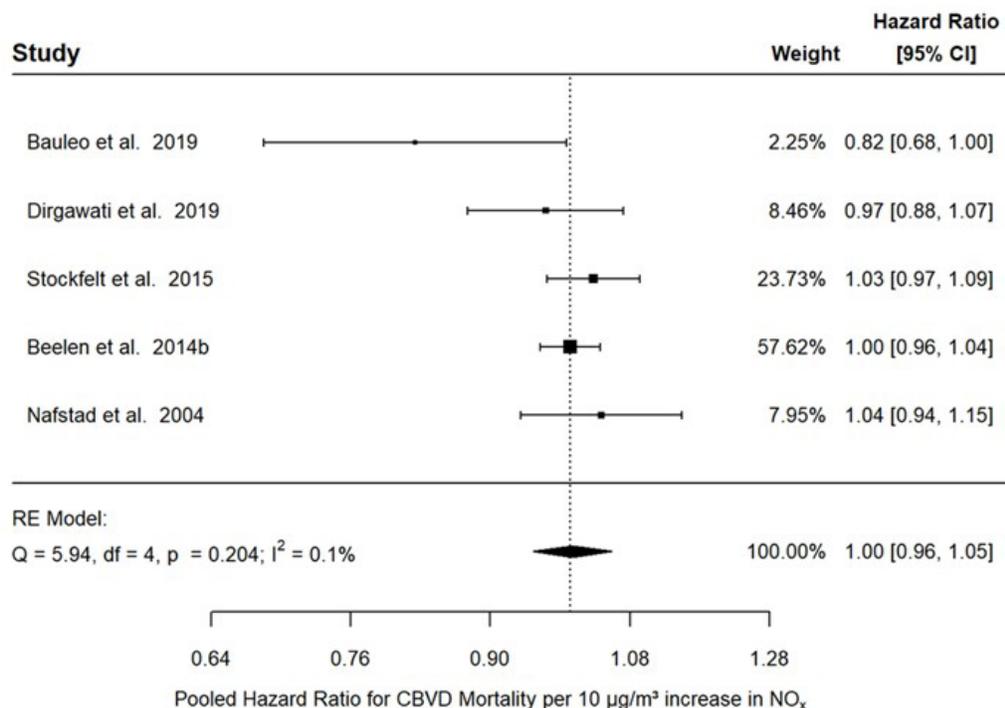
FIGURE 3.12: Association between CHD mortality and long-term exposure to NO_x in the general population



When the analysis was limited to studies using dispersion modelling to assess exposure, which included all but one study from the main analysis, the pooled RE remained positive but was not significant (RE: 1.01; 95% CI: 0.78–1.30) and heterogeneity increased (I² = 91.16%). In contrast, the pooled RE and heterogeneity from the main analysis were robust to the sensitivity analyses based on RoB (i.e., excluding studies with high or probably high RoB in the exposure assessment or confounder domains). Leave-one-out analysis indicated the following: 1) Nafstad et al. (2004) was the main source of heterogeneity as omitting this study removed heterogeneity from the main analysis, and 2) omitting Beelen et al. (2014b) and Stockfelt et al. (2015) increased the uncertainty around the RE. There was no evidence of a publication bias as demonstrated by the Begg’s (p = 0.7500) and Egger’s (p = 0.2366) tests and the trim-and-fill method suggested that one hypothetical study was needed to make the funnel plot symmetrical.

For CBVD mortality (including stroke mortality), two of the five REs were positive and borderline significant. The forest plot and results of the random-effects meta-analysis for CBVD mortality and NO_x in the general population are presented in **Figure 3.13**. Five studies were included in the meta-analysis with REs ranging from 0.82 to 1.04. The pooled analysis indicated a null association (RE: 1.00; 95% CI: 0.96–1.05) between NO_x and CBVD mortality with minimal heterogeneity that was likely not of importance (I² = 0.10%).

FIGURE 3.13: Association between CBVD mortality and long-term exposure to NO_x in the general population



Except for the higher heterogeneity observed for dispersion modelling ($I^2 = 70.44\%$), subgroup analysis based on the exposure assessment method (i.e., LUR modelling or dispersion modelling) did not indicate a difference from the main analysis. In contrast, sensitivity analyses based on RoB (i.e., excluding studies with high and probably high RoB for the confounder or exposure assessment domain) or limiting the analysis to studies exclusively evaluating CBVD mortality (excluding stroke mortality) resulted in a positive association (RE: 1.01) with borderline significance (95% CI: 0.97–1.04 and 95% CI: 0.94–1.07, respectively). In each of these instances, one study was excluded from the main analysis. Similarly, these studies (Bauleo et al., 2019 and Dirgawati et al., 2019) were the only ones noted to influence the main analysis in the leave-one-out analysis. Neither test for publication bias indicated the presence of a bias (Egger’s test $p = 0.2724$; Begg’s test $p = 0.4833$) and trim-and-fill analysis suggested that one hypothetical study was needed to make the funnel plot symmetrical.

Four studies examined the association between CSD mortality and NO_x, one of which provided the REs by quintile of exposure. No exposure-response relationship could be determined from this study (Andersson et al., 2020). Four of the seven REs reported for CSD mortality were positive, of which three were borderline significant. Similarly, two of the three REs pertaining to MI mortality were positive and borderline significant. One RE was reported for each of cardiac disease mortality and ACE mortality; neither indicated a positive association.

NO

The literature searches identified three studies conducted in Canada, the USA, and Asia evaluating the association between circulatory causes of mortality and NO; the study details are depicted in Appendix A.3. They were drawn from the general population with cohorts ranging in size from 41,869 (Alexeeff et al., 2018) to 406,232 (Gan et al., 2011). NO exposure was assessed by LUR models ($n = 2$) or hybrid models ($n = 1$) and were based on the residential address or postal code. Mean NO ranged from 6.0 (Alexeeff et al., 2018) to 489 $\mu\text{g}/\text{m}^3$ (Barratt et al., 2018). The studies each examined one or more endpoints pertaining to circulatory mortality, including mortality from CSD ($n = 1$), CHD ($n = 3$), and CBVD ($n = 2$). They included adjustments for the key confounders of age, sex, and SES, as well as additional confounders, but Gan et al. (2011) did not adjust for smoking. Based on a limited number of REs for each mortality endpoint, mixed results were observed for CHD and CBVD and there was no evidence of an association for CSD.

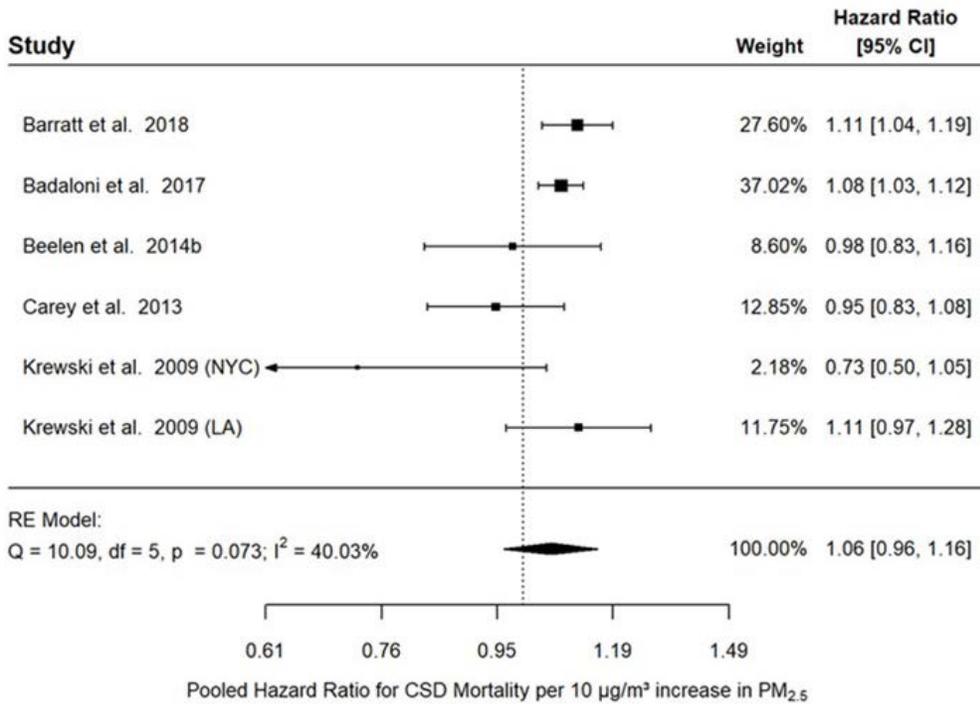
3.3.2. PM

PM_{2.5}

The literature searches identified 12 studies evaluating the association between circulatory causes of mortality and PM_{2.5} that was indicative of TRAP exposure (section 2.1.2). Study details including study population, exposure assessment, confounders, and REs are provided in Appendix A.4. Half of the studies were conducted in Europe ($n = 6$), while one study was conducted in Canada. All of the studies were conducted in cohorts drawn from the general population, which ranged in size from 10,126 (Dirgawati et al., 2019) to 1,265,058 (Cesaroni et al., 2013). For exposure assessment, the most commonly employed methods were LUR modelling ($n = 7$) and dispersion modelling ($n = 4$); exposures were assigned based on the residential address, postal code, or neighbourhood. The lowest mean or median exposures were estimated for a study conducted in Vancouver, British Columbia (4.08 $\mu\text{g}/\text{m}^3$; Gan et al., 2011) and the highest exposure was estimated for a study conducted in Hong Kong, China (42.4 $\mu\text{g}/\text{m}^3$; Barratt et al., 2018). Each of the studies included adjustments for the key confounders of age, sex, and SES, and typically included additional confounders. With respect to smoking, three studies did not include adjustment, either direct or indirect, for individual-level smoking (Naess et al., 2007; Gan et al., 2011; Cesaroni et al., 2013).

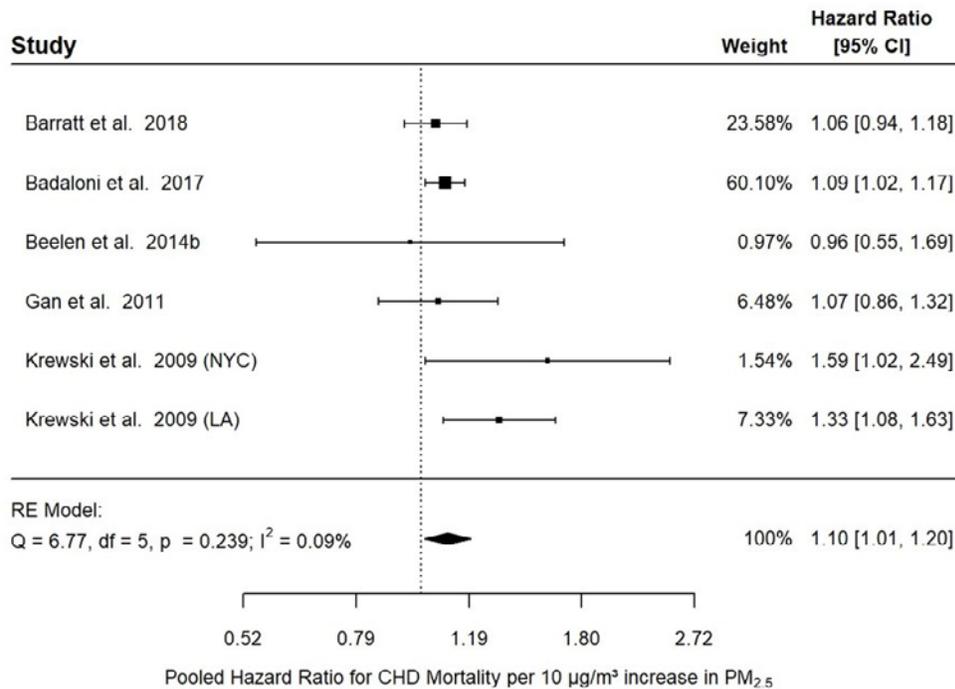
Most of the studies identified evaluated CSD mortality ($n = 9$, including 2 cardiopulmonary disease [CPD] mortalities), with fewer studies considering specific causes of mortality including CHD ($n = 6$), CBVD ($n = 3$) and stroke ($n = 1$), and MI ($n = 2$). Summarized in Appendix A.4 is the most appropriately adjusted RE identified from each study, for each relevant outcome. For CSD mortality, 10 of 13 individual REs were positive, of which 7 were significant and 1 was borderline significant. The forest plot and random-effects meta-analysis for CSD mortality and PM_{2.5} are presented in Figure 3.14. Six studies were included in the meta-analysis with standardized REs ranging from 0.73 to 1.11. The pooled RE for the association between PM_{2.5} and CSD mortality was borderline significant at 1.06 (95% CI: 0.96–1.16) and the heterogeneity was moderate ($I^2 = 40.03\%$). Leave-one-out analysis indicated that the main analysis was robust (pooled RE varied between 1.02 and 1.08). Neither test for publication bias indicated the presence of a bias (Egger's test $p = 0.08633$; Begg's test $p = 0.2722$). Also, trim-and-fill analysis indicated that two hypothetical studies, with positive associations, would be required to make the funnel plot symmetrical.

FIGURE 3.14: Association between CSD mortality and long-term exposure to PM_{2.5} in the general population



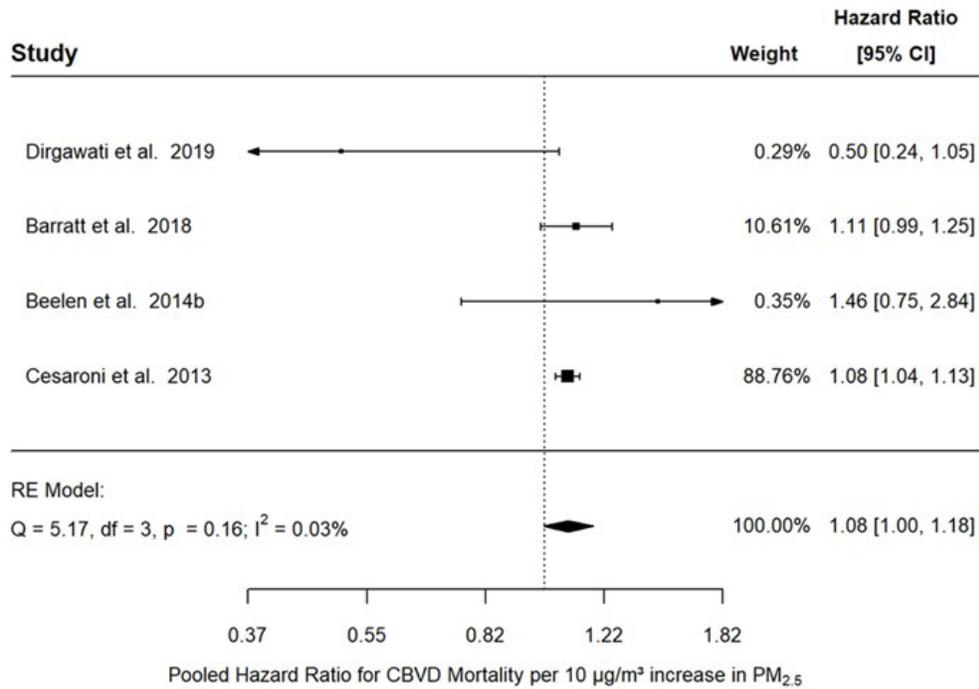
For CHD mortality, seven of the eight individual REs were positive, of which four were significant and three were borderline significant (summarized in Appendix A.4). The forest plot and random-effects meta-analysis for CHD mortality and PM_{2.5} are presented in **Figure 3.15**. Six studies were included in the meta-analysis with standardized REs ranging from 0.96 to 1.59. The pooled RE for the association between PM_{2.5} and CHD mortality was significant at 1.10 (95% CI: 1.01–1.20) and the heterogeneity was minimal and likely not of importance (I² = 0.09%). Leave-one-out analysis indicated that the main analysis was robust (pooled RE varied between 1.09 and 1.15). There was no indication of publication bias, as trim-and-fill analysis did not identify any missing studies and the tests did not indicate a bias (Egger’s test p = 0.3804; Begg’s test p = 1). From the sensitivity analyses, when the analysis was limited to studies with low and probably low RoB for the confounder domain, the pooled RE was robust (RE: 1.13) but there was increased uncertainty around the RE (95% CI: 0.97–1.32) and heterogeneity became moderate (I² = 39.74%).

FIGURE 3.15: Association between CHD mortality and long-term exposure to PM_{2.5} in the general population



For CBVD mortality including stroke, three of the four studies reported a positive association, of which two were significant or borderline significant (summarized in Appendix A.4). The forest plot and random effects meta-analysis for this association are presented in **Figure 3.16**. For the four studies included in the meta-analysis, the standardized REs ranged from 0.50 to 1.46. The pooled RE for the association between PM_{2.5} and CBVD mortality (including stroke) was borderline significant at 1.08 (95% CI: 1.00–1.18) and the heterogeneity was minimal and likely not of importance (I² = 0.03%). Leave-one-out analysis indicated that two studies (Barratt et al., 2018 and Cesaroni et al., 2013) had the greatest impact on the pooled estimate, as no association was observed when one of these studies was removed. Neither test for publication bias indicated the presence of a bias (Egger’s test p = 0.7566; Begg’s test p = 1.000). Also, trim-and-fill analysis indicated that no hypothetical studies would be required to make the funnel plot symmetrical. The sensitivity analyses, excluding the study that only considered stroke (Dirgawati et al., 2019), resulted in a significant association (RE: 1.08 [95% CI: 1.02–1.15]), and analysis based on RoB (i.e., excluding studies with probably high or high RoB in the confounder domain) resulted in a null association (RE: 0.99 [95% CI: 0.30–3.31]).

FIGURE 3.16: Association between CBVD mortality (including stroke) and long-term exposure to PM_{2.5} in the general population



For the other specific causes of circulatory mortality, there was an insufficient number of studies to conduct a meta-analysis. A borderline significant increase was reported for CHD mortality and no associations were observed for MI mortality.

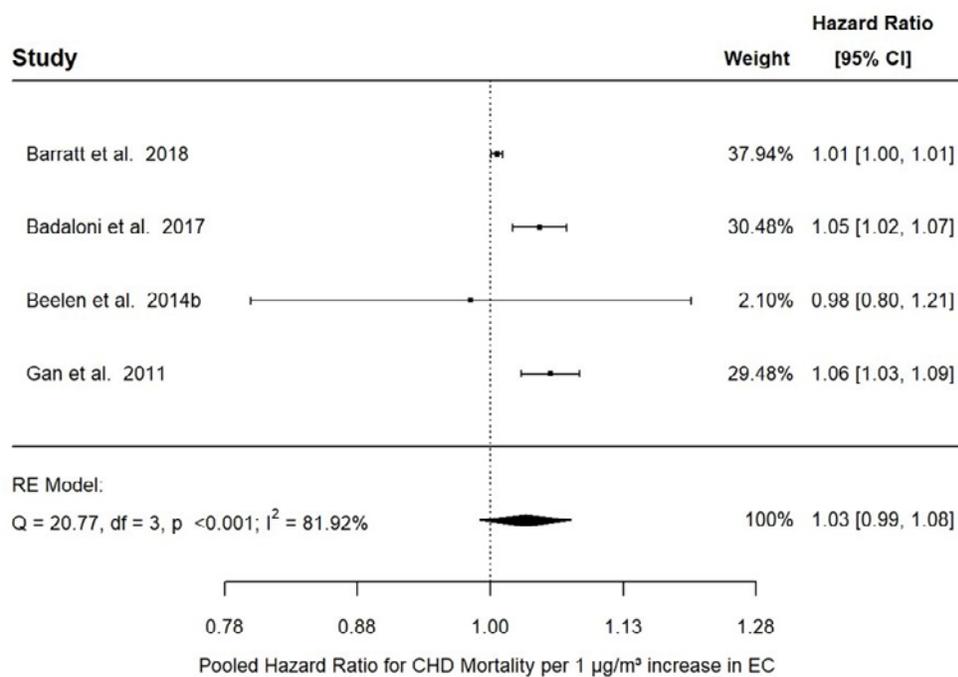
EC, PM_{2.5 abs}, and BC

Eight studies were identified that evaluated exposure to PM_{2.5 abs} or BC and circulatory mortality. Study details are provided in Appendix A.5. Studies were conducted in Canada (n = 1), Europe (n = 3), Asia (n = 2), the USA (n = 1), and Australia (n = 1). Each of the studies considered general population cohorts and study sizes ranged from 10,126 (Dirgawati et al., 2019) to 1,249,108 (Badaloni et al., 2017). Exposure assessment methods included LUR modelling (n = 6), hybrid modelling (n = 1), and dispersion modelling (n = 1) and exposure was assigned based on the residential address or postal code. Based on EC-equivalents, the mean or median exposures ranged from 0.45 (Alexeef et al., 2018) to 16.4 µg/m³ (Barratt et al., 2018). Adjustments for the key confounders of age, sex, and SES were accounted for in each of the studies; direct or indirect adjustment for smoking was accounted for in each study, except for Gan et al. (2011) and Badaloni et al. (2017).

The studies considered mortality associated with CSD (n = 6), CHD (n = 4), CBVD (n = 3) and stroke (n = 1), and MI (n = 2). Summarized in Appendix A.5 is the most appropriately adjusted RE identified from each study. There was an insufficient number of studies with poolable data to conduct a meta-analysis for these outcomes, except CHD and CBVD including stroke.

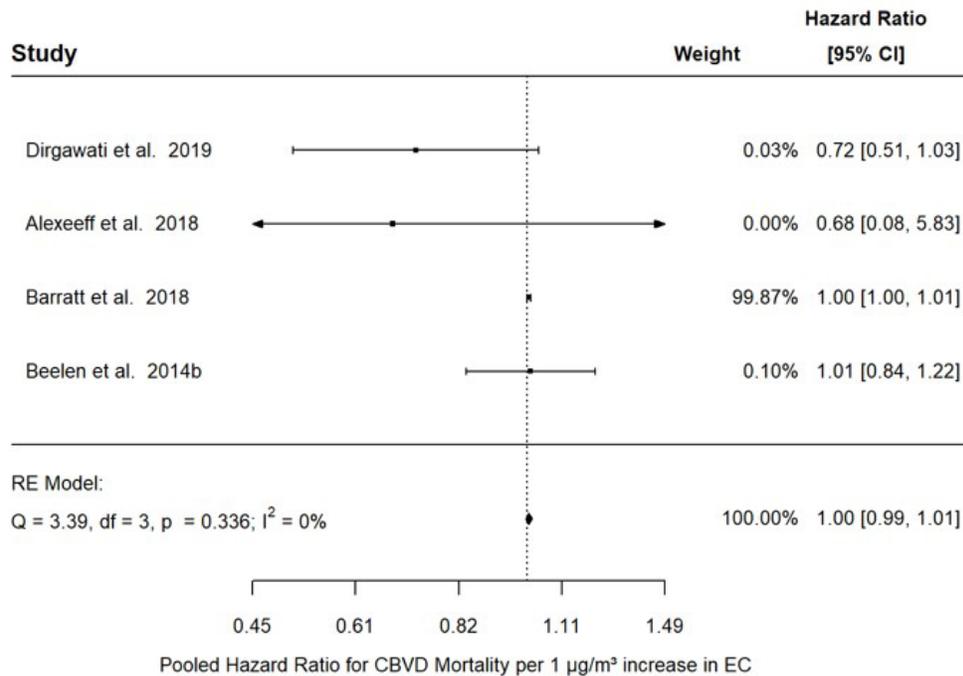
For CHD, the EC-equivalent standardized REs ranged from 0.98 to 1.06 and the pooled RE was positive and borderline significant with a HR of 1.03 (95% CI: 0.99–1.08) (**Figure 3.17**). Heterogeneity was substantial ($I^2 = 81.92\%$) and was largely attributed to Barratt et al. (2018) as no heterogeneity ($I^2 = 0\%$) was observed when this study was removed from the meta-analysis in the leave-one-out analysis. Leave-one-out analysis also indicated the main analysis was robust (pooled RE varied between 1.02 and 1.05). Neither test for publication bias suggested the presence of a bias (Egger’s test $p = 0.9973$; Begg’s test $p = 0.75$) while trim-and-fill analysis indicated that one hypothetical study would be required to make the funnel plot symmetrical. As each of the primary studies in the main analysis was evaluated as low or probably low RoB for the exposure assessment and confounding domains, a sensitivity analysis based on RoB was not conducted. Subgroup analysis based on the exposure assessment was also not conducted since all the studies utilized LUR models.

FIGURE 3.17: Association between CHD mortality and long-term exposure to EC in the general population



For CBVD including stroke, the results were mixed with the EC-equivalent standardized REs ranging from 0.68 to 1.01. The pooled RE for the association between EC and CBVD mortality (including stroke) was null at 1.00 (95% CI: 0.99–1.01) and there was no heterogeneity ($I^2 = 0\%$) (**Figure 3.18**). Leave-one-out analysis indicated that two studies (Barratt et al., 2018 and Beelen et al., 2014b) had the largest influence on the main analysis. Neither test for publication bias indicated the presence of a bias (Egger’s test $p = 0.3354$; Begg’s test $p = 0.3333$). Also, trim-and-fill analysis indicated that one hypothetical study would be required to make the funnel plot symmetrical. Excluding the study that only considered stroke (Dirgawati et al., 2019) also resulted in a null association (RE: 1.00 [95% CI: 1.00–1.01]).

FIGURE 3.18: Association between CBVD mortality (including stroke) and long-term exposure to EC in the general population



For CSD mortality, five of the studies reported a positive association, of which four were significant; however, the analysis of the ESCAPE cohorts did not report an association (Beelen et al., 2014b).

PM₁₀ and PM_{coarse}

The literature searches identified seven studies of PM₁₀ and one study of PM_{coarse} that had an association with circulatory mortality. As the literature available for PM_{coarse} is limited, this assessment will focus on the PM₁₀ literature. Study details including study population, exposure assessment, confounders, and REs are provided in Appendix A.6. Each of the studies was conducted in Europe; five of the studies were based on general population cohorts and two were population-based case-control studies. No studies conducted in Canada were identified in the literature searches. The sample sizes ranged from 3,249 (Rosenlund et al., 2006) to 1,249,108 (Badaloni et al., 2017). For exposure assessment, four of the studies utilized dispersion modelling, three employed LUR modelling, and exposures were assigned at the residential address-, postal code-, or neighbourhood-level. For PM₁₀, the mean exposures ranged from 2.2 (Rosenlund et al., 2009) to 48.1 µg/m³ (Beelen et al., 2014b). Each of the studies adjusted for the key confounders of age, sex, and SES; adjustments for smoking were included in each of the studies except for Naess et al. (2007) and Rosenlund et al. (2009).

For PM₁₀, the studies evaluated CSD mortality (n = 4) and specific causes of circulatory mortality including MI (n = 3), CHD (n = 2), and CBVD (n = 1). There was an insufficient number of studies with poolable data to conduct a meta-analysis for any of these outcomes. For CSD mortality, seven REs were provided in the studies, of which six were positive with four of these statistically significant. For MI mortality, the results were mixed with two studies reporting an association (one significant

and one non-significant) and two with null associations. Similarly, for CHD mortality, one study reported a borderline significant association and another a null association. For CBVD mortality, the single study reported a non-significant association.

3.3.3. Other TRAP pollutants: CO and benzene

CO

The literature searches identified two population-based case-control studies conducted in Stockholm, Sweden evaluating the association between circulatory mortality and CO; the study details are depicted in Appendix A.8. CO exposure was assessed by dispersion modelling and assigned based on the residential address; median CO ranged from 62.6 to 64.2 $\mu\text{g}/\text{m}^3$. Both studies reported positive associations that were borderline or statistically significant for CO exposure and mortality caused by MI. They accounted for the key confounders of age, sex, and SES and one study adjusted for smoking.

Benzene

Only one study was identified in the literature searches to examine the association between long-term exposure to benzene, as a marker of TRAP, and circulatory mortality. This Canadian study by Villeneuve et al. (2013) was conducted in the general population of Ontario and accounted for the key confounders including an indirect adjustment for smoking. It reported a positive association that was borderline significant for exposure to benzene and CSD mortality (summarized in Appendix A.7).

3.3.4. Traffic and the road network infrastructure

Traffic proximity

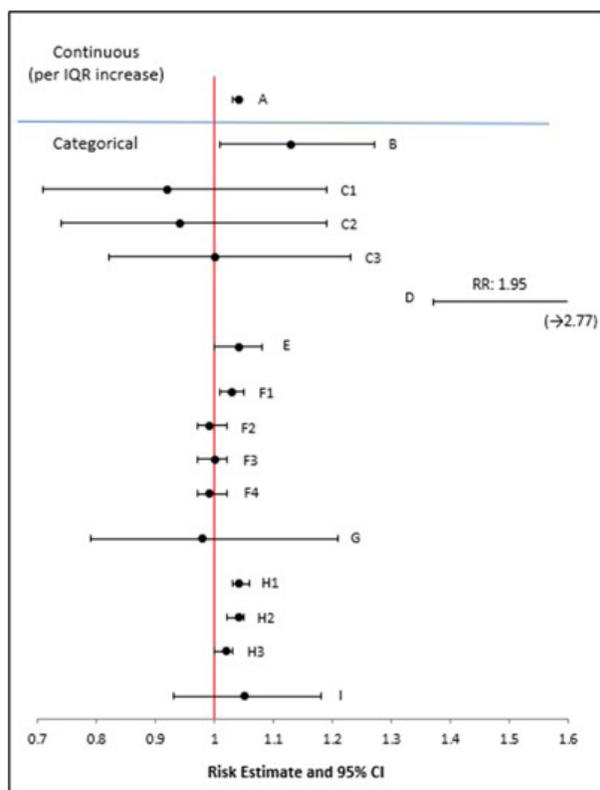
Traffic proximity or distance to roadway was the most commonly used metric of traffic and the road network infrastructure that examined the association between traffic and circulatory mortality with 17 studies, of which 15 were conducted on the general population and 2 on patient populations. The study details regarding study population, exposure assessment, confounders, and REs are provided in Appendix A.9.

For the general population, the majority of the studies were conducted in Europe ($n = 9$) followed by Canada ($n = 3$), the USA ($n = 2$), and Asia ($n = 1$), and ranged in size from 3,287 (Kulick et al., 2018) to 2,644,370 (Cakmak et al., 2019). All of the studies conducted in the USA, Canada, and Asia were based on unique cohorts while those conducted in Europe were based on five cohorts: NLCS-AIR (Hoek et al., 2002; Beelen et al., 2008, 2009; Brunekreef et al., 2009); SALIA (Gehring et al., 2006; Heinrich et al., 2013); the Swiss National Cohort (Huss et al., 2010); the Diet, Cancer, and Health Cohort Study (Raaschou-Nielsen et al., 2012); and the Rome Longitudinal Study (Cesaroni et al., 2013). Studies conducted in the general population each examined one or more endpoints pertaining to circulatory mortality including mortality from CSD ($n = 13$, including 3 CPD mortality), CHD ($n = 7$), CBVD ($n = 5$) and stroke ($n = 1$), acute MI ($n = 1$), sudden cardiac death ($n = 1$), HF ($n = 1$), and cardiac dysrhythmia ($n = 1$). Most of the 15 studies accounted for the key confounders of age, sex, SES, and smoking. Specifically, all 15 studies accounted for age, sex, and individual SES and/or area-level SES but 5 studies did not adjust for smoking (Gan et al., 2010; Huss et al., 2010; Cesaroni et al., 2013; Chen et al., 2013; Cakmak et al., 2019). Many studies also considered additional confounders. Proximity to traffic was directly measured in a GIS. It was based on the exact residential address

(European and American studies), the residential postal code (Canadian studies), or the geographic centre of each village for rural residents and the location of the primary health centre for urban residents (Iranian study). No consistent definitions or categories were used to assess traffic proximity across the studies.

The associations between traffic proximity and risk of CSD mortality in the general population are summarized in **Figure 3.19**; only unique cohorts and non-transformed data are included in the forest plot. Two studies considered traffic proximity as a continuous variable. In a Canada-wide study, Cakmak et al. (2019) reported a positive and significant association. In comparison, Kulick et al. (2018) did not observe any associations based on log-transformed proximity. When traffic proximity was evaluated as a categorical variable, 8 of the 15 REs were positive, of which 5 were significant and 3 were borderline significant. Of the three studies that examined exposure-response relationships, both Huss et al. (2010) and Cesaroni et al. (2013) identified an increased risk with increased exposure while Kulick et al. (2018) did not.

FIGURE 3.19: Forest plot of risk estimates for long-term exposure to traffic proximity and CSD mortality in the general population

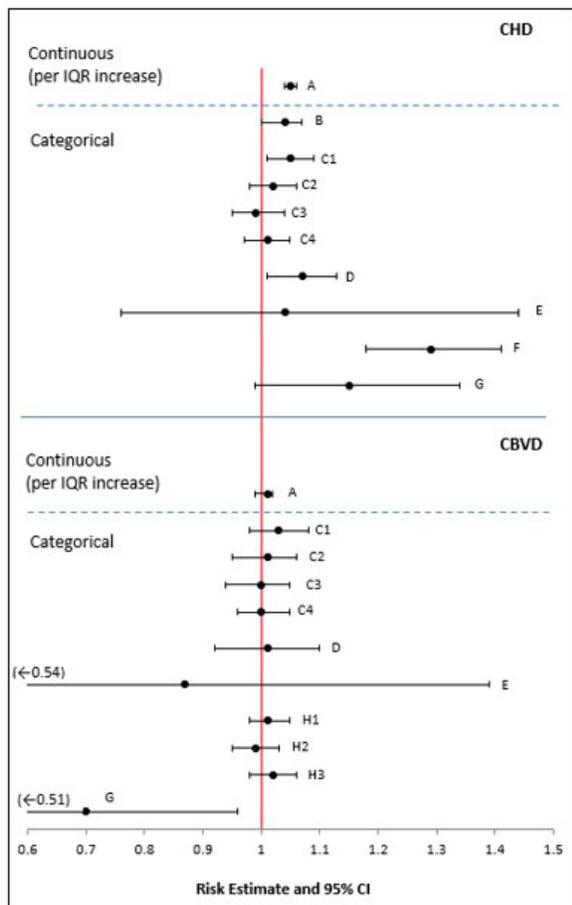


- A. CanCHEC Cohort, Canada (Cakmak et al., 2019); total length of local roads ≤ 200 m radius from residence, per 1,108.6 m increase
- B. Golestan Cohort Study, Asia (Hadley et al., 2022); living ≤ 100 m from a minor highway or ≤ 500 m from a major highway
- C. The Northern Manhattan Cohort, USA (Kulick et al., 2018); distance to roadway categorized as C1: <100 m; C2: 100 to <200 m; C3: 200 to <400 m (reference group ≥ 400 m)
- D. SALIA Cohort, Europe (Heinrich et al., 2013); living ≤ 50 m from a major roadway ($\geq 10,000$ vehicles/day)
- E. Ontario Tax Cohort, Canada (Chen et al., 2013); living ≤ 50 m from a major road or <100 m from a highway; pooled risk estimate for Toronto, Hamilton, and Windsor
- F. Rome Longitudinal Study, Europe (Cesaroni et al., 2013); distance to high traffic road with $>10,000$ vehicles/day; F1: <50 m; F2: 50–100 m; F3: 100–150 m; F4: 150–250 m (reference group ≥ 250 m)
- G. Diet, Cancer, and Health Cohort Study, Europe (Raaschou-Nielsen et al., 2012); living ≤ 50 m from a major roadway ($\geq 10,000$ vehicles/day)
- H. Swiss National Cohort, Europe (Huss et al., 2010); distance to main road; H1: <50 m; H2: 50–99 m; H3: 100–199 m (reference group ≥ 200 m)
- I. NLCS-AIR Cohort, Europe (Brunekreef et al., 2009); living near a major road (≤ 100 m from a freeway or ≤ 50 m from a major road with 10,000 motor vehicles/day)

CHD and CBVD (including stroke) mortality are the only specific causes of circulatory mortality for

which REs were identified for traffic proximity in three or more unique cohorts. The risk of CHD and CBVD mortality in the general population are summarized in **Figure 3.20**; only unique cohorts are included in the forest plot. For CHD mortality, only one Canadian study considered traffic proximity as a continuous variable. In this Canada-wide study, Cakmak et al. (2019) reported a positive and significant association. When traffic proximity was evaluated as a categorical variable, most of the REs (i.e., eight of nine) were positive, of which three were significant and five were borderline significant. An increased risk with increased exposure was also observed in the only study that examined exposure-response relationships (Cesaroni et al., 2013). For CBVD mortality, a positive, borderline significant association was reported in the only study that considered traffic proximity as a continuous variable (Cakmak et al., 2019). However, when traffic proximity was evaluated as a categorical variable, only 5 of the 10 REs were positive and borderline significant. Additionally, an increased risk with increased exposure was observed in one of the two studies that examined exposure-response relationships (Huss et al., 2010; Cesaroni et al., 2013).

FIGURE 3.20: Forest plot of risk estimates for long-term exposure to traffic proximity and CHD and CBVD mortality in the general population



- A. CanCHEC Cohort, Canada (Cakmak et al., 2019); total length of local roads ≤ 200 m radius of residence, per 1,108.6 m increase
- B. NHS, the USA (Hart et al., 2014); living < 500 m from nearest A1 (primary roads, e.g., interstate highways), A2 (primary major, non-interstate highways and major roads), or A3 (smaller, secondary roads, usually with more than two lanes) roads
- C. Rome Longitudinal Study, Europe (Cesaroni et al., 2013); distance to high traffic road with $> 10,000$ vehicles/day; C1: < 50 m; C2: 50–100 m; C3: 100–150 m; C4: 150–250 m (reference group ≥ 250 m)
- D. Ontario Tax Cohort, Canada (Chen et al., 2013); living ≤ 50 m from a major road or < 100 m from a highway; pooled risk estimate for Toronto, Hamilton, and Windsor
- E. Diet, Cancer, and Health Cohort Study, Europe (Raaschou-Nielsen et al., 2012); living ≤ 50 m from a major roadway ($\geq 10,000$ vehicles/day)
- F. Vancouver metropolitan residents, Canada (Gan et al., 2010); living near a major road (≤ 50 m from major road or ≤ 150 m from highway)
- G. NLCS-AIR, Europe (Beelen et al., 2009); living near a major road (≤ 100 m from motorway or ≤ 50 m from local road with traffic intensity $> 10,000$ motor vehicles/24 h)
- H. Swiss National Cohort, Europe (Huss et al., 2010); distance to main road; F1: < 50 m; F2: 50–99 m; F3: 100–199 m (reference group ≥ 200 m)

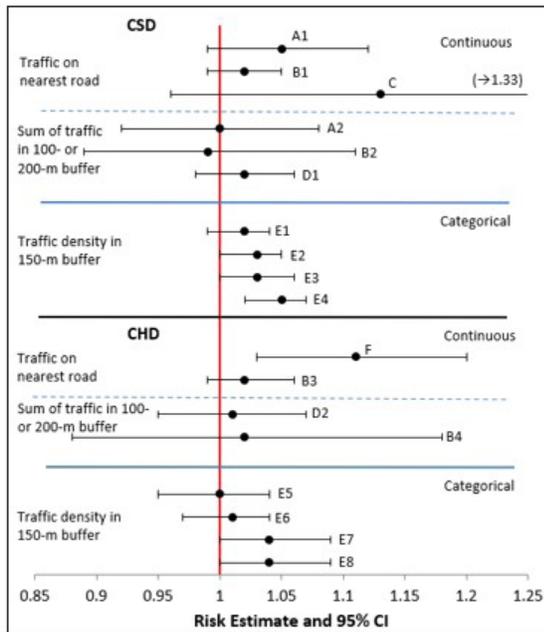
A limited number of studies also evaluated other causes of circulatory mortality (summarized in Appendix A.9). An increased risk with increased exposure was observed for MI mortality and a positive significant association was reported for SCD mortality. In contrast, no association was found for HF and cardiac dysrhythmia.

Two Canadian studies examined the association between exposure to traffic proximity and circulatory mortality in patient populations (summarized in Appendix A.9). These studies ranged in size from 2,360, comprising patients from a respiratory disease clinic in Toronto, Ontario (Jerrett et al., 2009), to 5,228, comprising patients who underwent pulmonary function testing at a clinic in Hamilton, Ontario (Finkelstein et al., 2005). Each study accounted for key confounders of age, sex, and SES, while smoking was only accounted for in Jerrett et al. (2009). A positive, borderline significant or significant association was observed between traffic proximity and CSD mortality in each study and between traffic proximity and CBVD mortality in one study.

Traffic density

Seven studies were identified in the literature search evaluating the risk of circulatory mortality and measures of traffic density. Study details including study population, exposure assessment, confounders, and REs are provided in Appendix A.10. The studies were conducted in Europe (n = 6) and Asia (n = 1). Each study was based on general population cohorts and ranged in size from 12,098 (Pan et al., 2021) to 1,265,058 (Cesaroni et al., 2013). Beelen et al. (2008, 2009) and Brunekreef et al. (2009) were conducted in the NLCS-AIR cohort and had identical results. Each of the studies accounted for the key confounders of age, sex, and SES, and smoking was accounted for in each of the studies except for Cesaroni et al. (2013). Each of the studies evaluated CSD mortality; specific causes of circulatory mortality were evaluated in four of the studies (Beelen et al., 2009, 2014; Raaschou-Nielsen et al., 2012; Cesaroni et al., 2013). The studies mostly reported positive, borderline significant associations for CSD or CHD mortality and measures of traffic density near the residence (summarized in **Figure 3.21**). Cesaroni et al. (2013) noted a significant trend of increasing risk for both CSD and CHD for the quintiles of exposure. Beelen et al. (2009) reported a significant association for CHD mortality. For CBVD, mixed results were noted between the three studies, and, for other specific causes (e.g., MI, HF, dysrhythmia), the single analysis reported positive associations.

FIGURE 3.21: Forest plot of risk estimates for long-term exposure to traffic density and CSD and CHD mortality in the general population



- A. NLCS-AIR Cohort, Europe (Brunekreef et al., 2009); A1: traffic on nearest road (per 10,000 vehicles/day); A2: sum of traffic intensity in 100-m buffer (per 335,000 vehicles/day)
- B. ESCAPE, Europe (Beelen et al., 2014b); B1, B3: traffic on nearest road (per 5,000 vehicles/day); B2, B4: sum of traffic intensity in 100-m buffer (per 4×10^6 vehicle-m/day)
- C. REVEAL-HBV, Asia (Pan et al., 2021); log vehicle/day
- D. Diet, Cancer, and Health Cohort Study, Europe (Raaschou-Nielsen et al., 2012); D1, D2: per doubling of traffic within 200 m buffer
- E. Rome Longitudinal Study, Europe (Cesaroni et al., 2013); traffic density in 150-m buffer (vehicle-m/day); E1, E5: $(0.25-1.63) \times 10^6$; E2, E6: $(1.63-3.23) \times 10^6$; E3, E7: $(3.23-6.66) \times 10^6$; E4, E8: $\geq 6.66 \times 10^6$ (reference: $<0.25 \times 10^6$)
- F. NLCS-AIR Cohort, Europe (Beelen et al., 2009); traffic on nearest road (per 10,000 vehicle/day)

Summary

The association between TRAP and circulatory mortality was evaluated in 39 cohort and 2 case-control studies; all but 2 studies were based on the general population and the majority were conducted in Europe. These studies evaluated mortality from CSD as a group, as well as from more specific causes, including CHD and CBVD (including stroke). Over 60% of the studies assessed exposure to TRAP by modelling individual traffic-related pollutants; the remainder used metrics of traffic and the road network infrastructure to assess the contribution of traffic emissions to ambient air pollution. Nearly all the studies accounted for the key confounders of age, sex, SES, and smoking and many considered additional confounders. Pooled analyses were conducted on the general population studies.

For CSD mortality, pooled analyses of the two pollutants evaluated (NO_2 and $\text{PM}_{2.5}$) indicated a positive association with pooled estimates of 1.05 and 1.06, respectively; both associations were borderline significant. Heterogeneity was considerable for NO_2 and moderate for $\text{PM}_{2.5}$. The meta-analysis results were supported by the qualitative analysis of 1) the other pollutants (i.e., NO_x , BC, $\text{PM}_{2.5 \text{ abs}}$, PM_{10} , and benzene) and of 2) the different metrics for traffic and the road network infrastructure, which demonstrated some evidence of an exposure-response relationship.

For CHD mortality, the pooled analyses indicated a positive association for each of the pollutants evaluated (i.e., NO_2 , NO_x , $\text{PM}_{2.5}$, and EC); these associations with pooled REs ranging from 1.02 to 1.10 were significant or borderline significant. Heterogeneity was likely not of importance for NO_2 and $\text{PM}_{2.5}$, but substantial for NO_x and EC. The meta-analysis results were supported by the qualitative analysis of the different metrics for traffic and the road network infrastructure with demonstration of an exposure-response relationship. In contrast, the evidence for NO and PM_{10} was mixed and the limited number of studies did not support conducting a pooled analysis.

For CBVD mortality, the pooled analyses of the pollutants evaluated produced mixed results. A positive association of borderline significance was identified for NO₂ and PM_{2.5} with REs of 1.01 and 1.08, respectively, but a null association was determined for NO_x and EC. Heterogeneity was likely not of importance for each of the four pollutants. Mixed results were also observed for the qualitative analysis of the metrics of traffic and the road network infrastructure. Evidence from NO and PM₁₀ was limited and did not support conducting a pooled analysis.

There was also some evidence of positive associations for other causes of circulatory mortality and various traffic-related air pollutants but this evidence was limited and did not support conducting a pooled analysis.

3.4. RESPIRATORY MORTALITY

Based on the overlap of ICD codes, individual studies refer to respiratory mortality as mortality from respiratory disease, pulmonary disease, non-malignant respiratory disease, and respiratory disease excluding lung cancer. While some studies included mortality from all respiratory disorders, others did not include lung diseases due to external agents. For this risk assessment, and consistent with HEI (2022), these health outcomes were considered similar and are referred to as respiratory mortality (or respiratory disorder [RD] mortality in the appendix). Respiratory mortality was evaluated in 20 of the 64 articles evaluating the association between long-term exposure to TRAP and mortality. An evaluation of the studies examining the effects of long-term exposure to TRAP and respiratory mortality are presented below by TRAP pollutant or metric. These studies evaluated mortality from respiratory disorders as a group, as well as from more specific causes (e.g., chronic obstructive pulmonary disease [COPD], pneumonia, and influenza/pneumonia).

3.4.1. Nitrogen oxides (NO, NO₂, and NO_x)

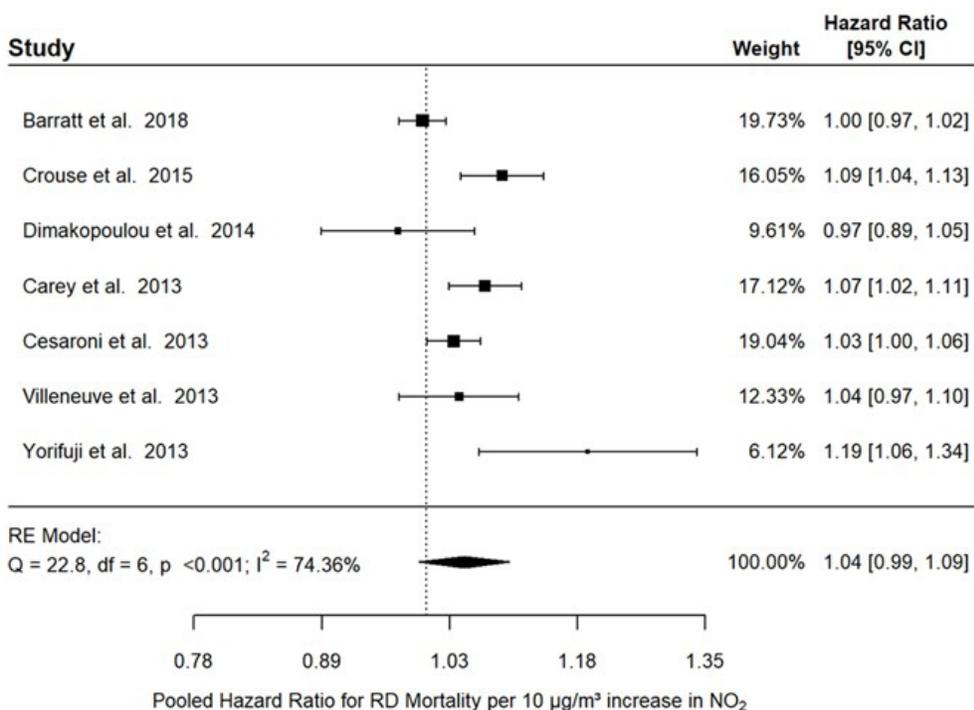
NO₂

The literature searches identified 12 studies evaluating the association between respiratory causes of mortality and NO₂. Study details pertaining to this health endpoint including study population, exposure assessment, confounders, and REs are provided in Appendix A.1. The studies were conducted in Canada (n = 4), Europe (n = 4), and Asia (n = 4). All but one Canadian study (Jerrett et al., 2009) were drawn from the general population with a study size ranging from 12,029 (Yorifuji et al., 2010) to 1,265,058 (Cesaroni et al., 2013). For exposure assessment of the studies conducted in the general population, LUR modelling (n = 9) was the most common method used, followed by dispersion modelling (n = 2). Exposures were assigned based on the residential address or postal code, or at the neighbourhood level, and the mean exposures ranged from 5.2 to 107 µg/m³. The lowest exposures were assigned to one of the Swedish cohorts included in the ESCAPE study (Dimakopoulou et al., 2014) while the highest exposures were noted in a study conducted in Hong Kong, China (Barratt et al., 2018). Studies conducted in the general population each examined one or more endpoints pertaining to respiratory mortality. Most of the studies identified evaluated respiratory mortality (n = 9), with fewer studies considering specific causes of mortality including COPD (n = 6); influenza and pneumonia (n = 2); and pneumonia alone (n = 2). All 11 studies accounted for age and sex, as well as individual SES and/or area-level SES; 3 studies did not adjust for smoking (Naess et al., 2007; Cesaroni et al., 2013; Gan et al., 2013). Many studies also considered additional confounders.

The most appropriately adjusted RE identified from each study for each relevant outcome is specified in Appendix A.1.

For the general population, six of the nine REs pertaining to respiratory mortality were positive, of which four were statistically significant and two were borderline significant. The forest plot and results of the random-effects meta-analysis for respiratory mortality and NO₂ are presented in **Figure 3.22**. Seven studies were included in the meta-analysis for the general population with REs ranging from 0.97 to 1.19. The pooled RE for the association between NO₂ and respiratory mortality was borderline significant at 1.04 (95% CI: 0.99–1.09) and the heterogeneity was substantial ($I^2 = 74.36\%$).

FIGURE 3.22: Association between respiratory mortality and long-term exposure to NO₂ in the general population



The subgroup and sensitivity analyses conducted did not indicate a difference from the main analysis. Specifically, both the pooled RE and the heterogeneity were robust when limiting the analysis to studies that used LUR modelling to assess exposure ($n = 6$) or to those with low and probably low RoB for the confounder domain ($n = 5$). Leave-one-out analysis indicated the results were robust as the pooled RE ranged from 1.03 to 1.05 and the heterogeneity remained substantial. There was no indication of publication bias, as trim-and-fill analysis did not identify any missing studies and the tests did not indicate a bias (Egger's test $p = 0.3593$; Begg's test $p = 0.3813$).

For COPD mortality in the general population, eight of the nine REs were positive, of which one was statistically significant and six were borderline significant. Four of the REs were derived from the same study (Naess et al., 2007) and correspond to different age groups and sex. For this exposure-outcome pair, no meta-analysis was conducted as there was an insufficient number of studies that

corresponded to unique cohorts and that had the necessary data to conduct a quantitative analysis.

A limited number of studies were identified in the literature searches pertaining to NO₂ exposure and mortality from influenza and pneumonia (combined) and from pneumonia alone in the general population. Two studies were identified for each outcome and both studies were conducted in the same cohort for each of the outcomes. Although no association was identified for mortality from pneumonia alone, a positive, borderline significant association was reported for mortality from influenza and pneumonia (combined).

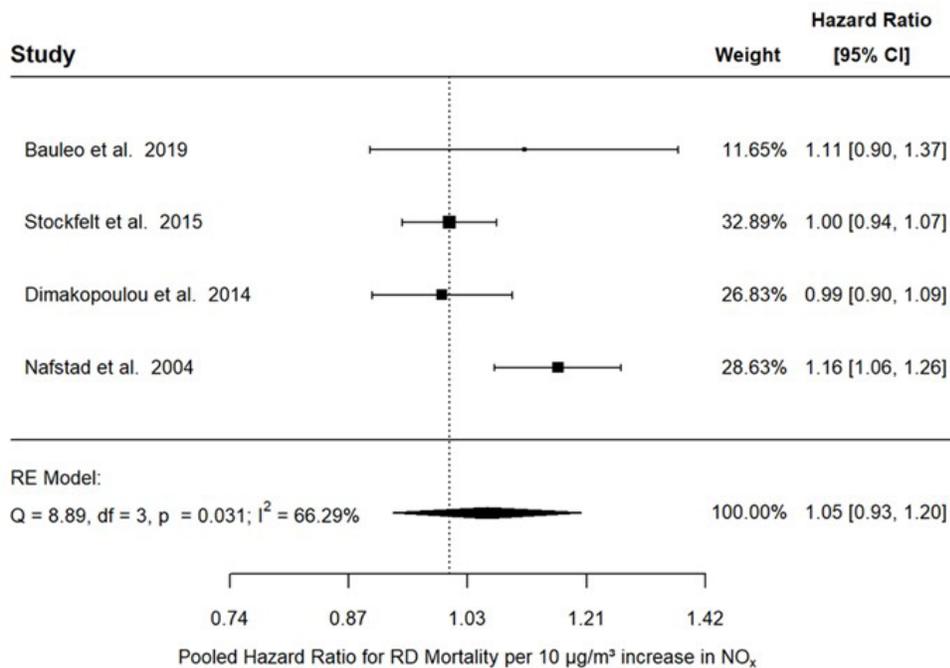
The only study to examine the association between long-term exposure to NO₂ and respiratory mortality in a patient population was conducted in adult patients from a respiratory disease clinic in Toronto, Ontario, (Jerrett et al., 2009). This Canadian study accounted for the key confounders including smoking and reported a positive but not significant association between NO₂ and respiratory mortality (summarized in Appendix A.1).

NO_x

The literature searches identified four studies, all conducted in Europe and drawn from the general population, evaluating the association between respiratory mortality and NO_x. Study details including study population, exposure assessment, confounders, and REs are provided in Appendix A.2. The cohorts ranged in size from 7,494 (Stockfelt et al., 2015) to 307,553 (Dimakopoulou et al., 2014). The majority of the studies used dispersion modelling (n = 3) while one study used an LUR model to assess NO_x exposure. All studies assigned NO_x exposure at the residential address; the mean (or median) exposures ranged from 5.80 to 96.1 µg/m³. The lowest exposures were estimated in a study conducted in Civitavecchia, Italy (Bauleo et al., 2019) while the highest exposures were modelled in an Italian cohort included in the ESCAPE study (Dimakopoulou et al., 2014). All four studies examined respiratory mortality and one study also evaluated COPD mortality. The studies accounted for the key confounders of age, sex, and SES (individual- and/or area-level) and all but one study (Bauleo et al., 2019) also adjusted for smoking. They also typically considered additional confounders.

The most appropriately adjusted RE from each study for each relevant outcome is summarized in Appendix A.2. For respiratory mortality, two of the four REs were positive of which one was statistically significant. The forest plot and results of the random-effects meta-analysis for respiratory mortality and NO_x in the general population are presented in **Figure 3.23**. Four studies were included in the meta-analysis for the general population with REs ranging from 0.99 to 1.16. The pooled RE was borderline significant at 1.05 (95% CI: 0.93–1.20) and heterogeneity was substantial (I² = 66.29%).

FIGURE 3.23: Association between respiratory mortality and long-term exposure to NO_x in the general population



When the analysis was limited to studies using dispersion modelling to assess exposure, which included all but one study from the main analysis, the pooled RE remained positive but was not significant (RE: 1.08; 95% CI: 0.88–1.33). Similarly, the pooled RE from the main analysis was robust to the sensitivity analyses based on RoB (i.e., excluding studies with high or probably high RoB in the exposure assessment or confounder domains). Heterogeneity remained substantial for all subgroup and sensitivity analyses. Leave-one-out analysis indicated that Nafstad et al. (2004) was the main source of heterogeneity as omitting this study removed heterogeneity from the main analysis. It was also the only study that, when omitted, resulted in a null association. A positive but non-significant association was observed when each of the three other studies were omitted. There was no indication of publication bias, as trim-and-fill analysis did not identify any missing studies and the tests did not indicate a bias (Egger’s test $p = 0.6812$; Begg’s test $p = 0.7500$).

Only one RE was identified for exposure to NO_x and COPD mortality. This RE was positive and borderline significant.

NO

Two studies evaluating the association between respiratory mortality and NO were identified in the literature searches; both were based on the general population. The study details are depicted in Appendix A.3. One study was conducted on a cohort of 465,360 participants in Vancouver, British Columbia (Gan et al., 2013) and the other on a cohort of 60,548 participants residing in Hong Kong, China (Barratt et al., 2018). Both studies estimated exposure using LUR models with

a mean NO ranging from 32.1 (Gan et al., 2013) to 489 $\mu\text{g}/\text{m}^3$ (Barratt et al., 2018). Both studies included adjustments for the key confounders of age, sex, and SES, but Barratt et al. (2008) also adjusted for smoking as well as additional confounders. A positive association that was borderline significant was reported for COPD mortality and NO in each of the studies; however, no association was observed for respiratory mortality or pneumonia mortality and NO.

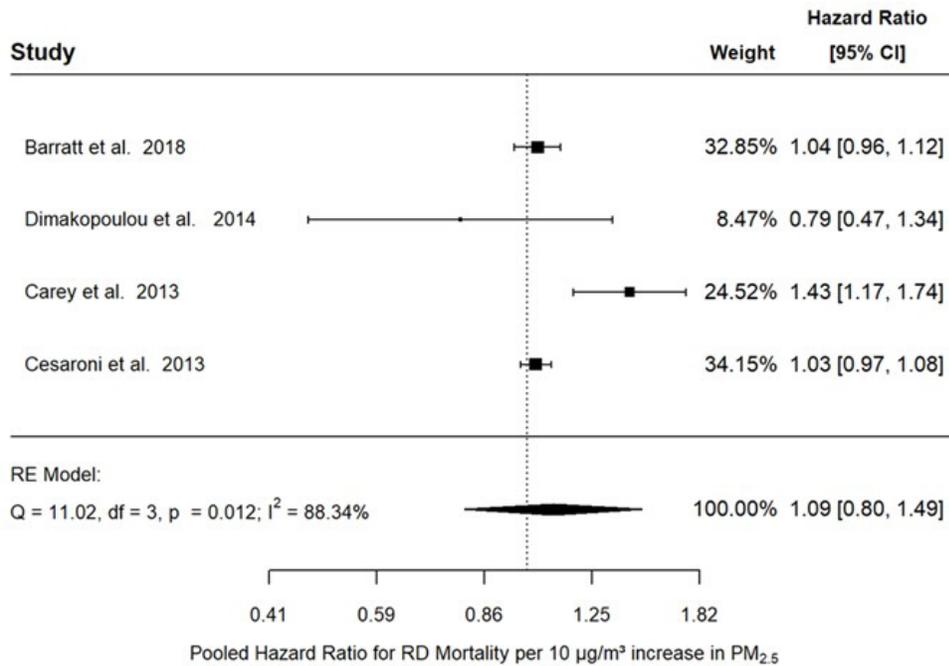
3.4.2. PM

PM_{2.5}

The literature search identified seven studies evaluating the association between long-term PM_{2.5} exposure and respiratory mortality. Study details including study population, exposure assessment, confounders, and REs are provided in Appendix A.4. Each of the studies considered general population cohorts and were conducted in Canada (n = 1), Europe (n = 4), and Asia (n = 2). The cohort sizes ranged from 60,458 (Barratt et al., 2018) to 1,265,058 (Cesaroni et al., 2013). The exposure assessments were derived from either LUR modelling (n = 4) or dispersion modelling (n = 3), with exposures assigned at either the residential address, postal code, or neighbourhood level. The lowest mean or median exposures were estimated for a study conducted in Vancouver, British Columbia (4.10 $\mu\text{g}/\text{m}^3$, Gan et al., 2013) and the highest exposure was estimated for a study conducted in Hong Kong, China (42.4 $\mu\text{g}/\text{m}^3$; Barratt et al., 2018). Each of the studies included adjustments for the key confounders of age, sex, and SES, and typically included additional confounders. With respect to smoking, three studies did not include an adjustment, either direct or indirect, for individual-level smoking (Naess et al., 2007; Gan et al., 2011; Cesaroni et al., 2013).

Five of the studies evaluated respiratory mortality, four evaluated COPD mortality, and two evaluated pneumonia mortality. Summarized in Appendix A.4 is the most appropriately adjusted RE identified from each study, for each relevant outcome. For respiratory mortality, four of the studies reported a positive association, of which one was significant and three were borderline significant, and one study reported no association. The forest plot and random-effects meta-analysis for respiratory mortality and PM_{2.5} are presented in **Figure 3.24**. Four studies were included in the meta-analysis with standardized REs ranging from 0.79 to 1.43. The pooled RE for the association between PM_{2.5} and respiratory mortality was non-significant at 1.09 (95% CI: 0.80–1.49) and the heterogeneity was substantial ($I^2 = 88.34\%$). Leave-one-out analysis indicated that the main analysis was robust (pooled RE varied between 1.03 and 1.13) and no one study distorted the overall results. Neither test for publication bias indicated the presence of a bias (Egger's test $p = 0.7017$; Begg's test $p = 1.000$). Also, trim-and-fill analysis indicated that one hypothetical study would be required to make the funnel plot symmetrical.

FIGURE 3.24: Association between respiratory mortality and long-term exposure to PM_{2.5} in the general population



For COPD mortality, each of the seven associations were positive, of which one was significant and five were borderline significant. Only two studies evaluated pneumonia mortality and reported null associations. There was an insufficient number of studies with poolable data to conduct a meta-analysis for any of these outcomes.

EC, PM_{2.5 abs}, and BC

Four studies were identified that evaluated exposure to PM_{2.5 abs} or BC and respiratory mortality. Study details are provided in Appendix A.5. The studies were conducted in Canada (n = 1), Europe (n = 1), and Asia (n = 2). Each of the studies considered general population cohorts and study sizes ranged from 60,548 (Barratt et al., 2018) to 465,360 (Gan et al., 2013). Each study used LUR modelling to assess exposures, which were assigned at the residential address or postal code level. Exposures, based on EC-equivalents, were 1.1 µg/m³ for the studies conducted in Canada and Europe, and 12 µg/m³ for the studies conducted in Asia. Adjustments for the key confounders of age, sex, and SES were accounted for in each of the studies; direct or indirect adjustment for smoking was accounted for in each study, except for Gan et al. (2013).

The studies considered mortality associated with respiratory disorders (n = 3), COPD (n = 4), and pneumonia (n = 2). The two studies conducted in Asia (Barratt et al., 2018; Yang et al., 2018) were based on the same cohort and had identical results for each cause-specific mortality. For respiratory disease and pneumonia mortality, a negative association was noted in each of the studies. For COPD, a positive, borderline significant association was reported for the Canadian study (Gan et al., 2013), while a negative association was reported in the two Asian studies (Barratt et al., 2018; Yang et al., 2018). There was an insufficient number of studies with poolable data to conduct a meta-analysis for any of these outcomes.

PM₁₀ and PM_{coarse}

The literature search identified three studies of PM₁₀ and one study of PM_{coarse} and the association with respiratory morbidity. Study details are provided in Appendix A.6. Each of the studies was conducted in Europe, based on general population cohorts with study sizes ranging from 143,842 (Naess et al., 2007) to 830,842 (Carey et al., 2013). For exposure assessment, two studies utilized dispersion modelling (Naess et al., 2007; Carey et al., 2013) and one employed LUR modelling (Dimakopoulou et al., 2014); exposures were assigned at the residential address, postal code, or neighbourhood level. For PM₁₀, the mean exposures ranged from 3.0 (Carey et al., 2013) to 10 µg/m³ (Dimakopoulou et al., 2014). Adjustments for the key confounders of age, sex, and SES were accounted for in each of the studies; direct or indirect adjustment for smoking was accounted for in each study, except for Naess et al. (2007).

Two studies evaluated respiratory mortality and PM₁₀ with conflicting results as one reported a significant, positive association (Carey et al., 2013) and the other a borderline significant, negative association (Dimakopoulou et al., 2014). No association was also observed for respiratory mortality and PM_{coarse}. For COPD, one study reported positive associations (either significant or borderline significant) with PM₁₀ (Naess et al., 2007). There was an insufficient number of studies with poolable data to conduct a meta-analysis for any of these outcomes.

3.4.3. Other TRAP pollutants: benzene

Only one study was identified in the literature searches that examined the association between long-term exposure to benzene, as a marker of TRAP, and respiratory mortality. This Canadian study by Villeneuve et al. (2013) was conducted in the general population of Ontario, accounted for the key confounders including indirect adjustment for smoking, and reported a borderline significant, positive association (summarized in Appendix A.7).

3.4.4. Traffic and the road network infrastructure

Traffic proximity

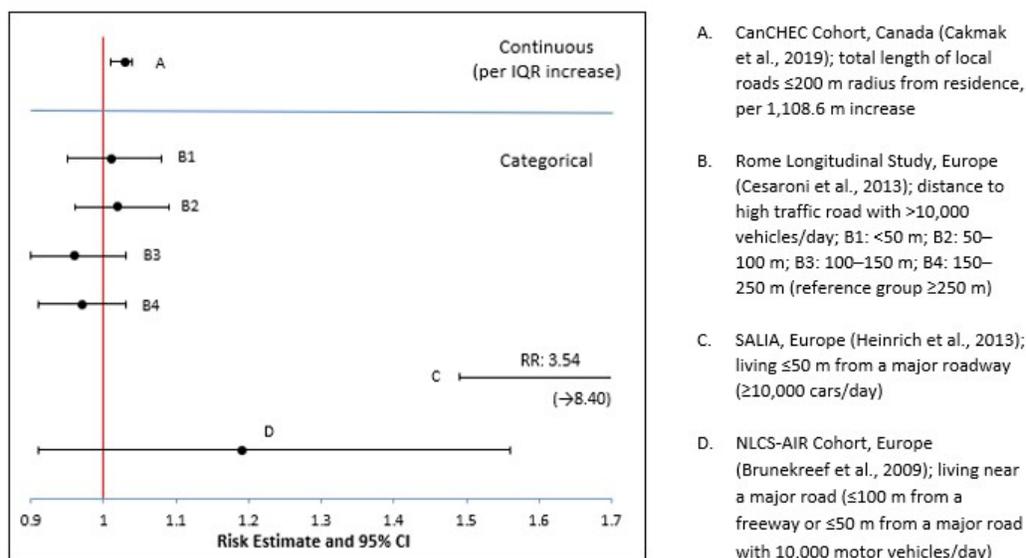
The literature search identified six studies that examined the association between traffic proximity or distance to roadway and respiratory mortality. Five of these studies were conducted on the general population and one on a patient population. The study details are provided in Appendix A.9.

For the general population, four studies were conducted in Europe and one study was conducted in Canada. The studies had a cohort design and ranged in size from 4,752 (Heinrich et al., 2013) to 2,644,370 (Cakmak et al., 2019). They were based on unique study populations, with the exception of two studies conducted in Europe that were both based on the NLCS-AIR cohort (Beelen et al., 2008; Brunekreef et al., 2009). The five studies evaluated mortality from respiratory diseases as a group; one study also examined COPD mortality. All studies accounted for the key confounders of age, sex, and SES (individual- and/or area-level), of which three studies also adjusted for smoking. Some studies considered additional confounders. Proximity to traffic was directly measured in a GIS, based on the exact residential address (European studies) or residential postal code (Canadian study). No consistent definitions or categories were used to assess traffic proximity across the studies.

The associations between traffic proximity and risk of respiratory mortality in the general population are summarized in **Figure 3.25**; only unique cohorts are included in the forest plot. Traffic proximity was considered a continuous variable in only one study. In this Canada-wide study, Cakmak

et al. (2019) reported a positive, significant association. When traffic proximity was evaluated as a categorical variable, four of the six REs were positive, of which two had a wide 95% CI, one was significant, and the remainder were borderline significant. The two REs that showed no association corresponded to distances farther away from high traffic roads (i.e., 100–150 m and 150–250 m) and were part of a study examining exposure-response relationships (Cesaroni et al., 2013). A RE indicating a positive, borderline significant association was also reported for COPD mortality by Cakmak et al. (2019).

FIGURE 3.25: Forest plot of risk estimates for long-term exposure to traffic proximity and respiratory mortality in the general population

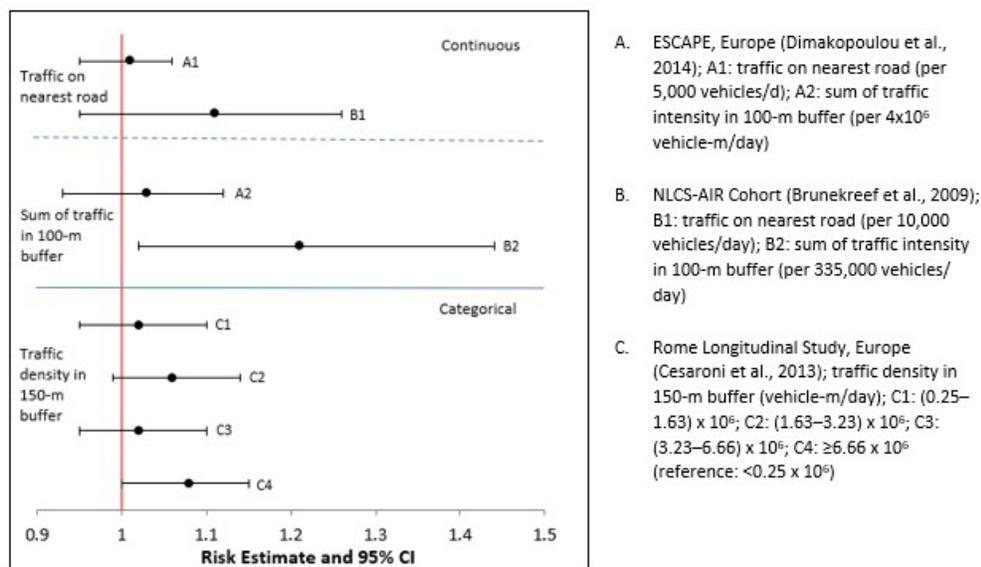


Only one study was identified in the literature searches to examine the association between traffic proximity and respiratory mortality in a patient population. This Canadian study (Finkelstein et al., 2005) conducted in patients who underwent pulmonary function testing at a clinic in Hamilton, Ontario, accounted for the key confounders of age, sex, and SES, and reported no association (summarized in Appendix A.9).

Traffic density

Four studies were identified in the literature search evaluating the risk of respiratory mortality and measures of traffic density. Study details including study population, exposure assessment, confounders, and REs are provided in Appendix A.10. Each of the studies was conducted in Europe based on general population cohorts, and ranged in size from 105,296 (Brunekreef et al., 2009) to 1,265,058 (Cesaroni et al., 2013). Beelen et al. (2008) and Brunekreef et al. (2009) were conducted in the NLCS-AIR cohort and had identical results. Each of the studies accounted for the key confounders of age, sex, and SES, and smoking was accounted for in each of the studies except for Cesaroni et al. (2013). The studies considered respiratory mortality; no specific causes of mortality were considered. An increased risk of respiratory mortality based on traffic density near the residence was reported in each of the studies (summarized in **Figure 3.26**), with most REs being borderline significant or significant.

FIGURE 3.26: Forest plot of risk estimates for long-term exposure to traffic density and respiratory mortality in the general population



3.4.5. Summary

The association between TRAP and respiratory mortality has been investigated in 20 studies of a cohort design; all but two studies were conducted in the general population. These studies evaluated mortality from respiratory disorders as a group, as well as from more specific causes, including COPD. The majority of these studies were conducted in Europe and Canada and assessed exposure to TRAP by modelling individual traffic-related pollutants. Nearly all the studies accounted for the key confounders of age, sex, SES, and smoking and many considered additional confounders. Pooled analyses were conducted on the general population.

For respiratory mortality (from all respiratory disorders), the pooled analyses indicated a positive association for each of the pollutants evaluated (i.e., NO_2 , NO_x , and $\text{PM}_{2.5}$), and these associations with pooled REs ranging from 1.04 to 1.16 were borderline significant for NO_2 and NO_x , but non-significant for $\text{PM}_{2.5}$. Heterogeneity was substantial for each of the three pollutants. The evidence for an association was supported by the qualitative analysis of the different metrics for traffic and the road network infrastructure with some demonstration of an exposure-response relationship. For the other pollutants (i.e., NO , $\text{PM}_{2.5 \text{ abs}}$, BC , PM_{10} , and benzene), the evidence did not support the pooled analyses but was based on a limited number of studies that were not poolable.

Pooled analyses could not be conducted for any specific cause of respiratory mortality. For COPD mortality, most or all of the REs for NO_2 , NO_x , NO , $\text{PM}_{2.5}$, and PM_{10} were positive and significant or borderline significant. The evidence was limited to only one or two studies for the other specific causes of respiratory mortality.

CHAPTER 4:

RISK CHARACTERIZATION AND EVALUATION OF CAUSALITY

4.1. EVIDENCE FROM LONG-TERM EPIDEMIOLOGICAL STUDIES

As a result of the limited number of studies identified for a diverse range of patient populations, characterization of risk and determination of causality were only conducted for the general population.

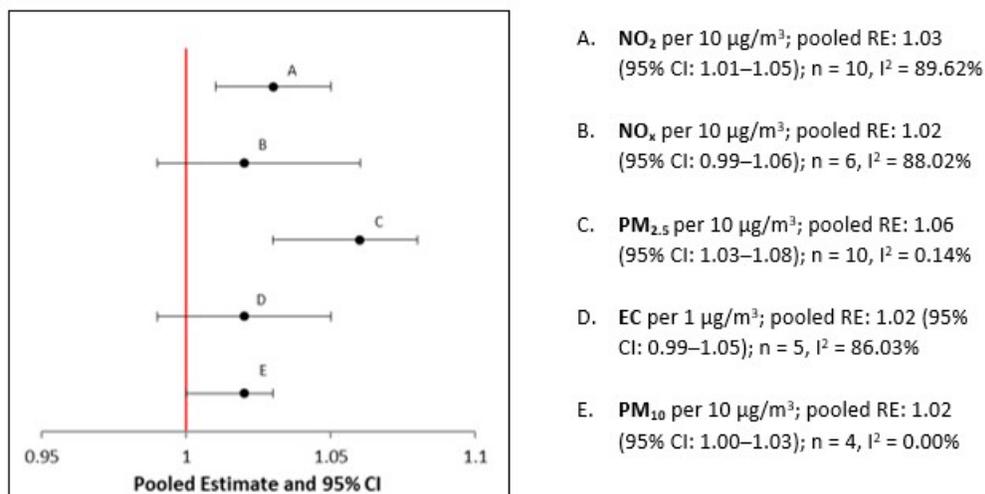
4.1.1. All-cause mortality

For this assessment, all-cause mortality refers to the total number of deaths as well as deaths that were not the result of an accident or suicide; the two were jointly evaluated as the fraction of non-accidental causes of death is generally high (Chen and Hoek, 2020). Forty-seven studies investigated the association between TRAP and all-cause mortality (section 3.2). The majority of these studies were based on the general population. All used a cohort study design and are therefore able to provide a temporal sequence for the observed health outcome. Mortality was ascertained using registry data, including national death records, insurance records, and hospital records. The studies were conducted mainly in Europe and North America. As such, the results from these studies were considered relevant to a Canadian assessment given the similarities in air pollution mixture, standard of living, health care, climate, and so on between Canada, the USA, and European countries. There were also a smaller number of studies in Asia and Australia. Over 60% of the studies assessed exposure to TRAP by modelling individual pollutants, of which a sufficient number of studies (i.e., equal to or greater than four studies) were identified for NO_2 , NO_x , $\text{PM}_{2.5}$, EC, and PM_{10} to conduct quantitative analysis. The remaining studies used metrics of traffic and the road network infrastructure as indirect measures of exposure. Nearly all the studies accounted for the key confounders of age, sex, SES, and smoking and many considered additional confounders (e.g., lifestyle, diet, or health status). The majority of the studies were considered to be of high quality based on the RoB analysis.

Pooled analyses were undertaken to objectively examine the consistency, exposure-response relationship, and strength of the association between all-cause mortality and TRAP for the general population. Random effects models were employed to address heterogeneity in the primary studies. The pooled estimates of these analyses are presented in the forest plot below (**Figure 4.1**) for each of the following traffic-related air pollutants: NO_2 , NO_x , $\text{PM}_{2.5}$, EC, and PM_{10} . Together, these analyses represent 35 unique observations. A positive association was determined for each of the pollutants with pooled REs ranging from 1.02 to 1.06 per increment of pollutant; all were significant or borderline significant. While the magnitudes of the pooled estimates are not readily comparable, all demonstrated an exposure-response relationship. The pooled REs were also robust to subgroup and sensitivity analyses, when applicable. There was an insufficient number of studies conducted in Canada or North America to conduct subgroup analysis by region but when studies were grouped

by exposure assessment method, the pooled estimates and level of significance remained largely unchanged. Similarly, the main analysis was robust when excluding studies with high or probably high RoB in the confounder or exposure domain. Confidence in the association between all-cause mortality and TRAP is further supported by having included studies with different population characteristics (e.g., geographical region, age distribution, and size and type of population) in the pooled analyses as potential biases are unlikely to affect REs in the same direction in different populations. Additionally, the pooled analyses were supported by the qualitative analysis of the different metrics for traffic and the road network infrastructure, which also provided some indication of an exposure-response relationship.

FIGURE 4.1: Forest plot of pooled risk estimates for exposure to TRAP and risk of all-cause mortality in the general population; n represents the number of studies included in the meta-analysis, and I^2 the heterogeneity.



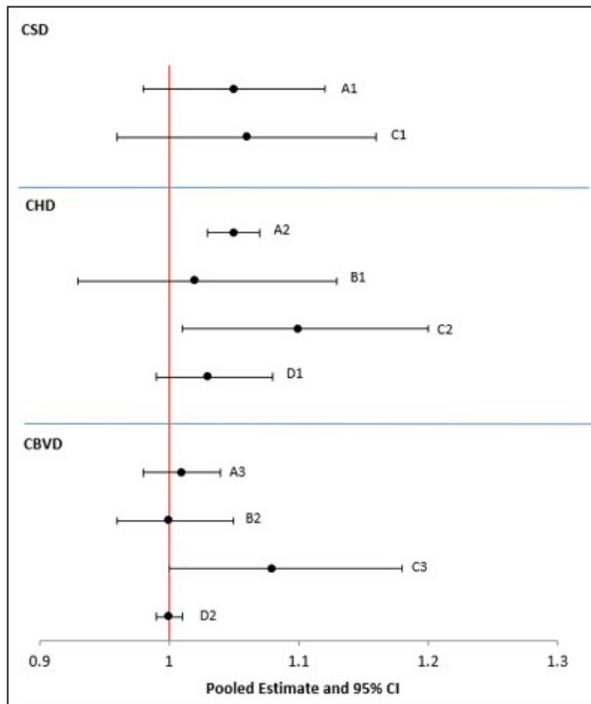
Heterogeneity varied considerably across the pollutants evaluated as depicted in **Figure 4.1**. Pollutants with greater traffic specificity, such as NO_2 , NO_x , and EC, exhibited substantial heterogeneity compared with $\text{PM}_{2.5}$ and PM_{10} , which displayed no or limited heterogeneity. This was expected given that pollutants with greater traffic specificity have greater spatial variation in TRAP exposure estimates, which vary according to factors such as traffic volume and configuration of the roadway network. For NO_2 , the substantial heterogeneity observed is consistent with analyses reported by HEI (2022) and Huangfu and Atkinson (2020). As illustrated in the forest plots in section 3.2, heterogeneity was mainly due to the magnitude of the individual REs and not to the direction of the association. Unlike for NO_x and EC, where heterogeneity was attributed to one or two REs, no individual RE influenced the heterogeneity in the NO_2 analysis. Sources of heterogeneity can be attributed to methodological differences among the primary studies, including exposure assessment methodologies, study location, distinct inclusion and exclusion criteria, population characteristics (e.g., age ranges), and adjustment for confounders and covariates. The variable range of exposures between the primary studies, the sources of TRAP (e.g., the proportion of gasoline vs. diesel vehicles can impact the nature of the TRAP mixture), as well as the large variations in the size of the primary studies may have also contributed to heterogeneity.

4.1.2. Circulatory mortality

Forty-one studies investigated the association between long-term exposure to TRAP and circulatory mortality; all but two studies were based on the general population (section 3.3). They evaluated mortality from CSD as a group and/or from more specific causes. This assessment focused on CSD, CHD, and CBVD due to the limited number of studies identified for the other health outcomes. All the studies pertaining to CSD, CHD, and CBVD were of a cohort study design and, as such, a temporal sequence could be determined for the observed health outcome. Mortality was ascertained using registry data, including national death records, insurance records, and hospital records. The studies were conducted mainly in Europe and North America. As such, the results from these studies were considered relevant to a Canadian assessment, given the similarities in air pollution mixture, standard of living, health care, climate, and so on between Canada, the USA, and European countries. There were also a smaller number of studies in Asia and Australia. Over 60% of the studies assessed exposure to TRAP by modelling individual pollutants; the remaining studies used metrics of traffic and the road network infrastructure as indirect measures of exposure. Nearly all the studies accounted for the key confounders of age, sex, SES, and smoking and many considered additional confounders (e.g., lifestyle, diet, or health status). The majority of the studies were considered to be of high quality based on the RoB analysis.

When a sufficient number of studies (i.e., equal to or greater than four studies) were identified, pooled analyses were undertaken to objectively examine the consistency, exposure-response relationship, and strength of the association between the circulatory mortality health outcomes evaluated (i.e., CSD, CHD, and CBVD) and TRAP for the general population. Random effects models were employed to address heterogeneity in the primary studies. The pooled estimates of these analyses are presented in the forest plot below (**Figure 4.2**).

FIGURE 4.2: Forest plot of pooled risk estimates for exposure to TRAP and risk of circulatory mortality in the general population; n represents the number of studies included in the meta-analysis, and I² the heterogeneity.



- A. NO₂ per 10 µg/m³;**
 A1: pooled RE: 1.05 (95% CI: 0.98–1.12), n = 7, I² = 96.64%;
 A2: pooled RE: 1.05 (95% CI: 1.03–1.07), n = 9, I² = 0.40%;
 A3: pooled RE: 1.01 (95% CI: 0.98–1.04), n = 8, I² = 0.56%.
- B. NO_x per 10 µg/m³;**
 B1: pooled RE: 1.02 (95% CI: 0.93–1.13), n = 4, I² = 77.84%;
 B2: pooled RE: 1.00 (95% CI: 0.96–1.05), n = 5, I² = 0.10%.
- C. PM_{2.5} per 10 µg/m³;**
 C1: pooled RE: 1.06 (95% CI: 0.96–1.16), n = 6, I² = 40.03%;
 C2: pooled RE: 1.10 (95% CI: 1.01–1.20), n = 6, I² = 0.09%;
 C3: pooled RE: 1.08 (95% CI: 1.00–1.18), n = 4, I² = 0.03%.
- D. EC per 1 µg/m³;**
 D1: pooled RE: 1.03 (95% CI: 0.99–1.08), n = 4, I² = 81.92%;
 D2: pooled RE: 1.00 (95% CI: 0.99–1.01), n = 4, I² = 0.00%.

For CSD mortality, quantitative analysis was conducted for two pollutants: NO₂, the most direct measure of TRAP exposure, and PM_{2.5}. They represent 13 unique observations. A borderline significant, positive association was determined for both pollutants with pooled REs of 1.05 and 1.06 per 10 µg/m³ increase in pollutant for NO₂ and PM_{2.5}, respectively. The pooled REs for NO₂ were generally robust to the subgroup, sensitivity, and leave-one-out analyses conducted. They were also supported by the qualitative analysis of NO, EC, and PM₁₀ for which the REs were not pooled, and by the qualitative analysis of the different metrics for traffic and the road network infrastructure, which demonstrated some evidence of an exposure-response relationship. However, mixed results were observed for the qualitative analysis of NO_x.

For CHD mortality, pooled REs representing 23 unique observations were derived for NO₂, NO_x, PM_{2.5}, and EC. A positive association was determined for each of the pollutants with pooled REs ranging from 1.02 to 1.13 per incremental increase in pollutant; all were significant or borderline significant. The subgroup and sensitivity analyses, when conducted, resulted in pooled REs of similar magnitude to the main analysis. Similarly, no NO₂ or EC study was found to influence the main analysis but a couple of studies, when omitted, increased the uncertainty around the pooled RE for NO_x and PM_{2.5}. This evidence was supported by the qualitative analysis of the different metrics for traffic and the road network infrastructure, which demonstrated a clear exposure-response relationship. In contrast, the evidence from the other pollutants (i.e., NO and PM₁₀) was limited and did not indicate an evident association between CHD mortality and TRAP.

For CBVD mortality, the pooled analyses of the pollutants evaluated (NO_2 , NO_x , $\text{PM}_{2.5}$, and EC) produced mixed results. Specifically, a weak positive association of 1.01 and a stronger positive association of 1.08 per increment of pollutant were identified for NO_2 and $\text{PM}_{2.5}$, respectively, while null associations were determined for NO_x and EC. Both positive associations were of borderline significance and the pooled REs represented 21 unique observations. Inconsistent results were also observed for the qualitative analysis of the metrics of traffic and the road network infrastructure and evidence from the other pollutants was limited.

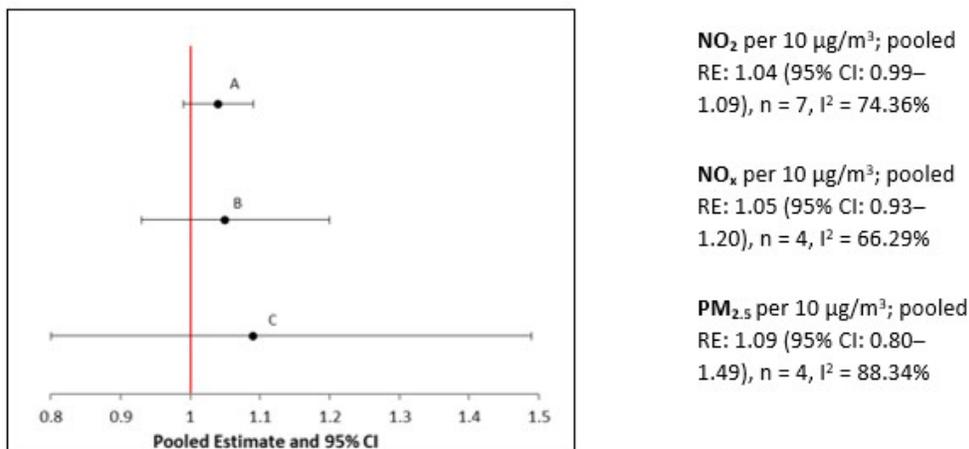
Heterogeneity varied considerably across the pollutants and circulatory mortality outcomes evaluated as depicted in **Figure 4.2**. The pooled estimate for the majority of the exposure-outcome pairs, including NO_2 – CHD mortality, $\text{PM}_{2.5}$ – CHD mortality, and TRAP pollutants for which quantitative analysis was undertaken (i.e., NO_2 , NO_x , $\text{PM}_{2.5}$, and EC) – CBVD mortality displayed little or no heterogeneity. In contrast, heterogeneity was considerable ($I^2 = 96.68\%$) in the pooled analysis for NO_2 and CSD mortality. Two thirds of the REs in the NO_2 – CSD mortality analysis had effect estimates in the same direction and no individual RE influenced the heterogeneity. Substantial heterogeneity ($I^2 = 77.84\%$) was also observed for the NO_x – CHD mortality analysis; this heterogeneity was attributed to one study (Nafstad et al., 2004) as omitting this study from the pooled analysis resulted in minimal heterogeneity. In contrast, omitting one of three studies (Krewski et al., 2009 [NYC cohort]; Carey et al., 2013; Beelen et al., 2014a) from the pooled analysis of $\text{PM}_{2.5}$ and CSD mortality decreased heterogeneity from moderate ($I^2 = 40.03\%$) to minimal ($I^2 \leq 0.12\%$). The variability in heterogeneity can be explained by the extent to which a number of factors, including the methodological differences among the primary studies (described in section 4.1.1), the range of exposures between the primary studies, and the size of the primary study, are similar or dissimilar across the pooled studies.

4.1.3. Respiratory mortality

Twenty studies investigated the association between long-term exposure to TRAP and respiratory mortality; all but two studies were based on the general population (section 3.4). They evaluated mortality from all respiratory disorders (respiratory mortality) and/or from more specific causes. Due to the limited number of studies identified for other specific respiratory causes, this assessment only addresses COPD mortality as a specific cause. Similar to the previous health outcomes evaluated in this assessment, all the studies were of a cohort study design and, as such, a temporal sequence could be determined for the observed health outcome. Mortality was ascertained using registry data, including national death records, insurance records, and hospital records. The studies were conducted mainly in Europe and Canada and, as described previously, the results from these studies were considered relevant to a Canadian assessment. The majority of the studies assessed exposure to TRAP by modelling individual pollutants; the remaining studies used metrics of traffic and the road network infrastructure as indirect measures of exposure. Nearly all the studies accounted for the key confounders of age, sex, SES, and smoking and many considered additional confounders (e.g., lifestyle, diet, or health status). The majority of the studies were considered to be of high quality based on the RoB analysis.

For the general population, pooled analyses were conducted for respiratory mortality and long-term exposure to the following three pollutants representing TRAP exposure: NO_2 , NO_x , and $\text{PM}_{2.5}$. Random effects models were employed to address heterogeneity in the primary studies. The pooled estimates of these analyses representing 15 unique observations are presented in the forest plot below (**Figure 4.3**). A positive association was determined for each of the pollutants with pooled REs ranging from 1.04 to 1.09 per $10 \mu\text{g}/\text{m}^3$ increase in pollutant, indicating consistency and strength in the association as well as an exposure-response relationship. Although the association was borderline significant for NO_2 and NO_x , it was non-significant and imprecise for $\text{PM}_{2.5}$ as depicted by the large 95% CI. For NO_2 , the subgroup and sensitivity analyses, when conducted, resulted in pooled REs of similar magnitude and precision to the main analysis. In contrast, for NO_x , while the pooled RE was robust, statistical significance was not observed in these analyses. A null association was also noted for NO_x when Nafstad et al. (2004) was omitted in the leave-one-out analysis. For $\text{PM}_{2.5}$, the pooled estimates from the subgroup and sensitivity analyses varied from the main analysis and the 95% CI remained large; this was attributed to the limited number of studies ($n = 2$ or 3) in these analyses. The positive association between respiratory mortality and TRAP exposure was supported by the qualitative analysis of the different metrics for traffic and the road network infrastructure, which demonstrated some evidence of an exposure-response relationship but also included some imprecise associations. The evidence from the qualitative analysis of the other pollutants representing TRAP exposure was limited and did not support an association between respiratory mortality and TRAP exposure.

FIGURE 4.3: Forest plot of pooled risk estimates for exposure to TRAP and risk of respiratory mortality in the general population; n represents the number of studies included in the meta-analysis, and I^2 the heterogeneity.



Heterogeneity was substantial in the pooled REs for all three pollutants (as indicated in **Figure 4.3**) and remained substantial in all the subgroup and sensitivity analyses that were conducted with an n greater than or equal to 3. Unlike for NO_2 where no one study influenced heterogeneity, no heterogeneity in the pooled RE was observed when Nafstad et al. (2004) and Carey et al. (2013) were omitted in the leave-one-out analysis for NO_x and $\text{PM}_{2.5}$, respectively. The sources of heterogeneity are described in section 4.1.3.

Pooled analysis was not conducted for COPD mortality and exposure to TRAP as there was an insufficient number of studies from unique cohorts that had the necessary data to conduct a quantitative analysis. The qualitative analysis indicated mostly positive associations that were either significant or borderline significant for NO₂, NO_x, NO, PM_{2.5}, and PM₁₀.

4.2. BIOLOGICAL EVIDENCE

HEI (2010) identified that the health effects of TRAP exposure were mediated through oxidative stress, which occurs when levels of reactive oxygen species (ROS) or free radical generation exceeds the antioxidant defence systems in cells. This leads to oxidative damage to lipids, proteins, and DNA, and can result in impairment of cellular function and cell death. Additionally, the altered redox state of the cell results in activation of gene expression of cytokines, chemokines, and adhesion molecules that participate in inflammatory responses, contributing to the cycle of oxidative tissue injury. HEI (2022) expanded on this and identified numerous inter-related pathways by which TRAP exposure can lead to adverse health outcomes. Inhaled TRAP particles penetrate the lungs and initiate a suite of responses including:

- lung inflammation, which can result in inflammatory mediators entering systemic circulation mediating a systemic inflammatory response;
- direct formation of biological intermediates (e.g., oxidized macromolecules) that can enter systemic circulation and mediate a systemic inflammatory response;
- neuroendocrine activation, which can elicit respiratory symptoms and alter cardiorespiratory function; and
- translocation of particles from the lungs into the blood stream where they can have direct impacts on the vasculature or other organs/tissues in the body.

These mechanisms of action can also lead to cardiovascular impairment, and ultimately circulatory morbidity and mortality, through impacts on the heart (e.g., altered heart rate variability [HRV], arrhythmia), vasculature (e.g., impaired endothelial function, altered vasoconstriction, exacerbation of atherosclerosis), and blood (e.g., increased coagulability, impaired platelet activity).

HEI (2022) also identified that TRAP exposure elicits adverse respiratory outcomes via action on airway oxidative stress and tissue damage, airway reactivity and remodelling, inflammatory pathways and immunological responses, and enhanced sensitization to aeroallergens. The mechanisms of action are complex and are influenced by genetic susceptibility, compromised lung function, and increased susceptibility to bacterial and viral pathogens.

Similar mechanisms of action centred on ROS generation, oxidative stress, and inflammatory responses were identified in the previous risks assessment of TRAP by Health Canada, providing biological plausibility for asthma, allergies, and lung function (Health Canada, 2020) and selected cancer outcomes (Health Canada, 2022c). As noted in those assessments, although the experimental studies mainly considered short-term exposures, the biological responses are informative to provide mechanistic insight into the effects observed in the long-term epidemiological studies.

A review of recent primary literature also identified adverse effects of TRAP exposure on the circulatory and respiratory systems (table summaries provided in section 4 of the supporting documentation). Panel studies that evaluated the biological responses of the circulatory system to real-world traffic exposures identified the following: alterations in HRV, blood pressure, and heart rate; increased biomarkers of systemic oxidative stress, inflammation, and cardiac injury; and/or endothelial dysfunction and arterial stiffness (Mallach et al., 2023; Zhang et al., 2022; Han et al., 2021; Hudda et al., 2021; Wang et al., 2022; Biel et al., 2020; Liang et al., 2018; Cole-Hunter et al., 2016; Kubesch et al., 2015; Ladva et al., 2018; Sarnat et al., 2014; Chu et al., 2016; Mirowsky et al., 2015; Jiang et al., 2016; Weichenthal et al., 2014; Brucker et al., 2013; Bartell et al., 2013; Huang et al., 2013; Chuang et al., 2013; Shields et al., 2013). Most of these panel studies were conducted in the USA (n = 7), followed by Asia (n = 6) and Canada (n = 3). Controlled exposure studies focused on short-term DE exposure and reported HRV and blood pressure alterations, increased biomarkers of systemic oxidative stress and inflammation, vasoconstriction, and altered blood chemistry (Cosselman et al., 2020; Sack et al., 2016; Jiang et al., 2014; Tong et al., 2014; Krishnan et al., 2013). A small number of studies in laboratory animals considered either roadside exposures or particles collected from roadsides and evaluated longer durations (e.g., weeks to months). These studies observed oxidative stress and inflammation in cardiac tissue that was associated with fibrosis (Edwards et al., 2020) and evidence of increased progression of atherosclerosis (Zhao et al., 2020).

For respiratory system impacts of TRAP exposure, the panel studies of real-world traffic exposures and controlled exposure studies of DE reported oxidative stress and inflammation of the airways and/or altered lung function metrics (Orach et al., 2022; Xu et al., 2022; Han et al., 2019; Wang et al., 2022; Jiang et al., 2019; Matt et al., 2016; Sarnat et al., 2014; Zhao et al., 2015). These studies were primarily conducted in Asia. Studies in experimental animals identified that TRAP and traffic particles increased oxidative stress and induced inflammatory responses in lungs and airways; altered lung function and induced airway hyperresponsiveness; and resulted in respiratory tissue changes, including thickening of alveolar walls, smooth muscle hypertrophy, matrix remodelling, and cellular degeneration (Xiao et al., 2022; Jheng et al., 2021; Chuang et al., 2020; Chan et al., 2019; Samara et al., 2015). In addition, in vitro studies in respiratory tissue cell lines reported ROS generation, oxidative stress, inflammatory responses, and reduced cell viability associated with traffic particles (Gong et al., 2022; Van Den Heuvel et al., 2016; Mirowski et al., 2015; Shang et al., 2013).

Considered together, multiple lines of evidence provide a biological basis for adverse health impacts on the circulatory and respiratory systems. For all-cause mortality, cancer along with circulatory and respiratory causes are among the leading non-accidental causes of death in Canada (Statistics Canada, 2022). The mechanistic information summarized in this section provides possible pathways by which TRAP exposure can disrupt or alter cellular and tissue function, which can enhance disease progression and ultimately lead to mortality. Overall, the experimental evidence reviewed in this assessment and Health Canada (2022c) provide the biological plausibility for all-cause as well as circulatory and respiratory mortality.

4.3. DETERMINATION OF CAUSALITY

4.3.1. All-cause mortality

For all-cause mortality (sections 3.2 and 4.1.1), based on the following lines of evidence:

- i. The positive association between long-term TRAP exposure and all-cause mortality determined for each of the air pollutants associated with exposure to TRAP (i.e., NO₂, NO_x, PM_{2.5}, EC, and PM₁₀). For each of the pollutants, the pooled REs ranged from 1.02 to 1.06 per increment of pollutant and were significant (for NO₂ and PM_{2.5}) or borderline significant (for NO_x, EC, and PM₁₀), indicating an exposure-response relationship, and consistency in the association across several pollutants.
- ii. Considerable qualitative evidence from the various metrics of traffic and road network infrastructure, which also supported the presence of an exposure-response relationship.
- iii. Support from the biological evidence, which provides a biological basis for adverse health impacts on the circulatory and respiratory systems, as circulatory and respiratory causes are among the leading non-accidental causes of death.

Overall, it is concluded that there is sufficient evidence of a causal relationship between long-term exposure to TRAP and all-cause mortality.

4.3.2. Circulatory mortality

For CSD mortality (sections 3.3 and 4.1.2), based on the following lines of evidence:

- i. The positive, borderline significant associations between long-term TRAP exposure and CSD mortality determined for NO₂ and PM_{2.5}, with pooled REs of 1.05 and 1.06 per increment, respectively, indicating an exposure-relationship and consistency in the evidence. This is supported by qualitative analysis from other TRAP pollutants (i.e., BC, PM_{2.5 abs}, PM₁₀, and benzene), noting the limited evidence for these pollutants.
- ii. Support from the qualitative evidence based on the various metrics of traffic and road network infrastructure, which also indicated the presence of an exposure-response relationship.
- iii. Support from the biological evidence, which provides a biological basis for adverse health impacts on the circulatory system.

Overall, it is concluded that there is sufficient evidence that the relationship between long-term TRAP exposure and CSD mortality is likely to be causal.

For CHD mortality (sections 3.3 and 4.1.2), based on the following lines of evidence:

- i. The positive, significant association between long-term TRAP exposure and CHD mortality determined for NO₂ and PM_{2.5} with pooled REs of 1.05 and 1.10 per increment, respectively, and borderline significant associations for NO_x and EC with pooled REs of 1.02 and 1.03 per increment, respectively. These quantitative syntheses indicate an exposure-relationship and consistency in the evidence for these pollutants; however, mixed results were noted from the limited studies of NO and PM₁₀.

- ii. Support from the qualitative evidence based on the various metrics of traffic and road network infrastructure, which also indicated the presence of an exposure-response relationship.
- iii. Support from the biological evidence, which provides a biological basis for adverse health impacts on the circulatory system.

Overall, it is concluded that there is sufficient evidence that the relationship between long-term TRAP exposure and CHD mortality is likely to be causal.

For CBVD mortality (sections 3.3 and 4.1.2), based on the following lines of evidence:

- i. The mixed results between long-term TRAP exposure and CBVD mortality for the TRAP pollutants. Specifically, a positive, borderline significant association was determined for NO₂ and PM_{2.5} with REs of 1.01 and 1.08 per increment, respectively; however, a null association was identified for NO_x and EC. The qualitative analysis for NO and PM₁₀ was limited to support an association.
- ii. Limited support from the qualitative evidence based on the various metrics of traffic and road network infrastructure, with no clear evidence of an exposure-response relationship.
- iii. Support from the biological evidence, which provides a biological basis for adverse health impacts on the circulatory system.

Overall, it is concluded that there is inadequate evidence to infer a causal relationship between long-term TRAP exposure and CBVD mortality.

4.3.3. Respiratory mortality

For respiratory mortality (sections 3.4 and 4.1.3), based on the following lines of evidence:

- i. The positive, borderline significant associations between long-term TRAP exposure and respiratory mortality determined for NO₂ and NO_x, with pooled REs of 1.04 and 1.05 per increment, respectively, indicating an exposure-relationship and consistency in the evidence. For PM_{2.5}, a positive association was identified, with a pooled RE of 1.09; however, it was non-significant and imprecise. Limited qualitative evidence was noted for the other pollutants (i.e., NO, PM_{2.5 abs}, BC, PM₁₀, and benzene).
- ii. Support from the qualitative evidence based on the various metrics of traffic and road network infrastructure, which also suggested the presence of an exposure-response relationship.
- iii. Support from the biological evidence, which provides a biological basis for adverse health impacts on the respiratory system.

Overall, it is concluded that the evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term TRAP exposure and respiratory mortality.

For COPD mortality (sections 3.4 and 4.1.3), based on the following lines of evidence:

- i. Although a quantitative synthesis could not be conducted for COPD mortality, most or all of the REs for the various TRAP pollutants (i.e., NO₂, NO_x, NO, PM_{2.5}, and PM₁₀) were positive and significant or borderline significant.
- ii. Support from the biological evidence, which provides a biological basis for adverse health impacts on the respiratory system.

Overall, it is concluded that the evidence is suggestive of, but not sufficient to infer, a causal relationship between long-term TRAP exposure and COPD mortality.

CHAPTER 5: CONCLUSION

Using systematic review techniques, including meta-analysis, this risk assessment evaluated the epidemiological literature regarding the associations between long-term exposure to TRAP and mortality. These associations were assessed along with relevant biological evidence gathered from mechanistic data from recent risk assessments of TRAP and recent primary literature as part of a weight of evidence approach to determine the causal role of long-term TRAP exposure in the health endpoints of all-cause mortality, CSD mortality, CHD mortality, CBVD mortality, respiratory mortality, and COPD mortality.

Based on the overall weight of evidence, **it is concluded that:**

- i. there is **sufficient evidence of a causal relationship** between long-term exposure to TRAP and all-cause mortality;
- ii. there is **sufficient evidence** that the relationship between long-term TRAP exposure and CSD mortality **is likely to be causal**;
- iii. there is **sufficient evidence** that the relationship between long-term TRAP exposure and CHD mortality **is likely to be causal**;
- iv. there is **inadequate evidence to infer a causal relationship** between long-term TRAP exposure and CBVD mortality;
- v. the evidence is **suggestive of, but not sufficient to infer, a causal relationship** between long-term TRAP exposure and respiratory mortality;
- vi. the evidence is **suggestive of, but not sufficient to infer, a causal relationship** between long-term TRAP exposure and COPD mortality.

Key uncertainties and gaps

The conclusions of this risk assessment were formed in consideration of the epidemiological and biological literature evaluating the health effects associated with exposure to TRAP pollutants. For the causes of mortality considered in this assessment, the scientific evidence was mainly based on NO_2 , NO_x , $\text{PM}_{2.5}$, PM_{10} , EC, traffic proximity, and traffic density. Although these markers are typically used to assess or quantify TRAP exposure, a definitive causative agent for the health impacts was not identified from the studies. Given the expected high degree of correlation between the individual TRAP components, further studies and use of multi-pollutant models would be required to identify the causative agent or agents within the TRAP mixture responsible for the health effects.

The exposure assessment framework described in section 2.1.2 was stringently applied to confirm TRAP specificity. As such, between-cities analyses and national scale studies with no city-specific adjustment were excluded from this assessment as they are more influenced by climate, topography, presence of point-source emitters, and overall city size (Crouse et al., 2015). While this limited the evidence base for this assessment, it allowed identification of studies in which the exposure contrasts were more likely attributable to TRAP sources. Additional studies with intra-city analyses would help

to expand the TRAP-specific literature database. As most of the primary studies estimated TRAP exposures at the residential address only, the accuracy by which TRAP exposure is assigned could also be improved in future studies by considering the mobility of the study participants and/or residential address changes.

The quantitative analyses in this risk assessment were highly comparable to those reported by HEI (2022), which is expected given the similarities in the approaches taken. However, key differences in the analyses were noted, including differences in the literature search periods and application of the inclusion/exclusion criteria. This led to some differences in the studies included in the quantitative synthesis and resulted in small variations in some of the pooled estimates.

In nearly all the studies evaluated, mortality from all causes and specific causes were ascertained using registry data and/or causes of mortality classified based on ICD codes. Mortality registries are generally complete, as is linkage of individuals to these registries. Of the small number of studies that did not rely on registry data, the information was taken from medical records, which were also considered to be reliable sources of this information. Mortality from a broad group of diseases such as circulatory and respiratory diseases are also less likely to be misclassified compared with specific causes of diseases such as CHD, CBVD, and COPD. As ICD codes have been updated over time and studies have used different versions of this code, there may be some inconsistencies on how specific causes of circulatory and respiratory mortality were classified. Additionally, five studies reported cardiopulmonary or cardiorespiratory mortality, without presenting the results for circulatory and respiratory mortality separately. These studies were considered a measure of circulatory mortality, as these causes dominate the combined category but could also result in the misclassification of the outcomes.

REs from all studies but one had some level of adjustment for confounders (e.g., age, sex, SES, smoking, and lifestyle factors); however, the level of adjustment was variable between the studies. Consistency in the inclusion and specification of the key confounders would improve the robustness of the quantitative syntheses. Additionally, the potential contributing role of environmental features such as traffic noise, green space, and neighbourhood walkability in the outcomes were considered in only a limited number of studies. Further studies exploring the potential confounding effects of these factors could help refine the risk attributable to TRAP exposure.

Although a substantial body of primary literature was identified for TRAP exposure and mortality, the size of the evidence base varied considerably depending on type of mortality. For all-cause mortality, the literature database was well developed, resulting in the most number of exposure-outcome pairs and unique observations, thus providing greater certainty in the causality conclusion. In comparison, the causality conclusions drawn for circulatory and respiratory mortality and their subtypes were based on a less developed epidemiological literature database, resulting in fewer exposure-outcome pairs and unique observations. While the overall evidence was more limited, the consistency, strength, and exposure response of the association was sufficient to evaluate the relationship and determine the level of causality. For other causes of mortality such as CBVD, CHD, MI, and HF, only a limited number of epidemiological studies were identified; as a result, the causal relationship could not be determined. Additional studies on these health outcomes would be useful in further characterizing and understanding the role of TRAP exposure in mortality. Similarly, only a limited number of studies were conducted on populations that may be disproportionately impacted,

including patient populations; as such, this was inadequate to support a conclusion for all-cause or any specific causes of mortality. Furthermore, additional studies addressing the potential sex-based differences in risk of mortality from specific causes of mortality (e.g., higher cardiovascular risk in males) and the influence of TRAP exposure on these differential risks would be informative.

For this risk assessment, the biological and mechanistic evidence was derived from existing reviews of TRAP by Health Canada (2020, 2022c) and HEI (2010, 2022) as well as a search of the primary literature from the past 10 years (i.e., 2013–2023). Based on the scientific evidence considered in this assessment, additional biological studies would be beneficial to further elucidate the mechanisms of action for the role of TRAP in mortality, particularly with respect to the effects of long-term exposure. At present, the majority of the experimental evidence is based on short-term exposures and supports a role for TRAP exposure in cellular and tissue dysfunction and enhancement of disease progression, which can ultimately lead to mortality. From the experimental evidence reviewed in this risk assessment, the proposed mechanisms of action have identified the central role of inflammation and oxidative stress, suggesting a possible overlap or one or more shared pathways of effect. A more thorough understanding of the mechanism would also help identify the component or components of TRAP that are the causative agent or agents of the observed health effects. This information could be used to inform policies or programs that would reduce or mitigate exposure to one or more specific pollutants.

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APPENDIX. STUDY DETAILS BY EXPOSURE METRIC

The study details regarding study population, exposure assessment, confounders, and REs are provided in this appendix by pollutant or metric of traffic and the road network infrastructure.

A.1. STUDY DETAILS FOR MORTALITY BY LONG-TERM EXPOSURE TO NO₂

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Canada—General population								
Gan et al., 2011	Cohort (1994–2002)	Vancouver metropolitan residents, British Columbia, aged 45–85 y Males: 45.3% Mean age (SD): 58.7 (10.4) y	LUR model (residential postal code) Mean (SD): 32.1 (8.0) µg/m ³ Median: 30.6 µg/m ³ IQR: 8.4 µg/m ³ Range: 15.3–57.7 µg/m ³	Age, sex, area-level SES, pre-existing comorbidities	406,232	CHD: 3,104	8.4 µg/m ³	CHD: RR = 1.04 (1.01–1.08)
Chen et al., 2013	Ontario Tax Cohort (1982–2004)	Residents in Toronto, Hamilton, or Windsor, Ontario 35–85 y, randomly selected from Ontario Tax Cohort All 3 cities: Males: 50% Mean age: 52 y	LUR model (residential postal code) Toronto: Mean: 12.7 ppb IQR: 4.1 ppb Hamilton: Mean: 15.5 ppb IQR: 2.9 ppb Windsor: Mean: 12.1 ppb IQR: 2.5 ppb	Age, sex, individual-level SES, area-level SES, indirect adjustment for smoking (data from 2001 CCHS), marital status	Pooled (Hamilton, Toronto, Windsor): 205,440	CSD: 19,380 CHD: 10,460 CBVD: 4,130	5 ppb (9.4 µg/m ³)	CSD: Pooled ^b Rate ratio = 1.07 (1.02–1.11) CHD: Pooled ^b Rate ratio = 1.08 (1.02–1.14) CBVD: Pooled ^b Rate ratio = 0.96 (0.89–1.03)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Gan et al., 2013	Cohort (1994–2002)	Vancouver metropolitan residents, British Columbia, aged 45–85 y Males: 47.1% Mean age (SD): 59.4 (10.7) y	LUR model (residential postal code) Mean (SD): 32.2 (8.1) µg/m ³ Median: 30.7 µg/m ³ IQR: 8.4 µg/m ³ Range: 15.3–57.7 µg/m ³	Age, sex, area-level SES	465,360	COPD: 541	8.4 µg/m ³	COPD: RR = 1.04 (0.95–1.12)
Villeneuve et al., 2013	Ontario Tax Cohort (1982–2004)	Randomly selected income tax filing Canadians in 10 urban areas of Ontario, restricted to Toronto, aged ≥35 y Males: 50.4%	LUR model (residential postal code) Mean (SD): 28.93 (6.34) ppb IQR: 5.92 ppb Median: 26.54 ppb Range: 13.59–60.60 ppb	Age, sex, individual-level SES, area-level SES, marital status indirectly adjusted for smoking	58,760	All-cause: 18,020 CSD: 6,060 RD: 1,410	5.92 ppb (11.13 µg/m ³)	All-cause: Rate ratio = 1.01 (0.99–1.04) CSD: Rate ratio = 1.02 (0.98–1.05) RD: Rate ratio = 1.04 (0.97–1.12)
Crouse et al., 2015	Cohort CanCHEC (1991–2006)	Cohort participants aged ≥25 y who completed long-form census from 10 cities (individually) across Canada Males: 48.0%	LUR model (within city; residential address) Mean: 4.7–17.6 ppb IQR: 1.3–7.7 ppb Min: 0.0–7.5 ppb Max: 16.5–60.4 ppb	Age, sex, individual-level SES, area-level SES, indirect adjustment for smoking and BMI, Aboriginal ancestry, minority status, other individual- and area-level SES indicators	735,590	All-cause: 80,660 CSD: 27,600 CHD: 16,550 CBVD: 5,440 RD: 6,450	5 ppb (9.4 µg/m ³)	All-cause: Pooled HR = 1.05 (1.04–1.07) CSD: HR = 1.04 (1.02–1.07) CHD: HR = 1.05 (1.02–1.09) CBVD: HR = 1.02 (0.97–1.07) RD: HR = 1.08 (1.03–1.12)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Canada—Patient population								
Jerrett et al., 2009	Cohort (1992–2002)	Adult patients from respiratory disease clinic in Toronto, Ontario Males: 48% Age (median): 60 y	LUR model (residential postal code) Median: 22.9 ppb IQR: 4 ppb	Age, sex, area-level SES, individual-level smoking, BMI, and lung function	2,360	All-cause: 298 CSD: 80 RD: 75	4 ppb (7.52 µg/m ³)	All-cause: Relative risk (RR) = 1.17 (1.00–1.36) CSD: RR = 1.45 (1.10–1.92) RD: RR = 1.06 (0.67–1.49)
USA—General population								
Alexeeff et al., 2018	Cohort (2010–2015)	Adult members of the Kaiser Permanente Northern California health care system living in Oakland, CA during the study period; those with history of CSD were excluded Males: 47.0%	Hybrid or other model (residential address) Mean (SD): 9 (3.8) ppb Median: 9.8 ppb IQR: 5.1 (12.1–7.0) ppb Min-max: 2.0–60.8 ppb	Age, sex, area-level SES, individual-level smoking, race, BMI, health status	41,869	CHD: 130 CBVD: 27	3.8 ppb (7.14 µg/m ³)	CHD: HR = 1.09 (0.89–1.34) CBVD: HR = 1.38 (0.93–2.06)
Europe—General population								
Rosenlund et al., 2006	Case-control Stockholm Heart Epidemiology Program (1992–1994)	Population-based case-control in Stockholm, Sweden; first events of MI in population aged 45–70 y Males (cases; controls): 66%; 65% Mean age (SD): 60.9 (6.8) y; 60.9 (6.8) y	Dispersion model (residential address) Cases: Median (5th–95th): 14.2 (3.0–32.0) µg/m ³ Controls: Median (5th–95th): 13.5 (3.4–32.2) µg/m ³	Age, sex, individual-level SES, individual smoking, diabetes, physical activity	3,210	MI: 272	30 µg/m ³	MI: OR = 1.51 (0.96–2.37)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Naess et al., 2007	Cohort (1992–1998)	Residents aged 51–90 y of 470 neighbourhoods in Oslo, Norway	Dispersion model (neighbourhood-level) Mean: 39 µg/m ³ Range: 2–73 µg/m ³	Age, sex, individual-level SES, other SES indicators	143,842	CSD: 51–70 y Men: 2007 Women: 946 71–90 y Men: 4,531 Women: 7,480 COPD: 51–70 y Men: 233 Women: 203 71–90 y Men: 503 Women: 516	Quartile increase (not specified)	CSD: 51–70 y Men: 1.08 (1.04–1.13) Women: HR = 1.07 (1.00–1.14) 71–90 y Men: HR = 1.02 (0.99–1.05) Women: HR = 1.01 (0.99–1.04) COPD: 51–70 y Men: HR = 1.21 (1.05–1.39) Women: HR = 1.06 (0.92–1.21) 71–90 y Men: HR = 1.04 (0.95–1.14) Women: HR = 1.07 (0.97–1.17)
Rosenlund et al., 2008	Cohort (1998–2000)	Residents in Rome, Italy aged 35–84 y who experienced first coronary event Males: 68.3% Fatal cases within 28 days captured	LUR model (residential address; census block) 5th–95th percentile: 33.0–60.1 µg/m ³	Age, sex, area-level SES	11,167	CHD: 4,654	10 µg/m ³	CHD: RR = 1.07 (1.02–1.12)
Rosenlund et al., 2009	Case-control (1985–1996)	Population-based case-control in Stockholm, Sweden; first events of MI in population 15–79 y Males (cases; controls): 69%; 49% Fatal cases captured	Dispersion model (residential address) Cases: Median (5th–95th): 12.9 (1.7–33.3) µg/m ³ Controls: Median (5th–95th): 11.8 (1.5–32.8) µg/m ³	Age, sex, individual-level SES, calendar year	301,273	MI: 8,809	30 µg/m ³	MI: OR = 1.23 (1.15–1.32)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Cesaroni et al., 2012	Cohort Rome Longitudinal Study (2001–2006)	Adults aged 45–80 y who resided in Rome, Italy ≥ 5 y Limited to participants that did not change address during study period	LUR model (residential address) Mean (SD): 43.9 (8.3) $\mu\text{g}/\text{m}^3$ Median: 44.8 $\mu\text{g}/\text{m}^3$ IQR: 10.4 (49.4–39.0) $\mu\text{g}/\text{m}^3$ Range: 13.0–75.2 $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, marital status, place of birth	684,013	All-cause: 45,006	10 $\mu\text{g}/\text{m}^3$	All-cause: HR = 1.04 (1.03–1.05)
Raaschou-Nielsen et al., 2012	Diet, Cancer, and Health Cohort Study (1993–2009)	Adults aged 50–64 y living in the Copenhagen and Aarhus areas, born in Denmark, and with no previous cancer diagnosis. Males: 47.5% Median age: 56.1 y	Hybrid model (residential address) Mean: 16.9 $\mu\text{g}/\text{m}^3$ Median: 15.1 $\mu\text{g}/\text{m}^3$ Range: 10.5–59.6 $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, individual smoking, lifestyle and dietary variables, occupational exposure, marital status	52,061	All-cause: 5,534 CSD: 1,285 CHD: 548 CBVD: 292	Per doubling (logbase 2 transformed) $\mu\text{g}/\text{m}^3$	All-cause: Mortality rate ratio (MRR) = 1.08 (0.98–1.18) CSD: MRR = 1.27 (1.06–1.51) CHD: MRR = 1.12 (0.85–1.47) CBVD: MRR = 1.11 (0.76–1.63)
Carey et al., 2013	Cohort Clinical Practice Research Datalink (2003–2007)	Patients aged 40–89 y of 205 clinics in England, United Kingdom; fully registered for at least 1 year on Jan 1, 2003 Males: 48.4%	Dispersion model (residential postcode centroid) Mean (SD): 22.5 (7.4) $\mu\text{g}/\text{m}^3$ Range: 4.5–60.8 $\mu\text{g}/\text{m}^3$ IQR: 10.7 $\mu\text{g}/\text{m}^3$	Age, sex, area-level SES, individual-level smoking, BMI	830,429	All-cause: 82,421 CSD: 28,726 RD: 10,500	10.7 $\mu\text{g}/\text{m}^3$	All-cause: HR = 1.02 (1.00–1.04) CSD: HR = 0.99 (0.97–1.02) RD: HR = 1.07 (1.03–1.12)
Cesaroni et al., 2013	Cohort Rome Longitudinal Study (2001–2010)	Adults aged ≥ 30 y who resided in Rome, Italy ≥ 5 y Males: 45.5% <60 y: 61.3% 60–75 y: 26.8% ≥ 75 y: 11.9%	LUR model (residential address) Mean (SD): 43.6 (8.4) $\mu\text{g}/\text{m}^3$ Median: 44.5 $\mu\text{g}/\text{m}^3$ IQR: 10.7 (49.2–38.5) $\mu\text{g}/\text{m}^3$ Range: 13.0–75.2 $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, marital status, place of birth	1,265,058	All-cause: 144,441 CSD: 60,318 CHD: 22,562 CBVD: 13,576 RD: 8,825	10 $\mu\text{g}/\text{m}^3$	All-cause: HR = 1.03 (1.02–1.03) CSD: HR = 1.03 (1.02–1.04) CHD: HR = 1.05 (1.03–1.06) CBVD: HR = 1.01 (0.99–1.03) RD: HR = 1.03 (1.00–1.06)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Beelen et al., 2014a	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Mean age at baseline (SD): 41.1 (11.8)–70.3 (8.1) y Females: 47.7%–100%	LUR model (residential address) Range of means (SD): 5.2 (2.5)–59.8 (10.5) µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	367,251	All-cause: 29,076	10 µg/m ³	All-cause: HR = 1.01 (0.99–1.03)
Beelen et al., 2014b	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females (range): 63% (48%–100%) Mean age at baseline (range): 50.5 (41.1–70.3) y	LUR model (residential address) Range of means (SD): 5.2 (2.5)–59.8 (10.5) µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	367,383	CSD: 9,994 CBVD: 2,484 CHD: 4,992 MI: 2,264	10 µg/m ³	CSD: HR = 1.01 (0.97–1.06) CBVD: HR = 1.01 (0.93–1.10) CHD: HR = 1.00 (0.91–1.09) MI: HR = 0.98 (0.88–1.09)
Dimakopoulou et al., 2014	Cohort ESCAPE (1990s–2007)	16 cohorts from 11 countries; general population Females (range): 47.7%–100% Mean age range at baseline: 41.9–73.0 y	LUR model (residential address) Range of means (SD): 5.2 (2.5)–53.1 (10.8) µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	307,553	RD: 1,559	10 µg/m ³	RD: HR = 0.97 (0.89–1.05)
Nieuwenhuijsen et al., 2018	Cohort SIDIAP (2010–2014)	Adults ≥18 y, registered in SIDIAP and living in Barcelona; SIDIAP represents 80% of total population of Catalonia (Spain) Males: 53% Average age: 50.9 y	LUR model (census tract) Geometric mean (95% CI): 53.42 (53.40–53.45) µg/m ³ p25–p75: 48.18–59.70 µg/m ³	Age, sex, area-level SES, individual-level smoking	792,649	All-cause: 28,391	5 µg/m ³	All-cause: HR = 1.01 (1.00–1.02)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Europe—Patient population								
Rosenlund et al., 2008	Cohort (1998–2005)	Residents in Rome, Italy aged 35–84 y who survived first coronary event (1998–2000) Follow-up: 4.0–7.5 y Males: 72.3%	LUR model (residential address; census block) Mean (SD): 46.8 (9.8) µg/m ³ IQR: 11.5 µg/m ³ Range: 24–73 µg/m ³	Age, sex, area-level SES	6,513	All-cause: 1,802	10 µg/m ³	All-cause: RR = 0.95 (0.89–1.02)
Maheswaran et al., 2010	Cohort (1995–2006)	Patients residing in London, United Kingdom who experienced first-ever stroke 1995–2005 Across categorized exposure concentrations: Females: 48.6%–50.8% Mean age (SD): 70.2–70.7 (14.3–14.8) y	Hybrid model (residential address) Mean (SD): 41 (3.3) µg/m ³ Range: 32.2–103.2 µg/m ³	Age, sex, area-level SES, individual-level smoking, ethnicity, comorbidities, medical variables	3,320	All-cause: 1,856	10 µg/m ³	All-cause: HR = 1.28 (1.11–1.48)
Desikan et al., 2016	Cohort (2005–2012)	South London Stroke Register (United Kingdom), a population-based register of incident strokes Males: 52.3% Mean Age (SD): 68.8 (15.8) y	Dispersion model (residential postcode) Mean (SD): 44.59 (4.29) µg/m ³ Median: 44.05 µg/m ³ IQR: 5.04 µg/m ³ (46.87–41.83) µg/m ³	Age, sex, area-level SES, ethnicity, strokespecific variables	1,800	All-cause: 729	5.04 µg/m ³	All-cause: HR = 0.97 (0.87–1.08)
Tonne et al., 2016	Cohort (2003–2010)	Patients >25 y from Greater London, United Kingdom admitted to hospital with MI from hospitals that had >10 STEMI or non-STEMI admissions Males: 68% Mean age (SD): 68 (14) y	Dispersion model (residential postcode centroid) Mean (SD): 37.1 (6.4) µg/m ³ Median: 36.3 µg/m ³ IQR: 7.9 (40.6–32.6) µg/m ³	Age, sex, area-level SES, individual-level smoking, ethnicity, medical history, MI, and STEMI-specific variables	18,138	All-cause: 5,129	8 µg/m ³	All-cause: HR = 1.04 (0.99–1.10)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Asia—General population								
Yorifuji et al., 2010	Shizuoka Elderly Cohort (1999–2006)	Adults ≥65 y living in Shizuoka, Japan in 1999 Females: 48%–49% Mean age (SD): 74 (5.4–5.5) y Excluded participants who moved during study period	LUR model (residential address) Mean (SD): 25 (12) µg/m ³ Range: 19–75 µg/m ³ (709 participants assigned negative concentration)	Age, sex, individual-level SES, individual-level smoking, BMI, comorbidities	12,029	All-cause: 1,232 CSD: 394 CHD: 91 Other cardiac diseases ^c : 106 CBVD: 191 RD: 199 I&P: 108 COPD: 35	10 µg/m ³	All-cause: HR = 1.02 (0.96–1.08) CSD: HR = 1.15 (1.03–1.28) CHD: HR = 1.27 (1.02–1.58) Other cardiac diseases ^c : HR = 1.19 (0.97–1.47) CBVD: HR = 1.09 (0.94–1.27) RD: HR = 1.19 (1.02–1.38) I&P: HR = 1.18 (0.96–1.45) COPD: HR = 1.11 (0.78–1.56)
Yorifuji et al., 2013	Shizuoka Elderly Cohort (1999–2009)	Adults ≥65 y living in Shizuoka, Japan in 1999 Females: 48.9% Mean age (SD): 74 (5.4) y Excluded participants who moved during study period	LUR model (residential address) Mean (SD): 22 (15) µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, BMI, comorbidities	13,412	All-cause: 1,663 CSD: 520 CHD: 110 Other cardiac diseases ^c : 156 CBVD: 248 RD: 281 I&P: 159 COPD: 50	10 µg/m ³	All-cause: HR = 1.12 (1.07–1.18) CSD: HR = 1.24 (1.15–1.33) CHD: HR = 1.29 (1.12–1.48) Other cardiac diseases ^c : HR = 1.27 (1.15–1.46) CBVD: HR = 1.19 (1.06–1.34) RD: HR = 1.19 (1.06–1.34) I&P: HR = 1.15 (0.99–1.35) COPD: HR = 0.98 (0.75–1.29)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Barratt et al., 2018	Elderly Health Service Cohort (1998–2011)	Hong Kong, China residents ≥65 y enrolled in Department of Health Elderly Health Service of the Hong Kong Government; participants lived in high-rise buildings below the 20th floor with openable windows streetside Males: 32.6% Mean age (SD): 70.2 (5.5) y	LUR model (residential address) Mean (SD): 96 (17) µg/m ³ Range: 43–177 µg/m ³ IQR: 23 µg/m ³ Median: 94 µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, indirect adjustment for smoking, BMI, physical activity, other SES indicators	60,548	All-cause: 16,006 CSD: 4,656 CHD: 1,810 CBVD: 1,621 RD: 3,150 Pneumonia: 2,057 COPD: 940	26 µg/m ³	All-cause: HR = 1.00 (0.97–1.03) CSD: HR = 1.00 (0.95–1.05) CHD: HR = 1.09 (1.00–1.18) CBVD: HR = 1.00 (0.91–1.09) RD: HR = 0.99 (0.93–1.06) Pneumonia: HR = 0.98 (0.90–1.06) COPD: HR = 1.02 (0.90–1.15)
Yang et al., 2018	Cohort (2001–2011)	Hong Kong, China residents ≥65 y enrolled in Department of Health Elderly Health Service of the Hong Kong Government Males: 33% Mean age (SD): 70.2 (5.5) y	LUR model (residential address) Median: 104 µg/m ³ IQR: 25.6 µg/m ³	Age, sex, individual and area-level SES, individual-level smoking, indirect adjustment for smoking, BMI, physical activity, other SES indicators	61,386	Not explicit	25.6 µg/m ³	All-cause: HR = 1.00 (0.97–1.03) CSD: HR = 1.00 (0.95–1.06) CHD: HR = 1.09 (1.00–1.18) CBVD: HR = 1.00 (0.91–1.09) RD: HR = 0.99 (0.93–1.06) Pneumonia: HR = 0.98 (0.90–1.06) COPD: HR = 1.02 (0.90–1.16)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Australia—General population								
Dirgawati et al., 2019	Cohort Health in Men Study (HIMS) (1996–2012)	Men aged ≥65 y, original recruited for a randomized control trial on abdominal aortic aneurism in Perth Mean age (SD): 72.1 (4.4) y	LUR model (residential address) Mean (SD): 13.4 (4.1) µg/m ³	Age, sex, individual-level SES, individual-level smoking, BMI	All-cause: 11,627 Stroke: 10,126	All-cause: 6,284 Stroke: 325	10 µg/m ³	All-cause: HR = 1.06 (1.00–1.13) Stroke: HR = 0.93 (0.72–1.19)
Hanigan et al., 2019	Cohort 45 and Up Study (2006–2015)	Participants ≥45 y and <80 y residing in Sydney Males: 47.6%	Hybrid model (residential address) Mean (SD): 17.75 (4.80) µg/m ³ Median: 17.14 µg/m ³ Min-max: 8.48–72.43 µg/m ³ IQR: 6.08 (20.33–14.25) µg/m ³	Age, sex, individual- and area-level SES, individual-level smoking, alcohol consumption, BMI, marital status, physical activity, and other demographic variables	75,145	All-cause: 3,280	5 µg/m ³	All-cause: HR = 1.03 (0.98–1.07)

Abbreviations: BMI: body mass index; CanCHEC: Canadian Census Health and Environment Cohort; CBVD: cerebrovascular disease; CCHS: Canadian Community Health Survey; CHD: coronary heart disease; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CSD: circulatory system disease; ESCAPE: European Study of Cohorts for Air Pollution Effects; I&P: influenza and pneumonia; HR: hazard ratio; IQR: interquartile range; LUR: land-use regression; LUR: land-use regression; MI: myocardial infarction; MRR: mortality rate ratio; OR: odds ratio; ppb: parts per billion; RD: respiratory disorder; RR: relative risk; SES: socio-economic status; SD: standard deviation; SIDIAP: Sistema d'Informació pel Desenvolupament de la Investigació en Atenció Primària; STEMI: ST-elevation myocardial infarction; y: year.

^a Where applicable, the following conversion factor was applied: 1 ppb = 1.88 µg/m³ (as referenced in Appendix 5c of HEI, 2022).

^b Pooled estimate of fully adjusted RRs was obtained using a fixed-effect model with the inverse-variance method.

^c Other cardiac diseases include dysrhythmias, heart failure, and cardiac arrest.

A.2. STUDY DETAILS FOR MORTALITY BY LONG-TERM EXPOSURE TO NO_x

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Europe—General population								
Nafstad et al., 2004	Cohort (1972–1998)	40–49-year-old men residing in Oslo, Norway	Dispersion model (residential address) 5-y median: 10.7 µg/m ³ Range of medians: 0.7–168.3 µg/m ³ IQR: 13.6 (20.4–6.8) µg/m ³	Age, sex, individual SES, individual smoking, physical activity, risk of cardiovascular diseases	16,209	All-cause: 4,227 CHD: 1,508 CBVD: 258 RD: 200	10 µg/m ³	All-cause: Risk ratio = 1.08 (1.06–1.11) CHD: Risk ratio = 1.08 (1.03–1.12) CBVD: Risk ratio = 1.04 (0.94–1.15) RD: Risk ratio = 1.16 (1.06–1.26)
Beelen et al., 2014a	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females: 47.7%–100% Mean age at baseline (SD): 41.1 (11.8)–70.3 (8.1) y	LUR model (residential address) Range of means (SD): 8.7 (5.7)–107.3 (24.1) µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	367,251	All-cause: 29,076	20 µg/m ³	All-cause: HR = 1.02 (1.00–1.04)
Beelen et al., 2014b	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females (range): 63% (48%–100%) Mean age at baseline (range): 50.5 (41.1–70.3) y	LUR model (residential address) Range of means (SD): 8.7 (5.7)–107.3 (24.1) µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	367,383	CSD: 9,994 CBVD: 2,484 CHD: 4,992 MI: 2,264	20 µg/m ³	CSD: HR = 1.02 (0.99–1.06) CBVD: HR = 1.00 (0.93–1.08) CHD: HR = 1.02 (0.96–1.09) MI: HR = 0.99 (0.91–1.08)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Dimakopoulou et al., 2014	Cohort ESCAPE (1990s–2007)	16 cohorts from 11 countries; general population Females (range): 47.7%–100% Mean age range at baseline: 41.9–73.0 y	LUR model (residential address) Range of means (SD): 8.7 (5.7)–96.1 (21.0) µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	307,553	RD: 1,559	10 µg/m ³	RD: HR = 0.99 (0.90–1.09)
Stockfelt et al., 2015	Cohort Multifactor Primary Prevention Study (1973–2007)	Men in Gothenburg, Sweden born 1915–1925 (except 1923) Mean age (range): 53.2 (48–58) y	Dispersion model (residential address) Median range: 17–44 µg/m ³ Range 5th–95th percentiles (between years): 10–31 µg/m ³ (in 2007) to 18–102 µg/m ³ (in 1983)	Age, sex, individual SES, individual smoking	7,494	All-cause: 4,047 CSD: 2,465 CHD: 1,584 MI: 953 CBVD: 442 RD: 268	10 µg/m ³	All-cause: HR = 1.02 (1.01–1.04) CSD: HR = 1.02 (1.00–1.04) CHD: HR = 1.02 (0.99–1.05) MI: HR = 1.03 (0.99–1.06) CBVD: HR = 1.03 (0.97–1.09) RD: HR = 1.00 (0.94–1.07)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Bauleo et al., 2019	Cohort (1996–2013)	All residents (18+ years) living in Civitavecchia, Italy on January 1, 1996 Females: 52.3%	Dispersion model (residential address) Mean (SD): 5.80 (3.86) µg/m ³ Median: 5.17 µg/m ³ 95th–5th: 12.77 µg/m ³	Age, sex, area-level SES, place of birth	71,362	All-cause: 13,687 CSD: 5,354 Cardiac diseases: 3,694 CHD: 1,623 ACE: 847 CBVD: 1,324 RD: 874 COPD: 358	12.77 µg/m ³	All-cause: HR = 0.98 (0.91–1.05) CSD: HR = 0.83 (0.74–0.93) Cardiac diseases: HR = 0.88 (0.77–1.01) CHD: HR = 0.83 (0.67–1.01) ACE: HR = 0.82 (0.62–1.08) CBVD: HR = 0.78 (0.61–0.99) RD: HR = 1.14 (0.87–1.49) COPD: HR = 1.34 (0.90–1.99)
Andersson et al., 2020	Cohort Primary Prevention Study (1970–2011)	Random third of all men in Gothenburg, Sweden born 1915–1925 Mean age (in 1978): 58.2 y Age range (in 1978): 53–63 y 80% of cohort died before 2011	Dispersion model (residential address) Mean NO _x decreased from 53 µg/m ³ in 1978 to 29 µg/m ³ in 2010 Reference group: <36.7 µg/m ³	Age, sex, individual-level SES, individual-level smoking, marital status, BMI, heredity, lifestyle variables, medical variables	6,304	All-cause: 3,182 CSD: 1,569	By quintile: 36.7–44.1 µg/m ³ vs. reference 44.1–53.3 µg/m ³ vs. reference 53.3–64.8 µg/m ³ vs. reference >64.8 µg/m ³ vs. reference	All-cause: by quintile: HR = 1.00 (0.89–1.11) HR = 1.08 (0.97–1.20) HR = 0.96 (0.86–1.08) HR = 1.05 (0.94–1.18) CSD: by quintile: HR = 1.00 (0.86–1.17) HR = 1.06 (0.90–1.23) HR = 0.94 (0.80–1.11) HR = 1.03 (0.87–1.21)
Carlsen et al., 2022	Malmö Diet and Cancer Cohort (1991–1996)	Random selection of individuals born from 1923 to 1950 in Malmö, Sweden; mean follow-up: 20 y Females: 60.3% Mean age (SD): 58.0 (7.6) y	Dispersion model (residential address) Mean (SD): 26.4 (8.8) µg/m ³ Median: 24.9 µg/m ³ 5th–95th: 14.8–42.8 µg/m ³ IQR: 9.62 µg/m ³	Age, sex, area-level SES, individual-level smoking, physical activity, health status, other lifestyle factors	25,823	MI: 650	9.62 µg/m ³	MI: HR = 1.09 (0.98–1.21)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Europe—Patient population								
Desikan et al., 2016	Cohort (2005–2012)	South London Stroke Register (United Kingdom), a population-based register of incident strokes Males: 52.3% Mean Age (SD): 68.8 (15.8) y	Dispersion model (residential address) Mean (SD): 78.98 (11.41) µg/m ³ Median: 77.42 µg/m ³ IQR: 13.99 (85.41–71.42) µg/m ³	Age, sex, area-level SES, ethnicity, stroke-specific variables	1,800	All-cause: 729	13.99 µg/m ³	All-cause: HR = 0.96 (0.85–1.08)
Tonne et al., 2016	Cohort (2003–2010)	Patients >25 y from Greater London, United Kingdom admitted to hospital with MI from hospitals that had >10 STEMI or non-STEMI admissions Males: 68% Mean age (SD): 68 (14) y	Dispersion model (residential address) Mean (SD): 61.8 (16.3) µg/m ³ Median: 59.0 µg/m ³ IQR: 19.2 (69.7–50.5) µg/m ³	Age, sex, area-level SES, individual-level smoking, ethnicity, medical history, MI and STEMI-specific variables	18,138	All-cause: 5,129	19.2 µg/m ³	All-cause: HR = 1.03 (0.98–1.08)
Asia—Patient/ Mix population								
Cohen et al., 2019	Cohort (2004–2017)	Patients undergoing percutaneous coronary interventions at the cardiology department, Rabin Medical Center, Israel Females: 24% Mean age (SD) at baseline: 69.2 (12.1) y	LUR model (residential address) Overall range: 5.5–86.4 ppb Exposure cut-off (low vs. high): 25 ppb Dispersion model (residential address) Range: 8.7–57.6 ppb Exposure cut-off (low vs. high): 25 ppb Hybrid model (residential address) High exposure (by LUR): 25.0–86.4 ppb High exposure (by dispersion modelling): 25.0–57.6 ppb	Age, sex, area-level SES, individual-level smoking, ethnicity, comorbidities Age, sex, area-level SES, individual-level smoking, ethnicity, comorbidities Age, sex, area-level SES, individual-level smoking, ethnicity, comorbidities	3,051	All-cause: 1,606	High vs. low (ppb)	All-cause: HR = 0.94 (0.83–1.06) All-cause: HR = 1.04 (0.94–1.16) All-cause: HR = 1.07 (0.98–1.18)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Cohen et al., 2021	Cohort (1992–2018)	Israeli residents; 2 patient-based cohorts of CHD and 2 population-based cohorts Patients matched (1:1) to CHD-free participants on age (±3 years) and sex Age- and sex-matched cohort (2,393 matched pairs) Females: 44% Mean (SD): 61.5 (14) y	LUR model (residential address) CHD-free: Median: 22.2 ppb Range: 2.6–74.8 ppb CHD: Median: 27.0 ppb Range: 5.6–76.4 ppb p-value <0.01	Age, sex, area-level SES, individual-level smoking, ethnicity, comorbidities	2,393	All-cause: CHD-free: 550 CHD: 908	10 ppb 15.5 µg/m ³	All-cause: CHD-free: HR = 1.00 (0.93–1.08) CHD: HR = 1.13 (1.05–1.22)
Australia—General population								
Dirgawati et al., 2019	Cohort Health in Men Study (HIMS) (1996–2012)	Men aged ≥65 y, originally recruited for a randomized control trial on abdominal aortic aneurism in Perth, Australia Mean age (SD): 72.1 (4.4) y	LUR model (residential address) Mean (SD): 32.3 (11.6) µg/m ³	Age, sex, individual-level smoking, BMI	All-cause: 11,627 Stroke: 10,126	All-cause: 6,284 Stroke: 325	10 µg/m ³	All-cause: HR = 1.02 (1.00–1.04) Stroke: HR = 0.97 (0.88–1.07)

Abbreviations: ACEi: acute coronary events; BMI: body mass index; CBVD: cerebrovascular disease; CHD: coronary heart disease; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CSD: circulatory system disease; ESCAPE: European Study of Cohorts for Air Pollution Effects; HR: hazard ratio; IQR: interquartile range; LUR: land-use regression; MI: myocardial infarction; ppb: parts per billion; RD: respiratory disorder; SD: standard deviation; SES: socio-economic status; STEMI: ST-elevation myocardial infarction; y: year.

^a Where applicable, the following conversion factor was applied: 1 ppb = 1.55 µg/m³ (as referenced in Appendix 5c of HEI, 2022).

A.3. STUDY DETAILS FOR MORTALITY BY LONG-TERM EXPOSURE TO NO

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Canada—General population								
Gan et al., 2011	Cohort (1994–2002)	Vancouver metropolitan residents, British Columbia, aged 45–85 y Males: 45.3% Mean age (SD): 58.7 (10.4) y	LUR model (residential postal code) Mean (SD): 32.0 (11.9) µg/m ³ Median: 29.3 µg/m ³ IQR: 13.2 µg/m ³ Range: 8.8–126.0 µg/m ³	Age, sex, area-level SES, pre-existing comorbidities	406,232	CHD: 3,104	13.2 µg/m ³	CHD: RR = 1.06 (1.02–1.10)
Gan et al., 2013	Cohort (1994–2002)	Vancouver metropolitan residents, British Columbia, aged 45–85 y Males: 47.1% Mean age (SD): 59.4 (10.7) y	LUR model (residential postal code) Mean (SD): 32.1 (12.0) µg/m ³ Median: 29.3 µg/m ³ IQR: 13.2 µg/m ³ Range: 8.8–126.0 µg/m ³	Age, sex, area-level SES	465,360	COPD: 541	13.2 µg/m ³	COPD: RR = 1.06 (0.97–1.16)
USA—General population								
Alexeeff et al., 2018	Cohort (2010–2015)	Adult members of the Kaiser Permanente Northern California health care system, living in Oakland, California during the study period; those with history of CSD were excluded Males: 47.0%	Hybrid or other model (residential address) Mean (SD): 4.9 (3.8) ppb [6.0 (4.7) µg/m ³] Median: 4.1 ppb IQR: 4.0 (6.4–2.4) ppb Min–max: 0.0 to 69.8 ppb	Age, sex, area-level SES, individual-level smoking, race, BMI, health status	41,869	CHD: 130 CBVD: 27	3.8 ppb (4.7 µg/m ³)	CHD: HR = 1.05 (0.88–1.25) CBVD: HR = 1.13 (0.86–1.49)
Europe—Patient population								
Desikan et al., 2016	Cohort (2005–2012)	South London Stroke Register (UK), a population-based register of incident strokes Males: 52.3% Mean age (SD): 68.8 (15.8) y	Dispersion model (residential address) Mean (SD): 34.39 (7.15) µg/m ³ Median: 33.40 µg/m ³ IQR: 8.86 (38.40–29.54) µg/m ³	Age, sex, area-level SES, ethnicity, stroke-specific variables	1,800	All-cause: 729	8.86 µg/m ³	All-cause: HR = 0.96 (0.85–1.08)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment ^a	Risk estimate (95% CI)
Asia—General population								
Barratt et al., 2018	Elderly Health Service Cohort (1998–2011)	Hong Kong, China, residents ≥65 y enrolled in Department of Health Elderly Health Service of the Hong Kong Government; participants lived in high-rise buildings below the 20 th floor with openable windows streetside Males: 32.6% Mean age (SD): 70.2 (5.5) y	LUR model (residential address) Mean (SD): 489 (119) µg/m ³ Range: 120–785 µg/m ³ IQR: 167 µg/m ³ Median: 486 µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, indirect adjustment for smoking, BMI, physical activity, other SES indicators	60,548	All-cause: 16,006 CSD: 4,656 CHD: 1,810 CBVD: 1,621 RD: 3,150 Pneumonia: 2,057 COPD: 940	167 µg/m ³	All-cause: HR = 0.99 (0.97–1.02) CSD: HR = 0.96 (0.91–1.00) CHD: HR = 0.98 (0.91–1.05) CBVD: HR = 0.96 (0.89–1.04) RD: HR = 1.00 (0.94–1.05) Pneumonia: HR = 0.99 (0.93–1.06) COPD: HR = 1.04 (0.94–1.15)

Abbreviations: BMI: body mass index; CBVD: cerebrovascular disease; CHD: coronary heart disease; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CSD: circulatory system disease; HR: hazard ratio; IQR: interquartile range; LUR: land-use regression; ppb: parts per billion; RD: respiratory disorder; RR: relative risk; SD: standard deviation; SES: socio-economic status; y: year.

^a Where applicable, the following conversion factor was applied: 1 ppb = 1.23 µg/m³ (as referenced in Appendix 5c of HEI, 2022).

A.4. STUDY DETAILS FOR MORTALITY BY LONG-TERM EXPOSURE TO PM_{2.5}

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Canada—General population								
Gan et al., 2011	Cohort (1994–2002)	Vancouver metropolitan residents, British Columbia, aged 45–85 y Males : 45.3%	LUR model (residential postal code) Mean (SD): 4.08 (1.63) µg/m ³ Median: 4.03 µg/m ³ IQR: 1.58 µg/m ³ Range: 0–10.24 µg/m ³	Age, sex, area-level SES, pre-existing comorbidities	406,232	CHD: 3,104	1.58 µg/m ³	CHD: RR = 1.01 (0.98–1.05)
Gan et al., 2013	Cohort (1999–2002)	Vancouver metropolitan residents, British Columbia, aged 45–85 y Males : 47.1%	LUR model (residential postal code) Mean (SD): 4.10 (1.64) µg/m ³ Median: 4.03 µg/m ³ IQR: 3.22–4.80 µg/m ³ Range: 0–10.24 µg/m ³	Age, sex, area-level SES, pre-existing comorbidities	465,360	COPD: 541	1.58 µg/m ³	COPD: RR = 1.02 (0.98–1.06)
USA—General population								
Jerrett et al., 2005	Cohort ACS-CPSII (1982–2000)	ACS-CPSII cohort members with a ZIP code in Los Angeles, California (no further details provided)	Hybrid or other model (residential postcode) Range: 9.0–27.1 µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking; included 40 individual confounders (lifestyle, dietary, demographic, and occupational, and educational factors) and 8 ecological variables for ZIP code (income, income inequality, education, population size, racial composition, and unemployment)	22,905	All-cause: 5,856 CPD: 3,136	10 µg/m ³	All-cause: HR = 1.11 (0.99–1.25) CPD: HR = 1.08 (0.92–1.27)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Krewski et al., 2009	Cohort ACS-CPSII (1982–2000)	ACS-CPSII cohort members with a ZIP code in New York City, New York Males: 56.3% Mean age (SD): 55.3 (10.7) y	LUR model (residential postcode) Mean (SD): 14.3 (1.78) $\mu\text{g}/\text{m}^3$ Decile difference (90% vs. 10%): 1.5 $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, individual-level smoking; included 40 individual confounders (lifestyle, dietary, demographic, occupational, and educational factors)	44,056	All-cause: 10,559 CPD: 4,625 CHD: 2,735	1.5 $\mu\text{g}/\text{m}^3$	All-cause: HR = 0.984 (0.948–1.020) CPD: HR = 0.953 (0.902–1.007) CHD: HR = 1.072 (1.003–1.147)
Krewski et al., 2009	Cohort ACS-CPSII (1982–2000)	ACS-CPSII cohort members with a ZIP code in Los Angeles, California Males: 57% Mean age (SD): 57 (10.6) y	LUR model (residential postcode) Mean (SD): 18.42 (6.01) $\mu\text{g}/\text{m}^3$ Median: 19.31 $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, individual-level smoking; included 40 individual confounders (lifestyle, dietary, demographic, occupational, and educational factors)	22,905	All-cause: 5,856 CPD: 3,136 CHD: 1,462	10 $\mu\text{g}/\text{m}^3$	All-cause: HR = 1.143 (1.033–1.266) CPD: HR = 1.114 (0.968–1.282) CHD: HR = 1.331 (1.084–1.634)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Europe—General population								
Naess et al., 2007	Cohort (1992–1998)	Residents 51–90 y of 470 neighbourhoods in Oslo, Norway	Dispersion model (neighbourhood-level) Mean: 15 µg/m ³ Range: 7–22 µg/m ³	Age, sex, individual-level SES, other SES indicators	143,842	All-cause: not explicit CSD: 51–70 y Men: 2007 Women: 946 71–90 y Men: 4,531 Women: 7,480 COPD: 51–70 y Men: 233 Women: 203 71–90 y Men: 503 Women: 516	Not specified	All-cause: Trend of increasing risk for each quartile of exposure (p < 0.001) for males and females and age group (51–70 y and 71–90 y) CSD: 51–70 y Men: HR = 1.10 (1.05–1.16) Women: HR = 1.14 (1.06–1.21) 71–90 y Men: HR = 1.05 (1.01–1.08) Women: HR = 1.03 (1.00–1.05) COPD: 51–70 y Men: HR = 1.27 (1.11–1.47) Women: HR = 1.09 (0.94–1.25) 71–90 y Men: HR = 1.10 (1.00–1.21) Women: HR = 1.05 (0.96–1.16)
Carey et al., 2013	Cohort Clinical Practice Research Datalink (2003–2007)	Patients aged 40–89 y of 205 clinics in England, United Kingdom; fully registered for at least 1 year on Jan 1, 2003 Males: 48.4%	Dispersion model (residential postcode) Mean (SD): 12.9 (1.4) µg/m ³ Range: 8.5–20.2 µg/m ³ IQR: 1.9 µg/m ³	Age, sex, area-level SES, individual-level smoking, BMI	830,842	All-cause: 82,475 CSD: 28,743 RD: 10,508	1.9 µg/m ³	All-cause: HR = 1.00 (0.98–1.02) CSD: HR = 0.99 (0.97–1.02) RD: HR = 1.07 (1.03–1.11)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Cesaroni et al., 2013	Cohort Rome Longitudinal Study (2001–2010)	Adults aged ≥ 30 y who resided in Rome, Italy, ≥ 5 y Males: 45.5% <60 y: 61.3% 60–75 y: 26.8% ≥ 75 y: 11.9%	Dispersion model (residential address) Mean (SD): 23.0 (4.4) $\mu\text{g}/\text{m}^3$ Median: 23.9 $\mu\text{g}/\text{m}^3$ IQR: 25.7 (6.0–20.3) $\mu\text{g}/\text{m}^3$ Range: 7.2–32.1 $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, marital status, place of birth	1,265,058	All-cause: 144,441 CSD: 60,318 CBVD: 13,576 CHD: 22,562 RD: 8,825	10 $\mu\text{g}/\text{m}^3$	All-cause: HR = 1.04 (1.03–1.05) CSD: HR = 1.06 (1.04–1.08) CBVD: HR = 1.08 (1.04–1.13) CHD: HR = 1.10 (1.06–1.13) RD: HR = 1.03 (0.97–1.08)
Beelen et al., 2014a	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females: 47.7%–100% Mean age at baseline (SD): 41.1 (11.8) to 70.3 (8.1) y	LUR model (residential address) Range of means (SD): 6.6 (1.2)–31.0 (1.7) $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	322,159	All-cause: 29,076	5 $\mu\text{g}/\text{m}^3$	All-cause: HR = 1.07 (1.02–1.13)
Beelen et al., 2014b	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females (range): 63% (48%–100%) Mean age at baseline (range): 50.5 (41.1–70.3) y	LUR model (residential address) Range of means (SD): 6.6 (1.2)–31.0 (1.7) $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	367,383	CSD: 9,994 CBVD: 2,484 CHD: 4,992 MI: 2,264	5 $\mu\text{g}/\text{m}^3$	CSD: HR = 0.99 (0.91–1.08) CBVD: HR = 1.21 (0.87–1.69) CHD: HR = 0.98 (0.74–1.30) MI: HR = 0.96 (0.70–1.32)
Dimakopoulou et al., 2014	Cohort ESCAPE (1990s–2008)	16 cohorts from 11 countries; general population Females range: 47.7%–100% Mean age range at baseline: 41.9–73.0 y	LUR model (residential address) Range of means (SD): 6.6 (1.2)–31.0 (1.7) $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	307,553	RD: 1,559	5 $\mu\text{g}/\text{m}^3$	RD: HR = 0.89 (0.66–1.12)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Badaloni et al., 2017	Cohort Rome Longitudinal Study (2001–2010)	Adults aged ≥ 30 y who resided in Rome, Italy, ≥ 5 y Males: 45.4% Mean age (SD): 55 (15) y	LUR model (residential address) Mean (SE): 20 (1.9) $\mu\text{g}/\text{m}^3$ Median: 19.1 $\mu\text{g}/\text{m}^3$ IQR: 1.7 (18.4–20.1) $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, indirect smoking status, place of birth	1,249,108	All-cause: 142,327 CSD: 59,434 CHD: 22,234	6.6 $\mu\text{g}/\text{m}^3$	All-cause: HR = 1.03 (1.01–1.05) CSD: HR = 1.05 (1.02–1.08) CHD: HR = 1.06 (1.01–1.11)
Nieuwenhuijsen et al., 2018	Cohort SIDIAP (2010–2014)	Adults ≥ 18 y, registered in SIDIAP and living in Barcelona; SIDIAP represents 80% of total population of Catalonia (Spain) Males: 53% Average age: 50.9 y	LUR model (census tract) Geometric mean (95% CI): 16.08 (16.07–16.08) $\mu\text{g}/\text{m}^3$ p25–p75: 14.95–17.72 $\mu\text{g}/\text{m}^3$	Age, sex, area-level SES, individual-level smoking	792,649	All-cause: 28,391	5 $\mu\text{g}/\text{m}^3$	All-cause: HR = 1.03 (0.99–1.06)
So et al., 2020	Danish Nurse Cohort (1993–2013)	Female nurses >44 y recruited in 1993 or who turned 44 y in 1993–1999, recruited in 1999; limited to Capital Region, Denmark Mean age (SD) at baseline: 53.2 (8.0) y	Hybrid or other model (residential address) At baseline: Mean (SD): 20.5 (3.9) $\mu\text{g}/\text{m}^3$ IQR: 4.39 $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, individual-level smoking, BMI, lifestyle variables, activity level, marital status, use of hormonal therapy	24,526	All-cause: 1,111	4.39 $\mu\text{g}/\text{m}^3$	All-cause: HR = 1.01 (0.94–1.09)
Carlsen et al., 2022	Malmö Diet and Cancer Cohort (1991–1996)	Random selection of individuals born between 1923 and 1950 in Malmö, Sweden Females: 60.3% Mean age (SD): 58.0 (7.6) y	Dispersion model (residential address) Mean (SD): 10.9 (1.9) $\mu\text{g}/\text{m}^3$ Median: 10.8 $\mu\text{g}/\text{m}^3$ 5th–95th: 8.5–15.7 $\mu\text{g}/\text{m}^3$ IQR: 1.63 $\mu\text{g}/\text{m}^3$	Age, sex, individual-level SES, area-level SES, individual-level smoking, physical activity, health status, other lifestyle factors	25,823	Ml: 650	1.63 $\mu\text{g}/\text{m}^3$	Ml: HR = 0.92 (0.74–1.15)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Europe—Patient population								
Desikan et al., 2016	Cohort (2005–2012)	South London Stroke Register (United Kingdom), a population-based register of incident strokes Males: 52.3% Mean age (SD): 68.8 (15.8) y	Dispersion model (residential postcode) Mean (SD): 15.35 (1.13) µg/m ³ Median: 15.26 µg/m ³ IQR: 1.86 (16.31–14.45) µg/m ³	Age, sex, area-level SES, ethnicity, stroke-specific variables	1,800	All-cause: 729	1.86 µg/m ³	All-cause: HR = 1.28 (1.08–1.53)
Tonne et al., 2016	Cohort (2003–2010)	Patients >25 y from Greater London, United Kingdom admitted to hospital with MI from hospitals that had >10 STEMI or non-STEMI admissions Males: 68% Mean age (SD): 68 (14) y	Dispersion model (residential postcode centroid) Traffic exhaust: Mean (SD): 0.6 (0.3) µg/m ³ Median: 0.6 µg/m ³ IQR: 0.3 (0.7–0.4) µg/m ³ Traffic non-exhaust: Mean (SD): 0.7 (0.3) µg/m ³ Median: 0.6 µg/m ³ IQR: 0.3 (0.8–0.5) µg/m ³	Age, sex, area-level SES, individual-level smoking, ethnicity, MI, and STEMI-specific variables	18,138	All-cause: 5,129	Traffic exhaust: 0.3 µg/m ³ Traffic non-exhaust: 0.3 µg/m ³	All-cause: Traffic exhaust: HR = 1.02 (0.98–1.06) Traffic non-exhaust: HR = 1.04 (1.00–1.08)
Asia—General population								
Barratt et al., 2018	Elderly Health Service Cohort (1998–2011)	Hong Kong, China, residents ≥65 y enrolled in Department of Health Elderly Health Service of the Hong Kong Government; participants lived in high-rise buildings below 20th floor with openable windows streetside Males: 32.6%	LUR model (residential address) Mean (SD): 42.4 (4.2) µg/m ³ Range: 27.2–42.2 µg/m ³ IQR: 5.5 µg/m ³ Median: 42.2 µg/m ³	Age, sex, individual and area-level SES, individual-level smoking, indirect adjustment for smoking, BMI, physical activity, other SES indicators	60,548	All-cause: 16,006 CSD: 4,656 CHD: 1,810 CBVD: 1,621 RD: 3,150 Pneumonia: 2,057 COPD: 940	5.5 µg/m ³	All-cause: HR = 1.03 (1.01–1.06) CSD: HR = 1.06 (1.02–1.10) CHD: HR = 1.03 (0.97–1.10) CBVD: HR = 1.06 (0.99–1.13) RD: HR = 1.02 (0.97–1.06) Pneumonia: HR = 1.00 (0.94–1.06) COPD: HR = 1.06 (0.97–1.15)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Yang et al., 2018	Elderly Health Service Cohort (2001–2011)	Hong Kong, China, residents ≥65 y enrolled in Department of Health Elderly Health Service of the Hong Kong Government Males: 33% Mean age (SD): 70.2 (5.5) y	LUR model (residential address) Median: 42.2 µg/m ³ IQR: 5.5 µg/m ³	Age, sex, individual and area-level SES, individual-level smoking, indirect adjustment for smoking, BMI, physical activity, other SES indicators	61,386	Not explicit	5.5 µg/m ³	All-cause: HR = 1.03 (1.01–1.06) CSD: HR = 1.06 (1.02–1.10) CHD: HR = 1.03 (0.97–1.10) CBVD: HR = 1.06 (0.99–1.13) RD: HR = 1.01 (0.97–1.06) Pneumonia: HR = 0.99 (0.94–1.06) COPD: HR = 1.06 (0.97–1.15)
Australia—General population								
Dirgawati et al., 2019	Cohort Health in Men Study (HIMS) (1996–2012)	Males aged ≥65 y, originally recruited for a randomized control trial on abdominal aortic aneurism in Perth, Australia Mean age (SD): 72.1 (4.4) y	LUR model (residential address) Mean (SD): 5.1 (1.7) µg/m ³	Age, sex, individual-level smoking, BMI	All-cause: 11,627 Stroke: 10,126	All-cause: 6,284 Stroke: 325	5 µg/m ³	All-cause: HR = 1.07 (0.98–1.16) Stroke: HR = 0.71 (0.49–1.02)
Hanigan et al., 2019	Cohort 45 and Up Study (2006–2015)	Participants ≥45 y and <80 y residing in Sydney, Australia; Males: 47.6%	Hybrid or other model (residential address) Mean (SD): 4.49 (0.61) µg/m ³ Median: 4.47 µg/m ³ Range: 2.78–13.81 µg/m ³ IQR: 0.82 (4.92–4.10) µg/m ³	Age, sex, individual- and area-level SES, individual-level smoking, alcohol consumption, BMI, marital status, physical activity, and other demographic variables	75,268	All-cause: 3,280	1 µg/m ³	All-cause: HR = 1.05 (0.98–1.12)

Abbreviations: ACS-CPSII: American Cancer Society—Cancer Prevention Survey II; BMI: body mass index; CBVD: cerebrovascular disease; CHD: coronary heart disease; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CPD: cardiopulmonary disease; CSD: circulatory system disease; ESCAPE: European Study of Cohorts for Air Pollution Effects; HR: hazard ratio; IQR: interquartile range; LUR: land-use regression; MI: myocardial infarction; RD: respiratory disorder; RR: relative risk; SD: standard deviation; SE: standard error; SES: socio-economic status; SIDIAP: Sistema d'Informació pel Desenvolupament de la Investigació en Atenció Primària; STEMI: ST-elevation myocardial infarction; y: year.

A.5. STUDY DETAILS FOR MORTALITY BY LONG-TERM EXPOSURE TO EC, PM_{2.5} abs^r AND BC

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Canada—General population								
Gan et al., 2011	Cohort (1994–2002)	Vancouver metropolitan residents, British Columbia, aged 45–85 y Males: 45.3%	LUR model (residential postal code) BC: Mean (SD): 1.49 (1.10) x 10 ⁻⁵ /m Median: 1.02 x 10 ⁻⁵ /m IQR: 0.94 x 10 ⁻⁵ /m Range: 0–4.98 x 10 ⁻⁵ /m	Age, sex, area-level SES, pre-existing comorbidities	406,232	CHD: 3,104	BC: 0.94 x 10 ⁻⁵ /m	CHD: RR = 1.06 (1.03–1.09)
Gan et al., 2013	Cohort (1999–2002)	Vancouver metropolitan residents, British Columbia, aged 45–85 y Males: 47.1%	LUR model (residential postal code) BC: Mean (SD): 1.50 (1.10) x 10 ⁻⁵ /m Median: 1.02 x 10 ⁻⁵ /m IQR: (0.83–1.80) x 10 ⁻⁵ /m Range: 0–4.98 x 10 ⁻⁵ /m	Age, sex, area-level SES, pre-existing comorbidities	465,360	COPD: 541	BC: 0.97 x 10 ⁻⁵ /m	COPD: RR = 1.02 (0.98–1.06)
USA—General population								
Alexeeff et al., 2018	Cohort (2010–2015)	Adult members of the Kaiser Permanente Northern California health care system, living in Oakland, California during the study period; those with history of CSD were excluded	Hybrid or other model (residential address) BC: Mean (SD): 0.36 (0.17) µg/m ³ Median: 0.4 µg/m ³ IQR: 0.2–0.5 µg/m ³ Min-max: -0.3 to 1.9 µg/m ³	Age, sex, area-level SES, individual-level smoking, race, BMI, health status	41,869	CSD: 130 CBVD: 27	BC: 0.17 µg/m ³	CSD: HR = 1.12 (0.94–1.33) CBVD: HR = 0.92 (0.58–1.45)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
USA—Patient population								
Von Klot et al., 2009	Cohort Worcester Heart Attack Study (1995–2005)	Adult patients aged ≥25 y from Worcester, MA, hospitalized with acute MI Males: 59% Age (mean): 69 (range 28–105) y	LUR model (residential address) EC: Mean: 0.42 µg/m ³ Range: 0.05–0.92 µg/m ³ IQR: 0.24 µg/m ³	Age, sex, individual-level smoking, marital status, medical history, clinical variables	3,169	All-cause: 1,714	EC: 0.24 µg/m ³	All-cause: HR = 1.19 (1.03–1.38)
Europe—General population								
Beelen et al., 2014a	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females: 47.7%–100% Mean age at baseline (SD): 41.1 (11.8) to 70.3 (8.1) y	LUR model (residential address) PM _{2.5,abs} ^a : Range of means (SD): 0.5 (0.1)–3.2 (0.4) x 10 ⁻⁵ /m	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	322,159	All-cause: 29,076	PM _{2.5,abs} ^a : 1 x 10 ⁻⁵ /m	All-cause: HR = 1.02 (0.97–1.07)
Beelen et al., 2014b	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females (range): 63% (48%–100%) Mean age at baseline (range): 50.5 (41.1–70.3) y	LUR model (residential address) PM _{2.5,abs} ^a : Range of means (SD): 0.5 (0.1)–3.2 (0.4) x 10 ⁻⁵ /m	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	367,383	CSD: 9,994 CBVD: 2,484 CHD: 4,992 MI: 2,264	PM _{2.5,abs} ^a : 1 x 10 ⁻⁵ /m	CSD: HR = 0.97 (0.89–1.06) CBVD: HR = 1.01 (0.82–1.24) CHD: HR = 0.98 (0.78–1.23) MI: HR = 0.97 (0.75–1.25)
Dimakopoulou et al., 2014	Cohort ESCAPE (1990s–2008)	16 cohorts from 11 countries; general population Females range: 47.7%–100% Mean age range at baseline: 41.9–73.0 y	LUR model (residential address) PM _{2.5,abs} ^a : Range of means (SD): 0.5 (0.1)–3.2 (0.4) x 10 ⁻⁵ /m	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	307,553	RD: 1,559	PM _{2.5,abs} ^a : 1 x 10 ⁻⁵ /m	RD: HR = 0.70 (0.47–0.93)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Badaloni et al., 2017	Cohort Rome Longitudinal Study (2001–2010)	Adults aged ≥ 30 y who resided in Rome, Italy, ≥ 5 y Males: 45.4% Mean age (SD): 55 (15) y	LUR model (residential address) $PM_{2.5,abs}^*$ Mean (SE): $3 (0.5) \times 10^{-5}/m$ Median: $2.6 \times 10^{-5}/m$ IQR: $0.4 (2.8-2.4) \times 10^{-5}/m$	Age, sex, individual-level SES, area-level SES, marital status, place of birth	1,249,108	All-cause: 142,327 CSD: 59,434 CHD: 22,234	$PM_{2.5,abs}^*$: $1.5 \times 10^{-5}/m$	All-cause: HR = 1.05 (1.03–1.06) CSD: HR = 1.06 (1.02–1.08) CHD: HR = 1.08 (1.03–1.12)
Nieuwenhuijzen et al., 2018	Cohort SIDIAP (2010–2014)	Adults ≥ 18 y, registered in SIDIAP and living in Barcelona; SIDIAP represents 80% of total population of Catalonia (Spain) Males: 53% Average age: 50.9 y	LUR model (census tract) $PM_{2.5,abs}^*$ Geometric mean (95% CI): 2.64 (2.64–2.64) $\times 10^{-5}/m$ p25–p75: 2.37–2.91 $\times 10^{-5}/m$	Age, sex, area-level SES, individual-level smoking	792,649	All-cause: 28,391	$PM_{2.5,abs}^*$: $1 \times 10^{-5}/m$	All-cause: HR = 1.02 (1.00–1.05)
Carlsen et al., 2022	Malmö Diet and Cancer Cohort (1991–1996)	Random selection of individuals born between 1923 and 1950 in Malmö, Sweden Females: 60.3% Mean age (SD): 58.0 (7.6) y	Dispersion model (residential address) BC: Mean (SD): 1.0 (0.1) $\mu g/m^3$ Median: 1.0 $\mu g/m^3$ 5th–95th: 0.8–1.1 $\mu g/m^3$ IQR: 0.15 $\mu g/m^3$	Age, sex, individual-level SES, area-level SES, individual-level smoking, physical activity, health status, other lifestyle factors	25,823	Mi: 650	BC: 0.15 $\mu g/m^3$	Mi: HR = 0.99 (0.86–1.13)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Asia—General population								
Barratt et al., 2018	Elderly Health Service Cohort (1998–2011)	Hong Kong, China, residents ≥65 y enrolled in Department of Health Elderly Health Service of the Hong Kong Government; participants lived in high-rise buildings below 20th floor with openable windows streetside Males: 32.6%	LUR model (residential address) BC: Mean (SD): 13.1 (6.7) µg/m ³ Min–max: 3.9–44.7 µg/m ³ IQR: 9.6 µg/m ³ Median: 12.1 µg/m ³	Age, sex, individual and area-level SES, individual-level smoking, indirect adjustment for smoking, BMI, physical activity, other SES indicators	60,548	All-cause: 16,006 CSD: 4,656 CHD: 1,810 CBVD: 1,621 RD: 3,150 Pneumonia: 2,057 COPD: 940	BC: 9.6 µg/m ³	All-cause: HR = 1.03 (1.00–1.05) CSD: HR = 1.07 (1.03–1.11) CHD: HR = 1.08 (1.01–1.15) CBVD: HR = 1.05 (0.98–1.13) RD: HR = 0.99 (0.94–1.04) Pneumonia: HR = 0.99 (0.93–1.05) COPD: HR = 0.98 (0.90–1.08)
Yang et al., 2018	Cohort (2001–2011)	Hong Kong, China, residents ≥65 y enrolled in Department of Health Elderly Health Service of the Hong Kong Government Males: 33% Mean age (SD): 70.2 (5.5) y	LUR model (residential address) BC: Median: 12.1 µg/m ³ IQR: 9.6 µg/m ³	Age, sex, individual and area-level SES, individual-level smoking, indirect adjustment for smoking, BMI, physical activity, monthly expenses, other area-level SES indicators	61,386	Not explicit	BC: 9.6 µg/m ³	All-cause: HR = 1.03 (1.00–1.05) CSD: HR = 1.07 (1.02–1.11) CHD: HR = 1.08 (1.01–1.15) CBVD: HR = 1.05 (0.98–1.13) RD: HR = 0.99 (0.94–1.04) Pneumonia: HR = 0.99 (0.93–1.05) COPD: HR = 0.98 (0.90–1.08)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Australia – General population								
Dirigawati et al., 2019	Cohort Health in Men Study (HIMS) (1996–2012)	Males aged ≥65 y, original recruited for a randomized control trial on abdominal aortic aneurism in Perth, Australia Mean age (SD): 72.1 (4.4) y	LUR model (residential address) PM _{2.5,abs} : Mean (SD): 0.9 (0.3) x 10 ⁻⁵ /m	Age, sex, individual-level SES, individual-level smoking, BMI	All-cause: 11,627 Stroke: 10,126	All-cause: 6,284 Stroke: 325	PM _{2.5,abs} : 1 x 10 ⁻⁵ /m	All-cause: HR = 1.12 (1.02–1.22) Stroke: HR = 0.70 (0.47–1.03)

Abbreviations: BC: black carbon; BMI: body mass index; CI: confidence interval; CBVD: cerebrovascular disease; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; CSD: circulatory system disease; EC: elemental carbon; ESCAPE: European Study of Cohorts for Air Pollution Effects; HR: hazard ratio; IQR: interquartile range; LUR: land-use regression; MI: myocardial infarction; PM_{2.5,abs}: PM_{2.5} absorbance; RD: respiratory disorder; RR: relative risk; SD: standard deviation; SES: socio-economic status; SIDAP: Sistema d'informació pel Desenvolupament de la Investigació en Atenció Primària; y: year.

A.6. STUDY DETAILS FOR MORTALITY BY LONG-TERM EXPOSURE TO PM₁₀ AND PM_{COARSE}

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Europe—General population								
Rosenlund et al., 2006	Case-control Stockholm Heart Epidemiology Program (1992–1994)	Population-based case-control in Stockholm, Sweden; first events of MI in population aged 45–70 y Males (cases; controls): 66%; 65% Mean age (SD): Cases; controls: 60.9 (6.8) y; 60.9 (6.8) y	Dispersion model (residential address) PM ₁₀ : Cases: Mean (5th–95th): 2.6 (0.5–6.0) µg/m ³ Controls: Mean (5th–95th): 2.4 (0.6–5.9) µg/m ³	Age, sex, individual-level SES, individual smoking, diabetes, physical activity	3,210	MI: 272	PM ₁₀ : 5 µg/m ³	MI: OR = 1.39 (0.94–2.07)
Naess et al., 2007	Cohort (1992–1998)	Residents 51–90 y of 470 neighbourhoods in Oslo, Norway	Dispersion model (neighbourhood-level) PM ₁₀ : Mean: 19 µg/m ³ Range: 7–30 µg/m ³	Age, sex, individual-level SES, other SES indicators	143,842	CSD: 51–70 y Men: 2007 Women: 946 71–90 y Men: 4,531 Women: 7,480 COPD: 51–70 y Men: 233 Women: 203 71–90 y Men: 503 Women: 516	PM ₁₀ : Not specified	CSD: 51–70 y Men: HR = 1.09 (1.04–1.15) Women: HR = 1.11 (1.04–1.19) 71–90 y Men: HR = 1.04 (1.01–1.08) Women: HR = 1.01 (0.99–1.04) COPD: 51–70 y Men: HR = 1.29 (1.12–1.48) Women: HR = 1.06 (0.92–1.22) 71–90 y Men: HR = 1.08 (0.98–1.18) Women: HR = 1.08 (0.98–1.19)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Rosenlund et al., 2009	Case-control (1985–1996)	Population-based case-control in Stockholm, Sweden; first events of MI in population 15–79 y Males (Cases; controls): 69%; 49% Fatal cases captured	Dispersion model (residential address) PM ₁₀ : Cases: Mean (5th–95th): 2.4 (0.3–6.2) µg/m ³ Controls: Mean (5th–95th): 2.2 (0.3–6.0) µg/m ³	Age, sex, individual-level SES	301,273	MI: 8,809	PM ₁₀ : 5 µg/m ³	MI: OR = 1.16 (1.09–1.24)
Carey et al., 2013	Cohort Clinical Practice Research Datalink (2003–2007)	Patients aged 40–89 y of 205 clinics in England, United Kingdom; fully registered for at least 1 year on Jan 1, 2003 Males: 48.4%	Dispersion model (residential postcode centroid) PM ₁₀ : Mean (SD): 19.7 (2.3) µg/m ³ Range: 12.6–29.8 µg/m ³ IQR: 3.0 µg/m ³	Age, sex, area-level SES, individual-level smoking, BMI	830,842	All-cause: 82,475 CSD: 28,743 RD: 10,508	PM ₁₀ : 3.0 µg/m ³	All-cause: HR = 1.00 (0.98–1.02) CSD: HR = 0.99 (0.97–1.02) RD: HR = 1.07 (1.03, 1.11)
Beelen et al., 2014a	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females: 47.7%–100% Mean age at baseline (SD): 41.1 (11.8) to 70.3 (8.1) y	LUR model (residential address) PM ₁₀ : Range of means (SD): 13.5 (3.1)–48.1 (4.1) µg/m ³ PM _{coarse} : Range of means (SD): 4.0 (2.0)–20.7 (2.6) µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	322,159	All-cause: 29,076	PM ₁₀ : 10 µg/m ³ PM _{coarse} : 5 µg/m ³	All-cause: PM ₁₀ HR = 1.04 (1.00–1.09) PM _{coarse} HR = 1.04 (0.98–1.10)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Beelen et al., 2014b	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females (range): 63% (48%–100%) Mean age at baseline (range): 50.5 (41.1–70.3) y	LUR model (residential address) PM ₁₀ : Range of means (SD): 13.5 (3.1)–48.1 (4.1) µg/m ³ PM _{coarse} : Range of means (SD): 4.0 (2.0)–20.7 (2.6) µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	367,383	CSD: 9,994 CBVD: 2,484 CHD: 4,992 MI: 2,264	PM ₁₀ : 10 µg/m ³ PM _{coarse} : 5 µg/m ³	CSD: PM ₁₀ HR = 1.02 (0.94–1.14) PM _{coarse} HR = 1.02 (0.91–1.13) CBVD: PM ₁₀ HR = 1.22 (0.91–1.63) PM _{coarse} HR = 1.17 (0.90–1.52) CHD: PM ₁₀ HR = 0.93 (0.77–1.13) PM _{coarse} HR = 0.92 (0.77–1.11) MI: PM ₁₀ HR = 0.94 (0.81–1.09) PM _{coarse} HR = 0.88 (0.71–1.10)
Dimakopoulou et al., 2014	Cohort ESCAPE (1990s–2008)	16 cohorts from 11 countries; general population Females range: 47.7%–100% Mean age range at baseline: 41.9–73.0 y	LUR model (residential address) PM ₁₀ : Range of means (SD): 13.5 (3.1)–48.1 (4.1) µg/m ³ PM _{coarse} : Range of means (SD): 4.0 (2.0)–20.7 (2.6) µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	307,553	RD: 1,559	PM ₁₀ : 10 µg/m ³ PM _{coarse} : 5 µg/m ³	RD: PM ₁₀ : HR = 0.86 (0.67–1.04) PM _{coarse} : HR = 0.95 (0.76–1.14)
Badaloni et al., 2017	Cohort Rome Longitudinal Study (2001–2010)	Adults aged ≥30 y who resided in Rome, Italy, ≥5 y Males: 45.4% Mean age (SD): 55 (15) y	LUR model (residential address) PM ₁₀ : Mean (SE): 37 (5.1) µg/m ³ Median: 35.2 µg/m ³ IQR: 4.7 (38–33.3) µg/m ³	Age, sex, individual-level SES, area-level SES, marital status, place of birth	124,9108	All-cause: 142,327 CSD: 59,434 CHD: 22,234	PM ₁₀ : 17.2 µg/m ³	All-cause: HR = 1.03 (1.01–1.04) CSD: HR = 1.04 (1.01–1.07) CHD: HR = 1.05 (1.00–1.09)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Nieuwenhuijzen et al., 2018	Cohort SIDIAP (2010–2014)	Adults ≥18 y, registered in SIDIAP and living in Barcelona; SIDIAP represents 80% of total population of Catalonia (Spain) Males: 53% Average age: 50.9 y	LUR model (census tract) PM ₁₀ : Geometric mean (95% CI): 38.29 (38.28–38.30) µg/m ³ p25–p75: 35.86–41.26 µg/m ³	Age, sex, area-level SES, individual-level smoking	792,649	All-cause: 28,391	PM ₁₀ : 10 µg/m ³	All-cause: HR = 1.00 (0.97–1.03)
Carlsen et al., 2022	Malmö Diet and Cancer Cohort (1991–1996)	Random selection of individuals born between 1923 and 1950 in Malmö, Sweden Females: 60.3% Mean age (SD): 58.0 (7.6) y	Dispersion model (residential address) PM ₁₀ : Mean (SD): 15.9 (2.2) µg/m ³ Median: 15.7 µg/m ³ 5th–95th: 12.3–2.04 µg/m ³ IQR: 2.71 µg/m ³	Age, sex, individual-level SES, area-level SES, individual-level smoking, physical activity, health status, other lifestyle factors	25,823	MI: 650	PM ₁₀ : 2.71 µg/m ³	MI: HR = 0.94 (0.78–1.14)
Europe—Patient population								
Maheswaran et al., 2010	Cohort (1995–2006)	Patients living in London, United Kingdom, in 2001 who experienced first-ever stroke 1995–2005 Females: 48.6%–50.8% Age (mean): 70.2–70.7 (SD: 14.3–14.8) y	Hybrid or other model (residential address) PM ₁₀ : Mean (SD): 25 (1.3) µg/m ³ Range: 22.7–52 µg/m ³	Age, sex, area-level SES, individual-level smoking, ethnicity, lifestyle variables, comorbidities, medical variables	3,320	All-cause: 1,856	PM ₁₀ : 10 µg/m ³	All-cause: HR = 1.52 (1.06–2.18)
Desikan et al., 2016	Cohort (2005–2012)	South London Stroke Register (United Kingdom), a population-based register of incident strokes Males: 52.3% Mean age (SD): 68.8 (15.8) y	Dispersion model (residential postcode) PM ₁₀ : Mean (SD): 24.84 (1.50) µg/m ³ Median: 24.91 µg/m ³ IQR: 2.21 (25.84–23.63) µg/m ³ PM _{coarse} : Mean (SD): 9.49 (0.69) µg/m ³ Median: 9.48 µg/m ³ IQR: 1.02 (9.94–8.92) µg/m ³	Age, sex, area-level SES, ethnicity, stroke-specific variables	1,800	All-cause: 729	PM ₁₀ : 2.21 µg/m ³ PM _{coarse} : 1.02 µg/m ³	All-cause: PM ₁₀ HR = 1.12 (0.98–1.29) PM _{coarse} HR = 0.98 (0.87–1.10)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Tonne et al., 2016	Cohort (2003–2010)	Patients >25 y from Greater London, United Kingdom, admitted to hospital with MI from hospitals that had >10 STEMI or non-STEMI admissions Males: 68% Mean age (SD): 68 (14) y	Dispersion model (residential postcode centroid) PM ₁₀ exhaust: Mean (SD): 0.7 (0.3) µg/m ³ Median: 0.6 µg/m ³ IQR: 0.3 (0.8–0.5) µg/m ³ PM ₁₀ non-exhaust: Mean (SD): 2.3 (0.9) µg/m ³ Median: 2.2 µg/m ³ IQR: 1.1 (2.8–1.7) µg/m ³	Age, sex, area-level SES, individual-level smoking, ethnicity, medical history, MI, and STEMI-specific variables	18,138	All-cause: 5,129	PM ₁₀ exhaust: 0.3 µg/m ³ PM ₁₀ non-exhaust: 1.1 µg/m ³	All-cause: PM ₁₀ exhaust HR = 1.02 (0.98–1.06) PM ₁₀ non-exhaust HR = 1.05 (1.00–1.09)

Abbreviations: BMI: body mass index; CBVD: cerebrovascular disease; CHD: coronary heart disease; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CSD: circulatory system disease; ESCAPE: European Study of Cohorts for Air Pollution Effects; HR: hazard ratio; IQR: interquartile range; LUR: land-use regression; MI: myocardial infarction; OR: odds ratio; RD: respiratory disorder; SD: standard deviation; SES: socio-economic status; SIDIA P: Sistema d'Informació pel Desenvolupament de la Investigació en Atenció Primària; STEMI: ST-elevation myocardial infarction; y: year.

A.7. STUDY DETAILS FOR MORTALITY BY LONG-TERM EXPOSURE TO BENZENE

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Canada—General population								
Villeneuve et al., 2013	Ontario Tax Cohort (1982–2004)	Randomly selected income tax filing Canadians in 10 urban areas of Ontario, restricted to Toronto, aged ≥35 y Males: 50.4%	LUR model (postal code) Mean (SD): 0.64 (0.10) µg/m ³ IQR: 0.13 µg/m ³ Median: 0.62 µg/m ³ Range: 0.47–1.17 µg/m ³	Age, sex, individual-level SES, area-level SES, indirectly adjusted for smoking	58,760	All-cause: 18,020 CSD: 6,060 RD: 1,410	0.13 µg/m ³	All-cause: Rate ratio = 1.03 (1.01–1.06) CSD: Rate ratio = 1.03 (0.98–1.07) RD: Rate ratio = 1.01 (0.91–1.12)

Abbreviations: CI: confidence interval; CSD: circulatory system disease; IQR: interquartile range; LUR: land-use regression; RD: respiratory disorder; SD: standard deviation; SES: socio-economic status; Y: year.

A.8. STUDY DETAILS FOR MORTALITY BY LONG-TERM EXPOSURE TO CO

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Europe—General population								
Rosenlund et al., 2006	Case-control Stockholm Heart Epidemiology Program (1992–1994)	Population-based case-control in Stockholm, Sweden; first events of MI in population aged 45–70 y Males: Cases; controls: 66%; 65% Mean age (SD): Cases; controls: 60.9 (6.8) y; 60.9 (6.8) y	Dispersion model (residential address) Cases: Median (5th–95th): 66.8 (13.9–295.7) µg/m ³ Controls: Median (5th–95th): 62.6 (13.3–283.4) µg/m ³	Age, sex, individual-level SES, individual smoking, diabetes, physical activity	3,210	MI: 272	300 µg/m ³	MI: OR = 1.22 (0.98–1.52)
Rosenlund et al., 2009	Case-control (1985–1996)	Population-based case-control in Stockholm, Sweden; first events of MI in population 15–79 y Males: Cases; controls: 69%; 49% Fatal cases captured	Dispersion model (residential address) Cases: Median (5th–95th): 64.2 (7.3–267.4) µg/m ³ Controls: Median (5th–95th): 55.8 (6.1–261.8) µg/m ³	Age, sex, individual-level SES, calendar year	301,273	MI: 8,809	300 µg/m ³	MI: OR = 1.14 (1.07–1.21)

Abbreviations: CI: confidence interval; MI: myocardial infarction; OR: odds ratio; SES: socio-economic status; SD: standard deviation; STEMI: ST-elevation myocardial infarction; y: year.

A.9. STUDY DETAILS FOR MORTALITY BY LONG-TERM EXPOSURE TO TRAFFIC PROXIMITY

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Canada—General population								
Gan et al., 2010	Cohort (1994–2002)	Vancouver metropolitan residents, British Columbia, aged 45–85 y with provincial health insurance plan Males: 45%–47% Mean age (SD): 58.6–61.0 (10.0–10.9) y	GIS (residential postal code) Consistent exposure: ≤50 m from major road or ≤150 m from highway Reference group: living >150 m from highway or >50 m from major road	Age, sex, area-level SES, preexisting comorbidities	414,793	CHD: 3,133	Exposed vs. reference	CHD: RR = 1.29 (1.18–1.41)
Chen et al., 2013	Ontario Tax Cohort (1982–2004)	Residents in Toronto, Hamilton, or Windsor, Ontario, 35–85 y, randomly selected from Ontario Tax Cohort For all 3 cities: Males: 50% Mean age: 52 y	GIS (postal code) Exposed group: ≤50 m from major road or <100 m from highway Reference group: living >50 m from major road or >100 m from highway	Age, sex, individual-level SES, area-level SES, marital status	205,440 (Hamilton, Toronto, Windsor)	CSD: 19,380 CHD: 10,460 CBVD: 4,130	Exposed vs. reference	CSD: Pooled ^a Rate ratio = 1.04 (1.00–1.08) CHD: Pooled ^a Rate ratio = 1.07 (1.01–1.13) CBVD: Pooled ^a Rate ratio = 1.01 (0.92–1.10)
Cakmak et al., 2019	Cohort CanCHEC (1991–2011)	Canadian residents aged ≥25 y at baseline who completed long-form census Males (per quartile of local road length): 49.3%–51.0%	GIS (postal code centroid) Total length of local roads ≤200 m radius of residence: IQR: 1,108.6 m	Age, sex, individual-level SES, area-level SES, additional social determinants	2,644,370	All-cause: 351,515 CSD: 114,990 CHD: 70,370 CBVD: 23,850 RD: 33,630 COPD: 16,070	Total length of local roads ≤200 m radius of residence: 1,108.6 m	All-cause: HR = 1.05 (1.04–1.05) CSD: HR = 1.04 (1.03–1.04) CHD: HR = 1.05 (1.04–1.06) CBVD: HR = 1.01 (0.99–1.02) RD: HR = 1.03 (1.01–1.04) COPD: HR = 1.02 (1.00–1.04)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Canada—Patient population								
Finkelstein et al., 2004	Cohort (1992–2001)	Adults aged ≥40 y who underwent pulmonary function testing at a clinic in Hamilton, Ontario Males (control; exposed): 45%; 42% Median age (control; exposed): 60.4 y; 63.6 y	GIS (postal code) Exposed group: residence within 50 m of major road or 100 m of a highway Control group: living outside buffer	None	5,228	All-cause: 923	Exposed vs. control	All-cause: RR = 1.18 (1.02–1.38)
Finkelstein et al., 2005	Cohort (1992–2001)	Adults aged ≥40 y who underwent pulmonary function testing at a clinic in Hamilton, Ontario Males (control; exposed): 45%; 42% Median age (control; exposed): 60.4 y; 63.6 y	GIS (postal code) Exposed group: residence within 50 m of major road or 100 m of a highway Reference group: living outside buffer	Age, sex, area-level SES, BMI, clinical variables	5,228	CSD: 252 CBVD: 58 RD: 232	Exposed vs. reference	CSD: RR = 1.35 (1.03–1.75) CBVD: RR = 1.80 (1.07–3.03) RD: RR = 0.95 (0.71–1.27)
Jerrett et al., 2009	Cohort (1992–2002)	Adult patients from respiratory disease clinic in Toronto, Ontario Males: 48% Age (median): 60 y	GIS (postal code) Exposed group: residence within 50 m of major road or 100 m of a highway Control group: living outside buffer 24% of population lived <50 m from major road or <100 m from highway	Age, sex, area-level SES, individual-level smoking, BMI, clinical variables	2,360	All-cause: 298 CSD: 80	Exposed vs. control	All-cause: RR = 1.19 (0.92–1.53) CSD: RR = 1.48 (0.91–2.42)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
USA—General population								
Hart et al., 2013	Cohort Nurses' Health Study (1990–2008)	Married female United States registered nurses from all 50 states, 30–55 y at enrollment Mean age (SD): 63.8 (8.6)–64.4 (8.7) y (traffic quartiles)	GIS (residential address) Close to traffic ^c : residence within 50 m of A3 road or within 150 m of A1 or A2 road (for the majority of cohort and their person-years) Far: outside buffer Reference group: consistently far	Age, sex, individual-level SES, area-level SES, individual-level smoking, race, lifestyle variables, medical history, family background variables	84,562	All-cause: 11,502	Consistently close vs. reference Moved from far to close vs. reference Moved from close to far vs. reference	All-cause: HR = 1.05 (1.00–1.10) HR = 1.17 (1.00–1.37) HR = 0.98 (0.94–1.03)
Hart et al., 2014	Cohort Nurses' Health Study (1986–2012)	Married female US registered nurses from all 50 states, 30–55 y at enrollment Mean age (SD): 64.3 (10.0) y	GIS (residential address) Traffic proximity to nearest A1–A3 road ^b Linear models for distances of 0 to 499 m compared with addresses ≥500 m away	Age, sex, individual-level SES, area-level SES, individual-level smoking, race, lifestyle variables, medical history, co-morbidities, family background variables	107,130	SCD ^c : 523 Fatal CHD: 1,159	Linear (per 100 m closer)	SCD: HR = 1.06 (1.01–1.11) Fatal CHD: HR = 1.04 (1.00–1.07)
Kulick et al., 2018	Cohort The Northern Manhattan Study (1993–2016)	Stroke-free multiethnic urban population aged ≥40 y residing in Northern Manhattan, New York Males: 37.2% Mean age (SD) at baseline: 69 (14) y	GIS (residential address) Median distance from major roadway (A1 or A2) ^b : 248.1 m IQR: 253.7 (389.8–136.1) m Reference group: ≥400 m 17% of cohort lived <100 m from a major roadway	Age, sex, individual-level SES, area-level SES, individual-level smoking, race, activity lifestyles, medical variables	3,287	All-cause: 1,854 CSD: 803	<100 m vs. reference 100 - <200 m vs. reference 200 - <400 m vs. reference log-transformed continuous variable (per IQR): 253.7 m	All-cause: HR = 0.95 (0.81–1.13) HR = 1.04 (0.90–1.21) HR = 1.04 (0.91–1.18) HR = 1.00 (0.95–1.06) CSD: HR = 0.92 (0.71–1.19) HR = 0.94 (0.74–1.19) HR = 1.00 (0.82–1.23) HR = 0.98 (0.89–1.07)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
USA—Patient population								
Medina-Ramón et al., 2008	Cohort Worcester Heart Failure Study (2000–2005)	Adult residents of Greater Worcester, Massachusetts, hospitalized with heart failure and discharged alive in 2000 Males: 43.8% Mean age: 76.1 ± 12.5 y	GIS (zip code) Distance to major roadway: Median: 1,640 m IQR: 2008 (2,899–891) m	Age, sex, area-level SES, ethnicity, medical history, and clinical variables	1,389	All-cause: 1,055	Distance to major roadway: 2,008 m	All-cause: HR = 1.00 (0.93–1.08)
Wilker et al., 2013	Cohort (1999–2012)	Patients aged ≥21 y admitted at Beth Israel Deaconess Medical Center with ischemic stroke; residents of greater Boston metropolitan area, Massachusetts Females: 54.55% Median age (IQR): 72 (21)–79 (20) y (by category)	GIS (residential address) Distance to roadway with >10,000 vehicles/day Reference group: >400 m	Age, sex, area-level SES, individual-level smoking, medical history, comorbidities	1,683	All-cause: 950	≤100 m vs. reference >100–200 m vs. reference >200–400 m vs. reference	All-cause: HR = 1.20 (1.01–1.43) HR = 1.08 (0.88–1.31) HR = 0.99 (0.82–1.20) P for trend: 0.02
Europe—General population								
Hoek et al., 2002	Cohort NLCS (1986–1994)	Adults aged 55–69 y residing in the Netherlands Males (alive; dead): 46%; 64% Mean age (alive; dead): 61 y; 63 y	GIS (residential address) Exposed group: residence within 100 m of a freeway or within 50 m of a major urban road	Age, sex, individual-level SES, area-level SES, individual-level smoking, Quetelet index	3,464	All-cause: 489 CPD: 158	Exposed (background concentration of black smoke [BS]) Exposed (background concentration of NO ₂)	All-cause: RR = 1.41 (0.94–2.12) RR = 1.41 (0.94–2.11) CPD: RR = 1.95 (1.09–3.51) RR = 1.94 (1.08–3.48)
Gehring et al., 2006	Cohort SALIA (1985–2003)	Females in mid50s of German nationality living in 10 areas in 7 cities in North Rhine-Westphalia, Germany Age: 50–59 y	GIS (residential address) Distance to major roads (defined as roads with ≥10,000 cars/day) Exposed group: ≤50 m Reference group: >50 m	Sex, individual-level SES, individual-level smoking	4,230	All-cause: 385 CPD: 139	Exposed vs. reference	All-cause: RR = 1.29 (0.93–1.78) CPD: RR = 1.70 (1.02–2.81)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Beelen et al., 2008	Cohort NILCS-AIR (1986–1996) Full cohort analyses	Adults aged 55–69 y living in 204 municipalities throughout the Netherlands Males (cases; non-cases): 65.5%; 45.4% Median age (IQR) (cases; non-cases): 64 (60–67) y; 61 (58–65) y	GIS (residential address) Exposed group: living near a major road (≤ 100 m of motorway or ≤ 50 m of local road with traffic intensity $> 10,000$ motor vehicles/24 h) Reference group: not living near a major road	Age, sex, area-level SES, individual-level smoking	117,528	All-cause: 15,287 CSD: 5,397 RD: 904	Exposed vs. reference Model include BS background concentration	All-cause: RR = 1.05 (0.97–1.12) CSD: RR = 1.05 (0.93–1.18) RD: RR = 1.19 (0.91–1.56)
Beelen et al., 2009	Cohort NILCS-AIR (1986–1996) Full cohort analyses	Adults aged 55–69 y living in 204 municipalities throughout the Netherlands Males (cases; non-cases): 69.1%; 47.2% Median age (IQR) (cases; non-cases): 64 (61–67) y; 62 (58–65) y	GIS (residential address) Exposed group: living near a major road (≤ 100 m of motorway or ≤ 50 m of local road with traffic intensity $> 10,000$ motor vehicles/24 h) Reference group: not living near a major road	Age, sex, area-level SES, individual-level smoking	117,528	CSD: 6,137 CHD: 3,521 CBVD: 1,175 HF: 422 Cardiac dysrhythmia: 399	Exposed vs. reference Model includes BS background concentration	CSD: RR = 1.05 (0.93–1.18) CHD: RR = 1.15 (0.99–1.34) CBVD: RR = 0.70 (0.51–0.96) HF: RR = 0.94 (0.59–1.49) Cardiac dysrhythmia: RR = 1.13 (0.70–1.82)
Brunekreef et al., 2009 (HEI report)	Cohort NILCS-AIR (1986–1996) Full cohort analyses	Adults aged 55–69 y living in 203 municipalities throughout the Netherlands Males (cases; other subjects): 65.5%; 45.4% Median age (range) (cases; other subjects): 64 (54–70) y; 61 (54–70) y	GIS (residential address) Median: 485 m IQR: 279 (501 st –22) m Range: 5–501 st m Exposed group: living near a major road (≤ 100 m of a freeway or ≤ 50 m of a major road with 10,000 motor vehicles/day) Reference group: not living near a major road	Age, sex, area-level SES, individual-level smoking, regional variation	105,296	All-cause: 17,674 CSD: 6,279 RD: 1,046	Exposed vs. reference Model includes average BS background concentration	All-cause: RR = 1.05 (0.97–1.12) CSD: RR = 1.05 (0.93–1.18) RD: RR = 1.19 (0.91–1.56)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Huss et al., 2010	Swiss National Cohort (2000–2005)	Swiss National Cohort of persons aged 30+ y (Switzerland) Females (per distance to main road quartile) ranged from 52%–53% Median age (per distance to main road quartile) ranged from 50.2–51.2 y	GIS (residential address) Distance to main road (major road network and interconnecting road network) Reference group: ≥ 200 m	Age, sex, individual- and area-level SES factors	4,580,311	CSD: 177,836 Acute MI: 15,532 Stroke: 25,231	<50 m vs. reference 50–99 m vs. reference 100–199 m vs. reference	CSD: HR = 1.04 (1.03–1.06) HR = 1.04 (1.02–1.05) HR = 1.02 (1.00–1.03) Acute MI: HR = 1.10 (1.05–1.15) HR = 1.08 (1.03–1.14) HR = 0.98 (0.93–1.04) Stroke: HR = 1.01 (0.98–1.05) HR = 0.99 (0.95–1.03) HR = 1.02 (0.98–1.06)
Raaschou-Nielsen et al., 2012	Diet, Cancer, and Health Cohort Study (1993–2009)	Adults aged 50–64 y living in the Copenhagen and Aarhus areas, born in Denmark, and with no previous cancer diagnosis Males: 47.5% Median age: 56.1 y	GIS (residential address) Exposed group: living within 50 m of a major road ($\geq 10,000$ vehicles/day) Reference group: living >50 m % of participants living within 50 m: 8.0% % living outside 50 m: 92%	Age, sex, individual-level SES, area-level SES, lifestyle and dietary variables, occupational exposure, marital status	52,061	All-cause: 5,534 CSD: 1,285 CHD: 548 CBVD: 292	Exposed vs. reference	All-cause: MRR = 0.94 (0.85–1.05) CSD: MRR = 0.98 (0.79–1.21) CHD: MRR = 1.04 (0.76–1.44) CBVD: MRR = 0.87 (0.54–1.39)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Cesaroni et al., 2013	Cohort Rome Longitudinal Study (2001–2010)	Adults aged ≥ 30 y who resided in Rome, Italy, ≥ 5 y Males: 45.5% <60 y: 61.3% 60 – 75 y: 26.8% ≥ 75 y: 11.9%	GIS (residential address) Distance to high traffic road with $>10,000$ vehicles/day Mean (SD): 232 (224) m Median: 165 m IQR: 228 (308–80) m Range: 2–946 m Reference group: ≥ 250 m	Age, sex, individual-level SES, area-level SES, marital status, place of birth	1,265,058	All-cause: 144,441 CSD: 60,318 CHD: 22,562 CBVD: 13,576 RD: 8,825	<50 m vs. reference 50–100 m vs. reference 100–150 m vs. reference 150–250 m vs. reference	All-cause: HR = 1.02 (1.00–1.01) HR = 1.01 (0.99–1.03) HR = 1.01 (0.99–1.02) HR = 0.99 (0.98–1.01) P for trend: 0.004 CSD: HR = 1.03 (1.01–1.05) HR = 0.99 (0.97–1.02) HR = 1.00 (0.97–1.02) HR = 0.99 (0.97–1.02) P for trend: 0.043 CHD: HR = 1.05 (1.01–1.09) HR = 1.02 (0.98–1.06) HR = 0.99 (0.95–1.04) HR = 1.01 (0.97–1.05) P for trend: 0.034 CBVD: HR = 1.03 (0.98–1.08) HR = 1.01 (0.95–1.06) HR = 1.00 (0.94–1.05) HR = 1.00 (0.96–1.05) P for trend: 0.305 RD: HR = 1.01 (0.95–1.08) HR = 1.02 (0.96–1.09) HR = 0.96 (0.90–1.03) HR = 0.97 (0.91–1.03) P for trend: 0.390
Heinrich et al., 2013	Cohort SALIA (1985–2008)	Females in mid-50s of German nationality living in 10 areas in 7 cities in North Rhine-Westphalia, Germany Age: 50–59 y Overall response rate: 70% Follow-up time median (max): 18.4 (21.9) y	GIS (residential address) Proximity to major roadway ($\geq 10,000$ cars/day) Exposed group: ≤ 50 m Reference group: >50 m	Age, sex, individual-level SES, individual-level smoking	4,752	All-cause: 740 CPD: 268 RD: 35	Exposed vs. reference	All-cause: RR = 1.42 (1.12–1.79) CPD: RR = 1.95 (1.37–2.77) RD: RR = 3.54 (1.49–8.40)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Europe—Patient population								
Nawrot et al., 2011	Cohort (1997–2009)	Patients who underwent lung transplantation in 1997–2008 with long-term follow-up at UZ Leuven, Belgium Females (close to major road; farther away from major road): 53%; 41% Mean age (close to major road; farther away from major road): 47.5±14.3 y; 46.3±13.9 y	GIS (residential address) Proximity to a major road (i.e., highways, national roads or large local roads) Exposed group: ≤171 m (assigned based on lowest tertile) Reference group: >171 m	Age, sex, individual-level SES, transplantation-specific variables	281	All-cause: 61	Exposed vs. reference	All-cause: HR = 1.99 (1.09–3.61)
Goeminne et al., 2014	Cohort (2006–2013)	Patients aged 18–65 y with non-cystic fibrosis bronchiectasis who visited outpatient clinic at University Hospital in Leuven, Belgium Females: 55% Median age (IQR): 53 (37–59) y	GIS (residential address) Distance to a major road (no additional information)	Age, sex, individual-level SES, individual-level smoking, clinical variables	183	All-cause: 15	10-fold increase in distance (m)	All-cause: HR = 0.28 (0.10–0.77)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Ruttens et al., 2017	Cohort (1987–2013) Macrolide-free group	Patients who underwent lung transplantation during study period in 13 major lung transplant centres across 10 European countries Males: 52% Mean age (SD): 45.5 (13.8) y	GIS (residential address) Distance to freeway: IQR: 1,233 m Mean (SD): 4,959 (5,232)–50,387 (77672) m Distance to major road: IQR: 241 m Mean (SD): 1,477 (1601)–5,785 (7559) m Total road length within different buffers: IQR for: 50 m: 108 m 100 m: 279 m 200 m: 752 m 500 m: 4092 m 1000 m: 15403 m	Age, sex, transplantation-specific variables	3,556	All-cause: 1,937	Distance to freeway: 1,233 m Distance to major road: 241 m Total road length within buffers: 108 m (50 m buffer) 279 m (100 m buffer) 756 m (200 m buffer) 4,092 m (500 m buffer) 15,403 m (1,000 m buffer)	All-cause: HR = 0.987 (0.964–1.012) HR = 1.000 (0.976–1.024) HR = 1.055 (0.955–1.112) HR = 1.111 (1.025–1.202) HR = 1.094 (1.030–1.779) HR = 1.085 (1.000–1.130) HR = 1.047 (0.985–1.131)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Asia—General population								
Hadley et al., 2022	Golestan Cohort Study (2004–2008)	Adults aged 40–75 y residing across northeastern Golestan, Iran; ~80% from 326 rural villages (ranging in size from 20 to 150 residents); 20% randomly selected from Gonbad City (130,000 residents) Females: 57% Mean age (SD): 52.1 (8.9) y	GIS (geographic centre of village for rural residents; location of primary health centre for residents of Gonbad City) Proximity to traffic Exposed group: living within 100 m of a minor highway or within 500 m of a major highway Reference group: not exposed	Age, sex, individual-level SES, area-level SES, individual-level smoking, ethnicity, marital status, medical history, substance use	45,052	All-cause: 5,996 CSD: 2,733	Exposed vs. reference	All-cause: HR = 1.04 (0.96–1.12) CSD: HR = 1.13 (1.01–1.27)

Abbreviations: BMI: body mass index; BS: black smoke; CanCHEC: Canadian Census Health and Environment Cohort; CBVD: cerebrovascular disease; CHD: coronary heart disease;

CI: confidence interval; COPD: chronic obstructive pulmonary disease; CPD: cardiopulmonary disease; CSD: circulatory system disease; GIS: geographic information system; HF: heart failure;

HR: hazard ratio; IQR: interquartile range; MI: myocardial infarction; MRR: mortality rate ratio; NLCS: Netherlands Cohort Study on Diet and Cancer; RD: respiratory disorder; RR: relative risk;

SALIA: Study on the influence of air pollution on lung function, inflammation and ageing; SCD: sudden cardiac death; SD: standard deviation; SES: socio-economic status; y: year.

^a Pooled estimate of fully adjusted RRs was obtained using a fixed-effect model with the inverse-variance method.

^b A1 (primary roads, e.g., interstate highways), A2 (primary major, non-interstate highways and major roads), or A3 (smaller, secondary roads, usually with more than two lanes)

^c Defined as death or cardiac arrest occurring within 1 hour of the onset of symptoms.

^d All subjects living >500 m from a major road were assigned a distance of 501 m.

^e Major road network (e.g., motorways, slip roads, and other roads of high importance); interconnecting road network (main roads between towns and main traffic connections within the larger cities).

^f Minor highway (two-lanes connecting smaller population centres); major highway (multi-lane connecting major population centres)

A.10. STUDY DETAILS FOR MORTALITY BY LONG-TERM EXPOSURE TO TRAFFIC DENSITY

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
USA—Patient population								
Medina-Ramón et al., 2008	Cohort Worcester Heart Failure Study (2000–2005)	Adult residents of Greater Worcester, Massachusetts, hospitalized with heart failure and discharged alive in 2000 Males: 43.8% Mean age: 76.1 ± 12.5 y	Traffic within 100 m of residence (vehicle-km/day) Median: 448 IQR: 1,379 (1,579–200) Traffic within 300 m of residence (vehicle-km/day) Median: 4,451 IQR: 9,425 (11,389–1,964)	Age, sex, area-level SES, ethnicity, medical history, and clinical variables	1,389	All-cause: 1,055	Traffic within 100-m buffer: 1,379 vehicle-km/day Traffic within 300-m buffer: 9,425 vehicle-km/day	All-cause: HR = 1.13 (1.03–1.23) HR = 1.07 (0.98–1.16)
Blount et al., 2017	Cohort (2000–2012)	All reported pediatric and adult tuberculosis cases in California Males: 60.8% and 58.3% for high and low traffic density, respectively Median age at diagnosis (IQR): 46.2 (30.5–62.2) y and 47.7 (30.8–64.5) y for high and low traffic density, respectively	Traffic (vehicle-km/hr) around residence: 100-m to 400-m buffers: Range of means: 216–2,977 Range of medians: 106–1,525 Traffic at nearest major road around residence (vehicles/day): 100-m to 400-m buffers: Range of means: 19,160–20,985 Range of medians: 12,000–12,610 Traffic of highest-trafficked road (vehicles/day): 100-m to 400-m buffers: Range of means: 24,876–53,332 Range of medians: 15,700–29,000	Age, sex, individual-level SES, ethnicity, lifestyle variables, tuberculosis-specific variables	32,875	All-cause: 2,305	Traffic (vehicle-km/hr) around residence: 100-m buffer 200-m buffer 300-m buffer 400-m buffer Traffic at nearest major road around residence (vehicles/day): 100-m buffer 200-m buffer 300-m buffer 400-m buffer Traffic of highest-trafficked road (vehicles/day): 100-m buffer 200-m buffer 300-m buffer 400-m buffer	All-cause: Trend analyses P-trend = 0.005 P-trend = 0.04 P-trend = 0.09 P-trend = 0.36 P-trend = 0.002 P-trend = 0.004 P-trend = 0.006 P-trend = 0.01 P-trend <0.001 P-trend = 0.005 P-trend = 0.01 P-trend = 0.46

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Europe—General population								
Beelen et al., 2008	Cohort NILCS-AIR (1986–1996) Full cohort analyses	Adults aged 55–69 y Includes 204 municipalities (small rural communities and major cities) throughout the Netherlands Males: 65.5% in case subjects; 45.4% in other subjects Median age: 64 y (range 54–70 y) in case subjects; 61 y (range 54–70 y) in other subjects	Traffic on nearest road to residence (vehicles/day): Mean (SD): 2,284 (3,767) Range: 1–104,275 Sum of traffic in 100-m buffer around residence (vehicles/day): Mean (SD): 140,903 (116,104) Range: 0–893,722	Age, sex, area-level SES, individual-level smoking	117,528	All-cause: 15,287 CSD: 5,397 RD: 904	Traffic on nearest road: 10,000 vehicles/day Sum of traffic in 100m buffer: 335,000 vehicles/day	All-cause: RR = 1.03 (1.00–1.08) RR = 1.02 (0.97–1.07) CSD: RR = 1.05 (0.99–1.12) RR = 1.00 (0.92–1.08) RD: RR = 1.11 (0.95–1.26) RR = 1.21 (1.02–1.44)
Beelen et al., 2009	Cohort NILCS-AIR (1986–1996) Full cohort analyses	Adults aged 55–69 y living in 204 municipalities throughout the Netherlands Males (cases; non-cases): 69.1%; 47.2% Median age (IQR) (cases; non-cases): 64 (61–67) y; 62 (58–65) y	GIS (residential address) Using GIS and digital road network (from year 2001) to characterize traffic intensities in 1986 Mean (SD): 2,284 (3,767) motor vehicles/24 h Min-max: 1–104,275 motor vehicles/24 h	Age, sex, area-level SES, individual-level smoking	117,528	CSD: 6,137 CHD: 3,521 CBVD: 1,175 HF: 422 Cardiac dysrhythmia: 399	10,000 motor vehicles/day Model include BS background concentration	CSD: RR = 1.05 (0.99–1.12) CHD: RR = 1.11 (1.03–1.20) CBVD: RR = 0.82 (0.68–1.00) HF: RR = 1.07 (0.86–1.23) Cardiac dysrhythmia: RR = 1.04 (0.79–1.36)
Brunekreef et al., 2009	Cohort NILCS-AIR (1986–1996) Full cohort analyses	Adults aged 55–69 y living in 203 municipalities (small rural communities and major cities) throughout the Netherlands Males: 65.5% in case subjects; 45.4% in other subjects Median age: 64 y (range 54–70 y) in case subjects; 61 y (range 54–70 y) in other subjects	Traffic of nearest road to residence (vehicles/day): Median: 10,171 IQR: 3,758 (13,758–0,000) Range: 10,000–114,968 Sum of traffic in 100-m buffer around residence (vehicles/day): Median: 104,125 IQR: 91,230 (166,787–75,557) Range: 0–2,867,610	Age, sex, area-level SES, individual-level smoking, regional variation	105,296	All-cause: 17,674 CSD: 17,674 RD: 1,046	Traffic on nearest road: 10,000 vehicles/day Sum of traffic in 100m buffer: 335,000 vehicles/day	All-cause: RR = 1.03 (1.00–1.08) RR = 1.02 (0.97–1.07) CSD: RR = 1.05 (0.99–1.12) RR = 1.00 (0.92–1.08) RD: RR = 1.11 (0.95–1.26) RR = 1.21 (1.02–1.44)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Raaschou-Nielsen et al., 2012	Diet, Cancer and Health cohort study (1993–2009)	Adults aged 50–64 y living in Copenhagen and Aarhus areas, born in Denmark and no previous cancer diagnosis Males: 47.5% Median age: 56.1 y	Traffic within 200-m buffer of residence (10 ³ vehicle-km/day): Median: 2.5 5th–95th percentile: 0.3–15.1	Age, sex, individual-level SES, area-level SES, individual smoking, lifestyle and dietary variables, occupational exposure, marital status	52,061	All-cause: 5,534 CSD: 1,285 CHD: 548 CBVD: 292	Per doubling of traffic within 200-m buffer	All-cause: MRR = 1.01 (0.99–1.03) CSD: MRR = 1.02 (0.98–1.06) CHD: MRR = 1.01 (0.95–1.07) CBVD: MRR = 1.02 (0.94–1.11)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Cesaroni et al., 2013	Cohort Rome Longitudinal Study (2001–2010)	Adults aged ≥ 30 y who resided in Rome, Italy, ≥ 5 y Males: 45.5% <60 y: 61.3% 60–75 y: 26.8% ≥ 75 y: 11.9%	Traffic in 150-m buffer around residence (vehicle-m/day): Mean (SD): 4.1×10^6 (5.3×10^6) Median: 5.4×10^6 IQR: 4.9×10^6 – 5.5×10^6 Range: 0 – 88.9×10^6	Age, sex, individual-level SES, area-level SES, marital status, place of birth	1,265,058	All-cause: 144,441 CSD: 60,318 CHD: 22,562 RD: 8,825	Traffic within 150-m buffer by quintile (vehicle-m/day) $\times 10^6$: Q1: $<0.25 \times 10^6$ Q2: $(0.25$ – $1.63) \times 10^6$ Q3: $(1.63$ – $3.23) \times 10^6$ Q4: $(3.23$ – $6.66) \times 10^6$ Q5: $\geq 6.66 \times 10^6$	All-cause: Q1: HR = 1.00 Q2: HR = 1.02 (1.00–1.04) Q3: HR = 1.03 (1.01–1.05) Q4: HR = 1.03 (1.01–1.05) Q5: HR = 1.04 (1.03–1.06) P-trend: <0.001 CSD: Q1: HR = 1.00 Q2: HR = 1.02 (0.99–1.04) Q3: HR = 1.03 (1.00–1.05) Q4: HR = 1.03 (1.00–1.06) Q5: HR = 1.05 (1.02–1.07) P for trend: 0.001 CHD: Q1: HR = 1.00 Q2: HR = 1.00 (0.95–1.04) Q3: HR = 1.01 (0.97–1.04) Q4: HR = 1.04 (1.00–1.09) Q5: HR = 1.04 (1.00–1.09) P for trend: 0.009 RD: Q1: HR = 1.00 Q2: HR = 1.02 (0.95–1.10) Q3: HR = 1.06 (0.99–1.14) Q4: HR = 1.02 (0.95–1.10) Q5: HR = 1.08 (1.00–1.15) P for trend: 0.065

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Beelen et al., 2014a	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females: 47.7%–100% Mean age at baseline (SD): 41.1 (11.8) to 70.3 (8.1) y 20 cohorts included for traffic intensity on nearest road 21 cohorts included for traffic intensity on major roads within 100-m buffer	Traffic of nearest road to residence (vehicle-km/day): Range of means (SD): 845 (1,523)–9,034 (12,466) Traffic on major roads within 100-m buffer (vehicle-km/day): Range of means (SD): 102 (418)–1,000 (15,000)	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	Traffic on nearest road: 349,916 Traffic on major roads in 100-m buffer: 357,380	All-cause: Sum of all cohorts: 29,076	Traffic on nearest road: 5,000 vehicle-km/day Traffic on major roads in 100-m buffer: 4,000,000 vehicle-m/day	All-cause: HR = 1.01 (1.00–1.03) HR = 1.01 (0.98–1.05)
Beelen et al., 2014b	Cohort ESCAPE (1990s–2008)	22 cohorts from 13 countries; general population Females (range): 63% (48%–100%) Mean age at baseline (range): 50.5 (41.1–70.3) y	Traffic of nearest road to residence (vehicle-km/day): Range of means (SD): 845 (1,523)–9,034 (12,466) Traffic on major roads within 100-m buffer (vehicle-km/day): Range of means (SD): 102 (418)–11,000 (15,000)	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	Traffic on nearest road: 349,916 Traffic on major roads in 100-m buffer: 357,380	CSD: 9,994 CBVD: 2,484 CHD: 4,992 MI: 2,264	Traffic on nearest road: 5,000 vehicles/day Traffic on major roads in 100-m buffer: 4,000,000 vehicle-m/day	CSD: HR = 1.02 (0.99–1.05) HR = 0.99 (0.89–1.11) CBVD: HR = 1.02 (0.98–1.07) HR = 1.04 (0.90–1.19) CHD: HR = 1.02 (0.99–1.06) HR = 1.02 (0.88–1.18) MI: HR = 1.03 (0.99–1.07) HR = 1.04 (0.89–1.22)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Dimakopoulou et al., 2014	Cohort ESCAPE (1990s–2008)	16 cohorts from 11 countries; general population Females range: 47.7%–100% Mean age range: 41.9–73.0 y	Traffic intensity on nearest road to residence (vehicle/day): Median (range): 0–4,366 Sum of traffic in 100-m buffer around residence (vehicles*road length/day): Median (range): 0–5,711,495	Age, sex, individual-level SES, area-level SES, individual-level smoking, environmental tobacco smoke, dietary and lifestyle variables, marital status, other SES indicators	307,553	RD: 1,559	Traffic on nearest road: 5,000 vehicles/day Sum of traffic in 100-m buffer: 4,000,000 vehicles*m/day	RD: HR = 1.01 (0.95–1.06) HR = 1.03 (0.93–1.12)
Europe—Patient population								
Goeminne et al., 2014	Cohort (2006–2013)	Patients aged 18–65 y with non-cystic fibrosis bronchiectasis who visited outpatient clinic at University Hospital in Leuven, Belgium Females: 55% Median age (IQR): 53 (37–59) y	Distance-weighted traffic density in a 100- or 200-m buffer around residential address Exposure distribution not provided	Age, sex, individual-level SES, individual-level smoking, clinical variables	183	All-cause: 15	10-fold increase distance-weighted traffic density	All-cause: 100-m buffer: HR = 3.80 (1.07–13.51) 200-m buffer: HR = 4.14 (1.13–15.22)
Tonne et al., 2016	Cohort (2003–2010)	Residents from Greater London, UK, aged >25 y admitted to hospital with MI from hospitals that had >10 STEMI or non-STEMI admissions Males: 68% Mean age (SD): 68 y (14) y	Volume of heavy goods vehicles (HGV) on major roads within a buffer around postcode centroid (per 1,000 vehicle-km): 100-m to 300-m buffer: Range of means (SD): 84.9 (166.5)–823.27 (1,005.3) Range of medians: 0–583.4 Range of IQR: 120.7–823.27	Age, sex, area-level SES, individual-level smoking, ethnicity, medical history, MI, and STEMI-specific variables	18,138	All-cause: 5,129	HGV traffic (per 1,000 vehicle-km): Within 100-m buffer: 120.7 Within 200-m buffer: 476.6 Within 300-m buffer: 856.1	All-cause: HR = 1.02 (1.00–1.04) HR = 1.02 (0.99–1.05) HR = 1.01 (0.98–1.04)

Reference	Cohort (Study period)	Study population	Exposure assessment method and distribution	Confounders and/or covariates	Total N	Cases	Increment	Risk estimate (95% CI)
Asia—General population								
Pan et al., 2021	Cohort REVEAL-HBV (2000–2014)	Adults aged 30–65 y in 1991 living in Taipei and Pingtung, Taiwan	Total vehicle traffic at monitoring site nearest to residence: Mean (SD): 8,569 (6,270) vehicles/day Median distance from residence to monitoring site: 1.56 km	Age, sex, individual-level smoking, BMI and other health/lifestyle variables	12,098	CSD: 382	Log vehicle/day	CSD: HR = 1.13 (0.96–1.33)

Abbreviations: BMI: body mass index; BS: black smoke; CBVD: cerebrovascular disease; CHD: coronary heart disease; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CSD: circulatory system disease; ESCAPE: European Study of Cohorts for Air Pollution Effects; GIS: geographic information system; HGV: heavy goods vehicles; HF: heart failure; HR: hazard ratio; IQR: interquartile range; MI: myocardial infarction; MRR: mortality rate ratio; NLCS: Netherlands Cohort Study on Diet and Cancer; REVEAL-HBV: Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer Hepatitis B Virus; RD: respiratory disorder; RR: relative risk; SES: socio-economic status; SD: standard deviation; STEMI: ST-elevation myocardial infarction; y: year.