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Long-term Exposure to Nitrogen Dioxide and Mortality: A Systematic Review and Meta-analysis

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Abstract

Long-term Exposure to Nitrogen Dioxide and Mortality: A Systematic Review and Meta-analysis

By Shiwen Huang

Background: Ambient air pollution is among the greatest environmental risks to human health. However, little is known about the health effects of nitrogen dioxide (NO2), a traffic-related air pollutant. Herein, we aimed to conduct a meta-analysis to investigate the long-term effects of NO2 on mortality.

Methods: We conducted a systematic search for studies that were published up to February 2020 and performed a meta-analysis of all available epidemiologic studies evaluating the associations between long-term exposure to NO2 with all-cause, cardiovascular, and respiratory mortality. Overall pooled effect estimates as well as subgroup-specific pooled estimates (e.g. location, exposure assessment method, exposure metric, study population, age at recruitment, and key confounder adjustment) and 95% confidence intervals were calculated using random-effects models. Risk of bias assessment was accessed by following WHO global air quality guidelines. Publication bias was accessed by visually inspecting funnel plot and Egger's liner regression was used to test of asymmetry.

Results: Our search initially retrieved 1,349 unique studies, of which 34 studies met the inclusion criteria. The pooled hazard ratio (HR) for all-cause mortality was 1.06 (95%CI: 1.04-1.08, n=28 studies, I2=98.6%) per 10 ppb increase in annual NO2 concentrations. The pooled HRs for cardiovascular and respiratory mortality per 10 ppb increment were 1.11 (95%CI: 1.07-1.16, n=20 studies, I2=99.2%) and 1.05 (95%CI: 1.02-1.08, n=17 studies, I2=94.6%), respectively. The sensitivity analysis pooling estimates from multi-pollutant models suggest an independent effect of NO2 on mortality. Funnel plots indicate that there is no evidence for publication bias in our study.

Conclusion: We provide robust epidemiological evidence that long-term exposure to NO2, a proxy for traffic-sourced air pollutants, is associated with a higher risk of all-cause, cardiovascular, and respiratory mortality that might be independent of other common air pollutants.

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1. Introduction

Ambient air pollution is among the greatest environmental risks to human health, and was reported to be responsible for 4.2 million deaths in 2016 worldwide [1]. Over the past decades, mounting epidemiological evidence has documented the adverse effects of particulate matter and ozone on human health [2-8]. Recently, there has been increased interest in nitrogen dioxide (NO_2), another traffic-related air pollutant.

Although NO_2 has multiple ecological sources, combustion of fossil fuels and motor vehicle emissions represent the primary source of NO_2 in the environment [9]. Previous work has considered NO_2 as an indicator of traffic pollution, given its strong correlation with other components of mobile exhaust. Additionally, NO_2 levels have been used to characterize other ambient air pollutants, such as NOx and ozone [10-12]. More recent work has focused on NO_2 as a possible independent contributor to adverse health effects. A growing body of evidence has reported associations between NO_2 and respiratory and cardiovascular disease-related mortality [13-15]. For example, Jerrett, Finkelstein [16], reported that long-term exposure to NO_2 is positively associated with cardiovascular (RR=1.45, 95%CI: 1.11-1.91) and respiratory mortality (RR=1.06, 95%CI: 0.79-1.43). However conflicting results have emerged, as Bentayeb, Wagner [17] reported null associations between NO_2 and cardiovascular mortality (HR=0.88, 95%CI: 0.51-1.54) and respiratory mortality (HR=0.76, 95%CI: 0.48-1.18). It should be noted that such discrepancies in the data is highly dependent upon location of measurement, time of measurement, sample sizes, study population, study designs, as well as other factors [18]. Thus, a more robust

estimate is needed to improve the understanding of the relationship between NO_2 and overall mortality, in addition to respiratory and cardiovascular disease-related mortality.

To date, three meta-analyses, Faustini et al. (2014)[19], Atkinson et al. (2018)[9] and Huangfu et al. (2020)[20], integrated existing studies published prior to January 2013, October 2016, and January 2018, respectively, all of which reported a link between long-term exposure to NO_2 (e.g., annual mean or multiple-year average) and overall and cause-specific mortality. However, previous studies mainly focused on cohorts in the United States and Europe, and cohorts in Asia and Oceania were limited. Recently, an emerging interest in the health effects of NO_2 has motivated the study and publication of NO_2-exposed cohorts that provide a more global representation of the affected populations. Given this increased interest, to date, the latest epidemiological studies on long-term NO_2 have not been incorporated in any systematic review, presenting a serious gap in our understanding of the current data.

In the present study, we performed a systematic literature search with no location restriction and performed a meta-analysis of all available up-to-date epidemiological studies to examine the association between long-term exposure to ambient NO_2 and mortality endpoints, including all-cause, cardiovascular, and respiratory mortality. We have incorporated 6 new studies compared with Huangfu et al. (2020)[9, 20]with a total of 15 million study population in this meta-analysis that have not been included in the previous ones.

2. Methods

2.1 Search strategy

We conducted a systematic search using both PubMed and EMBASE to identify epidemiologic studies that evaluated long-term exposure to NO_2 and mortality. We restricted our search to all-language studies that were published up to February 29, 2020.

We used the following search terms: ("nitrogen dioxide" OR "NO_2" OR "NO_X" OR "nitrogen oxide" OR "traffic-related air pollution" OR "traffic related air pollution") AND ("mortality" OR "cardiovascular mortality" OR "respiratory mortality") AND ("epidemiology" OR "epidemiological" OR "epidemiologic" OR "cohort" OR "case-control" OR "case control"). We limited our search to human studies. Synonyms of NO and mortality were included using Medical Subheadings (MeSH) terms.

2.2 Study selection

We excluded toxicity studies, in vitro studies, book chapters, commentaries, letters to the editor, conference abstracts, review articles, meta-analyses, and studies that were not written in English. We also excluded epidemiology studies that did not provide risk estimates for NO_2 exposure, or that reported extremely high risk estimates (HR>5), or that did not evaluate all-cause, cardiovascular, or respiratory mortality. In addition, for studies examining the same cohort, we included only the most updated and comprehensive study.

The included population-based studies of all ages exposed to long-term concentration of NO_2 (> 1 year). Outcomes included in our study were all-cause, cardiovascular, and respiratory mortality.

Following the PRISMA guidelines, four authors (initial name SH, HL, MW, YQ) independently evaluated titles and abstracts found in the 2 databases (n=1,774). Reference lists of review articles and meta-analyses were also reviewed to further identify epidemiology studies of NO_2 exposure and mortality (n=1). This resulted in a total of 159 potentially relevant articles for full-text review by four independent authors (SH, HL, MW, YQ). The eligibility of each study was independently assessed by two investigators (SH and YQ, or HL and MW) and the discrepancy was resolved through discussion with a third investigator. The protocol was registered at OSF and the link is provided at the bottom of the Figure 1. Detailed description of PECOS question is provided in Supplemental Table S1.

2.3 Data extraction

Data extraction and accuracy assessment were done by four independent authors (SH, HL, MW, YQ) on July 2020. Extracted information was entered into an Excel database, which included titles, authors' names, publication year, country, study design, study period, cohort name, sample size, age range, sex distribution, time period of exposure assessment, exposure assessment method, exposure levels, exposure increment, effect measure, effect estimate and its standard error, and co-pollutant adjustment as well as adjustment for other confounders. For each study, we extracted the effect estimates from the main model or with the most stringent adjustment of potential confounders. Several studies employed both single- and multiple-pollutant models. In this situation, we extracted estimates from both models, and used estimates from the former in the main analyses and the other in sensitivity analysis.

2.4 Statistical analysis

After data extraction, all effect estimates were converted to HR (95%CI) per 10 ppb increase in NO_2 concentrations. Unit conversion is followed by Air Pollution Information System[21] and assumed ambient pressure of 1 atmosphere and a temperature of 25 degrees Celsius (1 ppb = 1.88 $\mu g/m^3$).Forest plots were used to display the brief study information and HRs in each study graphically as well as the pooled results.

We tested for heterogeneity in the reported effect estimates, and we provided the p-values of the I^2-based Cochran Q test and the I^2 metric of inconsistency [22]. We considered I^2 >50% to represent substantial heterogeneity [23]. An inverse variance random effects model was used to provide the pooled estimates. We performed stratified analyses to explore potential sources of heterogeneity by either cohorts or methodological characteristics. These included (1) study location: we divided study locations into four regions including North America, Europe, Asia and Oceania; (2) exposure assessment method: we separated the exposure assessment method to fixed monitor sites, land use regression (LUR) and other exposure assessment methods; (3) exposure metrices: annual single year average verses multiple year average; (4) study population: general population cohorts versus cohorts using subjects with preexisting disease; (5) age at recruitment; (6) key confounders adjustment for individual measures of BMI and smoking versus no adjustment. We screened for publication bias using funnel plot analysis with standard error as the measure of study size and Egger's liner regression test of asymmetry [24, 25].

We conducted a series of sensitivity analyses to assess the robustness of results. We added back the studies with duplicated cohorts (n=8) and with extremely high HRs (n=2) and reran the meta-analysis. We also extracted estimates from the multi-pollutant models in the sensitivity analysis, if both single- and multi-pollutant models were fit. Moreover, we also excluded the articles that include high risk for each domain if available and rerun the model. Additionally, if $I^2 \geq 50\%$, we fit Hartung-Knapp-Sidik-Jonkman random effects models and compare the results with those from the DerSimonian-Laird random effects models. Statistical significance was assessed at the $\alpha = 0.05$ level, unless otherwise reported. All statistical analyses were conducted in R version 4.0.1 using packages "meta", "metagen" and "robvis".

2.5 Risk of bias assessment

A Risk of Bias (RoB) tool was developed by a working group convened by WHO for the assessment of cohort studies in air pollution epidemiology [26]. The tool consists of six domains: confounding, selection bias, exposure assessment, outcome assessment, missing data and selective reporting, each divided to one to four subdomains. In total, there are 13 sub-domains each potentially rated as low, moderate, or high risk of bias [27]. If any single sub-domain is rated medium or high RoB then the domain is rated similarly. RoB was applied to each NO_2-outcome pair for studies included in a meta-analysis. For all-cause mortality, assessment of RoB for the confounding sub-domain "Were all confounders considered adjusted for in the analysis?" important confounders were: age, sex, body mass index (BMI) and individual- or area-level socio-economic status (SES). For respiratory mortality we also added smoking.

3. Results

3.1 Characteristics of the eligible studies

Our study selection process is presented in Figure 1, which represents the PRISMA Flowchart. A total of 159 peer-review articles were identified for our search in PubMed and EMBASE. 125 studies did not meet with the inclusion criteria and were excluded. The reason for the exclusion were: 9 studies not related to NO_2 concentration; 75 studies not in correct endpoint of interest; 15 studies not in qualified results; 8 studies published as editorial pieces or conference; 1 review study; and 7 studies not published in English. Of these, after title and abstract screening, we identified a total of 44 articles that fulfilled our initial inclusion criteria, of which eight were excluded because the same cohort was analyzed in other more recent publications (i.e., duplicated cohorts). Particularly, two studies reporting extreme estimates (HR>5) based on the Shenyang cohort were excluded for the further analyses, given that there were expressed concerns about the validity of the results (Supplemental Table S2) [28, 29]. As a result, 34 studies based on 32 separate cohorts were included in the final meta-analysis (3 studies were based on the same cohort but reported the risk estimates on three endpoints separately), comprising 10 studies from North America (7 from USA and 3 from Canada), 17 studies from Europe, 5 studies from Asia, and 2 studies from Oceania (Table 1). The measure of association reported in most studies was a hazard ratio along with 95% confidence intervals, while two studies reported relative risks (and 95% confidence intervals). Of the 34 studies, 28 studies examined all-cause mortality, 20 studies examined cardiovascular mortality, and 17 studies examined respiratory mortality. Particularly, Sanyal et al. (2018) [30]

reported results for two partial-overlapping cohorts, including the ESPS survey data (Health, Health Care and Insurance Survey) and the CépiDc database (French Epidemiology Centre on Medical Causes of Death). We extracted results based on the CépiDc database due to the larger sample size and is therefore relatively more representative of the study. The study period, exposure assessment method, and exposure levels varied across the included studies. Most studies included both sexes, but two studies recruited only females [31, 32] and three studies recruited only males [33-35]. One article [36] studied males and females separately. Table 1 summarizes detailed characteristics for the studies included in the final meta-analysis.

3.2 Risk of bias assessment

The risk of bias assessment for each study is shown in traffic light plot (Figure 2) in six different domains. The traffic light plot indicates that the quality for all studies was moderate to high. None of our studies had a 'high' or 'probably high' risk rating in all the key elements (exposure assessment, outcome assessment, and confounding) and therefore no studies were excluded from the analyses. Detailed rationale for each domain for subdomain of each study are provided in supplement material Table S3 a-c.

3.3 Results of the meta-analysis

Table 2 presents the pooled effect estimates and heterogeneity for each of the three endpoints of interest. Despite substantial heterogeneity across studies, and the fact that estimates vary by region and exposure assessment method, the results generally suggest an association of NO_2 with all three

endpoints. Figures 3-5 respectively summarize the studies examining all-cause, cardiovascular, and respiratory mortality associated with traffic-related air pollution as measured by NO_2.

3.4 All-cause mortality

The overall pooled meta-estimate for all-cause mortality was 1.06 (95%CI: 1.04-1.08, n=28 studies) per 10 ppb increase in long-term NO_2 exposure (Figure 3). The pooled HRs for studies in Asia (HR=1.13, 95%CI: 0.83-1.54, n=4 studies) and Oceania (HR=1.12, 95%CI: 1.01-1.23, n=2 studies) were larger than that in North America (HR=1.06, 95%CI: 1.03-1.09, n=9 studies) and Europe (HR=1.03, 95%CI: 1.02-1.05, n=13 studies). The estimated heterogeneity across all 28 studies was substantially high, with I^2 of 98.6% ($P<0.05$). We also observed considerable heterogeneity across the studies in North America (I^2=97.9%), Europe (I^2=88.4%), and Asia (I^2=99.1%). Notably, there is no heterogeneity for studies in Oceania partially because of insufficient study numbers (I^2=0%, n=2 studies).

Four studies investigated the associations with mortality in cohorts selected on the basis of preexisting disease: STEMI [37], respiratory disease [16], stroke [38] and lung cancer [39]. Meta-analysis gave a summary HR of 1.14 (95%CI: 1.02, 1.28) compared with 1.05 (95%CI: 1.04, 1.07) from the general population. Eight studies recruited old population (age>60 years) and twenty studies recruited all age population. Meta-analysis reported substantial difference in HR for different age at recruitment, 1.08 (95%CI: 1.02, 1.14) versus 1.05 (95%CI: 1.04, 1.07), respectively. Meta-analytic summary estimates stratified by BMI and smoking status adjustment are also

reported in Table 2. Moderate heterogeneity was also observed in the studied that used exposure estimates derived from LUR (I^2=61.3%).

3.5 Cardiovascular mortality

The overall meta-estimate for cardiovascular mortality was 1.11 (95%CI: 1.07-1.16, n=20 studies) per 10 ppb increase in long-term NO_2 exposure (Figure 4). The pooled estimate was higher in studies from Asia (HR=1.39, 95%CI: 1.02-1.88, n=3 studies), compared to the studies in North America (HR=1.09, 95%CI: 1.05-1.12, n=7 studies) and Europe (HR=1.05, 95%CI: 1.00-1.09, n=10 studies), which was marginally significant. The overall heterogeneity between 21 studies was significantly high, with I^2 of 99.2% (P<0.05). Like all-cause mortality, there was also considerable heterogeneity across the studies in North America (I^2=88.8%), Europe(I^2=86.9%), and Asia(I^2=92.8%). Larger summary of HRs was observed in cohorts with an older age (age>=60 years, HR=1.26, 95%CI: 1.02-1.55); and in studies by using fixed-site monitor (HR=1.24, 95%CI: 0.96-1.60). Meta-analytic summary estimates stratified by BMI and smoking status adjustment are also reported in Table 2.

3.6 Respiratory mortality

The overall meta-estimate for respiratory mortality was 1.05 (95%CI: 1.02-1.08, n=17 studies) per 10 ppb increase in long-term NO_2 exposure (Figure 5). The stratified analysis by continent disclosed that the pooled estimate in Asia (HR=1.16, 95%CI: 1.00-1.34, n=3 studies) was larger than the estimates in North America (HR=1.03, 95%CI: 1.02-1.04, n=5 studies) and Europe

(HR=1.04, 95%CI: 0.98-1.09, n=9 studies). The overall heterogeneity between 17 studies was significantly high, with I^2 of 94.6% (P<0.05). In addition, we observed a substantial heterogeneity across the studies in Europe (I^2=92.8%) and a moderate heterogeneity in Asia (I^2=63.0%), while the heterogeneity for North America was null (I^2=0%). Larger summary of HRs was also observed in cohorts with an older age (age≥60 years, HR=1.10, 95%CI: 0.94-1.28); in studies using fixed-site monitor (HR=1.06, 95%CI: 0.96-1.18); and in cohorts with BMI (HR=1.09, 95%CI: 1.02-1.16) as well as smoking (HR=1.06, 95%CI: 1.02-1.09) adjustment (Table 2). We observed low heterogeneity in the studied that used LUR exposure assessment method (I^2=34.9%) as well as the studies that did not adjust for smoking (I^2=0%). We also found moderate heterogeneity for the studies that recruited at an elder age (age≥60, I^2=60.7%) for the respiratory mortality (Table 2).

3.7 Publication bias

The funnel plots were visually symmetrical for cardiovascular mortality as well as respiratory mortality endpoint and asymmetrical for all-cause mortality endpoint (Figure 6). To further quantify the funnel asymmetry, we performed the Egger's linear regression test. The P-value was 0.26 for all-cause mortality, 0.21 for cardiovascular mortality, and 0.17 for respiratory mortality, indicating no evidence of publication bias in all three endpoints.

3.8 Sensitivity analysis

Table 3 summarizes the sensitivity analyses for long-term NO_2 exposure and mortality. We calculated pooled effect estimates only for studies using multi-pollutant models, and the results

were essentially the same. Adding back the studies that reported extremely high HRs, the meta-estimates for cardiovascular and respiratory mortality were moderately elevated as expected and were nearly identical for all-cause mortality. We also removed the articles that identified as"high risks" for each domain and performed a subgroup analysis and the results were also identical for every domain (supplement Table S4).

4. Discussion

In this systematic review, we identified 34 studies from 32 separate globally representative cohorts that evaluated the effect of long-term exposure to NO_2 on all-cause, cardiovascular, and respiratory mortality. Our study provides evidence that long-term NO_2 exposure is positively associated with all three endpoints, with the largest effect estimates in Asia. No evidence of publication bias was observed, and none of our studies had a 'high' or 'probably high' risk rating within the risk of bias assessment, therefore, no studies were excluded from the meta-analysis. The sensitivity analysis in which we replaced the results from the single-pollutant models with those from the multi-pollutant models, when available, presented nearly identical results. This suggests that NO_2 has independent effects on each of the health outcomes defined in this study.

Three recent meta-analyses have respectively evaluated studies published prior to January 2020[20], October 2016 [9], and January 2013 [19, 20], all of which reported substantial heterogeneity and significant associations between long-term exposure to NO_2 and all-cause, cardiovascular, and respiratory mortality, consistent with our present findings. Our study updates existing evidence by

incorporating 6 new studies published from January 2018 through February 2020, indicating a growing evidence base. These 6 new studies include 15 million additional participants, which represent a 170% increase in sample size analyzed in previous meta-analyses, creating the largest evidence base to date. Moreover, 3.5 million, 1.6 million, and 0.4 million deaths were newly included for all-cause mortality, cardiovascular, and respiratory mortality, respectively. There are two studies conducted in Australia [34, 40], where for the first time long-term NO_2-mortality associations in Oceania were investigated, and a meta-estimate of 1.12 (95CI%: 1.01-1.23) with no heterogeneity (I^2=0) was reported. These results were not included in previous studies; therefore, our analysis covers a broader geographical area. Compared to previous reviews, our overall meta-estimates are slightly larger with the addition of new studies with updated cohorts, longer follow-up periods, or better exposure estimates. We also examined the publication bias which had rarely been done in previous NO_2-mortality meta-analysis [9, 19], and we found that all our eligible studies lie symmetrically around our pooled effect sizes.

We registered our protocol to OSF and followed our a-priori decisions as reflected in the protocol. We did not register our protocol to PROSPERO which is the major registration platform of systematic reviews and this could be a limitation of our study.

Consistent with previous meta-analyses, our study observed a large degree of heterogeneity for all NO_2-outcomes pairs across enrolled studies, indicating a significant variation among results that could not be expected by chance alone. Although such heterogeneity does not impact our determination of consistency in causal inference, it is still essential to explore why the results are

so disparate with each other [41]. We explored possible sources of heterogeneity by performing subgroup analyses using variables that can biologically or based on prior knowledge drive these associations. For instance, we stratified analyses by exposure assessment method (i.e. fixed-site monitor versus LUR versus other) and we found that the monitor-based studies had the highest estimates for all three endpoints, which is consistent with Atkinson et al. (2018) [9]. One possible reason is that amongst the limited studies that based on fixed monitors, the study populations were mainly comprised of elderly population that are typically vulnerable to air pollution [38, 39]. Apart from these sources, high statistical heterogeneity could attribute to methodological diversity or differences in outcome assessments. The methodological diversity is due to, first, substantial variation of sample size across different studies, ranging from 2,000 to 44.5 million [42]. Other possible factors further relate to the variation of study demographics, such as location of the study population, study population, and NO_2 concentration levels and different levels of confounding adjustment, which made the studies suffer from different degrees of bias and lead to diverse estimates. For instance, Atkinson et al. (2013) [43] adjusted for 4 covariates including age, sex, Body mass index, and smoking status, and reported an effect on all-cause mortality of 1.13 (95%CI: 1.07, 1.20) per 10 ppb increase in NO_2 levels. In contrast, Katanoda et al. (2011) [44] adjusted for 17 potential confounders such as lifestyle, dietary, socioeconomic status, marital status, and medical history and reported an estimated effect on all-cause mortality of 0.97 (95%CI: 0.91, 1.04) per 10 ppb increase in NO_2 levels. Moreover, the ICD code for cause-specific mortality can be slightly different, which may also result in high heterogeneity. Even though the high heterogeneity suggests that the studies are not all estimating the same quantity, it does not necessarily suggest

that the true exposure effect varies.

Accurate exposure estimates are crucial for environmental epidemiology studies. Recently, satellite data have been widely used in high-resolution air pollution level predictions, such as daily 1-km $PM_{2.5}$ and ozone prediction [45, 46]. However, high-resolution NO_2 prediction models utilizing satellite information are very sparse [47], and only two latest cohort studies from Denmark and Australia included in our meta-analysis were able to integrate satellite retrieved NO_2 estimates [40, 48]. The NO_2 levels in studies included in the meta-analysis tended to be derived from fixed-site monitors, LUR and CHIMERE chemistry transport models that yielded larger exposure measurement errors, as compared to more advanced exposure techniques such as machine learning. Further, fixed-site monitors are usually insufficient to adequately capture the spatial and temporal variability within a large area. Though geospatial statistical methods (such as LUR and Kriging) allow characterizing the spatial variation of exposure, they do not generally capture temporal variability in exposure, because they are commonly averaged over on a year, bi-annually or more. Chemical transport models usually increase the spatial variability to a few hundred kilometers, still not comparable to the satellite-based approach. Epidemiology studies with finer-resolution NO_2 exposure estimates (and consequent less exposure measurement error) are in urgent need.

Toxicological studies suggest possible mechanisms via which NO_2 might contribute to mortality. For example, NO_2 is related to increased levels of oxidative free radicals and inflammation [49, 50]. Numerous experimental studies demonstrated that air pollution promotes a systemic vascular oxidative stress reaction [51]. Radical oxygen species can cause endothelial dysfunction, monocyte

activation, and certain pro-atherosclerotic changes in lipoproteins, thereby initiating plaque formation, exacerbating disease, and increasing mortality [51].

Previous epidemiologic reviews concluded that even though some evidence between NO_2 and mortality is suggestive, it is still not sufficient to infer a causal relationship between long-term exposure to ambient NO_2 and mortality [9, 52]. In most of the epidemiological studies, ambient NO_2 is positively related to mortality, but we cannot rule out the possibility that such an association may be due to confounding variables, such as socioeconomic status (SES), behavioral factors, and co-pollutants (e.g., O_3, $PM_{2.5}$, PM_{10}, SO_2). Because different studies may adjust for different confounding variables as well as co-pollutants and such different adjustment could affect the result of effect estimates. Moreover, substantial high heterogeneity between the study results can also weaken the causality argument. Therefore, we believe that based on current evidence, the causal association for estimating the burden of NO_2 on mortality and life expectancy is still moderate. Although this study cannot provide a confirmed causal relationship between NO_2 and mortality, it can still help to evaluate the scientific debate as the meta-analysis improves the precision and validity of estimates as increased amounts of data are utilized. The pooled effect estimates we provided can also be useful for future health impact assessment.

5. Conclusion

In conclusion, we provide robust epidemiological evidence that long-term exposure to NO_2, a proxy for traffic-sourced air pollutants, is associated with a higher risk of all-cause, cardiovascular, and

respiratory mortality that might be independent of other criteria air pollutants. This finding can inform public health policy regarding the health effects of traffic pollution on taking appropriate measures to reduce exposure to traffic pollution, especially in vulnerable populations.

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7. Tables

Table 1. Descriptive characteristics of cohorts included

Country	Study	Study period	Total population	Mean age (SD) or range (yrs)	Exposure assessment	Mean annual exposure (SD) or range	Study population
North America							
USA	Lipfert et al. (2006)	1997-2001	26,843	51 (12)	Air monitoring sites	21.5 (6.1) ppb	Washington University- EPRI Veterans cohort
	Hart et al. (2011)	1985-2000	53,814	42.1 (9.9)	Spatial smoothing exposure model	14.2 (7.1) ppb	US Trucking Industry cohort
	Lipsett et al. (2011)	1997-2005	12,366	≥ 20	Air monitoring stations	33.59 (9.63) ppb	California Teachers Study (CTS)
	Hart et al. (2013)	1990-2008	84,562	30-55	Generalized additive models	13.9 ppb*	Nurses' Health Study (NHS)
	Eckel et al. (2016)	1988-2009	352,053	69.3 (11.0)	Air monitoring stations	21.9 (10.2) ppb	Lung cancer patients
	Turner et al. (2016)	1982-2004	669,046	≥ 30	Land use regression	11.6 (5.1) ppb	American Cancer Society's Cancer Prevention Study II (ACS CPS-II)
	Eum et al. (2019)	2000-2008	14.1million	65-120	Air monitoring stations	14.2 ppb*	U.S. Medicare cohort
Canada	Jerrett et al. (2009)	1992-2002	2,360	60*	Land use regression	22.9 ppb	Toronto respiratory cohort
	Chen et al. (2013)	1982-2004	205,440	35-85	Land use regression	12.1-21.7 ppb[#]	The Ontario Tax Cohort
	Crouse et al. (2015)	1991-2006	2,521,525	25-89	Land use regression	11.6 (6.7) ppb	Canadian Census Health and Environment Cohort (Can CHEC)
Europe							
Norway	Næss et al. (2007)	1992-1998	77,891	51-70	Air dispersion model	NA	Oslo cohort

Netherlands	Beelen et al. (2008)	1987-1996	120,852	58-67	Interpolation, regressions, and GIS[&]	36.9 (8.2) μg/m^3	The Netherlands Cohort Study on Diet and Cancer (NLCS)
	Fischer et al. (2015)	2004-2011	7,218,363	≥ 30	Land use regression	31 μg/m^3*	The Dutch Environmental Longitudinal Study (DUELS)
UK	Maheswaran et al. (2010)	1995-2006	3,320	70.3 (14.6)	Air monitoring Sites	41 (3.3) μg/m^3	South London Stroke cohort
	Carey et al. (2013)	2003-2007	830,429	40-89	Air dispersion model	22.5 (7.4) μg/m^3	Clinical Practice Research Datalink
	Tonne and Wilkinson (2013)	2004-2010	154,204	68 (13)	Gaussian dispersion model	18.8 μg/m^3	Myocardial Ischaemia National Audit Project (MINAP)
	Halonen et al. (2016)	2003-2010	>8,000,000	≥ 25	KCL urban dispersion model	38.9 (6.21) μg/m^3	London cohort
	Dehbi et al. (2017)	1989-2015	7,529	48.45 (7.0)	Land use regression	28.80 μg/m^3*	National Study of Health and Development (NSHD) + Southall and Brent Revisited (SABRE)
Italy	Cesaroni et al. (2013)	2001-2010	1,265,058	≥ 30	Land use regression	43.6 (8.4) μg/m^3	Rome Longitudinal Study (RoLS)
Denmark	Hvidtfeldt et al. (2019)	1993-2015	49,564	50-64	THOR/AirGIS dispersion model	25.0 μg/m^3*	The Diet, Cancer and Health cohort
France	Bentayeb et al. (2015)	1989-2013	20,327	43.7 (3.5)	CHIMERE chemistry-transport model	23 (12.1) μg/m^3	Gazel cohort
	Sanyal et al. (2018)	1999-2012	13,239	≥ 15	CHIMERE chemistry-transport model	4.55-46.96 μg/m^3	French cohort
Spain	de Keijzer et al. (2017)	2009-2013	44,561,414	NA	CALIOPE air quality forecasting system	9.48 μg/m^3	Spain cohort

	Nieuwenhuijsen et al. (2018)	2010-2014	792,649	50.9 (18.3)	Land use regression	53.42 μg/m^3	SIDIAP cohort
Multi-countries	Beelen et al. (2014)	1985-2007[a]	367,251	All ages	Land use regression	5.2-59.8 μg/m^3	European Study of Cohorts for Air Pollution Effects (ESCAPE)
	Beelen et al. (2014)	1985-2007[a]	367,383	All ages	Land use regression	5.2-59.8 μg/m^3	European Study of Cohorts for Air Pollution Effects (ESCAPE)
	Dimakopoulou et al. (2014)	1985-2007[a]	307,553	All ages	Land use regression	5.2-59.8 μg/m^3	European Study of Cohorts for Air Pollution Effects (ESCAPE)
Asia							
Japan	Katanoda et al. (2011)	1983-1995	63,520	≥ 40	Air monitoring stations	1.2-33.7 ppb	Three-prefecture Cohort Study
	Yorifuji et al. (2013)	1999-2009	13,412	74 (5.4)	Land use regression	22 (15) μg/m^3	The Shizuoka elderly cohort
China	Chen et al. (2016)	1998-2009	39,054	44.29 (13.95)	Air monitoring stations	40.66 μg/m^3	Four Northern Chinese city
	Yang et al. (2018)	1998-2011	66,820	70.2 (5.5)	Land use regression	104 (25.6) μg/m^3	Hong Kong Elderly Health Service Cohort
South Korea	Kim et al. (2017)	2007-2013	136,094	42.05 (14.83)	Air monitoring stations	34.45 (12.92) ppb	National Health Insurance Service-National Sample (NHIS-NSC) cohort
Oceania							
Australia	Dirgawati et al. (2019)	1996-2012	11,627	72.1 (4.4)	Land use regression	13.4 (4.1) μg/m^3	Health in Men Study (HIMS)
	Hanigan et al. (2019)	2007-2015	75,145	45-79	Satellite-based spatial regression model	17.75 (4.80) μg/m^3	"45 and up study" Cohort

Notes: [a] baseline study period; * median; [#] mean annual exposure concentrations are 12.1 ppb in Windsor, 15.5 ppb in Hamilton, and 21.7 ppb in Toronto; [&] Sum of regional (interpolation), urban (regressions), and local traffic (GIS).

SIDIAP: Sistema d'Informació pel Desenvolupament de la Investigació en Atenció Primària

NA indicates Not Applicable, SD standard deviation.

Table 2. Pooled effects of nitrogen dioxide on all-cause, cardiovascular, and respiratory mortality

	All-cause mortality			Cardiovascular mortality			Respiratory mortality		
	Studies (n)	**HR (95% CI)**	**I2 (%)**	**Studies (n)**	**HR (95% CI)**	**I^2 (%)**	**Studies (n)**	**HR (95% CI)**	**I^2 (%)**
Full meta-estimate	28	1.06 (1.04, 1.08)	98.6	20	1.11 (1.07, 1.16)	99.2	17	1.05 (1.02, 1.08)	94.6
Continent									
North America	9	1.06 (1.03, 1.09)	97.9	7	1.09 (1.05, 1.12)	88.8	5	1.03 (1.02, 1.04)	0
Europe	13	1.03 (1.02, 1.05)	88.4	10	1.05 (1.00, 1.09)	86.9	9	1.04 (0.98, 1.09)	92.8
Asia	4	1.13 (0.83, 1.54)	99.1	3	1.39 (1.02, 1.88)	92.8	3	1.16 (1.00, 1.34)	63.0
Oceania	2	1.12 (1.01, 1.23)	0	-	-	-	-	-	-
Exposure assessment method									
Fixed-site monitor	7	1.10 (1.04, 1.16)	99.3	3	1.24 (0.96, 1.60)	97.0	3	1.06 (0.96, 1.18)	95.4
Land use regression	10	1.05 (1.04, 1.06)	61.3	9	1.09 (1.05, 1.13)	82.1	7	1.04 (1.01, 1.07)	34.9

Other	11	1.02 (1.01, 1.03)	80.3	8	1.07 (1.00, 1.15)	81.5	7	1.03 (0.89, 1.18)	92.4
Exposure metric									
Single year	10	1.06 (1.04, 1.08)	76.4	8	1.09 (1.06, 1.12)	81.9	7	1.10 (1.03, 1.17)	86.5
Multiple year	16	1.06 (1.03, 1.07)	98.8	11	1.14 (1.07, 1.22)	99.5	9	1.03 (0.99, 1,07)	96.3
Study population									
General population	24	1.05 (1.04, 1.07)	98.3	19	1.11 (1.06, 1.15)	99.2	16	1.05 (1.02, 1.08)	94.9
Preexisting disease	4	1.14 (1.02, 1.28)	85.5	1	NA	NA	1	NA	NA
Age at recruitment									
≥60	8	1.08 (1.02, 1.14)	98.1	4	1.26 (1.02, 1.55)	87.6	4	1.10 (0.94, 1.28)	60.7
All age	20	1.05 (1.04, 1.07)	97.4	16	1.09 (1.05, 1.13)	94.3	13	1.05 (1.00, 1.10)	93.7
Key confounders adjustment for individual measures									
BMI									
Yes	16	1.08 (1.04, 1.11)	97.3	11	1.14 (1.09, 1.20)	90.7	10	1.09 (1.02, 1.16)	83.2
No	12	1.05 (1.02, 1.08)	98.9	9	1.06 (1.02, 1.11)	92.3	7	1.02 (0.97, 1.08)	95.3
Smoking									
Yes	21	1.03 (1.01, 1.05)	97.8	14	1.07 (1.02, 1.24)	99.5	14	1.06 (1.02, 1.09)	95.3
No	7	1.11 (1.06, 1.17)	99.4	6	1.20 (1.12, 1.30)	94.0	3	1.04 (1.02, 1.06)	0

Table 3. Sensitive analysis of NO_2 and all-cause, cardiovascular, and respiratory mortality

	All-cause mortality			Cardiovascular mortality			Respiratory mortality		
	Studies (n)	HR (95% CI)	I^2 (%)	Studies (n)	HR (95% CI)	I^2 (%)	Studies (n)	HR (95% CI)	I^2 (%)
All countries									
Including duplicate cohorts (a)	35	1.07 (1.05, 1.08)	98.3	25	1.13 (1.08, 1.17)	99.0	20	1.06 (1.03, 1.09)	93.7
Including extremely high effect estimates (b)	28	1.06 (1.04, 1.07)	98.6	21	1.20 (1.15, 1.26)	99.4	18	1.12 (1.08, 1.17)	97.8
Including both (a) and (b)	35	1.07 (1.05, 1.08)	98.3	26	1.21 (1.16, 1.26)	99.2	21	1.12 (1.08, 1.17)	97.4
Studies using multi-pollutant model	9	1.05(1.02, 1.08)	98.4	7	1.09 (1.02, 1.16)	99.7	5	1.00 (0.97, 1.03)	97.0
Two- pollutants model	2	1.00 (0.93, 1.09)	99.7	1	NA	NA	2	1.01 (0.96, 1.06)	95.4
Three- pollutants model	5	1.03 (1.01, 1.07)	91.1	5	1.02 (0.99, 1.06)	86.9	3	0.99 (0.99, 0.99)	0
Hartung-Knapp-Sidik-Jonkman model									
Full meta-estimate	28	1.07 (1.03, 1.12)	98.6	20	1.15 (1.04, 1.27)	99.2	17	1.04 (0.96, 1.13)	94.6
Continent									
North America	9	1.06 (1.00, 1.12)	97.9	7	1.13 (0.93, 1.37)	88.8	5	1.03 (0.99, 1.06)	0
Europe	13	1.05 (0.99, 1.12)	88.4	10	1.09 (0.96, 1.25)	86.9	9	1.01 (0.88, 1.17)	92.8

Asia	4	1.13 (0.79, 1.61)	99.1	3	1.39 (0.68, 2.82)	92.8	3	1.16 (0.77, 1.75)	63.0
Oceania	2	1.12 (1.11, 1.13)	0	-	-	-	-	-	-

8. Figures

Figure 1. Flow chart of the study selection process.

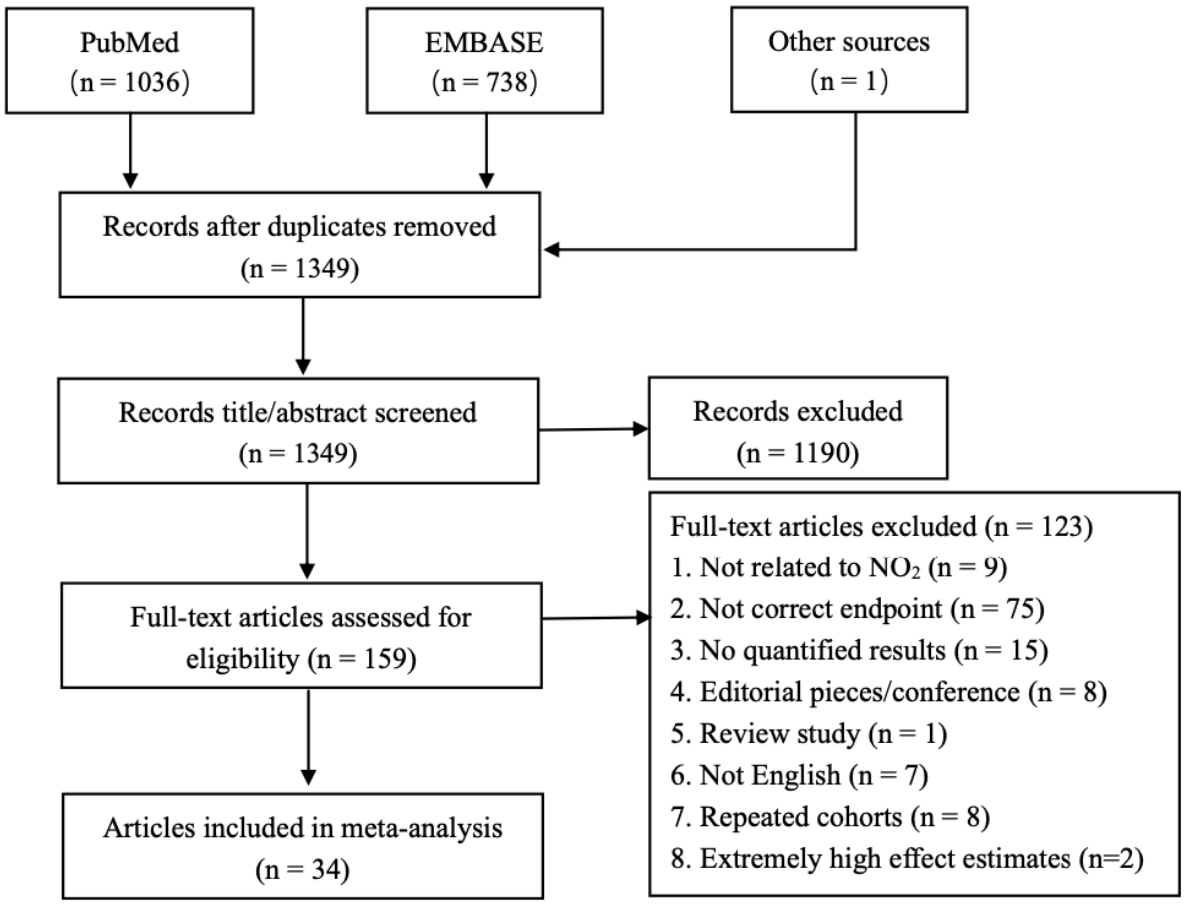


Figure 2. Traffic light plot of risk of bias assessment for each study.

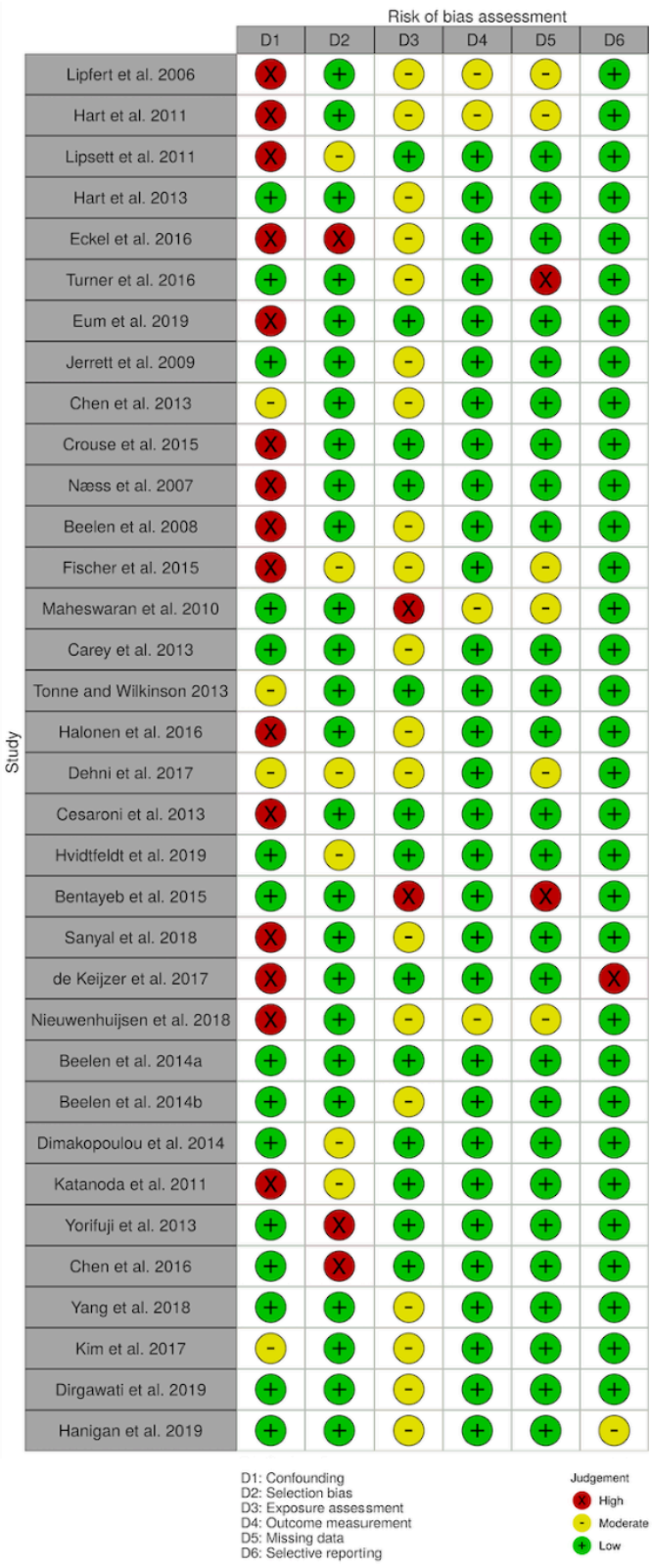


Figure 3. Forest plot of study-specific hazard ratio (HR) of all-cause mortality associated with a 10-ppb increase in exposure to NO_2. The meta-estimate and weights in the forest plot are estimated from random effects meta-analyses.

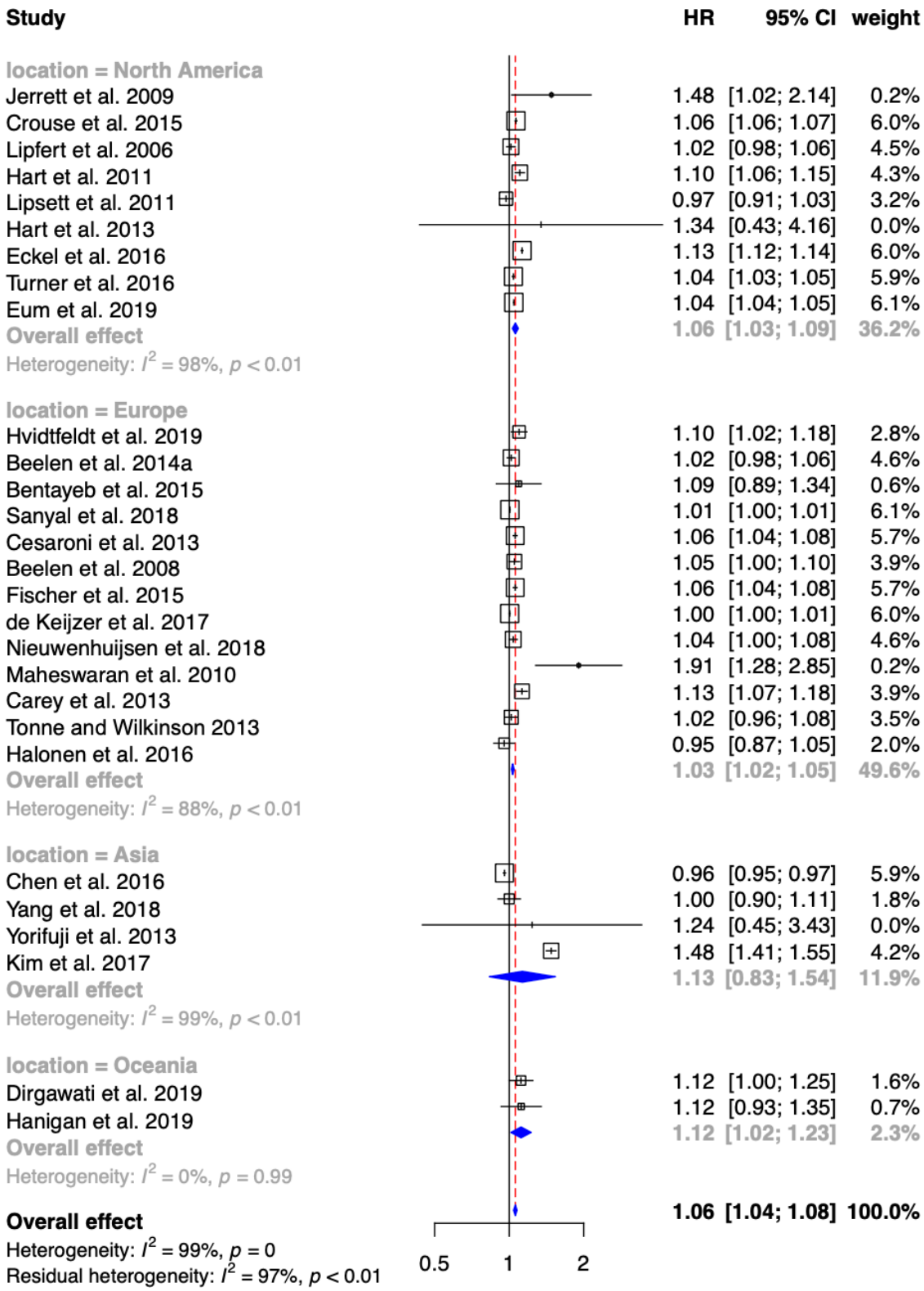


Figure 4. Forest plot of study-specific hazard ratio (HR) of cardiovascular mortality associated with a 10-ppb increase in exposure to NO2. The meta-estimate and weights in the forest plot are estimated from random effects meta-analyses.

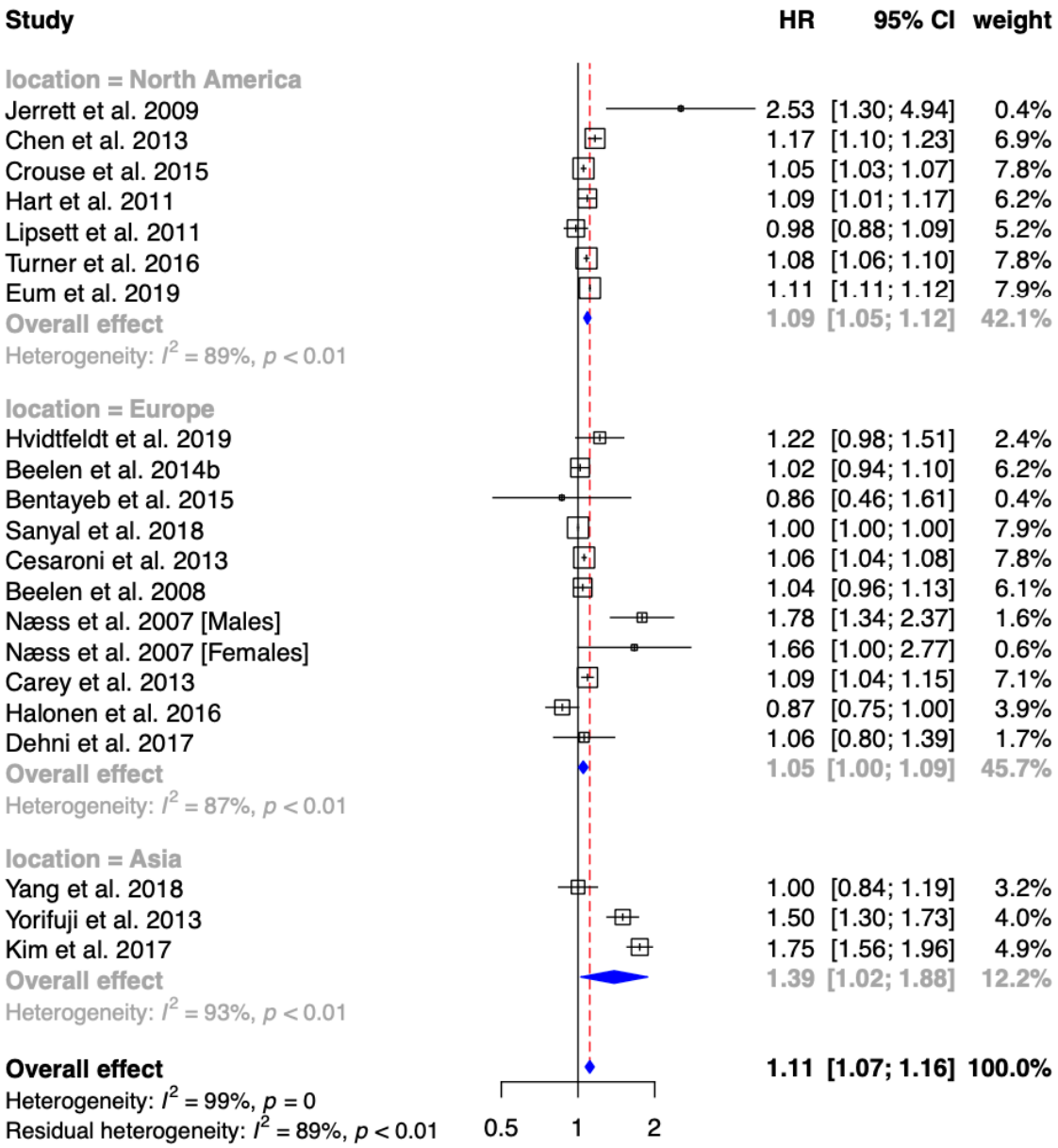


Figure 5. Forest plot of study-specific hazard ratio (HR) of respiratory mortality associated with a 10-ppb increase in exposure to NO_2. The meta-estimate and weights in the forest plot are estimated from random effects meta-analyses.

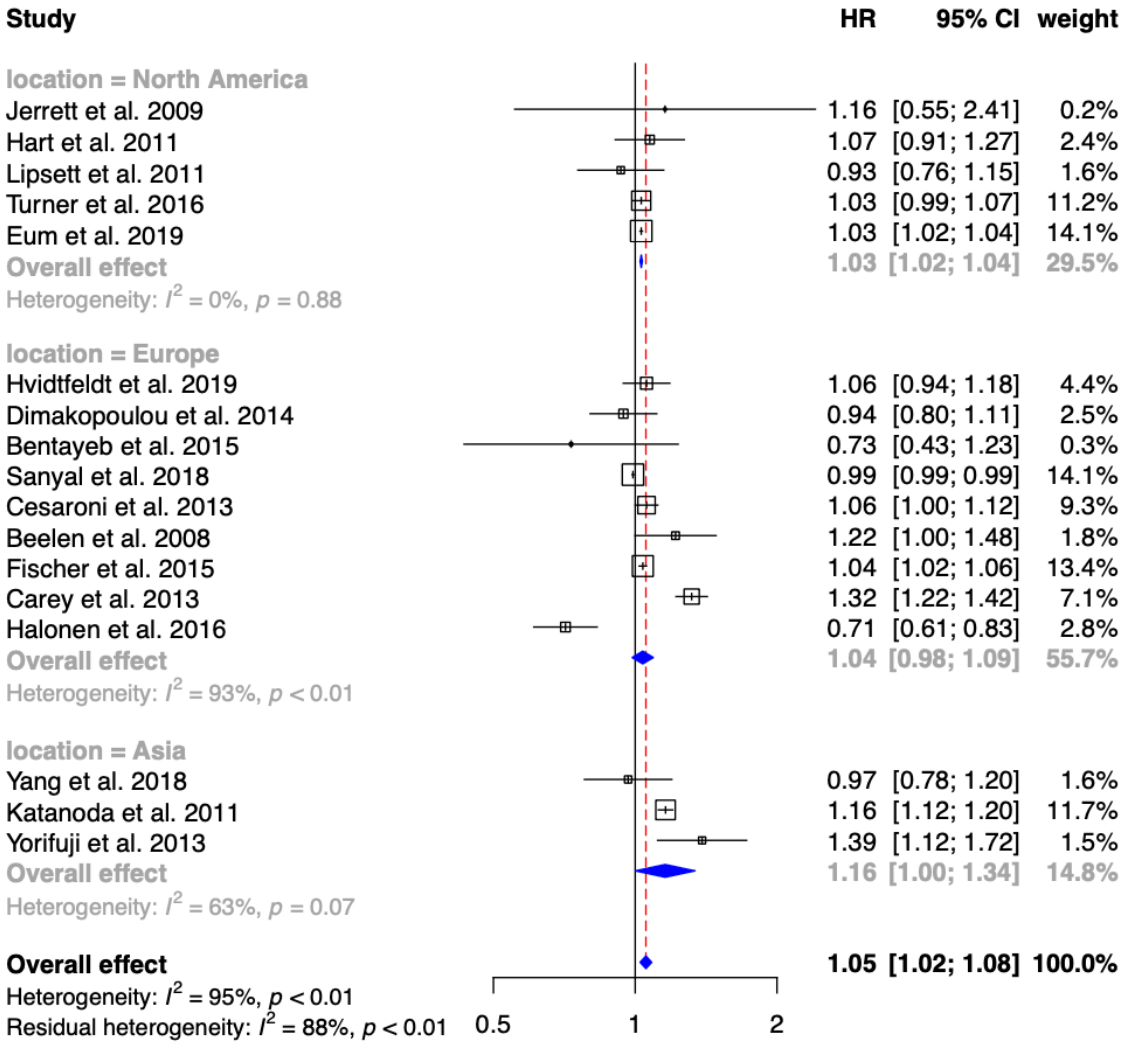
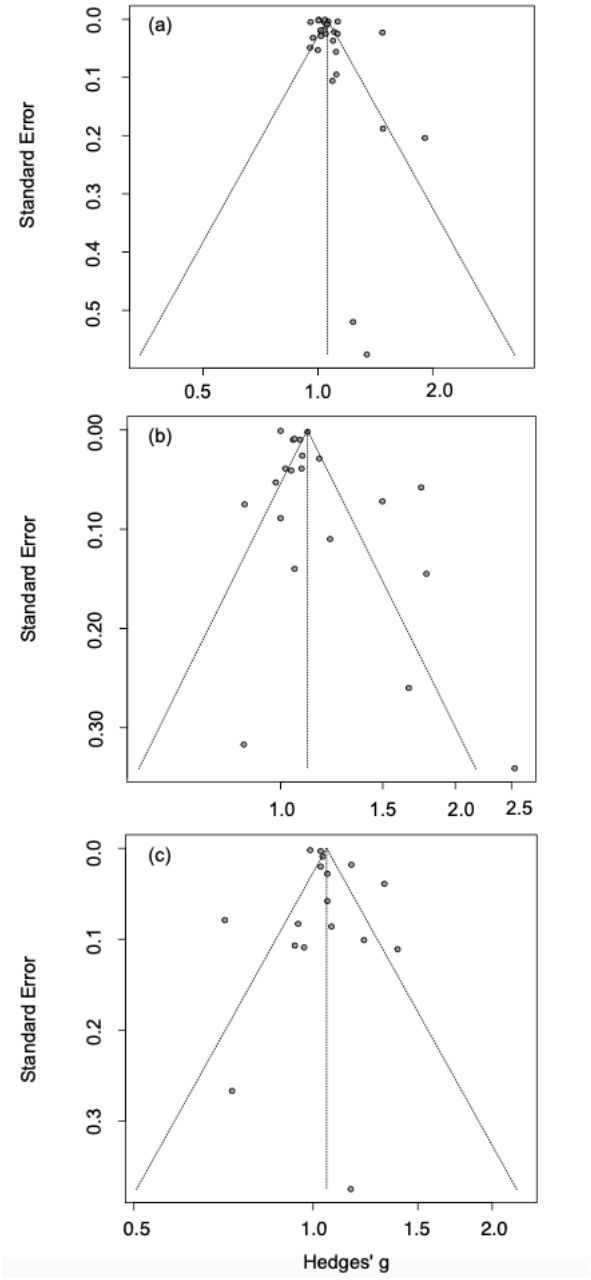


Figure 6. Funnel plots for (a) all-cause mortality, (b) cardiovascular mortality, and (c) respiratory mortality.



9. Appendix

Table S1
Explicit PECOS question

PECOS	Inclusion	Exclusion
Population	• Population-based human studies (including sub-groups at risk: children, pregnant women, elderly, or patients with underlying conditions), of all ages, developed and developing areas, both urban and rural. No geographical restrictions. • Study population expose to NO_2 via inhalation through ambient air	• Study population exposed to NO_2 in occupational settings or indoor exposure exclusively
Exposure	• Long-term exposure (year or more) to ambient air NO_2 expressed in a concentration unit (ppb and $\mu g/m^3$ respectively).	• Less than one year of data available
Comparator	• Exposure to per concentration increased unit of the air pollutant of interest in the same population	• Measures of association and uncertainty not provided
Outcome	• Health outcomes selected in relation to long-term exposure include (ICD 10 codes, version	• Outcomes other than mortality, including infant

	2016 in brackets): **all cause (A00-Z99); respiratory (J00-J99); COPD (J40-47) mortality** [Note: Studies vary in selection of codes.]		mortality due to neonatal exposure of pollutant
Study	• Prospective and retrospective epidemiological studies in humans Published peer reviewed (or accepted for publication i.e. in press) journal articles in English,)	• Qualitative studies • No adjustment for socio-economic status (individual or area) • Studies where no original data were analyzed • Reviews and methodological papers • Non-human studies (in vivo, in vitro, other)	

Table S2

Excluded studies with reasons (n=125 studies).

Not related to NO_2 (n=9 studies)

1. Ren, C. and S. Tong, Temperature modifies the health effects of particulate matter in Brisbane, Australia. Int J Biometeorol, 2006. **51**(2): p. 87-96.
2. Liu, C.C., et al., Ambient exposure to criteria air pollutants and risk of death from bladder cancer in Taiwan. Inhal Toxicol, 2009. **21**(1): p. 48-54.
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Table S3a
Detailed rationale for confounding and selection bias

Study	Confounding	Rationale	Selection bias	Rationale
Lipfert et al. 2006	High-risk	Do not adjust for sex.	Low-risk	No evidence of selection bias in this study
Hart et al. 2011	High-risk	Quote: "We do not have information on other risk factors for mortality, such as cigarette smoking, body mass index (BMI), medication use, high cholesterol or blood pressure diagnoses, or existing comorbidities.....however, there is likely some residual confounding if they are also associated with pollution." Comment: Do not adjust for critical confounder like BMI and SES.	Low-risk	No evidence of selection bias in this study
Lipsett et al. 2011	High-risk	Do not adjust for critical confounder SES.	Moderate-risk	Quote: "Of the 124,614 women living in California at baseline, we excluded..These exclusions left 101,784 women in the analytic cohort for the mortality analyses of all pollutants." Comment: may result in marginal bias
Hart et al. 2013	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	Quote: "with response rates above 90%"
Eckel et al. 2016	High-risk	Do not adjust for BMI.	High-risk	Quote: "The air pollution monitoring network is less dense in rural areas; so, exclusion of patients living >25 km from a monitor differentially excludes patients in rural areas."

Turner et al. 2016	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	No evidence of selection bias in this study.
Eum et al. 2019	High-risk	Do not adjust for BMI and other additional confounders.	Low-risk	No evidence of selection bias in this study.
Jerrett et al. 2009	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	No evidence of selection bias in this study.
Chen et al. 2013	Moderate-risk	comment: Indirect adjustment for smoking or BMI.	Low-risk	Quote: "Subjects were selected randomly from among Canadians who filed federal income."
Crouse et al. 2015	High-risk	Do not adjust for age, sex	Low-risk	Quote: "it is a population-based cohort of subjects who were ≥ 25 years of age at baseline; a usual resident of Canada on the census reference day."
Næss et al. 2007	High-risk	Do not adjust for BMI and other potential confounders.	Low-risk	Quote: "A total of 143,842 individuals were identified as the source population. For all of these persons, information on ..... was available and was included in the analysis." Comment: No evidence of selection bias in this study.
"Beelen et al. 2008	High-risk	Do not adjust for BMI.	Low-risk	No evidence of selection bias in this study.
Fischer et al. 2015	High-risk	Do not adjust for BMI and additional confounders.	Moderate-risk	Quote: "The follow-up period of the cohort was from 1 January 2004 to 1 January 2011. Subjects were lost to follow-up if their final record in the longitudinal file ended before 1 January 2011 and death was not registered as a reason for termination. Emigration was the main cause of censoring."
Maheswaran et al. 2010	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	Quote: "Nonresponse was followed up by contact with the patients' general

				practitioners, the health services authority, and next of kin." Comment: Low risk of selection bias here.
Carey et al. 2013	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	Quote: "we identified 836,557 patients ....A total of 950 patients had no census information and were dropped from the analyses."
Tonne and Wilkinson 2013	Moderate-risk	Do not directly adjust for BMI.	Low-risk	No evidence of selection bias in this study.
Halonen et al. 2016	High-risk	Do not adjust for BMI.	Low-risk	No evidence of selection bias in this study.
Dehni et al. 2017	Moderate-risk	Do not directly adjust for BMI.	Moderate-risk	Quote: "The cohort responding at the data collection at age 60–64 remains broadly representative of the general population, despite some loss to follow-up for more deprived groups."
Cesaroni et al. 2013	High-risk	Do not adjust for BMI.	Low-risk	No evidence of selection bias in this study.
Hvidtfeldt et al. 2019	Low-risk	All critical and other/additional potential confounders adjusted.	Moderate-risk	Quote: "Of the 57,053 enrolled participants, we excluded 581 because of cancers prior to baseline, 2084 because residential address history and thus exposure were unavailable at some point in the period from 1979 to baseline, and 4624 because of missing information on the potential confounders. The total study population included 49,564 participants."
Bentayeb et al. 2015	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	No evidence of selection bias in this study.
Sanyal et al. 2018	High-risk	Do not adjust for sex.	Low-risk	No evidence of selection bias in this study.

de Keijzer et al. 2017	High-risk	Do not adjust for BMI.	Low-risk	No evidence of selection bias in this study.
Nieuwenhuijsen et al. 2018	High-risk	Do not adjust for age, BMI and additional confounders.	Low-risk	Quote: "SIDIAP is a primary care computerized medical record of a representative sample of 5.8 million people (80% of the population) in Catalonia (Spain)."
Beelen et al. 2014a	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	Quote: "All cohorts were samples from the general population."
Beelen et al. 2014b	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	No evidence of selection bias in this study.
Dimakopoulou et al. 2014	Low-risk	All critical and other/additional potential confounders adjusted.	Moderate-risk	Quote: "Cohorts were included in the study if the number of respiratory mortality cases exceeded seven during the follow-up period and if data for the most important potential confounders were available." Comment: Suspect having selection bias
Katanoda et al. 2011	High-risk	Do not adjust for critical confounder SES.	Moderate-risk	Quote: "A self-administered questionnaire was distributed to 118820 individuals identified based on residence registries in cooperation with the municipal government of each area, and responses were returned by 100615 (84.7%). Individuals were excluded from the study if they had resided in the study areas for less than 10 years (n = 19 542) or provided incomplete answers to questions related to smoking status, pack-years (ever smokers only), smoking status of family members, frequency of vegetable and fruit consumption, or use

				of indoor charcoal or briquette braziers (sumi or rentan in Japanese) for heating (n = 17 553)." Comment: moderate level of non-response rate and the smokers may tend to participate the study
Yorifuji et al. 2013	Low-risk	All critical and other/additional potential confounders adjusted.	High-risk	Quote: "response rate: 63%"
Chen et al. 2016	Low-risk	All critical and other/additional potential confounders adjusted.	High-risk	Comment: 39,054 / 48,114 Considerable rate of loss to follow up
Yang et al. 2018	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	No evidence of selection bias in this study.
Kim et al. 2017	Moderate-risk	Do not directly adjust for BMI.	Low-risk	Quote: "The NHIS-NSC is a population-based cohort including 1 025 340 individuals who were randomly sampled from the population database—equivalent to %2% of the Korean population." "In this study, participants aged ≥18 years who resided in Seoul between 2007 and 2013 were selected from the NHIS- NSC. Those with a previous history of cardiovascular disease such as AMI, CHF, and stroke were excluded."
Dirgawati et al. 2019	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	No evidence of selection bias in this study.
Hanigan et al. 2019	Low-risk	All critical and other/additional potential confounders adjusted.	Low-risk	No evidence of selection bias in this study.

Table S3b
Detailed rationale for exposure assessment and outcome measurement

Study	Exposure assessment	Rationale	Outcome measurement	Rationale
Lipfert et al. 2006	Moderate-risk	Quote: "the analysis does not account for differences in residential construction that could modify exposures to air pollution or noise."	Moderate-risk	Comment: Do not provide ICD code, suspect have outcome misclassification.
Hart et al. 2011	Moderate-risk	Quote: "Additionally, although in surveys of this cohort the average time living in the current residence is 17 years, we cannot be certain that we have the correct home address for all participants in all years. This would add to the nondifferential misclassification of exposures and may help to explain some of the nonsignificant results we observe."	Moderate-risk	Quote: "For many of the outcomes this may lead to some misclassification in the cause-specific analyses, because some outcomes may not always be appropriately coded."
Lipsett et al. 2011	Low-risk	The exposure models used in study can adequately predict the exposure.	Low-risk	Quote: "Although some of these participants may have experienced silent events, it is unlikely that such misclassification of disease would be differentially distributed by pollutant exposure. Also, these outcomes were measured here only as hospitalizations or deaths, which could have resulted in incomplete ascertainment. Nevertheless, there is no reason to think that such unrecorded events would have biased the results in a differential manner."
Hart et al. 2013	Moderate-risk	Quote: "it is possible that the 2007 roads do not accurately represent the US roadway system in earlier years. However, the most likely scenario	Low-risk	Quote: "We assessed incident cases of Mi, defined as first nonfa- tal or fatal

		is that new roads have been built and that existing roads have gotten larger. if this is the case, some of the earlier addresses consid- ered close to roadways may have in fact not been close. this misclassification would bias the results toward the null."		Mi (icD-9 codes 410–414; icD-10 codes i20–i25) from 1990 to 2008."
Eckel et al. 2016	Moderate-risk	Quote: "We focused on air pollution exposures with large-scale regional variability using spatial interpolation of air quality monitoring data, which does not capture the effects of traffic-related pollution (TRP) that varies over a finer spatial scale."	Low-risk	Quote: "Our study population included lung cancer cases (ICD-O-3 site code C34) diagnosed in 1988–2009 and registered by the California Cancer Registry (CCR)."
Turner et al. 2016	Moderate-risk	Quote: "leading to potential misclassification of both air pollution concentrations" comment: also, the exposure level in 2006 might not be representative of the variable from 1982-2004."	Low-risk	Quote: "Deaths were classified by underlying cause using the International Classification of Diseases, 9th and 10th revisions."
Eum et al. 2019	Low-risk	The exposure models used in study can adequately predict the exposure.	Low-risk	Quote: "Using the International Classification of Disease (ICD–10) codes, we identified deaths from non-accidental and accidental causes of mortality, as well as three major causes including CVD, respiratory disease, and cancer."
Jerrett et al. 2009	Moderate-risk	Quote: "Although the measurement period for NO2 was at or beyond the end of mortality follow-up, there is evidence suggesting spatial exposure contrast observed from these shorter periods captures the essential aspects of the chronic exposure experience for the cohort."	Low-risk	No systematic error in the measurement of the outcome.
Chen et al. 2013	Moderate-risk	Quote: "the land use regression models were developed toward the end of our study and might	Low-risk	Quote: "this (outcome) measurement error was likely independent of exposure."

		not characterize exposure adequately during earlier periods of our study."		
Crouse et al. 2015	Low-risk	The exposure models used in study can adequately predict the exposure.	Low-risk	Quote: “The date of death and the underlying cause of death were extracted from death certificates coded by nosologists to the International Classification of Diseases, 9th Revision (ICD-9) for deaths before 2000, and to the 10th Revision (ICD-10) for those that occurred from 2000 onward.”
Næss et al. 2007	Low-risk	The exposure models used in study can adequately predict the exposure.	Low-risk	No systematic error in the measurement of the outcome.
Beelen et al. 2008	Moderate-risk	Quote: “In summary, long-term exposure to outdoor air pollution at the 1986 home address was estimated for all participants as the sum of regional, urban, and local traffic contributions." Comment: The exposure at 1986 may not be representitive of the exposure status from 1987-1996, and the time varying change does not take into account. However, other article suggests that the exposure status did not vary much and such method won't lead to serious bias.	Low-risk	Quote: “Mortality was assessed between 1 January 1987 and 31 December 1996. Mortality data were obtained from the Dutch Central Bureau of Genealogy and the Dutch Central Bureau of Statistics.” Comment: No evidence of error in outcome measurement.
Fischer et al. 2015	Moderate-risk	Quote: “Exposures were estimated by a LUR model for the year 2001 and assigned to the follow-up period 2004–2011. Although the exposure assignment precedes the follow-up period, we are not sure that the 2001 annual average adequately represents a longer exposure window, which is relevant for long-term exposure. However, there is evidence from the literature that spatial distribution of air pollution	Low-risk	Quote: “A database with mortality data was available from Statistics Netherlands. We selected nonaccidental mortality [International Classification of Diseases, 10th Revision (ICD-10) codes A00-R99], circulatory disease mortality (ICD-10 codes I00-I99), respiratory disease mortality (ICD-10 codes J00-J99), and

		is stable over 10-year periods....people might have moved since 2004 to unknown addresses and therefore changed their exposure."		lung cancer mortality (ICD-10 codes C33–C34)."
Maheswaran et al. 2010	High-risk	Quote: "We used modeled exposure estimates from a single year, and pollution levels could have varied across the study period....Exposures derived from prediction models are associated with nontrivial prediction error, but properly incorporating that error into health effects models is difficult, and the optimal procedure for doing so is still uncertain." Comment: The exposure assessment method may biased the effect estimate.	Moderate-risk	Comment: Do not provide ICD code, suspect have outcome misclassification.
Carey et al. 2013	Moderate-risk	Quote: "Misclassification is also likely to have resulted from assigning pollution estimates at a 1 km2 resolution." Comment: potential misclassification and do not take time-varying changes of exposure into consideration	Low-risk	Quote: "The underlying cause of death [coded according to the International Classification of Diseases, 9th Revision (ICD-9; WHO 1977)] for deceased subjects was retrieved from the Lazio regional health information system."
Tonne and Wilkinson 2013	Low-risk	The exposure models used in study can adequately predict the exposure.	Low-risk	Quote: "Vital status was obtained from the Office of National Statistics."
Halonen et al. 2016	Moderate-risk	Quote: "exposure misclassification due to secondary housing may partly explain the negative associations observed in the low deprivation groups."	Low-risk	Quote: "The underlying cause of death was classified using the 10th revision of the International Classification of Diseases (ICD10)"
Dehni et al. 2017	Moderate-risk	Quote: "Great- Britain-wide air pollution maps were produced with a resolution of 100m×100mforBSandSO2, and200m×200mforNO2.TheX-Ycoordinates of the residence of participants were overlaid with these maps to assign concentration estimates.	Low-risk	Quote: "Cohort participants are flagged on the NHS central register so that all deaths are identified, and CVD mortality diagnosed as International Classification of Disease-Ninth Edition [ICD-9] codes 390–459 and

		Model building employed 80% of the sites for BS and SO2, and 75% of the sites for NO2. The remaining sites were retained for model validation, and hold-out r2 values of 0.34, 0.31 and 0.62 were obtained for BS, SO2 and NO2 respectively. Two sets of air pollution estimates were available. Firstly, concentration estimates of sulphur dioxide [SO2], black smoke [BS] and nitrogen dioxide [NO2] were available for 1991, based on contemporaneous air pollution monitoring data" Comment: There are two different cohorts used in this study		ICD- Tenth Edition [ICD-10] chapter I codes. The follow-up for mortality was until the end of 2014 for NSHD and November 2015 for SABRE"
Cesaroni et al. 2013	Low-risk	Queto: "We are fairly confident that the spatial gradient of pollutants within the city remained stable over time."	Low-risk	No systematic error in the measurement of the outcome.
Hvidtfeldt et al. 2019	Low-risk	Quote: "In brief, the system enables the calculation of ambient air pollution concentration at high temporal (hourly basis) and spatial (individual address) resolutions."	Low-risk	Quote: "We defined the cause of death ac- cording to the underlying cause of death recorded on death certificates. Participants who died from external causes such as injuries, accidents and suicides (ICD-10 codes S–Z) were censored at date of death. In addition, we investigated cardiovascular (ICD10 codes 'I00'–'I99') and respiratory (ICD10 codes 'J00'–'J99' and 'C34') subgroups of mortality."
Bentayeb et al. 2015	High-risk	Queto: "Final data contained uncer-tainties due to the low number of monitoring stations (measurements) in the initial years of the study, especially for PM2.5 and benzene. This resulted in an underestimation of exposure, ...Moreover,	Low-risk	Quote: "We considered all causes apart from suicides and accidents (ICD-9 codes 001-799 and ICD-10 codes A00-R99), cardiovascular mortality (ICD-9 codes: 390-459;

		our exposure assessment did not consider traffic emissions which may have led to an underesti- mation of concentrations in urban areas."		ICD-10 codes: I00-I99), and respiratory mortality (ICD-9 codes 460-519 or ICD-10 codes J00-J98) including lung cancer (ICD-9 code 162 or ICD-10 codes C33-C34)."
Sanyal et al. 2018	Moderate-risk	Quote: "In addition, exposure to indoor air pollution, like wood stoves and fireplaces, was not considered in our study"	Low-risk	Quote: "However, the ESPS survey data is questionnaire-based, where individuals were asked about the occurrence of a disease during the past 12 months."
de Keijzer et al. 2017	Low-risk	The exposure models used in study can adequately predict the exposure.	Low-risk	Quote: "Mortality data for natural causes (International Classification of Dis- eases codes: ICD-9: 001–799, ICD-10:A00–R99) of years 2009–2013 were obtained from the Spanish Mortality Register"
Nieuwenhuijsen et al. 2018	Moderate-risk	Quote: "These models predicted 62–76% of variation in pollutant levels in our study area during 2008–2009."	Moderate-risk	Comment: Do not provide ICD code, suspect have outcome misclassification.
Beelen et al. 2014a	Low-risk	Quote: "Land use regression models were developed to explain the spatial variation of measured annual average air pollution concentrations within each area."	Low-risk	Quote: "Natural-cause mortality was defined on the basis of the underlying cause of death recorded on death certificates as International Classification of Diseases (ICD)-9 codes 001–779 and ICD-10 codes A00–R99."
Beelen et al. 2014b	Moderate-risk	Quote: "the land-use regression models used for exposure assessment were based on air pollution measurements in the period 2008–2011, whereas the cohort studies included in eScaPe started in the past....spatial air pollution contrasts often	Low-risk	Quote: "Outcomes were defined on the basis of the underlying cause of death recorded on death certificates: all cVD mortality (International Classification of Diseases [ICD]-9: 400–440; ICD-10: i10-i70), ischemic

		remained the same, even with a decrease in concentrations over time."		heart disease mortality (ICD-9: 410–414; ICD-10: i20-i25), Mi mortality (ICD-9: 410; ICD-10: i21, i22), and cerebrovascular disease mortality (ICD-9: 430–438; ICD-10: i60-i69)"
Dimakopoulou et al. 2014	Low-risk	The exposure models used in study can adequately predict the exposure.	Low-risk	Quote: "Nonmalignant respiratory mortality was defined on the basis of the underlying cause of death recorded on death certificates. Nonmalignant respiratory mortality included ICD-9 codes 460 to 519 or ICD-10 codes J00 to J99."
Katanoda et al. 2011	Low-risk	The exposure models used in study can adequately predict the exposure.	Low-risk	Quote: "Causes of death were confirmed by vital statistics obtained with official permission, and coded according to the International Classification of Diseases, 9th revision (ICD-9)."
Yorifuji et al. 2013	Low-risk	The exposure models used in study can adequately predict the exposure.	Low-risk	Quote: "The underlying causes of death were coded according to the 10th International Classification of Disease (ICD-10)."
Chen et al. 2016	Low-risk	The exposure models used in study can adequately predict the exposure.	Low-risk	Quote: "More than 98% of all known causes of death were recorded in this survey. We classified deaths according to the cause of death using the International Classification of Disease-10 (ICD-10) (C33, C34 for lung cancer) coding system."
Yang et al. 2018	Moderate-risk	Quote: "a lack of highly spatially resolved historical measurement data is clearly a weakness for our exposure assessment."	Low-risk	Quote: "Deaths were coded according to the International classification of Diseases, 10th Revision (ICD-10;

				WHO 2010) including natural cause mortality (A00–R99), overall cardiovascular disease (I00–I99) and overall respiratory disease (J00–J47 and J80–J99).”
Kim et al. 2017	Moderate-risk	Quote: “Each individual’s exposure to air pollutants was determined by linking the location of the monitoring stations to the ZIP code of his or her residence.”	Low-risk	Quote: “AMI was defined as a hospitalization with ICD-10 codes I21 to 23 as the primary or secondary diagnosis. CHF was defined based on discharge diagnosis (ICD-10 codes I11.0, I13.0, I13.2, I25.5, I42, I50, O90.3) after a hospitalization. Stroke was defined by discharge diagnosis (ICD-10 codes: I60–64) among patients who had been hospitalized and undergone brain imaging studies such as computed tomography and magnetic resonance imaging. Ischemic and hemorrhagic strokes were defined by ICD-10 codes I63 to 64 and I60 to 62, respectively. Composite cardiovascular events were defined as a composite of cardiovascular death, AMI, CHF, and stroke.”
Dirgawati et al. 2019	Moderate-risk	Quote: “Time spent away from home was not recorded, thus could be exposure misclassification.”	Low-risk	Quote: “Mortality and hospitalization data were recorded using the clinical modification of the ninth revision of the In- ternational Statistical Classification of Diseases (ICD-9-CM)”
Hanigan et al. 2019	Moderate-risk	Quote: “For NO2, we used estimated concentrations for 2007 from a spatial regression	Low-risk	Quote: “Mortality data from 2007 to 2015 was extracted from the NSW

	model using satellite and land use data (Knibbs et al., 2014; Knibbs et al., 2016). Knibbs et al. (2014) found that year to year differences were small for the NO2 model between 2006 and 2011 so we assumed the 2007 data were representative of long-term exposures."	Register of Births Deaths and Marriages (RBDM) and linked to '45 and Up Study' participants."

Table S3c
Detailed rationale for missing data and selective reporting

Study	Missing data	Rationale	Selective reporting	Rationale
Lipfert et al. 2006	Moderate-risk	Quote: "Sample sizes may be reduced due to missing ambient air quality data."	Low-risk	No evidence of selective report.
Hart et al. 2011	Moderate-risk	Quote: "Only 81% of the cohort was successfully geocoded to the street level. However, in sensitivity analyses conducted in just those individuals geocoded to the street level, the conclusions were not different than those from the whole cohort" Comment: high proportion of missing data for exposure value but the result are not seriously biased	Low-risk	No evidence of selective report.
Lipsett et al. 2011	Low-risk	Quote: "we excluded those who...were missing information for continuous variables used in the regression models"	Low-risk	No evidence of selective report.
Hart et al. 2013	Low-risk	No missing data of either outcome or exposure were detected in this study.	Low-risk	No evidence of selective report.
Eckel et al. 2016	Low-risk	No missing data of either outcome or exposure were detected in this study.	Low-risk	No evidence of selective report.
Turner et al. 2016	High-risk	Quote: "The majority of exclusions were due to missing or invalid residence (n = 385,422) or covariate (n = 130,119) data."	Low-risk	No evidence of selective report.
Eum et al. 2019	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Jerrett et al. 2009	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Chen et al. 2013	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.

Crouse et al. 2015	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Næss et al. 2007	Low-risk	Quote: “All death certificates ....., with no missing cases." Comment: No missing data of either outcome or exposure were incepted in this study.	Low-risk	All estimates of subgroups have been reported.
Beelen et al. 2008	Low-risk	Quote: “The exact residential address at baseline was available for all study participants. All cohort members consented to participation by completing a mailed, self-administered questionnaire.” Comment: No evidence of missing data	Low-risk	No evidence of selective report.
Fischer et al. 2015	Moderate-risk	Quote: “Subjects were lost to follow-up if their final record in the longitudinal file ended before 1 January 2011 and death was not registered as a reason for termination.”	Low-risk	No evidence of selective report.
Maheswaran et al. 2010	Moderate-risk	Quote: “Six hundred seventy-two of the 3320 patients moved during the study period, with 118 moving out of Greater London.....For these patients, their exposure was taken as the average of pollution values at the start and end of their follow-up period. For patients who had moved out of Greater London, pollution values could not be assigned to their postal code location at the end of their follow-up time. We therefore used half their follow-up time, censored their contribution to the study at that point, and used the pollution value at the time of stroke.”	Low-risk	No evidence of selective report.

		Comment: High proportion of missing data of exposure but having method mentioned in the study to fix the issue		
Carey et al. 2013	Low-risk	Comment: Using appropriate method to cope with missing value	Low-risk	No evidence of selective report.
Tonne and Wilkinson 2013	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Halonen et al. 2016	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Dehni et al. 2017	Moderate-risk	Quote:" despite some loss to follow-up for more deprived groups "	Low-risk	No evidence of selective report.
Cesaroni et al. 2013	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Hvidtfeldt et al. 2019	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Bentayeb et al. 2015	High-risk	Quote: “Unfortunately, data on cause-specific mortality were not available after 2010 to extend analyses to 2013.”	Low-risk	No evidence of selective report.
Sanyal et al. 2018	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
de Keijzer et al. 2017	Low-risk	No missing data of either outcome or exposure were incepted in this study.	High-risk	Comment: the data stratified by urban and rural areas but did not provide corresponding HR
Nieuwenhuijsen et al. 2018	Moderate-risk	Quote: “the limitations are that some potential confounders are missing or were not available on individual level, specifically individual level SES.”	Low-risk	No evidence of selective report.
Beelen et al. 2014a	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	All estimates of subgroups have been reported.
Beelen et al. 2014b	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.

Dimakopoulou et al. 2014	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Katanoda et al. 2011	Low-risk	Comment: Subjects with missing data were exclude in this study	Low-risk	No evidence of selective report.
Yorifuji et al. 2013	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Chen et al. 2016	Low-risk	Quote: "In addition, 2743 (0.6%) with missing residence location detail." Comment: low level of missing rate	Low-risk	No evidence of selective report.
Yang et al. 2018	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Kim et al. 2017	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Dirgawati et al. 2019	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Low-risk	No evidence of selective report.
Hanigan et al. 2019	Low-risk	No missing data of either outcome or exposure were incepted in this study.	Moderate-risk	Quote: "the results were sensitive to some covariates such as marital status, sufficient physical activity, area-level SES and missing data imputation."

Table S4. Pooled effects of subgroup analyses for per risk of bias domain when exclude high risks studies

Domain	All-cause mortality			Cardiovascular mortality			Respiratory mortality		
	Studies (n)	HR (95% CI)	I2 (%)	Studies (n)	HR (95% CI)	I^2 (%)	Studies (n)	HR (95% CI)	I^2 (%)
Confounding	15	1.11 (1.04, 1.17)	97.0	11	1.20 (1.10, 1.30)	90.2	8	1.09 (0.97, 1.22)	83.6
Selection bias	25	1.06 (1.04, 1.08)	98.0	19	1.10 (1.05, 1.14)	99.2	16	1.05 (1.02, 1.08)	94.8
Exposure assessment	26	1.06 (1.04, 1.07)	98.7	19	1.11 (1.07, 1.16)	99.2	16	1.05 (1.03, 1.09)	94.9

Missing data	26	1.06 (1.04, 1.08)	98.7	18	1.12 (1.07, 1.17)	99.3	15	1.06 (1.03, 1.09)	95.2
Selective reporting	27	1.06 (1.04, 1.08)	98.6	20	1.11 (1.07, 1.16)	99.2	17	1.05 (1.02, 1.08)	94.6