Ambient Air Pollution and Clinical Dementia: Systematic Review and Meta-analysis

Journal:	*BMJ*
Manuscript ID	BMJ-2022-071620
Article Type:	Original research
Date Submitted by the Author:	29-Apr-2022
Complete List of Authors:	Wilker, Elissa H.; Harvard TH Chan School of Public Health Boston MA, Department of Epidemiology; Harvard TH Chan School of Public Health, Department of Environmental Heath Wilker, Elissa; Harvard University HSPH, Osman, Marwa; Harvard TH Chan School of Public Health, Department of Environmental Heath Weisskopf, Marc; Harvard TH Chan School of Public Health Boston MA, Department of Epidemiology; Harvard TH Chan School of Public Health, Department of Environmental Heath
Keywords:	Dementia, Epidemiology

Ambient Air Pollution and Clinical Dementia: Systematic Review and Meta-analysis

Elissa H. Wilker ScD[1,2], Marwa Osman[2], and Marc G. Weisskopf PhD, ScD[1,2]

[1]Department of Epidemiology, Harvard TH Chan School of Public Health Boston MA.
[2]Department of Environmental Heath, Harvard TH Chan School of Public Health, Boston MA.

Corresponding Author:

Marc Weisskopf, PhD, ScD
665 Huntington Ave, Bldg. 1, Suite 1402
Boston MA 02115
Ph: 617.384.8872
Email: mweissko@hsph.harvard.edu

Funding Sources: Harvard Chan NIEHS Center for Environmental Health (P30 ES000002) and Biogen.
Competing interests: EHW received salary support from Alexion, Inc.

Abstract

Background: Air pollution exposure is a possible modifiable risk factor for dementia and epidemiologic evaluation of this relation has grown rapidly. We synthesize the existing literature, considering differences by study factors that could influence findings.

Methods: Studies describing associations between EPA criteria air pollutants and proxies of traffic pollution were identified from Embase and PubMed through August 2021. Information on study characteristics and key findings were extracted for each study and results were meta-analyzed where at least three studies used comparable approaches. Differences in data source, study type, and variability in exposure reported were also explored.

Results: Thirty-seven studies were identified and 11 could be meta-analyzed for $PM_{2.5}$. Results were expressed per standard deviation or interquartile range. The overall HR for $PM_{2.5}$ was 1.07 (95% CI: 1.04-1.10). The HR among 4 cohort studies was 1.20 (95% CI: 1.09-1.32) and among 6 studies using administrative data was 1.04 (95% CI: 1.00-1.07). Wider confidence intervals were observed for associations with NO_2 (HR=1.04; 95% CI: 0.99-1.10; n=5 studies) and NOx (HR=1.08; 95% CI: 0.99-1.16; n=4 studies), and there was no clear association with O_3 (HR=0.98; 95% CI: 0.93-1.04; n=3 studies).

Conclusion: The evidence suggests that $PM_{2.5}$ is a risk factor for dementia. However, the meta-analyzed HRs are subject to limitations that require interpretation with great caution. Outcome ascertainment approaches differ across studies and each exposure assessment approach likely is only a proxy for etiologically relevant exposure as it relates to clinical dementia outcomes. Studies that evaluate critical periods of exposure, pollutants other than $PM_{2.5}$, and that actively assess all participants for outcomes, are needed.

Keywords: Air pollution; dementia; meta-analysis; systematic review.

Introduction

The global burden of dementia has been increasing in recent years and it has been estimated more than 55.2 million people worldwide are living with this condition.[1] However, interventions to delay or prevent the onset of dementia remain scarce. In recent years, ambient air pollution has emerged as a potentially modifiable risk factor for dementia based on long-standing evidence that supports an association between exposure to air pollution and cardiovascular disease,[2,3] stroke,[4] and, somewhat more recently, cognitive impairment.[5,6] Studies have also shown that reductions in air pollution levels are associated with reduced mortality.[7,8] While the number of studies evaluating the association between ambient air pollution and dementia has increased over the past decade, the methodologies used have varied widely. Previous systematic reviews have either avoided combining estimates across studies because of these differences, or attempted to review and combine estimates without acknowledgement of these issues. Therefore, we conducted a systematic review and meta-analysis of the literature on associations between ambient pollutants and clinical dementia to synthesize the findings and evaluate how potential biases may impact the interpretation of results that aggregate these data using the work to inform policy and clinical practice.

Methods

Literature Search

The protocol was registered under PROSPERO (CRD42021277083). Two people (EW and MO) performed a literature search of the PubMed, and EMBASE databases through August 2021 using free text and Medical Subject Headings for Alzheimer's Disease and dementia and exposures related to EPA criteria pollutants or traffic pollution and its surrogates (see Appendix). All articles with an abstract suggesting it was relevant were reviewed. Studies were eligible for review if they included adults aged ≥18, the study design included longitudinal follow up; the exposure period considered was a year or more, and the investigators reported hazard ratios, odds ratios, relative risks or rate ratios and 95% confidence intervals (CI) for the association between exposure to ambient pollutants and clinical dementia. Studies that evaluated associations between ambient pollution and cognitive function, brain imaging, or biomarkers associated with dementia were excluded.

Data Extraction

Using a standardized form, two readers (EW and MW) independently and in duplicate extracted data from selected articles. Measures of association were reported with 95% CI, unit of exposure (μg/m^3, ppb, etc), scaling factor (e.g. 1, 5, 10μg/m^3) and covariate adjustment. Forms are available on request.

Assessment of Study Quality/Bias Assessment

Study quality was assessed by evaluating factors thought to be critical for study design, analysis, and data interpretation. We described potential biases in Table 2. We assumed that *exposure misclassification* was less of a concern in studies that utilized more temporally and spatially resolved exposure estimates (e.g. spatiotemporal model with exposure assigned at participant's address) than in those that assigned exposures based on the surrounding area (e.g. nearest monitor to a residence, or model average over a large area). *Outcome misclassification* was evaluated based on whether case ascertainment was active (i.e. all participants were regularly screened for dementia) or passive, and whether cases were identified primarily through insurance claims, medical records, or other sources. For *control of confounding* we focused on whether and how the study adjusted for indicators of socioeconomic status, which are more likely to introduce confounding of ambient air pollutant measures than personal behaviors.[9] We considered individual level adjustment for SES most appropriate. Whether studies adjusted for potential mediators on the causal pathway between ambient pollutant exposures and dementia outcomes was also considered. Whenever possible, results that did not include adjustment for mediators were included in meta-analyses. When results were only reported with adjustment for potential mediators, we included the estimate and noted this limitation. *Selection bias and loss to follow-up* was evaluated based on whether the study discussed attrition, addressed loss to follow-up, or included sensitivity analyses to determine the impact of these factors on the analysis.

Statistical Analysis

Inverse-variance-weighted random-effect meta-analyses were conducted to pool estimates from individual studies for pollutants when three or more studies were available using comparable approaches with similar definitions of exposure and outcome. I^2 was determined to quantify between-study heterogeneity. Data were presented scaled to an approximation of the standard deviation to account for the variation in exposure observed within each study. Where interquartile range was not available,

standard deviation was used. Subgroup analyses were also performed to evaluate differences in associations between cohort studies and those that used administrative databases and separately by geographic regions (North America, Europe, Asia). In most cases, results from single pollutant models were available. Where a multipollutant model was provided, we commented on whether estimates were substantially altered.

Results

Our initial review identified 116 publications in Pubmed and 148 in Embase with a total of 173 unique publications published through August 2021 (**Figure 1**). A total of 37 publications met inclusion criteria, (**Table 1**). There were 25 studies on $PM_{2.5}$ and 12 on nitrogen dioxide (NO_2), nitrogen oxides (NO_x), ozone (O_3) or a combination of these pollutants and $PM_{2.5}$. All of the publications were from the past ten years, with 19 published in 2020 or later, including 6 of the 12 studies that made use of cohort studies. While the majority of studies were reported from North America (n=19), there were several studies from Sweden and other countries in Europe (n=11) and a few studies in Asia from Taiwan and Hong Kong (n=7). Most studies estimated pollutants at participants' home addresses as a proxy of exposure, but many studies, particularly those using administrative data, assigned exposure at a cruder scale such as postal code. Most studies used a one-year average of exposure but time scales were up to 10 years.[10]

The timing of exposure assessment and dementia assessment is shown in **Figure 2A and B**. Cohort studies typically followed individuals who were free of dementia at baseline and assessed exposure and dementia at multiple points during follow-up using case ascertainment, which typically involved a combination of self-report, in-person exams, or review of medical records. Studies using administrative data obtained exposure information at multiple points and relied on passive ascertainment for dementia diagnoses by reviewing medical records for dementia ICD codes (See Supplemental Table 1 for codes). For most studies, the period of exposure preceded the assessment of outcomes, but for the studies from the Betula cohorts, addresses from the 1990s were linked to exposures assessed 2009-10.[11-15] Some land use regression (LUR) models used were based on measurements in one year that were then propagated to other years, typically based on ratios over time from the LUR years to other years at routine monitor sites.[10,16-22]

Study quality assessment is described in **Table 2.** Many of the studies using administrative data assigned exposure as a city average rather than at residence. Administrative data studies typically relied on medical claims data to identify cases of dementia. Five studies of the thirty-seven[17,20,22-24] used Canadian health databases and cited a validation study for the case-finding algorithm against patient charts that reported for individuals ≥20 years of age a sensitivity of 75% (79% for those ≥65 years of age) and a specificity of ~100% (positive and negative predictive values of 79% and ~100%, respectively).[25] This does not, however, rule out underdiagnosis relative to cases in the general population (since the validation gold standard had to be in the hospital) or differences in diagnostic delay. While administrative studies typically had more limited control of confounding by socioeconomic status than cohort studies, some of the administrative data studies used analysis approaches such as central site exposure assignment that eliminate, or at least greatly reduce, confounding by individual-level factors related to SES.[26-29] Many of the cohort studies commented on, and sometimes provided information on, attrition. Most performed inverse probability weighting of estimates to account for possible informative attrition.[11,12,14-16,30] Studies of administrative data provided little information on the potential for loss to follow-up, although most made use of data sources that were nationwide, or province/state-wide, therefore such attrition was likely low.

Among the thirty-seven studies, seven were excluded from meta-analyses because they used the same data source as a previous paper.[11,13,15,20,31-33] In this case, we included the findings from the largest or primary analysis study. Meta-analyses could be conducted for a subset of the publications included. Among the 11 studies on $PM_{2.5}$, five used data from cohort studies,[10,12,16,34] and six utilized information from administrative data and claims.[17,18,22,35-37] Other reasons $PM_{2.5}$ estimates were not meta-analyzed were because they did not model exposure continuously,[38,39] used death as the outcome (n=3)[21,40,41] (one paper included in the meta-analysis supplemented case identification with mortality records[10]), used study designs/analytic approaches that did not estimate a hazard ratio (HR; n=4),[19,27-29] were a reanalysis of (or overlapped greatly with the population of) a previously analyzed cohort (n=2),[20,31] or did not report on all-cause dementia (n=3).[24,26,42] Among meta-analyzed studies, five were from Europe,[10,12,16,18,35] five from North America,[17,22,34,37,43] and one from Hong Kong.[36] One of the publications from the BETULA cohort study considered $PM_{2.5}$ from local sources (traffic and stoves) and did not have data on regional $PM_{2.5}$, but assumed its contribution to variation in the study area was small.[12] This study had a mean (SD) of 0.95 (0.34) $\mu g/m^3$. Among the other nine studies in the meta-

analysis, the median/mean exposure levels ranged from 7.9 to 35.2 μg/m^3, with measures of spread (SD or IQR) that ranged from 0.08 to 4.8 μg/m^3. Six of the studies had mean exposure concentrations below the current US Environmental Protection Agency (EPA) annual standard of 12 μg/m^3.[10,12,17,22,37,43]

For $PM_{2.5}$, the HR per sd/IQR was 1.07 (95%CI: 1.04-1.10) (**Figure 3**). Of the 16 studies of $PM_{2.5}$ not included in the meta-analysis, two did not model a continuous exposure, but one of these found a statistically significant higher risk of dementia at exposures above 12 μg/m^3,[38] and the other found a statistically significant higher rate of AD hospitalization above 10 μg/m^3, but not for non-AD dementia.[39] Among the 14 others not included, one found no association,[21] while all the others found a higher rate of dementia with higher levels of pollution. The association did not reach statistical significance in 5 of the studies.[19,20,24,29,42] Three included studies suggested a leveling off of the association between $PM_{2.5}$ and dementia at higher concentrations, but the concentration at which the leveling started was often where data got more sparse and differed in the three studies (about 8.5, 15, and 35 μg/m^3).[10,36,37]

There were suggestive associations with NO_2 (HR=1.04; 95% CI: 0.99-1.10; n=5 studies;[16-18,22,35] 4 not meta-analyzed[20,21,24,44]) and NOx (HR=1.08; 95% CI: 0.99-1.16; all n=4 studies meta-analyzed,[10,14,18,30]), and no association with O_3 (HR=0.98; 95% CI: 0.93-1.04; n=3 studies;[17,18,35] 3 not meta-analyzed[42,44,45]) (**Figure 3**. Forest plots for pollutants on a unit exposure basis are shown in **Supplemental Figure 1**. No other pollutant had at least 3 studies that could be meta-analyzed (**Figure 1**). All of the studies for NO_2 not included in the meta-analysis showed elevated effect estimates, except for AD specifically in one study.[24] Two studies not included for O_3 showed statistically significant elevated effect estimates, although they assessed dementia differently (dementia diagnosis versus mortality),[42,45] while the other was null.[44]

Due to some of the differences in approaches used by cohort and administrative data studies, we estimated a combined hazard ratio by study type (cohort or administrative). For $PM_{2.5}$, the HR for the SD/IQR among five cohort studies was 1.20 (95% CI: 1.09-1.32) and among six studies using administrative data was 1.04 (95% CI: 1.00-1.07) (**Figure 4A**). Among the studies of each type, there was statistically significant heterogeneity, and the heterogeneity between these groups was also statistically significant. When analyzed separately by region (**Figure 4B)**, the HR for a 1 SD/IQR

change in exposure in Europe was 1.11 (95% CI: 1.03-1.20), while the HR was 1.06 (95% CI: 1.02-1.10) for North America, and in the one study in Asia was 1.06 (95% CI: 1.0-1.11). Given the small number of studies that could be meta-analyzed for other pollutants, we could not examine differences by study type or region.

Both the exposure averaging and follow-up varied substantially (**Figure 2**). Seven studies averaged exposure over a one-year period, two used a five-year average, and two used a 10-year average. Usually, the averaging period used was in the year or years before the year of the outcome, but ranged from approximately 15 years before the outcome to roughly 9 years after. The studies also involved different amounts of follow-up time. Among the eleven $PM_{2.5}$ studies included in the meta-analysis, two of the studies had 6-8 years of follow-up, six had 12-13, and three had 15-16 years. The follow-up period for most studies began around 2000, with seven of these studies beginning 1998-2001, although two began in 1993/1994[12,43] and the other two began 2005-2008.[34,35] Most studies adjusted for socioeconomic factors that could be determinants of pollution exposure such as education, material deprivation indices, or other individual or area-based indicators. One study did not adjust for socioeconomic status,[12] three studies included no individual adjustment and included group level information for socioeconomic status,[17,22,35] and other studies had only limited adjustment,[31,34,37] but effect estimates were similar regardless of approach. One study only presented results co-adjusted for other pollutants,[44] while three studies provided single pollutant and co-pollutant adjusted models.[18,42,45] Results for O_3 were generally unchanged or stronger when co-adjusted for other pollutants,[18,42,45] except in one study following SO_2 adjustment,[46] possibly as a result of SO_2 oxidation. Results for NO_2 and NOx were unchanged when co-adjusted for other pollutants,[18] and in one study, results for $PM_{2.5}$ were not changed with adjustment for NO_2, and null with adjustment for CO.[46]

Discussion

The findings from this systematic review and meta-analysis suggest that there is consistent evidence of an association between ambient air pollution and clinical dementia, particularly for ambient $PM_{2.5}$ exposure, even below current US EPA standards. Results were generally similar by regions of the world and adjustment factors, and effect sizes were larger from cohort studies, which may be due to less outcome misclassification than in administrative studies. However, the interpretation of a given estimate from a meta-analysis of air pollution and dementia must be viewed in light of many factors that can

contribute to results heterogeneity, such as exposure and outcome measurement error, different approaches to assigning exposure, spatiotemporal resolution of exposure assignment, individual behavioral factors, and uncertainty in the etiologically relevant window of exposure. In addition, data from other pollutants remains limited. The sources of bias described below highlight the importance of evaluating patterns across these studies rather than identifying a specific point estimate from meta-analysis.

Outcome Misclassification

Administrative data provide an advantage over established cohort studies in capturing point of service and health care utilization. However, they may be subject to diagnostic delay and under-diagnosis due to reliance on diagnostic codes and pharmaceutical prescriptions if individuals do not seek or have good access to care early on in disease stages,[47] and this may differ by socioeconomic status (SES), race and ethnicity.[48] For most cohort studies, patients were followed at regular study intervals and all study subjects were screened for dementia (active case identification) with cognitive testing, physician diagnosis, medical records, and claims, which should be highly sensitive and less misclassified, despite some diagnostic delay and loss to follow-up. If outcome misclassification is independent of exposure, the causal effect would be underestimated. However, if lower socioeconomic status is related to diagnostic delay, and there is a greater delay in dementia diagnosis among participants with a lower socioeconomic status (SES),[49] the direction of bias of a causal effect estimate should be downwards, making it harder to detect a causal effect. For PM, at least in the US, levels are on average lower among non-Hispanic whites,[50,51] who also tend to have higher health utilization such that cases are more likely to be ascertained.[52] To the extent that control of these factors is insufficient, the typical relation they have with PM exposures (e.g. less among those with lower SES and the non-Hispanic white population) is such that bias of a causal effect estimate should be downwards, making it harder to detect such a causal effect. This potential source of bias could occur for other air pollutants too, but may be less pronounced for some, like O_3, for which disparities in exposure can be smaller.[51]

A related point is the issue of detection bias, where known health effects of air pollutants can lead to more interaction with the medical system and thus earlier identification of dementia even if the air pollution has no direct biological effect on dementia. This would cause a bias away from the null, leading to spurious, non-causal associations, and administrative datasets with passive outcome capture

are more susceptible to this than cohort studies, where outcomes are pursued for all participants. Note that this is different from, for example, air pollution leading to cardiovascular effects (mediators) that in turn lead to higher risk of dementia, which could be a mechanism by which an air pollutant increases risk for dementia. Since cohort studies are also much less prone to underdiagnosis and differential diagnostic delay, these biases are unlikely to account for the positive findings seen among cohort studies included in this review. Although there is the possibility of detection bias causing spurious positive findings in studies with administrative data, underdiagnosis and diagnostic delay are likely to act in the opposite direction. Thus, we consider the significant, but much smaller, positive associations seen in the studies with administrative data as corroborating evidence of the results of the cohort studies.

Exposure Misclassification

An advantage of ambient air pollution exposure assessment rather than personal exposure assessment is that it protects against some types of confounding bias, in particular from confounding by personal behaviors.[9] However, using any ambient exposure measurement approach to estimate individual exposure will result in some level of exposure measurement error. This error is most likely independent of whether someone subsequently develops dementia, at least after accounting for covariates that may relate to residence, and so non-differential, which can involve both classical and Berksonian error.[53,54] Classical error will typically bias any true relation towards the null,[55] making it harder to detect a causal effect, whereas Berksonian error would not lead to a biased estimate, but it reduces the precision of the estimated association. A bias away from the null may occur when less granular exposure averages are used and true variation in exposure of the population are underestimated, but such bias can only happen if there is a true underlying causal effect of the pollutant.[54]

Finer spatio-temporal resolution or population-weighted exposure assignment is preferable. Exposure assessment error could also account for a positive finding between air pollution and dementia if pollutant levels were systematically over-estimated among those who develop dementia as a result of factors like socioeconomic status or race that relate to likelihood of identifying cases.[48] Finer resolution exposure assignment makes this less likely and in any case most studies controlled for these factors reasonably well. Studies using administrative databases generally used less spatially refined exposure assignment than the cohort studies and had lower associations. However, spatial variability of pollutants varies. $PM_{2.5}$ and O_3 tend to have less spatial variation than NOx and CO, which are driven more by

primary emissions and factors that vary on a finer scale. Any biases from exposure measurement error are greater with more spatial variation in the pollutant.[56]

A related issue is the extent to which the exposure averaging windows correlate with exposures during any etiologically relevant exposure window. The included studies averaged exposures over different time periods, with different intervals evaluated for the association between pollutant exposure and subsequent dementia. Further, correlation with any etiologically relevant window could be affected by changes in urbanization, pollutant reduction policies, and other factors. The more such factors lead to less correlation with exposure during an etiologically-relevant window, the harder it would be to identify an effect since a study effect estimate would be attenuated relative to any true causal effect. Overall, these exposure measurement issues are unlikely to account for the observed higher risk of dementia with higher pollutant levels.

Participation Bias and Loss to Follow-up

Participation bias and loss to follow-up are unlikely to affect studies of administrative data since these typically have data on everyone meeting eligibility. While some regional administrative studies could be susceptible to loss to follow-up and residential mobility if some people leave the state/province, this is likely to minimally impact results.[17,20,22-24,27,29,39] In contrast, cohort studies could be more affected because participants must opt in and actively participate in follow-up. Dementia status and predictors of dementia, including cognitive decline and ill health,[30,57,58] are predictors of initial study participation and loss to follow-up. Since air pollution is associated with a higher risk of several diseases, this may lead to lower participation rates and more loss to follow-up. Loss to follow-up as a consequence of pollutants and dementia risk typically cause a downward bias of the association,[5960] and so would mask a causal effect of air pollution on dementia risk. Most cohort studies acknowledged this potential issue and some describe the extent of attrition or attempt to address it using inverse probability weighted censoring. In one study, estimates were higher in a model that used inverse probability weighted censoring,[30] as expected based on the anticipated downward bias from a selection bias due to these environmental exposure driven patterns of differential loss to follow-up.[59,60] Since the bias, if present at all, would be downward, these concerns are unlikely to account for the observed higher risk of dementia with higher levels of pollution.

Confounding

Lower socioeconomic status (SES) and minority population group are typically associated with higher PM2.5 exposure,[50,51] and, at least in the US, with a lower probability of a dementia diagnosis, or a delayed one.[47,48,61] Therefore, inadequate control should lead to a downward bias in the estimated associations. While this SES-air pollution relation is consistent in most studies from North America, at least for $PM_{2.5}$, data from Europe are mixed and studies from Asia remain limited.[62] Also, the pattern may be weaker or different for other ambient pollutants, like O_3.[51] While some studies also adjusted for individual-level behavior variables such as smoking, alcohol intake, body mass index, or physical activity, this did not alter findings from the SES adjusted findings. This suggests that individual behavioral factors may be predictors or consequences of SES, but are not independent predictors of ambient pollution levels and so do not introduce confounding of ambient exposure estimates.[9] The relation between SES and pollution, and any outcome misclassification differing by SES, is unlikely to be the same across continents, yet results were similar in different regions. Thus, while we cannot rule out residual and unmeasured confounding, it is unlikely that confounding bias from SES could account for the positive associations seen between PM and dementia risk that were similar across regions.

Air pollutants can be correlated in their variability over time. Therefore, associations with health outcomes may be at least partially explained by other pollutants or constituents with similar temporal patterns. Only a few of the studies we examined reported findings with and without adjustment for co-exposure to other pollutants. In general, the results suggested that the main findings held, but more studies are needed to identify specific pollutants resulting in higher dementia risk to understand the mechanisms involved in this association.

A separate issue relates to adjustment for potential mediators. While adjusting for potential predictors of the outcome in a continuous model may improve precision, this is not the case for standard adjustment with a binary outcome,[63] and it is critical not to adjust for downstream consequences of pollution that may raise dementia risk, such as cardiovascular conditions or diabetes. In the absence of mediator-outcome confounding, this could produce a downward bias, but if there is mediator-outcome confounding, bias could go in any direction.[64] Furthermore, because of uncertainty about etiologically relevant exposure windows for air pollution, adjusting for such factors at baseline can be problematic.

Limitations

Several different approaches are used to evaluate exposure to outdoor air pollution and these differences result in different correlations between the measure used in the analysis and true individual exposures to pollution of outdoor origin, and therefore to heterogeneity in study findings if there is a true causal effect. Adding to the difficulty is the uncertainty around the etiologically relevant exposure window if there is a true causal effect. It is likely that any exposure measure used in a study, averaged over some time window, is acting as a proxy measure (with some correlation less than 1) of exposure during a true etiologically relevant window. These factors that contribute to reduced correlation of the exposure measure used with personal exposures in the etiologically relevant time period will contribute both to heterogeneity in meta-analysis results and underestimation of the association between air pollution and dementia. The heterogeneity from exposure assignment is most likely unrelated to whether an individual develops dementia or not, particularly after control for factors that may relate to identifying dementia cases, in which case study findings are almost always biased towards the null compared with any true causal effects.[54,55] We did not see large differences by mean exposure level of the different studies, which could suggest a linear exposure-response relationship, but this should be taken with caution since the same uncertainties in assigning exposure and relevant etiologic window compromise interpretation of dose-response relations.

Another limitation is that hazard ratios have inherent issues related to the conditioning on surviving to any given point in time.[65] If there is a true causal effect that is not constant over time (possibly because of differing susceptibility in the exposed population), hazard ratios can get smaller with longer follow-up as a true causal effect over one period of follow up is combined with lower or null effects over different follow up periods. Most of the studies we analyzed had follow-up times of 6-8 years, but even in those that had different follow-up times, the results were similar, suggesting this is likely to not be greatly affecting the findings. Finally, the majority of the literature focused on $PM_{2.5}$, but we sought to include other pollutants where feasible.

Conclusions and future directions

In summary, the studies included in our meta-analysis all show that higher long-term exposure to ambient $PM_{2.5}$ is associated with a higher rate of dementia. These findings provide strong evidence for a

causal effect of $PM_{2.5}$ on dementia risk, and our bias assessment suggests that this is likely a conservative estimate of the association. More studies would still be valuable, particularly studies using active case identification approaches, which should be more robust to the potential sources of bias addressed above. Studies of pollutants other than $PM_{2.5}$ are also clearly needed. As more studies examine pollutants other than $PM_{2.5}$, the consideration of multiple pollutants (including $PM_{2.5}$) and $PM_{2.5}$ components simultaneously will be important. Finally, studies that seek to identify etiologically relevant time windows for exposure are needed, as well as those that can provide additional insight into underlying mechanisms that are affected by exposure to ambient pollutants.

References

1. World Health Organization. Global status report on the public health response to dementia. Geneva: World Health Organization, 2021.
2. Brauer M, Casadei B, Harrington RA, Kovacs R, Sliwa K, Group WHFAPE. Taking a Stand Against Air Pollution-The Impact on Cardiovascular Disease: A Joint Opinion From the World Heart Federation, American College of Cardiology, American Heart Association, and the European Society of Cardiology. *Circulation* 2021; **143**(14): e800-e4.
3. Rajagopalan S, Brauer M, Bhatnagar A, et al. Personal-Level Protective Actions Against Particulate Matter Air Pollution Exposure: A Scientific Statement From the American Heart Association. *Circulation* 2020; **142**(23): e411-e31.
4. Ljungman PL, Mittleman MA. Ambient air pollution and stroke. *Stroke* 2014; **45**(12): 3734-41.
5. Power MC, Adar SD, Yanosky JD, Weuve J. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic review of epidemiologic research. *Neurotoxicology* 2016; **56**: 235-53.
6. Weuve J, Bennett EE, Ranker L, et al. Exposure to Air Pollution in Relation to Risk of Dementia and Related Outcomes: An Updated Systematic Review of the Epidemiological Literature. *Environmental health perspectives* 2021; **129**(9): 96001.
7. Dominici F, Peng RD, Zeger SL, White RH, Samet JM. Particulate air pollution and mortality in the United States: did the risks change from 1987 to 2000? *American journal of epidemiology* 2007; **166**(8): 880-8.
8. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. *American journal of respiratory and critical care medicine* 2006; **173**(6): 667-72.
9. Weisskopf MG, Webster TF. Trade-offs of personal vs. more proxy exposure measures in environmental epidemiology. *Epidemiology* 2017; **28**(5): 635-43.
10. Grande G, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D. Association Between Cardiovascular Disease and Long-term Exposure to Air Pollution With the Risk of Dementia. *JAMA neurology* 2020; **77**(7): 801-9.
11. Andersson J, Oudin A, Sundstrom A, Forsberg B, Adolfsson R, Nordin M. Road traffic noise, air pollution, and risk of dementia - results from the Betula project. *Environmental research* 2018; **166**: 334-9.
12. Astrom DO, Adolfsson R, Segersson D, Forsberg B, Oudin A. Local Contrasts in Concentration of Ambient Particulate Air Pollution (PM2.5) and Incidence of Alzheimer's Disease and Dementia: Results from the Betula Cohort in Northern Sweden. *J Alzheimers Dis* 2021; **81**(1): 83-5.
13. Oudin A, Andersson J, Sundstrom A, et al. Traffic-Related Air Pollution as a Risk Factor for Dementia: No Clear Modifying Effects of APOEvarepsilon4 in the Betula Cohort. *J Alzheimers Dis* 2019; **71**(3): 733-40.
14. Oudin A, Forsberg B, Adolfsson AN, et al. Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study. *Environmental health perspectives* 2016; **124**(3): 306-12.
15. Oudin A, Segersson D, Adolfsson R, Forsberg B. Association between air pollution from residential wood burning and dementia incidence in a longitudinal study in Northern Sweden. *PloS one* 2018; **13**(6): e0198283.

16. Mortamais M, Gutierrez LA, de Hoogh K, et al. Long-term exposure to ambient air pollution and risk of dementia: Results of the prospective Three-City Study. *Environment international* 2021; **148**: 106376.
17. Chen H, Kwong JC, Copes R, et al. Exposure to ambient air pollution and the incidence of dementia: A population-based cohort study. *Environment international* 2017a; **108**: 271-7.
18. Cerza F, Renzi M, Gariazzo C, et al. Long-term exposure to air pollution and hospitalization for dementia in the Rome longitudinal study. *Environmental health : a global access science source* 2019; **18**(1): 72.
19. Dimakakou E, Johnston HJ, Streftaris G, Cherrie JW. Is Environmental and Occupational Particulate Air Pollution Exposure Related to Type-2 Diabetes and Dementia? A Cross-Sectional Analysis of the UK Biobank. *Int J Environ Res Public Health* 2020; **17**(24).
20. Ilango SD, Chen H, Hystad P, et al. The role of cardiovascular disease in the relationship between air pollution and incident dementia: a population-based cohort study. *International journal of epidemiology* 2020; **49**(1): 36-44.
21. Klompmaker JO, Hoek G, Bloemsma LD, et al. Surrounding green, air pollution, traffic noise exposure and non-accidental and cause-specific mortality. *Environment international* 2020; **134**: 105341.
22. Smargiassi A, Sidi EAL, Robert LE, et al. Exposure to ambient air pollutants and the onset of dementia in Quebec, Canada. *Environmental research* 2020; **190**: 109870.
23. Chen H, Kwong JC, Copes R, et al. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. *Lancet* 2017b; **389**(10070): 718-26.
24. Yuchi W, Sbihi H, Davies H, Tamburic L, Brauer M. Road proximity, air pollution, noise, green space and neurologic disease incidence: a population-based cohort study. *Environmental health : a global access science source* 2020; **19**(1): 8.
25. Jaakkimainen RL, Bronskill SE, Tierney MC, et al. Identification of Physician-Diagnosed Alzheimer's Disease and Related Dementias in Population-Based Administrative Data: A Validation Study Using Family Physicians' Electronic Medical Records. *J Alzheimers Dis* 2016; **54**(1): 337-49.
26. Kioumourtzoglou MA, Schwartz JD, Weisskopf MG, et al. Long-term PM2.5 Exposure and Neurological Hospital Admissions in the Northeastern United States. *Environmental health perspectives* 2016; **124**(1): 23-9.
27. Nunez Y, Boehme AK, Weisskopf MG, et al. Fine Particle Exposure and Clinical Aggravation in Neurodegenerative Diseases in New York State. *Environmental health perspectives* 2021; **129**(2): 27003.
28. Bishop KC, Ketcham JD, Kuminoff NV. Hazed and Confused: The Effect of Air Pollution on Dementia. Cambridge, MA: NATIONAL BUREAU OF ECONOMIC RESEARCH, 2018.
29. van Wijngaarden E, Rich DQ, Zhang W, et al. Neurodegenerative hospital admissions and long-term exposure to ambient fine particle air pollution. *Annals of epidemiology* 2021; **54**: 79-86 e4.
30. Paul KC, Haan M, Yu Y, et al. Traffic-Related Air Pollution and Incident Dementia: Direct and Indirect Pathways Through Metabolic Dysfunction. *J Alzheimers Dis* 2020; **76**(4): 1477-91.
31. Lee M, Schwartz J, Wang Y, Dominici F, Zanobetti A. Long-term effect of fine particulate matter on hospitalization with dementia. *Environ Pollut* 2019; **254**(Pt A): 112926.
32. Ran J, Zhang Y, Han L, et al. The joint association of physical activity and fine particulate matter exposure with incident dementia in elderly Hong Kong residents. *Environment international* 2021a; **156**: 106645.

33. Yu Y, Haan M, Paul KC, et al. Metabolic dysfunction modifies the influence of traffic-related air pollution and noise exposure on late-life dementia and cognitive impairment: A cohort study of older Mexican-Americans. *Environ Epidemiol* 2020; **4**(6): e122.
34. Sullivan KJ, Ran X, Wu F, et al. Ambient fine particulate matter exposure and incident mild cognitive impairment and dementia. *J Am Geriatr Soc* 2021; **69**(8): 2185-94.
35. Carey IM, Anderson HR, Atkinson RW, et al. Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. *BMJ Open* 2018; **8**(9): e022404.
36. Ran J, Schooling CM, Han L, et al. Long-term exposure to fine particulate matter and dementia incidence: A cohort study in Hong Kong. *Environ Pollut* 2021b; **271**: 116303.
37. Shi L, Wu X, Danesh Yazdi M, et al. Long-term effects of PM2.5 on neurological disorders in the American Medicare population: a longitudinal cohort study. *Lancet Planet Health* 2020; **4**(12): e557-e65.
38. Cacciottolo M, Wang X, Driscoll I, et al. Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. *Translational psychiatry* 2017; **7**(1): e1022.
39. Rhew SH, Kravchenko J, Lyerly HK. Exposure to low-dose ambient fine particulate matter PM2.5 and Alzheimer's disease, non-Alzheimer's dementia, and Parkinson's disease in North Carolina. *PloS one* 2021; **16**(7): e0253253.
40. Bowe B, Xie Y, Yan Y, Al-Aly Z. Burden of Cause-Specific Mortality Associated With PM2.5 Air Pollution in the United States. *JAMA Netw Open* 2019; **2**(11): e1915834.
41. Ho HC, Fong KNK, Chan TC, Shi Y. The associations between social, built and geophysical environment and age-specific dementia mortality among older adults in a high-density Asian city. *Int J Health Geogr* 2020; **19**(1): 53.
42. Jung CR, Lin YT, Hwang BF. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. *J Alzheimers Dis* 2015; **44**(2): 573-84.
43. Shaffer RM, Blanco MN, Li G, et al. Fine Particulate Matter and Dementia Incidence in the Adult Changes in Thought Study. *Environmental health perspectives* 2021; **129**(8): 87001.
44. Li CY, Li CH, Martini S, Hou WH. Association between air pollution and risk of vascular dementia: A multipollutant analysis in Taiwan. *Environment international* 2019; **133**(Pt B): 105233.
45. Zhao N, Pinault L, Toyib O, Vanos J, Tjepkema M, Cakmak S. Long-term ozone exposure and mortality from neurological diseases in Canada. *Environment international* 2021; **157**: 106817.
46. Jung C, Lin Y, Hwang B. Air pollution and newly diagnostic autism spectrum disorders: a population-based cohort study in Taiwan. *PloS one* 2013; **8**(9): e75510.
47. Tyas SL, Tate RB, Wooldrage K, Manfreda J, Strain LA. Estimating the incidence of dementia: the impact of adjusting for subject attrition using health care utilization data. *Annals of epidemiology* 2006; **16**(6): 477-84.
48. Power MC, Gianattasio KZ, Ciarleglio A. Implications of the Use of Algorithmic Diagnoses or Medicare Claims to Ascertain Dementia. *Neuroepidemiology* 2020; **54**(6): 462-71.
49. Lin PJ, Emerson J, Faul JD, et al. Racial and Ethnic Differences in Knowledge About One's Dementia Status. *J Am Geriatr Soc* 2020; **68**(8): 1763-70.
50. Tessum CW, Paolella DA, Chambliss SE, Apte JS, Hill JD, Marshall JD. PM2.5 polluters disproportionately and systemically affect people of color in the United States. *Sci Adv* 2021; **7**(18).
51. Liu J, Clark LP, Bechle MJ, et al. Disparities in Air Pollution Exposure in the United States by Race/Ethnicity and Income, 1990-2010. *Environmental health perspectives* 2021; **129**(12): 127005.
52. Barnes LL. Alzheimer disease in African American individuals: increased incidence or not enough data? *Nat Rev Neurol* 2022; **18**(1): 56-62.

53. Zeger S, Thomas D, Dominici F, et al. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environmental health perspectives* 2000; **May;108**(5): 419-26.
54. Goldman GT, Mulholland JA, Russell AG, Gass K, Strickland MJ, Tolbert PE. Characterization of Ambient Air Pollution Measurement Error in a Time-Series Health Study using a Geostatistical Simulation Approach. *Atmos Environ (1994)* 2012; **57**: 101-8.
55. Kioumourtzoglou M, Spiegelman D, Szpiro A, et al. Exposure measurement error in PM2.5 health effects studies: A pooled analysis of eight personal exposure validation studies. *Environ Heal* 2014; **13**(1): 2.
56. Sarnat SE, Klein M, Sarnat JA, et al. An examination of exposure measurement error from air pollutant spatial variability in time-series studies. *Journal of exposure science & environmental epidemiology* 2010; **20**(2): 135-46.
57. de Graaf R, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *American journal of epidemiology* 2000; **152**(11): 1039-47.
58. Mein G, Johal S, Grant RL, Seale C, Ashcroft R, Tinker A. Predictors of two forms of attrition in a longitudinal health study involving ageing participants: an analysis based on the Whitehall II study. *BMC Med Res Methodol* 2012; **12**: 164.
59. Weisskopf MG, Sparrow D, Hu H, Power MC. Biased Exposure-Health Effect Estimates from Selection in Cohort Studies: Are Environmental Studies at Particular Risk? *Environmental health perspectives* 2015.
60. Weuve J. Magnitude matters: beyond detection in the presence of selection in research on socioeconomic inequalities in health. *Epidemiology* 2013; **24**(1): 10-3.
61. Laurent O, Bard D, Filleul L, Segala C. Effect of socioeconomic status on the relationship between atmospheric pollution and mortality. *J Epidemiol Community Health* 2007; **61**(8): 665-75.
62. Hajat A, Hsia C, O'Neill MS. Socioeconomic Disparities and Air Pollution Exposure: a Global Review. *Curr Environ Health Rep* 2015; **2**(4): 440-50.
63. Robinson LD, Jewell N. Some surprising results about covariate adjustment in logistic regression models. *International Statistical Review / Revue Internationale de Statistique* 1991; **59**(2): 227-40
64. Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. *International journal of epidemiology* 2013; **42**(5): 1511-9.
65. Hernan MA. The hazards of hazard ratios. *Epidemiology* 2010; **21**(1): 13-5.

Table 1: Characteristics of studies included in the systematic review.

First author, year	Geographic Location	Study Population	Exposures	Age distribution in years	Percent Male	Exposure averaging period	Outcome
Cohort Studies							
Oudin, 2016	Umea, Sweden	BETULA Cohort	NO_x	Median 70 (range 55-85)	43%	Annual average	DSM-IV All-Cause Dementia; and Vascular dementia, Alzheimer's disease separately
Oudin, 2018	Umea, Sweden	BETULA Cohort	$PM_{2.5}$ from wood burning, stove or boilers; traffic	Median 70 (range 55-85)	43%	Annual average	DSM-IV All-Cause Dementia
Andersson, 2018	Umea, Sweden	BETULA Cohort	NO_x	Median 70 (range 55-85)	43%	Annual average	DSM-IV All-Cause Dementia
Oudin, 2019	Umea, Sweden	BETULA Cohort	NO_x	Median 70 (range 55-85)	43%	Annual average	DSM-IV All-Cause Dementia and Alzheimer's disease separately
Astrom 2021	Umea, Sweden	BETULA Cohort	$PM_{2.5}$	Median 70 (range 55-85)	43%	Annual average	DSM-IV All-Cause Dementia
Cacciotollo, 2017	USA	WHIMS Cohort	$PM_{2.5}$	Range 65-79	0%	3-year rolling average	All-Cause Dementia
Grande, 2020	Stockholm, Sweden	SNAC-K Cohort	$PM_{2.5}$, NO_x	Mean 74, sd 11; range 60+	37%	5-year rolling average	DSM-IV All-Cause Dementia
Paul, 2020	California, USA	SALSA Cohort	TRAP (NO_x)	Mean 70, sd 7; range 60-101	42%	Annual average	DSM-IV All-Cause Dementia
Yu, 2020	California, USA	SALSA Cohort	TRAP (NO_x)	Mean 70, sd 7; range 60-101	42%	Annual average	DSM-IV All-Cause Dementia
Mortamais 2021	Bordeaux, Montpellier, and Dijon, France	3C Study Cohort	$PM_{2.5}$, NO_2, BC	Median 73, Range 65+	38%	Annual average	DSM-IV All-Cause Dementia; and Vascular dementia, Alzheimer's disease separately

Shaffer 2021	Puget Sound region, WA	Adult Changes in Thought Cohort	$PM_{2.5}$	Mean 75, SD 6.3, range 65+	42%	10 year rolling average	All-cause Dementia
Sullivan, 2021	Allegheny County, Pennsylvania, USA	MYHAT Cohort	$PM_{2.5}$	Mean 77, sd 7; range 65+	38%	Annual average	Clinical Dementia Rating (CDR) Staging All-Cause Dementia
Administrative Database Studies							
Chang, 2014	Taiwan	Administrative Insurance Database (NHIRD)	NO_2, CO	Mean 61, sd 9; Range 50+	46%	Annual average	All-cause Dementia
Jung, 2015	Taiwan	Systematic Random Sample of Administrative Insurance Database (LHID2000 drawn from NHIRD)	O_3, $PM_{2.5}$	Median within 70-74; Range 65+	54%	Annual average	Alzheimer's Disease
Kioumourtzoglou, 2016	Northeast USA	Medicare data from Northeast USA	$PM_{2.5}$	Mean 76, sd 8; Range 65+	43%	Annual average	Alzheimer's Disease
Chen, 2017a	Ontario, Canada	Health Administrative database (ONPHEC)	$PM_{2.5}$, NO_2, O_3	Mean 67; Range 55-85	47%	5 year rolling average	All-Cause Dementia
Chen, 2017b	Ontario, Canada	Health Administrative database (ONPHEC)	DTR	Mean 67; Range 55-85	47%	<50m, 50-100, 101-200, 201-300, >300 & log distance	All-Cause Dementia
Carey, 2018	London, England	Primary care administrative database (CPRD)	$PM_{2.5}$, Traffic $PM_{2.5}$, NO_2, O_3	Median within 60-69; Range 50-79	50%	Annual average	All-Cause Dementia
Bishop, 2018	USA	Medicare hospitalization database	$PM_{2.5}$	Range 65+	Not stated	Annual average	All-Cause Dementia
Zhang, 2019	Taiwan	Systematic Random Sample of Administrative Insurance Database (LHID2000 drawn from NHIRD)	hydrocarbons and non-methane hydrocarbons	Mean 63, sd 9; Range 50+	52%	5-year average	All-Cause Dementia
Li, 2019	Taiwan	Administrative Insurance Database (NHIRD)	PM_{10}, SO_2, O_3, NO_2, and CO	Mean 79, sd 7; Range 65+	53%	3, 5, and 7 yr average	Vascular Dementia

Cerza, 2019	Rome, Italy	Rome Longitudinal Study followed through administrative hospital discharge data	PM_{10}, $PM_{2.5}$, PMcoarse, NO_2, NO_x, O_3, $PM_{2.5}$ absorbance	Mean 75, sd 7; Range 65-100	42%	Annual average	Vascular, Senile, and Alzheimer's Dementia separately
Lee, 2019	Florida, North Carolina, Georgia, Tennessee, Alabama, South Carolina, and Mississippi, USA	MedPAR Medicare and fee-for-service hospitalization data	$PM_{2.5}$	Mean 70, sd 7; Range 65+	44%	Annual average	All-Cause Dementia; and Vascular dementia, Alzheimer's disease, other dementias separately
Bowe, 2019	USA	US VHA database with NDI linkage	$PM_{2.5}$	Median 64; Interquartile range 56-76	94%	Annual average	Dementia Mortality
Yuchi, 2020	Vancouver, Canada	MSP health and vital statistics databases	$PM_{2.5}$, BC, NO_2, NO, DTR	Median (case/non-case) 76/57; Range 45-84	(case/non-case) 41%/48%	Annual average, DTR (highway and major road each <50m, <150m)	Alzheimer's disease and non-AD Dementia separately
Dimakakou, 2020	United Kingdom	UK Biobank Cohort	$PM_{2.5}$	Median within 57-66; Range 37-73	46%	Annual average	All-Cause Dementia
Ho, 2020	Hong Kong, China	Hong Kong Administrative Death Data	$PM_{2.5}$, BC	Range 65+	53%	"Long-term" (Averaging period not given)	All-Cause Dementia Mortality
Ilango, 2020	Ontario, Canada	NPHS and CCHS linked to administrative health database	$PM_{2.5}$, NO_2	Mean 60, sd 11; Range 45+	42%	3-year average	All-Cause Dementia
Klompmaker, 2020	Netherlands	PHM cohort linked to administrative mortality data	PM_{10}, PMcoarse, $PM_{2.5}$, $PM_{2.5}$ absorbance, NO_2	Median 63; Range 30+	46%	Annual average	Non-Alzheimer's Dementia Mortality
Shi, 2020	USA	MedPAR Medicare and fee-for-service hospitalization data	$PM_{2.5}$	Mean 70, sd 7; Range 65+	45%	Annual average	All-Cause Dementia

Smargiassi, 2020	Québec, Canada	QIDCSS linked to administrative health database	$PM_{2.5}$, NO_2, DTR	Median within 65-74; Rnage 65+	45%	Annual average (NO2), 2-year average (PM2.5), DTR: per 150m and quintiles	All-Cause Dementia
Nunez, 2021	New York, USA	NY (USA) SPARCS hospital and emergency department database	$PM_{2.5}$	NY Hospital admission count data	NY Hospital admission count data	Annual average	Alzheimer's disease
Rhew, 2021	North Carolina, USA	NC SCHS mortality and HCUP inpatient databases	$PM_{2.5}$	Range 65+	(Exposed/control) 41%/45%	7-year average	Alzheimer's disease
Ran, 2021a,b	Hong Kong, China	EHS Cohort followed through administrative hospital data	$PM_{2.5}$	Median within 65-74; Range 65+	34%	Annual average	All-Cause Dementia; and Vascular dementia, Alzheimer's disease separately
Van Wijngaarden, 2021	Buffalo, Rochester, Albany, Bronx, Manhattan, and Queens, New York, USA	NY (USA) SPARCS hospital and emergency department database	$PM_{2.5}$	Range 18+	NY Hospital admission count data	Annual average	Alzheimer's disease Other Dementia
Zhao, 2021	Canada	CanCHEC followed with administrative mortality data	O_3	Range 25+	48%	Annual average	Non-Alzheimer's Dementia

Abbreviations:
BC: Black Carbon
3C Study: Three Cities Study;
CanCHEC: Canadian Census Health and Environment Cohort;
CCHS: Canadian Community Health Survey;
CPRD: Clinical Practice Research Datalink;
DTR: Distance to Road
EHS: Chinese Elderly Health Service;

HCUP: Healthcare Cost and Utilization Project;
LHID2000: longitudinal health insurance database 2000;
MedPAR: Medicare Provider and Analysis Review;
MSP: Medical Services Plan;
MYHAT: Monongahela-Youghiogheny Healthy Aging Team;
NDI: National Death Index;
NHIRD: National Health Insurance Research Database of Taiwan;
NPHS : Canadian National Population Health Survey;
ONPHEC: Ontario Population Health and Environment Cohort;
PHM: Public Health Monitor;
QIDCSS: Québec Integrated Chronic Disease Surveillance System;
SALSA: The Sacramento Area Latino Study on Aging;
SCHS: State Center for Health Statistics;
Sd: Standard Deviation;
SNAC-K: Swedish National Study on Aging and Care in Kungsholmen;
SPARCS: Statewide Planning and Research Cooperative System;
WHIMS: Women's Health Initiative Memory Study;
VHA: Veterans Health Administration.

Table 2: Bias assessment of studies included in the systematic review[1].

First author, year	Exposure Assessment	Misclassification and measurement error of outcome	Control of Confounding	Selection Bias/loss to follow up
Cohort Studies				
Oudin, 2016	LUR (50x50m grid) based on 4 week-long measurements in 2009-10; assigned 1993-1995 residence.	Active: In-person assessment supplemented with medical records	Appropriate confounding control	Used censoring to address loss to follow-up
Oudin, 2018	Source(s) specific model at 50x50m grid and assigned at residence level	Active: In-person assessment supplemented with medical records	Individual education level as SES adjustment	Used censoring to address loss to follow-up
Andersson, 2018	LUR (50x50m grid) based on 4 week-long measurements in 2009-10; assigned 1993-1995 residence.	Active: In-person assessment supplemented with medical records	Appropriate confounding control	Used censoring to address loss to follow-up
Oudin, 2019	LUR (50x50m grid) based on 4 week-long measurements in 2009-10; assigned 1993-1995 residence.	Active: In-person assessment supplemented with medical records	Individual education level as SES adjustment	Used censoring to address loss to follow-up
Åström, 2021	Source(s) specific model at 50x50m grid and assigned at residence	Active: In-person assessment supplemented with medical records	No adjustment for SES	Used censoring to address loss to follow-up
Cacciottolo, 2017	Spatiotemporal model based on US EPA AQS assigned to residence	Active: Screening followed by in-person assessment	Adjustment for mediators	No discussion of issue of loss to follow up
Grande, 2020	Emission sources and dispersion model at 60x60 km with interpolation for years between data sources	Active: In-person assessment supplemented with death and medical records	Adjustment for potential mediators	Attrition rate mentioned
Paul, 2020	CALINE4 dispersion model within 1.5 km of residence	Active: In-person screening, with neuropsychological exam follow up reviewed by neurologist and neuropsychologist review	Appropriate control	Weighting to address possible informative follow-up
Yu, 2020	CALINE4 dispersion model within 1.5 km of residence	Active: In-person screening, with neuropsychological exam follow up reviewed by neurologist and neuropsychologist review	Appropriate control	Weighting to address possible informative follow-up
Mortamais, 2021	LUR (ESCAPE) assigned at residence. Some extrapolations over time.	Active: 3 phases of in-person outcome assessment, included review by geriatric specialist	Appropriate confounding adjustment	IPW for attrition bias
Shaffer, 2021	Spatiotemporal model based on LUR and geospatial smoothing, with data from 5 types of $PM_{2.5}$ monitors	Active: In-person assessments and follow-up physical and neuropsychological evaluations reviewed by consensus	Appropriate confounding adjustment	Completeness of Follow-up Index
Sullivan, 2021	US EPA downscaling model at census tract level	Active: in-person CDR assessment by trained interviewers	Individual education level as SES adjustment	No information on loss to follow up and attrition
Administrative Database Studies				

Chang, 2014	Monitor from residential district of participant's most frequently used clinic for respiratory care	Passive: ICD codes	Adjustment for potential mediators	Likely none because it is National Health Care database
Jung, 2015	Inverse distance weighting of 3 closest monitors within 25km for 100m grid cells averaged to residential postcode level (~1 urban block, ~10x larger rurally); some back-extrapolation for PM2.5	Passive: ICD codes	Adjustment for potential mediators	Likely none because it is National Health Care database
Kioumourtzoglou, 2016	Average of all monitors within a city	Passive: ICD codes	Zip-code level income as SES adjustment	Likely none. All ≥65 and it is National Health Care database
Chen, 2017a	Postcode level (block or large building) exposure assignment; PM2.5: AOD and transport-based model at 1x1 km; NO2: LUR; O3: Physically-based prediction model and ground monitoring at 21x21 km. Some extrapolations over time.	Passive: ICD codes	Neighborhood level SES adjustment (income, education, unemployment, immigration status)	Likely low because it is Province-wide data and required residence >5 years
Chen, 2017b	Distance to major roads based on postal code (block or large building)	Passive: ICD codes	Adjustment for potential mediators; Neighborhood level SES adjustment (income, education, unemployment, immigration status)	Likely low because it is Province-wide data and required residence >5 years
Carey, 2018	Postcode level (~15 households) assignment; Dispersion model at 20x20 km in 2004	Passive: Read codes for dementia within the Quality and Outcomes Framework	Neighborhood level adjustment for SES (Index of Multiple Deprivation)	Censored if contributing GP practice withdrew from CPRD; individual patient loss to follow-up not known
Bishop, 2018	Assigned at zip code level weighting nearest monitors	Passive: ICD codes and dementia drug use	Modeling approach removes confounding by individual factors; adjustment for potential mediators	Likely low. All ≥65; Nationwide data
Zhang, 2019	Postcode level (~1 urban block, ~10x larger rurally) exposure assignment from spatial interpolation of monitor data.	Passive: ICD codes	No SES adjustement and adjustment for mediators	Likely none because it is National Health Care database
Li, 2019	Exposure assigned to residence based on spatial interpolation of monitor data to 250x250 m grid	Passive: ICD codes	Appropriate confounding control; no single pollutant models, only co-adjusted for other pollutants	Case-control study
Cerza, 2019	LUR (ESCAPE) assigned at residence; Some extrapolations over time; O3 from FARM chemical transport model at 1x1 km	Passive: ICD codes	Appropriate confounding control	Loss to follow-up discussed
Lee, 2019	Zip code level data from AOD based 1x1 km model	Passive: ICD codes	Medicaid eligibility as individual SES indicator and zip-code area education	Likely low. All ≥65; only lost if move out of one of the included states

Bowe, 2019	County-level 2006 exposure from US EPA CMAQMS	Passive: ICD codes for mortality	control of county level SES only	Little issue of loss to follow up for mortality
Yuchi, 2020	Post code level (~1 urban block, larger in rural areas) LUR (10m resolution) exposure assignment.	Passive: ICD codes	Neighborhood level adjustment for SES, adjustment for potential mediators for non-AD analyses	Likely none because it is Province-wide data and required residence during entire exposure and follow up period
Dimakakou, 2020	LUR (ESCAPE) model assigned at residence; Some extrapolations over time.	Passive: ICD codes	Area deprivation index adjustment for SES	Limited information on loss to follow up and attrition
Ho, 2020	LUR at 10m resolution	Passive: ICD codes	Adjustment for being employed at time of death as indicator of individual SES and area based indicators	Likely none as it is Hong Kong mortality data
Ilango, 2020	Postcode level (block or large building) exposure assignment; PM2.5: AOD and transport-based model at 1x1 km; NO2: LUR. Some extrapolations over time.	Passive: ICD codes	Appropriate confounding control	Likely low because it is Province-wide data and required residence >5 years
Klompmaker, 2020	LUR (ESCAPE) model assigned at residence; Some extrapolations over time.	Passive: ICD codes for mortality	Appropriate confounding control	Likely none as it is National mortality data
Shi, 2020	Ensemble model at postal code level (~7500 people; varying areas—mean 92 km^2)	Passive: ICD codes	Medicaid eligibility as individual SES indicator and area-level indicators	Likely low. All ≥65; Nationwide data
Smargiassi, 2020	Post code level (average area 10,038 m^2) exposure assignment. PM2.5: AOD and transport-based model at 1x1 km; NO2: LUR at 2x10 km. Some extrapolations over time.	Passive: ICD codes	Area based SES adjustment	Likely low because it is Province-wide data and required residence >4 years
Nunez, 2021	AOD-based model at 1x1 km, assigned at city level	Passive: ICD codes	County-specific analysis not affected by individual level variables; appropriate control for city-level SES	Quasi-Poisson method of counts per county, not follow up
Rhew, 2021	AOD-based model at 1.1x1.1 km resolution; assigned at zip code level	Passive: ICD codes (mortality and hospital)	Area based SES adjustment	Odds Ratio; likely only lose people if they move out of state
Ran, 2021[a]	AOD-based model at 1x1 km, assigned at residence	Passive: ICD codes	Appropriate confounding control	Likely none as it is Hong Kong-wide data
Ran, 2021[b]	AOD-based model at 1x1 km, assigned at residence	Passive: ICD codes	Appropriate confounding control	Likely none as it is Hong Kong-wide data
Van Wijngaarden, 2021	US EPA AQS monitor data assigned at city level	Passive: ICD codes	City-specific analysis not affected by individual level variables; appropriate control for city-level SES	Quasi-Poisson method of counts per city, not follow up

Zhao, 2021	Chemical transport model at 21 km resolution; assigned at post code level	Passive: ICD codes	Appropriate confounding control	Likely low. Nationwide data

[1]Blue shading indicates particularly good methods for the issue considered. Note, however, that for exposure assessment, while finer resolution is generally better, for pollutants with less spatial variation (e.g. $PM_{2.5}$, secondary pollutants like O_3), the issues with less resolution are less pronounced than for pollutants with more spatial variation (e.g. NO_2, NOx).

Abbreviations:
AOD: Aerosol Optical Depth;
AQS: Air Quality System;
CMAQMS: Community Multiscale Air Quality Modeling System;
CPRD: Clinical Practice Research Datalink;
ESCAPE: European Study of Cohorts for Air Pollution Effects;
FARM: Flexible Air quality Regional Model;
ICD: International Classification of Diseases;
LUR: Land Use Regression model;
US EPA: United States Environmental Protection Agency

Figure legends

Figure 1: Flowchart of literature search.

Dark blue boxes indicate the number of publications included at each stage of selection process. White boxes indicate reasons for removal and exclusion at each stage.

Figure 2: Graphic Representation of Exposure and Outcome Assessment in the Administrative (Panel A) and Cohort (Panel B) Studies Included in the Systematic Review.

Red lines indicate period of exposure assessment. Blue lines indicate period of outcome assessment for administrative studies (Panel A) and blue circles indicate follow-up visits (Panel B). For SNAC-K cohort, visits occurred every 6 yrs for participants age 60-77 years old and every 3 years for older participants and are indicated by the larger and smaller blue circles respectively (Panel B).

Figure 3: Random effects meta-analysis of pollutant associations for 1 SD/IQR.

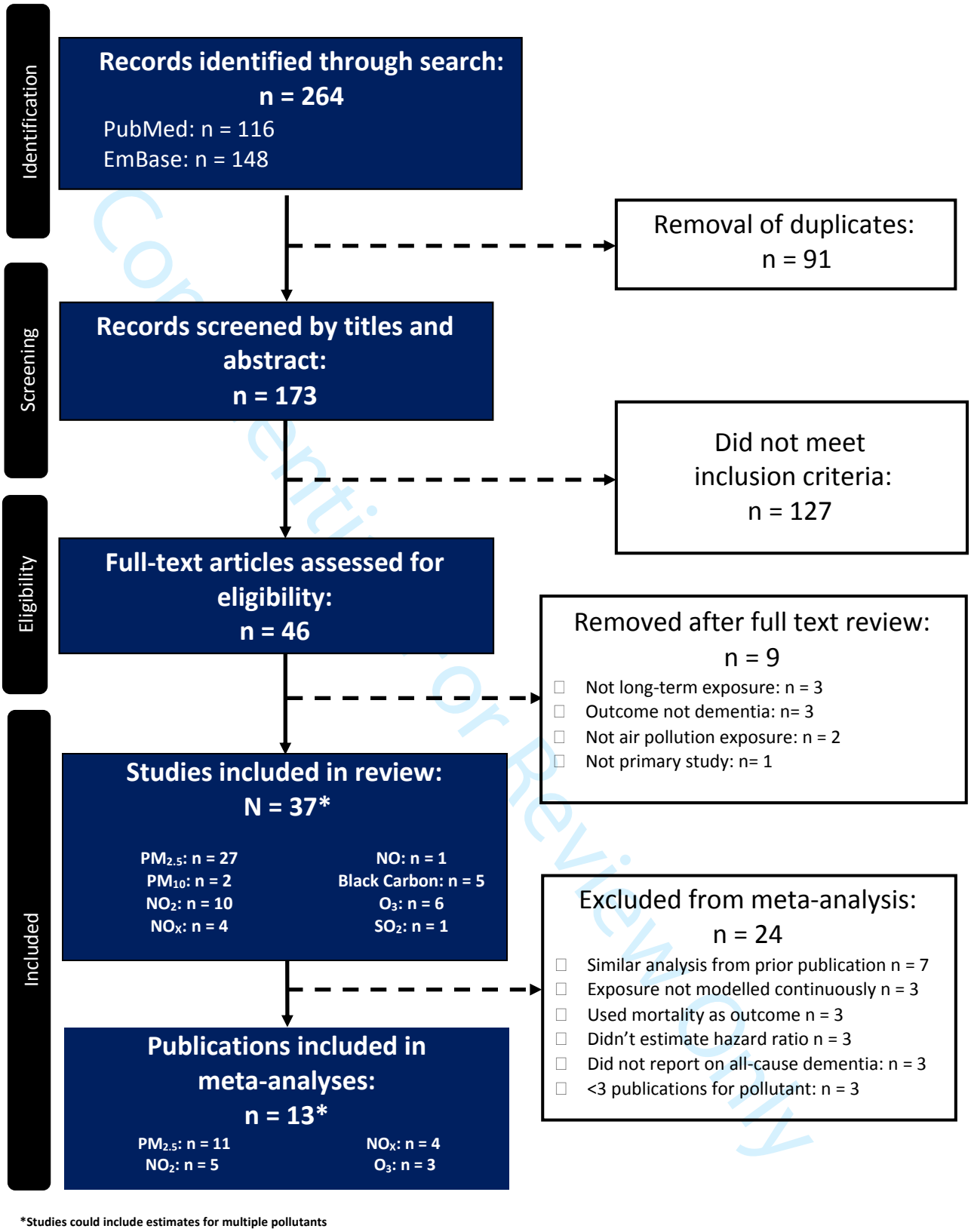
Shaded boxes represent the relative weight of the studies. Meta-analysis estimates for each pollutant are in bold. All measures of spread (SD or IQR) were reported in $\mu g/m^3$. DL: DerSimonian and Laird method.

Figure 4: $PM_{2.5}$ SD/IQR estimates by study type and region.
Cohort studies were those that estimated associations from established cohort studies; Administrative studies made use of data such as claims and medical records. Shaded boxes represent the relative weight of the studies. Meta-analysis estimates for each pollutant are in bold. All measures of spread (SD or IQR) were reported in $\mu g/m^3$. DL: DerSimonian and Laird method.

Supplemental Figure 1: Random effects meta-analysis of $PM_{2.5}$ associations.

Associations are scaled to a 1 $\mu g/m^3$ change in $PM_{2.5}$, 10 $\mu g/m^3$ change in NO_2 and NO_x and 5 $\mu g/m^3$ change in O_3. Shaded boxes represent the relative weight of the studies. DL method indicates DerSimonian and Laird approach. Meta-analysis estimates for each pollutant are in bold. All measures of spread (SD or IQR) were reported in $\mu g/m^3$.

Figure 1: Flowchart of literature search.



*Studies could include estimates for multiple pollutants

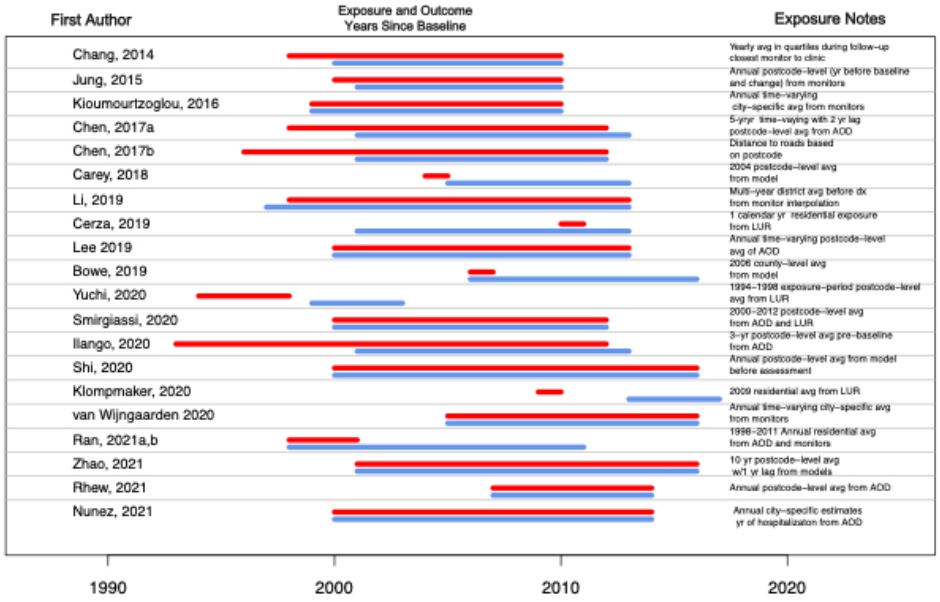


Figure 2A: Red lines indicate period of exposure assessment. Blue lines indicate period of outcome assessment for administrative studies (Panel A) and blue circles indicate follow-up visits (Panel B). For SNAC-K cohort, visits occurred every 6 yrs for participants age 60-77 years old and every 3 years for older participants and are indicated by the larger and smaller blue circles respectively (Panel B).

222x140mm (72 x 72 DPI)

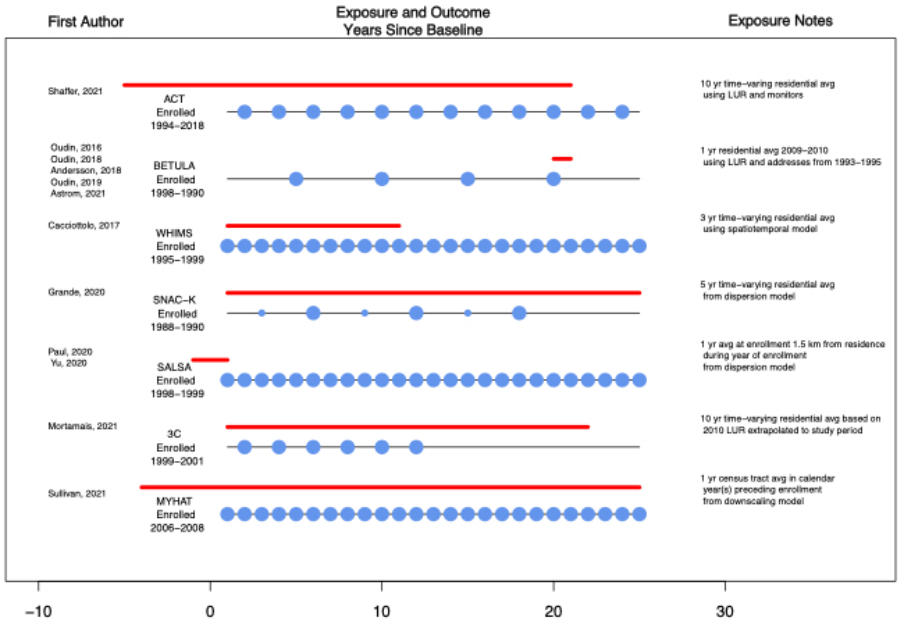


Figure 2b: Red lines indicate period of exposure assessment. Blue lines indicate period of outcome assessment for administrative studies (Panel A) and blue circles indicate follow-up visits (Panel B). For SNAC-K cohort, visits occurred every 6 yrs for participants age 60-77 years old and every 3 years for older participants and are indicated by the larger and smaller blue circles respectively (Panel B).

253x161mm (72 x 72 DPI)

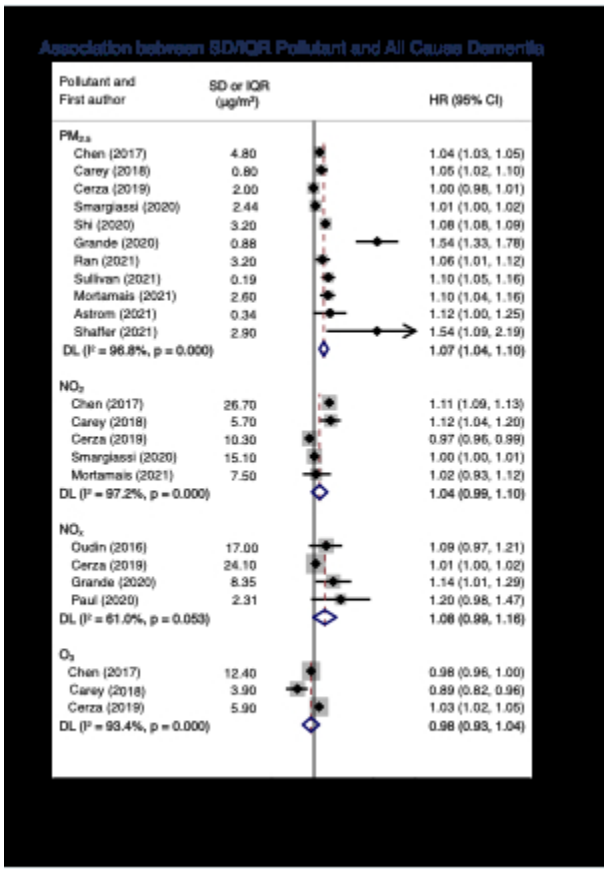


Figure 3:Shaded boxes represent the relative weight of the studies. Meta-analysis estimates for each pollutant are in bold. All measures of spread (SD or IQR) were reported in μg/m3. DL: DerSimonian and Laird method.

105x152mm (72 x 72 DPI)

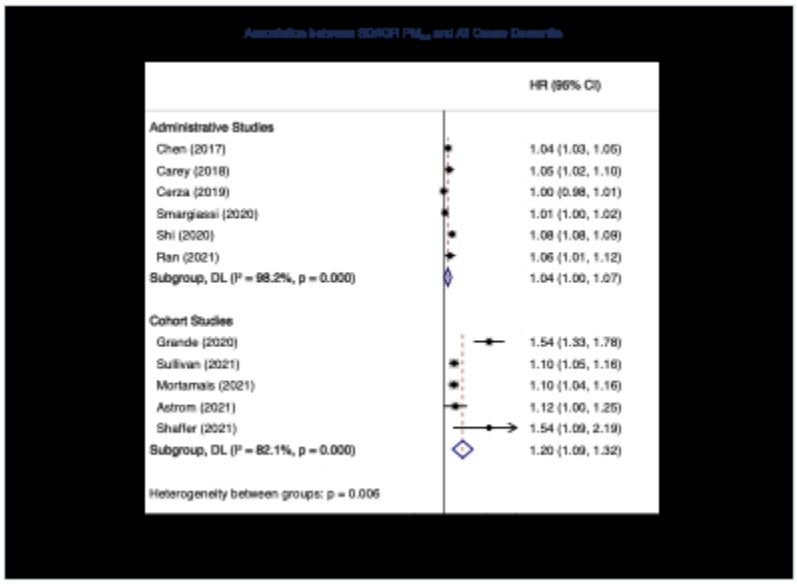


Figure4a: Cohort studies were those that estimated associations from established cohort studies; Administrative studies made use of data such as claims and medical records. Shaded boxes represent the relative weight of the studies. Meta-analysis estimates for each pollutant are in bold. All measures of spread (SD or IQR) were reported in µg/m3. DL: DerSimonian and Laird method.

139x101mm (72 x 72 DPI)

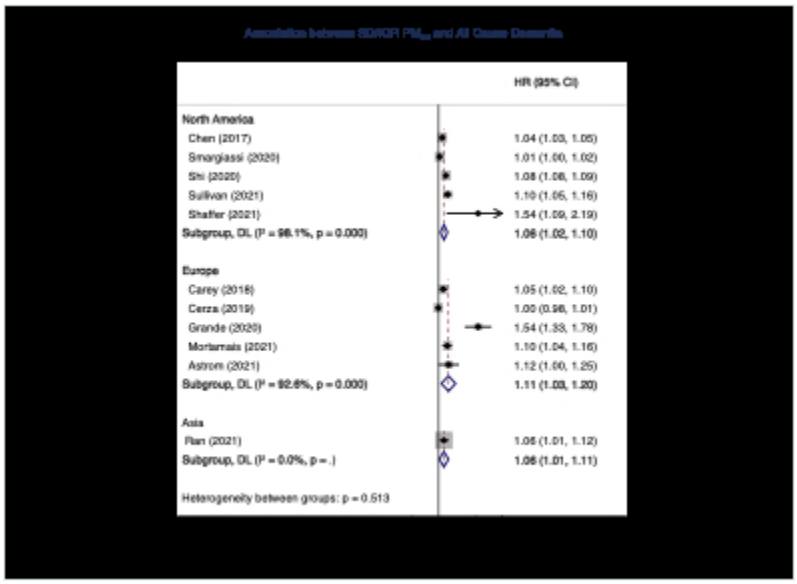


Figure 4b: Cohort studies were those that estimated associations from established cohort studies; Administrative studies made use of data such as claims and medical records. Shaded boxes represent the relative weight of the studies. Meta-analysis estimates for each pollutant are in bold. All measures of spread (SD or IQR) were reported in µg/m3. DL: DerSimonian and Laird method.

139x101mm (72 x 72 DPI)