# Long-term Air Pollution Exposure and Incident Dementia: A Systematic Review and Meta-Analysis

Authors: Clare B. Best Rogowski (MPhil)[a, &], Christiaan Bredell (MB BChir)[b, c, &], Yan Shi (MB BChir)[b], Alexandra Tien-Smith (MPhil)[a], Magdalena Szybka (MB BChir)[b], Kwan Wai Fung (MB BChir)[b], Lucy Hong (MB BChir)[b], Veronica Phillips (PhD)[d], Professor Zorana Jovanovic Andersen (PhD)[e], Stephen J. Sharp (MSc)[a], Professor James Woodcock (PhD)[a], Professor Carol Brayne (MD)[f], Annalan Navaratnam (MFPH)[a], Haneen Khreis (PhD)[a, g *]

[&] Joint first authors
* Corresponding author: Dr Haneen Khreis, Addenbrooke's Hospital, Level 3 Institute of Metabolic Science, University of Cambridge School of Clinical Medicine, Cambridge CB2 0SL, United Kingdom, Phone: +44(0)1223 769200, Email: hrk38@medschl.cam.ac.uk

a. MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge CB2 0SL, United Kingdom
b. University of Cambridge School of Clinical Medicine, Cambridge CB2 0SL, United Kingdom
c. Hinchingbrooke Hospital, North West Anglia NHS Foundation Trust, Huntingdon, PE29 6NT, United Kingdom
d. University of Cambridge Medical Library, University of Cambridge School of Clinical Medicine, Hills Rd, Cambridge CB2 0SP, United Kingdom
e. Section of Environmental and Health, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 15 Øster Farimagsgade 5, 1014 Copenhagen, Denmark
f. Cambridge Public Health, University of Cambridge, Cambridge CB2 0SR, United Kingdom
g. Texas A&M Transportation Institute, 3135 Texas A&M University System, College Station, Texas 77843-3135, United States

***Panel:*** **Research in context**

**Evidence before this study**

Before undertaking this study, we reviewed the existing literature, including systematic reviews and meta-analyses, on the associations between various air pollutants and dementia incidence. We found key gaps, such as limited evidence for $NO_2$, $NO_x$, and $BC/PM_{2.5\ Absorbance}$, a lack of certainty of evidence assessment, and few subgroup or sensitivity analyses to explore the sources of large observed heterogeneity. Additionally, we assessed that the number of relevant primary studies had grown tremendously since the previous systematic reviews' publications. We then developed and published a protocol to guide our work.

This systematic review and meta-analysis searched Medline, Embase, Cochrane Library, Cinahl, Global Health, PsycINFO, Scopus, and Web of Science, covering studies through October 2023. Eligible studies were observational epidemiological studies that included participants > 18, examined long-term outdoor air pollution exposure (≥1 year), and quantitatively investigated exposure to a clinical dementia diagnosis in adults without dementia at baseline. Excluded studies exclusively reported on cognitive impairment, surrogate dementia markers (e.g., imaging, and biochemical markers), or lacked quantitative exposure or exposure-response estimates. We assessed risk of bias and certainty of evidence using standard tools from the OHAT Handbook.

Out of 15,619 screened records, 51 studies met the inclusion criteria, 40 were eligible for the meta-analysis, and 34 were included (population represented: 29,364,106). The meta-analyses revealed significant positive associations between $PM_{2.5}$ (Hazard Ratio (HR) per 5 μg/m³: 1.08 (95%CI: 1.02-1.14), $BC/PM_{2.5\ absorbance}$ (per 1 μg/m³: 1.13 (95%CI: 1.01-1.27) and $NO_2$ (per 10 μg/m³: 1.03 (95%CI: 1.01-1.05) and dementia incidence. Our certainty of evidence assessment indicated that we had a moderate level of certainty. Our risk of bias assessment of each included study was generally low, though a few studies had high bias in specific categories.

**Added value of this study**

This study offers the most comprehensive exposure-response estimates to date for use in burden of disease, health impact assessments and air quality regulation. It is the largest meta-analysis to explore the associations between air pollution and dementia incidence, covering pollutants not previously analysed. Subgroup analyses by dementia subtype, study location, outcome ascertainment and exposure assessment methods provide new insights into why evidence strength may vary across groups.

**Implications of all the available evidence**

Our findings reinforce and extend the evidence that long-term exposure to outdoor air pollution is a risk factor for the onset of dementia. Reducing pollution exposure would lower dementia rates, and stricter air quality standards are likely to yield significant health, social, and economic benefits.

# Abstract

A rapidly-evolving evidence-base suggests that exposure to air pollution increases dementia's incidence. We conducted a systematic review and meta-analysis according to a published protocol. Prespecified inclusion criteria required primary observational studies of individuals over 18 years and a quantitative report on the association between long-term outdoor air pollution and subsequent dementia incidence. Risk of bias, publication bias, and confidence in the evidence were assessed. Fifty-one papers met the inclusion criteria and 40 were eligible for some meta-analysis, with a population of 29,364,106 participants,[1] mostly from high-income countries. Of those 40 papers, 34 papers with continuous effect estimates whose pollutant-exposure met the threshold of three or more papers were included in the meta-analysis. Meta-analyses revealed significant positive associations between $PM_{2.5}$, $NO_2$, and $BC/PM_{2.5\ Absorbance}$ and dementia incidence. There was considerable heterogeneity between studies in the pooled analyses for most exposure-outcome associations. Sensitivity analyses supported findings. Subgroup analyses suggested a larger association between $PM_{2.5}$ and $NO_2$ with vascular dementia than Alzheimer's disease. The overall Certainty of Evidence was moderate. This paper adds to the body of evidence that outdoor air pollutants are risk factors for dementia.

[1]This is a sum of the populations, rather than samples, represented by the studies included in the meta-analysis.

# Body

## Introduction

Dementia refers to the acquired and often progressive loss of function across multiple cognitive domains such that it impairs an individual's personal, social, and occupational function (1). Dementia is a clinical syndrome which can be caused by multiple disease processes. Estimated to affect over 57.4 million people, Alzheimer's disease (AD) and other dementias ranked as the eighth leading cause of death in 2021 globally (2, 3). Its global burden is projected to increase to 152.8 million cases by 2050 (3). The impacts on both society and the individual are significant, and, while there are some indications that its prevalence is decreasing in some higher income countries, signalling the potential to modify population risk, there are no signs that the incidence of dementia decreasing outside of Europe and North America (4). Therefore, there remains an urgent need to investigate and address causes of this syndrome.

The most recent Lancet Commission on Dementia Prevention, Intervention, and Care (2024) identified air pollution as one of 14 modifiable risk factors for dementia, based on published evidence (5). Air pollution is a relatively recently recognised risk factor, supported by primary studies reporting an association between dementia and exposure to a number of air pollutants, including particulate matter (PM) of different sizes ($PM_{2.5}$, $PM_{2.5\text{-}10}$, $PM_{10}$), Black Carbon (BC) or $PM_{2.5\ Absorbance}$, and gases (ground-level Ozone ($O_3$)), Nitrogen Dioxide ($NO_2$), Carbon Monoxide (CO), Sulphur Oxides ($SO_x$) and Nitrogen Oxides ($NO_x$). The direction of association and strength of evidence, however, have varied by publication and pollutant, raising questions about confidence in the evidence base and reasons underlying observed heterogeneity (6-10). Considering the then-emerging nature of this investigation and mixed findings of primary studies, a series of systematic reviews and meta-analyses were published from 2015 to synthesise the rapidly growing body of evidence. These works have concluded that $PM_{2.5}$ exposure is associated with an increased risk of developing dementia but yielded less clear findings on the associations with $PM_{2.5\text{-}10}$, $PM_{10}$, $PM_{2.5\ Absorbance}$,

BC, $O_3$, $NO_2$, CO, $SO_x$, and $NO_x$ and the differential effects on study-diagnosed dementia subtype (11-20). Importantly, many of these works were either systematic reviews without meta-analyses, included few primary studies in their meta-analysis, had inadequate definitions of case ascertainment, focused exclusively on the relationship between dementia and one (e.g., $PM_{2.5}$), or a limited number of air pollutants, and differed in the strength, significance and direction of association (12, 13, 15-17, 20). Some of these studies focus on particular study-diagnosed subtypes (labelled as AD and vascular dementia (VaD), for example), which are subject to considerable uncertainty when tested against pathological findings after death, including the fact that most dementia in the ninth decade and beyond is mixed in nature, and such pathologies are found in most people who die without having developed dementia (21, 22).

The latest systematic review and meta-analysis were published by Wilker et al. and included 51 studies published up to July 2022, only 16 of which were included in the meta-analysis (19). The authors concluded that there was evidence to support an association between dementia and $PM_{2.5}$ (14 studies), and more limited support for an association with $NO_2$ (9 studies) and NOx (5 studies). Additionally, they did not find a clear association with $O_3$ (4 studies). They assessed most studies to be at high risk of bias. This study provided important estimates but was limited in the number of pollutants included in its meta-analysis with limited data for $NO_2$, and no data for $PM_{10}$, or $BC/PM_{2.5\ absorbance}$. These pollutants are included in our meta-analysis. Secondly, Wilker et al. did not perform a subgroup analysis by dementia study-diagnosed subtype. Finally, it lacked an overall certainty of evidence assessment and a publication bias assessment, which the authors noted as a limitation (19).

Since 2022, a surge in publications has provided an opportunity for a new, more comprehensive systematic review and meta-analysis. The primary aim of this study is to deepen the understanding of the relationship between air pollution and dementia incidence, while bolstering the evidence base for strategies to prevent or delay its onset. New studies include additional pollutants like $NO_2$, $NO_x$, $PM_{10}$, and $BC/PM_{2.5\ absorbance}$, offering a larger data pool for analysis, including subgroup effects, dementia subtype variations, and

potential clarification of earlier inconsistencies and heterogeneities. This expanded data also facilitates assessments of study quality and evidence certainty, and highlights areas for methodological improvement in future research. Ultimately, this study provides updated estimates for future burden of disease and health impact assessments and inform discussions on the mechanisms by which air pollution contributes to dementia, as well as policy on air quality limits and targets.

## Methods

A protocol for this systematic review was published in December 2022 (23), and registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023414413). The deviations from this protocol are listed in Table S1 (Supplementary Material pg. 1) and are mostly minor and more inclusive in nature.

## Literature Search

### *Search Strategy*

Medline (via Ovid), Embase (via Ovid), Cochrane Library, Cinahl (via Ebscohost), Global Health (via Ebscohost), PsycINFO (via Ebscohost), Scopus, and Web of Science (Core Collection) were searched twice (once from inception to October 2022 and again from October 2022 to October 2023) using peer-reviewed and piloted search terms (S1; Supplementary Material pg. 10) developed through a review of existing literature, a selection of indicator papers, and pilot searches, according to the published protocol (23).

### *Eligibility Criteria*

Studies were eligible if they were based on the results of a primary case-control, cohort, cross-sectional, or ecological studies of individuals over 18 years of age, investigated exposure to outdoor air pollution of a year or more (long-term), and quantitatively reported the association between single air pollution exposures and a subsequent physician diagnosis of dementia in adults free of disease at baseline. To be included, cross

sectional studies must have a design adequate to answer the research question 'is there an association between preceding exposure to air pollution and subsequent risk of the selected health outcome reported as incidence or life-time prevalence in healthy/disease-free individuals at baseline?'. In cross-sectional studies, only life-time prevalence was acceptable in previously healthy/disease-free individuals at baseline. We excluded papers that exclusively used outcomes such as cognitive impairment or self-diagnosis of dementia, and papers that did not provide a quantitative exposure estimate or used a proximity model for exposure assessment. Complete inclusion and exclusion criteria are in Table S2 (Supplementary Material pg. 2) and the published protocol (23).

*Selection Process*

Deduplication of the search results was completed in EndNote then Zotero and then Rayyan. Remaining papers were title and abstract screened by two independent reviewers. Papers included by both independent reviewers, or included by one and excluded by the other, underwent full-text screening by two reviewers; any remaining conflict was resolved by a third reviewer. The list of studies excluded at both the title and abstract (Table S7) and full text screening stages (Table S8), alongside the reason for exclusion are included in the supplementary material. The original search included multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis, the topic of another paper, alongside dementia. Following title and abstract screening, papers were divided by outcome for separate data extraction and analysis.

*Data Extraction*

Using a standardised and piloted form through multiple iterations (Table S9), data was extracted independently by two reviewers. Duplicate sheets were compared, and discrepancies were resolved through escalation to and discussion with a third reviewer. Unadjusted and adjusted measures of association (effect estimates) were recorded with their reported 95% confidence intervals, unit of exposure ($\mu g/m^3$, ppb, etc), scaling factor (e.g., 1 $\mu g/m^3$, 5 $\mu g/m^3$, 10 $\mu g/m^3$), and covariates adjustment. Additional data on study type,

location, year, length of follow-up, population, exposure assessment, and funding were also recorded. The complete list of extracted data points is included in S2 (Supplementary Material pg. 15) and includes 41 items per paper. If one paper reported more than one effect estimate per pollutant, the estimate which met pre-specified criteria in the published protocol (Table S3; Supplementary Material pg. 2) was extracted (23). For example, if multiple adjusted effect estimates were reported for an individual pollutant, we extracted the effect estimate with the most restrictive analysis model (i.e., which adjusted for the greatest number of factors), if that adjustment was appropriate. We considered an adjustment to be inappropriate if it included intermediate conditions and/or effect modifiers such as stroke, heart failure, ischemic heart disease, diabetes, and depression. If the only available adjusted effect estimates included such comorbidities, these effect estimates were used, per the published protocol (23). A sensitivity analysis was, however, later run excluding effects estimates which adjusted for comorbidities from the meta-analysis.

If information could not be determined for a paper, we attempted to contact the authors to clarify, and if no response was received after three attempts, we coded it as 'Not Available'.

*Risk of Bias Assessment*

Using the Office of Health Assessment and Translation (OHAT) tool, two independent reviewers assessed Risk of Bias (RoB) for each included study (internal validity), with modifications implemented after piloting the tool at the outset (24). While the OHAT tool includes 11 questions, 4 of these questions were excluded, because they are related to Experimental Animal and Human Controlled Trials, making them inapplicable. For each of the 7 remaining questions, one of the following four answers was selected: definitely low risk of bias, probably low risk of bias, probably high risk of bias, definitely high risk of bias. Discrepancies between reviewers were discussed and a consensus was reached and, therefore, no conflicts or discrepancies needed to be escalated to the third senior reviewer, per the protocol. The full RoB assessment is shown in Table S4 (Supplementary Material pg.3). *Certainty of Evidence Assessment*

Two reviewers rated the confidence in evidence bodies using the OHAT approach for systematic review and evidence integration for literature-based health assessments (24). The studies were grouped together and given an initial confidence rating of "high confidence", "moderate confidence", "low confidence", or "very low confidence" based on study design features which indicate the ability of a study to assess causality. Because observational studies do not have "controlled exposure", one of the four key features in rating certainty of evidence, the highest rating the body of evidence could attain was "moderate confidence" provided they had the other three categories: "exposure prior to outcome", "individual outcome data", and "comparison group used". Since our eligibility criteria selected for certain study design features, the body of evidence had an initial confidence rating of moderate, as all included studies had the other three categories. The confidence rating of the body of studies was upgraded or downgraded based on the presence or absence of various factors. The presence of factors which led to a downgrade in the confidence rating were risk of bias, unexplained consistency, indirectness, imprecision, and publication bias. The presence of factors which led to an upgrade in the confidence rating were a large magnitude of effect, a dose response relationship (i.e., evidence of a gradient), and cross-population and cross-study-design consistency. The certainty of evidence summary is shown in Table S5 (Supplementary Material pg. 6-8).

*Statistical Analysis*

Standardisation

Following data extraction, all papers were combined for statistical analysis. Given that some of the included studies used the same study population, we only included the most recent study with the longest follow-up in meta-analysis to avoid double counting. Meta-analyses were conducted when three or more independent studies reported an exposure-outcome pair (i.e., $PM_{2.5}$ and Dementia, $PM_{10}$ and Dementia). For each pollutant, adjusted and unadjusted effect estimates, and their 95% CI were harmonised to a prespecified exposure increment representing World Health Organization Standards (where no annual WHO guideline values exist, per the protocol, we calculated new concentration increments to approximately equal to 10% of the maximum concentrations encountered in any of the included studies) and entered in a Hartung and

Knapp random-effects model (23). Conversions were conducted using the approach utilized Chen and Hoek (2020), which has previously been used in various meta-analyses related to air pollution exposure (25). This process is detailed in Table S6 (Supplementary Material pg. 9). Conversions between ppb and ug/$m^3$ were completed for $NO_2$, $NO_x$, and $BC/PM_{2.5\ absorbance}$ using the following conversions factors from the Health Effects Institute Special Report: for $NO_2$ x*1.88, for $NO_x$ x*1.55, for $BC/PM_{2.5\ absorbance}$, values recorded in $10^{-5}$/m were converted to ug/$m^3$ using (x*1.1)/1.25 (26). Conversions for $O_3$ (annual) between ppb and ug/$m^3$ were completed using x*1.96 using the conversion factor from the UK Department for Environment, Food & Rural Affairs (27).

Meta-Analysis

The Der Simonian and Laird (DSL) inverse-variance method, with the Hartung Knapp (HK) modification was used to weight the harmonised effects estimates for directness of comparison with other meta-analyses (28). The standard DSL method does not take into account the uncertainty in the estimation of the between-studies variance, which may be high, particularly when the number of studies included in the meta-analysis is low, and hence could result in an inflated false positive rate (29). Therefore, we applied the DSL method with the HK modification, which has been shown to result in a more adequate error rate (30). Based on reasoning reported in previous articles investigating pollutant similarities, and reflected in the included studies, we treated BC and $PM_{2.5\ absorbance}$ as interchangeable in this meta-analysis (31, 32). When outcomes are rare (i.e., <10-20%), the hazard ratio (HR) and odds ratio (OR) can be approximated to a risk ratio (RR) (33). Given that dementia is a rare outcome, pooling the HR and OR together in one meta-analysis in this case was considered acceptable. The analysis of unadjusted effect estimates was designed to give insight into the effects of (residual) confounding factors.

Quantifying Heterogeneity

Between-study inconsistency was assessed using the $I^2$ statistic and the Cochran Q-test (Q). 95% prediction intervals (PIs), calculated from the between-studies variance (tau-squared) and describing a range within

which 95% of true effects are expected to lie, were reported as a more intuitive and interpretable description of the amount of variability in the meta-analysis (34) (35).

### Subgroup Analyses

The published protocol outlined that we would conduct subgroup analyses by geographical location, sex, age, ethnicity, exposure assessment method, outcome definition and ascertainment (23). Not enough papers (≥3) recorded data on sex, age, or ethnicity to conduct subgroup analyses. Therefore, subgroup analyses were undertaken based on continent, exposure assessment method, and outcome definition and ascertainment. Additionally, subgroup analyses by study-diagnosed dementia subtype were completed. While not all subgroups had more than three studies, subgroup analyses with at least two subcategories with three or more studies are commented on in this manuscript, as we considered this to allow for a somewhat meaningful comparison within those groups.

### Sensitivity Analyses

We performed the following sensitivity analyses: 1) excluding studies which were determined to have 'probably high risk of bias'; 2) excluding studies which rely on patient self-report of physician diagnosis for outcome assessment, where the potential of reporting error is higher compared to administrative medical (e.g., hospital) records; 3) using the Paule-Mandel (PM) with the HK modification in place of the DSL, given reports that the DSL is negatively biased in scenarios with small studies and with a rare binary outcome (36); 4) excluding the study with the largest weight (smallest SE) from each meta-analysis; 5) excluding studies with models which were adjusted for co-morbidities. There were two sensitivity analyses which were planned per the protocol but could not be run primarily due to the lack of studies, as detailed in Table S1 (Supplementary Material pg. 1).

## Visualising the shape of the Exposure Response Functions (ERF)

As outlined in our protocol, we planned to formally assess the shape of a pollutant's ERF when four or more independent studies reported an exposure-outcome pair across the exposure range, and those studies included effect estimates for at least three exposure categories, excluding the reference category. However, none of the exposure-outcome pairs met these pre-specified criteria. As a result, we did not formally evaluate ERF shapes, per our protocol, but instead visualised the data, adjusting the thresholds of the three exposure categories to include, rather than exclude, the reference category. Given the limited data, we deemed simple visualisation in this instance more appropriate, reserving methods like cubic splines for future analysis when more robust data becomes available.

## Assessment of Publication Bias

We visually examined publication bias with funnel plots and conducted the Egger's linear regression test to estimate the potential publication bias in cases of ten or more studies, per the protocol.

## Visualisation

The results of all meta-analyses are displayed using forest-plots. The standardisation of effect estimates was only possible for continuous variables.

All data-analysis was conducted in R version 4.2.2 using the “meta”, “dmetar”, “metafor”, “tidyverse”, “readxl”, “ggplot2”, “ggeasy”, “reshape2”, “DescTools”, “tm”, “stringr”, and “dplyr” packages (37-39).

## Role of Funder

The funders had no role in the study design or in the collection, analysis, interpretation of data, writing of the manuscript, or decision to submit the article for publication.

## Results

### *Primary Results*

Our initial search in October 2022 identified 8319 unique publications across eight databases. From this, 141 papers were full-text screened. 107 of those papers were excluded because they were either non-dementia related or met one of the other exclusion criteria. 34 papers published from the inception of the search engine until October 2022, met our inclusion criteria and were included in data extraction. Our secondary search conducted in October 2023 identified 1005 unique publications. 137 papers were identified for full- text screening and 17 were included in data extraction (Figure 1). Across both searches, in total, 51 papers were included.

Table 1 provides a summary of each paper. Most studies began at age 55, 60, or 65. The maximum reported age of a participant was 115 and the minimum reported was 37, though not all studies recorded their minimum and maximum age. Reported follow-up periods ranged from a minimum of 3 to a maximum of 22.7 years, though most studies reported follow-up either as a median or mean.

20 studies were conducted in Europe, 17 in North America, 12 in Asia, and 2 in Australia. 43 studies reported on dementia, 26 on AD, 17 on VaD, 1 on frontotemporal dementia (FTD), and 1 on mixed VaD/AD. Whether each paper was included in the meta-analysis was also documented in Table 1.

Forty studies reported on $PM_{2.5}$, 28 on $NO_2$, 17 on $PM_{10}$, 12 on $NO_x$, 10 on $BC/PM_{2.5\ absorbance}$, 10 on annual $O_3$ ($O_3$ was separated between warm season and annual), and 6 on $PM_{2.5-10}$. All studies except 3 were cohort studies. Of those 3, 1 was a case-control study (Wu et al. (2015)), and 2 combined cohort data with a nested case-control (Li et al. (2019) and Yuchi et al. (2020)).

Exposure assessment methods varied across studies and were divided into seven categories, based on an assessment of included papers and relevant literature on exposure assessment methods (40-42). The most popular method was Land Use Regression Models (LURs). Other methods included dispersion models, chemical transport models (CTMs), spatial interpolation techniques, statistical or machine-learning models (separate from LUR), monitoring station data, and hybrid models which combined a number of these approaches in one.

Five studies relied on some form of patient self-report of physician dementia diagnosis (at times validated by medical records), while the remaining 46 used a variety of methods including review of medical records, neuropsychological exams, and validated algorithms of health records to determine if an individual had a diagnosis of dementia, AD, VaD, or FTD (43-47). The reviews of medical records were either based on DSM (Diagnostic and Statistical Manual of Mental Disorders) coding or ICD (International Classification of Diseases) billing codes.

The RoB and Certainty of Evidence results are displayed in Tables S4 and S5. Only seven studies recorded a probably high RoB in one category, either for the use of some form of self-report of a physician diagnosis, a failure to report some analyses outlined in their methods, or the use of a non-peer reviewed categorization of pollutant exposure (qualifying under the category of "other bias") (43-49).

*Meta-analysis*

Several of the 51 papers used the UK Biobank population or other large cohort populations (Medicare, Betula Cohort, GEMS, 3C Population, EHS: Taiwan, SALSA, WHIMS, NHIRD). While all papers were included for data extraction and the systematic review, per the protocol, only the most recent paper with the longest follow-up was selected for the meta-analysis. This led to the removal of ten papers from the meta-analysis solely for reasons of population overlap: Andersson et al. (2018), Chen et al. (2023), Ran et al. B (2021), Yuan et al. (2023), Ma et al. (2023), Chang et al. (2014), Raichlen et al. (2022), Cacciottolo et al. (2017), Li et al. (2022), Dimakakou et al. (2020)) (7, 10, 47, 50-56). A detailed explanation of the exclusion due to population overlap is provided in S18 (Supplementary Material pg. 53-54).

Following the removal of papers based on the same population, 41 remained for the meta-analysis. An additional paper (Xie et al. 2023) was removed from the meta-analysis due to a failure to record a CI in their presentation of the data bringing the final number of papers to 40 (58). Of those 40, 34 recorded pollutant-exposure pairs that reached the threshold of 3 or more papers and where therefore recorded in the meta-analysis results. The 34 papers included in the meta-analyses originated from 11 countries: 15 originated in North America, 10 in Europe, 7 from Asia, and 2 from Australia

**$PM_{2.5}$**

For $PM_{2.5}$, 21 studies were included in the meta-analysis. The pooled effect estimate per 5 μg/m³ was 1.08 (95% CI: 1.02 to 1.14; Figure 2). The $I^2$ was 95% and Q was statistically significant ($p<0.01$). The PI was 1.00 to 1.16.

Two studies in the pooled analysis had wide CIs. These values were rescaled to per 1 μg/m³ and then manually checked. The wide CIs were determined to be the result of scaling up; the CIs were wide for

small increases in $PM_{2.5}$ exposure (per 0.88 μg/m$^3$ for Grande et al. (2020); per 1 μg/m$^3$ for Sullivan et al. (2021)) compared to the other included studies and scaling them up to per 5 μg/m³ made them even wider.

**$NO_2$**

For $NO_2$, 16 studies were included. The pooled effect estimate per 10 μg/m$^3$ was 1.03 (95% CI: 1.01 to 1.05; Figure 3). The $I^2$ was 84% and Q was statistically significant ($p<0.01$). The PI was 1.00 to 1.07.

**$NO_x$**

For NOx, 5 studies were included. The pooled effect estimate per 10 μg/m$^3$ was 1.05 (95% CI: 0.97 to 1.13; Figure 4). The $I^2$ was 44%, Q was not statistically significant ($p=0.13$), and the PI was 0.92 to 1.19.

**$BC/PM_{2.5\ Absorbance}$**

For $BC/PM_{2.5\ Absorbance}$, 6 studies were included. The pooled effect estimate per 1 μg/m³ was of 1.13 (95% CI: 1.01 to 1.27; Figure 5). $I^2$ was 97%, Q was statistically significant ($p<0.01$), and the PI was 0.72 to 1.78.

**$PM_{10}$**

For $PM_{10}$, 4 studies were included. The pooled effect estimate per 15 μg/m$^3$ was 1.52 (95% CI: 0.80 to 2.87; Figure 6). $I^2$ was 82%, Q was statistically significant ($p<0.01$), and the PI was 0.20 to 11.61.

**$O_3$ (annual)**

For annual $O_3$, 4 studies were included. The pooled effect estimate per 45 μg/m$^3$ was 0.82 (95% CI: 0.35 to 1.92; Figure S3A; Supplementary Material pg. 16). $I^2$ was 69%, Q was statistically significant ($p=0.02$), and the PI was 0.17 to 3.95.

No other pollutants reached the threshold of three studies for meta-analysis. Across these primary analyses, $I^2$ was 69% and above for $PM_{2.5}$, $PM_{10}$, $O_3$, $NO_2$, $BC/PM_{2.5\ Absorbance}$ and 44% for $NO_x$, implying that the variability in effect size estimates may be due to sampling error. However, $I^2$ may be less reliable with fewer included studies. The PIs for $PM_{2.5}$ and $NO_2$ did not dip below one, lending further support to the significance of those results.

*Subgroup Analysis*

By Subtype of Dementia

When analysed by study-diagnosed subtype of dementia, the pooled effect estimate for $PM_{2.5}$ was 1.09 (95% CI: 1.01 to 1.19) for AD, while for VaD it was 1.50 (95% CI: 0.69 to 3.26) per 5 $\mu g/m^3$ (Figure S4A; Supplementary Material pg. 17). Heterogeneity was high in both subgroups. While larger in magnitude, the effect estimate for VaD was not statistically different from that for AD (p=0.13).

For $NO_2$, the effect estimate for AD was 1.03 (95% CI: 0.93 to 1.15) while for VaD it was 1.13 (95% CI: 1.02 to 1.26) per 10 $\mu g/m^3$ (Figure S4B; Supplementary Material pg. 18). Though different in magnitude, the difference was not statistically significant between the subgroups (p=0.20).

For $BC/\ PM_{2.5\ Absorbance}$ the effect estimate for VaD was 1.26 (95% CI: 0.95 to 1.66) and was higher than AD at 1.14 (95% CI: 0.85 to 1.52) per 1 $\mu g/m^3$ (Figure S4C; Supplementary Material pg. 19). The difference was not statistically significant (p=0.41).

For $PM_{10}$, the effect estimate for VaD was 1.01 (95% CI: 0.74 to 1.37) and was lower than AD at 1.20 (95% CI: 0.60 to 2.40) per 15 $\mu g/m^3$ (Figure S4D; Supplementary Material pg. 20). The difference was not statistically significant (p=0.31).

By Continent

When analysed by continent, the effect estimate per 5 μg/m$^3$ $PM_{2.5}$ was 1.39 (95% CI: 0.80 to 2.44) for Europe, and 1.07 (1.01 to 1.13) for North America, with substantial heterogeneity in each of the continents. While the effect estimates differed across continents, the difference was not statistically significant (p=0.56; Figure S5A; Supplementary Material pg. 21). For $NO_2$, the effect estimate for Europe was 1.09 (95% CI: 0.96 to 1.23), while for North America it was 1.02 (95% CI: 1.01 to 1.04) per 10 μg/m$^3$ (Figure S5B; Supplementary Material pg. 22). Inconsistency was lower in the European subgroup, but heterogeneity was high in both analyses. This difference between subgroups was not statistically significant. There were two few studies to comment on $BC/PM_{2.5\ absorbance}$ (Figure S5C; Supplementary Material pg. 23).

By Exposure Assessment Methods

When analysed by exposure assessment method, the difference between the pooled effect estimates for $PM_{2.5}$ was not statistically significant (p=0.47; S6A; Supplementary Material pg. 24). Only the pooled effect estimates from studies which used LUR models or hybrid models, the subgroups with the largest number of studies, remained close to statistically significant. The difference between subgroups for $NO_2$ was close to statistically significant (p=0.07), though only the LUR subgroup remained statistically significant on its own, and it was the category with the largest number of studies (S6B; Supplementary Material pg. 25).

By Outcome Ascertainment Methods

For $PM_{2.5}$ the pooled effect estimates differed significantly (p=0.02) between outcome ascertainment methods (S7A; Supplementary Material pg. 26). Only the pooled effect estimates from studies which used medical records and a hybrid method, the subgroup with the largest number of studies, remained statistically significant. The other subgroups of studies (used physician diagnosis, Administered Exams) had larger, non-statistically significant pooled effect estimates but a much smaller number of studies. For $NO_2$, the

pooled effect estimates did not differ significantly between outcome ascertainment methods (p=0.51) and none of the subgroups remained statistically significant (S7B; Supplementary Material pg. 27).

Additional Subgroup Analyses

Due to the small number of studies that met the inclusion criteria for some pollutants, no further subgroup analyses could be conducted for those pollutants.

*Sensitivity Analyses*

Additionally, while we outlined that we would conduct sensitivity analyses by study design, this was not feasible as the three studies that used some form of case-control study design only recorded values for AD and VaD (Yuchi et al. (2020) only used nested case-control for their AD results) (59-61).

Paule-Mandel Estimator instead of Der-Simonian and Laird

Use of the PM estimator instead of the DSL yielded variable changes in the effect estimates but no changes to our conclusions. The effect estimate for dementia and $PM_{2.5}$ was much higher (1.43 (95% CI: 1.05 to 1.96)) (S8A; Supplementary Material pg. 28). For dementia and $PM_{10}$, it was slightly lower (1.47 (95% CI: 0.77 to 2.79) (S8B; Supplementary Material pg. 29). For $NO_2$, it was marginally higher (1.05 (95% CI: 1.01 to 1.09)) (S8C; Supplementary Material pg. 30), while for NOx, the PM only slightly raised the pooled effect estimate (1.06 (95% CI: 0.96 to 1.16)) (S8D; Supplementary Material pg. 31). In all PM cases, the confidence intervals and PIs were wider than with the DSL, except for $PM_{10}$ where both the confidence interval and the PI were narrower.

Removal of Self-report

Of the studies included in the meta-analysis, both Wood et al. (2022) and Trevenen et al. (2022) relied on patient self-report of a physician diagnosis, and both were removed from the analysis (the others: Parra et

al. (2022), Mukadam et al. (2022) and Dimakakou et al. (2020) also relied on self-report, validated with the UK Biobank algorithm, but were not included in the meta-analysis due to an overlap in population and/or insufficient number of studies for their exposure-outcome pairs).

For $PM_{2.5}$, the removal of these two papers altered the CI of the pooled effect estimate from 1.08 (95% CI: 1.02 to 1.14) to 1.08 (95% CI: 1.02 to 1.15) (S9A; Supplementary Material pg. 32). Given that Wood et al. (2022) was 35.8% of the weight in the meta-analysis of $PM_{10}$ and dementia, the pooled effect estimate changed from 1.52 (95% CI: 0.80 to 2.87) to 1.83 (95% CI: 1.31 to 2.55) with the removal of that study (S9B; Supplementary Material pg. 33). For $NO_2$, the removal of both papers changed the CI of the pooled effect from 1.03 (95% CI: 1.01 to 1.05) to 1.03 (95% CI: 1.01 to 1.06) (S9C; Supplementary Material pg. 34). For BC/ $PM_{2.5\ absorbance}$ the removal of Trevenen et al. (2022) increased the pooled effect estimate from 1.13 (95% CI: 1.01 to 1.27) to 1.15 (95% CI: 1.00 to 1.32), however it rendered it non-statistically significant (S9D; Supplementary Material pg. 35). The meta-analysis could not be conducted for annual $O_3$ because with the removal of Wood et al., it no longer met the criteria for analysis. Trevenen et al. (2022) and Wood et al. (2022) did not appear in other meta-analyses.

Excluding Studies with High Risk of Bias

All five studies which relied on some form of self-report of a physician diagnosis received a probably high risk of bias rating in the detection domain: Wood et al. (2022), Trevenen et al. (2022), Parra et al. (2022), Mukadam et al. (2022), and Dimakakou et al. (2020). In addition, two other studies received a rating of probably high risk of bias in one domain (He et al. (2022) and Ilango et al. (2020)). A sensitivity analysis was conducted, per the protocol, by excluding those that reported a high risk of bias in one domain (He et al. (2022), Parra et al. (2022), Mukadam et al. (2022) and Dimakakou et al. (2022) did not appear in any primary meta-analyses). Removing Ilango et al. (2020), Trevenen et al. (2022), and Wood et al. (2022) altered the pooled effect estimate for $PM_{2.5}$ from 1.08 (95% CI: 1.02 to 1.14) to 1.08 (95% CI: 1.01 to 1.15)

(Figure S10A; Supplementary Material pg. 36). For $NO_2$, removing Ilango et al. (2020), Trevenen et al. (2022), and Wood et al. (2022) altered the upper end of the confidence interval (from 1.03 (95% CI:1.01 to 1.05) to 1.03 (95% CI: 1.01 to 1.06) (S10B; Supplementary Material pg. 37). For $PM_{10,}$ removing Wood et al. (2022), increased the effect estimate from 1.52 (95% CI: 0.80 to 2.87) to 1.83 (95% CI: 1.31 to 2.55), though the number of included studies reduced from four to three (Figure S10C; Supplementary Material pg. 38). For $BC/PM_{2.5\ Absorbance}$, removing Wood et al. (2022) increased the pooled effect estimate, however it rendered it non-statistically significant (from 1.13 (95% CI: 1.01 to 1.27) to 1.15 (95% CI: 1.00 to 1.32) (Figure S10D; Supplementary Material pg. 39). No studies were removed from the $NO_{x,}$ meta-analysis.

Excluding the Study with the Largest Weight

Excluding the studies with the largest weights had very little impact on the overall pooled effect estimates for $PM_{2,5}$ , $NO_2$ , $NO_{x,}$ and $O_3$ as demonstrated in the leave one out sensitivity analysis (Figure S11A,B,C, F; Supplementary Material pgs. 40-41). For $BC/PM_{2.5\ absorbance}$, omitting Shi et al. (2023), which was 24% of the weight, lowered the confidence interval from 1.13 (95% CI: 1.01 to 1.27) to 1.06 (95% CI: 0.96 to 1.17) per 1 $\mu g/m^3$. Generally, the $BC/PM_{2.5\ absorbance}$ meta-analysis was sensitive to omitting individual papers in the leave one out sensitivity analysis (Figure S11D; Supplementary Material pg. 42). Omitting Wood et al. (2022) in the $PM_{10}$ analysis, which was 35.8% of the weight, shifted the pooled effect estimate away from the null from 1.52 (95% CI: 0.80 to 2.87) to 1.83 (95% CI: 1.31 to 2.55) (Figure S11E; Supplementary Material pg.42). Removing Zhang, B. et al. (2023) from the $O_3$ analysis lowered the pooled effect estimate from 0.82 (95%CI: 0.35 to 1.92) to 0.76 (95% CI: 0.12 to 4.90) (Figure S11F; Supplementary Material pg. 42).

Excluding Studies which Adjusted for Comorbidities

Excluding the studies which adjusted for comorbidities in their models from the meta-analysis had small effects on the overall pooled effect estimates for $PM_{2.5}$ , $NO_2$, $NO_x$ and $PM_{10}$ and did not change our

conclusions (Figure S12 A-C and E; Supplementary Material pg.43,44). For BC/$PM_{2.5\ absorbance}$, the removal of Yuchi et al. (2020) and Zhang, Z. et al. (2023) raised the effect estimate from 1.13 (95% CI: 1.01 to 1.27) to 1.18 (95% CI:1.00 to 1.39), though it rendered it non-significant (Figure S12D; Supplementary Material pg. 44).

Assessments of Publication Bias

Only $NO_2$ and $PM_{2.5}$ and dementia reached the threshold of ten studies for assessing small studies effects and using Egger's linear regression test. The studies for $PM_{2.5}$ are asymmetrical, with a large concentration of studies near the top with very low standard error (Figure S13A; Supplementary Material pg. 45). There are a few studies on the right-hand side of the graph with no studies to balance it out in the left-hand, suggesting there may be studies missing due to publication bias. The results of Egger's linear regression test (2.29, p=0.03) provide further evidence of funnel plot asymmetry. In a symmetrical funnel plot, studies with negative or non-significant effect sizes would likely appear on the left-hand side of the plot. The asymmetry indicates that fewer studies are reporting smaller or negative effects, which could either be due to publication bias or scarcity of such studies due to the presence of a true positive effect. The $NO_2$ studies are less asymmetrical and there is a suggestion of missing studies on the left-hand-side of the plot, again indicating potential publication bias (Figure S13B; Supplementary Material pg.46). The intercept of 1.19 (p=0.10) from Egger's linear regression test does not differ significantly from zero. Again, these results may indicate a true positive effect.

Categorical Exposure Response Functions (ERFs)

Five studies reported categorical effect estimates for $PM_{10}$ and AD, though for differing ranges of exposures (Figure S14A; Supplementary Material pg. 47). Two studies reported monotonic relationships (He et al. (2022), and Wu et al. (2015)), while the remaining three reported non-monotonic relationships. Four studies reported categorical effect estimates for $NO_2$ and AD, again for differing ranges of exposures. One study

reported a monotonic relationship (Chen et al. (2023)) and the other three reported non-monotonic relationship (Figure S14B; Supplementary Material pg. 47). Four studies reported categorical effect estimates for $PM_{2.5}$ and AD. Two reported monotonic relationships (Chen et al. (2023), and He et al. (2022)) and two reported non-monotonic relationships (Figure S14C; Supplementary Material pg. 48). We determined that the data would not yield a more meaningful synthesis than the visual presentation in Figures S14A-C. No other pollutant-outcome pairs reached the threshold of four papers (excluding studies with population overlap in line with our overall meta-analysis conduct).

## Discussion

This systematic review and meta-analysis found that there is a positive and statistically significant association between $PM_{2.5}$, $NO_2$, $BC/PM_{2.5\ absorbance}$, and the incident dementia in disease-free individuals at baseline. There was no evidence for an association with incident dementia for $NO_x$ , $PM_{10}$ and annual $O_3$ based on a limited number of studies. These results are in line with findings of recent meta-analyses which largely focused on the associations between $PM_{2.5}$ and dementia. We also produce new evidence in support of significant associations between $NO_2$, $BC/PM_{2.5\ absorbance}$ and dementia.

Abolhasani et al. reported a significant association between $PM_{2.5.}$ and dementia (1.03 (95% CI: 1.02 to 1.05) per 1 $\mu g/m^3$), a borderline statistically significant result with $NO_2$ (1.03 (95% CI:1.00 to 1.07) per 10 $\mu g/m^3$) and some evidence of association with $NO_x$ (1.05 (95% CI: 0.99 to 1.13) per 10 $\mu g/m^3$) (18). Similarly, Wilker et al. found evidence of an association between $PM_{2.5}$ and dementia (1.04 (95% CI:0.99 to 1.09) per 2 $\mu g/m^3$), with higher associations when restricting the meta-analysis to the 7 studies that used active case ascertainment (1.42 (95% CI: 1.00 to 2.02) per 2 $\mu g/m^3$), and a suggestive but non-significant association with $NO_2$ (1.02 (95% CI: 0.98 to 1.06) per 10 $\mu g/m^3$) and $NO_x$ (1.05 (95% CI: 0.98 to 1.13) per 10 $\mu g/m^3$) (19). Notably, our meta-analysis included more studies than in both these meta-analyses. This review therefore strengthens the accumulating evidence for an association with $PM_{2.5}$, adding 7 studies to the most recent meta-analysis by Wilker et al. (2023), and it builds on recent insufficient, but suggestive, evidence for associations with $NO_2$ and $NO_x$, and provides new evidence for $BC/PM_{2.5\ absorbance}$.

For all pollutants except $NO_x$, there was significant heterogeneity across the included studies. This likely reflects the range in the exposure assessment methods, the outcome ascertainment methods, the demographic characteristics of the study populations, the varying geographical and socioeconomic contexts of the studies, differences in the air pollution composition, and potentially underlying susceptibility factors. Large parts of this may be due to a lack of standard methods to assess exposure to air pollution in addition

to the limitations of standard methods such as their inability to capture personal mobility and associated exposures, the effects the clinical heterogeneity of dementia has on standardising case ascertainment and diagnosis, as well as potentially true differences in response. Subgroup analyses revealed that the pooled effect estimate $PM_{2.5}$, $BC/PM_{2.5\ absorbance}$, and $NO_2$ and VaD were higher compared to AD, although not statistically significant. Meta-analyses had previously been completed for $PM_{2.5}$ and AD/VaD and found similar results, but not for the range of pollutants analysed here (62).

The subgroup analyses by continent indicate that there are also potential differences in $NO_2$, $PM_{2.5}$ and $BC/PM_{2.5\ Absorbance}$ effect estimates between continents, though none of the differences were statistically significant. For $NO_2$ in particular, the difference may speak to different $NO_2$ sources across continents, for example, the larger share of diesel vehicles in Europe versus in North America. Additional subgroup analyses by exposure assessment method indicate differences in effect estimates between exposure assessment methods for $NO_2$ and $PM_{2.5}$ with a close to statistically significant result ($p=0.07$ for $NO_2$). Differences in pooled effect estimates were also noted between outcome ascertainment methods for both pollutants, with the difference reaching statistical significance in the case of $PM_{2.5}$. These results indicate that additional research into exposure assessment methods prior to future meta-analyses may be necessary to assess whether certain exposure assessment perform better for capturing effects, and further attempts should be made to capture the true variance in the exposure of participants. Initial reports indicate that the performance of LUR, Bayesian maximum entropy (BME), or mixed models is affected by the temporal scale and degree of spatial heterogeneity. Therefore, the preferred model for a given environment depends on several contextual factors (63-65). The results on outcome ascertainment method may reflect the differences in the number of studies using each outcome ascertainment method (with those not reaching statistical significance having fewer studies). However, future work should focus on producing high quality reproducible outcome ascertainment methods that can be applied across different populations.

The results from the sensitivity analysis using the PM estimator were very similar to those in the primary analysis, except for $PM_{2.5}$, where the point estimate of the effect size was higher and the confidence interval wider. It has previously been shown that in some circumstances the PM estimator can introduce substantial positive bias while the DSL method may be negatively biased, so the true effect may lie somewhere in between (66). The remaining sensitivity analyses supported this paper's primary findings for all pollutants except $BC/PM_{2.5\ absorbance}$, as removing studies with patient self-report of physician diagnosis, studies with a rating of probably high risk of bias in one domain, studies with co-morbidities, and studies with the largest weight in the meta-analysis did not alter the conclusions. However, for $BC/PM_{2.5\ absorbance}$, removing the studies with self-report of physician diagnosis, studies with a rating of probably high risk of bias in one domain, and those with co-morbidities made the results non-significant, indicating that those results should be viewed more critically. Finally, the leave one out sensitivity analysis showed rather robust pooled effect estimates for all pollutants, except for $PM_{10}$ and $BC/PM_{2.5\ Absorbance}$, which was sensitive to the removal of individual studies. Future work when more data on the associations with $BC/PM_{2.5\ Absorbance}$ becomes available will be useful in elucidating that association.

*Findings in Context*

Epidemiological evidence plays a crucial role in building evidence for a causative relationship between air pollution and dementia. Our findings contribute to this case for a causal relationship, and complement evidence for the biological plausibility of the association (67). Several mechanisms have been proposed to explain how air pollution may cause dementia, though this remains an active area of research, and a comprehensive review of these mechanisms is beyond the scope of this paper. These mechanisms primarily involve neuroinflammation and oxidative stress, both of which play a well-established role in the pathogenesis of dementia (68-70). Air pollution is thought to trigger these processes through direct entry to the brain or via the same systemic effects that impact the risk of lung and cardiovascular diseases (71-73).

Neuropathological evidence of direct brain entry of air pollution exists across species in both animal and human studies. Dogs living in cities with high levels of air pollution were found to have metal accumulation in a gradient from olfactory mucosa to frontal cortex, suggesting the olfactory mucosa and nerve as a point of entry (73, 74). Blood-brain barrier disruptions, reactive astrocytosis, and neurofibrillary tangles are seen on electron microscopy of samples of the dogs' brains, matching the pathology seen in brains of humans with AD (74). Moreover, in rodent models, exposures to certain air pollution components were found to cause transcriptional activation of NF-kB, a key pro-inflammatory transcription factor, which may promote sustained production of neurotoxins such as reactive oxygen species through downstream activation of pathways including enzymes such as NADPH oxidases (72). Similar findings have been replicated in humans: on autopsy, compared to controls, children and young adults in a city with high air pollution have visible particulate matter in their olfactory bulb and increased expression of pro-inflammatory factors including cyclooxygenase-2, interleukin-1-beta, NFkB, and CD14 in their olfactory bulb, frontal cortex, substantia nigrae, and/or vagus nerves (75). Other cases saw evidence of tau hyperphosphorylation and amyloid-beta plaques, increased expression of NFkB, tumour necrosis factor (TNF), interferon (IFN) and toll-like receptors, as well as frontal disruption of the blood brain barrier (75, 76).

Beyond direct brain entry, systemic pathways may also contribute to the pathogenesis of dementia. Air pollutants can enter circulation from the lungs and travel to solid organs, initiating local and wide-spread inflammation (77-79). Ozone provides an example of how transcriptional modification may occur via indirect effects. There is evidence from mouse models that ozone causes a peripheral immune response after entry through the lungs, involving the upregulation of factors such as the High Mobility Group Box 1 (HMGB1) protein (72, 80). This impairs the protective microglial response in the brain by reducing the expression of the triggering receptor expressed on myeloid cells 2 (TREM2), leading to increased accumulation of amyloid-beta plaques in a dose-dependent manner. Recently, research identified additional mechanisms, such as increased pulmonary production of lipopolysaccharide (LPS), which disrupts

305 microglial signalling and polarisation. This adds to the growing evidence that peripheral circulating factors
306 contribute to microglial dysregulation (81, 82). Air pollution has also been found to directly induce protein
307 misfolding, which may contribute to neurodegeneration through the endoplasmic reticulum stress response
308 (83).
309
310 With relevance to VaD, previous literature has demonstrated the strong association between air pollution and
311 cardiovascular disease and stroke; this may represent a significant intermediate mediator of the effect of air
312 pollution which may combine with direct effects (49, 84, 85). However, it is worth noting that alongside
313 causative mechanisms which are thought to be unique to AD, cardiovascular disease is also associated with AD,
314 and not just VaD (86, 87). Our findings therefore contribute to building the evidence-base for a causal link
315 between air pollution and dementia, including AD and VaD, by providing epidemiological evidence supporting
316 putative and biologically plausible mechanisms of air pollution's action on neurodegeneration (67).
317
318 The effect estimates for AD were smaller than for VaD (except in the case of $PM_{10}$), although the difference
319 between these subgroups was non-significant. However, there are several important considerations to
320 contemplate when interpreting this finding. Firstly, the subgroup analyses are still limited by the small
321 number of included studies and generally lack statistical power. Secondly, most of the studies do not make
322 a pathological diagnosis of either AD or VaD, but rather rely on non-validated, non-standardised methods
323 of diagnosis which are not the clinicopathological diagnosis required to make an accurate subtype grouping
324 (86, 88). Even if a pathological diagnosis is present, there is often poor correlation between pathological
325 features on post mortem and a clinical diagnosis (21). Thirdly, there is increasing recognition that AD and
326 VaD, although distinct clinical entities, often co-exist as a form of 'mixed dementia' and likely exist at
327 different points on a single spectrum, and potentiate each other (21, 89-91). This means that there are
328 significant barriers to being able to conclude this is a true effect. Notwithstanding these concerns over the
329 boundaries and diagnosis of these disease entities, there may be several additional explanations of this
330 result.

There may be differences in the rate of case ascertainment between VaD and AD in the included studies which may have contributed, at least partially, to this difference. This is made more likely by the fact that VaD and AD may follow different clinical trajectories, which affect the point at which a diagnosis is sought, the rate at which symptoms appear, the method of diagnosis, and whether someone is diagnosed with a particular subtype of dementia (92, 93). Accordingly, we cannot assume that we have captured the true effect of these pollutants on the development of AD and VaD to the same degree (86, 87). Notably, there was substantial heterogeneity in the effect estimates with respect to AD, but generally less for VaD (except in the case of $PM_{2.5}$ where both VaD and AD had high heterogeneity). This suggests that there may be considerable heterogeneity in the clinical aspect of the disease, or the methodology of assessing exposure and outcome, or likely both. It is unclear why this heterogeneity seems more prominent for AD and whether additional data would paint a different picture; this is made even more surprising by the fact that VaD is generally more variable in its clinical presentation and has diagnostic criteria which has evolved more recently when compared to AD (94, 95). This difference seems to exist even within the context of a lack of overall standardisation of dementia subtype diagnosis. However, this subgroup analysis is informative to the extent that it is consistent with the fact that vascular risk factors and cardiovascular disease, including stroke, are often used to make a differential diagnosis of VaD (96), and therefore, may represent the recognised impact of air pollution on cardiovascular disease (85). We emphasise the need to develop consistent and standardised ways of dementia case ascertainment and more accurate methods for subtype grouping.

We also investigated how the association of $NO_2$, BC/$PM_{2.5}$ absorbance, and $PM_{2.5}$ with dementia varied by continent, although these differences were not statistically significant. This difference in the effect of could be due to the sources of air pollution. For example, while the transport sector is the largest source of $NO_2$ worldwide, more diesel than gasoline is burned in Europe compared to North America and a typical diesel car emits much more $NO_2$ than a gasoline-powered car (54, 55). These results replicate findings by Wilker et al. (2023), who also showed higher effect estimates in Europe when compared to North America

and noted that low exposure variance studies were based in Europe which may have led to the larger effect estimates in that region (19). Further investigation is necessary to understand the source of this difference.

*Limitations*

Firstly, there are limitations with respect to the studies included. A substantial limitation in air pollution and health research lies in the modelling of human exposure. Although assessment methods may effectively estimate air pollution exposure at the selected spatial resolution, they fail to capture individual/personal exposure variations due to individual movements throughout time and space and differences in dosage from varying inhalation rates by age, sex, race, nostril shape, and physical activity levels which all contribute to particle deposition in the body (75). The use of home address as a proxy for exposure assessment disregards time spent at work, other settings, or during commuting, which are exposure micro-environment that vary between individuals (97-99). This limitation may bias the results towards the null. Despite individual-level limitations, the pooled effect estimates derived from this analysis provide valuable insights into the population-level impacts and would allow the estimation of potential benefits of regulatory interventions. There is a need, however, to further refine exposure assessment methodologies and enhance their accuracy, reliability and representation of more complex real-world conditions.

The exposure assessment methods used, and the durations they are modelled for, additionally introduce uncertainty to the results presented in this study. The included papers used a variety of exposure assessment methods (including LUR, Dispersion models, CTM, etc.). Each model incorporates various uncertainties based on their set-up, input data, calculations, and underlying assumptions, and they accordingly have varying performances, including by air pollutant, and are fit for different purposes and geographical contexts. In addition to uncertainties stemming from the choice of exposure assessment methods, further uncertainty arises from the differences in time windows used in the included studies. Exposure windows ranged from a minimum of one year to a maximum of 22 years, with studies representing nearly every

duration within this range (44). Additionally, several studies also reported effect estimates for multiple exposure windows (e.g., 1, 3, and 5 years). These studies which provide such data include Shim et al. (2023), Li et al. (2019), and Zhang, B et al. (2023) (59, 100, 101). Per the protocol, we selected the model which related to the longest or most cumulative exposure window during the follow-up period with the assumption that this is the most relevant biological window. However, with the data we extracted, future research could assess how the different exposure windows within these papers compared to provide a more nuanced discussion of relevant exposure windows and their influence on the reported associations. Exploring the impact of these windows across different pollutants could provide insights into any varying temporal sensitivity of the associations. Since the confidence intervals in this meta-analysis do not account for uncertainty stemming from the different exposure assessment methods, they should be interpreted with caution, as they may underestimate the true extent of uncertainty present in models.

There are known and widespread limitations in the commonly used exposure assessment methods to examine the health effects of air pollutants. Specifically, although this paper looks at single pollutant models, air pollution exists as a complex mixture of multiple correlated pollutants, and the measurements of pollutants do not exist as mutually distinct categories. Although we may be tempted to conclude that some pollutants have stronger evidence linking them to dementia than others, an important consideration is the validity of the almost ubiquitous approach of treating exposure to each pollutant as occurring in isolation and being independent of other pollutants. This caution should frame our results. Exposure to air pollution occurs almost exclusively as a mixture, which makes interpretation of single pollutant models challenging. Reporting an association between a single pollutant and dementia may disregard the presence of interactions between pollutants, including permissive and synergistic effects (102-104). Categories of air pollutants are not mutually distinct: for example, major contributors and precursors to particulate matter include nitrogen oxides (105). This represents a major gap in our understanding and shortcoming of our methodology, which will be challenging to address: various approaches have been suggested but are challenging to implement

partly due to the correlated nature of exposures (102, 106-108). Per the protocol, if three or more studies reported on the same multi-pollutant models, we aimed to conduct an additional multi-pollutant assessment. The only multi-pollutant model for which there were sufficient studies to explore the relationship was $PM_{2.5}$, controlling for $NO_2$ (Yu et al. (2023), Smargiassi et al. (2020), Yan et al. (2022)). We find no evidence of a significant relationship in this pooled analysis (1.02, 95% CI: 0.99 to 1.05) (S15A; Supplementary Material p.49). We recommend future research undertake this to investigate and further assess how the multi-pollutant models compare to the single-pollutant models that were included in this review to provide more robust insights into the relationship between these pollutants and the outcome of dementia.

Furthermore, the papers with data on participants' ethnicity revealed that they were majority White. This is a limitation for the generalisability of results since there is evidence that marginalised groups have a higher exposure to air pollution which is not fully explained by socioeconomic status or geography (109, 110). This difference is made more significant by the evidence that reducing air pollution exposure has a higher benefit for reducing mortality for such marginalised groups (111, 112). Three studies reported effect estimates by ethnic group Mukadam et al. (2022), in their analysis for $PM_{2.5}$ and dementia, found a higher effect estimate for the Black population (1.38 (95% CI: 0.82 to 2.34) for those above 10 $ug/m^3$ compared to those below 10 $ug/m^3$) compared to White (1.06 (95% CI: 1.00-1.12)) and South Asian populations (0.97 (95% CI: 0.97 to 1.66)) (46). Younan et al. (2022), in their analysis of $PM_{2.5}$ and AD, similarly found a higher effect estimate for the Black population (2.11 (95% CI: 1.30 to 3.44) per 3.73 $ug/m^3$) compared to the White population (1.07 (95% CI: 0.84 to 1.38)) (113). In contrast, Zhang, B. et al. (2023) in their analysis of $PM_{2.5}$ and dementia found a higher effect estimate for non-hispanic White (1.13 (95% CI: 1.03 to 1.23) per 3.7 $ug/m^3$) compared to non-hispanic Black (1.03 (95% CI: 0.91 to 1.17)), and Hispanic (1.04 (95% CI: 0.95 to 1.14)) (100). While these studies lend some insights into the potential differing association between air pollution and dementia incidence across ethnicity, future work should ensure better and more

adequate representation across ethnicities. Additionally, most of the studies are based in high-income countries.

The above factors together limit the generalisability of our results, as the particular social and structural context, such as level of education and socioeconomic status, as well as the prevalence of other comorbidities and life expectancy of a population, mediates the effect of air pollution on dementia. This has implications for addressing inequalities in burden of disease across countries but the problem of addressing health inequalities is preceded by the problem of defining them and the current dearth of studies into risk factors such as air pollution for dementia in low- and middle-income countries.

Secondly, there are limitations with respect to the meta-analysis process. The conversion of hazard ratios to the same exposure increment assumed constant ambient temperature and pressure, which may introduce inaccuracies due to natural fluctuations in temperature and pressure throughout the year (114). However, given the lack of specific information from the included studies, these conversions were deemed the most appropriate approach and follow standard analytical practices. There are also further relevant study population characteristics future work should investigate, such as whether rural and urban settings are equally represented and if observed effects differ between those settings. This represents a potential source of confounding bias, as well as being relevant to health inequalities. Similarly, we have recorded whether studies adjusted for socioeconomic status, and at which level, but have not extracted the data to enable the investigation of effect estimates stratified by socioeconomic status.

The adjusted meta-analysis included hazard ratios that were adjusted for different covariates and at varying levels (as described in Table 1). These ranged from clinical factors such as the presence of co-morbidities and body mass index, to lifestyle factors such as smoking and drinking, and socioeconomic factors. For example, some adjusted for individual participant income, while others adjusted for neighbourhood-level

socioeconomic position. This variation in adjustment methods limits the comparability of the effect estimates and could be investigated with meta-regression in future work. To partially address this issue, we also conducted preliminary analyses with the extracted unadjusted effect estimates when three or more were available. For $PM_{2.5}$ and dementia, the pooled effect estimate for the unadjusted values was 1.20 (95% CI: 0.95 to1.52) with eight papers (Figure S16A; Supplementary Material pg. 50). For $NO_2$, the pooled effect estimate for the unadjusted values was 1.05 (95% CI: 0.93 to1.18) with five papers (Figure S16B; Supplementary Material pg. 51). That the unadjusted effect estimates were higher for both $NO_2$ and $PM_{2.5}$ suggest that confounding factors were inflating the apparent association. Given that the number of studies in the unadjusted analysis is much smaller than the primary analysis, our interpretation remains very limited.

Finally, although our data extraction process adhered to gold-standard protocols with two independent reviewers (CR and YS), an internal review (HK) identified discrepancies, prompting a third independent verification of all extracted data. For instance, Oudin et al. (2018) was initially excluded because the original reviewers agreed the study, focusing on indoor stoves, did not meet the criteria for outdoor air pollution exposure (115). However, a subsequent review revealed the study included a model addressing outdoor air pollution, warranting its inclusion. Conversely, Tan et al. (2021) was initially included under the assumption that participants were disease-free at baseline, but further scrutiny found this could not be confirmed (116). These findings underscore the importance of additional verification steps beyond gold-standard practices. Requiring a third unaffiliated reviewer as an external check could enhance accuracy, although it added significant time and resource demands. Future opportunities may lie in leveraging artificial intelligence tools to streamline error-prone tasks, serving as an impartial reviewer, and potentially reducing the burden of manual oversight (117).

*Assessment of Confidence in the Body of Evidence*

We developed and published a protocol for this systematic review and meta-analysis a priori, and followed this precisely, lowering the risk of bias, and addressing factors that can decrease confidence in the body of evidence: "indirectness" and "imprecision" (23). The risk of bias of individual studies, as assessed by the OHAT tool, across the studies was at worst 'probably low risk of bias', with only seven having a 'probably high risk of bias' in one domain due to the use of some form of self-report of physician diagnosis (though at times verified through an algorithm) (Dimakakou et al. (2020), Parra et al. (2022), Trevenen et al. (2022), Mukadam et al. (2022), Wood et al. (2022)), failure to record certain information (Ilango et al. (2020)), and the use of a non-peer reviewed blog for determining the cut-offs for "good, moderate, and poor" air quality (He et al. (2022)). We conducted a RoB assessment for each individual paper to assess the data collection, analysis, and processing at the most granular level possible. This provided us with a fine-tuned assessment of the potential bias of each included paper. We did not categorically address potential bias at the journal level, as we could not find a validated method by which to do so.

In our Certainty of Evidence Assessment, we found the overall confidence in the body of evidence to be moderate (Table S5; Supplementary Material pg. 6-8). There was unexplained inconsistency and heterogeneity across results and evidence of publication bias, and these factors decreased our confidence. A range of heterogeneity is expected in meta-analyses, and has been a hallmark of air pollution epidemiology, and is not necessarily of concern, given that predefined eligibility criteria for the meta-analysis were sound and that the data were correctly extracted by two independent reviewers and verified by a third (118). However, the presence of cross-population and cross-study design consistency, and the evidence of a dose-response relationship in ERFs, increased our confidence in the body of evidence to moderate (Table S5; Supplementary Material pg. 6-8).

Per the protocol, a sensitivity analysis was conducted removing the seven studies that recorded a probably high risk of bias. The removal of such papers had only a negligible effect on the pooled effect estimates.

Grouping and running the analysis separately for studies with “Definitely low risk of bias” and “Probably low risk of bias” combined, versus those studies that included “Probably high risk of bias” also had a negligible effect (S17A,B; Supplementary Material pg. 52-53). Overall, the results of various sensitivity analyses led us to the same conclusions on the associations between pollutants and dementia.

As discussed, studies also maintained major differences in adjustment for confounders, outcome ascertainment and exposure assessment methods. Subgroup analyses were undertaken to assess those differences. Per the protocol, we aimed to increase comparability by selecting effect estimates from the papers which did not adjust for potential comorbidities, including cardiovascular disease. Finally, while our assessment of publication bias for those exposure-outcome pairs with more than ten papers indicate potential publication bias, given the presence of funnel plot asymmetry, these results may be true if there was a true positive effect estimate as well.

Taken together, the robustness of our protocol, the results of the certainty of evidence, risk of bias and various sensitivity and subgroup analyses, provide us with further confidence in the synthesised body of evidence and provide areas for further investigation.

*Implications*

Our results strengthen the evidence that outdoor air pollution is a risk factor for dementia. This suggests that efforts to reduce exposure to these pollutants in a population would help reduce the burden of dementia and that stricter limits for several pollutants are necessary with major contributors like the transport and industry sectors, signalling target areas for regulatory interventions. Reducing the air quality limits on $PM_{2.5}$, $NO_2$, to below current limits, and introducing limits on $BC/PM_{2.5\ absorbance}$ is likely to yield long-term health, social and economic benefits, relieving the healthcare system's burden by reducing dementia cases, income loss, and the significant toll on families and caregivers.

## Conclusion

Our results strengthen and expand the evidence that $PM_{2.5}$, $NO_2$, and $BC/PM_{2.5\ absorbance}$ are risk factors for the onset of dementia including both study-diagnosed VaD and AD. This suggests that efforts to reduce exposure to these pollutants would help reduce the global burden of dementia. The extent of air pollution signals an urgent need for regional, national, and international policy interventions to combat air pollution equitably. Additionally, our meta-analysis reports on differences between effect estimates for AD and VaD and between continents. Interpretation of these differences remains limited by a limited data pool, and further research is necessary into the causal pathways and sources of air pollution, which may impact the development of dementia. Future work should aim to better represent low- and middle-income countries, include adequate diverse study populations, including diverse races and populations across varying degrees of urbanisation and socioeconomic status, to ensure global health inequalities are identified and addressed. This will ultimately inform a truly global and equitable approach to reduce the burden of dementia.

## References


1. Gale SA, Acar D, Daffner KR. Dementia. The American Journal of Medicine. 2018;131(10):1161-9.
2. Naghavi M, Ong KL, Aali A, Ababneh HS, Abate YH, Abbafati C, et al. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2013;2021: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet. 2024;403(10440):2100-32.
3. Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. The Lancet Public Health. 2022;7(2):e105-e25.
4. Wolters FJ, Chibnik LB, Waziry R, Anderson R, Berr C, Beiser A, et al. Twenty-seven-year time trends in dementia incidence in Europe and the United States. Neurology. 2020;95(5):e519-e31.
5. Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. The Lancet. 2024;404(10452):572-628.
6. Chen H, Kwong JC, Copes R, Tu K, Villeneuve PJ, van Donkelaar A, et al. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. The Lancet. 2017;389(10070):718-26.
7. Cacciottolo M, Wang X, Driscoll I, Woodward N, Saffari A, Reyes J, 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-e.
8. Hu K, Hale JM, Kulu H, Liu Y, Keenan K. A Longitudinal Analysis of the Association Between Long-Term Exposure to Air Pollution and Cognitive Function Among Adults Aged 45 and Older in China. The Journals of Gerontology: Series B. 2023;78(3):556-69.
9. Iain MC, Anderson HR, Richard WA, Sean DB, Derek GC, David PS, 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.
10. Chang K-H, Chang M-Y, Muo C-H, Wu T-N, Chen C-Y, Kao C-H. Increased Risk of Dementia in Patients Exposed to Nitrogen Dioxide and Carbon Monoxide: A Population-Based Retrospective Cohort Study. PLOS ONE. 2014;9(8):e103078.
11. Tang J, Chen A, He F, Shipley M, Nevill A, Coe H, et al. Association of air pollution with dementia: a systematic review with meta-analysis including new cohort data from China. Environmental Research. 2023;223:115048.
12. 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.
13. Fu P, Guo X, Cheung FMH, Yung KKL. The association between PM2.5 exposure and neurological disorders: A systematic review and meta-analysis. Science of The Total Environment. 2019;655:1240-8.
14. Zhao Y-L, Qu Y, Ou Y-N, Zhang Y-R, Tan L, Yu J-T. Environmental factors and risks of cognitive impairment and dementia: A systematic review and meta-analysis. Ageing Research Reviews. 2021;72:101504.

15. Tsai T-L, Lin Y-T, Hwang B-F, Nakayama SF, Tsai C-H, Sun X-L, et al. Fine particulate matter is a potential determinant of Alzheimer's disease: A systemic review and meta-analysis. Environmental Research. 2019;177:108638.
16. Peters R, Mudway I, Booth A, Peters J, Anstey KJ. Putting Fine Particulate Matter and Dementia in the Wider Context of Noncommunicable Disease: Where are We Now and What Should We Do Next: A Systematic Review. Neuroepidemiology. 2021;55(4):253-65.
17. Weuve J, Bennett Erin E, Ranker L, Gianattasio Kan Z, Pedde M, Adar Sara D, 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).
18. Abolhasani E, Hachinski V, Ghazaleh N, Azarpazhooh MR, Mokhber N, Martin J. Air Pollution and Incidence of Dementia. Neurology. 2023;100(2):e242.
19. Wilker EH, Osman M, Weisskopf MG. Ambient air pollution and clinical dementia: systematic review and meta-analysis. BMJ. 2023;381:e071620.
20. Cristaldi A, Fiore M, Oliveri Conti G, Pulvirenti E, Favara C, Grasso A, et al. Possible association between PM2.5 and neurodegenerative diseases: A systematic review. Environmental Research. 2022;208:112581.
21. Savva George M, Wharton Stephen B, Ince Paul G, Forster G, Matthews Fiona E, Brayne C. Age, Neuropathology, and Dementia. New England Journal of Medicine.360(22):2302-9.
22. Kalaria R. Similarities between Alzheimer's disease and vascular dementia. Journal of the Neurological Sciences. 2002;203:29-34.
23. Khreis H, Bredell C, Wai Fung K, Hong L, Szybka M, Phillips V, et al. Impact of long-term air pollution exposure on incidence of neurodegenerative diseases: A protocol for a systematic review and exposure-response meta-analysis. Environment International. 2022;170:107596.
24. OHAT. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Institute of Environmental Health Sciences, US Department of Health and Human Services; 2019.
25. Chen J, Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. Environment International. 2020;143:105974.
26. Institute HE. Chapter 5 Appendix 5C, Special Report 23, Systematic Review and Meta-analysis of Selected Health Effects of LongTerm Exposure to Traffic-Related Air Pollution. Online: Health Effects Insitute; 2022.
27. DEFRA. Conversion Factors Between ppb and μg m-3 and ppm and mgm-3. Online: UK Defra.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7(3):177-88.
29. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Research Synthesis Methods. 2016;7(1):55-79.
30. IntHout J, Ioannidis JPA, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Medical Research Methodology. 2014;14(1):25.

31. Durant JL, Beelen R, Eeftens M, Meliefste K, Cyrys J, Heinrich J, et al. Comparison of ambient airborne PM2.5, PM2.5 absorbance and nitrogen dioxide ratios measured in 1999 and 2009 in three areas in Europe. Science of The Total Environment. 2014;487:290-8.
32. Savouré M, Lequy É, Bousquet J, Chen J, de Hoogh K, Goldberg M, et al. Long-term exposures to PM2.5, black carbon and NO2 and prevalence of current rhinitis in French adults: The Constances Cohort. Environment International. 2021;157:106839.
33. Gallis JA, Turner EL. Relative Measures of Association for Binary Outcomes: Challenges and Recommendations for the Global Health Researcher. Annals of Global Health. 2019.
34. Cochrane Handbook for Systematic Reviews of Interventions version 6.3. In: JJ Deeks JH, DG Altman editor.: Cochrane; 2022.
35. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I² index? Psychological Methods. 2006;11(2):193-206.
36. Bender R, Friede T, Koch A, Kuss O, Schlattmann P, Schwarzer G, et al. Methods for evidence synthesis in the case of very few studies. Research Synthesis Methods. 2018;9(3):382-92.
37. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing Meta-Analysis With R: A Hands-On Guide. 1st ed. Boca Raton, FL and London: Chapman & Hall/CRC Press; 2021 2021.
38. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software. 2010;36(3):1 - 48.
39. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. dmetar: Companion R Package For The Guide 'Doing Meta-Analysis in R'. 2019.
40. WHO. Overview of methods to assess population exposure to ambient air pollution. Geneva: World Health Organization; 2023.
41. Lotrecchiano N, Barletta D, Poletto M, Sofia D. Comparison of spatial interpolation techniques for innovative air quality monitoring systems. Results in Engineering. 2023;17:100937.
42. Power MC, Bennett EE, Lynch KM, Stewart JD, Xu X, Park Eun S, et al. Comparison of PM2.5 Air Pollution Exposures and Health Effects Associations Using 11 Different Modeling Approaches in the Women's Health Initiative Memory Study (WHIMS). Environmental Health Perspectives. 2024;132(1):017003.
43. Parra KL, Alexander GE, Raichlen DA, Klimentidis YC, Furlong MA. Exposure to air pollution and risk of incident dementia in the UK Biobank. Environmental Research. 2022;209:112895.
44. Trevenen ML, Heyworth J, Almeida OP, Yeap BB, Hankey GJ, Golledge J, et al. Ambient air pollution and risk of incident dementia in older men living in a region with relatively low concentrations of pollutants: The Health in Men Study. Environmental Research. 2022;215:114349.
45. Wood D, Evangelopoulos D, Beevers S, Kitwiroon N, Katsouyanni K. Exposure to Ambient Air Pollution and the Incidence of Dementia in the Elderly of England: The ELSA Cohort. International Journal of Environmental Research and Public Health [Internet]. 2022; 19(23).
46. Mukadam N, Marston L, Lewis G, Livingston G. Risk factors, ethnicity and dementia: A UK Biobank prospective cohort study of White, South Asian and Black participants. PLOS ONE. 2022;17(10):e0275309.

47. 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. International Journal of Environmental Research and Public Health [Internet]. 2020; 17(24).
48. He F, Tang J, Zhang T, Lin J, Li F, Gu X, et al. Impact of air pollution exposure on the risk of Alzheimer's disease in China: A community-based cohort study. Environmental Research. 2022;205:112318.
49. Ilango SD, Chen H, Hystad P, van Donkelaar A, Kwong JC, Tu K, 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.
50. Li J, Wang Y, Steenland K, Liu P, van Donkelaar A, Martin RV, et al. Long-term effects of PM2.5 components on incident dementia in the northeastern United States. The Innovation. 2022;3(2):100208.
51. Raichlen DA, Furlong M, Klimentidis YC, Sayre MK, Parra KL, Bharadwaj PK, et al. Association of Physical Activity with Incidence of Dementia Is Attenuated by Air Pollution. Medicine & Science in Sports & Exercise. 2022;54(7).
52. Ma H, Li X, Zhou T, Wang M, Heianza Y, Qi L. Long-term exposure to low-level air pollution, genetic susceptibility and risk of dementia. International Journal of Epidemiology. 2023;52(3):738-48.
53. Yuan S, Huang X, Zhang L, Ling Y, Tan S, Peng M, et al. Associations of air pollution with all-cause dementia, Alzheimer’s disease, and vascular dementia: a prospective cohort study based on 437,932 participants from the UK biobank. Frontiers in Neuroscience. 2023;17.
54. Ran J, Zhang Y, Han L, Sun S, Zhao S, Shen C, et al. The joint association of physical activity and fine particulate matter exposure with incident dementia in elderly Hong Kong residents. Environment International. 2021;156:106645.
55. Chen G-C, Nyarko Hukportie D, Wan Z, Li F-R, Wu X-B. The Association Between Exposure to Air Pollution and Dementia Incidence: The Modifying Effect of Smoking. The Journals of Gerontology: Series A. 2023;78(12):2309-17.
56. Andersson J, Oudin A, Sundström 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.
57. Oudin A, Forsberg B, Adolfsson Annelie N, Lind N, Modig L, Nordin M, et al. Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study. Environmental Health Perspectives. 2016;124(3):306-12.
58. Xie J, Lu C. Is there a casual relation between air pollution and dementia? Environmental Science and Pollution Research. 2023;30(9):23248-62.
59. Li C-Y, Li C-H, Martini S, Hou W-H. Association between air pollution and risk of vascular dementia: A multipollutant analysis in Taiwan. Environment International. 2019;133:105233.
60. Wu Y-C, Lin Y-C, Yu H-L, Chen J-H, Chen T-F, Sun Y, et al. Association between air pollutants and dementia risk in the elderly. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2015;1(2):220-8.
61. 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. 2020;19(1):8.

62. Cheng S, Jin Y, Dou Y, Zhao Y, Duan Y, Pei H, et al. Long-term particulate matter 2.5 exposure and dementia: a systematic review and meta-analysis. Public Health. 2022;212:33-41.
63. He J, Christakos G, Jankowski P. Comparative Performance of the LUR, ANN, and BME Techniques in the Multiscale Spatiotemporal Mapping of PM2.5 Concentrations in North China. IEEE Journal of Selected Topics in Applied Earth Observations and Remote Sensing. 2019;12(6):1734-47.
64. Cowie CT, Garden F, Jegasothy E, Knibbs LD, Hanigan I, Morley D, et al. Comparison of model estimates from an intra-city land use regression model with a national satellite-LUR and a regional Bayesian Maximum Entropy model, in estimating NO2 for a birth cohort in Sydney, Australia. Environmental Research. 2019;174:24-34.
65. Adam-Poupart A, Brand A, Fournier M, Jerrett M, Smargiassi A. Spatiotemporal Modeling of Ozone Levels in Quebec (Canada): A Comparison of Kriging, Land-Use Regression (LUR), and Combined Bayesian Maximum Entropy–LUR Approaches. Environmental Health Perspectives. 2014;122(9):970-6.
66. Langan D, Higgins JPT, Jackson D, Bowden J, Veroniki AA, Kontopantelis E, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. Research Synthesis Methods. 2019;10(1):83-98.
67. Hill AB. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine. 1965(5):295-300.
68. Bennett S, Grant MM, Aldred S. Oxidative Stress in Vascular Dementia and Alzheimer's Disease: A Common Pathology. Journal of Alzheimer's Disease. 2008;17(2):245-57.
69. Heneka MT, van der Flier WM, Jessen F, Hoozemanns J, Thal DR, Boche D, et al. Neuroinflammation in Alzheimer disease. Nature Reviews Immunology. 2024.
70. Houldsworth A. Role of oxidative stress in neurodegenerative disorders: a review of reactive oxygen species and prevention by antioxidants. Brain Communications. 2024;6(1):fcad356.
71. Jayaraj RL, Rodriguez EA, Wang Y, Block ML. Outdoor Ambient Air Pollution and Neurodegenerative Diseases: the Neuroinflammation Hypothesis. Current Environmental Health Reports. 2017;4(2):166-79.
72. Finch CE, Thorwald MA. Inhaled Pollutants of the Gero-Exposome and Later-Life Health. The Journals of Gerontology: Series A. 2024;79(7):glae107.
73. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends in Neurosciences. 2009;32(9):506-16.
74. Calderón-Garcidueñas L, Azzarelli B, Acuna H, Garcia R, Gambling TM, Osnaya N, et al. Air Pollution and Brain Damage. Toxicologic Pathology. 2002;30(3):373-89.
75. Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, Torres-Jardón R, Nuse B, Herritt L, et al. Long-term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid β-42 and α-Synuclein in Children and Young Adults. Toxicologic Pathology. 2008;36(2):289-310.
76. Calderón-Garcidueñas L, Kavanaugh M, Block M, D'Angiulli A, Delgado-Chávez R, Torres-Jardón R, et al. Neuroinflammation, Hyperphosphorylated Tau, Diffuse Amyloid Plaques, and Down-Regulation of the Cellular Prion Protein in Air Pollution Exposed Children and Young Adults. Journal of Alzheimer's Disease. 2012;28(1):93-107.
77. Elder A, Oberdörster G. Translocation and effects of ultrafine particles outside of the lung. Clinics in Occupational and Environmental Medicine. 2006;5:785–96.

78. Jankowska-Kieltyka M, Roman A, Nalepa I. The Air We Breathe: Air Pollution as a Prevalent Proinflammatory Stimulus Contributing to Neurodegeneration. Frontiers in Cellular Neuroscience. 2021;15:239.
79. Harmon AC, Hebert VY, Cormier SA, Subramanian B, Reed JR, Backes WL, et al. Particulate matter containing environmentally persistent free radicals induces AhR-dependent cytokine and reactive oxygen species production in human bronchial epithelial cells. PLOS ONE. 2018;13(10):e0205412.
80. Greve HJ, Dunbar AL, Lombo CG, Ahmed C, Thang M, Messenger EJ, et al. The bidirectional lung brain-axis of amyloid-β pathology: ozone dysregulates the peri-plaque microenvironment. Brain. 2023;146(3):991-1005.
81. Kang H, Huang D, Zhang W, Wang J, Liu Z, Wang Z, et al. Pulmonary Flora-Derived Lipopolysaccharide Mediates Lung-Brain Axis through Activating Microglia Involved in Polystyrene Microplastic-Induced Cognitive Dysfunction. Advanced Science. 2024;11(47):2404966.
82. Mumaw CL, Levesque S, McGraw C, Robertson S, Lucas S, Stafflinger JE, et al. Microglial priming through the lung—brain axis: the role of air pollution-induced circulating factors. The FASEB Journal. 2016;30(5):1880-91.
83. Onoda A, Kawasaki T, Tsukiyama K, Takeda K, Umezawa M. Carbon nanoparticles induce endoplasmic reticulum stress around blood vessels with accumulation of misfolded proteins in the developing brain of offspring. Scientific Reports. 2020;10(1):10028.
84. 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.
85. de Bont J, Jaganathan S, Dahlquist M, Persson Å, Stafoggia M, Ljungman P. Ambient air pollution and cardiovascular diseases: An umbrella review of systematic reviews and meta-analyses. Journal of Internal Medicine. 2022;291(6):779-800.
86. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. The Lancet Neurology. 2008;7(9):812-26.
87. Tini G, Scagliola R, Monacelli F, La Malfa G, Porto I, Brunelli C, et al. Alzheimer's Disease and Cardiovascular Disease: A Particular Association. Cardiology Research and Practice. 2020;2020(1):2617970.
88. Brayne C. The elephant in the room — healthy brains in later life, epidemiology and public health. Nature Reviews Neuroscience. 2007;8(3):233-9.
89. Wharton SB, Simpson JE, Ince PG, Richardson CD, Merrick R, Matthews FE, et al. Insights into the pathological basis of dementia from population-based neuropathology studies. Neuropathology and Applied Neurobiology. 2023;49(4):e12923.
90. Nichols E, Merrick R, Hay SI, Himali D, Himali JJ, Hunter S, et al. The prevalence, correlation, and co-occurrence of neuropathology in old age: harmonisation of 12 measures across six community-based autopsy studies of dementia. The Lancet Healthy Longevity. 2023;4(3):e115-e25.
91. Emrani S, Lamar M, Price CC, Wasserman V, Matusz E, Au R, et al. Alzheimer's/Vascular Spectrum Dementia: Classification in Addition to Diagnosis. Journal of Alzheimer's Disease. 2019;73(1):63-71.

813 92. Laukka EJ, MacDonald SWS, Fratiglioni L, Bäckman L. Preclinical Cognitive
814 Trajectories Differ for Alzheimer's Disease and Vascular Dementia. Journal of the International
815 Neuropsychological Society. 2012;18(2):191-9.
816 93. Tolea MI, Morris JC, Galvin JE. Trajectory of Mobility Decline by Type of Dementia.
817 Alzheimer Disease & Associated Disorders. 2016;30(1).
818 94. Bir SC, Khan MW, Javalkar V, Toledo EG, Kelley RE. Emerging Concepts in Vascular
819 Dementia: A Review. Journal of Stroke and Cerebrovascular Diseases. 2021;30(8):105864.
820 95. Groves WC, Brandt J, Steinberg M, Warren A, Rosenblatt A, Baker A, et al. Vascular
821 Dementia and Alzheimer's Disease: Is There a Difference? The Journal of Neuropsychiatry and
822 Clinical Neurosciences. 2000;12(3):305-15.
823 96. Erkinjuntti T. Differential diagnosis between Alzheimer's disease and vascular dementia:
824 evaluation of common clinical methods. Acta Neurologica Scandinavica. 1987;76(6):433-42.
825 97. Kennedy D, Bates RR, Watson AY. Air pollution, the automobile, and public health.
826 1988.
827 98. Ujimoto KV, Chapin FS. Review of Human Activity Patterns in the City: Things People
828 Do in Time and in Space. Social Indicators Research. 1975;2(2):261-4.
829 99. Flowerdew ADJ. A. Szalai. The Use of Time. Daily activities of urban and suburban
830 populations in twelve countries. The Economic Journal. 1974;84(335):691-4.
831 100. Zhang B, Weuve J, Langa KM, D'Souza J, Szpiro A, Faul J, et al. Comparison of
832 Particulate Air Pollution From Different Emission Sources and Incident Dementia in the US.
833 JAMA Internal Medicine. 2023;183(10):1080-9.
834 101. Shim J-I, Byun G, Lee J-TT. Long-term exposure to particulate matter and risk of
835 Alzheimer's disease and vascular dementia in Korea: a national population-based Cohort Study.
836 Environmental Health. 2023;22(1):35.
837 102. Mauderly Joe L, Samet Jonathan M. Is There Evidence for Synergy Among Air
838 Pollutants in Causing Health Effects? Environmental Health Perspectives. 2009;117(1):1-6.
839 103. Levy I, Mihele C, Lu G, Narayan J, Brook Jeffrey R. Evaluating Multipollutant Exposure
840 and Urban Air Quality: Pollutant Interrelationships, Neighborhood Variability, and Nitrogen
841 Dioxide as a Proxy Pollutant. Environmental Health Perspectives. 2014;122(1):65-72.
842 104. Dominici F, Peng RD, Barr CD, Bell ML. Protecting Human Health From Air Pollution:
843 Shifting From a Single-pollutant to a Multipollutant Approach. Epidemiology. 2010;21(2).
844 105. Gu B, Zhang L, Van Dingenen R, Vieno M, Van Grinsven HJM, Zhang X, et al. Abating
845 ammonia is more cost-effective than nitrogen oxides for mitigating PM2.5 air pollution. Science.
846 2021;374(6568):758-62.
847 106. Fazakas E, Neamtiu IA, Gurzau ES. Health effects of air pollutant mixtures (volatile
848 organic compounds, particulate matter, sulfur and nitrogen oxides) – a review of the literature.
849 2024;39(3):459-78.
850 107. Szyszkowicz M. An approach to represent a combined exposure to air pollution. Int J
851 Occup Med Environ Health. 2015;28(5):823-30.
852 108. Chen X, Gehring U, Dyer GMC, Khomenko S, de Hoogh K, Tonne C, et al. Single- and
853 two-pollutant concentration-response functions for PM2.5 and NO2 for quantifying mortality
854 burden in health impact assessments. Environmental Research. 2024;263:120215.
855 109. Liu J, Clark Lara P, Bechle Matthew J, Hajat A, Kim S-Y, Robinson Allen L, et al.
856 Disparities in Air Pollution Exposure in the United States by Race/Ethnicity and Income, 1990–
857 2010. Environmental Health Perspectives. 2021;129(12):127005.

110. Woo B, Kravitz-Wirtz N, Sass V, Crowder K, Teixeira S, Takeuchi DT. Residential Segregation and Racial/Ethnic Disparities in Ambient Air Pollution. Race and Social Problems. 2019;11(1):60-7.
111. Josey Kevin P, Delaney Scott W, Wu X, Nethery Rachel C, DeSouza P, Braun D, et al. Air Pollution and Mortality at the Intersection of Race and Social Class. New England Journal of Medicine. 2023;388(15):1396-404.
112. Jbaily A, Zhou X, Liu J, Lee T-H, Kamareddine L, Verguet S, et al. Air pollution exposure disparities across US population and income groups. Nature. 2022;601(7892):228-33.
113. Younan D, Wang X, Gruenewald T, Gatz M, Serre ML, Vizuete W, et al. Racial/Ethnic Disparities in Alzheimer's Disease Risk: Role of Exposure to Ambient Fine Particles. The Journals of Gerontology: Series A. 2022;77(5):977-85.
114. Wang P, Cao J-j, Shen Z-x, Han Y-m, Lee S-c, Huang Y, et al. Spatial and seasonal variations of PM2.5 mass and species during 2010 in Xi'an, China. Science of The Total Environment. 2015;508:477-87.
115. 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.
116. Tan J, Li N, Wang X, Chen G, Yan L, Wang L, et al. Associations of particulate matter with dementia and mild cognitive impairment in China: A multicenter cross-sectional study. The Innovation. 2021;2(3):100147.
117. Ge L, Agrawal R, Singer M, Kannapiran P, De Castro Molina JA, Teow KL, et al. Leveraging artificial intelligence to enhance systematic reviews in health research: advanced tools and challenges. Systematic Reviews. 2024;13(1):269.
118. Higgins JPT. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. International Journal of Epidemiology. 2008;37(5):1158-60.

# Funding Sources

Haneen Khreis and James Woodcock have received funding from the European Research Council (ERC) under the Horizon 2020 research and innovation programme (Grant agreement No. 817754) and from the European Union's, Horizon Europe Framework Programme (HORIZON) under GA No 101094639 - The Urban Burden Of Disease Estimation For Policy Making (UBDPolicy). The funders had no role in the study design or in the collection, analysis, interpretation of data, writing of the manuscript, or decision to submit the article for publication.

# Declarations of Interest

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

# Acknowledgements

We would like to acknowledge Shazia Absar (MB BChir) for her contributions to the initial abstract screening stages of this paper.

# Keywords

Air pollution, dementia, environmental epidemiology, vascular dementia, Alzheimer's disease

# Figures Legend

Figure 1: PRISMA Flow Diagram of Systematic Review Process

Figure 2: $PM_{2.5}$ adjusted random-effects meta-analyses. Individual and summary random effects estimates for associations between $PM_{2.5}$ per 5 μg/m³ and dementia. (HK) refers to the Hartung and Knapp random-effects model.

Figure 3: $NO_2$ adjusted random-effects meta-analyses. Individual and summary random effects estimates for associations between $NO_2$ per 10 μg/m³ and dementia. (HK) refers to the Hartung and Knapp random-effects model.

Figure 4: $NO_x$ adjusted random-effects meta-analyses. Individual and summary random effects estimates for associations between $NO_x$ per 10 μg/m³ and dementia. (HK) refers to the Hartung and Knapp random-effects model.

Figure 5: BC/ $PM_{2.5\ Absorbance}$ adjusted random-effects meta-analyses. Individual and summary random effects estimates for associations between BC/ $PM_{2.5\ Absorbance}$ per 1 $\mu g/m^3$ and dementia. (HK) refers to the Hartung and Knapp random-effects model.

Figure 6: $PM_{10}$, adjusted random-effects meta-analyses. Individual and summary random effects estimates for associations between $PM_{10}$ per 15 μg/m³ and dementia. (HK) refers to the Hartung and Knapp random-effects model.

# Contributors

CBR: Primary acquisition, analysis concept, analysis, and interpretation of data. Primary drafting of the manuscript, figures, tables, and supplementary material. Critical revision of the manuscript for important intellectual content. Administrative, technical, or material support.

CB: Analysis, interpretation, and checking of data. Primary drafting of the manuscript. Critical revision of the manuscript for important intellectual content. Administrative, technical, or material support. Drafting portions of original protocol manuscript in Khreis et al. (2022). Impact of long-term air pollution exposure on incidence of neurodegenerative diseases: a protocol for a systematic review and exposure-response meta-analysis. Environment international, 170, p.107596.

YS: Initial acquisition and analysis of data.

ATS: Initial acquisition of data.

MS: Acquisition and analysis of data. Drafting portions of original protocol manuscript in Khreis et al. (2022). Impact of long-term air pollution exposure on incidence of neurodegenerative diseases: a protocol for a systematic review and exposure-response meta-analysis. Environment international, 170, p.107596.

KWF: Acquisition and analysis of data. Drafting portions of original protocol manuscript in Khreis et al. (2022). Impact of long-term air pollution exposure on incidence of neurodegenerative diseases: a protocol for a systematic review and exposure-response meta-analysis. Environment international, 170, p.107596.

LH: Acquisition and analysis of data. Drafting portions of original protocol manuscript in Khreis et al. (2022). Impact of long-term air pollution exposure on incidence of neurodegenerative

diseases: a protocol for a systematic review and exposure-response meta-analysis. Environment international, 170, p.107596.

VP: Acquisition of data, Critical revision of the manuscript for important intellectual content. Drafting portions of original protocol manuscript in Khreis et al. (2022). Impact of long-term air pollution exposure on incidence of neurodegenerative diseases: a protocol for a systematic review and exposure-response meta-analysis. Environment international, 170, p.107596.

ZJA: Concept. Critical revision of the manuscript for important intellectual content.

SS: Advice on statistical analysis. Critical revision of the manuscript for important intellectual content.

JW: Concept. Critical revision of the manuscript for important intellectual content.

CaB: Concept and design. Critical revision of the manuscript for important intellectual content.

AN: Supervision, Critical revision of the manuscript for important intellectual content.

HK: Concept and design, Acquisition, analysis concept, and interpretation of data, Primary drafting and editing of the manuscript, Oversight and leadership responsibility for the research activity planning and execution, Supervision from conception to completion, including of all versions of the manuscript and data analysis, Critical revision of the manuscript for important intellectual content, Administrative, technical, or material support, Guarantor. Primary drafting and first authorship of the original protocol manuscript in Khreis et al. (2022). Impact of long-term air pollution exposure on incidence of neurodegenerative diseases: a protocol for a systematic review and exposure-response meta-analysis. Environment international, 170, p.107596.

# Data Sharing Statement

Data extracted for this systematic review and meta-analysis will be made available to others (as Table S9) with publication. The study protocol is already published (Khreis et al. (2022)) and accessible. The R code is available to be shared, should others seek to look at it and may be requested by contacting the corresponding author.