Long-term air pollution exposure and incident dementia: a systematic review and meta-analysis

Clare B Best Rogowski, Christiaan Bredell*, Yan Shi, Alexandra Tien-Smith, Magdalena Szybka, Kwan Wai Fung, Lucy Hong, Veronica Phillips, Zorana Jovanovic Andersen, Stephen J Sharp, James Woodcock, Carol Brayne, Annalan Navaratnam, Haneen Khreis*

Summary

Background A rapidly evolving evidence base suggests that exposure to outdoor air pollution is a risk factor for the onset of dementia, with an upturn in publications since 2022. We sought to synthesise and critically assess this evidence base accounting for the latest studies.

Methods In this systematic review and meta-analysis, we searched MEDLINE, Embase, Cochrane Library, CINAHL, Global Health, PsycINFO, Scopus, and Web of Science Core Collection from database inception up to Oct 23, 2023, for primary observational studies of adults (aged ≥18 years) that provided a quantitative analysis of the association between long-term (≥1 year) exposure to outdoor air pollutants and a subsequent physician diagnosis of dementia. When three or more independent studies reported an exposure–outcome pair, effect estimates of the association were extracted and harmonised to a prespecified exposure increment, and included in inverse-variance weighted random-effects meta-analyses. Between-study inconsistency was assessed using the I^2 statistic and the Cochran Q test. Study-level risk of bias and confidence in the overall body of evidence were assessed with the Office of Health Assessment and Translation tool, and publication bias was examined. The protocol for this review was registered with PROSPERO, CRD42023414413.

Findings The search generated 15 619 records, of which 51 studies met the inclusion criteria for data extraction. After excluding studies due to population overlap and missing continuous effect estimates, 32 studies reported on exposure–outcome pairs that met the threshold of three or more studies, and were included in meta-analyses of adjusted effect estimates for incident dementia and/or in subgroup analyses of dementia subtypes. In meta-analyses of incident dementia, we identified a dementia diagnosis to be significantly associated with long-term exposure to $PM_{2·5}$ (21 studies, n=24 030 527, pooled adjusted hazard ratio (HR) per 5 μg/m^3 increase in exposure, 1·08 [95% CI 1·02–1·14]; I^2=95%), nitrogen dioxide (16 studies, n=17 228 429, pooled adjusted HR per 10 μg/m^3 increase, 1·03 [1·01–1·05]; I^2=84%), and black carbon/$PM_{2·5\ absorbance}$ (six studies, n=19 421 865, pooled adjusted HR per 1 μg/m^3 increase, 1·13 [1·01–1·27]; I^2=97%). We found no significant association for exposure to nitrogen oxides (five studies, n=241 409, pooled adjusted HR per 10 μg/m^3 increase, 1·05 [0·97–1·13]; I^2=44%), PM_{10} (four studies, n=246 440, pooled adjusted HR per 15 μg/m^3 increase, 1·52 [0·80–2·87]; I^2=82%), or annual ozone (four studies, n=419 972, pooled adjusted HR per 45 μg/m^3 increase, 0·82 [0·35–1·92]; I^2=69%), with moderate to considerable heterogeneity between studies in these pooled analyses. Of the 32 studies overall, three (9%) had a probably high risk of bias in one of seven domains; all other studies had ratings of probably to definitely low risk of bias. The overall certainty of evidence of studies in the systematic review was moderate.

Interpretation This analysis adds to the body of evidence that outdoor air pollutants are risk factors for dementia, indicating that reduced exposure to pollution could reduce dementia rates and stricter air quality standards would likely provide substantial health, social, and economic benefits.

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*Joint first authors

MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, UK (C B Best Rogowski MPhil, A Tien-Smith MPhil, S J Sharp MSc, Prof J Woodcock PhD, A Navaratnam MFPH, H Khreis PhD); **University of Cambridge School of Clinical Medicine, Cambridge, UK** (C Bredell MB BChir, Y Shi MB BChir, M Szybka MB BChir, K W Fung MB BChir, L Hong MB BChir); **Hinchingbrooke Hospital, North West Anglia NHS Foundation Trust, Huntingdon, UK** (C Bredell); **University of Cambridge Medical Library, University of Cambridge School of Clinical Medicine, Cambridge, UK** (V Phillips PhD); **Section of Environmental Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark** (Prof Z Jovanovic Andersen PhD); **Cambridge Public Health, University of Cambridge, Cambridge, UK** (Prof C Brayne MD); **Texas A&M Transportation Institute, Texas A&M University System, College Station, TX, USA** (H Khreis)

Correspondence to:
Dr Haneen Khreis, MRC Epidemiology Unit, Level 3 Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge School of Clinical Medicine, Cambridge CB2 0SL, UK
hrk38@medschl.cam.ac.uk

Introduction

Dementia, a clinical syndrome involving progressive cognitive decline that impairs daily functioning, was estimated to affect more than 57·4 million people globally in 2019, and ranked as the eighth leading cause of death worldwide in 2021.[1–3] The impacts on society and individuals are substantial,[4] and there remains an urgent need to investigate and address causes of this syndrome.

The 2024 *Lancet* Commission on dementia prevention, intervention, and care identified air pollution as one of 14 modifiable risk factors for dementia, supported by studies reporting an association between dementia and several air pollutants.[5–10] However, the direction of associations and strength of evidence vary by pollutant and study, highlighting uncertainty and heterogeneity in the evidence base. Considering the then-emerging nature of studies

Research in context

Evidence before this study

Before undertaking this study, we reviewed the existing literature as detailed in our published protocol for this study (Khreis et al. *Environ Int* 2022; **170:** 107596). This review included summarising systematic reviews (2015–22) on long-term outdoor air pollution exposure and risk of dementia, Parkinson's disease, multiple sclerosis, and motor neuron disease, and engaging in an review of the materials and a non-comprehensive review of the literature, including systematic reviews and meta-analyses, on the associations between various outdoor air pollutants and dementia incidence. We identified key gaps, such as little evidence on nitrogen dioxide (NO_2), nitrogen oxides, and black carbon (BC)/$PM_{2·5\ absorbance}$, a paucity of certainty of evidence assessment, and few subgroup or sensitivity analyses to explore the sources of large observed heterogeneity. Additionally, we found that the number of relevant primary studies had markedly increased since the previous systematic review publications. We subsequently developed and published a protocol for an updated systematic review and meta-analysis, which sought to deepen the understanding of the relationship between outdoor air pollution and dementia incidence, expand analyses to additional pollutants, subgroups, and subtypes of dementia, assess study quality and certainty of evidence, address previous inconsistencies, and provide updated estimates.

Added value of this study

Drawing on 32 studies (pooled population, n=26 180 535), this meta-analysis assessed the effect of long-term (≥1 year) exposures to single outdoor air pollutants on the risk of a subsequent diagnosis of dementia and dementia subtypes. Meta-analyses of individual pollutants identified incident dementia to be significantly positively associated with long-term exposure to $PM_{2·5}$, BC/$PM_{2·5\ absorbance}$, and NO_2. Our certainty of evidence assessment indicated a moderate level of certainty across the overall body of evidence. Our risk of bias assessment indicated generally low risk of bias, although three studies that contributed adjusted effect estimates in meta-analyses had probably high risk of bias in one domain. To our knowledge, this study provides the most comprehensive exposure-response estimates to date for use in burden of disease analyses, 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. Our subgroup analyses by dementia subtype, continent, outcome ascertainment, and exposure assessment methods also provide insights into how evidence strength varies across groups, and highlighted areas for future research.

Implications of all the available evidence

Our findings reinforce and build on existing evidence that long-term exposure to outdoor air pollution is a risk factor for the onset of dementia. Reducing pollution exposure could lower dementia rates, and stricter air quality standards would likely provide substantial health, social, and economic benefits.

looking at this putative association, and mixed findings of primary studies, a series of systematic reviews and meta-analyses were published. These reports concluded that $PM_{2·5}$ exposure might be associated with an increased risk of dementia, but yielded less clear findings on the associations with other pollutants and the differential effects on study-diagnosed dementia subtype.[11–20] Importantly, many of these works were 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 pollutant or assessed a limited number of air pollutants, or differed in the strength, significance, and direction of association.[12,13,15–17,20] Some of these studies focused on particular study-diagnosed subtypes (labelled as Alzheimer's disease and vascular dementia, for example), which are subject to considerable uncertainty as most dementia in older people is mixed in nature.[21,22]

The latest systematic review and meta-analysis was published by Wilker and colleagues and included 51 studies published up to July, 2022, 16 of which were included in the meta-analysis.[19] The authors concluded that there was some evidence to support a possible association between $PM_{2·5}$ and dementia (14 studies), and that this association was more robust when the meta-analysis was restricted to studies that used active case ascertainment (seven studies). There was more limited support for an association with nitrogen dioxide (NO_2; nine studies) and nitrogen oxides (NOx; five studies) and these associations were considered suggestive at the time.[19] They did not find a clear association with ozone (O_3; four studies). Most studies were at high risk of bias. This analysis provided important estimates but was limited in pollutants, the subgroup analyses performed (with no analysis by study-diagnosed dementia subtype), and by the absence of an overall certainty of evidence assessment and publication bias assessment.[19]

Since 2022, a surge in publications has provided an opportunity for a new, more comprehensive review. As such, in the present paper we present the findings of a systematic review and meta-analysis, which sought to deepen understanding of the relationship between outdoor air pollution and dementia incidence, expand analyses to additional pollutants and subgroups, assess study quality and certainty, address previous inconsistencies, and provide updated estimates to inform future burden of disease or health impact assessments, the study of mechanisms, and air quality policy.

Methods

Search strategy and selection criteria

A protocol for this systematic review and meta-analysis was published in December, 2022,[23] and registered with PROSPERO, CRD42023414413. Deviations from this protocol for the present systematic review and meta-analysis are listed in appendix 1 (p 2) and were mostly minor and more inclusive in nature.

The detailed methods are included in appendix 1 (pp 16–21), and are summarised herein. We conducted two searches of 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, once from database inception to Oct 11, 2022, and again from inception to Oct 23, 2023, using peer-reviewed and piloted search terms (appendix 1 pp 22–27).[23] Based on the original protocol, the literature searches included multiple sclerosis, Parkinson's disease, and motor neuron disease, the topics of another paper under review, alongside dementia.[23] Following title and abstract screening, articles were divided by outcome for separate full-text screening and data extraction and analysis.

Studies were eligible if they were based on the results of a primary case–control, cohort, cross-sectional, or ecological study of adults (aged ≥18 years), investigated exposure to outdoor air pollution for 1 year or longer (long term), quantitatively reported the association between single air pollutant exposures and a subsequent physician diagnosis of dementia (including subtypes: Alzheimer's disease, vascular dementia, or mixed Alzheimer's and vascular dementia; with diagnosis based on clinical diagnosis or assessment including medical, prescription, or insurance records or administered examinations, or self-report of a physician diagnosis) in adults without dementia at baseline, and were published in English. Administered examinations consisted of standardised cognitive assessments performed by trained assessors. We did not specify criteria relating to the sex of study participants. Complete inclusion and exclusion criteria are listed in appendix 1 (p 3) and the published protocol.[23]

Deduplication of the search results was completed in EndNote (version 21) followed by Zotero (version 6) and then Rayyan (version 1.2.2). Remaining articles were title and abstract screened by two independent reviewers (CBBR and AT-S). Articles 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 (HK).

Data analysis

With use of a standardised and piloted form developed through multiple iterations (appendix 2), data were extracted independently by two reviewers (CBBR and YS). Duplicate sheets were compared, and discrepancies were resolved through escalation to and discussion with a third reviewer (HK). Available unadjusted and adjusted measures of association (effect estimates: odds ratio [OR], risk ratio [RR], or hazard ratio [HR]) were recorded with their reported 95% CIs, unit of exposure (eg, $\mu g/m^3$ or parts per billion), scaling factor (eg, per 1 $\mu g/m^3$, 5 $\mu g/m^3$, or 10 $\mu g/m^3$ increment of exposure), and covariate adjustment. Additional data on study type, country, publication year, length of follow-up, population, exposure assessment, and funding were also recorded. The complete list of extracted data is included in appendix 1 (p 28).

See Online for appendix 1

Following data extraction, all studies were combined for analysis. Given that some of the included studies used the same study cohort, we included only the most recent study with the longest follow-up (prioritising follow-up duration over recency) in meta-analysis to avoid double counting. Meta-analyses were done when three or more independent studies reported an exposure–outcome pair. When more than one type of effect estimate per exposure–outcome pair was reported in a study, we selected the risk estimate for inclusion according to prespecified criteria (appendix 1 p 3). When outcomes are rare (ie, <10–20% incidence), the RR and OR can be approximated to HR.[24] Given that dementia is a rare outcome, pooling the HR, OR, and RR together in a single meta-analysis was considered acceptable. For each pollutant, adjusted and unadjusted effect estimates, when available, and their 95% CIs were harmonised to a prespecified exposure increment (appendix 1 p 4). Harmonised effect estimates were included in inverse-variance weighted random-effects meta-analyses, with use of the DerSimonian and Laird inverse-variance method with Hartung–Knapp modification to weight the harmonised estimates.[25] The pooled effect estimates were expressed as HRs. Separate meta-analyses were done with unadjusted and adjusted effect estimates, with the meta-analyses of adjusted estimates the main focus of this report. The standardisation of effect estimates was only possible for continuous variables. Thus studies reporting only categorical effect estimates were excluded from meta-analysis.

Between-study inconsistency was assessed using the I^2 statistic and the Cochran Q test (significant at $p<0{\cdot}05$). Heterogeneity was defined as low (<25%), moderate (25–50%), substantial (51–75%), or considerable (>75%). 95% prediction intervals (PIs), describing the range within which 95% of true effects were expected to lie, were calculated from the between-study variance (τ^2).

For pooled analyses including ten or more studies, we visually examined publication bias with funnel plots and conducted the Egger's linear regression test to estimate the potential publication bias. Regarding risk of bias for each included study (internal validity), two independent reviewers (CBBR and YS) assessed this bias using the Office of Health Assessment and Translation approach for systematic review and evidence integration for literature-based health assessments,[26] with modifications implemented after piloting the tool at the outset (appendix 1 p 18). No conflicts or discrepancies needed to be

See Online for appendix 2

escalated to a third reviewer. Finally, certainty of evidence was assessed by two reviewers (YS and CBBR; with discrepancies resolved by a third reviewer, ChB), who rated the confidence in the overall body of evidence using the Office of Health Assessment and Translation tool[26] (appendix 1 p 18).

Subgroup analyses were done based on continent, exposure assessment method, outcome definition and ascertainment, risk of bias, and by study-diagnosed dementia subtype (appendix 1 p 20). Herein, we present the subgroup analyses for exposure–outcome pairs when at least two subcategories had three or more studies, as we considered this to allow for a somewhat meaningful comparison within those groups. Differences between subgroups were tested with use of the meta package in R (version 4.2.2). In addition, we performed the following sensitivity analyses of the main analysis: using the Paule–Mandel method[27] with Hartung–Knapp modification in place of the DerSimonian–Laird method, given that the DerSimonian–Laird method might be negatively biased in scenarios with small studies and with a rare binary outcome;[16] excluding studies which relied on patient self-report of a physician diagnosis of dementia for outcome assessment, for which the potential of reporting error is higher than for administrative medical (eg, hospital) records; excluding studies which were determined to have one or more domain with at least probably high risk of bias; excluding the study with the largest weight (smallest standard error) from each meta-analysis via a leave-one-out approach; and excluding studies with models that were adjusted for comorbidities. As a further supplementary analysis, when three or more studies reported on the same multipollutant models, we conducted a meta-analysis.

Due to there being insufficient data to formally assess exposure-response functions, we conducted a simple visualisation of exposure-response pairs when we had at least four independent studies with at least three categories (levels) of exposure (ie, including studies that reported exposures and effect estimates categorically; appendix 1 p 21). For each pollutant, values for exposure categories were plotted against their respective effect estimates for each study.

All data analyses were conducted in R (version 4.2.2) with use of the meta, dmetar, metafor, tidyverse, readxl, ggplot2, ggeasy, reshape2, DescTools, tm, stringr, and dplyr packages. Statistical significance was assessed based on whether 95% CIs included the null.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Our initial search in October, 2022, identified 8319 unique publications across the eight databases. 66 publications were full-text screened, 32 of which were excluded because they met exclusion criteria or were a duplicate. The remaining 34 studies met our inclusion criteria and were included in data extraction. Our second search in October, 2023, identified 1005 unique publications, 59 of which were full-text screened, with 17 studies included in data extraction (figure 1). Thus, we extracted and reviewed data from 51 studies across both searches.[6,8,9,28–75]

Appendix 1 (pp 65–75) provides a summary of each study. In 34 (67%) of 51 studies, the minimum age of participants was 55, 60, or 65 years. The maximum reported age of a participant was 115 years and the minimum reported was 37 years, although not all studies recorded minimum and maximum age. For studies that recorded information on the distribution of sex, the proportion of female participants was between 43% and 72%. Three studies were exclusively in female participants[6,64,67] and one study was exclusively in male participants.[29] Reported follow-up periods ranged from 3 to 23 years, although many studies reported follow-up either as a median or mean. 20 (39%) studies were done in Europe, 17 (33%) in North America, 12 (24%) in Asia, and two (4%) in Oceania (both in Australia). Several studies reported on different dementia subtypes. 43 (84%) studies reported on dementia (including one study on non-Alzheimer's dementia[55]), 24 (47%) on Alzheimer's disease, 16 (31%) on vascular dementia, one (2%) on frontotemporal dementia, and one (2%) on mixed vascular dementia and Alzheimer's disease. The studies reported on one or more pollutant exposures, with 40 (78%) reporting on $PM_{2·5}$, 28 (55%) on NO_2, 17 (33%) on PM_{10}, 12 (24%) on NOx, ten (20%) on black carbon (BC)/$PM_{2·5\ absorbance}$, ten (20%) on annual O_3 (O_3 was reported on as warm-season or annual exposure, with two [4%] studies reporting on warm-season O_3), six (12%) on $PM_{2·5–10}$, five (10%) on carbon monoxide, five (10%) on sulphur dioxide, and three (6%) on nitrogen oxide. Additional pollutants were reported in two or fewer studies. 48 (94%) studies were cohort studies, two (4%) were cohort studies with a nested case–control analysis, and one (2%) was a case–control study.

Exposure assessment methods varied across studies and were divided into seven categories, based on an assessment of the included studies and relevant literature on exposure assessment methods,[76–78] with the most common method being land use regression models. Five studies relied on some form of patient self-report of a physician diagnosis of dementia (in some cases validated by medical records) and the remaining 46 studies used a variety of methods, including medical records, administered examinations, physician diagnosis, or a combination of two or more of these (hybrid).

Several of the 51 studies used the UK Biobank population or other large cohorts. Per the protocol, only the most recent study with the longest follow-up was included in the meta-analysis, prioritising follow-up duration over recency when multiple studies overlapped. This led to the removal of ten studies due to population overlap: Andersson et al (2018), Chen et al (2023), Ran et al (2021), Yuan et al (2023), Ma et al (2023), Chang et al (2014), Raichlen et al (2022),

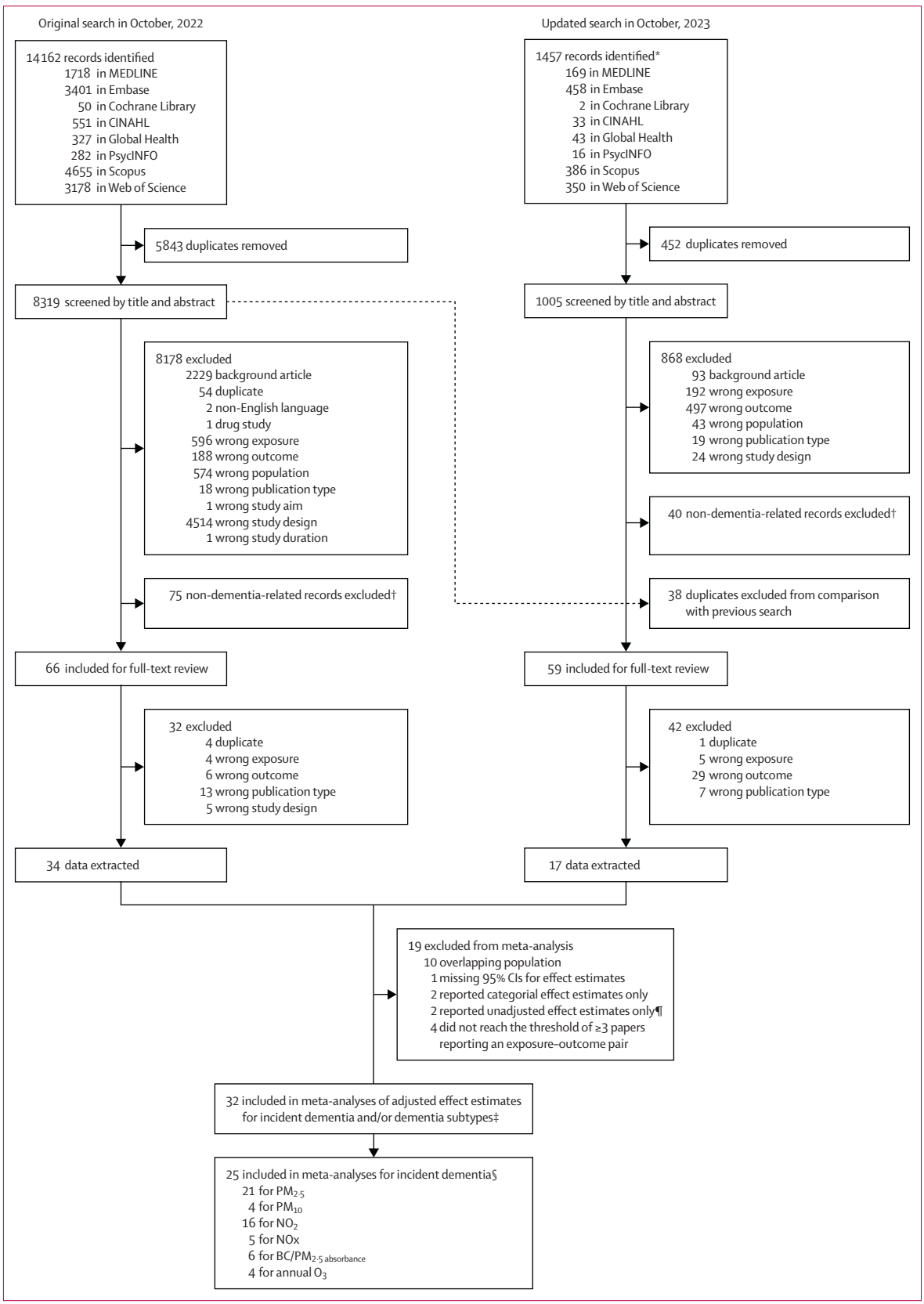

Figure 1: **PRISMA flow diagram of the systematic review process**
Lists of studies excluded at the title and abstract screening (appendix 3) and full-text screening stages (appendix 4) are included in the supplementary material. $BC/PM_{2·5\ absorbance}$=black carbon/$PM_{2·5\ absorbance}$. NO_2=nitrogen dioxide. NOx=nitrogen oxides. O_3=ozone. *1457 records identified after deduplicating records compared with the first search. †The search included multiple sclerosis, Parkinson's disease, and motor neuron disease, the topics of another paper, alongside dementia. Following title and abstract screening, articles were divided by outcome for separate full-text screening and data extraction and analysis. ‡Seven studies were included only in the subgroup analyses by study-diagnosed dementia subtype (appendix 1 pp 29–32). §Studies may have reported on more than one pollutant exposure in the following list. ¶Included in preliminary meta-analyses of unadjusted effect estimates (appendix 1 pp 61–62).

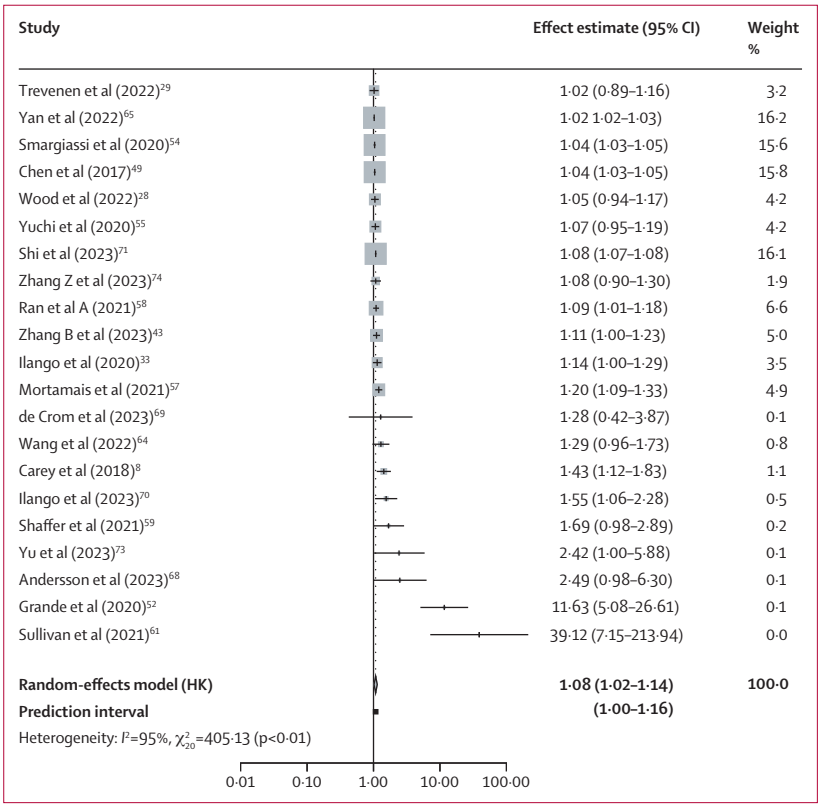

***Figure 2*: Random-effects meta-analysis of adjusted effect estimates for $PM_{2·5}$**
Individual estimates and pooled random-effects estimates for associations between $PM_{2·5}$ per 5 μg/m^3 increase in exposure and incident dementia. The pooled effect estimate was expressed as a hazard ratio. The x-axis is on log scale. Shaded boxes represent the point estimate for each study. The size of the boxes reflects the weight of the study in the meta-analysis. Errors bars represent the 95% CIs around each estimate. The pooled effect estimate is represented by a diamond, with the centre indicating the summary estimate and the horizontal points representing the 95% CI. The 95% prediction interval is represented by a square. HK=Hartung–Knapp.

See Online for appendix 3
See Online for appendix 4

Cacciottolo et al (2017), Li et al (2022), and Dimakakou et al (2020).[6,9,31,35–41] Details of exclusions due to population overlap are documented in appendix 1 (pp 10–12).

41 studies remained for meta-analysis. Xie et al (2023)[42] was subsequently removed due to not recording 95% CIs for effect estimates, bringing the number of studies to 40. Of those 40 studies, two were excluded from meta-analyses (He at al [2022][32] and Wu et al [2015][47]) as these studies reported categorical effect estimates only. Of the remaining 38 studies, 32 recorded adjusted effect estimates for exposure–outcome pairs that were reported in three or more studies (for $PM_{2·5}$, NO_2, NOx, $BC/PM_{2·5\ absorbance}$, PM_{10}, and annual O_3) and were therefore included in meta-analyses (pooled population, n=26 180 535; figure 1).[8,28,29,33,43–46,49,51–61,63–71,73–75] A summary of decisions to include or exclude studies and further conditions of inclusion are provided in appendix 1 (pp 65–75). 25 of the studies reporting dementia as the outcome were included in meta-analyses to assess the relationship of pollutant exposures with overall dementia. Of the remaining seven studies, six only reported on dementia subtypes (ie, Alzheimer's disease, vascular dementia, and mixed vascular dementia and Alzheimer's disease),[44–46,66,67,75] and one reported on dementia but was not the most recent study for the pollutant–outcome pair (this study also reported on mixed vascular dementia and Alzheimer's disease)[63]; these studies were included only in the subgroup analyses by study-diagnosed dementia subtype. Of the total 32 included studies overall, 15 (47%) were from North America, eight (25%) were from Europe, seven (22%) were from Asia, and two (6%) were from Oceania, spanning a total of 11 countries or territories (appendix 1 pp 65–75).

For $PM_{2·5}$, 21 studies with adjusted effect estimates were included in the meta-analysis for overall dementia (pooled population, n=24 030 527).[8,28,29,33,43,49,52,54,55,57–59,61,64,65,68–71,73,74] The pooled adjusted HR per 5 μg/m^3 increase in exposure was 1·08 (95% CI 1·02–1·14), indicating a significant association between $PM_{2·5}$ exposure and incident dementia (figure 2). The I^2 value was 95%, representing considerable statistical heterogeneity and Q was statistically significant (p<0·01). The 95% PI was 1·00–1·16. Two studies in the pooled analysis had wide 95% CIs.[52,61] These values were rescaled to a 1 μg/m^3 exposure increment and then manually checked. The wide 95% CIs were determined to be the result of scaling up; the 95% CIs were wide in the original studies for small increases in $PM_{2·5}$ exposure (per 0·88 μg/m^3 for Grande et al [2020];[52] per 1 μg/m^3 for Sullivan et al [2021][61]), which was not observed in the other studies.

For NO_2, 16 studies with adjusted effect estimates were included in the meta-analysis for dementia (pooled population, n=17 228 429).[8,28,29,33,43,49,54–57,60,64,69,70,73,74] The pooled adjusted HR per 10 μg/m^3 increase in exposure was 1·03 (95% CI 1·01–1·05), indicating a significant association (figure 3). The I^2 value was 84%, representing considerable heterogeneity, and Q was statistically significant (p<0·01). The 95% PI was 1·00–1·07.

For NOx, five studies with adjusted effect estimates were included in the meta-analysis for dementia (pooled population, n=241 409).[51–53,69,74] The pooled adjusted HR per 10 μg/m^3 increase in exposure was 1·05 (95% CI 0·97–1·13), suggesting no significant association (figure 4). The I^2 value was 44% indicating moderate heterogeneity, Q was not statistically significant (p=0·13), and the 95% PI was 0·92–1·19.

For $BC/PM_{2·5\ absorbance}$, six studies with adjusted effect estimates were included in the meta-analysis for dementia (pooled population, n=19 421 865).[29,55,57,69,71,74] The pooled adjusted HR per 1 μg/m^3 increase in exposure was 1·13 (95% CI 1·01–1·27; figure 5), suggesting a significant association. The I^2 value was 97% indicating considerable heterogeneity, Q was statistically significant (p<0·01), and the 95% PI was 0·72–1·78.

For PM_{10}, four studies with adjusted effect estimates were included in the meta-analysis for dementia (pooled population, n=246 440).[28,69,70,74] The pooled adjusted HR per 15 μg/m^3 increase in exposure was 1·52 (95% CI 0·80–2·87), suggesting no significant association (figure 6).

The I^2 value was 82% indicating considerable heterogeneity, Q was statistically significant (p<0·01), and the 95% PI was 0·20–11·61.

For annual O_3, four studies with adjusted effect estimates were included in the meta-analysis for dementia (pooled population, n=419 972).[8,28,43,73] The pooled adjusted HR per 45 μg/m^3 increase in exposure was 0·82 (95% CI 0·35–1·92), suggesting no significant association (appendix 1 p 28). The I^2 value was 69% indicating substantial heterogeneity, Q was statistically significant (p=0·02), and the 95% PI was 0·17–3·95.

For assessment of publication bias, only the meta-analyses of NO_2 and $PM_{2·5}$ reached the threshold of ten studies for assessing small-study effects with use of Egger's linear regression test. The studies for $PM_{2·5}$ produced an asymmetrical funnel plot, with a large concentration of studies near the top of the plot with low standard error, suggesting that small studies might be systematically missing due to publication bias (appendix 1 p 56). Egger's linear regression test (intercept=2·29, p=0·03) provided further evidence of funnel plot asymmetry. The NO_2 studies produced a more symmetrical funnel plot than those for $PM_{2·5}$, although there was evidence of missing studies on the lefthand-side of the plot, again indicating potential publication bias (appendix 1 p 57). The intercept of 1·19 (p=0·10) from Egger's linear regression test did not differ significantly from zero suggesting no significant asymmetry. These results suggested a true positive effect in the meta-analysis. The risk of bias (internal validity) and certainty of evidence results are presented in appendix 1 (pp 5–10). Three (9%) of the 32 studies included in the meta-analyses had a probably high risk of bias in one of seven domains;[28,29,33] all other studies had ratings of probably to definitely low risk of bias in the seven domains. We considered the certainty of evidence of all 51 studies identified in the systematic review, to allow interpretation of the results of meta-anlyses in the context of the entire body of relevant studies as a whole. In this assessment, the overall certainty of evidence was rated as moderate.

Appendix 1 (pp 29–38) presents the results of meta-analyses according to specified subgroups, for exposure–outcome pairs meeting the threshold of three or more studies in at least two subgroup categories. When analysed by study-diagnosed subtype of dementia, the pooled HR point estimates of effect size for $PM_{2·5}$, NO_2, and $BC/PM_{2·5\ absorbance}$ were numerically higher for vascular dementia than for Alzheimer's disease, although testing for subgroup differences showed the differences were not statistically significant (appendix 1 pp 29–31). For PM_{10}, the pooled HR point estimate for vascular dementia was numerically lower than for Alzheimer's disease, although again, the difference was not statistically significant (appendix 1 p 32). When analysed by continent, the pooled HR point estimate was numerically higher in Europe than in North America for $PM_{2·5}$ and, marginally, for NO_2, although the differences were not statistically significant (appendix 1 pp 33–34). When studies of $PM_{2·5}$ and NO_2 were analysed by exposure assessment method, no statistically significant differences were found (appendix 1 pp 35–36). When analysed by outcome ascertainment methods, the pooled HRs differed significantly between outcome ascertainment methods for $PM_{2·5}$ (appendix 1 p 37). Only the pooled HRs from studies that used medical records (the subgroup with the largest number of studies) or a hybrid method (a combination of two or more

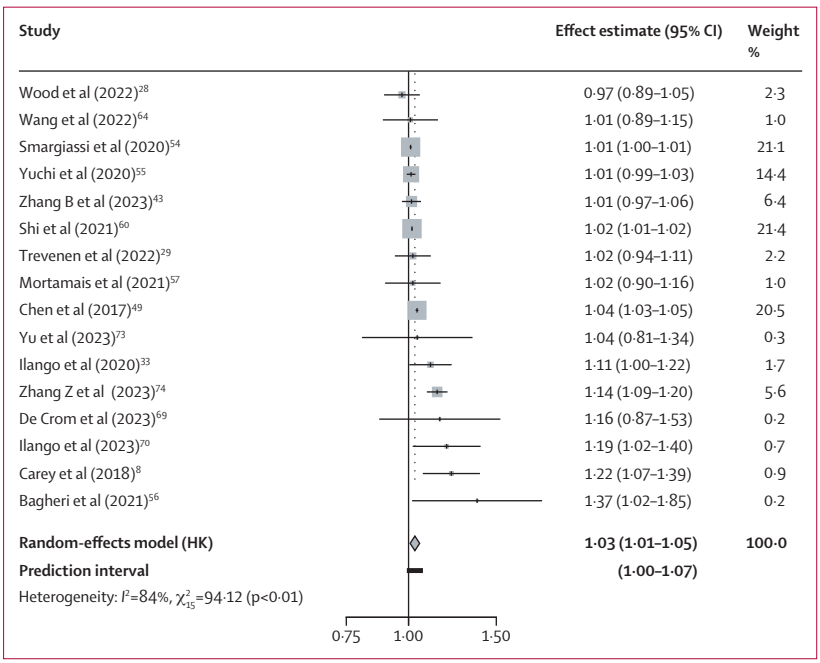

Figure 3: **Random-effects meta-analysis of adjusted effect estimates for NO_2**
Individual estimates and pooled random-effects estimates for associations between NO_2 per 10 μg/m^3 increase in exposure and incident dementia. The pooled effect estimate was expressed as a hazard ratio. The x-axis is on log scale. Shaded boxes represent the point estimate for each study. The size of the boxes reflects the weight of the study in the meta-analysis. Errors bars represent the 95% CIs around each estimate. The pooled effect estimate is represented by a diamond, with the centre indicating the summary estimate and the horizontal points representing the 95% CI. The 95% prediction interval is represented by a square. HK=Hartung–Knapp. NO_2=nitrogen dioxide.

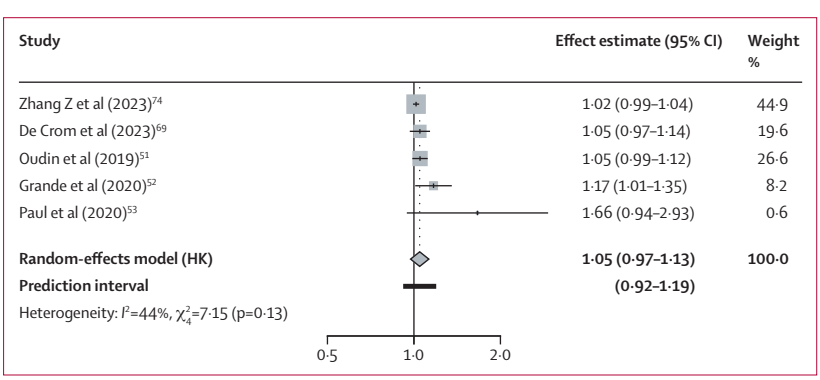

Figure 4: **Random-effects meta-analysis of adjusted effect estimates for NOx**
Individual estimates and pooled random-effects estimates for associations between NOx per 10 μg/m^3 increase in exposure and incident dementia. The pooled effect estimate was expressed as a hazard ratio. The x-axis is on log scale. Shaded boxes represent the point estimate for each study. The size of the boxes reflects the weight of the study in the meta-analysis. Errors bars represent the 95% CIs around each estimate. The pooled effect estimate is represented by a diamond, with the centre indicating the summary estimate and the horizontal points representing the 95% CI. The 95% prediction interval is represented by a square. HK=Hartung–Knapp. NOx=nitrogen oxides.

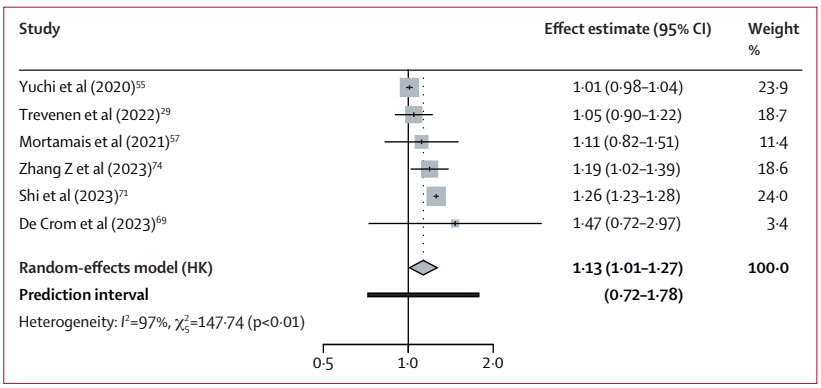

Figure 5: **Random-effects meta-analysis of adjusted effect estimates for BC/$PM_{2·5\ absorbance}$**
Individual estimates and pooled random-effects estimates for associations between BC/ $PM_{2·5\ absorbance}$ per 1 μg/m^3 increase in exposure and incident dementia. The pooled effect estimate was expressed as a hazard ratio. The x-axis is on log scale. Shaded boxes represent the point estimate for each study. The size of the boxes reflects the weight of the study in the meta-analysis. Errors bars represent the 95% CIs around each estimate. The pooled effect estimate is represented by a diamond, with the centre indicating the summary estimate and the horizontal points representing the 95% CI. The 95% prediction interval is represented by a square. HK=Hartung–Knapp. BC/$PM_{2·5\ absorbance}$=black carbon/$PM_{2·5\ absorbance}$.

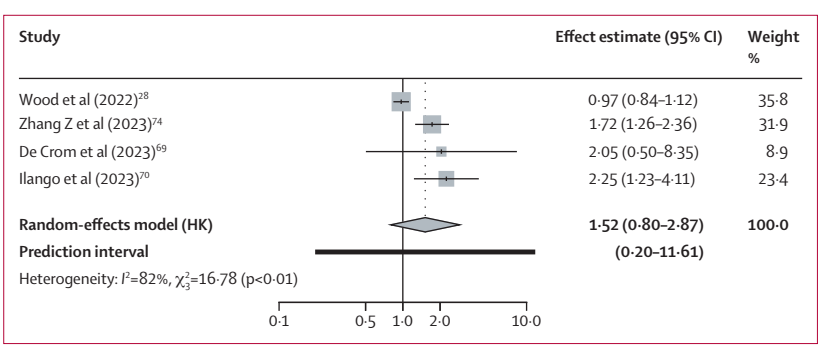

Figure 6: **Random-effects meta-analysis of adjusted effect estimates for PM_{10}**
Individual estimates and pooled random-effects estimates for associations between PM_{10} per 15 μg/m^3 increase in exposure and incident dementia. The pooled effect estimate was expressed as a hazard ratio. The x-axis is on log scale. Shaded boxes represent the point estimate for each study. The size of the boxes reflects the weight of the study in the meta-analysis. Errors bars represent the 95% CIs around each estimate. The pooled effect estimate is represented by a diamond, with the centre indicating the summary estimate and the horizontal points representing the 95% CI. The 95% prediction interval is represented by a square. HK=Hartung–Knapp.

outcome ascertainment methods) remained statistically significant. The other subgroups of studies (those that used physician diagnosis or administered examinations) had larger, non-statistically significant pooled HRs but smaller numbers of studies. For NO_2, the pooled HRs did not differ significantly between outcome ascertainment methods (appendix 1 p 38). When comparing studies with definitely or probably low risk of bias versus those with one or more domain with at least probably high risk of bias, the pooled HRs did not differ significantly between the subgroups for $PM_{2·5}$ or NO_2 (appendix 1 pp 63–64).

Five sensitivity analyses were done to check the robustness of findings in the main meta-analyses. Use of the Paule–Mandel method instead of the DerSimonian–Laird method yielded variable changes in the pooled HRs but no changes to overall conclusions (appendix 1 pp 39–42). For $PM_{2·5}$, NO_2, NOx, and annual O_3, the 95% CIs and 95% PIs were wider with the Paule–Mandel method than with the DerSimonian–Laird method, whereas for PM_{10}, both intervals were narrower, and for BC/$PM_{2·5\ absorbance}$, the 95% PI was narrower. The second sensitivity analysis removed studies in which dementia was based on patient self-report of a physician diagnosis. Of the studies included in meta-analyses, both Wood et al (2022)[28] and Trevenen et al (2022)[29] relied on patient self-report, and both were removed from meta-analyses (three other studies identified in the systematic review also relied on self-report, validated with the UK Biobank algorithm,[30,31,34] but were not included in the meta-analyses of adjusted effect estimates due to population overlap or an insufficient number of studies). For $PM_{2·5}$ and NO_2, the removal of the two studies altered the 95% CIs but did not change the conclusions (appendix 1 pp 43, 45). Similarly, for annual O_3, the removal of Wood et al (2022) changed the pooled HR and 95% CIs but did not change the conclusion (appendix 1 p 46). For BC/$PM_{2·5\ absorbance}$, the removal of Trevenen et al (2022) rendered the pooled HR non-statistically significant (appendix 1 p 46). For PM_{10}, the removal of Wood et al (2022) rendered the HR statistically significant (appendix 1 p 44). Sensitivity analysis excluding studies with one or more domain with at least probably high risk of bias altered the overall 95% CIs, but did not affect the statistical significance of the HRs for $PM_{2·5}$ and NO_2 (appendix 1 pp 47–48). For PM_{10}, removing the single study with probably high risk of bias (Wood et al [2022][28]) rendered the pooled HR significant, and for BC/$PM_{2·5\ absorbance}$, removing the single study with probably high risk of bias (Trevenen et al [2022][29]) rendered the HR non-significant (appendix 1 pp 49–50). For annual O_3, the removal of Wood et al (2022) did not change the conclusion (appendix p 50). In the leave-one-out sensitivity analysis, excluding the studies with the largest weights had little effect on the pooled HRs for $PM_{2·5}$ (Yan et al [2022][65]), NO_2 (Shi et al [2021][60]), and NOx (Zhang et al [2023][74]; appendix 1 pp 51–52). For O_3, excluding the largest-weight study (Zhang et al [2023][43]) widened the 95% CIs but had a small effect on the overall HR (appendix 1 p 53). For BC/$PM_{2·5\ absorbance}$, removing the largest-weight study (Shi et al [2023][71]) rendered the pooled HR non-significant, and for PM_{10}, removing the largest-weight study (Wood et al [2022][28]) rendered the pooled HR significant (appendix 1 p 53). Generally, the BC/$PM_{2·5\ absorbance}$ meta-analysis was sensitive to omitting individual studies in the leave-one-out sensitivity analysis. Sensitivity analysis excluding the studies that adjusted for comorbidities had small effects on the pooled HRs for $PM_{2·5}$, NO_2, and NOx, whereas for PM_{10} it widened the 95% CIs; for all of these pollutants, conclusions were unchanged (appendix 1 pp 54–55). For BC/$PM_{2·5\ absorbance}$, excluding the studies that adjusted for comorbidities rendered the overall HR non-significant (appendix 1 p 55).

We conducted preliminary meta-analyses with unadjusted effect estimates when three or more studies reporting unadjusted estimates for an exposure–outcome

pair were available. Thus, analyses were done for the associations of $PM_{2·5}$ and NO_2 exposure with dementia (appendix 1 pp 61–62). The pooled HR point estimates based on unadjusted values were numerically higher for $PM_{2·5}$ and, marginally, for NO_2, than in the meta-analyses of adjusted estimates. In supplementary assessment of multipollutant models, only one multipollutant model (for $PM_{2·5}$, controlling for NO_2) reached the threshold of three studies. We found no evidence of a significant relationship between $PM_{2·5}$ and dementia when controlling for NO_2 in this pooled analysis (adjusted HR 1·02 [95% CI 0·99–1·05]; appendix 1 p 60).

Exposure-response functions were constructed for PM_{10} and Alzheimer's disease, NO_2 and Alzheimer's disease, and $PM_{2·5}$ and Alzheimer's disease based on studies reporting categorial exposures and effect estimates. In each case, there were both monotonic and non-monotonic relationships represented (appendix 1 pp 58–59).

Discussion

In this systematic review and meta-analysis, we observed positive and statistically significant associations between incident dementia and previous long-term exposure to $PM_{2·5}$, NO_2, and $BC/PM_{2·5\ absorbance}$, in adults without dementia at baseline. We found no evidence for such an association with NOx, PM_{10}, and annual O_3, based on small numbers of studies.

Abolhasani and colleagues reported an adjusted HR for the association between $PM_{2·5}$ and dementia of 1·03 (95% CI 1·02–1·05) per 1 $\mu g/m^3$ increment; as well as adjusted HRs for the association with NO_2 (HR 1·03 [1·00–1·07] per 10 $\mu g/m^3$), NOx (HR 1·05 [0·99–1·13] per 10 $\mu g/m^3$), and O_3 (HR 1·01 [0·91–1·11] per 10 $\mu g/m^3$).[18] Wilker and colleagues reported an adjusted HR for the association between $PM_{2·5}$ and dementia of 1·04 (95% CI 0·99–1·09) per 2 $\mu g/m^3$ based on 14 studies, which increased in effect size when restricting the meta-analysis to seven studies that used active case ascertainment (HR 1·42 [1·00–2·02] per 2 $\mu g/m^3$).[19] They also reported adjusted HRs for the association with NO_2 (HR 1·02 [0·98–1·06] per 10 $\mu g/m^3$), NOx (HR 1·05 [0·98–1·13] per 10 $\mu g/m^3$), and O_3 (HR 1·00 [0·98–1·05] per 5 $\mu g/m^3$).[19] Our meta-analysis included more studies than these previous analyses. This review therefore strengthens evidence for an association with $PM_{2·5}$ while building on recent insufficient evidence for NO_2 and NOx and providing new evidence for $BC/PM_{2·5\ absorbance}$.

For all pollutants except NOx, we observed significant heterogeneity across studies. This finding likely reflects the range in the exposure assessment methods, outcome ascertainment methods, demographic characteristics of the study populations, varying geographical and socioeconomic contexts of the studies, differences in the air pollution composition, and potentially underlying susceptibility factors.

In subgroup analyses, we observed numerically higher point estimates of effect size for $PM_{2·5}$, $BC/PM_{2·5\ absorbance}$, and NO_2 for vascular dementia than for Alzheimer's disease, although the differences between subgroups were not statistically significant. Previous meta-analyses of $PM_{2·5}$ and Alzheimer's disease or vascular dementia found similar results, but not for the range of pollutants analysed here.[79] However, it is important to note that the subgroup analyses were limited by small numbers of studies, and that most of the studies did not make a pathological diagnosis of either Alzheimer's disease or vascular dementia, but rather relied on non-validated, non-standardised methods of diagnosis, which are not the clinicopathological diagnosis required to make an accurate subtype grouping.[21] There is also increasing recognition that Alzheimer's disease and vascular dementia, although distinct clinical entities, often co-exist as a form of mixed dementia, and likely exist at different points on a single spectrum and potentiate each other.[21,80–82]

The subgroup analyses by continent also showed some numerical differences in the point estimates of effect size for NO_2 and $PM_{2·5}$, albeit the differences were not statistically significant. The presence of some variation, albeit not statistically significant, in point estimates between subgroups according to exposure assessment method for $PM_{2·5}$ suggests the need for additional research before future meta-analyses to assess which methods perform best, including their ability to capture the true variance in the exposure of participants. Initial reports indicate that the performance of land use regression, Bayesian maximum entropy, and 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.[83–85] The subgroup results on outcome ascertainment method, with there being a statistically significant difference between subgroups for $PM_{2·5}$, might reflect the differences in the number of studies using each outcome ascertainment method (with the subgroups not reaching statistical significance having few studies). However, future work should focus on producing high-quality reproducible outcome ascertainment methods.

The results from the sensitivity analysis using the Paule–Mandel method were generally similar to those in the primary analysis, although with variation in 95% CIs; notably for $PM_{2·5}$, the point estimate of effect size was higher and the 95% CIs wider. It has previously been shown that in some circumstances the Paule–Mandel estimator can introduce substantial positive bias, whereas the DerSimonian–Laird method might be negatively biased, and thus the true effect could lie somewhere in between.[86] The remaining sensitivity analyses supported this paper's primary findings except in the $BC/PM_{2·5\ absorbance}$ and PM_{10} analyses. Future work when more data on the associations for $BC/PM_{2·5\ absorbance}$ and PM_{10} are available will be useful in elucidating those associations.

Epidemiological studies have a crucial role in providing 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.[87] Several

mechanisms, including direct and indirect effects, have been proposed to explain how air pollution might contribute to the development of dementia, often involving the well established roles of neuroinflammation and oxidative stress, although this remains an active area of research.[88–93]

Initial evidence for direct effects comes from dogs living in cities with high amounts of air pollution, which were found to have metal accumulation in a gradient from the olfactory mucosa to the frontal cortex, suggesting the olfactory mucosa and nerve to be a point of entry.[93,94] Blood–brain barrier disruptions, reactive astrocytosis, and neurofibrillary tangles were observed in samples of the dogs' brains on electron microscopy, matching the pathology in the brains of humans with Alzheimer's disease.[94] Furthermore, in rodent models and human autopsy studies, exposures to some air pollution components were found to cause transcriptional activation of NF-κB, a key proinflammatory transcription factor. Such transcriptional activation of NF-κB might promote sustained production of neurotoxins such as reactive oxygen species through downstream activation of pathways including enzymes such as NADPH oxidases.[92,95,96]

Systemic pathways might also contribute to the pathogenesis of dementia. Air pollutants can enter circulation from the lungs and travel to solid organs, initiating inflammation.[97–99] There is evidence from mouse models that O_3 causes a peripheral immune response after entry through the lungs, involving the upregulation of factors such as the HMGB1 protein.[92,100] This upregulation of HMGB1 impairs the protective microglial response in the brain by reducing the expression of TREM2, leading to increased accumulation of amyloid-β plaques in a dose-dependent manner.[101–105]

We acknowledge several limitations of our review and analyses. Firstly, there are limitations with respect to the studies included. A substantial limitation in air pollution and health research arises from the modelling of human exposure. Assessment methods fail to capture true personal exposure variations.[106] The use of home address as a proxy for exposure assessment disregards time spent at work or in other settings, or commuting, which are exposure microenvironments that vary between individuals, likely biasing the results toward the null.[107–109] Despite these individual-level limitations, our results provide valuable insights into the population-level effects and have applications in the estimation of potential benefits of regulatory interventions. However, there is a need for methodologies to be improved in terms of reliability and their representation of complex real-world conditions.

The exposure assessment methods used, and the durations exposures are modelled for, additionally introduce uncertainty to the results presented in this study. The included studies used a variety of exposure assessment methods (including land use regression models, dispersion models, and chemical transport models). Each model incorporates various uncertainties based on model set up, input data, calculations, and underlying assumptions, and accordingly the models have varying performances, including by air pollutant, and are fit for different purposes and geographical contexts.[43–45] Given that the 95% CIs in this meta-analysis do not account for uncertainty stemming from the different exposure assessment methods, they should be interpreted with caution, as they might underestimate the true extent of uncertainty present in the models.

A further important consideration, which represents a known limitation in this field, is that although we analysed single pollutants, air pollution exists as a complex mixture of multiple correlated pollutants. Therefore, effect estimates might not represent the effects of individual pollutants. This caution should frame our results. The single pollutant approach might disregard permissive and synergistic effects between pollutants.[110–112] Categories of air pollutants are not mutually distinct: for example, a major contributor to particulate matter is NOx.[113] Various approaches have been suggested to address this shortcoming but are challenging to implement partly due to the correlated nature of pollutant exposures.[110,114–116] The only multipollutant model for which there was sufficient studies to explore the relationship in a meta-analysis was for $PM_{2·5}$, controlling for NO_2 (pooling Yu et al [2023],[73] Smargiassi et al [2020],[54] and Yan et al [2022][65]). We found no evidence of a significant relationship between $PM_{2·5}$ and dementia when controlling for NO_2 in this pooled analysis. For robust evidence, we recommend that future research investigates and further assesses how multipollutant models compare to the single-pollutant models included in this review.

Another limitation relates to case ascertainment. Passive case ascertainment is cost-effective and enables investigation of large populations.[117] However, it might introduce potential confounding bias as participants with comorbidities caused by air pollution might have increased contact with a health-care system, which could bias away from the null. By contrast, under-ascertainment of cases, especially in groups such as Black Americans with increased exposure to air pollution, might lead to bias towards the null.[118,119]

The studies with data on participants' ethnicity showed that the populations were predominantly White. This is a limitation for the generalisability of results given that there is evidence that marginalised groups have increased exposure to air pollution, which is not fully explained by socioeconomic status or geography.[118,120,121] This difference is made more noteworthy by evidence suggesting that reducing air pollution exposure has a higher benefit for reducing mortality for such marginalised groups than for non-marginalised groups.[118,122] Additionally, most of the studies in this analysis were based in high-income countries. Collectively, these factors limit the generalisability of our results as they represent possible confounding factors, and emphasise the need for future work to capture the effect of air pollution on incident dementia in a wider range of social, cultural, and geographical contexts, including a distinction between rural and urban populations.

There are also limitations with respect to the meta-analysis process. The conversion of effect estimates to the same exposure increment assumed constant ambient temperature and pressure, which might have introduced inaccuracies due to natural fluctuations in temperature and pressure throughout the year.[123] However, given the absence of specific information on temperature and pressure from included studies, these conversions were deemed the most appropriate approach and followed standard analytical practices.

The meta-analyses included effect estimates that were adjusted for different covariates and at varying levels (as described in appendix 1 [pp 65–75]). 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 conducted preliminary meta-analyses with the extracted unadjusted effect estimates when three or more studies reporting unadjusted estimates were available. The finding that the point estimates of effect size from the unadjusted analyses were numerically higher for $PM_{2·5}$ and, marginally, for NO_2, than in the analyses of adjusted estimates suggests that confounding factors were inflating the apparent association. Given that the numbers of studies in the unadjusted analyses were smaller than in the primary analyses, this interpretation is limited.

Finally, although our data extraction process adhered to gold-standard protocols with two independent reviewers, an internal review (HK) identified discrepancies, prompting a third independent verification of all extracted data. These findings underscore the importance of additional verification steps beyond gold-standard practices, with the potential to enhance accuracy with a third unaffiliated reviewer as an external check. Future opportunities might exist in leveraging artificial intelligence tools to streamline error-prone tasks, which would serve as an impartial reviewer and potentially reduce the burden of manual oversight.[124]

As a strength of this analysis, we developed and published a protocol for this systematic review and meta-analysis a priori, and followed this with only slight deviations (appendix 1 p 2), lowering the risk of bias.[23] We also addressed factors that can decrease confidence in the body of evidence, such as studies with a probably high risk of bias, which we omitted in a sensitivity analysis. Additionally, we conducted a risk of bias assessment for each individual paper at the most granular level possible. We did not categorically address potential bias at the journal level.

In our certainty of evidence assessment, we found the overall confidence in the body of evidence to be moderate. 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 is characteristic of air pollution epidemiology. Such heterogeneity is not necessarily of major concern for this analysis, given that predefined eligibility criteria for the meta-analysis were defined through thorough discussions with leading experts and tested through pilot searches, and that data were correctly extracted by two independent reviewers and verified by a third.[125] The presence of cross-population and cross-study design consistency, and the evidence of an exposure-response relationship in exposure-response functions, increased our confidence in the body of evidence to moderate. Taken together, the robustness of our prepublished protocol and results of the certainty of evidence, risk of bias, and various predefined sensitivity and subgroup analyses provide us with confidence in the synthesised body of evidence and highlight areas for further investigation.

Building on existing evidence, our results show that $PM_{2·5}$, NO_2, and $BC/PM_{2·5\ absorbance}$ are risk factors for incident dementia. The findings suggest that efforts to reduce exposure to these pollutants would help to reduce the global burden of dementia. The widespread nature of air pollution signals an urgent need for policy interventions to combat exposure equitably. Additionally, our meta-analysis reports on variations in effect estimates for Alzheimer's disease and vascular dementia and between continents. Interpretation of these variations remains limited, and further research is necessary into the causal pathways and sources and toxicity of specific and multiple air pollutants, to determine impact on the development of dementia. Future research should aim to better represent low-income and middle-income countries and include diverse populations spanning different racial and ethnic groups, levels of urbanisation, and socioeconomic backgrounds. Such efforts would ultimately inform a truly global and equitable approach to reduce the burden of dementia, and yield long-term health, social, and economic benefits.

Contributors

CBBR: primary acquisition of data, 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. Had access to raw data and accessed and verified data. ChB: 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. Had access to raw data and accessed and verified data. Drafting portions of the original protocol manuscript (Khreis et al. *Environ Int* 2022; **170:** 107596). YS: initial acquisition and analysis of data. AT-S: initial acquisition of data. MS: acquisition and analysis of data. Drafting portions of the original protocol manuscript. KWF: acquisition and analysis of data. Drafting portions of the original protocol manuscript. LH: acquisition and analysis of data. Drafting portions of the original protocol manuscript. VP: acquisition of data. Critical revision of the manuscript for important intellectual content. Drafting portions of the original protocol manuscript. ZJA: concept. Critical revision of the manuscript for important intellectual content. SJS: 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. All authors: full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data extracted for this systematic review and meta-analysis will be made available to others (as appendix 2) with publication. The study protocol is already published 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 with a proposal.

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