Ambient air pollution and clinical dementia: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To investigate the role of air pollutants in risk of dementia, considering differences by study factors that could influence findings.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

EMBASE, PubMed, Web of Science, Psycinfo, and OVID Medline from database inception through July 2022.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Studies that included adults (≥18 years), a longitudinal follow-up, considered US Environmental Protection Agency criteria air pollutants and proxies of traffic pollution, averaged exposure over a year or more, and reported associations between ambient pollutants and clinical dementia. Two authors independently extracted data using a predefined data extraction form and assessed risk of bias using the Risk of Bias In Non-randomised Studies of Exposures (ROBINS-E) tool. A meta-analysis with Knapp-Hartung standard errors was done when at least three studies for a given pollutant used comparable approaches.

RESULTS

2080 records identified 51 studies for inclusion. Most studies were at high risk of bias, although in many cases bias was towards the null. 14 studies could be meta-analysed for particulate matter <2.5 µm in diameter ($PM_{2.5}$). The overall hazard ratio per 2 µg/m^3 $PM_{2.5}$ was 1.04 (95% confidence interval 0.99 to 1.09). The hazard ratio among seven studies that used active case ascertainment was 1.42 (1.00 to 2.02) and among seven studies that used passive case ascertainment was 1.03 (0.98 to 1.07). The overall hazard ratio per 10 µg/m^3 nitrogen dioxide was 1.02 ((0.98 to 1.06); nine studies) and per 10 µg/m^3 nitrogen oxide was 1.05 ((0.98 to 1.13); five studies). Ozone had no clear association with dementia (hazard ratio per 5 µg/m^3 was 1.00 (0.98 to 1.05); four studies).

CONCLUSION

$PM_{2.5}$ might be a risk factor for dementia, as well as nitrogen dioxide and nitrogen oxide, although with more limited data. The meta-analysed hazard ratios are subject to limitations that require interpretation with caution. Outcome ascertainment approaches differ across studies and each exposure assessment approach likely is only a proxy for causally relevant exposure in relation to clinical dementia outcomes. Studies that evaluate critical periods of exposure and pollutants other than $PM_{2.5}$, and studies that actively assess all participants for outcomes are needed. Nonetheless, our results can provide current best estimates for use in burden of disease and regulatory setting efforts.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42021277083.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Accumulating evidence suggests that air pollutants may contribute to the risk of dementia

Few meta-analyses have been performed and none that included more recent studies that use active case ascertainment, nor any that used in depth assessment of risk of bias with the Risk Of Bias In Non-randomized Studies of Exposure (ROBINS-E) tool

WHAT THIS STUDY ADDS

A systematic assessment of the literature that suggests exposure to particulate matter <2.5 microns in diameter (PM2.5) is associated with increased risk of dementia, and with somewhat less data, exposure to nitrogen dioxide and nitrogen oxide as well

The findings support the public health importance of limiting exposure to PM2.5 and other air pollutants and provides a best estimate of effect for use in burden of disease and policy deliberations

Introduction

More than 57 million people worldwide are living with dementia and the global burden continues to increase.[1] However, interventions to delay or prevent the onset of dementia are scarce. Long term ambient air pollution has been acknowledged as a potentially modifiable risk factor for dementia on the basis of long standing evidence that supports an association between exposure to air pollution and cardiovascular disease,[2 3] stroke,[4] and somewhat more recently, cognitive impairment.[5 6] Studies have also shown that reductions in air pollution concentrations are associated with reduced mortality.[7 8]

The number of studies evaluating the association between ambient air pollution and dementia has increased over the past decade, but studies have used different approaches to identify dementia cases, estimate long term exposures to ambient environmental exposures, and quantify the associations. Previous systematic reviews have either avoided combining estimates across studies because of these differences or attempted to review and combine estimates without acknowledgment of these issues.[5 6 9 10] Furthermore, no systematic review has been done since the publication of several studies that used active case ascertainment approaches. Additionally, none have evaluated bias by use of the new Risk of Bias In Non-randomised Studies of Exposures (ROBINS-E) tool,[11] which addresses bias issues in environmental studies in much greater detail than other assessment approaches. We therefore conducted a systematic review and meta-analysis of the

literature on associations between ambient pollutants and clinical dementia using the ROBINS-E to evaluate potential biases and identify how potential biases might impact the interpretation of aggregate results. A systematic and quantitative analysis of this type can provide results for use by regulatory agencies to inform policy and information for clinicians to discuss dementia risk with their patients.

Methods

Literature search

The protocol was registered under PROSPERO (CRD42021277083) on 10 November 2021. Two people (EW and MO) independently performed a literature search of the EMBASE, PubMed, Web of Science, Psycinfo, and OVID Medline databases from database inception through July 2022. Searches used free text and medical subject headings for Alzheimer's disease and dementia and exposures related to US Environmental Protection Agency (EPA) criteria pollutants or traffic pollution and its surrogates (online supplementary material 1). The literature review was developed on the basis of the researchers' experience, a preliminary review of existing literature, and discussions with research library staff. All articles with a potentially relevant abstract, or ones for which the relevance was unclear, were reviewed and downloaded to an Endnote 20 library (Clarivate, Philadelphia, PA, USA). Discrepancies were resolved by a third reviewer (MW). Studies were eligible for review if they included adults (≥18 years), a longitudinal follow-up, considered exposure periods of a year or more, and reported hazard ratios, odds ratios, relative risks or rate ratios and 95% confidence intervals for the association between ambient pollutant exposures and clinical dementia. We excluded studies that evaluated associations between ambient pollution and cognitive function, brain imaging, or biomarkers associated with dementia.

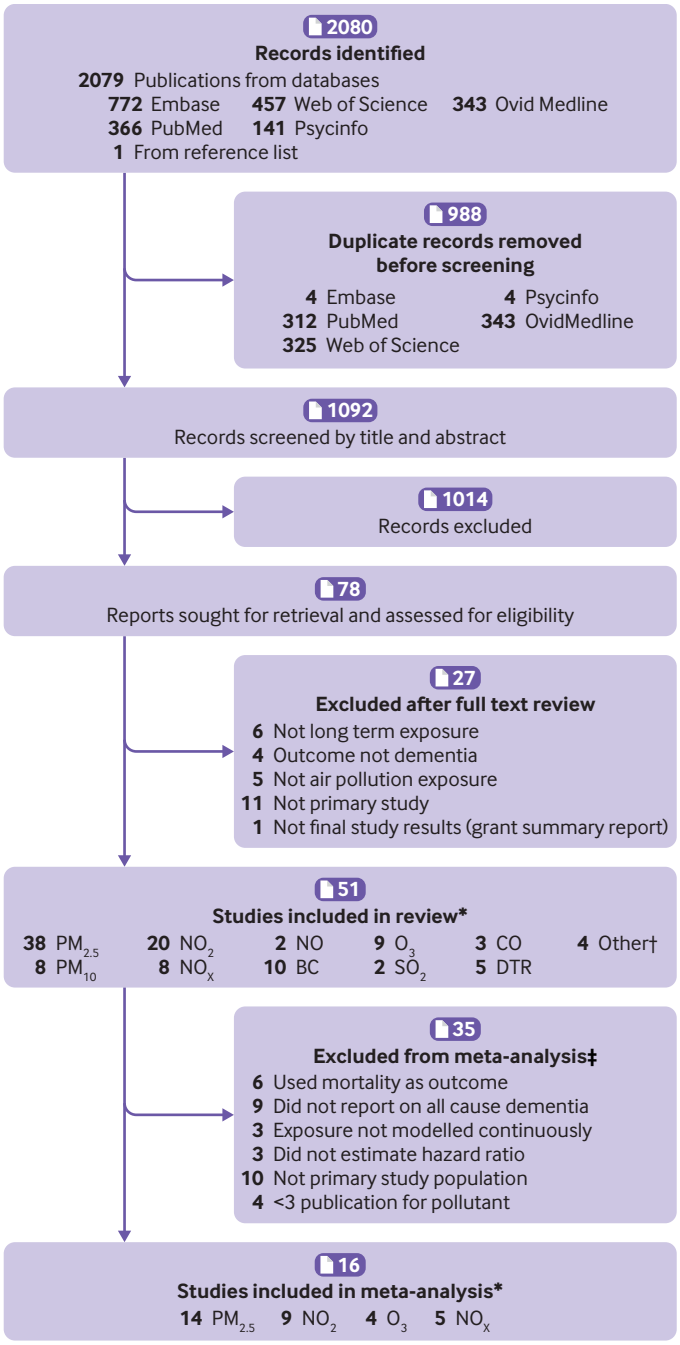

Fig 1 | Flowchart of literature search

Data extraction

Using a standardized form, two readers (EW and MW) independently and in duplicate extracted data from selected articles. Measures of association were recorded with 95% confidence intervals, unit of exposure (μg/m^3, ppb, etc), scaling factor (eg, 1 μg/m^3, 5 μg/m^3, 10 μg/m^3), and covariate adjustment. Results were reviewed for consensus and discrepancies were resolved among the authors. If information could not be determined for a paper, we attempted to contact the authors to clarify.

Risk of bias assessment

We used the ROBINS-E tool[11] to assess risk of bias to support detailed assessment of domain specific issues that can raise threats to causal inference. The ROBINS-E tool is designed to assess non-randomised studies and is adapted from the original ROBINS-I (Risk of Bias In Non-randomised Studies of Interventions tool[12] with a specific focus on environmental exposures. Bias is defined as a tendency for study results to differ systematically from the results expected from a hypothetical target randomised trial, conducted on the same participants and with no flaws in its conduct.[12] For this meta-analysis to best inform policy, we defined the hypothetical target trial as exposure to a standard unit increase in the annual average outdoor ambient exposure to the air pollutant in question because this criteria is what EPA regulations address. Using the ROBINS-E tool, we assessed the risk of bias in seven different methodological aspects (called domains). Per ROBINS-E protocol, risk of bias in each domain was graded as either low, some, high, or very high. We also considered whether the mechanisms of bias were

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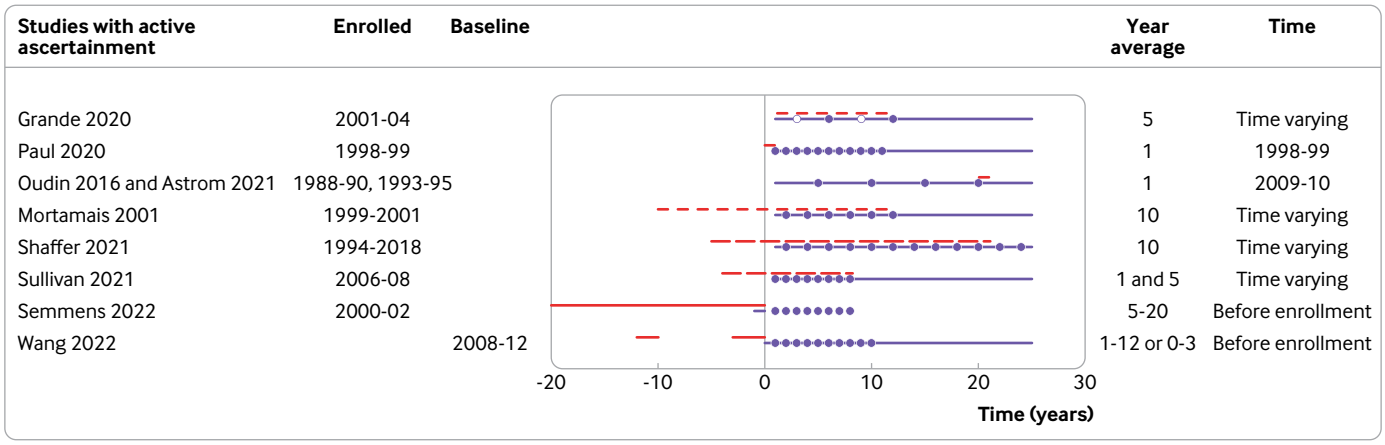

Fig 2 | Graphical representation of exposure and outcome assessment in studies with active ascertainment included in the meta-analyses. Red lines indicate period of exposure assessment and circles indicate outcome assessment and follow-up visits. For Grande 2020, visits occurred every six years for participants ages 60-77 years old indicated by the closed circles and every three years for older participants, indicated by the open circles.

likely to bias towards harm (ie, a higher hazard ratio) or away from harm (a lower hazard ratio) for effects of the air pollutant on dementia. Where authors disagreed on these risk of bias questions, we had a discussion and came to a consensus. Overall risk of bias for each study was then recorded as the highest risk of bias for any domain. Item level judgement for each domain of bias was recorded as the most dominant risk of bias.

Statistical analysis

Inverse variance weighted random effect models were used to pool estimates from individual studies for pollutants when three or more studies were available using comparable approaches with similar definitions of exposure and outcome.[13] We used Knapp-Hartung standard errors as these have been found to result in fewer type 1 errors when study population sizes differ and study number is small,[14] but because these standard errors also decrease power,[15] we also reported confidence limits using DerSimonian-Laird standard errors in the supplement. Estimates were converted from ppb to μg/m^3 where necessary using these conversions: 1 ppb NO_2=1.88 μg/m^3; 1 ppb NO_x=1.9125 μg/m^3; and 1 ppb O_3=1.96 O_3 μg/m^3. Tau2 was reported as the variance of the true effect sizes and I^2 as a measure of inconsistency across the findings of the studies. We did not include studies in meta-analyses if they did not estimate a hazard ratio or did not model exposure continuously (fig 1). We pooled estimates from studies that used different sets of confounding variables because each study aimed to identify the best effect estimates for the air pollutants, and issues of risk of bias related to confounding were discussed. Data were presented for a fixed unit change in exposure for each pollutant. We performed subgroup analyses to evaluate differences in associations by different study characteristics, and then we performed meta-regression to determine the significance of the association of the study characteristic with the meta-analysis results. In most cases, results from single pollutant models were available. Where a multipollutant model was provided, we commented on whether estimates were substantially altered. All statistical analyses were conducted in Stata version 17 (StataCorp, College Station, TX, USA). Additional plots were generated in RStudio v1.4. All hypothesis tests were two sided.

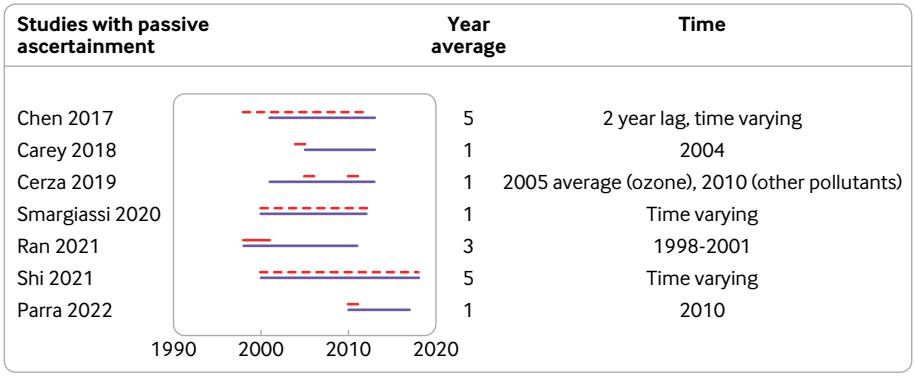

Fig 3 | Graphical representation of exposure and outcome assessment in studies that used passive ascertainment included in the meta-analyses. Purple lines indicate period of outcome assessment and red lines indicate exposure assessment

Table 1 | Study population and exposure characteristics of studies included in the meta-analyses

First author, year	Geographical location	Study population	Exposures	Age distribution in years	Percentage male	Exposure averaging period
Active case ascertainment studies						
Oudin, 2016[16]	Umea, Sweden	Betula Cohort	NO_x	Median 70; range 55-85	43%	Annual average
Astrom 2021[20]	Umea, Sweden	Betula Cohort	$PM_{2.5}$	Median 70; range 55-85	43%	Annual average
Wang, 2022[23]	USA	WHIMS-Echo	$PM_{2.5}$, NO_2,	60% >80	0%	3 year average for recent and remote exposures
Grande, 2020[25]	Stockholm, Sweden	SNAC-K Cohort	$PM_{2.5}$, NO_x	Mean 74, SD 11; range 60+	37%	5 year time varying average
Paul, 2020[26]	California, USA	SALSA Cohort	TRAP (NO_x)	Mean 70, SD 7; range 60-101	42%	Annual average
Mortamais 2021[29]	Bordeaux, Montpellier, and Dijon, France	3C Study Cohort	$PM_{2.5}$, NO_2	Median 73, range 65+	38%	10 year time varying average
Semmens, 2021[30]	Winston Salem NC, Hagerstown MD, Sacramento, CA and Pittsburgh, PA	Gingko Evaluation of Memory Study (GEMS)	$PM_{2.5}$, NO_2	Mean 78.4, SD 3.2	54%	5, 10, 20 year average
Shaffer 2021[31]	Puget Sound region, WA	Adult Changes in Thought Cohort	$PM_{2.5}$	Mean 75, SD 6.3, range 65+	42%	10 year time varying average
Sullivan, 2021[32]	Allegheny County, Pennsylvania, USA	MYHAT Cohort	$PM_{2.5}$	Mean 77, SD 7; range 65+	38%	Annual and 5 year time varying average
Passive case ascertainment studies						
Chen, 2017[37]	Ontario, Canada	Health Administrative database (ONPHEC)	$PM_{2.5}$, NO_2, O_3	Mean 67; range 55-85	47%	5 year time varying average
Carey, 2018[39]	London, England	Primary care administrative database (CPRD)	$PM_{2.5}$, NO_2, O_3	Median within 60-69; range 50-79	50%	Annual average
Cerza, 2019[43]	Rome, Italy	Rome Longitudinal Study followed through administrative hospital discharge data	$PM_{2.5}$, NO_2, NO_x, O_3,	Mean 75, SD 7; range 65-100	42%	Annual average
Smargiassi, 2020[52]	Québec, Canada	QIDCSS linked to administrative health database	$PM_{2.5}$, NO	Median within 65-74; range 65+	45%	Annual time varying average (NO_2); 2 year time varying average ($PM_{2.5}$)
Ran, 2021[56]	Hong Kong, China	EHS Cohort followed through administrative hospital data	$PM_{2.5}$	Median within 65-74; range 65+	34%	Annual average
Shi, 2021[59]	USA	Medicare denominator and Medicare Chronic Conditions	$PM_{2.5}$	Median within 65-74; range 65-114	41%	5 year time varying average
Parra, 2022[62]	UK	UK Biobank	$PM_{2.5}$, NO_2, N_Ox	60+	47%	Annual average

BC=Black Carbon; 3C Study=Three Cities Study; CPRD=Clinical Practice Research Datalink; EHS=Chinese Elderly Health Service; MYHAT=Monongahela-Youghiogheny Healthy Ageing Team; NO_2=nitrogen dioxide; NO_x=nitrogen oxide; O_3=ozone; ONPHEC=Ontario Population Health and Environment Cohort; $PM_{2.5}$=particulate matter <2.5 µm in diameter; QIDCSS=Québec Integrated Chronic Disease Surveillance System; SALSA=The Sacramento Area Latino Study on Ageing; SD=standard deviation; SNAC-K=Swedish National Study on Ageing and Care in Kungsholmen; TRAP=traffic related air pollution; WHIMS=Women's Health Initiative Memory Study

Patient and public involvement

This research question was developed on the basis of discussions with community members and people involved in environmental policy, but not by patients. Members of the public reviewed a version of this article before submission. We plan to disseminate these findings to the general public in a press release, through social media posts and the Harvard Chan National Institute of Environmental Health Sciences Center for Environmental Health website, and media outlets through Biogen. We have presented this work at scientific conferences and will continue to disseminate the results through academic presentations. We will also share the findings with specific interested parties involved with environmental policy, for example at the National Institutes of Health and National Institute of Environmental Health Sciences, the EPA, and relevant European Union committees.

Results

Study characteristics

Our initial review identified 2079 publications (1092 unique) across the different databases, and one additional article found from the reference lists of other papers (fig 1). A total of 51 publications met the inclusion criteria,[16-66] key characteristics of which are in the supplementary material 2 and 3. Particulate matter <2.5 µm in diameter ($PM_{2.5}$) was considered most frequently (n=38). All of the publications were from the past 10 years, with 33 (65%) in 2020 or later, including 13 (72%) of the 18 studies that used active case ascertainment. Most studies were in North America (n=25), followed by several in Sweden and other European countries (n=17), and a few in Asia (Taiwan, n=4; Hong Kong, n=3; China, n=1) and Australia (n=1).

Among the 51 studies, we only used 16 in the meta-analyses for several reasons (fig 1). When we excluded a study because the data source was the same as another paper,[18 19 27 28 44 49 57 58 63 65] we included the study that we considered primary (based on larger numbers or least risk of bias, etc). Active case ascertainment studies all used some form of screening of the entire study population followed by in-person evaluation for dementia among individuals who did not have dementia at baseline.

Table 2 | Bias aspects of studies included in the meta-analyses

First author, year	Misclassification and measurement error of outcome	Control of confounding: Socioeconomic control	Control of confounding: Time varying exposure control	Selection bias/loss to follow-up	Risk of bias*: A	B	C	D	Overall
Active case ascertainment studies									
Oudin, 2016[16]	Mostly active: in-person assessment supplemented with MR (some MR only)	Individual level adjustment	Not time varying exposure	Full follow-up	Some	Low	Low	Some	Some
Astrom 2021[20]	Mostly active: in-person assessment supplemented with MR (some MR only)	Individual level adjustment	Not time varying exposure	Full follow-up	Some	Low	Low	Some	Some
Wang, 2022[23]	Active: in-person or telephone screening followed by in-person assessment	Individual and area level adjustment; Adjustment for potential mediators	Not time varying exposures	Weighting to address loss to follow-up	High*	Low	Some	Low	High*
Grande, 2020[25]	Active: in-person assessment supplemented with death and medical records	Individual level adjustment; Adjustment for potential mediators	Time varying exposure with adjustment for time trend	6-11% loss to follow-up	High*	Low	Some	Low	High*
Paul, 2020[26]	Active: in-person screening, with neuropsychological exam follow-up reviewed by neurologist and neuropsychologist review	Individual and area level adjustment	Not time varying exposures	Weighting to address loss to follow-up	Some	Low	Some	Low	Some
Mortamais 2021[29]	Active: 3 phase in-person assessment, review by geriatric specialist	Individual level adjustment	Not time varying exposure	Weighting to address loss to follow-up	High	Low	Some	Low	High
Semmens, 2021[30]	Active; screening followed by neuropsychological battery, neurological evaluation and adjudication	Individual and area level adjustment	Not time varying exposure	Approaches to limit selective attrition in study design	Some	Low	Some	Low	Some
Shaffer 2021[31]	Active: in-person assessments, follow-up physical, neuropsychological evaluations reviewed by consensus	Individual and area level adjustment	Time varying exposure with adjustment for time trends	14% loss to follow-up	Some	Low	Some	Low	Some
Sullivan, 2021[32]	Active: in-person Clinical Dementia Rating assessment by trained interviewers (case=rating >1)	Individual level adjustment	Time varying exposure, no adjustment for time trends	No information on loss to follow-up	High	Low	High*	Low	High
Passive case ascertainment studies									
Chen, 2017[37]	Passive: ICD codes and prescriptions	Area level adjustment	Time varying exposures; reported no difference in results with time trend adjustment	Likely low; province wide data, required residence >5 years	High	High	Low	High*	High
Carey, 2018[39]	Passive: Primary care record Quality and Outcomes Framework Read Codes, and death ICD codes	Area level adjustment	Not time varying exposures	Censored if GP withdrew from CPRD; patient loss to follow-up not known	Some	High	Low	High*	High
Cerza, 2019[43]	Passive: ICD codes	Area level adjustment	Not time varying exposure	Loss to follow-up discussed	High	High	Low	High*	High
Smargiassi, 2020[52]	Passive: ICD codes and prescriptions	Area level adjustment	Time varying exposure with time trend adjustment	Likely low; province wide data, required residence >4 years	High	High	Low	High*	High
Ran, 2021[56]	Passive: ICD codes	Individual level adjustment	Not time varying exposure	Likely none; Hong Kong wide data	Some	High	Low	High*	High
Shi, 2021[59]	Passive: ICD codes	Individual (Medicaid eligibility) and area level adjustment	Time varying exposure with time trend adjustment	Likely low; all ≥65 years; nationwide data	Some	High	Low	High*	High
Parra, 2022[62]	Passive: ICD codes	Individual level adjustment	Not time varying exposure	Censoring for loss to follow-up	Some	High	Low	High*	High

AOD=Aerosol Optical Depth; AQS=Air Quality System; CPRD=Clinical Practice Research Datalink; GP=general practitioner; ICD=International Classification of Diseases; MR=medical records.
*Indicates that the likely direction of bias would be towards the null and no other bias is greater than some. Risk of bias domains: A=Confounding; B=Post-exposure intervention; C=Missing data; D=Measurement of the outcome. All studies were rated some risk of bias in the domains of "Measurement of the exposure" and "Selection of reported results," and low risk of bias in the domain of "Selection of participants."

Studies that used passive case ascertainment typically identified dementia via International Classification of Diseases codes in insurance claims data or medical records (supplementary material 4). Among the papers included in the meta-analyses, the timing of exposure and dementia assessment

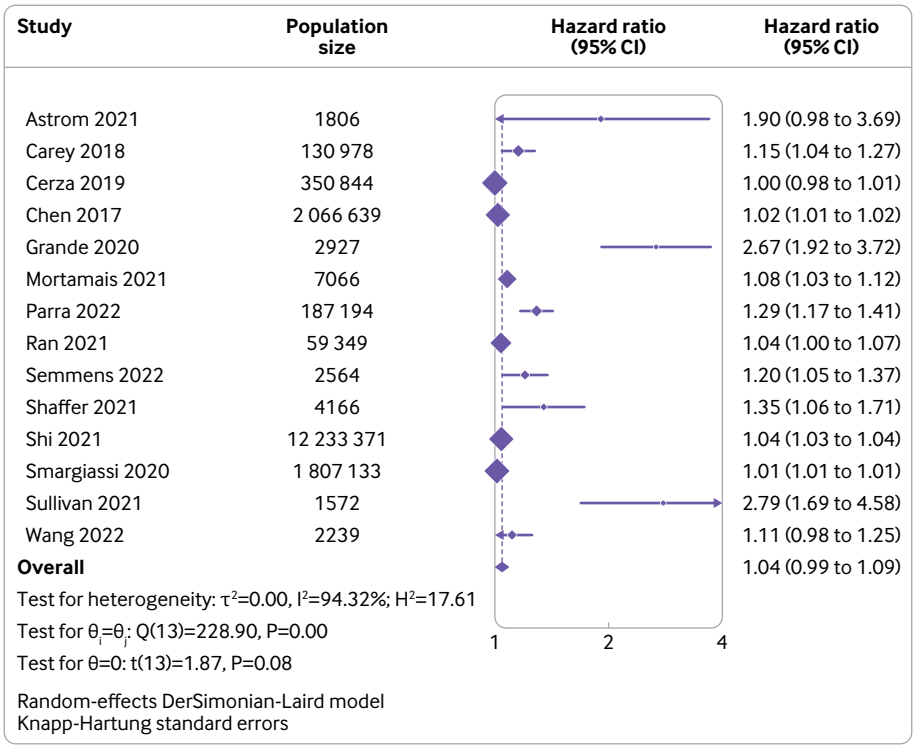

Fig 4 | Random effects meta-analysis for $PM_{2.5}$. Diamond size represents the relative weight of the studies. Study specific estimates are scaled to a standard unit change of 2 µg/m³. $PM_{2.5}$=particulate matter <2.5 µm in diameter

is shown in figure 2 and figure 3. In some studies, land use regression exposure models were based on measurements in one year that were then propagated to other years (rather than direct measures in those years), typically based on land use regression model year to other year ratios found in measurements at routine monitor sites.[29 37 52]

Risk of bias assessment

A detailed discussion of the reasoning for our bias assessments is provided in supplementary material 5. Key differences between studies were in the domains of confounding, postexposure interventions, missing data, and measurement of the outcome (online supplementary material 3). For confounding, we considered socioeconomic status, race and ethnicity, and time trends to be the largest threats of bias, likely towards harm.[67-75] When available, we took results unadjusted for potential mediators of the effect of air pollutants on dementia (eg, diabetes and cardiovascular conditions), but where only results adjusted for potential mediators were available, we considered the study at high risk of bias, but most likely away from harm.[76-78] For post-exposure interventions, we considered studies that used passive case ascertainment to be at high risk of bias from effects of air pollutants on the timing or presence of a dementia diagnosis (eg, from more interaction with medical systems because of other air pollution health effects[79]), likely towards harm. For missing data, because worse cognitive function has been shown to be associated with less participation and more loss to follow-up in cohort studies, as has ill health, which is associated with higher air pollution,[26 80 81] studies that did not address this effect were considered at higher risk of bias, although likely away from harm.[76 77 82] For measurement of the outcome, studies that used passive case ascertainment and relied on diagnostic codes, and sometimes prescriptions, in administrative datasets for identifying outcomes are subject to bias that likely goes away from harm.[67 68 83-86] In all other domains, risk of bias was rated low or some.

Quantitative synthesis

Meta-analyses could only be conducted with 16 of the studies (table 1 and table 2). Of 14 studies on $PM_{2.5}$, seven used active case ascertainment,[20 23 25 29 30-32] and seven used passive case ascertainment.[37 39 43 52 56 59 62] Among these 14 meta-analysed studies, seven were from North America,[23 30-32 37 52 59] six from Europe,[20 25 29 39 43 62] and one from Hong Kong.[56] One of the publications from the Betula cohort study considered $PM_{2.5}$ from local sources (traffic and stoves) and did not have data for regional $PM_{2.5}$, but assumed that its contribution to variation in the study area was small.[20] This study had a mean of 0.95 µg/m³ (standard deviation 0.34). Among the other 13 studies in the meta-analysis, the median/mean exposure levels ranged from 7.9 µg/m³ to 35.2 µg/m³, with measures of spread (standard deviation or interquartile range) that ranged from 0.08 to 4.8 µg/m³. Eight of the studies had mean exposure concentrations below the current EPA annual standard of 12 µg/m³ [20 23 25 31 37 52 59 62] with the highest mean at 10.5 µg/m³ and all but three were below 10 µg/m³ [23 31 37] which is being considered as a new EPA limit.[87]

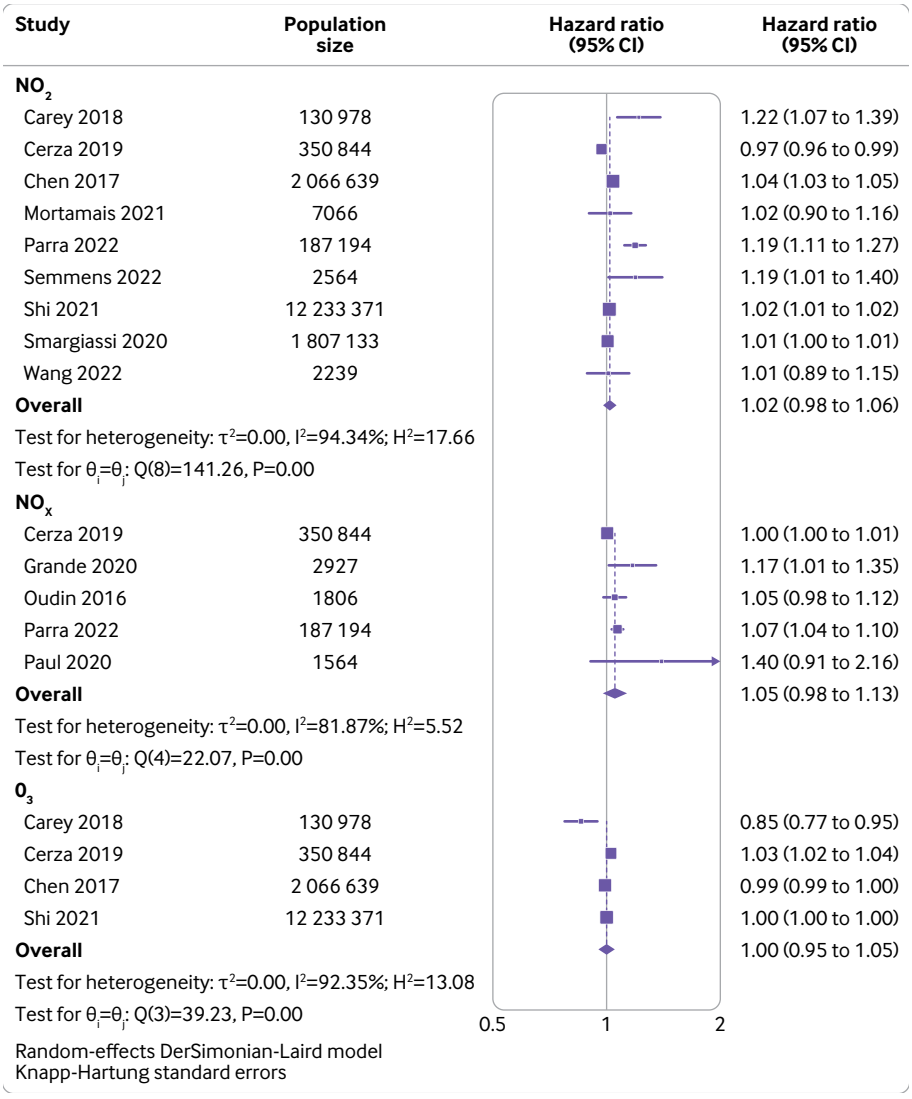

Fig 5 | Random effects meta-analysis for NO_2, NO_x, and O_3. Shaded boxes represent the relative weight of the studies. Study specific estimates for each pollutant are scaled to a standard unit change of 10 µg/m³ NO_2, 10 µg/m³ NO_x, and 5 µg/m³ O_3. NO_2=nitrogen dioxide; NO_x=nitrogen oxide; O_3=ozone

For $PM_{2.5}$, the overall hazard ratio per 2 µg/m³ was 1.04 (95% confidence interval 0.99 to 1.09; fig 4). Among studies with mean $PM_{2.5}$ exposures that were less than the EPA annual standard of 12 µg/m³ (n=8), the hazard ratio was also 1.04 (0.97 to 1.11). Two studies suggested a levelling off of the association between $PM_{2.5}$ and dementia at higher concentrations, but the concentration at which the levelling started was often where data were more sparse and differed in the two studies (about 8.5 µg/m³ and 35 µg/m³).[25 56] One other study that explored a possible non-linear dose response association found essentially a linear relation with exposure from 3 µg/m³ to 16 µg/m³.[59] Evidence suggested an association with NO_2 (per 10 µg/m³ hazard ratio 1.02 (0.98 to 1.06)) and NO_x (1.05 (0.98 to 1.13)), with all studies but one of each showing small but elevated hazard ratio (fig 5). No clear association was noted with O_3 (for 5 µg/m³, 1.00 (0.95 to 1.05); (fig 5). No other pollutant had at least three studies that could be meta-analysed (fig 1). Studies not included in our meta-analyses generally pointed to similar conclusions (online supplementary material 6).

Across the primary analyses conducted, values for I^2 were more than 90% and Tau^2 values were reported as 0.00, because of truncation, which reflects non-zero values of less than 0.001. When analysed separately by region (fig 6), the hazard ratio per 2 µg/m³ change in $PM_{2.5}$ exposure in North America was 1.03 (95% confidence interval 0.98 to 1.08), while in Europe the hazard ratio was 1.21 (0.90 to 1.63), and the one study in Asia was 1.04 (1.00 to 1.07). Although larger, the estimate for Europe was not statistically different from that in North America in the meta-regression (P=0.59). For $PM_{2.5}$, the hazard ratio per 2 µg/m³ among the seven passive case ascertainment studies was 1.03 (0.98 to 1.07) and among the seven active case ascertainment studies was 1.42 (1.00 to 2.02; fig 7), a difference that approached statistical significance in meta-regression (P=0.06). We excluded

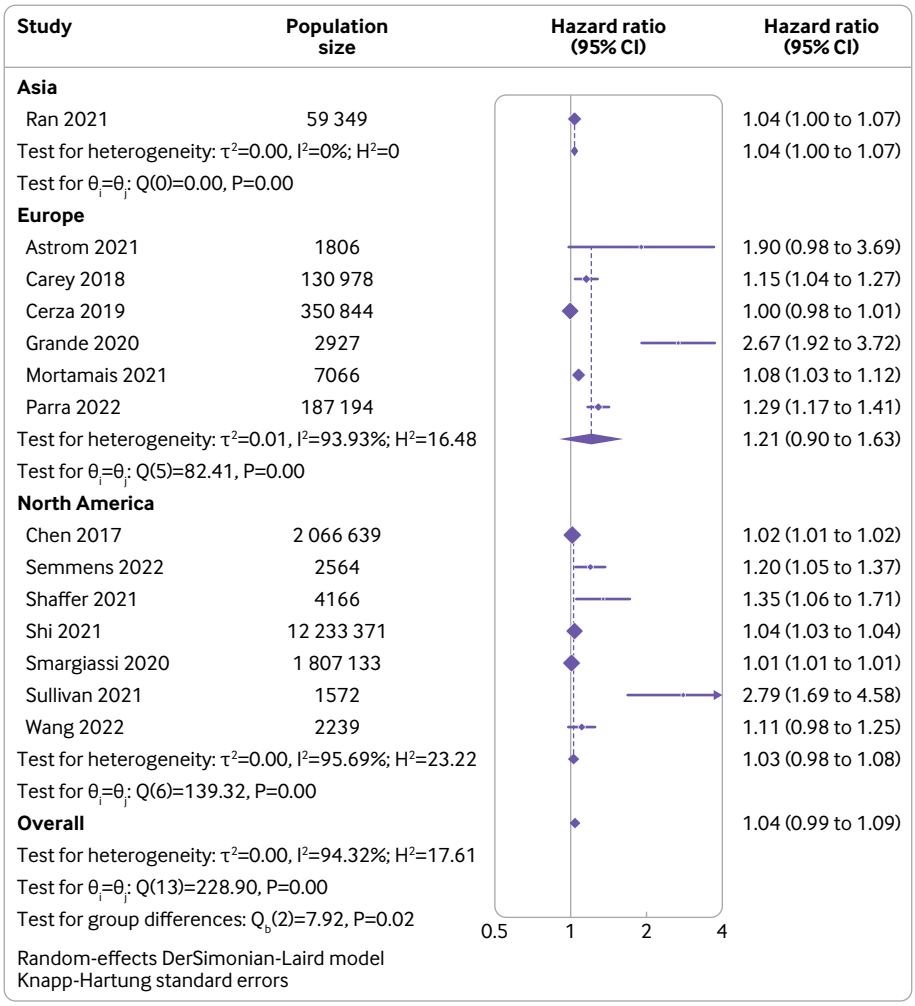

Fig 6 | $PM_{2.5}$ estimates by region. Region was characterised as North America, Europe, or Asia. Diamond sizes represent the relative weight of the studies. Study specific estimates are scaled to a standard unit change of 2 μg/m³ change in $PM_{2.5}$. $PM_{2.5}$=particulate matter <2.5 μm in diameter

the two active case ascertainment studies deemed at high risk of bias away from the null because of possible time trend bias,[29 32] after which the hazard ratio per 2 μg/m³ $PM_{2.5}$ among the remaining five studies was 1.45 (0.93 to 2.27). The hazard ratio per 10 μg/m³ NO_2 was also larger among active case ascertainment studies (hazard ratio 1.06; n=3), than among passive case ascertainment studies (hazard ratio 1.02; n=6). Seven studies of $PM_{2.5}$ used time varying exposure so follow-up after exposure was effectively within a year and the hazard ratio per 2 μg/m³ among this group was 1.03 (0.96 to 1.11).[25 29 31 32 37 52 59] Among the rest (none with time varying exposure), six had 7-13 years of follow-up,[23 30 39 43 56 62] while the one that used the Betula cohort had 20.[20] Among this group the hazard ratio was 1.11 (1.00 to 1.23; meta-regression P=0.05). There was little difference by exposure averaging period (meta-regression P=0.75) with a hazard ratio per 2 μg/m³ among the six studies that used a 1 year average of 1.06 (0.92 to 1.22) and among the eight that used longer averages of 1.05 (0.99 to 1.11). Given the small number of studies that could be meta-analysed for other pollutants, we could not examine differences by study characteristics for those.

Exposure variance appeared to change effect sizes. Among studies that used active case ascertainment, the three with the largest hazard ratios were the three with the smallest variance in $PM_{2.5}$ with a standard deviation of 0.7-0.34 μg/m³ and 0.08-0.19 μg/m³ depending on the year.[20 25 32] One of the other studies did not report the exposure standard deviation but was based in the USA where other studies typically had a standard deviation of more than 2 μg/m³,[30] while the other three had a standard deviation of 2.15 μg/m³ (estimated from the reported interquartile range of 2.9), 2.6 μg/m³, and 2.9 μg/m³.[23 29 31] Of these four higher $PM_{2.5}$ variance studies, we excluded one study deemed at high risk of time trend bias,[29] after which the hazard ratio per 2 μg/m³ $PM_{2.5}$ among the remaining three was 1.17 (0.96 to 1.43). The two largest hazard ratios among the studies that used passive case ascertainment also had the smallest standard deviation in that group of 0.7 (as estimated from a reported interquartile range of 0.9) and 1.25 μg/m³ (compared with 2.0 to 3.6 μg/m³).[39 62] Results with DerSimonian and Laird confidence limits are shown for all meta-analysis results in supplementary material 7. Few studies considered confounding by co-pollutants (supplementary material 8).

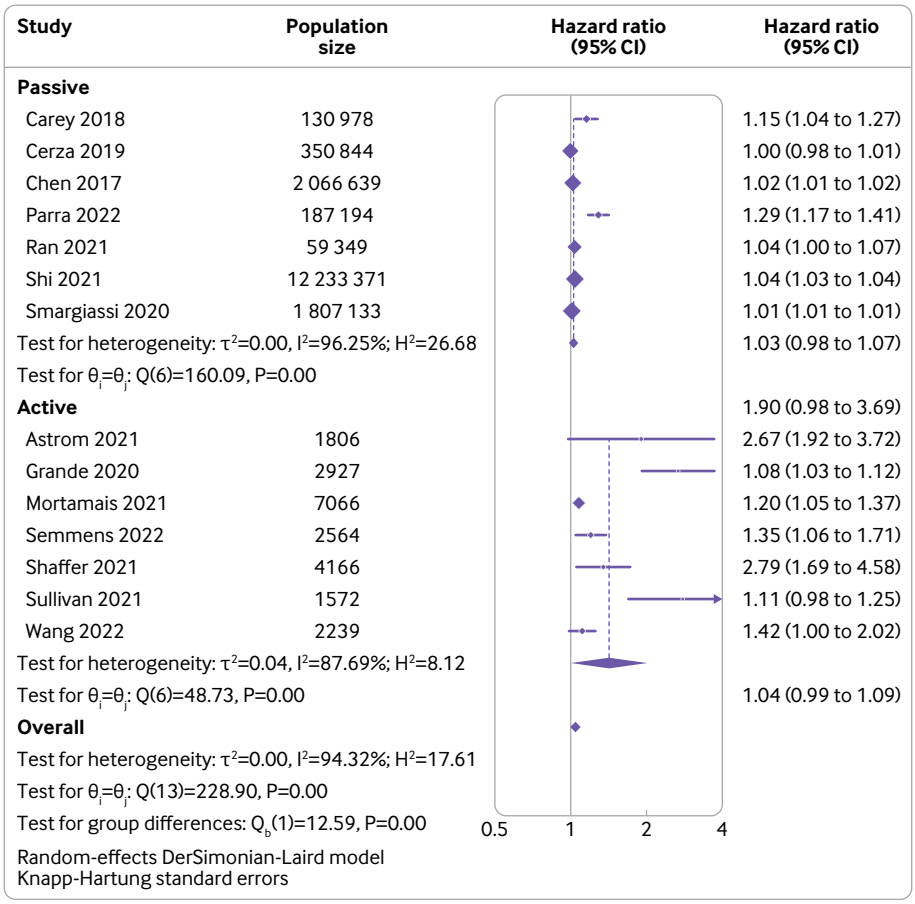

Fig 7 | $PM_{2.5}$ estimates by outcome ascertainment. Active ascertainment studies were those that estimated associations from established cohort studies; Passive ascertainment studies made use of data such as claims and medical records. Diamond sizes represent the relative weight of the studies. Study specific estimates are scaled to a standard unit change of 2 µg/m³ change in $PM_{2.5}$. $PM_{2.5}$=particulate matter <2.5 µm in diameter

Discussion

Principal findings

The findings from this systematic review and meta-analysis suggest consistent evidence of an association between ambient air pollution and clinical dementia, particularly for $PM_{2.5}$, even below the current EPA annual standard of 12 µg/m³, and well below the limits of the UK (20 µg/m³) and the European Union (25 µg/m³). Evidence is also suggestive for an association with NO_2 and NO_x, although with more limited data. Data for other pollutants are even more limited. Although the Knapp-Hartung confidence limits are wide and have better false positive error properties, the consideration of false positive versus false negative error might be different when considering an exposure that everyone is passively exposed to, such as air pollution, rather than, for example, a medication that has been actively prescribed. Our risk of bias assessment suggested that many of the studies have some level of risk of bias, but overall, the pattern of results does not suggest that the biases would have produced a false association. In many cases, any likely bias would be towards the null (away from harm), in particular bias from exposure and outcome misclassification. Although some concern of bias towards harm from confounding exists, studies that used methods that inherently avoided confounding by personal factors, such as socioeconomic status and race and ethnicity, also identified substantial risks of dementia associated with $PM_{2.5}$.[36 40 60]

The characteristic that made the biggest difference to the results was case ascertainment method, with hazard ratios for both $PM_{2.5}$ and NO_2 larger for studies that used active case ascertainment. The P value for this characteristic from the meta-regression was only 0.06, but this should be considered in light of the fact that fewer than 10 studies per group were included in this meta-regression (and all others), which has been recommended as a minimum to reliably estimate the effects of factors.[88] The smaller hazard ratio for passive case ascertainment studies likely is a result of more outcome misclassification when passive case ascertainment is used. Exposure measurement error would not generally differ by this characteristic. Outcome misclassification (or delay) by socioeconomic status and race and ethnicity likely would bias towards the null (away from harm) in the USA, at least for $PM_{2.5}$ and NO_2, given their relation with air pollution. Additionally, data from Europe for the association between air pollution and socioeconomic status are mixed, and studies from Asia are scarce.[86] Regardless, this misclassification bias is unlikely to affect studies that used active case ascertainment.

Bias to the null (away from harm) of any causal effect might also occur because the causally relevant window for air pollutant exposures is not known. The exposure windows assessed in the different studies might not capture the causally relevant window directly, but rather only correlate with it to different degrees. This effect would introduce further error in estimation of causally relevant exposure and so also contribute to biasing a causal effect estimate towards the null.[89 90] At the same time, if this relevant window is earlier than that measured in a study, decreasing trends over time in pollutants and their variance could lead to bias towards harm because a unit increase in the measured pollutant would represent a larger difference in the earlier pollutant level. However, this bias would not create a false association, but only potentially amplify a true one. The three largest effect sizes for $PM_{2.5}$ among studies that used active case ascertainment were noticeably in the studies that had the lowest exposure variances of all (standard deviation <1 μg/m^3).[20 25 32] Similarly, the two largest effect sizes for $PM_{2.5}$ among studies that used passive case ascertainment were also in those with the lowest exposure variances (standard deviation ≤1.25 μg/m^3ν ≥2 μg/m^3).[39 62] Four of these five studies of low exposure variance were in Europe, which could have accounted for the larger effect size seen overall in that region. These kinds of issues also lead to heterogeneity between studies: I^2 estimates were 90% or greater, and T^2 close to 0. The T^2 finding might occur when there is imprecision in the estimates and high variance within the study, leading to estimates that vary across studies. The bias most likely to cause a spuriously harmful association (bias away from the null) is that from postexposure intervention in studies that used passive case ascertainment (a form of detection bias). However, the overall results for those studies was a less harmful effect estimate than among the studies that used active case ascertainment. Therefore, bias away from harm (towards the null) from outcome misclassification was likely stronger.

Findings in context

The overall effect estimates for the associations were often small, but this finding is typical for studies of health effects of ambient air pollution.[79 91] When scaled to the same units (eg, effect estimates per 5 μg/m^3), the effect estimates that we found were very similar to those found for annual averages and many other outcomes (eg, cardiovascular mortality and respiratory mortality). The effect estimates associated with air pollution are smaller than those reported for other risk factors for dementia (eg, education and smoking),[69] but given the size of the population that is potentially exposed to air pollutants, the population health implications can be substantial.

The estimates that we report apply to the effect of a change in ambient air pollution concentrations in an area, which is what political bodies like the EPA or European Union regulate. However, the assumption is that any causal effect of the air pollutant would have to occur through actual personal exposure. The outdoor ambient concentration of pollutants is substantially mismatched with actual personal exposure because specific behaviours, such as time spent at home (where exposures are estimated), are not captured. The use of such ambient estimates protects against many kinds of confounding, but will result in bias towards the null of any causal effects through personal exposure levels.[92] Nonetheless, the effect estimate tied to the outdoor ambient pollutant measure would be expected to describe the population health benefits of regulatory related changes in outdoor ambient exposure levels.

Global estimates of dementia prevalence suggest an increase from 57 million in 2019 to 153 million in 2050.[1] The largest bulk of this comes from population ageing and population growth, but up to 40% of dementia prevalence has been estimated to be prevented by targeting modifiable risk factors.[69] Air pollution is only one of these possible risk factors so any effects of reducing air pollution would certainly be smaller, but air pollution is relatively directly targeted through regulation setting. The contribution of modifiable risk factors to dementia prevalence varies substantially in different regions of the world, with the lowest contribution in high income Asia Pacific region countries, and the highest in African, central European, and Latin American regions.[1] A reduction in air pollution limits would be likely to have differential impact on dementia prevalence worldwide too because pollution levels vary widely.[93-95] Nonetheless, reductions in air pollution levels anywhere would be expected to have an effect commensurate with the level of reduction enacted.

Many potential biological mechanisms have been suggested to underlie associations between air pollutant exposures and dementia. Cardiovascular effects of air pollutants are well known,[79 91] as are cardiovascular conditions as risk factors for dementia.[96 97] Although some papers suggest that vascular factors could mediate an association between air pollutants and dementia,[6 25 49] issues with these kinds of analyses can complicate interpretation.[6] Particulate matter exposure has been found to result in systemic inflammation, damage to the blood–brain barrier, changes in different neurotransmitter levels, and increases in neuroinflammation that can lead to neuronal death.[98-102] Microglia can be particularly relevant cells for these issues as the resident immune cells of the brain that respond to injury, produce local cytokines, and have been shown to actively eliminate synapses.[98 100 103] Toxic activation of microglia, possibly contributed to by air pollutant exposures, might lead to aberrant synapse elimination in older age that is part of the pathway to dementia. Demonstration of these types of mechanisms occurring in humans, however, is difficult. Although neuroimaging studies of brain effects of air pollutants are increasing, the literature is hard to synthesise and clear evidence for particular mechanisms of action linking air pollutant exposures to dementia is still elusive.[6]

Limitations

Few studies have used active case identification approaches, considered pollutants other than $PM_{2.5}$, and considered multiple pollutants simultaneously. Additionally, other exposures (eg, noise) that could co-vary with air pollutants might also need to be considered.[104] Studies that seek to identify the causally relevant time windows for exposure and further evaluate exposure-response associations are needed, as are those that can provide additional insight into underlying mechanisms that are affected by these exposures. Meta-analyses of hazard ratios have inherent issues that can compromise comparability across studies.[105] If a causal effect that is not constant over time is true, hazard ratios can change with longer follow-up after exposure. Typically, this biases a true effect towards the null with longer follow-up because susceptible individuals get the outcome and are censored. We found a slightly larger hazard ratio with a longer follow-up, which could instead suggest that effects of air pollutant exposures take some time to manifest. Lastly, assessment of the possibility of publication bias is difficult. The problems with the use of funnel plots to assess publication bias have been described,[106] and the issues of numbers of studies and other reasons (than publication bias) for heterogeneity between studies are issues of particular concern in the context of the air pollution and dementia literature.

Conclusions and policy implications

Our results suggest that exposure to ambient $PM_{2.5}$ is associated with a higher rate of dementia, and likely NO_2 and NO_x as well, but with more limited data. Our risk of bias assessment and results of stratified meta-analyses suggest that the predominant biases are probably away from harm rather than towards it. Nonetheless, the many limitations discussed in meta-analysing observational studies of environmental exposures, such as air pollution, mean that findings must be interpreted with caution. Nevertheless, given the available data, our results suggest that the best estimate for the effect of a 2 $\mu g/m^3$ higher concentration of $PM_{2.5}$ is a hazard ratio of 1.42 (95% confidence interval 1.00 to 2.02) based on the studies that used active case ascertainment. However, given concerns of time trend bias and causally relevant time windows, a more conservative estimate is 1.17 (0.96 to 1.43) after removing four studies for these reasons. With either estimate, the confidence limits are likely too wide given the number and characteristics of the included studies.[15] Our results strengthen the evidence that air pollutants are risk factors for dementia, further suggesting that efforts to reduce population exposures to these contaminants might help to reduce the personal, financial, and societal burden of dementia. To some degree, this reduction can be done on a personal level and clinicians should communicate the risks of air pollutant exposures to their patients. More importantly, steps can be taken at a broader public policy level. These findings can provide regulatory agencies and others with a best estimate for use in burden of disease estimation and regulation setting efforts, as well as inform summaries of risk factors for dementia.[69]

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Ethical approval: Because this was a review paper, no ethical approval was required.

Data sharing: No additional data was generated for this review. The data are that found in the referenced papers. Data collection forms are available upon request.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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Web appendix: Supplementary material