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# Putting Fine Particulate Matter and Dementia in the Wider Context of Noncommunicable Disease: Where are We Now and What Should We Do Next: A Systematic Review

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**Keywords**
Air pollution · Dementia · Cognitive impairment · Particulate matter · Noncommunicable disease

**Abstract**
***Introduction:*** A significant proportion of the global population regularly experience air quality poorer than that recommended by the World Health Organization. Air pollution, especially fine particulate matter ($PM_{2.5}$), is a risk factor for various noncommunicable diseases (NCDs) and is emerging as a risk factor for dementia. To begin to understand the full impact of $PM_{2.5}$, we review the longitudinal epidemiological evidence linking $PM_{2.5}$ to both dementia and to other leading NCDs and highlight the evidence gaps. Our objective was to systematically review the current epidemiological evidence for $PM_{2.5}$ as a risk factor for cognitive decline and incident dementia and to put this in context with a systematic overview of $PM_{2.5}$ as a potential risk factor in other leading NCDs. ***Methods:*** We performed 2 systematic reviews. A high-level review of reviews examining the relationship between $PM_{2.5}$ and leading NCDs and an in-depth review of the longitudinal epidemiological data examining relationships between $PM_{2.5}$ incident dementia and cognitive decline. ***Results:*** There were robust associations between $PM_{2.5}$ and NCDs although in some cases the evidence was concentrated on short rather than longer term exposure. For those articles reporting on incident dementia, all reported on longer term exposure and 5 of the 7 eligible articles found $PM_{2.5}$ to be associated with increased risk. ***Conclusion:*** The evidence base for $PM_{2.5}$ as a risk factor for dementia is growing. It is not yet as strong as that for other NCDs. However, varied measurement/methodology hampers clarity across the field. We propose next steps.


## Introduction

In recent years, the established literature linking poor air quality to adverse cardiopulmonary end points, including excess mortality [1], has expanded to include evidence of associations with incident dementia [2–4]. In 2018, we reviewed the evidence for air pollution and cognitive decline or dementia and noted that these adverse associations appear strongest when considering longer term exposures to ambient fine particulate matter ($PM_{2.5}$). $PM_{2.5}$ refers to particles with an average aerodynamic di-

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ameter of ≤2.5 μm and is composed of a mixture of chemical components, primary emissions, and products of secondary chemical reactions in the atmosphere, derived from a wide range of sources [5, 6]. The $PM_{2.5}$ ambient mass concentration, averaged over varying lengths of time, reflects the sum of all these sources and provides a single uniform metric to interrogate population health, often based on modeled attributions, but ultimately informed by widespread monitoring of this pollutant for regulatory and research purposes. Globally, the World Health Organization (WHO) estimates that around 91% of the population live in places where annual fine particulate matter ($PM_{2.5}$) levels regularly exceed the recommended WHO guideline level of 10 μg/m$^3$, with those in low- and middle-income countries most at risk [3].

Importantly, there are also established links between leading noncommunicable diseases (NCDs) (e.g., diabetes and stroke) and an increased risk of later dementia [5]. This is important since $PM_{2.5}$ may raise the risk of dementia via both direct and indirect pathways. For example, dementia risk may be increased via inflammatory respiratory disease pathways and/or cerebrovascular disease [6, 7]. Given the potential overlap between $PM_{2.5}$ as a risk factor for NCDs and a fast emerging risk factor for dementia, it is important to understand its population-level impact. Here we draw together the epidemiological evidence linking $PM_{2.5}$ exposure to incident leading NCDs (using review of review methodology) and also systematically review the longitudinal epidemiological evidence on the relationship between $PM_{2.5}$ and incident dementia and cognitive decline. We present the extent and scope of the evidence to date, highlighting the gaps and proposing the next steps.

## Methods

Standard systematic review methodology [8] was used to undertake 2 complementary literature searches. The first was a high-level systematic update focused on $PM_{2.5}$ as a risk factor for leading NCDs followed by an in-depth systematic review examining the relationship between $PM_{2.5}$ and incident cognitive decline and dementia. For both reviews, there were 2 independent analysts (R.P. and J.P.). The lead analyst carried out the literature searches. All identified abstracts, or titles where abstracts were unavailable, were double reviewed and a list of potentially relevant references compiled independently by the 2 analysts. These lists were compared, and differences were resolved by discussion. Once the list of possible references was agreed, full-text articles were obtained, independently read, and assessed for relevance. Data were extracted by the lead analyst and checked by the 2nd analyst. Standard extraction tables were used.

*Major Noncommunicable Diseases and $PM_{2.5}$*

Leading NCDs were defined as cardiovascular disease (myocardial infarction, heart failure, and stroke), respiratory disease (COPD and asthma), lung cancer, diabetes mellitus, or chronic kidney disease (CKD), based on the WHO top 10 NCD causes of death [9]. To evaluate the relationship between exposure to $PM_{2.5}$ and leading NCDs, the databases MEDLINE, Embase, and PsycInfo® were searched from inception to January 31, 2020. A review of reviews methodology was selected as a systematic method frequently used to summarize large volumes of data from an established literature and to ensure inclusion of most comprehensive and recent evidence [10, 11]. Search terms included (air pollut* or particulate or $PM_{10}$ or $PM_{2\,5}$ or Roadway or Vehicle or Diesel.ti.) and (systematic review.ti or systematic.af) (see online suppl. Text 1; for all online suppl. material, see www.karger.com/doi/10.1159/000515394). Utilizing methodologies adapted from those that underpin guideline development [12], we included only the most recent systematic review reporting on incident or worsening NCD and exposure to $PM_{2.5}$. We did not include cross-sectional relationships, diagnoses that may predispose to NCDs (e.g., insulin resistance, hypertension, and obesity), and data from child or adolescent populations, those reporting composite outcomes or solely fatal outcomes. Data were extracted from the systematic reviews on the number of constituent studies, the regions of the world where the studies had taken place, the way the exposure had been assessed, the $PM_{2.5}$ exposure estimates for the population, the assessment of incident disease, and the results. The Assessing the Methodological Quality of Systematic reviews (AMSTAR) version 2 (https://amstar.ca/Amstar-2.php) was used to evaluate the systematic reviews [13].

*Dementia, Cognitive Decline, and $PM_{2.5}$*

To evaluate the relationship between exposure to $PM_{2.5}$ and incident cognitive decline or dementia (including incident Alzheimer's Disease), the databases MEDLINE, Embase, and PsycInfo® were searched from 2018 to April 1, 2020, supplemented by a prior search from inception to September 2018 [14]. Search terms included (alzheime* or dementia or cogniti*) and (air pollut* or particulate matter or roadway or particle size or PM* or vehicle or diesel) (online suppl. text 1). The results were further strengthened using forward citation searching for each of the included articles published prior to September 2018 and examining each cited article against the inclusion and exclusion criteria. Articles were included if they reported on longitudinal studies evaluating the relationship between exposure to outdoor $PM_{2.5}$ and incident cognitive decline or dementia, in human adults aged 18 years and older. Studies reporting indoor exposure or examining passive smoking were excluded. Where more than one article reported on the same population, the article including the largest number of participants was included.

For the relationship between $PM_{2.5}$ and incident cognitive decline or dementia (including Alzheimer's Disease), information was collected on the dates of exposure, duration of follow-up, assessment of incident cognitive decline or dementia, $PM_{2.5}$ concentrations, region of the world where the studies had taken place, and the results. Where multiple results were available, the most conservative interpretation, that is, selecting the longest exposure and most adjusted model, was reported. Data were extracted on length, dates and measures of exposure, region of recruitment, number of participants and participant age, average $PM_{2.5}$ level, assessment of

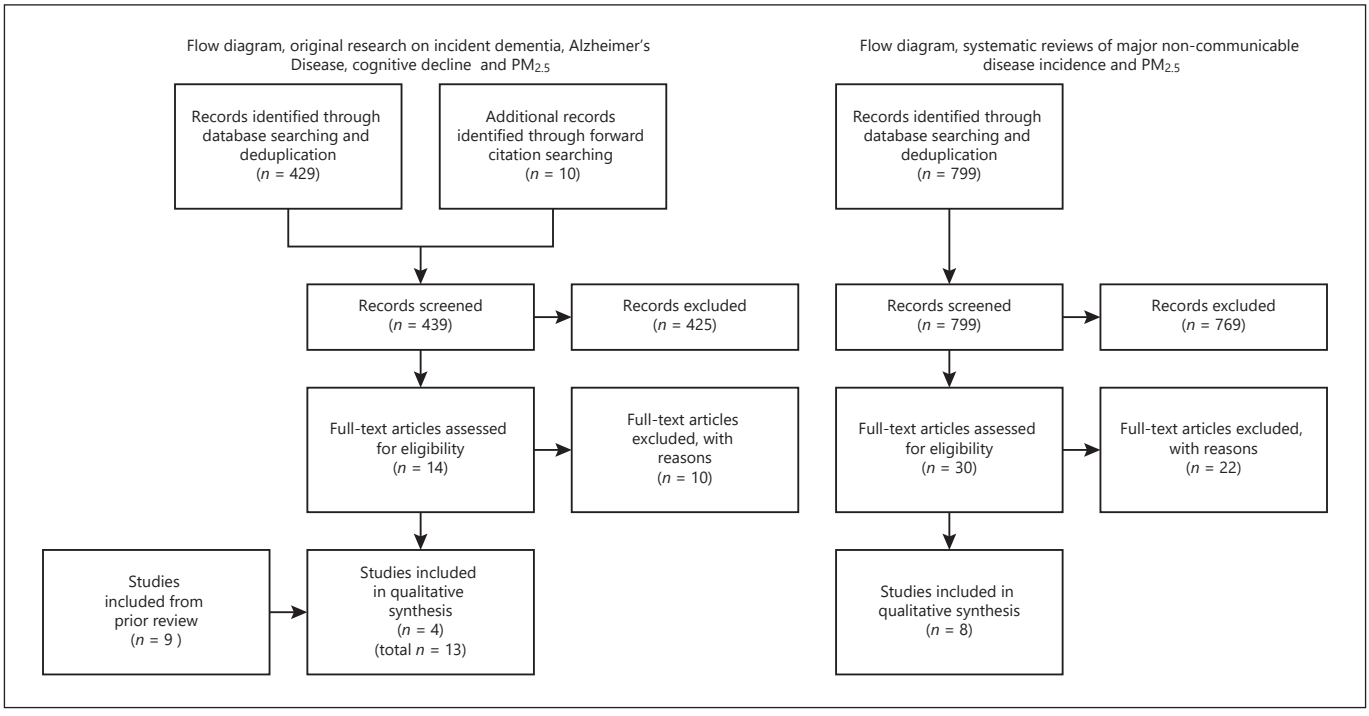


**Fig. 1.** Flow diagrams detailing the screening and inclusion processes.

dementia or cognitive decline, results, and evaluation of potential confounders. Each original research article was also assessed for bias against key criteria based on the Critical Appraisal Skills Programme (CASP©) cohort study checklist [15], and potential sources of bias in each study were tabulated.

## Results

*Major Noncommunicable Disease and $PM_{2.5}$*

For the searches of systematic reviews reporting on the relationship between exposure to $PM_{2.5}$ and incident NCD, 799 abstracts were screened and 30 assessed at the full-text stage. Twenty-two were excluded after full-text screening. Sixteen of these reviews had been superseded by more recent reviews, 2 were of the same year as alternative reviews, but more limited. In one review, it was not possible to separate out the results for adults and children, one did not separate out $PM_{2.5}$, one did not exclude cross-sectional data, and one focused on methodology (online suppl. Table 1). No reviews were excluded based on their assessment of exposure (duration or methodology). Figure 1 for a flow chart. Reviews included case control, crossover, and time series studies with 2 [16] to 59 [17] studies included in meta-analyses.

Systematic reviews were identified that reported on the association between $PM_{2.5}$ and incident or exacerbated respiratory disease (lung cancer [18] chronic obstructive airways disease [COPD] [17], asthma [19]), diabetes mellitus (DM) [20], cardiovascular disease (heart failure [21], stroke [22], myocardial infarction [MI] [23]), and chronic kidney disease (CKD) [16] (Table 1). Follow-up was both long term (3–34 years for the constituent studies on lung cancer [18]), 1–10 years for DM [20], 2 years for CKD [16], and short term with acute exposures of 0–3 days for COPD [17] and 0–7 days for stroke, heart failure, MI, and asthma [19, 21–23]. All meta-analyses reported a statistically significant relationship between their respective outcome and 10 μg/$m^3$ increment in $PM_{2.5}$ with most point estimates falling between 1 and 10% increase in risk. See Table 1 (in brief, estimated percentage increase and 95% confidence intervals from meta-analyses, for lung cancer: 9 (4–14), COPD: 2 (1–4), asthma: 3 (1–5), DM: 10 (4–17), heart failure: 112 (42–182), MI 2 (2–3), and stroke 1 (1–1)).

*Dementia, Cognitive Decline, and $PM_{2.5}$*

For the searches relating to the relationship between exposure to $PM_{2.5}$ and incident cognitive decline or dementia (2018-present), 439 abstracts were screened and 14 assessed at the full-text stage. Ten were excluded after

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**Table 1.** $PM_{2.5}$ exposure as a risk factor for Noncommunicable Disease (NCD)

| Author | Assessment of incident disease (NCD) | Number of studies | Region | Search dates | Exposure length | Range of $PM_{2.5}$ level, μg/m$^3$ Mean (standard deviation [SD]) | Results (10 μg/m$^3$ increment) |
|---|---|---|---|---|---|---|---|
| Hamra et al. [18] | Lung cancer incidence or mortality | 14 cohort or case control | Europe, North America, Asia | Unclear. To October 2013 | Unclear. Length of included studies ranged from 3 to 34 yr | 12.9 (SD 1.4) to 31.9 (SD 10.7) | RR 1.09 (1.04:1.14) $I^2$ 53% |
| Li et al. [17] | Chronic obstructive pulmonary disease exacerbations (emergency hospitalizations or mortality) | 59 case crossover or time series | Europe, North and South America, Asia, and Australia | Web of Science 1956–2016 Medline 1946–2016, Embase 1974–2005, Environmental sciences and pollution management index, CINAHL, Google Scholar, Cochrane database 2005–2016, CNKI | Short term. exposure lags from 0 to 3 days | 5.2–94.59 Overall mean 14.84 (SD 8.05) | RR 1.02 (1.01:1.04) for lag 1 $I^2$ 76.8% For a 3 day lag time RR 1.01 (1.01:1.02) |
| Zheng et al. [19] | Asthma emergency hospital visits or hospitalization | 6 case crossover or time series | Unclear for the studies included in the adult data meta-analysis. Overall studies were drawn from Europe, North America, Asia and Australia | Embase, PubMed, Cochrane Central Register of Controlled Trials, and EBM Reviews – Cochrane database of systematic reviews, Web of Science, Ovid and Highwire. Inception to March 2015 | Short term. Exposure lags from 0 to 7 days | Unclear for the studies included in the adult data meta-analysis. Overall average 24 h concentration ranged from 6.1 to 36.4 | RR 1.03 (1.01:1.05) $I^2$ 56% |
| Yang et al. [20] | Incident diabetes mellitus | 11 cohort studies | Europe, North America and Asia. | PubMed and web of Science Inception to March 2019 | Longer term exposure Average exposure reported in the constituent studies ranged from 1 to >10 yr exposure | Mean 4.1–35.8 | HR 1.10 (1.04:1.17) $I^2$ 74.4 |
| Shah et al. [21] | Heart failure hospitalization or mortality | 11 estimates from 10 case crossover or time series | Unclear, likely to include North America and other geographical areas. | Medline, Embase, Global Health, Cumulative Index to Nursing and Allied Health Literature, Web of Science 1948–July 2012 | Short term. Exposure lags from 0 to 7 days | Median 15.0 (IQR 10.8:17.6) | % Increase in risk 2.12 (1.42:2.82) $I^2$ 53% For a 2 day lag time % increase in risk 0.65 (0.13:1.18) |
| Luo et al. [23] | Incident myocardial infarction | 19 case crossover or time series | Europe, North and South, America, Asia, Australia | PubMed, Web of Science, Embase, Google Scholar to January 2015 | Short term. Exposure lags from 0 to 7 days | Not provided | OR 1.022 (1.015:1.030) $I^2$ 61.4% For a 2 day lag time RR 1.002 (0.995:1.009) |
| Shah et al. [22] | Incident hospitalization for stroke, or stroke mortality | 41 estimates from case crossover or time series | Europe, North and South, America, Asia, Australia and New Zealand | Medline, Embase 1948–2014, Global Health, Cumulative index to Nursing and Allied Health Literature (CINAHL), Web of Science | Short term. Exposure lags from 0 to 7 days | Not provided | RR 1.011 (1.011:1.012) $I^2$ 86% For a 2 day lag RR 1.013 (1.010:1.015) |

**Table 1** (continued)

| Author | Assessment of incident disease (NCD) | Number of studies | Region | Search dates | Exposure length | Range of $PM_{2.5}$ level, $\mu g/m^3$ Mean (standard deviation [SD]) | Results (10 $\mu g/m^3$ increment) |
|---|---|---|---|---|---|---|---|
| Wu et al. [16] | Incident chronic kidney disease | Only 2 studies where incident chronic kidney disease clearly reported | North America and Asia | Medline, Embase, Cochrane Library Inception to October 2019 | 2 yr averaged $PM_{2.5}$ and annual average and time varying $PM_{2.5}$ | Not provided | For the 2 studies: RR 1.06 (1.00:1.21) and RR 1.27 (1.17:1.38) $I^2$ N/A |

IQR, interquartile range; HR, hazards ratio; NCD, noncommunicable disease; $PM_{2.5}$, Particulate matter ≤2.5 μm in diameter; RR, relative risk; SD, standard deviation.

full-text screening (online suppl. Table 2), one did not report results for PM2.5, three either included prevalent dementia, or it was not possible to tell whether it was excluded, one reported only fatal outcomes, 3 appeared to report on subpopulations of studies already included, and 2 reported cross temporal analyses without measuring incident decline. Four articles were included ([24–27]), and these were supplemented with 9 articles that had been identified in our prior systematic review (covering the literature from inception to 2018) but which also met the inclusion criteria [28–36], Tables 2 and 3, and Figure 1 for the flow chart.

Seven studies reported on incident dementia [25, 27, 31–34, 36] (Table 2), 5 of the 7 studies reporting on incident dementia used administrative health records for case ascertainment, selecting out coded incident dementia based on the International Classification of Disease codes versions 9 or 10 ([27, 31, 33, 34], read codes (used in UK general practice) [34], and/or the Diagnostic Statistical Manual version 4 (DSM-IV) [31, 36]. The 3 smallest studies were research cohorts. These included (i) the Betula cohort from Sweden ($n$ = 1,806) [36], which reported additional review by old age psychiatrist, for dementia diagnosis, (ii) the Swedish National Study on Ageing and Care in Kungsholmen (SNAC-K) ($n$ = 2,927), which used physician review [25], and (iii) the Cacciolotto et al. [32] study population ($n$ = 3,647), which was drawn from the larger Women's Health Initiative Memory (WHIMS) Study. WHIMS was a research-based cohort with repeated assessments that diagnosed dementia with a multistep process using the extended Mini-Mental State Examination (MMSE) for screening. Those that screened positive received further neuropsychological and physician assessment plus imaging [32]. The studies that used health records were population based and reported on between 100,000 and over 2 million individuals [27, 31, 33, 34]. Although age was not consistently reported, the mean baseline age for all dementia studies was estimated at around 65 years. Exposure duration ranged from 1 [34] to 14 years [33] with $PM_{2.5}$ data collected at different time points from 1990 [36] to 2012 [33]. Five of the 7 studies reported a relationship between exposure to $PM_{2.5}$ and increased risk of incident dementia, but methodology varied between studies. Exposure was based around residential location, with several studies specifying details such as the use of postcodes or zip codes [31, 33] taking account of the history as well at the present residential location [32], or use of grids as small as 50 × 50 m in urban areas and 3,200 × 3,200 m in rural areas [36]. Annual exposure measures were most common [32–34, 36], but

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**Table 2.** $PM_{2.5}$ exposure as a risk factor for dementia

| | Longest exposure measure and date of exposure | Region of recruitment, number of participants at baseline | Participant age at baseline | $PM_{2.5}$ level | Measures of dementia | Measures of air pollution exposure | Results | Adjustments |
|---|---|---|---|---|---|---|---|---|
| Carey et al. [34] | Annual concentrations of air pollutants in 2004 (the year prior to baseline) | Population-based cohort<br>UK<br>130,978 | 50–79 | Mean 15.7 μg/m$^3$ (SD 0.8),<br>Median 15.6 IQR (15.2–16.1) | Incident dementia:<br>Incident dementia from general practice records (Read codes) and dementia listed as primary cause of death on death certificates (International Classification of Disease version 10) | Modeled annual concentrations of air pollutants in the year prior to baseline estimated using the KCLurban dispersion modeling system at a resolution of 20 × 20 m incorporating hourly meteorological measurements and empirically derived concentrations on emissions from the London Atmospheric Emissions inventory | Incident dementia:<br>$PM_{2.5}$ HR 1.06 (1.01, 1.13) per IQR change 0.95 μg/m$^3$ increment<br>Similar patterns for Alzheimer's Disease and vascular dementia | Age, sex, ethnicity, smoking, body mass index, index of Multiple Deprivation (area socioeconomic status), ischemic heart disease, stroke, diabetes, heart failure, nighttime noise. Each pollutant also adjusted for exposure to others |
| Chen et al. [33] | Annual mean concentration 1998–2012 | Population-based cohort, Ontario Canada<br>2,066,639 | Mean 66.8 (SD 8.2) | 5-yr cumulative exposure with<br>2-yr lag: 10.4 μg/m$^3$ (range: 1.1–49.7 μg/m$^3$; IQR: 4.8 μg/m$^3$) | Incident dementia:<br>Cases ascertained from health administrative data and defined as having one of more hospital admission with a diagnosis of dementia (International Classification of Disease versions 9 and 10) or 3 physician claims over a 2-yr period or a prescription relating to dementia. Note. Validated algorithm applied to health insurance database. Cases defined as dementia-related hospital admission, physician claims, prescriptions | Annual mean concentration of $PM_{2.5}$ (1 × 1 km) yearly between 1998 and 2012. Derived from satellite data, global atmospheric chemistry transport model (GEOS-Chem CTM) outputs, and calibrated with land cover, elevation, aerosol composition information using geographically weighted regression. Postal code represented centroids or blocks or residence | Incident dementia:<br>5-yr lag: $HR_{IQR}$ = 1.03 (1.02, 1.05) per IQR 4.8 μg/m$^3$) increment<br>10-yr lag: $HR_{IQR}$ = 1.03 (1.01, 1.06) per IQR 4.8 μg/m$^3$) increment | Age, sex, stratified region baseline SES (neighborhood-level income, education, unemployment rate, % of recent immigrants preexisting), urban residency, and a North/South indicator, comorbidities (diabetes, hypertension, coronary heart disease, stroke, heart failure, arrhythmias, traumatic brain injury), region-scale spatial patterns, urban residence, density of neurologist, geriatricians, internist, and family physicians<br>Secondary analysis: access to neurological care, neighborhood deprivation, linear term for time, excluded urban residency and North/South indicator |
| Jung et al. [31] | Taiwan data on $PM_{2.5}$ only available after 2006, hence this was extrapolated backwards using the mean ratio between $PM_{2.5}$ and $PM_{10}$ during 2006–2010 | Population based cohort<br>Taiwan<br>95,690 | >65 at follow-up | Mean annual average of $PM_{2.5}$ concentration, during 2006–2010: 33.56 μg/m$^3$ (SD = 9.20;<br>range 10.36–61.76) | Incident AD:<br>Case identification based on the Taiwanese National Insurance Research Database using the International Classification of Disease 9th Revision Clinical Modification. Incident AD defined as individuals who had received at least 2 consensus diagnoses between 2001 and 2010. Diagnoses are assigned by physicians based on history, physical examination, laboratory, and imaging investigations, Diagnostic criteria DSM-IV and NINCDS-ADRDA, or Hachinski ischemic scores | Taiwan data on $PM_{2.5}$ only available after 2006, hence this was extrapolated backward using the mean ratio between $PM_{2.5}$ and $PM_{10}$ during 2006–2010. Annual average $PM_{10}$ according to guidance from USA EPA. Data from 70 EPA sites across Taiwan at postcode level, interpolated using inverse distance weight method | Incident AD:<br>HR 1.03 (0.95:1.11) per IQR (13.21 μg/m$^3$) increment of baseline $PM_{2.5}$<br>HR = 2.38 (2.21:2.56) per IQR (4.34 μg/m$^3$) increase in change in $PM_{2.5}$ during follow-up<br>Similar results when adjusted for other pollutants | Age, sex, income, diabetes, diabetes mellitus, hypertension, myocardial infarction, stroke myocardial infarction, peripheral artery disease, asthma, chronic obstructive pulmonary disease, other pollutants multiple ($PM_{10}$, $O_3$, $CO_2$, $NO_2$, $SO_2$) |
| Cacciottolo et al. [32] | Yearly time series of $PM_{2.5}$ exposure 1999–2010 used to calculate a 3 yr moving average exposure. | Selective research cohort, women only,<br>USA<br>3,647 | 65–79 | 3-yr average exposure preceding the event >12 μg/m$^3$ categorized as high exposure | Incident dementia:<br>Annual screening of global cognitive function. Participants falling below prespecified cut-points received additional neuropsychological and functional assessment alongside clinical data and physician assessment used by a central blinded adjudication committee to reach dementia diagnosis<br>Diagnostic criteria DSM-IV | Yearly time series of $PM_{2.5}$ exposure generated from statistically validated BME method (estimates applied to geocoded residential location and combined with residential histories to calculate the 3-yr moving average exposure. BME method used to construct spatiotemporal models to estimate ambient concentrations of $PM_{2.5}$ which integrates nationwide monitoring data from the US EPA AQS and output of chemical transport models to characterize spatiotemporal interdependence of environmental data to estimate mean trends and covariance of the air pollution field over space and time. | Incident dementia:<br>For high exposure<br>HR = 1.92 (1.31, 2.80)<br>APOE*$PM_{2.5}$<br>ε3/3: HR = 1.68 (0.97, 2.92)<br>ε3/4: HR = 1.91 (1.17, 3.14)*<br>ε4/4: HR = 3.95 (1.18, 13.19)*<br>interaction $p$ = 0.43 | Age, geographic location, education, income, employment status, lifestyle factors (smoking, alcohol, physical activity), clinical characteristics (use of hormone treatment, depression, BMI, hypercholesterolemia, hypertension, diabetes, history of cardiovascular disease) |

**Table 2** (continued)

| | Longest exposure measure and date of exposure | Region of recruitment, number of participants at baseline | Participant age at baseline | $PM_{2.5}$ level | Measures of dementia | Measures of air pollution exposure | Results | Adjustments |
|---|---|---|---|---|---|---|---|---|
| Oudin et al. [36] | Annual mean concentration of $PM_{2.5}$ for 1990, 2000, 2010 | Population based cohort, Sweden 1,806 | ≥55 | Mean annual average of $PM_{2.5}$ concentration: 0.18 μg/m$^3$ (SD = 0.17 μg/m$^3$) | Incident dementia: Dementia was assessed at baseline and every 5 yr using medical records from hospital and primary care visits over the 5 yr period plus observations obtained at Betula study visits (health and cognitive evaluations). Extended review by a senior old age psychiatrist was included in Mini-Mental State Exam scores were ≤23 or where cognitive or functional status had declined from previous visit or where a participant expressed a perception of subjective memory loos or where cognitive or behavioral issues were noticed by the testing team. A quality assurance exercise with blinded re-evaluation. Diagnostic criteria DSM-IV Note Blinded re-evaluation was made of medical records of those with established dementia diagnosis, DSM-IV diagnosis, supplemented with medical record data | Used annual mean concentration of $PM_{2.5}$ for 1990, 2000, 2010 calculated by the Swedish Meteorological and Hydrological Institute which estimated concentrations using a wind model and a Gaussian air quality dispersion model. To estimate $PM_{2.5}$ from vehicular emissions the traffic flow for vehicles was collected for most major roads and modeled for elsewhere. Vehicle fleet composition derived from national vehicle registry, and emission factors for exhaust calculated based on the Handbook Emission factors for Road Transport. Model grids were of 3,200 × 3,200 m spatial resolution and 50 × 50 m in urban areas | Incident dementia: HR = 1.14 (0.59, 2.23) per 1 μg/m$^3$ increase in exposure | Education level, physical activity, smoking, sex, body mass index, waist-hip ratio (>recommended vs. ≤recommended), alcohol, age |
| Grande et al. [25] | Air pollution measure 5 yr prior to baseline, follow-up for 13 yr | Research cohort study, Sweden $N$ = 2,927 | 74.1 (10.7) | 8.4 μg/m$^3$ (SD 0.7) | Incident dementia: Three-step procedure including consensus physician diagnosis DSM-IV | Based on residential addresses with dispersion modeling based on local emission inventories. Gaussian dispersion model was applied to the emission databases with meteorological and climate data and using a quadtree receptor grid to allow high resolution in the vicinity of roads. Time varying 5-yr mean $PM_{2.5}$ | Incident dementia: HR 1.54 (1.33:1.78) per IQR difference of 0.88 μg/m$^3$ Authors also report a nonlinear relationship such that the increase in risk was steepest from low to mean level concentrations and flatter at higher levels | Age, sex, education, smoking, physical inactivity, socioeconomic status, early retirement, BMI, depression, baseline MMSE, and cardiovascular risk factors Additional analyses examined cardiovascular disease as a moderating or mediating factor and reported $PM_{2.5}$ associated with a stroke – dementia pathway |
| Yuchi et al. [27] | Exposure period 4 yr (1994-1998), follow-up period 4 yr (1999–2003) | Population-based cohort, Canada $N$ = 633,949 | 76 for non-Alzheimer's dementia, 57 for noncases | Median 4.1 μg/m$^3$ for non-Alzheimer's dementia, 4.0 μg/m$^3$ for noncases and for Alzheimers dementia | From hospital record ICD-9 coding, or 3 physician medical services claims in 3 yr, or prescriptions for acetyl cholinesterase inhibitors. Divided cases in non-Alzheimer dementia and Alzheimer's Dementia | Based on residential address and satellite-based estimation of $PM_{2.5}$ based on land use regression models. There were 25 monitoring sites for $PM_{2.5}$ | Per IQR 1.54 μg/m$^3$ Non-Alzheimer's dementia HR 1.02 (0.98:1.05) Alzheimer's Disease HR 0.90 (0.76:1.07 | For non-Alzheimer's dementia. Age, sex, comorbidities including traumatic brain injury, diabetes, hypertension, stroke, coronary heart disease, arrhythmia plus household income, ethnicity For AD, due to small numbers, analysis was via an age and sex matched case control with household income, education, ethnicity, and comorbidities as covariates |

AD, Alzheimer's disease; BME, Bayesian maximum entropy; EPA AQS, United States Environmental Protection Agency Air Quality System; BMI, body mass index; $CO_2$, carbon dioxide; DSM-IV, Diagnostic Statistical Manual for mental disorders; IQR, interquartile range; HR, hazards ratio; MMSE, Mini-Mental State Exam; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; $O_2$, nitrogen dioxide; NCD, noncommunicable disease; $O_3$, ozone; $PM_{2.5}$, particulate matter ≤2.5 μm in diameter; $PM_{10}$, particulate matter ≤10 μm in diameter; RR, relative risk; SD, standard deviation; SES, socioeconomic Status; $SO_2$, sulfur dioxide.

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**Table 3.** $PM_{2.5}$ as a risk factor for cognitive decline

| | Longest exposure measure and date of exposure | Region of recruitment, number of participants at baseline | Participant age at baseline | $PM_{2.5}$ level | Measures of cognitive decline | Measures of air pollution exposure | Results | Adjustments |
|---|---|---|---|---|---|---|---|---|
| Weuve et al. [28] | Averaged monthly exposure 1988–1995 | Research cohort USA (11 states) 19,409 | ≥70 yr | 14.2 μg/m$^3$ (SD = 3.0; range: 19.2–25.5 μg/m$^3$) | Global cognition (averaged z-scores from TICS 10-word list, EBMT, immediate recall, delayed recall, Digit Span Backward test, category fluency 2-yr change in global cognitive score z-scores | Averaged month-specific exposure from 1988 through to month preceding month) preceding baseline cognitive interview. Derived from EPA's AQS meteorological data and GIS smoothing models for geocoded residential location per participant. | Adjusted difference in 2-yr change in global cognitive score z-scores per 10 μg/m$^3$ increase (since 1988): −0.018 (−0.035, −0.002) | Age, cognitive assessment, education, husband's education, long-term physical activity, long-term alcohol consumption, time × covariate interactions (BMI, diabetes, smoking, aspirin use, ibuprofen use adjustments had no effect) Further adjustment in secondary analyses found similar results Secondary analyses: SES measures (percentage of adults who have less than high school education, median home value, median income) Additional analyses: self-reported emphysema and indicators of cardiovascular and cerebrovascular disease (high blood pressure, coronary heart disease, congestive heart failure, coronary artery bypass graft, transient ischemic attack, carotid endarterectomy) |
| Loop et al. [29] | Annual average exposure up to and including the date of the baseline visit (2003) | Research cohort USA (48 states) 20,150 | 64 (9.2) | Quartiles of $PM_{2.5}$ μg/m$^3$: 6.6–12.2 12.2–13.6 13.6–14.8 14.8–21.0 | Six item Screening telephone assessment (3-item recall and orientation in time) cognitively intact: scores ≥5/6; incident cognitive impairment: scores ≤4 | Annual average exposure using an algorithm combining EPA›s AQS ground-level monitoring data and NASA's MODIS aerosol optical depth satellite data to calculate daily $PM_{2.5}$ exposure per participant according to residence up to and including the date of the baseline visit. | Effect of 10 μg/m$^3$ increase in $PM_{2.5}$ >12 months, $n$ = 18,180 OR = 0.71 (0.38, 1.32) | Length of follow-up, temperature, season, incident stroke, age, race, region, education, income, behavioral factors (alcohol, smoking, exercise, BMI), depression, dyslipidemia, diabetes, hypertension |
| Tonne et al. [30] | 5-yr average (between 2002 and 2009) | Research cohort, London UK 2,867 | ~61 | 14.9 μg/m$^3$ (SD = 0.9; IQR: 1.1 μg/m$^3$) | Tests of reasoning (Alice Hein 1-I test) Short-term verbal memory (20-word-free recall test) Semantic verbal fluency Phonemic verbal fluency Administered 2002–2004 and 2007–2009 Cognitive test scores were converted to z-scores and standardized using distribution of that wave. Linear mixed models used to evaluate relationship between cognitive change and pollutant exposure. | Annual average concentration for years 2003–2009 modeled at resolution 20 × 20 m using the KCLurban dispersion modeling system which incorporates meteorological data, empirically derived PM relationships, and emission from the London Atmospheric Emission Inventory. Exposure at residence based on average concentration at model grid points within 25 m of the postcode center 5-yr average (preceding years of assessment in 2007–2009) | Cognitive change between 2 tests on reasoning, memory, semantic, and phonemic fluency per IQR increase 5-yr average: ns for all tests | Age, sex, ethnicity, marital status, education, SES (civil service employment grade), alcohol use, physical activity, time, age × time interaction, main effects of exposures |
| Cleary et al. [35] | 2001–2008. Annual mean concentrations starting year before each participants baseline. Analyses restricted to those participants with geographical data from 2005 to 2008 | Research cohort, USA (Nationwide) Selected those with baseline MMSE >26 2,048 | 76.6 (7.7) with MMSE ≥24 | Annual mean concentrations 9.7 μg/m$^3$ (range: 3.8–14.4 μg/m$^3$) | Change in MMSE, CDR-SB Mean annual cognitive change (1.3±0.02 on the MMSE and 1.0±0.02 on the CDR-SB [mean±SE of the mean]) is provided only for the whole cohort – i.e., including those with baseline MMSE >26 and 26 and below | Annual mean concentrations derived daily 24-h $PM_{2.5}$ concentrations in μg/m$^3$ starting year before baseline EPA's hierarchical Bayesian model data derived from ground-level monitoring data from the AQS and simulated ozone and from the CMAQ model (estimates available in 12×12 m resolution covering eastern states and 24×24 m nationwide) used. Yearly exposure estimates based on to ZIP codes of residence, or via interpolation. | ns Dose-dependent relationship between *APOE4* $PM_{2.5}$ interaction and cognitive decline. Lowest decline in those without *APOE4* allele and lowest exposure | Age, gender, education, race, APOE genotype, smoking, B12 deficiency, and population density |

**Table 3** (continued)

| | Longest exposure measure and date of exposure | Region of recruitment, number of participants at baseline | Participant age at baseline | $PM_{2.5}$ level | Measures of cognitive decline | Measures of air pollution exposure | Results | Adjustments |
|---|---|---|---|---|---|---|---|---|
| Cacciottolo et al. [32] | Yearly time series of $PM_{2.5}$ exposure 1999–2010 used to calculate a 3 yr moving average exposure | Selective research cohort, women only, USA 3,647 | 65–79 | 3-yr average exposure preceding the event >12 μg/m$^3$ categorized as high exposure | Incident accelerated decline in global cognitive function (operationally defined as having an 8-point loss in the Modified MMSE in 2 consecutive assessments) | Yearly time series of $PM_{2.5}$ exposure generated from statistically validated BME method estimates applied to geocoded residential location and combined with residential histories to calculate the 3-yr moving average exposure. BME method used to construct spatiotemporal models to estimate ambient concentrations of $PM_{2.5}$ which integrates nationwide monitoring data from the US EPA AQS and output of chemical transport models to characterize spatiotemporal interdependence of environmental data to estimate mean trends and covariance of the air pollution field over space and time | Cognitive decline HR = 1.81 (1.42, 2.32) APOE* cognitive decline ε3/3: HR = 1.65 (1.23, 2.23)* ε3/4: HR = 1.93 (1.29, 2.90)* ε4/4: HR = 3.64 (1.36, 9.69)* interaction $p = 0.29$ | Age, geographic location, education, income, employment status, lifestyle factors (smoking, alcohol, physical activity), clinical characteristics (use of hormone treatment, depression, BMI, hypercholesterolemia, hypertension, diabetes, history of cardiovascular disease) |
| Cullen et al. [24] | Mean annual concentration in 2010. Follow-up visit invitations 2012–2013 | Research cohort, UK Numbers vary depending on the cognitive test ~2,590 | 56.9 (8.1) | Median 9.55 (IQR 8.86:10.16) | Reasoning, reaction time, pair matching, and prospective memory tasks Change scores for reasoning, reaction time, and pairs matching followed an approximately normal distribution, and were analyzed with linear regression; Change on the prospective memory test was analyzed using logistic regression, | Measures were modeled at participants' baseline residential addresses. $PM_{2.5}$ was measured as annual average values in μg/m$^3$. Estimates for the year 2010 were modeled for each address using a Land use Regression model developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE; http://www.escapeproject.eu/) | Reasoning slope 0.0013 (95% CI −0.0860:0.0886) Reaction time −6.2530 (−11.1697: −1.3363) higher values of pollutant associated with improvement but becomes ns when $p$ value adjusted for false discovery rate) Pairs matching −0.0383 (−0.2428:0.1663) Prospective memory 1.0107 (0.7685:1.3293) | Duration between baseline and follow-up as well as baseline age, gender, ethnic group, Townsend score (socioeconomic), education, smoking status, physical activity time outdoors, major road proximity, traffic intensity, and population density category |
| Kulick et al. [26] | Calendar year prior to enrollment (enrollment in 3 cohorts 1992, 1999, 2010) | Research cohort, Washington, USA 4,821 | 76.3 (6.6) | Mean 13.5 (IQR 4:42) | Global composite and domain-specific cognitive scores from a neuropsych battery combined using z-scores Assessment every 18–24 months weighted linear mixed models for repeated measures | Estimates of residential ambient air pollution levels in the calendar year prior to first neuropsychological assessment were from the U.S. EPA Air Quality System and annual average values were used in a universal kriging regression framework to predict concentrations at individual addresses. Partial least square methods were used to include geographic covariates (roadway density, population density, urban land, agricultural land, forests, bodies of water), land use, and roadway proximity to improve predictions | Global cognition slope −0.093 (−0.12: −0.07) Memory domain −0.047 (−0.08: −0.02) Language domain −0.066 (−0.10: −0.03) Executive function −0.051 (−0.08: −0.02) | Visit number, visit by pollutant interaction, age, sex, race-ethnicity, education, neighborhood socioeconomic status, and an indicator for cohort wave to account for secular trends |

EPA, Environmental Protection Agency; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CMAQ, Community Multiscale Air Quality Modelling System; GIS, geographic information system; EBMT, East Boston Memory Test; EPA AQS, United States Environmental Protection Agency Air Quality System; BMI, body mass index; $CO_2$, carbon dioxide; DSM-IV, Diagnostic Statistical Manual for mental disorders; IQR, interquartile range; HR, hazards ratio; MMSE, Mini-Mental State Exam; NASA MODIS, NASA, Moderate Resolution Imaging Spectroradiometer; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; $O_2$ nitrogen dioxide; NCD, noncommunicable disease; $O_3$, ozone; $PM_{2.5}$, particulate matter ≤2.5 μm in diameter; $PM_{10}$, particulate matter ≤10 μm in diameter; RR, relative risk; SD, standard deviation; SES, socioeconomic status; $SO_2$, sulfur dioxide; TICS, Telephone Interview for Cognitive Status.

exact measures, timing, and calculation of exposure variables differed. The USA study [32] reported a 92% {hazard ratio (HR) 1.92 (95% confidence interval [CI]) 1.31:2.80} increased risk for exposure to levels above 12 μg/m$^3$ over 3 years, the Canadian study reported a 3% (HR 1.03 [1.02:1.05]) increased risk with an increment of 4.8 μg/m$^3$ [33], the UK study a 6% (HR 1.06 [1.01:1.13]) increased risk but for a 0.95 μg/m$^3$ incremental change in exposure [34], and one Swedish study a 54% (HR 1.54 [1.33:1.78]) increased risk per 0.88 μg/m$^3$ increase [25]. The other studies found no increased risk including the Taiwanese study [31] which reported exposure measures of 33.6 μg/m$^3$ and the study with the lowest concentrations, the Betula study reporting a mean annual average $PM_{2.5}$ concentration of 0.18 μg/m$^3$ (standard deviation [SD] 0.17 μg/m$^3$) [36].

The 7 studies reporting on incident cognitive decline all comprised research cohorts (Table 2). Two were recruited from the UK [24, 30] and 5 from the USA [26, 28, 29, 32, 35]. Studies ranged in size from 2,048 [35] to over 20,000 [29] participants. Air pollution measures were collected as early as 1988 [28] and as recently as 2010 [24, 26, 32]. The mean age of the cohorts ranged from 56.9 (SD 8.1) [24] to 76.3 (SD 6.6) [26] years. All reported on cognitive change or incident decline defined as a fall to below a threshold [29] or of a certain size [32]. Some chose to report cognitive domains or general cognitive assessment and 3 used screening tools [29, 32, 35]. The relationships between air pollution and cognition were largely nonsignificant [24, 29, 30, 35]. The exceptions were Weuve et al. [28] who reported a significant 2-year decrease in global cognitive z-score (per 10 μg/m$^3$ increase in $PM_{2.5}$) and the WHIMS cohort which found an 81% (HR 1.81 [1.42:2.32]) increase in incident cognitive decline (an 8-point decline in extended Mini-Mental State Exam in 2 consecutive assessments) in the higher exposure group [32]. Levels of $PM_{2.5}$ were similar across studies with mean concentrations of 14.9 [30] 14.2 [28], 13.6 (Median) [29], 13.5 [26], 9.7 [35], and 9.6 [24] μg/m$^3$.

*Assessment of Bias*

Overall, the risk of bias within studies reporting on the relationship between $PM_{2.5}$ and incident dementia, or cognitive decline was low to moderate (6 rated as low, 6 as low moderate, and 1 as moderate) see online suppl. Table 3. Included studies reported clear aims, appropriate methodology, comprehensive adjustment for confounders, standard methods for measurement of exposure, and use of health records or appropriate cognitive testing for outcomes. Improvements within individual studies would involve improving detailed assessment of exposure, using more comprehensive neuropsychological testing and more rigorous case ascertainment, selecting more representative populations, and investigating attrition more thoroughly. For NCDs, the reviews were largely rated as moderate quality using the rigorous AMSTAR 2 criteria [13] (6 as moderate and 2 low quality).

*Across the Evidence Base*

A greater risk of bias becomes evident when the studies are narratively synthesized and considered together as a body of research [37]. For the studies on dementia and cognitive decline, although the evidence is largely from older adults, the differing lengths of exposure, methods of modeling of exposure and outcome, and varied combinations of confounders and potential under or over adjustment in the analyses (we selected the most adjusted results) make the studies appear less comparable than when assessed individually. For example, it is not possible to know whether the same positive or negative relationships would be shown across the studies if the same $PM_{2.5}$ concentrations and exposure times had been used. Data are also drawn only from a limited number of high-income countries and are lacking for younger age-groups and longer term follow-up, particularly relevant for dementia where disease processes may start 10 or 20 years prior to symptom onset [38]. The reviews of other NCDs suffer from similar issues with some evidence only available for acute and very short-term exposure and some only for on longer term follow-up measures. Reviews demonstrate more global data than the studies of dementia, but most combine varied study designs and wide $PM_{2.5}$ concentration ranges. Finally, for all review and original research studies, included in this systematic review, $PM_{2.5}$ was defined based on its ambient mass concentration, which is insensitive to the significant regional differences in its composition [39–42].

## Discussion

Our aim was to systematically review the evidence relating to $PM_{2.5}$ and risk of dementia or cognitive decline, and to position this within a wider public health context. In addition, given that vascular disease itself is a risk factor for dementia [6, 7], we also performed a systematic review of the evidence for $PM_{2.5}$ and other relevant NCDs, to contextualize these observations with other established diseases previously associated with $PM_{2.5}$ exposures and sharing common underlying inflammatory pathways.

Overall, for studies on cognition, we found that the evidence supporting an association between fine particulate matter exposures was strongest for dementia. Studies on cognitive decline were inconclusive, with only 2 of the 7 studies reporting an elevated risk both of which used general measures of cognition. Most of the studies on incident dementia demonstrated an increased risk with higher $PM_{2.5}$ concentrations. Our results are broadly in agreement with prior reviews [43–45]. The systematic review evidence for the other NCDs was clearer than the evidence for cognition and dementia; however, exposure times for some outcomes were effectively based on acute time periods, whereas others were over the longer term. Interestingly, the results for dementia outcomes were obtained despite most studies adjusting broadly for the presence of other cardiovascular comorbidities, which may support an independent $PM_{2.5}$ dementia pathway. This potentially argues for a more direct linkage to Alzheimer's disease as opposed to vascular dementia, but this distinction needs further research beyond inference drawn from epidemiological observations.

Using the standard review methodology, we used published data and, in order to represent the evidence base on NCDs, selected a review of reviews method rather than reviewing primary research. Despite this, we undertook a rigorous systematic review approach and, while we can conclude that the emerging evidence base confirms that $PM_{2.5}$ is associated with increased risk of dementia and other NCDs, consideration of the whole picture reveals several limitations.

Individual studies and reviews revealed no definitive sources of bias on formal assessment; however, when considered holistically the gaps in the evidence become clearer. We raise several issues that need to be addressed before using the evidence to inform policy. These limitations fall within 3 categories: (i) those that may be overcome in the shorter term, (ii) those that require additional research, and (iii) those that cannot be easily remedied without additional data collection. We discuss each of these and make recommendations below.

1. **Limitations that may be overcome in the shorter term.** These include a lack of standardization in reporting and in analyses, varied adjustment for confounders, the potential for incomplete adjustment for confounders, including those that may influence lifestyle and health choices, a mixture of acute and longer term exposure estimates and a lack of enough accounting for attrition (particularly attrition due to other health conditions exacerbated by $PM_{2.5}$).

   **Recommendations:** The adoption of an agreed standardized data collection, processing, and analysis protocol and/or a 1 or 2 stage individual participant data meta-analysis (IPD-MA) to facilitate similar processing across studies. Examination of multiple NCD end points and analysis, taking account of competing end points and interactions is also needed, for example, looking at the direct and indirect pathways that may impact on dementia risk.
2. **Limitations that require additional research:** Variation in exposure attribution methods between studies, including an absence of detailed compositional information, despite clearly different source profiles between countries, and within countries over time. Because $PM_{2.5}$ is not a uniform chemical entity, its composition varies markedly between different regions [40, 41] as well as across time [40, 41]. While the epidemiological literature strongly focuses on $PM_{2.5}$, it is notable that preliminary work and evolving research hypotheses around the potential causal link between air pollution and dementia have focused on primary combustion and mechanical abrasion particles [39] which represent only a fraction of $PM_{2.5}$ mass and display marked spatial variation, not captured by the simple mass metric. As these fractions of $PM_{2.5}$ are not widely measured in regulatory networks and as models for these metrics are relatively recent [42], their association with dementia incidence has not been fully explored. This may be of particular importance for cognitive outcomes since the ultrafines (particles that are <100 nm in diameter) within $PM_{2.5}$ may translocate across biological barriers, for example, via olfactory neurons to the olfactory bulb. Often $NO_2$, for which widespread monitoring and well validated models are available, is used as a proxy for primary exhaust emissions from diesel vehicles, but the literature linking $NO_2$ to dementia, or indeed to associated cardiovascular risk factors remains equivocal [2, 14]. Furthermore, there remain significant gaps in our knowledge of the molecular triggers and causal pathways linking poor air quality to increased dementia risk.
   **Recommendations:** We need a better understanding of how $PM_{2.5}$ composition has varied over time and presently varies between different global regions, to fully interrogate and integrate studies drawn from different periods and locations. A better understanding of these issues will help inform causal inference and potentially improve our understanding of the drivers for some of the heterogeneity observed in the current evidence base. In addition, the extent to which $PM_{2.5}$ and its constituents interact with copollutant gases and volatile organic

species in the atmosphere, either additively or synergistically, to impact on the risk of one or more NCDs and pre-NCD states need to be clarified. This is particularly important where one NCD may impact on the risk of another, an area where evidence is severely lacking, such as for the relationship between cardiovascular disease and dementia [25]. Alongside this, we need a greater background understanding of the shape of the relationship between $PM_{2.5}$ and NCD outcomes and the role of other risk factors. For example, is the relationship linear or is there a point at which it has less of an impact (as implied by the recent Grande et al. [25] study)?

Furthermore, how does the background risk of the population, the life-course exposure, and population risk factor habits play a part? Relevant to this is a need to better assess personal exposure, to collect data from wider geographical and cultural areas, and to look by population subgroups where risk levels may vary. For example, women may be exposed to increased risk where they are the ones predominantly exposed to cooking on woodstoves, or men where they spend more time on busy streets outside the home.

3. **Limitations that cannot be easily remedied without new data collection:** There is bias inherent in the use of administrative health record data, a lack of sophisticated cognitive testing and an absence of long-term follow-up.

   **Recommendations:** An IPD-MA may help in resolving these limitations with the use of z-score change for cognition, but inevitably new studies are needed.

Overall, we can conclude it is likely that greater exposure to $PM_{2.5}$ increases the risk of dementia, and that there is some evidence that this effect is independent of other cardiovascular comorbidities. It is also notable that the magnitude of the relationship between incident dementia and $PM_{2.5}$ after adjustment for comorbidities is of a similar magnitude to that seen for cardiovascular disease. This would imply that the total health impact of ambient $PM_{2.5}$ may have been significantly underestimated. Understanding the potential associations with dementia is therefore critical and whilst the evidence base is growing and strengthening, before we can take the next steps and calculate population attributable risk, estimate cost implications and model the effects of risk reduction, we need a more sophisticated analysis of the current evidence and, ideally, new data collection. Air pollution is pervasive and global. It holds numerous inter-related health implications. Using a systematic review process to integrate what is already in the literature has allowed us to synthesize findings across the breadth of evidence necessary to evaluate such a global health phenomena and has allowed important commonalities across these fields to emerge. To develop our understanding of the relationship between air pollution and dementia, we must now look holistically beyond dementia.


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## Conflict of Interest Statement

The authors have no conflict of interest to report.


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## Author Contributions

Ruth Peters conceived the research, drafted the search terms, ran the searches, extracted the data, and drafted the article. Ian Mudway co-conceived the research, advised on the search terms, contributed to the drafting of the article and the critical interpretation of the results. Andrew Booth advised on the search terms, strategies and assessment of the evidence, and contributed to the drafting of the article and the critical interpretation of the results. Jean Peters co-conceived the research, double screened the articles, aided with extraction, and contributed to the drafting of the article and the critical interpretation of the results. Kaarin J. Anstey aided in the conceptualization of the article and contributed to the drafting of the article and the critical interpretation of the results.

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