Title: Putting fine particulate matter and dementia in the wider context of non-communicable disease, where are we now and what should we do next? A systematic review.

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Running title Critical overview of the evidence on $PM_{2.5,}$ dementia and non-communicable disease

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ABSTRACT

Introduction

A significant proportion of the global population regularly experience air quality poorer than that recommended by the WHO. Air pollution, especially fine particulate matter ($PM_{2.5}$) is a risk factor for various non-communicable diseases 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 non-communicable diseases 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 two 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 five of the seven 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.

Keywords

Dementia, non-communicable disease, air pollutants, particulate matter

INTRODUCTION

In recent years the established literature linking poor air quality to adverse cardiopulmonary endpoints, 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 long-term exposures to ambient fine particulate matter ($PM_{2.5}$). $PM_{2.5}$ refers to particles with an average aerodynamic diameter 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 modelled 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 $\mu g/m^3$, with those in low and middle income countries most at risk [3].

Importantly, there are also established links between leading Non-Communicable Diseases (NCD) (for example diabetes and stroke) and an increased risk of later dementia [5]. This is important since $PM_{2.5}$ may raise 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 two 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 two independent analysts (RP, JP). 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 two 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 non-communicable disease and $PM_{2.5}$

Leading NCDs were defined as cardiovascular disease (myocardial infarction, heart failure, stroke), respiratory disease (COPD, 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 31st January 2020. A review of reviews methodology was selected as a systematic method frequently used to summarise 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)) (supplementary text 1). Utilising 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, obesity), 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 PM2.5 exposure estimates for the population, the assessment of incident disease and the results.

The Assessing the Methodological quality of Systematic reviews (AMSTAR) version two (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 1st 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) (supplementary 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 citing 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, i.e. 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 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 non-communicable 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 full text stage. Twenty-two were excluded after full text screening. Sixteen of these reviews had been superseded by more recent reviews, two 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, Supplementary 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, cross-over and time series studies with two [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 [21, 23, 22, 19]. All meta-analyses reported a statistically significant relationship between their respective outcome and 10 $\mu g/m^3$ increment in $PM_{2.5}$ with most point estimates falling between a one and 10 percent 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), 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 full text screening (supplementary table 2), one did not report results for $PM_{2.5}$, three either included prevalent dementia, or it was not possible to tell whether it was excluded, one reported only fatal outcomes, three appeared to report on sub-populations of studies already included and two reported cross temporal analyses without measuring incident decline. Four articles were included ([24-27]) and these were supplemented with nine articles that had been identified in our prior systematic review (covering the literature from inception to 2018) but which also met inclusion criteria the [28-36] Tables 2 and 3 and figure 1 for the flow chart.

Seven studies reported on incident dementia [31-34, 36, 25, 27] (Table 2) Five of the seven 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 ([31, 33, 34, 27], Read codes (used in UK general practice) [34] and/or the Diagnostic Statistical Manual version 4 (DSM IV) [31, 36]. The three smallest studies were research cohorts. These included: i) the Betula cohort from Sweden (n=1806) [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=2927), which used physician review [25] and iii) the Cacciolotto et al study population (n=3647), which was drawn from the larger Women's Health Initiative Memory (WHIMS) Study [32]. WHIMS was a research-based cohort with repeated assessments that diagnosed dementia with a multi-step 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 [31, 33, 34, 27]. Although age was not consistently reported, the mean baseline age for all dementia studies was estimated at around 65 years. Exposure duration ranged from one [34] to 14 years [33] with $PM_{2.5}$ data collected at different time points from 1990 [36] to 2012 [33]. Five of the seven 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 50m x 50m in urban areas and 3200m x 3200m in rural areas [36]. Annual exposure measures were most common [32-34, 36] but 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 $\mu g/m_3$ over 3 years, the Canadian study reported a 3% (HR1.03 (1.02:1.05)) increased risk with an increment of 4.8 $\mu g/m^3$ [33], the UK study a 6% (HR1.06

(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% (HR1.54 (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 seven studies reporting on incident cognitive decline all comprised research cohorts, (Table 2). Two were recruited from the UK [30, 24] and five from the USA[28, 29, 32, 35, 26]. Studies ranged in size from 2048 [35] to over 20,000 [29] participants. Air pollution measures were collected as early as 1988 [28] and as recently as 2010 [32, 24] [26]. 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 three used screening tools [29, 35], [32]. The relationships between air pollution and cognition were largely non-significant [29, 30, 24], [35]. The exceptions were Weuve et al who reported a significant 2-yr decrease in global cognitive z-score (per 10 μg/m^3 increase in $PM_{2.5}$) [28] and the WHIMS cohort which found an 81% (HR1.81 (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 (six rated as low, six as low-

moderate and one as moderate) See supplementary 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] (six as moderate and two 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 modelling 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 contextualise 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 two of the seven studies reporting an elevated risk both of which used general measures of cognition. In contrast, 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 co-morbidities, 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 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, whilst 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 the detail for policy or planning These limitations fall within three 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 standardisation 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 standardised data collection, processing and analysis protocol and/or a one or two stage individual participant data meta-analysis (IPD-MA) to facilitate similar processing across studies. Examination of multiple NCD endpoints and analysis, taking account of competing endpoints 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]. Whilst 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 ultrafine particulate matter within PM2.5 may translocate across biological barriers, for example via olfactory neuron 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 co-pollutant 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 study [25])?

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 co-morbidities. It is also notable that the magnitude of the relationship between incident dementia and $PM_{2.5}$ after adjustment for co-morbidities 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 synthesise 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/DISCLOSURE STATEMENT

The authors have no conflict of interest to report

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 and 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 conceptualisation of the article contributed to the drafting of the article and the critical interpretation of the results.

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Table 1 $PM_{2.5}$ exposure as a risk factor for Non-Communicable Disease (NCD)

Author	Assessment of incident disease (NCD)	Number of studies	Region	Search dates	Exposure length	Range of $PM_{2.5}$ level µg/m3 Mean (Standard Deviation (SD))	Results (10 µg/m3 increment)
Hamra et al [2014] [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 3-34 years	12.9 (SD1.4) to 31.9 (SD10.7)	RR1.09 (1.04:1.14) I^2 53%
Li et al [2016] [17]	Chronic Obstructive Pulmonary Disease exacerbations (emergency hospitalisations or mortality)	59 case crossover or time series	Europe, North and South, America, Asia, Australia	Web of Science 1956-2016 Medline1946-2016, Embase 1974-2005, Environmental Sciences and Pollution Management Index, CINAHL, Google Scholar, Cochrane database 2005-2016, CNKI	Short term. Exposure lags from 0-3 days	5.2 to 94.59 Overall mean 14.84 (SD8.05)	RR1.02 (1.01:1.04) for lag 1 I^2 76.8% For a 3 day lag time RR1.01 (1.01:1.02)
Zheng et al [2015]	Asthma emergency hospital visits or	6 case crossover or time series	Unclear for the studies included in the adult data meta-analysis.	Embase, Pubmed, Cochrane Central Register of Controlled Trials and	Short term. Exposure lags from 0-7 days	Unclear for the studies included in the adult data	RR1.03 (1.01:1.05) I^2 56%

[19]	hospitalisation		Overall studies were drawn from Europe, North, America, Asia and Australia	EBM Reviews – Cochrane database of systematic reviews, Web of Science, Ovid and Highwire.Inception to March 2015		meta-analysis. Overall average 24 hour concentration ranged from 6.1-36.4	
Yang et al [2020] [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 more than 10 year exposure	Mean 4.1 to 35.8	HR1.10 (1.04:1.17) I^2 74.4
Shah et al [2013] [21]	Heart failure hospitalisation 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 0-7 days	Median 15.0 (IQR10.8:17.6)	% 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 [2015] [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 0-7 days	Not provided.	OR1.022 (1.015:1.030) I2 61.4% For a 2 day lag time RR1.002 (0.995:1.009)

Shah et al [2015] [22]	Incident hospitalisation 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 0-7 days	Not provided.	RR1.011 (1.011:1.012) I^2 86% For a 2 day lag RR1.013 (1.010:1.015)
Wu et al [2020] [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 year averaged $PM_{2.5}$ and annual average and time varying $PM_{2.5}$	Not provided.	For the 2 studies: RR1.06 (1.00:1.21) and RR1.27 (1.17:1.38) I^2 N/A

Abbreviations: IQR Inter-Quartile Range, HR Hazard Ratio, NCD Non-communicable Disease, PM2.5 Particulate matter ≤2.5μm in diameter, RR Relative Risk, SD Standard Deviation.

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

	Longest exposure measure and date of exposure	Region of recruit-ment, 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 2018 [34]	Annual concentrations of air pollutants in 2004 (the year prior to baseline)	Population based cohort UK 130978	50-79	Mean 15.7µg/m3 (SD 0.8) Median 15.6 IQR (15.2-16.1)	Incident dementia 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)	Modelled annual concentrations of air pollutants in the year prior to baseline estimated using the KCLurban dispersion modelling 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 $PM_{2.5}$ HR1.06 (1.01, 1.13) per IQR change 0.95 µg/m3 increment 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, night time noise. Each pollutant also adjusted for exposure to others.
Chen et al 2017 [33]	Annual mean concentration 1998-2012	Population based cohort, Ontario Canada 2066639	Mean 66.8 (S.D. 8.2)	5-yr cumulative exposure with 2-yr lag: 10.4µg/m3 (range: 1.1-49.7µg/m3; IQR: 4.8µg/m3)	Incident dementia 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	Annual mean concentration of $PM_{2.5}$ (1 x 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	Incident dementia 5-yr lag: HR_{IQR} = 1.03 (1.02, 1.05)Per IQR 4.8 ug/m3) increment 10-yr lag: HR_{IQR} = 1.03 (1.01, 1.06)	Age sex, stratified region baseline SES (neighborhood-level income, education, unemployment rate, % of recent immigrants pre-existing), urban residency and a North/South indicator,

					physician claims over a two-year 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	represented centroids or blocks or residence.	Per IQR 4.8 ug/m3) increment	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. Secondary analysis: access to neurological care, neighborhood deprivation, linear term for time, excluded urban residency and North/South indicator.
Jung et al 2015 [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	Populati on based cohort Taiwan 95690	>65 at follow up	Mean annual average of $PM_{2.5}$ concentrati on, during 2006-2010: 33.56 µg/m3 (*SD*=9.20; range 10.36-61.76)	Incident Alzheimer's Disease (AD) Case identification based on the Taiwanese National Insurance Research Database using the International Classification of Disease 9th Revision Clinical Modification.	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. 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 HR1.03 (0.95:1.11) per IQR (13.21 ug/m3) increment of baseline $PM_{2.5}$ HR2.38 (2.21:2.56) per IQR (4.34 ug/m3) increase in	age, sex, income, diabetes, diabetes mellitus, hypertension, myocardial infarction, stroke myocardial infarction, peripheral artery disease, asthma, chronic obstructive pulmonary disease, other pollutants

	PM_{10} during 2006-2010.				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		change in $PM_{2.5}$ during follow up. Similar results when adjusted for other pollutants.	multiple (PM_{10}, O_3, CO_2, NO_2, SO_2)
Cacciottolo et al., 2017 [32]	Yearly time series of $PM_{2.5}$ exposure 1999-2010 used to calculate a 3 year moving average exposure.	Selective research cohort, women only, USA 3647	65-79	3-year average exposure preceding the event >12µg/m3 categorised as high exposure	Incident dementia Annual screening of global cognitive function. Participants falling below pre-specified cut-points received additional neuropsychological and functional assessment alongside clinical data and physician assessment used by a central blinded adjudication committee to reach a dementia diagnosis Diagnostic criteria DSM-IV	Yearly time series of $PM_{2.5}$ exposure generated from statistically validated Bayesian Maximum Entropy method (BME) estimates applied to geocoded residential location and combined with residential histories to calculate the 3-y 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	Incident dementia. For high exposure HR=1.92 (1.31, 2.80) APOE*$PM_{2.5}$ ε3/3: HR=1.68 (0.97, 2.92) ε3/4: HR=1.91 (1.17, 3.14)* ε4/4: HR=3.95 (1.18, 13.19)* 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)

						the air pollution field over space and time.		
Oudin et al., 2018 [36]	Annual mean concentration of $PM_{2.5}$ for 1990, 2000, 2010	Population based cohort, Sweden 1806	≥55	Mean annual average of $PM_{2.5}$ concentration: 0.18 µg/m3 (*SD*=0.17 µg/m3)	Incident dementia Dementia was assessed at baseline and every 5 years using medical records from hospital and primary care visits over the 5 year 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 behavioural 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	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 modelled 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 3200 m x3200 m spatial resolution and 50 m x 50 m in urban areas	Incident dementia HR=1.14 (0.59, 2.23) per 1 µg/m3 increase in exposure	Education level, physical activity, smoking, sex, body mass index, waist-hip ratio (>recommended versus ≤recommended), alcohol, age.

					medical records of those with stablished dementia diagnosis, DSM-IV diagnosis, supplemented with medical record data			
Grande et al., 2020 [25]	Air pollution measure 5 years prior to baseline, follow up for 13 years	Research cohort study, Sweden N=2927	74.1 (10.7)	8.4µg/m^3 (SD 0.7)	Three step procedure including consensus physician diagnosis. DSM-IV	Based on residential addresses with dispersion modelling 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-year mean $Pm_{2.5}$	HR 1.54 (1.33:1.78) per IQR difference of 0.88 µg/m^3 Authors also report a non-linear 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 PM2.5 associated with a stroke – dementia pathway.

Yuchi., et al 2020 [27]	Exposure period 4 years (1994-8), follow-up period 4 years (1999-2003)	Population based cohort, Canada N=633949	76 for non-Alzheimers dementia, 57 for non-cases	Median 4.1 $\mu g/m^3$ for non-Alzheimers dementia, 4.0 $\mu g/m^3$ for non-cases and for Alzheimers dementia	From hospital record ICD-9 coding, or 3 physician medical services claims in 3 years, or prescriptions for acetylcholinesterase 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 $\mu g/m^3$ Non-Alzheimer's dementia HR1.02 (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 Alzheimer's Disease, due to small numbers, analysis was via an age and sex matched case control with household income, education, ethnicity and comorbidities as covariates

Abbreviations: 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 Inter-Quartile Range, HR Hazard 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 Non-communicable Disease, O_3 Ozone, $PM_{2.5}$ Particulate Matter ≤2.5μm in diameter, PM_{10} Particulate Matter ≤10μm in diameter, RR Relative Risk, SD Standard Deviation, SES Socioeconomic Status, SO_2 Sulphur dioxide.

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

	Longest exposure measure and date of exposure	Region of recruit-ment, number of participants at baseline	Part-icipant age at bas-eline	$PM_{2.5}$ level	Measures of cognitive decline	Measures of air pollution exposure	Results	Adjustments
Weuve et al 2012 [28]	Averaged monthly exposure 1988-1995	Research cohort USA (11 states) 19409	≥70 years	14.2 µg/m3 (*SD*= 3.0; range: 19.2-25.5 µg/m3)	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 10µg/m3 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 x 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 2013 [29]	Annual average exposure up to and including the date of the baseline visit (2003)	Research cohort USA (48 states) 20150	64 (. 9.2)	Quartiles of $PM_{2.5}$ µg/m3 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 10µg/m3 increase in $PM_{2.5}$ >12 months, n = 18180 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, body mass index), depression, dyslipidemia, diabetes, hypertension.
Tonne et al 2014 [30]	5-yr average (Between 2002-2009)	Research cohort, London UK. 2867	~61	14.9µg/m 3 (*SD*= 0.9; IQR: 1.1µg/m3	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 modelled at resolution 20 x 20 m using the KCLurban dispersion modelling system which incorporates meteorological data, empirically derived PMrelationships 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 centre. 5-y average (preceding years of assessment in 2007-2009)	Cognitive change between two tests on reasoning, memory, semantic and phonemic fluency per IQR increase 5-y average: ns for all tests	Age, sex, ethnicity, marital status, education, SES (civil service employment grade), alcohol use, physical activity, time, age x time interaction, main effects of exposures.
Cleary et al	2001-2008. Annual	Research cohort,	76.6 (7.7)	Annual mean	Change in MMSE, CDR-SB	Annual mean concentrations derived daily 24-hour $PM_{2.5}$	Ns	Age, gender, education, race, APOE genotype,

2018 [35]	mean concentrations starting year before each participants baseline. Analyses restricted to those participants with geographical data from 2005-2008.	USA (Nationwide) Selected those with baseline MMSE>26 2048	with MMSE ≥24	concentrations 9.7µg/m3 (range: 3.8-14.4µg/m3)	Mean annual cognitive change (1.3±0.02 on the MMSE and 1.0±0.02 on the CDR-SB (mean ± std. error of the mean)) is provided only for the whole cohort – ie including those with baseline MMSE >26 and 26 and below.	concentrations in µg/m3 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 12x12 m resolution covering eastern states and 24 x 24 m nationwide) used. Yearly exposure estimates based on to ZIP codes of residence, or via interpolation.	Dose-dependent relationship between *APOE4* $PM_{2.5}$ interaction and cognitive decline. Lowest decline in those without *APOE4* allele and lowest exposure	smoking, B12 deficiency and population density
Caccio ttolo et al., 2017 [32]	Yearly time series of $PM_{2.5}$ exposure 1999-2010 used to calculate a 3 year moving average exposure.	Selective research cohort, women only, USA 3647	65-79	3-year average exposure preceding the event >12µg/m3 categorised as high exposure	Incident accelerated decline in global cognitive function (operationally defined as having an 8-point loss in the Modified MMSE in two consecutive assessments)	Yearly time series of $PM_{2.5}$ exposure generated from statistically validated Bayesian Maximum Entropy method (BME) estimates applied to geocoded residential location and combined with residential histories to calculate the 3-y 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	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)

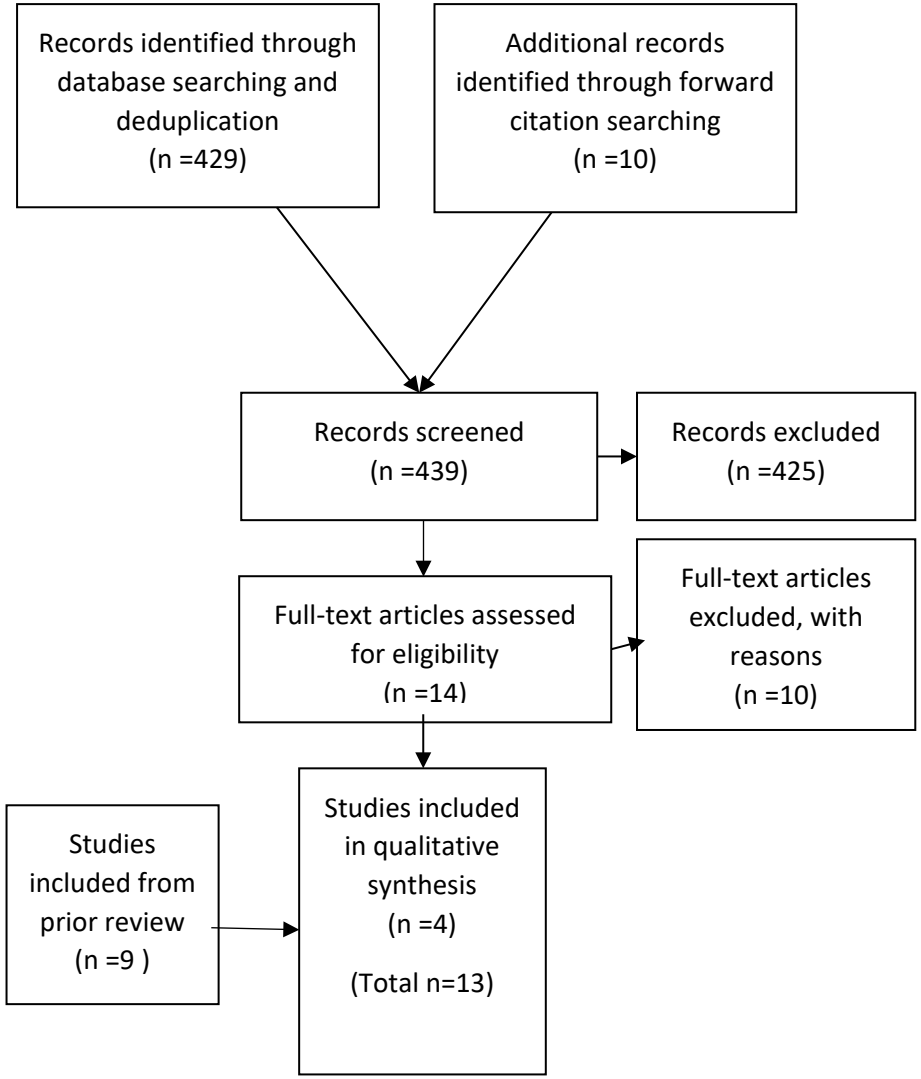
						pollution field over space and time.		
Cullen et al [2018] [24]	Mean annual concentration in 2010. Follow up visit invitations 2012-13	Research cohort, UK Numbers vary depending on the cognitive test ~2590	56.9 (8.1)	Median 9.55 (IQR8.86: 10.16)	Reasoning, reaction time, pair matching and prospective memory tasks Change scores for reasoning, reaction time and pairs matching followed an approximately normal distribution, and were analysed with linear regression; Change on the prospective memory test was analysed using logistic regression,	Measures were modelled at participants' baseline residential addresses. $PM_{2.5}$ was measured as annual average values in µg/m3. Estimates for the year 2010 were modelled 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 [2020] [26]	Calendar year prior to enrolment (enrolment in 3 cohorts 1992, 1999, 2010)	Research cohort, Washington, USA 4821	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. Environmental Protection Agency (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	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, neighbourhood socioeconomic status, and an indicator for cohort wave to account for secular trends.

						covariates (roadway density, population density, urban land, agricultural land, forests, bodies of water), land use, and roadway proximity to improve predictions		

Abbreviations: 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 Inter-Quartile Range, HR Hazard 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 Non-communicable Disease, O_3 Ozone, $PM_{2.5}$ Particulate Matter ≤2.5μm in diameter, PM_{10} Particulate Matter ≤10μm in diameter, RR Relative Risk, SD Standard Deviation, SES Socioeconomic Status, SO_2 Sulphur dioxide, TICS Telephone Interview for* Cognitive *Status.*

Figure 1

Flow diagram, original research on incident dementia, Alzheimer's Disease, cognitive decline and particulate matter 2.5



Flow diagram, systematic reviews of major non-communicable disease incidence and particulate matter 2.5