Review

A critical review of the epidemiological evidence of effects of air pollution on dementia, cognitive function and cognitive decline in adult population

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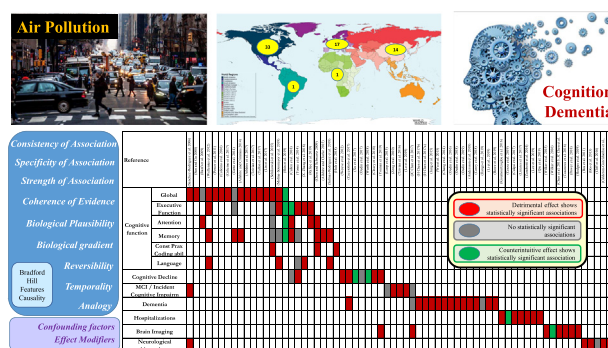[h] Institute of Clinical Neurosciences, University of Bristol, School of Medicine, Level 2 Learning and Research, Southmead Hospital, Bristol, UK

HIGHLIGHTS

- Epidemiological evidence suggests air pollution adversely affects cognitive function.
- Evidence suggests air pollution is causally associated with cognitive impairment.
- Evidence suggests air pollution is causally associated with increased risk of dementia.
- Residual confounding cannot be completely ruled out.
- Diversity of study designs, air pollutants and endpoints precludes meta-analysis.

GRAPHICAL ABSTRACT

ARTICLE INFO

ABSTRACT

Dementia is arguably the most pressing public health challenge of our age. Since dementia does not have a cure, identifying risk factors that can be controlled has become paramount to reduce the personal, societal and economic burden of dementia. The relationship between exposure to air pollution and effects on cognitive function, cognitive decline and dementia has stimulated increasing scientific interest in the past few years. This review of the literature critically examines the available epidemiological evidence of associations between exposure to ambient air pollutants, cognitive performance, acceleration of cognitive decline, risk of developing dementia, neuro-imaging and neurological biomarker studies, following Bradford Hill guidelines for causality.

The evidence reviewed has been consistent in reporting associations between chronic exposure to air pollution and reduced global cognition, as well as impairment in specific cognitive domains including visuo-spatial abilities. Cognitive decline and dementia incidence have also been consistently associated with exposure to air pollution. The neuro-imaging studies reviewed report associations between exposure to air pollution and white matter volume reduction. Other reported effects include reduction in gray matter, larger ventricular volume, and smaller corpus callosum. Findings relating to ischemic (white matter hyperintensities/silent cerebral infarcts) and hemorrhagic (cerebral microbleeds) markers of cerebral small vessel disease have been heterogeneous, as have observations on hippocampal volume and air pollution. The few studies available on neuro-inflammation tend to report associations with exposure to air pollution.

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Several effect modifiers have been suggested in the literature, but more replication studies are required. Traditional confounding factors have been controlled or adjusted for in most of the reviewed studies. Additional confounding factors have also been considered, but the inclusion of these has varied among the different studies. Despite all the efforts to adjust for confounding factors, residual confounding cannot be completely ruled out, especially since the factors affecting cognition and dementia are not yet fully understood.

The available evidence meets many of the Bradford Hill guidelines for causality. The reported associations between a range of air pollutants and effects on cognitive function in older people, including the acceleration of cognitive decline and the induction of dementia, are likely to be causal in nature.

However, the diversity of study designs, air pollutants and endpoints examined precludes the attribution of these adverse effects to a single class of pollutant and makes meta-analysis inappropriate.

Contents

1. Introduction

Dementia is a pressing public health challenge. Its prevalence is strongly age-related: doubling every 5–6 years over the age of 65 years. The number of people living with dementia worldwide is estimated at 50 million and expected to reach 152 million by 2050. Its current economic cost worldwide is US$818 billion/year (as of 2015) and it will rise in proportion to the numbers affected (WHO, 2019).

Interest in the possible effects of air pollutants on the brain began in about 2002 when Calderon-Garciduenas and colleagues reported that dogs exposed to air pollution in Mexico City showed neuropathological changes of the type associated with Alzheimer's disease (Calderon-Garciduenas et al., 2002). This work was an extension of studies undertaken in the 1990s on the effects of Mexico City air pollution on the olfactory epithelium of humans and dogs. More

recently, interest in possible effects on the brain has been strengthened by epidemiological studies, which suggest that exposure to air pollutants is associated with a decline of cognitive function and the development of dementia.

Magnetite nanoparticles have been found in the brain with a morphology that suggests an exogenous origin (Maher et al., 2016). Similar ferrous nanoparticles were found in air collected at traffic roadsides in the UK (Sanderson et al., 2016). These nanoparticles may be able to reach the brain via the olfactory nerves and olfactory bulb (Oberdörster et al., 2009), or via the circumventricular organs where the blood-brain barrier is more permeable (Banks et al., 1995). In addition, the blood-brain barrier could be made less impermeable by systemic inflammation (Varatharaj and Galea, 2017) for which exposure to air pollutants is a known risk factor (Araujo, 2011). The blood-brain barrier is also more permeable in the very young and old, making

these two life stages opportunities for the entry of nanoparticles into the brain, and potential elicitation of neurological damage.

In addition to the possible direct effects from nanoparticles reaching the brain, there are indirect mechanisms by which pollutants could potentially lead to brain injury. These include damage to the vasculature, leading to cerebral ischaemia or extravasation of neurotoxic proteins such as fibrinogen. Brain injury could also be secondary to systemic inflammatory responses to air pollution (Brockmeyer and D'Angiulli, 2016; Campbell, 2004; Kicinski et al., 2015; Mumaw et al., 2016b; Wang et al., 2009).

There is great interest in reducing risk of dementia by identifying preventable risk factors for the responsible diseases. Epidemiological evidence, linking exposure to air pollutants with adverse effects on cognition and the development of dementia, has expanded appreciably over the past 15 years. Several literature reviews were published between 2015 and 2019, including eight systematic reviews on the association between ambient air pollution exposure and cognitive function, cognitive decline and dementia (Clifford et al., 2016; Dimakakou et al., 2018; Fu et al., 2019; Killin et al., 2016; Peters et al., 2019; Peters et al., 2015; Power et al., 2016; Zhao et al., 2018). Some of the reviews included studies of several aspects of cognitive performance and cognitive decline (Attilio et al., 2018; Bejot et al., 2011; Cipriani et al., 2018; Cohen and Gerber, 2017; Costa et al., 2014; Kilian and Kitazawa, 2018; Xu et al., 2016). Others also included evidence from neuroimagining studies (Babadjouni et al., 2017; Dimakakou et al., 2018; Paul et al., 2019; Power et al., 2016; Russ, 2018). Some reviews have focused solely on cognitive function (Clifford et al., 2016; Tzivian et al., 2015b), neuroimaging data (de Prado Bert et al., 2018), dementia (Killin et al., 2016; Peters et al., 2019) or a clinical diagnosis of Alzheimer's disease (Yegambaram et al., 2015). A few reviews have focused on specific air pollutants, such as ozone (O_3) (Zhao et al., 2018) or fine particulate matter (Fu et al., 2019). Only one of the review papers analysed the available evidence on cognitive performance with reference to the Bradford Hill features of causality (Clifford et al., 2016) and that review covered 13 studies prior to October 2015.

The current review covers epidemiological studies up to December 2019, and concerns the relationship between air pollution and multiple measures of cognitive performance and neurodegeneration, including global cognitive function and performance in specific cognitive domains (attention, executive function, memory, etc.); cognitive decline, mild and incident cognitive impairment; dementia, hospitalizations related to dementia; brain imagining and neurological biomarkers. This review critically analyses the literature following the guidance of Bradford Hill (Hill, 1965) on the features of causal associations. In addition, this review considers the various confounding factors as well as the evidence on effect modifiers.

2. Methodology

This paper updates the body of evidence that has been already reviewed in the various literature reviews published between 2015 and 2019. We assessed the original research papers included in the published reviews, and expanded those reviews by including more recently published studies, up to December 2019. To identify these additional papers, an extensive literature search was conducted using PubMed and Web of Science databases for papers published between January 2015 and December 2019. The following keywords were used to identify the studies: "air pollution", "air pollutants", "particulate matter", "PM", "PM_{10}", "$PM_{2.5}$", "nitrogen dioxide", "ozone", "black carbon", "diesel", "diesel exaust", "cognitive performance", "cognitive function", "cognitive decline", "mild cognitive impairment", "MCI", "dementia", "Alzheimer's disease", "MRI", "neuromarker", "neuroinflammation". In addition, the reference lists of pertinent papers and of the published reviews were checked to identify further studies.

Inclusion/exclusion eligibility criteria were developed: papers were included if they reported an association between either short- or long-

term exposure to ambient air pollution (considering both exposure to specific air pollutants and traffic) and cognitive performance, mild cognitive impairment, incident cognitive impairment, dementia, hospitalizations due to neurological disease, brain imagining, or neurological biomarkers. All study designs were included. Only studies on adult populations were considered for inclusion. Abstracts and unpublished studies were not included. No studies were excluded a priori for weakness of design or data quality.

The papers were first screened by titles and abstracts. When the information provided in the abstract was not detailed enough full-text documents were also reviewed The following information from the included epidemiological studies was collected: first author, year of publication, name of the study, location, study design, period of enrollment and follow up, sample size, sex and age, exposure assessment methodology, outcome, effect estimator used, and covariates adjusted for in the analysis.

The evidence was reviewed with emphasis on strength of association, dose-response functions, temporality, reversibility, consistency of association, specificity of association and biological plausibility. Interpretations of causal associations were made, based on the guidance of Bradford Hill (1965).

3. Results and discussion

3.1. Characteristics of identified studies

A total of 69 epidemiological studies, published between 2006 and 2019, were included in this review. Tables S1–S12 summarize information on each study. Sixteen studies reported the effect of exposure to ambient air pollution on global cognition (Table S1), 9 reported on executive function (Table S2), 6 on attention (Table S3), 11 on memory (Table S4), 3 on constructional praxis and coding ability (Table S5), 5 on language (Table S6), 9 on cognitive decline (Table S7), 7 on mild cognitive impairment and incident cognitive impairment (Table S8), 15 on dementia and a clinical diagnosis of Alzheimer's disease (Table S9), 6 on hospitalizations related to dementia and Alzheimer's disease (Table S10), 8 on brain imaging (Table S11) and 8 on neurological biomarkers (Table S12).

The studies used several different methods to estimate chronic exposure to air pollution, such as proximity models (e.g. distance to nearest road), allocating concentrations from the nearest monitoring site, using geostatistical models (e.g. krigging, inverse distance weighting), dispersion models, land use regression models and hybrid models (e.g. incorporating satellite measures, chemical transport models, Bayesian models). Studies assessing effects of short-term exposure to air pollution on hospital admissions estimated daily exposures by using district or regional level mean concentrations obtained from available monitoring stations within the region of interest.

Cognitive performance outcomes were assessed using different neuropsychological tests[1] (e.g. the Mini-Mental State Examination). Dementia diagnosis was assessed using information in health databases or medical records.

Half of the available literature originates from North America (33), followed by Europe (17) and Asia (14). One study reported data from Africa and another from South America. Ten studies reported on data from low- and middle-income countries.

3.2. Review of association reported in epidemiological studies on the effect of air pollution on cognitive decline and dementia

3.2.1. Global cognition

The effect of air pollution on global cognition – defined as a cognitive decline assessed using tests such as Mini-Mental State Examination

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[1] Neuropsychological tests are specific tasks defined to assess a brain function known to be associated with a specific brain structure or pathway in the brain.

(MMSE) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Total Score – has been evaluated on the basis of the evidence from sixteen papers (see Table S1).

Sanchez-Rodriguez et al. (2006) found that older residents in Mexico DC (aged >60) had significantly lower global cognition, measured by MMSE, compared with residents in rural areas (MMSE: 26.15 ± 0.35 vs 27.16 ± 0.28, $p < 0.05$) (Sanchez-Rodriguez et al., 2006). No formal assessment of air pollution was made, only a simple urban- rural comparison.

Sun and Gu (2008) studied the association between air pollution and cognitive performance among participants of the Chinese Longitudinal Health Survey. They used the Air Pollution Index (API), which is a composite index encompassing sulfur dioxide, nitrogen dioxide, particulate matter of <10 μm in diameter (PM_{10}), carbon monoxide (CO), and ozone concentrations. After adjusting for several meteorological, demographic, socio-economic, lifestyle and health factors, they reported that a 1-point increase in the API (in 1995) at the city level was associated with a significant mean difference of 1.51 points in the MMSE test (as measured in 2002) indicating poorer cognitive function in older adults (86.3 ± 11.4 years) (Sun and Gu, 2008).

Ranft et al. (2009) studied the effect of air pollution on cognitive function and attention in elderly women in the SALIA cohort in the Ruhr valley, Germany, and accounted for demographic, lifestyle, health and education variables. They found that living within 50 m of a busy road (>10,000 cars/day) during the 20 years prior to the test was related to poorer performance on the CERAD test ($\beta = -3.8$, 95% confidence interval (CI) -7.8, 0.1). The association with average PM_{10} for the period when the tests were undertaken (2002–2006) was weaker ($\beta = -0.6$, 95% CI -1.4, 0.2) and was reversed when PM_{10} exposures estimated for the age when tests were conducted (55 years) were used ($\beta = 0.4$, 95% CI 0.0, 0.9) (Ranft et al., 2009). In both cases, exposures were assigned using 5-year average concentrations measured at the nearest monitoring site. A follow up study on the SALIA cohort estimated exposures to nitrogen dioxide (NO_2), nitrogen oxide (NO_x), particulate matter of <2.5 μm in diameter ($PM_{2.5}$) and PM_{10} using a land use regression model (LUR) (Schikowski et al., 2015). A statistically significant association was found between increased NOx exposure and lower cognitive performance on CERAD testing ($\beta = -1.35$, 95% CI -2.59, -0.10) but not MMSE ($\beta = -0.04$, 95% CI -0.19, 0.12). No associations were found between traffic load, NO_2, PM_{10} or $PM_{2.5}$, and CERAD and or MMSE test scores.

Wellenius et al. (2012) found that participants in the MOBILIZE Boston study who were ≤77 years or who were college-educated, and who lived near busy traffic roadsides, had an increased risk of lower cognitive performance (MMSE <26). Odds ratios (OR) of 1.34 (95% CI 1.01, 1.76) and 1.54 (95% CI 1.10, 2.17) respectively, were reported as being associated with an interquartile range (IQR) decrease (851.2 m) in residential distance to a major road. They also studied the association with black carbon (BC), a diesel tracer, in the same population. An IQR increase in residential BC (0.11 μg/m³) estimated using a LUR model was positively, but statistically not significantly, associated with an increased risk of lower cognitive performance (OR = 1.15, 95% CI 0.99, 1.34). Power et al. (2011) reported that exposure to BC increased the odds of having a MMSE score of ≤25 by a factor of 1.3 (95% CI 1.1; 1.6) for each doubling of BC concentration and this was equivalent to aging by 1.9 years. Colicino and colleagues found the association between BC and cognitive function to be affected by telomere length, systemic inflammation (Colicino et al., 2017) and microRNA (miRNA) expression in carriers of particular miRNA-processing single nucleotide polymorphisms (SNPs) (Colicino et al., 2016).

Gatto et al. (2014) studied the effects of O_3, NO_2, and $PM_{2.5}$ among healthy, mainly Caucasian, women aged 60 ± 8 years living in Los Angeles, USA. No association was found between pollutant exposures and lower global cognition (Gatto et al., 2014).

A significant inverse association was found between $PM_{2.5}$ exposure and cognitive function for the highest (13.8–20.7 μg/m³) vs the lowest (4.5–9.9 μg/m³) category of exposure ($\beta = -0.26$, 95% CI -0.47; -0.05) in adults >50 years participating in the nationwide Health and Retirement Study in the US (Ailshire and Crimmins, 2014). Similar results were observed in the American's Changing Life's Survey, with a higher number of cognitive errors associated with $PM_{2.5}$ exposure (incidence rate ratio, IRR = 1.04, 95% CI 1.00, 1.08 per 1 μg/m³ of $PM_{2.5}$) (Ailshire et al., 2017). The Heinz Nixdorf Recall cohort study in Germany found an association between an IQR increase of $PM_{2.5}$ (1.43 μg/m³) and worse global cognition, but this was statistically significant only in those subjects exposed to high noise levels ($\beta = -0.48$, 95% CI -0.72, -0.23) (Tzivian et al., 2017).

An IQR increase in 1-year average $PM_{2.5}$ (4.25 μg/m³) and 2-year average NO_2 (6.66 ppb) concentrations was significantly associated with decreased cognitive function scores ($PM_{2.5}$: $\beta = -0.22$; 95% CI -0.44, -0.01 and NO_2: $\beta = -0.26$; 95% CI -0.45, -0.06) in participants of the National Social Life, Health and Aging Project cohort study, an effect equivalent to aging by 1.6 years ($PM_{2.5}$) and by 1.9 years (NO_2) (Tallon et al., 2017). A larger reduction was reported when a longer period was analysed. An IQR increase in 7-year average $PM_{2.5}$ (4.33 μg/m³) was associated with a decrease in cognitive function scores of -0.25 (95% CI -0.43, -0.06); whereas an IQR increase in 7-year average NO_2 concentration (7.42 ppb) was associated with a decrease in cognitive function score of -0.27 (95% CI -0.48, -0.07) (Tallon et al., 2017).

Exposure to $PM_{2.5}$ was significantly associated ($\beta = 0.10$ per 10 μg/m³ increase; 95% CI 0.02; 0.18) with poor cognitive performance on the WHODAS-2 test (higher score means greater impairment) in participants of the Study on global AGEing and Adult Health in six low- and middle-income countries (China, India, Ghana, Mexico, Russia and South Africa) (Lin et al., 2017).

A study in Chile compared MMSE scores in four groups of women aged 69.8 ± 4.3, living in Santiago de Chile (polluted environment) and Viña del Mar (clean environment), further subdivided according to engagement in a physical training programme. Active women in the clean environment (29 ± 1.3) had higher MMSE scores than did sedentary women (24.3 ± 2.9) or active women (28.4 ± 1.5) in the polluted environment (Molina-Sotomayor et al., 2019).

Exposure to $PM_{2.5}$ and PM_{10} was associated with lower MMSE scores in adults aged 70–84 years in The Korean Frailty and Aging Cohort Study, whereas exposure to NO_2, O_3 and CO was associated with higher scores (Shin et al., 2019).

3.2.2. Specific cognitive domains

3.2.2.1. Executive function.
The characteristics of the nine epidemiological studies on air pollution and executive function[2] are summarized in Table S2.

Decreasing distance to a busy traffic roadside was associated with reduced executive function as measured by the time required to complete the trail-making test (TMT) part B and TMT interference (Wellenius et al., 2012). An IQR decrease in residential distance to a major roadway (851 m) was linked with a significant increase of the scores (slower performance) on the TMT part B of 10.5 s (95% CI, 4.0, 17.1). The impact for those subjects living closer to major roadways was equivalent to an age increase of 4 years in those living further away. No associations were found between increased BC exposure and poorer executive function (Wellenius et al., 2012).

Gatto et al. (2014) reported that exposure to the highest (>49 ppb) compared to the lowest level of O_3 (≤34 ppb) showed a nonsignificant association with lower executive function ($\beta = -0.66$, 95% CI -1.35; 0.03). No association was found between exposure to NO_2 and executive function.

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[2] Executive function refer to a set of mental processes that facilitate planning, attention control, remembering and following instructions, problem solving, inhibitory control and juggling multiple tasks successfully.

Significantly reduced reasoning ability was associated with increased exposure to $PM_{2.5}$, $PM_{2.5 \text{ exhaust}}$, PM_{10} and $PM_{10 \text{ exhaust}}$ in the Whitehall II study (Tonne et al., 2014).

No association was found between traffic load, NO_2, NOx, $PM_{2.5}$ and $PM_{2.5 \text{ abs}}$ exposures and worse executive function in the SALIA study (Schikowski et al., 2015).

In the UK Biobank cohorts, Cullen et al. (2018) found associations between air pollution, estimated from a 100 m × 100 m land use regression model, and executive function, that were inconsistent in direction and of very small magnitude. An increase of 1 μg/m³ in PM_{10} was associated with a better response in the reasoning test (β = 0.0111; 95% CI 0.0054; 0.0169) on a scale 1–13. Increases of NO_2 (1 μg/m³) were also associated with better reasoning scores (β = 0.0032; 95% CI 0.0013; 0.0050). No association was found between $PM_{10-2.5}$ or NO_x with reasoning (Cullen et al., 2018).

Cumulative exposure to air pollution, as measured by the average APIs over 30 days to 3 years, was associated with worse mathematics test scores (β = −0.004 ± 0.002[3] for 30 days; β = −0.016 ± 0.007 for 3 years) in participants of a nationally representative longitudinal survey database in China. No associations were found with 1-day or 7-day APIs. The longer the cumulative exposure, the greater the effect: an increase in the 30-day mean API by 1 standard deviation lowered the mathematics test scores by 0.068 ± 0.011, whereas an increase in the 3-year mean API decreased the scores by 0.211 ± 0.033 (Zhang et al., 2018).

Molina-Sotomayor et al. (2019) found that a group of elderly women living in a clean area in Viña del Mar (Chile) had significant better scores, although not adjusted for any confounding variables, than those in a polluted area in Santiago de Chile in time and space orientation, and calculation ability (Molina-Sotomayor et al., 2019).

Results from The Korean Frailty and Aging Cohort Study found that $PM_{2.5}$ was associated with worse scores in the Digit Backward Span test and the Frontal Assessment Battery. Sulfur dioxide (SO_2) was also related to lower scores in the Digit Backward Span, whereas NO_2 was associated with worse performance in the Frontal Assessment Battery and O_3 with better scores (Shin et al., 2019).

A study conducted among the general population in Tehran found that exposure to high residential traffic, self-reported by participants in a questionnaire, was associated with worse scores on the TMT part B test compared with the scores in those participants reporting low residential traffic (β = 0.127 s; 95% CI 0.024 s; 0.325 s) (Rafiee et al., 2020).

3.2.2.2. Attention. Table S3 summarizes the characteristics of the five epidemiological studies evaluating the association between air pollution exposure and attention.

Ranft et al. (2009) reported a significant inverse association between long-term (20 years) exposure to traffic, defined as living within 50 m of a busy road, and attention (β = −5.1, 95% CI −8.2, −2.0). No association was found between PM_{10} exposure, based on concentrations measured at the nearest monitoring site, and decreased attention (β = 0.0 to 0.2).

Chen and Schwartz (2009) analysed the effect of PM_{10} and O_3 on attention among the participants of the Third US National Health and Nutrition Examination Survey. A significant inverse association was found between O_3 and attention. Indeed, each 10 ppb increase in 1-year average O_3 prior to examination increased by 0.57 s (95% CI, 0.08, 1.06) the time to complete the serial-digit learning test (SDLT) test (measuring attention and short-term memory) and it increased the number of trials needed to achieve the set criterion (β = 0.28, 95% CI 0.06, 0.51). This was equivalent to being 5.3 years older. No association was found between PM_{10} exposure and decreased attention (Chen and Schwartz, 2009).

No statistically significant associations were reported between traffic load, NO_2, NOx, PM_{10}, $PM_{2.5}$ and $PM_{2.5 \text{ abs}}$ and attention in the SALIA study conducted in the North Rhine-Westfalia area (Germany) (Schikowski et al., 2015).

Analysis of the UK Biobank cohort suggested that exposure to $PM_{2.5}$ is associated with a slower reaction time (rate ratio 1.0032, 95% CI 1.0012, 1.0053 per unit (μg/m³)), with values above 1 indicating relatively longer reaction times. Similarly, an IQR increase of NO_x (14.67 μg/m³) was also associated to poorer attention (rate ratio 1.0002, 95% CI 1.0001 1.0003). No association was found with PM_{10}, $PM_{10-2.5}$ or NO_2 (Cullen et al., 2018).

Shin et al. (2019) reported that exposures to PM_{10}, $PM_{2.5}$ and NO_2 were associated with worse scores in the digit forward span test, whilst CO, SO_2 and O_3 were associated with better scores in The Korean Frailty and Aging Cohort Study (Shin et al., 2019).

Rafiee et al. (2020) reported worse attention scores in the TMT part A test for those subjects self-reported to live in an area with high residential traffic compared with subjects in areas with low residential traffic (β = 0.118 s; 95% CI 0.062 s; 0.238 s).

3.2.2.3. Memory. Eleven studies analysed the association between air pollution exposure and memory (see Table S4).

Chen and Schwartz (2009) reported a significant association between preceding 1-year average O_3 exposure (but not for PM_{10}) and reduced short-term memory, measured with the SDLT test as discussed above (Chen and Schwartz, 2009).

Wellenius et al. (2012) found that an inter-quartile range decrease (851 m) in residential distance to a major road was associated with reduced immediate recall scores in the Hopkins Verbal Learning Test-Revised (HVLT-R). Significant associations were only found among participants aged ≤77 years (β = −0.6, 95% CI −1.1, −0.1) and in those with a college education (β = −0.66, 95% CI −1.15, −0.17). They also reported that an IQR reduction in distance to a main road was associated with reduced delayed memory (β = −0.59, 95% CI −0.87, −0.3 in subjects aged ≤77 and β = −0.4, 95% CI −0.7, −0.1 in subjects with a college education). No associations were found between living close to a major roadway and performance on the HVLT-R word recognition (β = 0.07, 95% CI −0.1, 0.2) or working memory (β = −0.04, 95% CI −0.15, 0.07). Overall, they reported that the memory impairment was equivalent to being 2 years older. They also reported that an IQR increase in BC exposure (IQR = 0.11 μg/m³) was associated with a significant HVLT-R immediate recall reduction (β = −0.36, 95% CI −0.71, −0.01). No association was found between BC exposure and delayed recall or working memory (Wellenius et al., 2012).

The US Health and Retirement study found a significant association between exposure in the third (12.185–13.796 μg/m³) and highest (13.797–20.661 μg/m³) quartiles of $PM_{2.5}$ compared to the lowest (4.5–9.9 μg/m³) and reduction in episodic memory, a marker of early cognitive decline (Ailshire and Crimmins, 2014). The scores for episodic memory were β = −0.35, 95% CI −0.51, −0.19 and β = −0.17, 95% CI −0.33; −0.01 for the third and fourth quartiles, respectively.

A 10 μg/m³ increment of $PM_{2.5}$ was linked with an increased odds ratio of errors in working memory and orientation tests (OR = 1.53, 95% CI 1.02, 2.30) in the American Changing Life survey (Ailshire and Clarke, 2015).

In the German SALIA study, Schikowski et al. (2015) reported that traffic load, NO_2 and NO_x were associated (non-significantly) with reduced episodic and semantic memory, whereas PM_{10}, $PM_{2.5}$ and $PM_{2.5abs}$ showed an opposite (non-significant) trend.

Reduced memory was associated with increased exposure to $PM_{2.5}$, $PM_{2.5 \text{ exhaust}}$, PM_{10} and $PM_{10 \text{ exhaust}}$ in the Whitehall II study, but the results were not statistically significant (Tonne et al., 2014).

Gatto et al. (2014) reported that exposure to $PM_{2.5}$ was significantly associated with lower verbal learning scores (β = −0.32 per 10 μg/m³ $PM_{2.5}$, 95% CI −0.63, 0.00). In addition, subjects exposed to ambient

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[3] Regression coefficient ± standard error.

exposure to $NO_2 > 20$ ppb had lower logical memory scores (β −0.62 95% CI −1.35, 0.11) than those exposed to ≤10 ppb (Gatto et al., 2014).

Cullen et al. (2018) found associations between NO_2 (1 μg/m^3) and worse visuospatial memory (β = 0.032; 95% CI 0.0013; 0.0050) in the UK Biobank cohort. No association was found for PM_{10}, $PM_{10-2.5}$, NO_2 or NOx with numeric or prospective memory, or for PM_{10}, $PM_{10-2.5}$ or NOx with visuospatial memory (Cullen et al., 2018).

$PM_{2.5}$ exposure was associated with significantly poorer cognitive performance in the three-word memory test (OR = 1.37; 95% CI 1.08; 1.74) in a nationally representative sample of older adults from the National Survey of Health and Nutrition in Mexico (Salinas-Rodriguez et al., 2018).

A group of physically active women living in a relatively unpolluted area in Chile had better recall scores than a group of sedentary women living in a polluted area in Santiago de Chile, but similar registration scores. No differences were observed between physically active groups in the two environments (Molina-Sotomayor et al., 2019).

In the Korean Frailty and Aging Cohort Study, $PM_{2.5}$ exposure was associate with worse Word List, Word List Recall, Recall Storage and Word List Recognition test scores. Exposure to CO was associated with lower Word List and Word Recall List test scores, and exposure to SO_2 with lower Word List Recall and Recall Storage test scores. NO_2 exposure was associated with better Word List test scores but worse scores in the Word Recall List. PM_{10} levels were associated with better Word List scores, exposure to O_3 was associated with better Word List Recall and Recall Storage test scores (Shin et al., 2019).

3.2.2.4. Constructional praxis and coding ability. Three studies assessed the impact of air pollution on constructional praxis[4] and another study looked at coding ability (see Table S5).

Schikowski et al. (2015) found a significant association between an IQR increase of exposure to NO_2 (β = −0.27, 95% CI −0.45, −0.10, IQR = 9.6 μg/m^3), NOx (β = −0.25, 95% CI −0.42, −0.08, IQR = 23.4 μg/m^3), and PM_{10} (β = −0.15, 95% CI −0.29, −0.01, IQR = 2.2 μg/m^3) and reduced performance in the Figure Copying test that assesses constructional praxis. Traffic load within 100 m (IQR = 26.7 k car-km/day), $PM_{2.5}$ (IQR = 1.9 μg/m^3) and $PM_{2.5abs}$ (IQR = 0.4 m$^{-1} \times 10^{-5}$) were not significantly (β = −0.19 to −0.10) associated with constructional praxis. In subjects with the *APOE* ε4 allele the association between all the air pollutants and reduced constructional praxis was stronger (p-value for interaction <0.01) suggesting that ε4 was an effect modifier.

PM_{10} levels were associated with worse visuo-construction performance scores in the SALIA cohort study (β = −0.25, 95% CI −0.40, −0.11, IQR = 8.0 μg/m^3), $PM_{2.5}$ (β = −0.21, 95% CI −0.36, −0.06, IQR = 4.9 μg/m^3), as was NO_2 (β = −0.26, 95% CI −0.50, −0.03, IQR = 13.8 μg/m^3) (Huls et al., 2018).

Chen and Schwartz (2009) found a significant association between annual ozone increase (10 ppb), measured during the year prior to testing, and reduced coding ability, measured by the symbol-digit substitution test (SDST) (β = 0.12, 95% CI 0.01, 0.23). No association was found with an increase of 10 μg/m^3 in PM_{10} (β = 0.0, 95% CI −0.04, 0.05).

3.2.2.5. Language. Five studies have analysed the association between air pollution and language skills (see Table S6).

Wellenius et al. (2012) found a significant association between decreasing distance to a major road (IQR = 851.2 m) and poor performance in language, as measured using letter fluency tests (β = −1.4, 95% CI −2.7, −0.2) and category fluency tests (β = −0.7, 95% CI −1.1, −0.3) in the MOBILIZE study. The decline in performance was equivalent to aging by 4 years.

In a nationally representative sample of older adults in the National Survey of Heatlh and Nutrition in Mexico, exposure to $PM_{2.5}$ was associated with impaired verbal fluency (β = −0.72, 95% CI −1.05, −0.4, per 10 μg/m^3) (Salinas-Rodriguez et al., 2018).

In a longitudinal survey of a nationally representative cohort in China, language scores were negatively associated with cumulative exposures to air pollution, measured with the API, averaged from 7 days to 3 years (β = −0.013 ± 0.005[5] for 7-day exposure; β = −0.086 ± 0.021 for 3-year exposure). No associations were found between 1-day API and verbal test performance. The negative effect over 7 days and 3 years was more pronounced for language test scores than for mathematics test scores and the longer the cumulative exposure, the more marked the effect. An increase in the 7-day mean API by 1 standard deviation lowered the verbal scores by 0.278 ± 0.026, whereas an increase in the 3-year mean API decreased the verbal scores by 1.132 ± 0.108 (Zhang et al., 2018).

No significant associations were found between language tests scores and BC exposures in the MOBILIZE study (Wellenius et al., 2012). Similarly, the Whitehall II study conducted in London, found no significant associations for $PM_{2.5}$, $PM_{2.5 exhaust}$, PM_{10} or $PM_{10 exhaust}$ with semantic or phonemic fluency (Tonne et al., 2014).

No differences in language scores were observed between women living in clean and polluted areas in Chile (Molina-Sotomayor et al., 2019).

3.2.3. Cognitive decline

The characteristics of the nine epidemiological studies on air pollution and cognitive decline[6] are summarized in Table S7.

Weuve et al. (2012) found associations between an increase of 10 μg/m^3 $PM_{2.5}$ and global cognitive decline (β = −0.018; 95% CI −0.035; −0.002) and $PM_{10-2.5}$ (β = −0.020; 95% CI −0.032; −0.008) over a 7-year follow up period in the Nurse's Health Study (USA) (Weuve et al., 2012). This was equivalent to aging by 2 years.

Cacciottolo et al. (2017) reported that participants of the Women's Health Initiative Memory Study (WHIMS, USA) living in areas with high $PM_{2.5}$ exposure (>12 μg/m^3) had a greater hazard ratio (HR) for accelerated cognitive decline (1.81; 95% CI 1.42, 2.32) over a 10-year period than did women in low-pollution areas ($PM_{2.5}$ ≤ 12 μg/m^3). The HRs were higher in ε4 homozygotes (HR = 3.64; 95% CI 1.36, 9.69) than ε3 homozygotes (HR = 1.65; 95% CI 1.23, 2.23) but the difference was not statistically significant (p-value interaction >0.05) (Cacciottolo et al., 2017).

In the Whitehall II Study, long-term exposure to air pollutants showed only non-significant associations, per IQR increase, with a decline in reasoning and memory over a 5-year period; $PM_{2.5}$ (IQR = 1.1 μg/m^3), $PM_{2.5 exhaust}$ (IQR = 0.27 μg/m^3), PM_{10} (IQR = 1.8 μg/m^3) and $PM_{10 exhaust}$ (IQR = 0.30 μg/m^3). $PM_{2.5}$ was associated with a small decline in semantic and phonemic verbal fluency, and no relationship was found with $PM_{2.5 exhaust}$ nor $PM_{10 exhaust}$. Higher $PM_{2.5}$ of 1.1 μg/m^3 (yearly lag 4) was associated with a 0.03 (95% confidence interval = −0.06 to 0.002) 5-year decline in standardized memory score and a 0.04 (−0.07 to −0.01) decline when restricted to participants remaining in London between study waves (Tonne et al., 2014).

In the Chinese Longitudinal Healthy Longevity Survey, participants who had lived all or part of their lives in rural environments reported faster cognitive decline than did participants who had always lived in urban environments. Xu et al. (2017) suggested that the faster decline in rural subjects could be related to lower access to socioeconomic benefits, such as retirement pension and access to health care. Another possible confounder was the "healthy migrant effect" with healthier subjects moving to urban areas in search of better economic opportunities (Tong and Piotrowski, 2012).

A longitudinal analysis did not find any association between long-term exposure to NOx and change of episodic memory over a 5-

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[4] Constructional praxis is to assemble, join, or articulate independent parts to form a single unitary structure. For example, building a tower out of blocks.

[5] Regression coefficient ± standard error.

[6] Cognitive decline refers to the reduction on cognitive abilities occurred over a period of time.

year period ($\beta = 0.005$, 95% CI-0.018, 0.027 per 1 $\mu g/m^3$ NO_x increase) in participants of the Betula study (Sweden), in an area with relatively low NO_x exposures (21 ± 16 $\mu g/m^3$)(Oudin et al., 2017).

In a cohort of older Puerto Rican adults living in Greater Boston, one-year moving average exposures to BC (53 $\mu g/m^3$) were significantly associated with decreased verbal memory (-0.38; 95% CI: -0.46, -0.30), recognition (-0.35; 95% CI: -0.46, -0.25), mental processing (-1.14; 95% CI: -1.55, -0.74), and executive function (-0.94; 95% CI: -1.31, -0.56). Similar associations were found for nickel. Associations for sulfur, and silicon, and $PM_{2.5}$ were generally null, although sulfur (-0.51; 95% CI -0.75, -0.28 per 390 ng/m^3) silicon (-0.25; 95% CI: -0.36, -0.13 per 11 ng/m^3) and $PM_{2.5}$ (-0.35; 95% CI: -0.57, -0.12 per 1.75 $\mu g/m^3$) were associated with decreased recognition (Wurth et al., 2018).

Regional ozone concentrations were associated with a faster cognitive decline in individuals with normal cognition at baseline, who were followed by the National Alzheimer's Coordinating Centre (USA). The score in the cognitive dementia sum-of-boxes test was lower in the first tertile than the third tertile of ozone exposure ($\beta = -0.27$, 95% CI -0.4, -0.1) in the normal cognition group, with higher scores representing faster cognitive decline. Subjects who had one or more $\varepsilon 4$ alleles experienced faster cognitive decline. No effect was observed in subjects who entered the study with baseline cognitive impairment. No effect was observed for $PM_{2.5}$ exposure (Cleary et al., 2018).

No association was found for PM_{10}, $PM_{10-2.5}$, NO_2 or NO_x with cognitive decline in the domains of memory (numeric, visuospatial, prospective), reasoning, or reaction time in the UK Biobank cohort (Cullen et al., 2018).

Exposure to $PM_{2.5}$ over the preceding 3-year period (IQR = 2.81 $\mu g/m^3$) was associated with greater annual declines in immediate recall ($\beta = -19.3\%$, 95% CI -1.9%, -36.2%) and new learning ($\beta = -14.8\%$, 95% CI -4.4%, -24.9%) in participants of the Women's Health Initiative (WHI) Memory Study, who also participated in the subsequent ancillary studies: WHI Study of Cognitive Aging (WHISCA) and the WHI Memory Study of Magnetic Resonance Imaging (WHIMS-MRI). No association was found between 3-year average $PM_{2.5}$ exposure and decline in delayed-recall or composite scores (Younan et al., 2020).

3.2.4. Mild and incident cognitive impairment

Table S8 summarizes the characteristics of the seven epidemiological studies on air pollution and mild and incident cognitive impairment.[7]

The REGARDS study conducted across 48 contiguous US states found that an increase of 10 $\mu g/m^3$ exposure to $PM_{2.5}$ was not associated with incident cognitive impairment 0.98 (95% CI 0.72; 1.34) (Loop et al., 2015).

Similarly, an IQR increase in $PM_{2.5}$ (3.9 $\mu g/m^3$) or diesel PM (0.35 $\mu g/m^3$) was not associated with mild cognitive impairment (MCI) in older women in the WHIMS study (HRs 0.93, 95% CI 0.79, 1.09; and 0.95,95% CI 0.82, 1.11, respectively) (J.C. Chen et al., 2017).

In contrast, Zeng et al. (2010) found that elderly residents in China with higher exposure to air pollution, measured as API, had a significantly increased risk of cognitive impairment (MMSE < 18) (OR = 1.09, 95% CI 1.01, 1.18) (Zeng et al., 2010).

Results of the Heinz Nixdorf Recall study also suggest an association between increased 1-year IQR exposure to $PM_{2.5}$ (1.44 $\mu g/m^3$) and MCI (OR = 1.16; 95% CI 1.05, 2.24), especially for amnestic MCI (OR = 1.22; 95% CI 1.0.8, 1.38) (Tzivian et al., 2016). The authors reported a synergic effect between $PM_{2.5}$ and noise, with increased risk of MCI (OR = 1.30; 95% CI 1.01, 1.67) among subjects exposed to higher noise levels ($L_{DEN} \geq 60$).

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[7] Mild cognitive impairment (MCI) refers to the stage between the cognitive decline associated with normal aging and the cognitive decline that occurs in dementia. MCI causes a slight but measurably lower performance in one or more cognitive domains, such as memory and executive function but without the loss of ability on ADLs seen in dementia.

Sanchez-Rodriguez et al. (2006) also observed a higher prevalence of cognitive impairment (MMSE <23 points) in older residents in Mexico DC (18%) than in rural areas (11%) (crude OR 1.96, 95% CI 0.79, 5.21) (Sanchez-Rodriguez et al., 2006). No formal assessment of air pollution exposure concentrations was made in this study.

Lo et al. (2019) reported that long-term exposure to PM_{10} and O_3 was significantly associated with cognitive impairment in the Taiwan Longitudinal Study on Aging (OR = 1.094, 95% CI: 1.020, 1.174 for an increase of 10 $\mu g/m^3$ in PM_{10} levels; OR = 1.878, 95% CI: 1.363, 2.560 for an increase of 10 ppb in O_3 levels).

IQR increases in 1-month (8.3 $\mu g/m^3$) and 2-month (7.9 $\mu g/m^3$) $PM_{2.5}$ were associated with worsening of symptoms related to Alzheimer's disease and mild cognitive impairment, as assessed during outpatient visits, in participants of the Clinical Research Center for Dementia of South Korea (CREDOS) Study. The risk was increased 17.1% (95% CI 2.7–33.5%) for a 1-month IQR $PM_{2.5}$ increase and 20.7% (95% CI 1.8–43.1%) for a 2-month increase. Larger risks were observed for mild cognitive impairment patients, with increases of 40.7% (95% CI 18.3–67.3%) and 24.9% (95% CI -3.1–61.1%) for 1- and 2-month IQR increases. The distress of Alzheimer's diseases carers was also evaluated, and increased 29% (95% CI 8.1–53.9) and 36.1% (95% CI 9.1–69.8%) for 1-month and 2-month IQR $PM_{2.5}$ increases. The $PM_{2.5}$ results remained statistically significant for worsening of Alzheimer's disease symptoms and caregiver distress for 1-month and 2-month exposures when adjusted in two-pollutant models for NO_2, SO_2 or O_3, but not for CO. Two-pollutant models remained statistically significant for 1-month averages for aggravated symptoms of mild cognitive impairment (Lee et al., 2019).

3.2.5. Dementia, Alzheimer's disease

Fifteen studies have assessed the association between exposure to air pollution and dementia and Alzheimer's disease (see Table S9).

A significant positive association was found between residential proximity to traffic (<50 m) and risk of incident dementia (ascertained from provincial health administrative databases with validated algorithms) in the Ontario Population Health and Environment Cohort of over 2 million participants in Toronto, Canada (HR = 1.07, 95% CI 1.06; 1.08), with a significant trend in risk. The strongest associations were found for residents of the main cities in Ontario (Canada) and for urban residents (H. Chen et al., 2017a). A follow-up analysis of the same cohort found $PM_{2.5}$ to be significantly associated with dementia incidence, with a HR of 1.04 (95% CI, 1.03–1.05) for every IQR (3.4 $\mu g/m3$) increase in exposure to $PM_{2.5}$. NO_2 (per IQR increase of 11.3 ppb) was also associated with increased incidence of dementia (HR = 1.10; 95% CI: 1.08–1.12). These estimates translated to 6.1% of dementia cases attributable to $PM_{2.5}$ and NO_2 (H. Chen et al., 2017b).

Another population-based cohort study in Ontario, the National Population Health Survey and the Canadian Community Health Survey, reported only non-statistically significant associations between exposure to NO_2 and dementia incidence (HR = 1.10, 95% CI 0.99; 1.19 per 5 ppb) and between exposure to $PM_{2.5}$ and dementia (HR = 1.29, 95% CI 0.99; 1.64 per 10 $\mu g/m^3$) (Ilango et al., 2020).

In the Women's Health Initiative Memory Study (WHIMS) of 4500 older women across USA, exposure to $PM_{2.5}$ was significantly associated with an increased risk of incident dementia (HR = 1.92, 95% CI 1.31; 2.80) for the highest (>12 $\mu g/m^3$) vs the lowest (≤12 $\mu g/m^3$) $PM_{2.5}$ residential exposure averaged during the 3 years prior to the incident event (Cacciottolo et al., 2017).

However, a recent reanalysis of the WHIMS cohort found no association between an interquartile increment (3.9 $\mu g/m^3$) of annual $PM_{2.5}$ exposure and the incidence of dementia (HR = 0.99, 95% CI 0.81, 1.22). There was also no association between an IQR increment of diesel particulate matter exposure (0.35 $\mu g/m^3$) and the risk of developing dementia (HR = 1.02; 95% CI 0.83, 1.25) (J.C. Chen et al., 2017).

An increase of exposure of 4.34 $\mu g/m^3$ annual $PM_{2.5}$ was positively associated with a significantly increased risk of incidence of Alzheimer's

disease (physician-diagnosed) (HR = 2.38, 95% CI 2.21; 2.56) in a cohort of circa 100 k participants randomly selected from the National Health Insurance Research Database (NHIRD) of Taiwan in the year 2000 (Jung et al., 2015). In another study in Taiwan (Wu et al., 2015), exposure to the highest (≥49.23 µg/m³) compared to the lowest (<44.95 mg/m³) tertile of PM_{10} was linked in a case-control analysis with an increased risk of vascular dementia (OR = 3.61, 95% CI 1.67; 7.81) and Alzheimer's disease (OR = 4.17, 95% CI 2.31; 7.54). In contrast, a nested case-control study within the Taiwan NHIRD database found no association between risk of incident vascular dementia and 3-year, 5-year or 7-year average exposure to PM_{10} (Li et al., 2019).

Another cohort study using data from the NHIRD of Taiwan during 2000–2010 found an association between exposure to NO_2 and risk of incident dementia. For the highest quartile of exposure to NO_2 (>9826 ppb) versus the lowest quartile (<6652 ppb), the adjusted HR for dementia was 1.54 (95% CI 1.34–1.77). Results were consistent across the sexes (Chang et al., 2014). Li et al. (2019) found an increase in the odds ratio of incident vascular dementia (OR = 1.06, 95% CI 1.01; 1.11 per 1 ppb) with 7-year average exposure to NO_2, in a nested case-control study within NHIRD. (These results are similar to those in the population based study in Toronto (H. Chen et al., 2017a) reported above).

A United States Veterans Health Administration (VA) study reported that an IQR increase in baseline $PM_{2.5}$ exposure was associated with dementia mortality (HR = 1.09, 95% CI 1.06–1.12). Participants exposed to the highest $PM_{2.5}$ quartile (13.9–20.1 µg/m³) had a higher incidence of dementia (IR = 0.70, 95% CI 0.68; 0.72 per 1000 person-years) than participants in the lowest $PM_{2.5}$ quartile (4.8–10 µg/m³) (Bowe et al., 2019).

NO_x exposure was associated with incident dementia risk in the Betula study in Sweden (circa 2000 participants). Associations were observed for dementia (AD or VaD) with a HR of 1.60 (95% CI 1.02–2.10), for the highest quartile of NOx exposure (>26 µg/m³) compared to the lowest quartile (4.8–9 µg/m3). However, no significant association was found for 10 µg/m³ increase in NOx (HR 1.05, 95% CI 0.98–1.12). The association was stronger in a subgroup analysis that excluded younger participants (HR = 1.71; 95% CI 1.08–2.73 for the highest vs the lowest quartile; HR = 1.08, 95% CI 1.00–1.16 per 10 µg/m³ NOx increase). Stratified analysis by diagnosis yielded similar results with a HR for AD of 1.38 (95% CI 0.87–2.14) and a HR for VaD of 1.47 (95% CI 0.83–2.61) for the highest versus the lowest quartile of NOx exposure. The HR for a 10 µg/m³ increase in NOx was 1.05 (95% CI 0.97–1.15) for AD and 1.02 (95% CI 0.92–1.14) for VaD (Oudin et al., 2016). In a recent analysis from the Betula study restricted to data from participants who were *APOE* ε4-positive, Oudin et al. (2019) reported increased hazard ratio for incident dementia (AD or VaD) in the 3rd (HR = 1.52, 95% CI 1.08; 2.12) and 4th (HR = 1.41; 95% CI 1.01; 1.98) quartiles of exposure compared to the lowest quartile. However, no significant association was found for 10 µg/m³ increase in NOx (HR = 1.03; 95% CI 0.97; 1.10). For AD, hazard ratios were higher in the 3rd (HR = 1.72; 95% CI 1.12; 2.65) but not the 4th (HR = 1.53; 95% CI 0.99; 2.36) quartile, with no significant association per 10 µg/m³ NOx increase (HR = 1.04, 95% CI 0.96; 1.13) (Oudin et al., 2019).

In a follow up analysis of the Betula Study, subjects in the 3rd (17–26 µg/m³) and 4th (≥26 µg/m³) quartiles for exposure compared to 1st (<9 µg/m³) quartile of traffic-related NO_x had an increased risk of developing dementia (HR_{3ile} = 1.48; 95% CI 1.03–2.12; HR_{4ile} = 1.41; 95% CI 0.97, 2.03). The effect was not modified by modelled residential traffic noise levels (Andersson et al., 2018). A further analysis showed that $PM_{2.5}$ from local residential wood burning was associated with dementia incidence (HR = 1.55; 95% CI 1.00; 2.41 per 1 µg/m³ increase). A stronger association was found among subjects who also had a wood-burning stove at home (HR = 1.74; 95% CI 1.10–2.75) compared to participants without wood-burning stoves at home. $PM_{2.5}$ from traffic exhaust was also associated with an increased risk of dementia incidence (HR 1.66; 95% CI 1.16–2.3 and 1.41 95% CI 0.97–2.04 for the third and fourth quartiles respectively) (Oudin et al., 2018).

Carey et al. (2018) found an increased incidence of all cause dementia in London associated with NO_2 (HR = 1.15, 95% CI 1.04–1.28; IQR = 7.47 µg/m³), $PM_{2.5}$ (HR = 1.06, 95% CI 1.01–1.13; IQR = 0.95 µg/m³) and traffic-related $PM_{2.5}$ (HR = 1.08, 95% CI 0.99–1.18; IQR = 0.58 µg/m³), but not with ozone. NO_2 exposure also increased the risk of incidence of Alzheimer's disease (HR = 1.23, 95% CI 1.07–1.43), vascular dementia (HR = 1.15, 95% CI 0.96–1.39) and non-specific dementia (HR = 1.13, 95% CI 0.99–1.28) per IQR increase. Similar, but smaller, effects were observed for $PM_{2.5}$ and for traffic-related $PM_{2.5}$ (Carey et al., 2018).

Ozone exposure has also been associated with an increased risk of Alzheimer's disease in some studies. A study in Taiwan reported that an IQR increase in 10.91 ppb of O_3 was associated with a HR of 3.12 (95% CI, 2.92–3.33) for incidence of Alzheimer's disease (Jung et al., 2015). Another Taiwanese study reported that participants exposed to the highest tertile of ozone (≥21.56 ppb) had an adjusted OR of 2.09 (95% CI 1.01–4.33) for dementia and an OR of 2.00 (95% CI 1.14–3.50) for Alzheimer's disease compared to the lowest tertile (<20.2 ppb) (Wu et al., 2015). On the other hand, no association was found between 3-year, 5-year or 7-year O_3 exposure and risk of incident vascular dementia in a nested case-control study of the NHIRD cohort in Taiwan (Li et al., 2019). Likewise, the study by Chen et al. in Toronto did not find the risk of incident dementia to be linked with the concentration of O_3 (IQR: 12.4 µg/m³) (H. Chen et al., 2017a); nor did that by Carey et al. in London (Carey et al., 2018).

Chang et al. (2014) reported that randomly selected participants from the NHIRD cohort in Taiwan who were in the highest quartile of exposure to CO (>296.2 ppb) compared to the lowest one (<196.2 ppb) had significantly more risk of incident dementia (HR 1.61, 95% CI 1.39–1.85), consistent between men and women. A nested case-control study in the same NHIRD cohort found an increased odds ratio of incident vascular dementia for people whose 7-year average CO exposure was in the 2nd (OR = 1.46, 95% CI 1.11–1.93), 3rd (OR = 1.53, 95% CI 1.10–2.13) or 4th (OR = 1.53, 95% CI 1.03–2.27) quartile compared to the 1st quartile (Li et al., 2019). No associations were found with SO_2 exposure in the same study.

3.2.6. Hospital admissions due to Alzheimer's disease and dementia

Table S10 summarizes the characteristics of the six studies that have analysed the association between air pollution and hospital admissions due to Alzheimer's disease and dementia.

Short-term exposure to $PM_{2.5}$ was not associated with an increase in hospitalizations due to Alzheimer's disease (0.20%; 95% CI −1.26%, 1.69%) or dementia (0.92%; 95% CI −0.44%, 2.30%) for each 10 µg/m³ increase in the two days preceding the episode, in a national case-crossover analysis among Medicare enrollees aged ≥65 years in 121 US communities. On the other hand, age was found to be a significant modifier (p-value$_{interaction}$ = 0.009) for Alzheimer's disease hospitalization, with an increased risk of 3.48% (95% CI 0.83–6.19) for subjects between 65 and 75 years. Mortality after hospitalization for Alzheimer's disease was also associated with short-term $PM_{2.5}$ exposure (1.04%; 95% CI 0.36–1.72%) and dementia (0.94%; 95% CI 0.01–1.89%) (Zanobetti et al., 2014).

Kioumourtzoglou et al. (2016) estimated the effects of long-term city-wide $PM_{2.5}$ concentrations on first hospital admissions for dementia, Alzheimer's disease and Parkinson's disease (primary or secondary cause) in 9.8 million elderly subjects across 50 north-eastern US cities over 11 years. Significant associations for all three outcomes were reported, with an HR of 1.08 (95% CI 1.05–1.11) for dementia, 1.15 (95% CI 1.11–1.19) for Alzheimer's disease per 1 µg/m³ increase in annual $PM_{2.5}$ concentration (Kioumourtzoglou et al., 2016).

A similar study in Rome estimated the effects of long-term exposure to air pollution on first hospital admission for dementia. First hospital admission for vascular dementia was associated with PM_{10}, $PM_{2.5}$, PM_{coarse}, $PM_{2.5\,abs}$, NO_2 and NO_x, with hazard ratios ranging 1.05 to 1.15 (p < 0.05) for a 10 µg/m³, except $PM_{2.5}$, PM_{coarse} (5 µg/m³) and NOx (20 µg/m³), and with distance to heavy traffic roadside (HR =

1.17, 95% CI 1.10–1.24 for <50 m). In contrast, exposure to most of these pollutants was associated with reduced hazard ratios for first time hospitalization for Alzheimer disease or "senile dementia", ranging between 0.91 and 0.96 (p < 0.05). For first time hospitalization related to dementia, the hazard ratio associated with long-term exposure to NO_2 was 0.97 (95% CI 0.96–0.99 for 10 μg/m³), whereas the hazard ratios reported for exposure to NOx and O_3 were 1.01 (95% CI 1.00–1.02 for 20 μg/m³) and 1.06 (95% CI 1.03–1.08 for 10 μg/m³) respectively (Cerza et al., 2019).

In a Madrid study, short-term exposure to $PM_{2.5}$ carried a significantly increased risk of Alzheimer's disease hospital admission (primary cause): for an increment in $PM_{2.5}$ IQR of 20 μg/m³ the RR after a 2-day lag was 1.38 (95% CI 1.15–1.65) (Culqui et al., 2017). For a 10 μg/m³ increase in O_3 concentration (lag 5), the RR of daily hospital admission for dementia was 1.09 (95% CI 1.04–1.15) (Linares et al., 2017). Excessive heat and noise also affected Alzheimer's and dementia hospital admissions (Culqui et al., 2017; Linares et al., 2017).

Qiu et al. (2019) used electronic hospital records to evaluate the risk attributable to $PM_{2.5}$, PM_{10} and PM_{coarse}, for hospital admission for dementia in Sichuan Province in all tertiary and secondary hospitals in the area. A 10 μg/m³ increase of PM_{coarse} on lag 1, lag 2 and lag 0–2 was significantly associated with dementia hospitalization; PM_{10} and $PM_{2.5}$ were not associated. The attributable fraction and number of hospitalizations were 7.22% (95% CI 0.63%, 12.81%) and 66 (95% CI 0, 6118) cases respectively for a 10 μg/m³ increase in PM_{coarse} (Qiu et al., 2019).

3.2.7. Neuroimaging

Eight studies, on four American cohorts and one British one, assessed the effects of air pollution on brain morphology, white matter lesions and small vessel ischemic disease (see Table S11).

A 2 μg/m³ increase in $PM_{2.5}$ exposure was associated with smaller brain volume (β = −0.26%, 95% CI, −0.53–0.004) in the Framingham Offspring Study: equivalent to 1 year of brain aging (Wilker et al., 2015). However, in the Massachusetts Alzheimer's Disease Research Centre Longitudinal Cohort, brain parenchymal fraction (a measure of brain atrophy) was not related to $PM_{2.5}$ or residential proximity to traffic (Wilker et al., 2016).

Structural brain magnetic resonance imaging of 1400 community-dwelling older women participating in the WHIMS study and who did not have dementia revealed reductions in total white matter (WM) volume (of 6.23 ± 1.28[8] cm³, 95% CI 3.72–8.74) and in WM association areas (of 4.47 ± 1.12 cm³, 95% CI 2.27–6.67) per inter-quartile (3.49 μg/m³) increase in cumulative yearly $PM_{2.5}$ (1999–2006) and −2.04 ± 0.59 cm³ in frontal, −0.73 ± 0.34 cm³ parietal and −1.70 ± 0.33 cm³ temporal association regions (J.C. Chen et al., 2017; Chen et al., 2015).

Voxel-based morphometry analysis by Casanova et al. (2016) demonstrated that long-term (3-year average) $PM_{2.5}$ exposure preceding MRI scans in participants in the WHIMS study was associated with smaller subcortical WM volume, especially in the frontal lobe and less marked in the temporal, parietal and occipital lobes.

An inconsistent relationship was found between WM volumes and exposure to diesel particulate matter (estimated by the U.S. EPA National-Scale Air Toxics Assessment (NATA) Program[9]). In the frontal and temporal association areas WM volume was reduced for an IQR increase (0.31 μg/m³) in the 1st-3rd quartiles of concentration (0.01–0.55 μg/m³) but increased for those in the 4th quartile of concentration (0.55–3.93 μg/m³) (J.C. Chen et al., 2017). $PM_{2.5}$ level showed an inverse association with white matter hyperintensity volume (WMH), a marker of small vessel disease. (β = −0.19, 95% CI −0.38, −0.001). A

similar but non-significant trend, although not significant, was observed for residential proximity to major roads and WMH, such that living closer to a major road was associated with lower WMH volume (Wilker et al., 2016; Wilker et al., 2015). In a follow-up analysis restricted to subjects with probable Alzheimer's disease, Wilker et al. (2016) did not find WMH to be significantly associated with residential traffic nor a 2 μg/m³ increment in $PM_{2.5}$.

Wilker et al. reported an association between long-term air pollution and higher risk of covert brain infarcts (OR 1.37 per 2 μg/m³ increase of $PM_{2.5}$, 95% CI 1.02–1.85) (Wilker et al., 2015). No association was found between microbleeds and either exposure to $PM_{2.5}$ or living closer to a major road (Wilker et al., 2016). The severity of small-vessel ischaemic disease in the brain as a whole, WM, GM or brain association areas was not related to exposure to $PM_{2.5}$ or diesel particulate matter (J.C. Chen et al., 2017).

$PM_{2.5}$ exposure estimated over a 6-year period was not associated with GM volume in MRI scans of older women participating in the WHIMS study (J.C. Chen et al., 2017; Chen et al., 2015). A subsequent analysis of the same cohort found that 3-year average $PM_{2.5}$ exposure was related to smaller cortical GM volumes on voxel-wise morphology, the effects being clustered in the bilateral superior, middle and medial frontal gyri (Casanova et al., 2016). Further analysis of the WHIMS cohort found that exposure to diesel particulate matter was associated with smaller GM volumes (J.C. Chen et al., 2017). The largest effect was reported for the association areas of the brain (−12.72 ± 1.88) followed by the frontal (−6.64 ± 0.91), parietal (−3.85 ± 0.55) and temporal (−2.23 ± 0.63) lobes, on comparison between participants with diesel PM exposures in the fourth quartile (median = 0.78 μg/m³) and those in the first to third quartiles (median = 0.29 μg/m³) (J.C. Chen et al., 2017).

The Atherosclerosis Risk in Communities (ARIC) study found Minnesota participants with higher mean $PM_{2.5}$ and PM_{10} exposures over 5 to 20 years prior to the MRI scans to have smaller deep-gray matter volumes (β = −0.02 SD-unit brain volume, 95% CI −0.04–0.0 per 1 μg/m³ increase in PM_{10}). Increased $PM_{2.5}$ concentrations were associated with smaller total (β = −0.09 SD-unit brain volume, 95% CI −0.16 to −0.01) and regional brain volumes (β ranging from −0.08 to −0.1). This association was not present in participants from the other three study regions. No other MRI marker (total brain, frontal, occipital, parietal or temporal brain volumes, hippocampus or Alzheimer's disease signature[10]) was associated with $PM_{2.5}$ or PM_{10} exposure (Power et al., 2018).

No association between exposure to air pollutants ($PM_{2.5}$ or diesel particulate matter) and hippocampal volumes has been found in any of the American cohort studies (Casanova et al., 2016; J.C. Chen et al., 2017; Chen et al., 2015; Wilker et al., 2015). Mean annual concentrations of $PM_{2.5}$ for the year 2010 were associated with smaller left hippocampal volume (−10.78 mm³) in participants of UK Biobank (Hedges et al., 2019). No associations were observed for PM_{coarse}, PM_{10}, NO_2 or NO_x with left or right hippocampal volumes.

Exposure to diesel particulate matter was associated with a significant increase in ventricular volume (0.96 ± 0.43 cm³) per IQR increase (0.31 μg/m³), in keeping with an atrophic effect on the brain (J.C. Chen et al., 2017). No association was found between $PM_{2.5}$ and ventricular volume (J.C. Chen et al., 2017).

An IQR increase (3.49 μg/m³) in cumulative yearly $PM_{2.5}$ (1999–2006) was associated with a reduction of corpus callosum volume (−0.12 ± 0.04 cm³) (J.C. Chen et al., 2017; Chen et al., 2015), but no such association was observed by Casanova et al. (2016).

In the WHIMS study, no association was reported between exposure to $PM_{2.5}$ or diesel particulate matter and changes in the basal ganglia (J.C. Chen et al., 2017).

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[8] Regression coefficients ± standard error.
[9] The U.S. EPA National-Scale Air Toxics Assessment (NATA) Program estimates ambient concentrations of around 50 of the more prevalent and higher risk hazardous air pollutants from emission inventories using a blend of chemical transport models with a dispersion model (AERMOD).

[10] Alzheimer's Disease signature region refer to multiple gray matter regions atrophied in Alzheimer's disease, such as parahippocampal, entorhinal, inferior parietal lobules, hippocampus, precuneuos and cuneus.

Younan et al. (2020) reported that average exposure to PM$_{2.5}$ over 3 years preceding an MRI scan was associated with an increased Alzheimer's Disease Pattern Similarity score ($\beta_{PM2.5}$ = 0.018, 95% CI 0.001–0.034). This score is a structural brain MRI-based neuroanatomic biomarker reflecting gray matter atrophy in areas vulnerable to Alzheimer's disease neuropathology (Younan et al., 2020). It was derived using a voxel-wise supervised machine learning algorithm (Casanova et al., 2018; Casanova et al., 2013; Casanova et al., 2011).

More generally it is worth noting that in most of the relevant studies, the regions of the brain reported to show morphological changes associated with air pollution are those important for higher cognitive functions such as working memory, episodic memory retrieval and executive function (Casanova et al., 2016).

3.2.8. Human studies on neuroinflammation

Table S12 summarizes eight studies of associations between air pollution and markers of neuroinflammation.

Sanchez-Rodriguez et al. (2006) found the proportion of elderly subjects with elevated oxidative stress biomarker levels measured in blood and cognitive impairment to be greater in urban (25%) than rural environments (9%). Subjects in urban areas had significantly higher levels of lipoperoxides[11] and lower levels of superoxide dismutase[12] and glutathione peroxidase.[13] The authors found the MMSE score showed significant inverse correlation with lipoperoxides, total antioxidant status and age, and correlated positively with superoxide dismutase level.

Shaffer et al. (2019) evaluated associations between vascular cell adhesion molecule-1 (VCAM-1)[14] and E-selectin[15] in cerebrospinal fluid (CSF) and short-term (7-day average) and long-term (1-year) preceding PM$_{2.5}$ exposure. In cognitively normal adults, PM$_{2.5}$ exposure over the preceding week was associated with elevated VCAM-1 (35.4 ng/ml, 95% CI 9.7–61.1 ng/ml per 5 μg/m^3) and E-selectin (53.3 pg/ml, 95% CI 11.0–95.5 pg/ml per 5 μg/m^3) in CSF; PM$_{2.5}$ exposure over the preceding year was associated with elevated VCAM-1 only (51.8 ng/ml, 95% CI 6.5–97.1 ng/ml per 5 μg/m^3). No associations were found in individuals with mild cognitive impairment or Alzheimer's disease (Shaffer et al., 2019).

Bos et al. (2011) reported that serum brain-derived neurotrophic factor (BDNF)[16] did not increase after cycling near a traffic roadside, whilst it did increase when cycling whilst breathing filtered air. BDNF plays a key role in brain plasticity and is thought to be linked with enhanced cognition and improved memory function. The lack of increase of BDNF on exercise was seen as a potentially deleterious effect. The results were consistent between subjects training in urban and rural environments (Bos et al., 2013).

In a randomised controlled crossover study, Liu et al. (2017) exposed fifty healthy non-smoking volunteers to coarse, fine and ultrafine concentrated ambient particles. The authors found significant associations between levels of biological molecules such as endotoxin and β-1,3-D-glucan, present in the coarse and fine concentrated ambient particles, and blood C-terminal hydrolase L1 and astrocytic calcium-binding protein B (S100b), which are biomarkers of damage to the blood brain barrier. No association was found with ultrafine concentrated ambient particles (Liu et al., 2017).

Cliff et al. (2016) did not find any relationship between short-term exposure to diesel exhaust and several biomarkers of neurotoxicity: S100b, neuron-specific enolase (NSE),[17] and serum BDNF in an double blinded cross-over study (Cliff et al., 2016).

Calderon-Garciduenas et al. (2013) reviewed their work in children and youngsters in Mexico City and reported neuropathological changes in children and young adults similar to those in Alzheimer's disease. There was increased neuro-inflammation and vascular damage: upregulated mRNA cyclooxygenase-2, interleukin-1β and CD14, and clusters of mononuclear cells around blood vessels and activated microglia in the frontal and temporal cortex, subiculum and brain stem. They also found deposits of amyloid-β42, α-synuclein, hyperphosphorylated tau, and evidence of oxidative stress, neuronal damage and death (Calderon-Garciduenas et al., 2013). Children in Mexico City (with high levels of air pollution) also had low serum BDNF concentrations (Calderon-Garciduenas et al., 2016).

3.3. Assessment of the evidence-base with regard to the question of causality of the reported associations

A majority of the reviewed epidemiological studies have shown a positive association between air pollution exposure and detrimental effects on cognitive decline and dementia. However, the possible effects of publication bias need to be considered: it is possible that studies with negative or null results are less likely to be published, especially as the study of the effects of environmental factors on cognition and dementia is a relatively new field (Xu et al., 2016). If we assume no major publication bias, the question of causality can be approached as outlined by Bradford Hill (1965). Bradford Hill set out nine considerations, which we address below.

3.3.1. Strength of association

Bradford Hill pointed out that it was more likely that strong than weak associations were causal in nature: if the former were caused by confounding factors linked to the putative causal agent, those factors should not be difficult to identify, whereas for weak associations possible confounding factors might be difficult to identify. In general, associations between air pollutants and effects on health tend to be weak rather than strong, and it is clear that the question of causality cannot be decided on the basis of strength of association alone. Weak associations might be causal in nature; the weakness or strength of an association does not of itself control the likelihood of causality. In addition, it should be noted that weak, but causal, associations might be very important in terms of their implications for public health if a large proportion of the population is exposed.

The reviewed literature suggests that long-term exposure to air pollution is associated with a small to modest reduction in global cognitive performance, attention, memory, and language function, and with concomitant morphological changes in the brain (Chen and Schwartz, 2009; Power et al., 2011; Wellenius et al., 2012; Weuve et al., 2012; Wilker et al., 2015), as summarized in Table 1. The effects on cognitive function are similar to those of aging 1 to 5 years.

As described in Section 3.2, the reported associations between indices of air pollution and endpoints indicating effects on the brain are, in general, weak. They are, however, not notably weaker than other associations in the air pollution field, and the potential risks are considerable, as highlighted by a recent cohort study in London: subjects in the upper quartile of NO$_2$ exposure (>41.5 μg/m^3) were at a 40% greater risk of dementia (95% CI 1.12–1.74) compared to those in the lowest quartile (<31.9 μg/m^3) (Carey et al., 2018). Overall, there is evidence for weak associations, and some high-quality studies reporting strong associations of substantial potential public health importance.

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[11] Lipids molecules that have been degraded by oxidation.
[12] Superoxide dismutase is an enzyme that catalyses the detoxification of the superoxide radical in cells.
[13] Glutathione peroxidase is an antioxidant enzyme, considered a major defense in low-level oxidative stress, which reduces H$_2$O$_2$ and lipid peroxides to water and lipid alcohols, respectively.
[14] Vascular cell adhesion molecule-1 (VCAM-1) is expressed on cytokine-activated endothelium and helps regulate vascular adhesion and transendothelial migration of leukocytes (e.g. macrophages and T cells) during inflammatory processes.
[15] E-selectin is expressed on endothelial cells after activation by interleukin 1 (IL-1), tumor necrosis factor α (TNFα) or bacterial lipopolysaccharides and it is crucial to control leukocyte accumulation in inflammatory responses.
[16] Brain-derived neurotrophic factor (BDNF) is a neurotransmitter modulator with an important role for neuronal survival and growth, and contributes to neuronal plasticity.
[17] Neuron-specific enolase (NSE) is a protein found in the cytoplasm of neurons, erythrocytes, platelets, and cells of neuroendocrine origin that has been linked with neuronal injury severity.

Table 1

Summary of characteristics and outcomes of studies reporting aging equivalent to the effect of long-term air pollution exposure on cognition included in literature review.

Reference/name of study	Location	Sample size	Age	Study design	Cognitive/neurological outcome	Coefficient[a]	Exposure	Aging equivalence
(Power et al., 2011) Normative Aging Study	Boston, USA	680 men	Range: 51–97 Mean: 71 ± 7	Prospective cohort Cross-sectional analysis of cognitive testing responses obtained between 1996 and 2007.	Global cognition	OR (MMSE <25) = 1.3 (95% CI 1.1, 1.6)	Doubling of BC	1.9 years
(Tallon et al., 2017) National Social Life, Health and Aging Project cohort	USA	3377	57–85	Prospective cohort Cross-sectional analysis of 2010–2011 survey	Global cognition	β (CCFM) = −0.22; (95% CI −0.44; −0.01)	PM$_{2.5}$ 1-year IQR increase (4.25 µg/m^3)	1.6 years
						β (CCFM) = −0.26; (95% CI −0.45; −0.06)	NO$_2$ 2-year IQR increase (6.66 ppb)	1.9 years
(Chen and Schwartz, 2009) NHANES-III	Nationwide, USA	1764 (879 men, 885 women)	Mean: 37.4 ± 10.9	Prospective cohort Cross-sectional analysis (1989–1991)	Attention & memory	β (SDLT) = 0.52 s; (95% CI 0.03; 1.01) β (No of trials SDLT) = 0.26 s; (95% CI 0.03; 0.48)	O$_3$ (10 ppb) O$_3$ (10 ppb)	5.3 years
(Wellenius et al., 2012) MOBILIZE Boston Study	Boston, USA	765 (276 men, 489 women)	≥65 Mean: 78.1 ± 5.4	Prospective cohort Longitudinal study (Baseline recruitment 2005–2008; median follow-up of 16.8 months)	Memory	β (HVLT-R immediate recall) = −0.6; (95% CI −1.1; −0.1) (subjects age ≤ 77)	Residential Traffic proximity IQR decrease (851.2 m).	2 years
						β (HVLT-R immediate recall) = −0.66; (95% CI −1.15; −0.17) (subject's education>college)	Residential Traffic proximity IQR decrease (851.2 m).	
						β (HVLT-R delayed memory) = −0.59; (95% CI −87; −0.31) (subjects age ≤ 77)	Residential Traffic proximity IQR decrease (851.2 m).	
						β (HVLT-R delayed memory) = −0.4; (95% CI −0.7; −0.1) (subject's education>college)	Residential Traffic proximity IQR decrease (851.2 m).	
					Language	β (letter fluency) = −1.4; (95% CI −2.7, −0.2)	Residential Traffic proximity IQR decrease (851.2 m).	4 years
						β (category fluency) = −0.7; (95% CI −1.1, −0.3)	Residential Traffic proximity IQR decrease (851.2 m).	
(Weuve et al., 2012) Nurses' Health Study Cognitive Cohort	USA	19,409 women	≥70	Prospective cohort Longitudinal study (Sub-cohort of NHS: 1995–2001; participants resurveyed in 1997–2004; 2002–2008)	Cognitive decline	β = −0.018; (95% CI −0.035; −0.002)	PM$_{2.5}$ (10 µg/m^3)	2 years
						β = −0.020; (95% CI −0.032; −0.008)	PM$_{10-2.5}$ (10 µg/m^3)	
(Wilker et al., 2015) Framingham Offspring Study	New England, USA	943	≥60	Prospective cohort Cross-sectional analysis of responses from the 7th examination (1998–2001)	Neuroimaging	β (brain volume) = −0.32% (95% CI, −0.59, −0.05)	PM$_{2.5}$ (2 µg/m^3)	1 year
						β (covert brain infarct) = 1.46 (95% CI, 1.10, 1.94)	PM$_{2.5}$ (2 µg/m^3)	
(J.C. Chen et al., 2017; Chen et al., 2015) Women's Health Initiative Memory Study (WHIMS)	USA	1403 women	71.0–89 years at baseline	Prospective cohort Cross-sectional analysis of scans conducted on 2005–2006	Neuroimaging	β (total WM brain volume) = −6.23 ± 1.28 cm^3 (95% CI 3.72; 8.74)	PM$_{2.5}$ annual IQR increment (3.49 µg/m^3)	1–2 years
						β (association areas WM brain volume) = −4.47 ± 1.12 cm^3 (95% CI 2.27; 6.67)		
						β (frontal WM) = −2.04 ± 0.59 cm^3		

Table 1 (*continued*)

Reference/name of study	Location	Sample size	Age	Study design	Cognitive/neurological outcome	Coefficient[a]	Exposure	Aging equivalence
						β (parietal WM) = −0.73 ± 0.34 cm^3		
						β (temporal WM) = −1.70 ± 0.33 cm^3		
						β (corpus callosum) = −0.12 ± 0.04 cm^3		

3.3.2. Consistency of association

The multiplicity of air pollutants and cognitive endpoints considered, the range of cognitive tests, and the different study designs in the literature preclude meta-analysis of the data. Within each study design, it is also difficult qualitatively to assess consistency of findings for a specific air pollutant and for particular cognitive domains.

Moreover, studies have been conducted in a wide range of geographical locations, each with a different mixture of air pollutants. For instance, in the USA gasoline emissions dominate urban air pollution. In Europe, diesel vehicle emissions make a larger contribution. The temporal profiles of air pollutant mixtures also vary. The enforcement of stricter fuel regulations (e.g. reduced sulfur content, unleaded gasoline) and technological advances in transport (e.g. improved fuel combustion) and industry (e.g. improved control of stack emissions) has resulted in considerable reduction in air pollutant emissions in recent years. In comparing different studies, the geographical and temporal patterns of air pollutants also need to be considered.

Most of the studies of the effects of air pollution on cognitive performance reviewed here have reported associations between exposure to at least one air pollutant and a decrement in global cognition (13 of 16) and constructional praxis (3 of 3). The findings have been less consistent with respect to executive function (5 of 9), attention (4 of 6), memory (7 of 11) and language (4 of 5), or for associations between air pollution and mild cognitive impairment (4 of 6) or cognitive decline (5 of 9).

Proximity to traffic (3 of 3) and CO (2 of 2) has consistently been associated with increased risk of dementia. NO_2/NO_x (7 of 8) and PM (6 of 9) have also been associated with dementia in most studies, but O_3 in only 2 of 5 studies. One large study (on approximately 9 million people) found that long-term exposure to $PM_{2.5}$ was associated with first-time hospital admissions for Alzheimer's disease and other causes of dementia (Kioumourtzoglou et al., 2016). This is consistent with population-based studies showing associations between short-term variations in air pollution and neurological disease-related hospital admissions in Madrid (Spain) (Culqui et al., 2017; Linares et al., 2017), Chengdu (China) (Qiu et al., 2019) and USA (in older adults) (Zanobetti et al., 2014). However, a study in Rome did not find consistent associations between air pollutants and first-time hospitalization for dementia (Cerza et al., 2019). Associations between $PM_{2.5}$, Alzheimer's disease symptoms and carers' distress was reported in South Korea (Lee et al., 2019).

Evidence of changes on neuroimaging in association with air pollution is more limited and less consistent. Studies on the WHIMS cohort have found associations between air pollution and reductions in white matter volume (Casanova et al., 2016; J.C. Chen et al., 2017; Chen et al., 2015). In three different US cohorts air pollution has not been associated with hippocampal volume (Casanova et al., 2016; J.C. Chen et al., 2017; Chen et al., 2015; Wilker et al., 2015), but left hippocampal volume was associated with air pollution in the UK Biobank cohort (Hedges et al., 2019). Exposure to particulate matter was associated with lower gray matter volume in the WHIMS and ARIC cohorts (Casanova et al., 2016; J.C. Chen et al., 2017; Power et al., 2018) and, in the WHISCA and WHIMS-MRI cohorts, with a pattern of atrophy of gray matter structures similar to that in Alzheimer's disease (Younan et al., 2020). Documented effects of exposure to air pollution on neuroimaging features of small vessel disease are inconsistent (J.C. Chen et al., 2017; Wilker et al., 2016; Wilker et al., 2015).

Studies on other biomarkers measured after chronic exposure to air pollutants are very limited in number (Calderon-Garciduenas et al., 2013; Sanchez-Rodriguez et al., 2006), and few studies are available on effects on biomarkers of short-term exposures.

Although most of the reviewed studies have found significant associations between concentrations of at least one air pollutant and markers of brain injury, and some have reported associations that suggest a deleterious effect but failed to reach statistical significance, a few studies have found contrary associations: proximity to traffic associated with a lower risk of white matter hyperintensities (Wilker et al., 2016; Wilker et al., 2015), better reasoning and prospective memory (Cullen et al., 2018), better verbal memory and visuospatial skills (Wurth et al., 2018), reduced risk of first time hospitalization related to dementia (Cerza et al., 2019), better scores on tests of global cognition, executive function, attention and memory (Shin et al., 2019), reduced cognitive decline (Xu et al., 2017), and a non-significant association between air pollution and improved cognitive performance (Tonne et al., 2014).

Although the various studies have examined the effects of a range of different pollutants, there is some correlation between different pollutants, especially in urban areas. It seems, therefore, reasonable to compare studies on different pollutants to gauge overall consistency. Our review has shown that there is reasonably strong consistency across the range of studies reported: stronger in the studies linking air pollution to incident dementia, and weaker in others (e.g. relating to executive function, mild cognitive impairment). There is only moderate consistency between the documented effects of different air pollutants on cognition and on brain structure and neuropathology.

The failure to detect an association between air pollution and cognitive performance, cognitive decline or dementia in some studies could be due to the fact that such an association does not exist. It could also be a consequence of using too crude a model to estimate exposure, e.g. relying on the nearest monitor (Chen and Schwartz, 2009; Gatto et al., 2014; Ranft et al., 2009), or using models with a coarse (10 km by 10 km) grid structure to estimate exposure (Loop et al., 2015). The lack of an association could be because the environmental concentrations in the particular study were too low to cause an observable effect as suggested by Oudin et al. (2017). It might also be due to not appropriately accounting for confounding/effect-modifying factors. For instance, Oudin et al. (2016) found a statistically significant effect only when the analysis took into account the age of participants. Likewise, Tonne et al. (2014) found statistically significant associations between exposure and cognitive decline only in subjects who had never moved from London, which authors suggested to be a consequence of reduced exposure misclassification. A lack of association might also be related to the misalignment between etiologic exposure windows and the measured/modelled exposure windows. Some studies have used air pollutant concentrations over a previous 1–2 year period as a surrogate for chronic exposure. There is an inherent difficulty faced by studies that

Table 2
Summary of consistency of associations between exposure to air pollution or traffic measures and outcomes included in the literature review.

N	Reference	Cognitive function						Cognitive decline	MCI/incident cognitive impairm	Dementia	Hospitalizations	Brain imaging	Neurological biomarkers	Low medium income country
		Global	Executive function	Attention	Memory	Const prax coding abil	Language							
1.	(Sanchez-Rodriguez et al., 2006)	Urban vs Rural							Urban vs Rural				Urban vs Rural	Yes
2.	(Sun and Gu, 2008)	API												Yes
3.	(Ranft et al., 2009)	Traffic PM_{10}		Traffic PM_{10}										No
4.	(Wellenius et al., 2012)	Traffic BC	Traffic BC		Traffic BC		Traffic BC							No
5.	(Power et al., 2011)	BC												No
6.	(Colicino et al., 2016)	BC												No
7.	(Colicino et al., 2017)	BC												No
8.	(Gatto et al., 2014)	$PM_{2.5}$ O_3 NO_2	$PM_{2.5}$ O_3 NO_2		$PM_{2.5}$ O_3 NO_2									No
9.	(Ailshire and Crimmins, 2014)	$PM_{2.5}$												No
10.	(Ailshire et al., 2017)	$PM_{2.5}$												No
11.	(Tzivian et al., 2017)	$PM_{2.5}$			$PM_{2.5}$									No
12.	(Tallon et al., 2017)	$PM_{2.5}$ NO_2												No
13.	(Lin et al., 2017)	$PM_{2.5}$												Yes
14.	(Schikowski et al., 2015)	NO_x NO_2 PM_{10} $PM_{2.5}$ $PM_{2.5}$ abs traffic load	NO_2 NO_x PM_{10} $PM_{2.5}$ $PM_{2.5}$ abs traffic load	NO_2 NO_x PM_{10} $PM_{2.5}$ $PM_{2.5}$ abs traffic load	NO_2 NO_x PM_{10} $PM_{2.5}$ abs traffic load	NO_2 NO_x PM_{10} $PM_{2.5}$ $PM_{2.5}$ abs traffic load								No
15.	(Molina-Sotomayor et al., 2019)	Clean vs Polluted	Clean vs Polluted		Clean vs Polluted		Clean vs Polluted							No
16.	(Shin et al., 2019)	$PM_{2.5}$ PM_{10} NO_2 O_3 CO SO_2	$PM_{2.5}$ PM_{10} NO_2 O_3 CO SO_2	$PM_{2.5}$ PM_{10} NO_2 O_3 CO SO_2	$PM_{2.5}$ PM_{10} NO_2 O_3 CO SO_2									No
17.	(Cullen et al., 2018)		PM_{10} NO_2 $PM_{2.5}$ PM_{coarse} NO_x	$PM_{2.5}$ PM_{10} PM_{coarse} NO_2 NO_x	NO_2 $PM_{2.5}$ PM_{10} PM_{coarse} NO_x			PM_{10}, NO_2 $PM_{10-2.5}$ NO_x						No
18.	(Tonne et al., 2014)				$PM_{2.5}$ $PM_{2.5}$ exhaust PM_{10} PM_{10} exhaust		$PM_{2.5}$ $PM_{2.5}$ exhaust PM_{10}, PM_{10} exhaust	$PM_{2.5}$ $PM_{2.5}$ exhaust PM_{10} PM_{10} exhaust						No
19.	(Zhang et al., 2018)	API	API				API							Yes
20.	(Rafiee et al., 2020)	Low vs	Low vs	Low vs										Yes

N	Reference	Cognitive function						Cognitive decline	MCI/incident cognitive impairm	Dementia	Hospitalizations	Brain imaging	Neurological biomarkers	Low medium income country
		Global	Executive function	Attention	Memory	Const prax coding abil	Language							
48.	(Ilango et al., 2020)									Traffic, PM2.5, O3				No
49.	(Li et al., 2019)									PM2.5, NO2				Yes
50.	(Bowe et al., 2019)									PM10, NO2, O3, CO, SO2				No
51.	(Kioumourtzoglou et al., 2016)									PM2.5	PM2.5			No
52.	(Cerza et al., 2019)										PM2.5, PM10, PMcoarse, PM2.5 abs, NO2, NOx, Traffic load			No
53.	(Culqui et al., 2017)										PM2.5			No
54.	(Linares et al., 2017)										O3			No
55.	(Zanobetti et al., 2014)										PM2.5			No
56.	(Qiu et al., 2019)										PM2.5, PM10, PMcoarse			Yes
57.	(Wilker et al., 2015)											PM2.5, Traffic distance		No
58.	(Wilker et al., 2016)											PM2.5, Traffic distance		No
59.	(J.C. Chen et al., 2017; Chen et al., 2015)											PM2.5, Diesel PM		No
60.	(Casanova et al., 2016)											PM2.5		No
61.	(Power et al., 2018)											PM2.5, PM10		No
62.	(Hedges et al., 2019)											PM2.5, PM10, PMcoarse, NO2, NOx		No
63.	(Bos et al., 2011)												Traffic vs filtered air	No
64.	(Bos et al., 2013)												Urban vs rural	No
65.	(Liu et al., 2017)												PM2.5, PM10-2.5	No
66.	(Cliff et al., 2016)												Diesel exhaust	No
67.	(Calderon-Garciduenas et al., 2008)												Urban vs Rural	Yes
68.	(Calderon-Garciduenas et al., 2016)												Urban vs	Yes
N	Reference	Cognitive function						Cognitive decline	MCI/incident cognitive impairm	Dementia	Hospitalizations	Brain imaging	Neurological biomarkers	Low medium income country
		Global	Executive function	Attention	Memory	Const prax coding abil	Language							
69.	(Shaffer et al., 2019)												Rural, PM2.5	No

N	Reference	Cognitive function						Cognitive decline	MCI/incide nt cognitive impairm	Dementia	Hospitalizati ons	Brain imaging	Neurologica l biomarkers	Low medium income country
		Global	Executive function	Attention	Memory	Const prax coding abil	Language							
48.	(Ilango et al., 2020)									Traffic PM2.5 O3				No
49.	(Li et al., 2019)									PM10 NO2 O3 CO SO2				Yes
50.	(Bowe et al., 2019)													No
51.	(Kioumourtzoglou et al., 2016)									PM2.5	PM2.5			No
52.	(Cerza et al., 2019)										PM2.5 PM10 PMcoarse PM2.5 ab NO2 NOx Traffic load			No
53.	(Culqui et al., 2017)										PM2.5			No
54.	(Linares et al., 2017)										O3			No
55.	(Zanobetti et al., 2014)										PM2.5			No
56.	(Qiu et al., 2019)										PM2.5 PM10 PMcoarse			Yes
57.	(Wilker et al., 2015)											PM2.5 Traffic distance		No
58.	(Wilker et al., 2016)											PM2.5 Traffic distance		No
59.	(J.C. Chen et al., 2017; Chen et al., 2015)											PM2.5 Diesel PM		No
60.	(Casanova et al., 2016)											PM2.5		No
61.	(Power et al., 2018)											PM2.5 PM10		No
62.	(Hedges et al., 2019)											PM10 PM2.5 PMcoarse NO2 NOx		No
63.	(Bos et al., 2011)												Traffic vs filtered air	No
64.	(Bos et al., 2013)												Urban vs rural	No
65.	(Liu et al., 2017)												PM2.5 PM10,2.5	No
66.	(Cliff et al., 2016)												Diesel exhaust	No
67.	(Calderon-Garciduenas et al., 2008)												Urban vs Rural	Yes
68.	(Calderon-Garciduenas et al., 2016)												Urban vs	Yes
N	Reference	Cognitive function						Cognitive decline	MCI/incide nt cognitive impairm	Dementia	Hospitalizati ons	Brain imaging	Neurologica l biomarkers	Low medium income country
		Global	Executive function	Attention	Memory	Const prax coding abil	Language						Rural	
69.	(Shaffer et al., 2019)												PM2.5	No

A pollutant is displayed in red and orange background if it shows detrimental statistically significant associations in at least one cognitive test in a specific domain, or in any type of dementia.

A pollutant is shown in black and gray background if the associations reported do not reach statistical significance for any of the cognitive tests in the specific domain, or any type of dementia.

A pollutant is shown in green and green background if the associations reported reach statistical significance in at least one cognitive tests in a specific domain, or any type of dementia, and shows an effect counterintuitive (e.g. higher exposure related with better cognition). Green takes preference over red or black.

All studies report the effect of long-term exposure to air pollution with the exception of those reporting associations between short-term exposure to air pollution exposure and risk of hospitalizations.

Table 3
Summary of consistency of associations between long-term exposure to air pollution or traffic measures and brain imaging outcomes included in the literature review.

References	Total brain volume	brain parenchymal fraction	WM brain volume	WM frontal	WM parietal	WM temporal	WM occipital	GM brain volume	GM frontal	GM parietal	GM temporal	GM occipital	Deep gray	GM in AD areas	Corpus callosum	Hippocampal	Basal ganglia	Ventricle	WMH	Micro-bleed	Covert brain infarcts	Small Vessel Disease
	Total brain		White matter					Gray matter								Regions of interest			Cerebral vessel disease			
(Wilker et al., 2015)	PM$_{2.5}$ Traffic-Distance															PM$_{2.5}$ Traffic-Distance			PM$_{2.5}$ Traffic-Distance		PM$_{2.5}$ Traffic-Distance	
(Wilker et al., 2016)		PM$_{2.5}$ Traffic-Distance																	PM$_{2.5}$ Traffic-Distance	PM$_{2.5}$ Traffic-Distance		
(J.C. Chen et al., 2017; Chen et al., 2015)	PM$_{2.5}$ DPM		PM$_{2.5}$ DPM	PM$_{2.5}$ DPM	PM$_{2.5}$ DPM	PM$_{2.5}$ DPM		PM$_{2.5}$ DPM	PM$_{2.5}$ DPM	PM$_{2.5}$ DPM	PM$_{2.5}$ DPM				PM$_{2.5}$	PM$_{2.5}$	PM$_{2.5}$	PM$_{2.5}$ DPM				PM$_{2.5}$
(Casanova et al., 2016)			PM$_{2.5}$	PM$_{2.5}$	PM$_{2.5}$	PM$_{2.5}$	PM$_{2.5}$		PM$_{2.5}$	PM$_{2.5}$	PM$_{2.5}$	PM$_{2.5}$			PM$_{2.5}$	PM$_{2.5}$	PM$_{2.5}$					
(Power et al., 2018)	PM$_{2.5}$ PM$_{10}$												PM$_{2.5}$ PM$_{10}$			PM$_{2.5}$ PM$_{10}$						
(Younan et al., 2020)														PM$_{2.5}$								
(Hedges et al., 2019)																PM$_{2.5}$ PM$_{10}$ PM$_{coarse}$ NO$_2$ NOx						

A pollutant is displayed in red and orange background if shows detrimental statistically significant associations in at least one cognitive test in a specific domain, or in any type of dementia.
A pollutant is shown in black and gray background if the associations reported do not reach statistical significance for any of the cognitive tests in the specific domain, or any type of dementia.
A pollutant is shown in green and green background if the associations reported reach statistical significance in at least one cognitive test in a specific domain, or any type of dementia, and shows an effect counterintuitive (e.g. higher exposure related with better cognition). Green takes preference over red or black.
DPM is diesel particulate matter.

have to estimate exposures based on relatively recent data, to assess risks that may depend on earlier-life or life-course exposure, as in the case of dementia.

Table 2 summarizes the consistency of findings across the spectrum of studied outcome measures, whereas Table 3 focusses on consistency of evidence from brain imaging studies.

3.3.3. Specificity of association

Bradford Hill (1965) described specificity of association as a feature of causal associations. In the present case, the putative cause is exposure to air pollution and the effects include a decline in cognitive performance, an increase in the incidence of dementia, and structural changes in the brain that are associated with poor cognition and dementia. As regards the effects, the reviewed papers have assessed global cognition, performance in specific cognitive domains (e.g. memory, attention), cognitive decline, mild cognitive impairment, incidence of dementia, neurological structural changes and neuroinflammation.

All the reviewed papers considered air pollution as the putative cause. Many of them included variables related to traffic-associated air pollution, such as distance to the nearest busy road, or level of black carbon (a tracer of diesel exhaust). Some focused on particulate matter, for which traffic is a major source, although other sources (e.g. resuspension, secondary formation in the atmosphere) exist. A few studies focused on the effect of gaseous air pollutants, such as NO_2/NO_x and ozone, for which traffic is an important primary and secondary source respectively. Some of the studies that reported comparative associations with PM, NO_2 or O_3 exposures, or that compared effects of PM with those of traffic distance, showed a larger effect for the gases or traffic measure than for PM. For instance, Schikowski et al. (2015) reported a stronger association with NO_2 than PM_{10} for constructional praxis; Chen and Schwartz (2009) reported a larger effect for O_3 than for PM_{10} on learning recall and short-term memory; Wellenius et al. (2012) found a stronger effect on immediate recall for exposure to traffic than exposures to BC. However, there were studies that showed a larger effect for PM than for other air pollutants. For instance, Tzivian et al. (2016) reported a larger effect for $PM_{2.5}$ than for NO_2 on amnestic MCI; and Gatto et al. (2014) ranked responses: $PM_{2.5} > O_3 > NO_2$ for verbal learning. For dementia, some studies found a larger effect for $PM_{2.5}$ than for gases (e.g. H. Chen et al., 2017a), whilst others found the opposite (Jung et al., 2015; Wu et al., 2015).

Overall, many different air pollutants have been considered, all associated with traffic emissions – although not exclusively so. It remains unclear which individual air pollutant or pollutants may be responsible for the effects observed.

Bradford Hill (1965) acknowledged that one-to-one relationships are infrequent and that several causes might have the same effect. This is indeed the case here, where several putative causes (air pollutants) and, also, confounding factors (described in detail below) might affect cognitive decline. Conversely, one agent, i.e. air pollution, might influence a variety of health outcomes, including different types of cancer, cardio-respiratory diseases, reproduction, cardio-metabolic disease and mortality (Dehbi et al., 2017; Gowers et al., 2012; Pope and Dockery, 2006; Pope et al., 2015; Samoli et al., 2016; Sram et al., 2005). A familiar example is smoking, which is associated with multiple adverse health outcomes. Hence, Bradford Hill (1965) emphasized the importance of identifying an underlying factor linking cause and effect (e.g. a specific biological mechanism linking exposure to air pollution with cognitive decline or dementia).

3.3.4. Temporality

Almost all reviewed studies have focused on the possible effects of chronic exposure to air pollutants. Such studies imply a sustained exposure to air pollutants prior to the discovery of effects and thus support a temporal relationship between exposure and effect. Only a few studies had a longitudinal design, with measurement of cognitive indices at baseline and follow-up, and exposure to air pollutants estimated from

the subjects' residential addresses. Most of the reviewed studies made the assumption that differences between recently measured exposures (or pollutant concentrations) closely reflect those in the past. Other studies estimated long-term exposure to air pollutants. The current section analyses temporality, focussing particularly on results from classical longitudinal studies.

The longitudinal studies that have estimated exposures over long periods of time have demonstrated significantly faster decline in cognition in participants with higher pollution exposures (Cleary et al., 2018; Lo et al., 2019; Tonne et al., 2014; Weuve et al., 2012; Wurth et al., 2018). The findings are supported by cross-sectional studies, showing that subjects exposed to the highest levels of (estimated) long-term air pollution performed worst in cognitive tests (Power et al., 2011; Ranft et al., 2009; Zeng et al., 2010) and had the highest hazard ratio for incident dementia (H. Chen et al., 2017b).

On the other hand, a longitudinal analysis in the Betula study in Northern Sweden did not find any association between long-term exposure to ambient NO_x and change in episodic memory, a marker of early cognitive decline. The authors suggested that the lack of an effect could be related to the low NO_x exposures of participants (estimated from outdoor exposure models), to other exposures such as domestic wood burning (an indoor source contributing to NO_2 exposure) not captured in their exposure model or to attrition in cognitively compromised participants (Oudin et al., 2017). Two follow-up analyses on participants in the Betula Study found that $PM_{2.5}$ from local residential wood burning and from traffic sources was associated with dementia incidence (Oudin et al., 2018), and that NO_2 from traffic was linked to a higher risk of developing dementia (Andersson et al., 2018).

3.3.5. Biological gradient

One of the Bradford Hill features requires the existence of a biological gradient, i.e. larger effects with higher exposures. Epidemiological analysis is based on regression analysis to define a gradient. If the coefficient and confidence intervals linking exposure with health effect have statistical significance, then it is accepted that the regression line suggests a real association and the gradient is established.

Significant dose-response functions (i.e. coefficients and 95% confidence intervals) are summarized in Tables S1 to S6 (Supporting Information) for global cognitive performance (Power et al., 2011; Sun and Gu, 2008; Zeng et al., 2010), executive function (Ranft et al., 2009; Wellenius et al., 2012), coding ability, attention (Chen and Schwartz, 2009), memory (Ailshire and Clarke, 2015; Chen and Schwartz, 2009; Wellenius et al., 2012), and language (Wellenius et al., 2012).

Table S7 reports dose-response functions for cognitive decline (Cacciottolo et al., 2017; Weuve et al., 2012), and memory decline (Ailshire and Crimmins, 2014; Tonne et al., 2014). Table S8 reports dose-response function for mild cognitive impairment.

Table S9 reports dose-response function for dementia and NO_2/NO_x (Andersson et al., 2018; Carey et al., 2018; Chang et al., 2014; H. Chen et al., 2017a), O_3 (Jung et al., 2015; Wu et al., 2015), PM (Cacciottolo et al., 2017; Carey et al., 2018; H. Chen et al., 2017a; Jung et al., 2015; Oudin et al., 2018; Wu et al., 2015) and traffic (Carey et al., 2018; H. Chen et al., 2017b).

All the statistically significant coefficients suggest a biological gradient. But it should also be noted that a constant dose-response has not been observed in all studies (Loop et al., 2015; Oudin et al., 2017).

3.3.6. Biological plausibility

There are several plausible mechanisms that could account for a link between air pollution and dementia. A detailed description of the toxicological evidence relating air pollution to risk of dementia is provided in the COMEAP report (COMEAP, in preparation).

The work investigating the mechanisms by which air pollutants might damage the brain began with a focus on ozone and has evolved to include ambient particles and, especially, metal-rich particles. Interest has focused on the initiation of an inflammatory response in the

brain (Block and Calderon-Garcidue nas, 2009; Gonzalez-Guevara et al., 2014; Heusinkveld et al., 2016; Levesque et al., 2011a; Levesque et al., 2011b) and the role of oxidative stress (Cole et al., 2016; Farfán-García et al., 2014; Guerra et al., 2013; Heusinkveld et al., 2016; Kalita et al., 2018; M'Rad et al., 2018; Rodríguez-Martínez et al., 2013). Both biological mechanisms have been implicated in neurodegenerative conditions such as cognitive decline and dementia (Calderon-Garciduenas et al., 2011; Calderon-Garciduenas et al., 2004; Calderon-Garciduenas et al., 2008). It is not clear whether the effects of pollutants are locally generated (i.e. resulting from a pollutant or reaction by-product which has entered the brain), or are secondary to adverse effects on the lung or in the systemic circulation. Nor is it clear whether the oxidative stress is the cause or the result of the neuroinflammation.

Air pollution has also been reported to be associated with accumulation of $A\beta 42$ and other misfolded protein aggregates (Calderon-Garciduenas et al., 2012; MohanKumar et al., 2008), changes in the blood-brain barrier (Block and Calderon-Garcidue nas, 2009; Liu et al., 2017), and white matter lesions (Calderon-Garciduenas et al., 2012; Calderón-Garcidueñas et al., 2015; Guxens and Sunyer, 2012) reflecting small vessel disease. The cerebrovascular changes are in keeping with a large body of evidence indicating that air pollution increases the risk of ischaemic cardiac and cerebral vascular disease (COMEAP, 2018). It is possible that age may affect the susceptibility to the effects of air pollutants on the brain (Mumaw et al., 2016a; Rivas-Arancibia et al., 2000; Woodward et al., 2017). However, the evidence on this is not yet clear.

3.3.7. Coherence of evidence

The reviewed studies provide coherent evidence that chronic exposure to air pollution has a deleterious impact across a range of interrelated outcome measures: cognitive performance, cognitive decline, memory, attention, constructional praxis, morphological changes in the brain (most notably white matter atrophy), alterations of neurological biomarkers, as well as incidence of dementia, aggravation of symptoms of dementia, and hospitalizations related to dementia. The consistency with which air pollution has been associated with adverse effects across a wide range of endpoints indicates a considerable level of coherence between the findings of the reported studies.

3.3.8. The experiment (reversibility)

Before discussing reversibility, it is important to consider this concept in the context of cognitive decline and dementia, as many of the potential underlying pathological alterations (e.g. formation of neurofibrillary tangles, degeneration of neurons, infarction of brain tissue) are unlikely themselves to be reversible. In the present discussion, reversibility refers to changing the slope of the biological gradient. For example, moving to a less polluted area might slow the rate of cognitive decline, reduce the incidence of dementia or increase the age of onset. This is a field of study that merits further research, as there is a paucity of evidence of the effect on cognitive trajectories of changing individual exposure to air pollution. Quasi-experimental designs where reversibility might be assessed include natural experiments that take account of policy changes aimed at mitigating air pollution (e.g. London Emission Zone, Dublin coal ban), in addition to carefully designed migration studies. Animal studies on reversibility of behavioural, imaging, biochemical or neuropathological markers of cognitive impairment would be complementary.

3.3.9. Reasoning by analogy

Although the mixtures of toxicologically active species are not identical, smoking can be considered as a high-dose parallel of the effects of ambient air pollutants on cognitive decline and dementia. The risk of developing Alzheimer's disease (as diagnosed clinically) was found to be significantly higher in active than former smokers (Durazzo et al., 2014; Ott et al., 1998; Peters et al., 2008). The risk of developing dementia and cognitive decline tended also to be greater in smokers than non-smokers or never-smokers, although this association did not

reach significance (Peters et al., 2008). Overall, the comparative risk of dementia associated with smoking - a high-dose parallel of ambient air pollutants - suggests that, once the source of toxic exposure is removed, the speed of cognitive decline or dementia progression slows, and there is evidence that white matter damage associated with smoking declines on cessation of smoking (Gons et al., 2011). If this were true for air pollution, it would have important consequences for public health policies, as reductions on air pollution exposure would be expected to reduce the rate of cognitive decline and the incidence of dementia.

3.4. Confounding factors

Identifying and controlling/adjusting for confounding factors in the assessment of the effects of air pollution on cognitive decline and dementia is difficult as there is much that we still do not know about factors that affect cognition and cerebrovascular health. For instance, a recent paper reported an association between air pollution and depression and anxiety (Roberts et al., 2019); yet depression (Onwby et al., 2006) and anxiety (Wilson et al., 2011) have also been identified as potential risk factors for cognitive decline and dementia. Hence further research is required to understand whether depression and anxiety act as confounders or mediators of an association between air pollution and dementia.

Factors that should be considered in the analysis of the effects of air pollution on cognitive decline and dementia include age, sex, education, socioeconomic status, ethnic background, smoking, alcohol intake, body mass index, co-morbidities - such as cardiovascular disease, cerebrovascular disease, diabetes and mental health - and sleep deprivation. Other factors related to exposures should include exposure to noise, environmental tobacco smoke (ETS), indoor sources (e.g. indoor biomass/wood burning), neurotoxicants (e.g. lead, mercury, pesticides, persistent organic pollutants) from dermal and/or dietary exposure routes.

Most of the studies we have reviewed have adjusted for a number of standard confounding factors such as personal characteristics and socioeconomic factors, (mainly age, sex, educational attainment) and co-morbidities (Killin et al., 2016; Tzivian et al., 2015a) that might have affected the observed association between air pollution and cognition or brain structure. Adjustments for other possible confounding factors were made in some studies, but this has been highly variable (Killin et al., 2016). Tables S1 and S12 detail the list of confounding factors that have been considered in the reviewed studies.

Studies have adjusted for individual-level factors when available. Area-level adjustment has been implemented when the relevant individual-level information was not available (e.g. H. Chen et al., 2017b adjusted for area-level socioeconomic factors and for individual-level co-morbidities: diabetes, brain injury). Individual-level adjustment would be expected to enhance accuracy and reduce bias. However, Goodman et al. (2011) concluded that limited residual socio-economic confounding existed in epidemiological studies that included comprehensive area-level adjustment. However, this cannot be extrapolated to other potential confounders, such as smoking, drinking or pre-existence of comorbidities, where area-level indicators might not be adequate.

Other factors that should ideally be considered in epidemiological analysis include social integration and participation in social networks (Zunzunegui et al., 2003), physical activity, contact with nature (i.e. access to green and blue spaces) (de Keijzer et al., 2019), sleep quality and quantity (Bliwise, 1993; Ju et al., 2013), depression, anxiety and stress (Wilson et al., 2011), all of which have been linked to cognitive performance and decline. With the exception of depression, stress and anxiety, these factors have not been accounted for in any of the reviewed studies.

Thus, although most of the studies have controlled for standard confounding factors, there are many possible confounders for which the studies have not accounted. Despite all the efforts to account for

potential confounding in the reviewed papers, possible residual confounding cannot be completely ruled out. Further research should include additional confounding factors identified (e.g. social interactions, sleep, physical activity) and should investigate whether the observed associations with traffic exposure reflect exposure to air pollution or some other correlated factor such as poorer socio-economic status, noise, or any of the myriad features of urban living.

The next section details the different confounding factors that have been included in the reviewed studies.

3.4.1. Review of evidence on confounding factors

It is possible that the neurocognitive responses considered in the studies reviewed here may not be caused by exposure to air pollution. Instead, they may reflect effects on cognition of other factors acting at different ages (Clifford et al., 2016). This section describes several putative causes and confounding factors that should be considered when investigating the association between exposure to air pollution and cognitive impairment. For a high probability of causality to be inferred, the Bradford Hill characteristics of causal associations should be established in the absence of confounding, or after controlling for any confounding factor that could not be removed in the studies reviewed.

Environmental factors other than air pollutants of current interest could also contribute to associations between air pollution and cognitive decline. Past chronic exposure to lead, e.g. from leaded gasoline, could confound the observed associations, since lead exposure is associated with poor cognitive functioning (Bakulski et al., 2012). In addition, lead exposure could still play a part as it is a minor constituent of air pollution from sources such as tyre wear and incinerators (Sanderson et al., 2014). Power et al. (2011) adjusted for past lead exposure and did not report significant changes in their results. Other environmental neurotoxicants, such as mercury, polychlorinated biphenyls, pesticides and ionizing radiation could also play a part or act as confounding factors (Xu et al., 2016). Whilst multiplicative and additive effects of these neurotoxicants with air pollution are possible, none of the reviewed studies has examined such an interaction (Xu et al., 2016).

Smoking and, in non-smokers, ETS has been associated with cognitive impairment (Llewellyn et al., 2009) and increased risk of dementia (Chen, 2012; Ott et al., 2004). Drinking alcohol is another potential confounding factor (Sabia et al., 2018; Xu et al., 2016).

The association between air pollution and Body Mass Index (BMI) is still unclear. BMI has been associated with lower cognitive ability (Dahl et al., 2010; Kerwin et al., 2010) and more rapid cognitive decline in later life (Dahl et al., 2010), and with global reduction and regional alterations in gray matter volume in healthy adults (Taki et al., 2008). In contrast, Deschamps et al. reported that elderly subjects with a BMI >23 had a lower risk of cognitive decline than did those with a BMI <23 (Deschamps et al., 2002). Traffic pollution was associated with increased BMI in children in a Southern California cohort (Jerrett et al., 2014), and with obesity, higher fat content and larger BMI in adults participating in The Framingham Heart Study (Li et al., 2016). Further studies are required to disentangle whether BMI is mediating the association between exposure to air pollution and cognitive decline, or is a confounder.

Indoor and personal exposures may differ from those estimated by means of geostatistical or proximity models used in most of the reviewed studies (Clifford et al., 2016; Xu et al., 2016). However, studies which adjusted for smoking (Ranft et al., 2009; Sun and Gu, 2008; Wellenius et al., 2012), ETS exposure (Ranft et al., 2009; Schikowski et al., 2015), alcohol consumption (Chen and Schwartz, 2009; Power et al., 2011; Sun and Gu, 2008; Weuve et al., 2012) and for indoor sources of pollution (Chen and Schwartz, 2009; Ranft et al., 2009) in their analyses still reported statistically significant associations between air pollution and cognitive performance.

Noise has been suggested as an environmental factor affecting cognitive performance. A study of police officers and office workers showed an effect of noise on arithmetic performance and logical reasoning, as well as on attention (Chiovenda et al., 2007), but authors did not investigate the possible interaction between air pollution and noise. Recent studies conducted in the Heinz Nixdorf Recall study found that noise acts synergistically with air pollution on global cognition and MCI (Tzivian et al., 2017). Air pollution had negative effects on general cognition irrespective of the noise level but the effect was more pronounced at higher noise levels. Noise showed a detrimental effect in relation to cognitive performance in single-agent models, but in two-pollutant models the negative effect remained only when higher concentrations of pollution were considered (Tzivian et al., 2017). Similar results were found when the effects of air pollution and noise on mild cognitive impairment (MCI) were investigated. Associations between $PM_{2.5}$ and MCI were stronger in participants with high noise exposure, whilst the effect of noise was enhanced in those subjects exposed to higher $PM_{2.5}$ concentrations (Tzivian et al., 2016). Carey et al. (2018) found in a London study that the effect of noise on incidence of dementia was no longer statistically significant when adjusted for $PM_{2.5}$ or NO_2. Likewise, no association was found between road traffic noise and risk of developing dementia in the Betula study: the effect of NO_2 was not modified by adjusting for noise, nor was significant interaction found between noise and NO_2 on dementia risk (Andersson et al., 2018). Short-term noise exposures have been associated with increased daily dementia-related hospital admissions (Linares et al., 2017). Few of the epidemiological studies reviewed adjusted for noise levels.

Reduced exposure to green spaces could also be a confounding factor. However, evidence of the effect of "greenness" on cognition is limited. Studies in children suggest that "lifelong residential greenness" is associated with increased attention and reduced reaction time (Dadvand et al., 2017), with greater progress in the development of working memory over a calendar year (Dadvand et al., 2015) and with higher cerebral gray and white matter volumes in regions associated with better working memory and reduced inattentiveness (Dadvand et al., 2018). Controlled laboratory studies of adults have indicated that access to green spaces may buffer stress and facilitate cognitive restoration after mental fatigue (Berto, 2005; Mantler and Logan, 2015).

Socioeconomic factors could also play a role. Several potential individual-level and area-level socioeconomic factors could affect the relationship between air pollution exposure and cognitive and neurodegenerative health outcomes. Deprived neighbourhoods are more likely to experience high levels of air pollution (Xu et al., 2016) and lower educational attainment, the latter being associated with an increased risk of dementia later in life (Stern, 2012). Power et al. (2016) suggested that socio-cultural background may affect the associations between air pollution and cognitive performance, whereas cognitive decline was less susceptible to socio-cultural background factors. Socioeconomic factors were also suggested to explain Xu et al.'s (2017) results of more rapid cognitive decline in residents of rural than urban areas, a finding at odds with the broad conclusions of the reviewed literature. The authors suggested that this effect might have been related to poor access to socioeconomic benefits, such as health care and retirement pensions, for subjects living in rural areas (Xu et al., 2017).

Sex has been identified as a confounder in a study which showed a stronger association in women than men between $PM_{2.5}$ exposure and cognitive disability in low and middle-income countries, although this finding could also have related to inadequately controlling for differences in indoor air exposure to pollutants (Lin et al., 2017). Poor early cognitive development is another possible confounder. People with lower cognitive development are likely to have poorer occupational prospects and lower socioeconomic status, and may be more exposed to pollution and subject to other risk factors for dementia (e.g. smoking) later in life.

Pre-existing comorbidities, such as stroke (Bejot et al., 2011; Kalaria et al., 2016), hypertension (Faraco and Iadecola, 2013), diabetes mellitus (Biessels et al., 2006), and depression (Byers and Yaffe, 2011; Tallon et al., 2017) increase the risk of cognitive decline and dementia.

Several of the reported studies excluded individuals with history of stroke or chronic disease. On the other hand, such exclusion may have affected the results by over-controlling for mediating factors (Clifford et al., 2016). Some studies which included adjustment for factors related to cardiovascular disease have shown an attenuation of pollution effect (Chen and Schwartz, 2009; Loop et al., 2013), suggesting that cardiovascular health could be contributory factor to the effect of air pollution on cognitive performance (Tzivian et al., 2015a).

3.5. Effect modifiers

Several possible effect modifiers, e.g. factors potentially influencing the coefficients linking air pollutant concentrations with effects on the brain, have been identified. These include *APOE* ε4, single nucleotide polymorphisms in microRNA (miRNA) processing genes, telomere length in leukocytes, pre-existent medical conditions (including diabetes mellitus, cardiovascular disease, cerebrovascular disease, mental health problems), BMI, smoking, alcohol consumption, sex, education (a surrogate of cognitive reserve) and neighbourhood social stressors.

The evidence for each of these factors is detailed below. In general, effect modifiers have been investigated in very few studies, and replication would be required to confirm or exclude any of the factors as effect modifiers. Very few potential effect modifiers have been investigated in more than one study, and the findings have been inconsistent: *APOE* ε4 (1 of 6 studies), diabetes mellitus (2 of 4), cerebrovascular disease (2 of 3), mental health problems (1 of 2), body mass index (1 of 2), sex (1 of 2). Pre-existing cardiovascular disease was rejected as an effect modifier in 3 of 3 studies and smoking was confirmed as an effect modifier in 2 of 2 studies.

3.5.1. Review of evidence on effect modifiers

In the SALIA cohort study, possession of *APOE* ε4 was associated with significant stronger concentration-effect relationships between traffic (p-value$_{interaction}$ = 0.0069) and PM$_{2.5abs}$ (p-value$_{interaction}$ = 0.0380) and reduced constructional praxis (Schikowski et al., 2015). Cacciottolo et al. (2017) reported that exposure to PM$_{2.5}$ was associated with larger hazard ratios for cognitive decline and dementia among ε4 carriers but that these interactions were not statistically significant. Cleary et al. (2018) reported faster cognitive decline rates in subjects harbouring at least one ε4 allele but the p-value$_{interaction}$ was not reported (Cleary et al., 2018). Wu et al. (2015) found no significant interactions between ε4 and air pollution for Alzheimer's disease or vascular dementia. Similarly the Betula study found no evidence for a modifying of ε4 on the association between NOx exposure and all-type dementia or AD (p-value for interaction >0.30 for both) (Oudin et al., 2019).

miRNAs are involved in neuroplasticity, neurodevelopment, synapse formation and maturation, and stress responses (Sharma and Lu, 2018). Altered miRNA levels have been reported in a variety of neurological disorders (Femminella et al., 2015; Maes et al., 2009; Miya Shaik et al., 2018; Sharma and Lu, 2018; Swarbrick et al., 2019), and in a rat model of vascular dementia (Ren et al., 2018). Single nucleotide polymorphisms in miRNA-processing genes were reported to affect the association between BC exposure and global cognition and MMSE scores (Colicino et al., 2016). The association between BC and MMSE was stronger in heterozygous carriers of the single nucleotide polymorphism rs11077 in gene *XPO5* (OR = 1.99; 95% CI 1.39–2.85; p-value$_{interaction}$ = 0.01, False Discovery Rate (FDR) = 0.09) and minor variant carriers of polymorphism rs2740348 in gene *GEMIN4* (OR = 1.34; 95% CI 1.05–1.7; p-value$_{interaction}$ = 0.01, FDR = 0.13). The association between BC and global-cognition was stronger in heterozygous carriers of polymorphism rs4968104 (SD −0.10; 95% CI −0.18 to −0.02; p-value$_{interaction}$ = 0.004, FDR = 0.04), and rs910924 (SD −0.09; 95% CI −0.17 to −0.02; p-value$_{interaction}$ = 0.01, FDR = 0.04) in *GEMIN4* relative to the major variant. All results are considered relevant for FDR < 0.15.

Leukocytes with longer telomere length have been shown to be more responsive to inflammatory stimuli. In a study of older men, Colicino et al. (2017) reported that the association between BC concentration and reduced cognitive function was strongest in those with longer leukocyte telomeres (p-value$_{interaction}$ = 0.04). A similar increase in effect was seen in those with high C-reactive protein levels (p-value $_{interaction}$ = 0.04). This work supports a link between inflammation and effects of air pollution on the brain.

Pre-existent medical conditions have been suggested as effect modifiers, although results are inconclusive. Subjects with diabetes mellitus (DM) or who had suffered a stroke had lower hazard ratios for dementia in association with PM$_{2.5}$ exposure in a study in Canada (p-value $_{interaction}$ = 0.003 and 0.030, respectively) (H. Chen et al., 2017a). The authors suggested that the additive effect from pollution might have been masked by the heightened baseline risk profile of patients with these comorbidities (H. Chen et al., 2017a). A recent London-based study found higher (and statistically significant) adjusted hazard ratios for incidence of dementia due to exposure to NO$_2$ in subjects without co-morbidities (i.e. IHD, stroke, DM or heart failure), although the interaction with comorbidities was non-significant (p-value $_{interaction}$ = 0.31) (Carey et al., 2018). The associations between exposure to PM$_{2.5}$ and diesel PM with white matter or gray matter volumes, mild cognitive impairment or dementia were not significantly modified by existing cardiovascular disease or DM, with the exception of diesel PM and gray matter parietal volumes, which varied with DM (p-value $_{interaction}$ = 0.03) (J.C. Chen et al., 2017). Tallon et al. (2017) did not find any influence of DM or hypertension on the association between air pollution (PM$_{2.5}$ and NO$_2$) and changes in cognitive function. However, the effect of PM$_{2.5}$ on cognitive decline was more pronounced in those without pre-existing stroke (p = 0.046), anxiety (p = 0.03) or stress (p = 0.01), all factors with p-value for interaction <0.05 (Tallon et al., 2017). On the other hand, Tzivian et al. (2016) found that whilst associations between PM$_{2.5}$ and mild cognitive impairment were stronger in subjects with depressive disorders, the interaction was non-significant (p-value $_{interaction}$ = 0.43). On a similar note, the National Social Health and Aging Project (NSHAP) cohort study examined the effect of mood disorders on the association between air pollution and cognitive decline and found that the impacts of PM$_{2.5}$ and NO$_2$ on cognitive performance were mediated by depression and stress, respectively (Tallon et al., 2017).

BMI was suggested as an effect modifier of the association between PM$_{2.5}$ and white matter volume in the parietal association region (p-value $_{interaction}$ = 0.03) and the association between diesel PM and ventricular volume (p-value $_{interaction}$ = 0.03) (J.C. Chen et al., 2017). BMI was not found to modify the association between PM$_{2.5}$ or NO$_2$ with changes in cognitive function (Tallon et al., 2017).

Smoking was reported to modify the effect of air pollution on cognition (p-value $_{interaction}$ = 0.02–0.04) (Ailshire and Crimmins, 2014; Tzivian et al., 2016). In addition, Tzivian et al. (2016) found that the association of PM$_{2.5}$ with mild cognitive impairment was stronger in subjects with no or moderate alcohol consumption (p-value $_{interaction}$ = 0.05) (Tzivian et al., 2016).

Sex may affect the association between exposure to air pollution and cognitive decline (Tzivian et al., 2015a). The detriment of performance on verbal tests was greater in elderly men than women exposed to air pollution in China, for a mean air pollution index representative of 30 days (p-value $_{interaction}$ < 0.01), 1 year and 3 years (p-value $_{interaction}$ < 0.05) (Zhang et al., 2018). A London-based study also reported a larger effect of air pollution on incidence of dementia in men, although this interaction was non-significant (Carey et al., 2018).

Education was investigated by Wellenius et al. (2012) and shown to modify the odds ratio of achieving a low score (<26) in the MMSE global cognition test (p-value $_{interaction}$ = 0.007) on an IQR decrease in residential distance to a major roadway (851 m), with a higher OR for subjects who had received college or higher education. A similar modifying effect of education was suggested for the association between IQR

decrease in residential distance to traffic roadside and trail-making test part B scores measuring executive function, but this was non-significant (p-value $_{interaction}$ = 0.085) (Wellenius et al., 2012).

Ailshire et al. (2017) reported an interaction (p-value$_{interaction}$ < 0.05) between air pollution and neighbourhood social stressors and reduced cognitive performance. A stronger inverse association between $PM_{2.5}$ and cognitive function was found among those subjects exposed to stressful neighbourhood conditions (i.e. general lack of upkeep of the neighbourhood, litter in the streets, deteriorating buildings, empty properties) (Ailshire et al., 2017). The findings remained significant after adjustment for several individual and community-level socioeconomic and demographic factors. The synergy between air pollution and neighbourhood stress in causing poor cognitive performance is consistent with the hypothesis that exposure to stress increases neuronal damage in response to toxic challenges (McEwen and Tucker, 2011).

3.6. Strengths and limitations of the literature reviewed

The reviewed papers cover a wide range of study designs, including longitudinal, case-control, cross-sectional, and time-series analysis from population-based and prospective cohorts. There are several large studies, with 8000 to 9.8 million subjects. Most of the studies met acceptable quality standards as far as cognitive tests, neuro-imaging and statistical methods are concerned.

Limitations include the difficulty in quantifying exposure and the risk of temporal and spatial misalignment, due to reliance on surrogate measures of exposure and the dependence on modeling and geostatistical interpolation. There are also limitations in the extent to which some of the endpoints studied (e.g. decline in attention) can be linked to mild cognitive impairment or dementia. Because of their spatial and temporal correlation, it is difficult to separate the effects of a variety of air pollutants. And although most of the studies have controlled for relevant confounding factors, not all studies have controlled for the same factors, and there remains the possibility of residual confounding. The strengths and limitations of the reviewed studies are discussed below.

The quality of most reviewed studies was adequate, after consideration of the exposure and outcome assessment and inclusion of confounding factors.

All of the studies on cognitive performance used standard cognitive tests. The MMSE has been widely used to assess general cognitive performance as well as cognitive impairment, though it was specifically designed as a screen for early impairment and is relatively poor at assessing some aspects of cognitive performance (Tombaugh and McIntyre, 1992). The threshold used to define impairment in the MMSE test varied among different studies from 18 to 26 out of a maximum score of 30 (Peters et al., 2015). In addition, whilst many studies focused on general cognition, relatively few analysed the cognitive domains comprehensively. For instance, Chen and Schwartz (2009) studied the effects of air pollution on attention, short-term memory, constructional praxis and coding ability, whilst Wellenius et al. (2012) focused on immediate, delayed and working memory, and language. Many other studies focused only on only one cognitive domain. Some studies assessed the effect of air pollution on dementia using prevalence and incidence of dementia documented in medical records (e.g. ICD-9 codes), which can lead to substantial misclassification. For example, a US-study identified that, in only 56% of subjects classified as having a dementia-associated disease according to their Medicare claims records, could the diagnosis be confirmed by more detailed clinical assessment (Taylor et al., 2009). This may be an example of over-diagnosis but under-diagnosis is also a problem since only around half of cases in the community are known to clinical services. Under-diagnosis in medical records may not be independent of air pollution exposure since subjects exposed to elevated air pollution are at higher risk of cardiorespiratory conditions, leading to frequent interaction with the medical community and perhaps an increased likelihood of diagnosis of dementia. Consistent with the advice of Power et al. (2016), some caution should be

exercised in interpreting the findings of studies relying on ICD-9 codes to evaluate the effect of air pollution on dementia.

Some cohort studies have included representative sex and ethnicity strata, whilst others included one sex only (e.g. Weuve et al., 2012) or assessed only a selected population group (e.g. Ranft et al., 2009). The age of the participants has been diverse though most studies have focused on the elderly, who are at greater risk of cognitive decline. However, subjects with the highest exposure and/or poorest levels of cognition are less likely to participate in this type of study and are more likely to discontinue participation in longitudinal studies, leading to selection bias. Some studies are clearly not representative of the general population (e.g. Wurth et al., 2018).

Most of the reviewed articles included versions of logistic and linear regression with adjustment for a range of relevant potential covariates, although some made very crude adjustments for socio-demographic confounders. Hence, the possibility of residual confounding remains. Those studies which appropriately adjusted for socio-demographic covariates tended to report associations. The magnitude of the risks reported from individual studies will be a function of the health outcomes and exposures to air pollution. Exposures need to be assigned to health outcomes, with both aligned in space and time, the latter allowing for the expected lag between exposures and outcome.

In the case of spatial alignment, assigning exposures to individuals and/or populations in an observational study will, of necessity, often involve a degree of approximation. Exposures are commonly based on measurements from ground monitors that are located in proximity to an individual's place of residence, or the average of measurements within an administrative area in which a population resides. Alternatively, assignment of exposures may be based on modelled concentrations, again often at the place of residence or, in aggregated form, to an administrative area. The use of air quality monitors, geo-statistical modeling, or surrogate measures of exposure based on distance to major roads may not adequately reflect individual exposures of subjects participating in the cohort studies. None of the studies has determined individual exposures or adjusted for personal activity patterns. The approaches used in the reviewed studies might be valid for pollutants that disperse homogeneously over the urban landscape (e.g. $PM_{2.5}$), but would be less appropriate for pollutants with a heterogeneous distribution influenced by local sources (e.g. BC, NO_x, O_3) or with shorter persistence times (e.g. $PM_{10-2.5}$). Measurement error may also explain some of the inconsistencies observed in the cognitive effect estimates.

Temporal alignment of health outcomes and exposures over time can be problematic due to the lack of availability of measurements (and/or modelled estimates) for specific pollutants of interest over the required time period, especially where long-term exposure is of interest. This can lead to misclassification of exposure over both space and time.

Examples of temporal misalignment include studies in which exposure data were gathered at times different from those of the cognitive tests (generally prior to cognitive testing), which is in line with the Bradford-Hill temporality feature of causality. Many of the reviewed studies assessed chronic exposure to air pollution at the current residence of the participants, using a single mean or a composite chronic exposure measure covering less than a 5-year period. Many studies used shorter periods (e.g. 1–2 year) (e.g. Ailshire and Clarke, 2015; Wilker et al., 2015), whilst other studies and those assessing incident dementia considered exposures of up to 7–14 years (H. Chen et al., 2017a; J.C. Chen et al., 2017; Jung et al., 2015; Wu et al., 2015). It may be important to assess the cumulative exposure of a subject given the residential history. However, length of residence at the same residential address was not mentioned in most of the studies. For those subjects who had changed residence, current residential exposures may not be good surrogates of long-term exposures. The approach might be appropriate if the measured and aetiological windows were close in time but the validity is questionable over longer intervals (Power et al., 2016). This is of special relevance in the current discussion, since the development of dementia involves a long prodromal phase, generally over 2 or

more decades. Hence recent exposures might not be reflective of the window of exposure critical for the health effect under consideration.

Many of the studies have a cross-sectional design. If the impact of air pollution on cognition is subtle, multiple testing with detailed neuro-psychological tests over time would be required to observe any significant effect. Hence, longitudinal design including multiple cognitive testing and exposure measurements over a period of time would be very useful to identify critical or sensitive periods within the life course.

Studies that included a large variation in estimated exposure were more likely to report significant associations, whereas those with small exposure variability were more likely to yield heterogeneous or largely null results. The magnitude and significance of risks may be sensitive to the characterisation of exposures in statistical models that are used to estimate the risks (and associated measures of uncertainty). The relationships between exposures and health outcomes may be non-linear but the use of non-linear models (for the exposure-health relationship) is not common in this setting. If the relationship is non-linear, then assuming linearity may result in biased estimates of risk. This may be overcome to some extent by categorising exposures but the choice of boundaries for individual categories can itself have an effect on the resulting risk estimates. In addition to the issues associated with the exposure-outcome relationship, the uncertainty associated with estimated exposures when using modelled estimates, or the temporal misalignment between exposures and health outcomes is rarely acknowledged. A complex form of 'measurement error' (Gryparis et al., 2009), can result in bias in both estimates and associated uncertainties and thus potentially in subsequent conclusions based on significance.

Bradford Hill's guidelines are mainly focused on avoiding Type I errors: i.e. rejecting the null hypothesis (i.e. that there is not an effect) when in fact it is true. It can be argued that under the precautionary principle, the Type II error, making the opposite mistake and accepting the null hypothesis that there is no effect when in fact there is an effect (i.e. the null hypothesis is false) is more important when public health is at risk. The problem in statistical terms is that as the risk of making a Type I error reduces, the risk of making a Type II error increases. The likelihood of avoiding a Type I error is defined by the p value (commonly 0.05); whereas the capability to avoid a Type II error is defined by the power of the statistical test. Increasing the number of subjects studied is the only way of avoiding both error types in well-designed epidemiological studies, e.g. free from bias and unmeasured confounding. The sample size of many of the cohort studies was large ($N > 700$) to very large ($N > 9.8$ million) implying high statistical power and high power to avoid Type I and Type II errors in the reported results. The large sample size also implies that effect sizes rather than statistical significance need to be considered. The effect sizes may be over-estimated by the inability to account for the effect that cognitive performance at earlier stages of life might have in defining exposure to air pollution. For example, people with higher cognitive abilities might migrate to urban areas, generally characterised with poor air quality, where more working opportunities are available, i.e. the healthy migrant effect. Although this earlier selection would not explain the effects of lifetime exposure. Some of the studies of a lower number of participants (190–400) nonetheless reported significant associations (e.g. Sanchez-Rodriguez et al., 2006). The studies assessing neurological biomarkers examined responses in small numbers of participants (typically 20–60), which probably contributed to the heterogeneity of the results, affecting their validity and generalizability.

The majority of the reviewed studies (58 out of 69) were conducted in high-income countries. Only eleven studies (Lin et al., 2017; Qiu et al., 2019; Salinas-Rodriguez et al., 2018; Sanchez-Rodriguez et al., 2006; Sun and Gu, 2008; Xu et al., 2017; Zeng et al., 2010; Zhang et al., 2018) examined associations in low- to middle-income countries and found results consistent with those in developed countries.

As the studies used a variety of cognitive tests to assess outcome, and a diverse range of air pollutants was considered (Clifford et al., 2016), formal meta-analysis was deemed not appropriate. Although the wide variety of study designs, exposure metrics and outcome measures contributes to the overall body of evidence, it is not possible to isolate a single well defined relationship that can be represented by a coefficient derived from meta-analysis. In addition, despite the large number of participants in some studies (8.000–750.000) and a few very large-scale studies based on electronic medical records in North America (2.2–9.8 millions), most of the studies have been of much smaller cohorts. The few very large studies would dominate meta-analysis calculations to an extent that would mean that any overall estimates might not fairly represent the current field of knowledge.

Coming to a view on the effects of different pollutants is also not possible at this stage as the pollutants responsible for the observed outcomes cannot be identified with confidence from the epidemiological literature. Likewise, it is difficult at this stage to evaluate whether air pollution exposure predominantly affects functioning in any particular cognitive domain (Power et al., 2016). In addition, the effect estimates are non-comparable, precluding evaluation of the likelihood of publication bias (Clifford et al., 2016; Power et al., 2016).

No study was found which had assessed the association between air pollution and markers of pathological accumulation of amyloid-β or hyperphosphorylated tau in older adults and elderly participants (Power et al., 2016). Also, whereas some studies assessed within-person change of cognitive function, none studied within-person brain structural changes related to air pollution (Power et al., 2016). Further studies should consider these research gaps.

3.7. Strengths and limitations of this literature review

The current review of the literature on the association between ambient air pollution exposure and cognition has strengths and limitations. A strength of the current review is its comprehensiveness exploring the epidemiological evidence across 12 different outcomes related to cognitive decline and dementia. By contrast, the earlier reviews failed to integrate many of these relevant areas, e.g. neurological biomarkers into an overall evaluation. Another strength of this review is that it is based on an exhaustive search of the literature and includes recently published epidemiological evidence (i.e., up to December 2019). Hence, the current work offers a comprehensive and up-to-date review of the available epidemiological evidence of the effect of air pollution on cognitive decline and dementia. In detail, the main strengths are as follows:

1. The number of studies included in this review (after initial assessment of a larger number) is substantially greater than in previous reviews (69 studies) and includes evidence published up to December 2019.

2. The studies cover many endpoints, such as global cognition, specific cognitive domains (i.e. executive function, attention, memory, constructional praxis and coding ability, language), cognitive function decline, mild cognitive impairment, diagnosis of dementia or Alzheimer's disease, hospital admissions, brain morphology, and neurological biomarkers. A similar approach was conducted by Power et al. (2016), but the current review expands the body of evidence from 18 to 69 papers and also includes evidence from neurological biomarkers.

3. Epidemiological studies have been included worldwide, without restrictions for study design. The studies are from many different locations in North America, Europe and Asia. Whilst most of the studies originate from developed countries, one study focused in six low and middle-income countries, six studied populations in China, five in Mexico and one in Iran.

4. The Bradford Hill criteria have been systematically applied to assess the causality of the association between air pollution exposure and cognitive decline and dementia. This expands the analysis of Clifford et al. (2016), who used this approach but focused only on cognitive performance and reviewed only 13 papers.

The limitations of the current review include:

1) This is not a systematic review. Despite this, it is a detailed review and we are confident that all relevant epidemiological papers on air pollution and cognitive decline published until December 2019 have been included.

2) A meta-analysis could not be performed due to the heterogeneity of the outcomes and the pollutants considered as well as the risk estimates used.

4. Conclusions

The evidence reviewed is consistent in reporting associations between chronic exposure to air pollution and reduced global cognition. The evidence is also generally consistent in reporting associations between air pollution and reduced performance in visuo-spatial abilities. The findings are heterogeneous as regards other cognitive domains such as executive function, attention, memory, language and mild cognitive impairment.

Cognitive decline and dementia incidence have consistently been associated with exposure to air pollution. The strength of association reported in some studies suggests a potentially important effect on public health.

All the reviewed studies of white matter volume found associations between exposure to air pollution and reduced white matter volume. Heterogeneous results were found for markers of cerebrovascular health: no association was found with small vessel ischaemic disease or microbleeds, but associations were reported for covert brain infarcts and (counterintuitively) a lower prevalence of white matter hypertintensities. Associations between air pollution and hippocampal volume were also heterogenoeus.

The few studies available on neuro-inflammation tend to report associations with chronic exposure to air pollution.

Several effect modifiers have been suggested in the literature. However, very few studies have analysed whether these factors act as effect modifiers and results are heterogeneous. More replication studies are required to evaluate whether these factors are effect modifiers.

The available evidence, which has been reviewed with reference to Bradford Hill's features of causal associations, suggests that long-term exposure to air pollutants is associated with cognitive decline and with the risk of development of dementia.

Temporal misalignment (of putative causes and effects) could potentially affect the documentation of associations between exposure to air pollution and cognitive and neurological changes. Most of the studies considered exposures representative of one to ten years prior to cognitive testing, dementia incidence or neuroimaging. However, exposures over that period of time might not be representative of exposures over a longer term (e.g. 30 years), which may well be more relevant to the effect under consideration.

However, the studies are not consistent in which pollutant they report as being most closely associated with these adverse effects on cognition. Some studies that have included traffic load or distance and components of air pollution have suggested associations with traffic but not with air pollutants (Ranft et al., 2009; Wellenius et al., 2012), whilst other have found associations with air pollutants but not with traffic load or distance (Schikowski et al., 2015; Wilker et al., 2015). It is therefore unclear whether the exposure mainly associated with cognitive decline and dementia is a specific component of air pollution, the urban air pollution mixture, or factors related to urbanicity and traffic exposure, such as poorer socio-economic status (i.e. poorer people tend to be near major traffic roadsides). It could be also related to any of the multiple features of urban living such as noise, stress, exposure to artificial light at night, poor access to green spaces, sedentarism, unbalanced diet. The diversity of study designs and the end-points makes meta-analysis inappropriate.

Typical confounding factors have been accounted for in the majority of the reviewed studies. Additional factors have been also controlled in some individual studies, but the adjustment of these factors has been heterogeneously implemented. A list of possible confounding factors, such as social interactions, physical activity, sleep deprivation and other factors related with urban living and which none of the studies has controlled for, has been identified. Despite all the efforts in controlling for confounding factors in the reviewed studies, residual confounding cannot be completely ruled out.

In the light of the above discussion it is our view that there is substantial epidemiological evidence suggestive of a causal association between exposure to a range of air pollutants and a number of effects on the nervous system including the acceleration of cognitive decline and the induction of dementia.

CRediT authorship contribution statement

Juana Maria Delgado-Saborit: Conceptualization, Methodology, Writing - Original draft preparation, Visualization, Writing - Reviewing and Editing. **Valentina Guercio:** Validation, Visualization, Writing - Reviewing and Editing. **Alison M Gowers:** Conceptualization, Methodology, Validation, Writing - Reviewing and Editing. **Gavin Shaddick:** Conceptualization, Methodology, Writing - Reviewing and Editing. **Nick C Fox:** Conceptualization, Methodology, Validation, Writing - Reviewing and Editing. **Seth Love:** Conceptualization, Methodology, Validation, Writing - Reviewing and Editing.

Declaration of competing interest

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

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Appendix A. Supplementary data

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