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Ambient Air Pollution, Noise, and Late-Life Cognitive Decline and Dementia Risk

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Abstract

Exposure to ambient air pollution and noise is ubiquitous globally. A strong body of evidence links air pollution, and recently noise, to cardiovascular conditions that eventually may also affect cognition in the elderly. Data that support a broader influence of these exposures on cognitive function during aging is just starting to emerge. This review summarizes current findings and discusses methodological challenges and opportunities for research. Although current evidence is still limited, especially for chronic noise exposure, high exposure has been associated with faster cognitive decline either mediated through cerebrovascular events or resulting in Alzheimer's disease. Ambient environmental exposures are chronic and affect large populations. While they may yield relatively modest-sized risks, they nevertheless result in large numbers of cases. Reducing environmental pollution is clearly feasible, though lowering levels requires collective action and long-term policies such as standard setting, often at the national level as well as at the local level.

INTRODUCTION

Exposure to ambient air pollution is ubiquitous globally and has been associated with various adverse health outcomes in children and adults, including asthma, cardiovascular disease, respiratory disorders, adverse pregnancy outcomes, and all-cause mortality (52, 79). A strong body of evidence links air pollution and, more recently, noise to cardiovascular conditions. But data that support an influence of these exposures on cognitive function across the life course and on late-life rates of cognitive decline and dementia risk are just beginning to accumulate. It is commonly thought that a mixture of Alzheimer's disease (AD) and vascular neuropathology synergize, contributing to cognitive decline and impairment and dementia late in life (3, 74, 75). Cardiovascular risk factors and disease are linked with cognitive decline and dementia risk, suggesting that air pollution and noise exposure may contribute indirectly to cognitive decline and dementia risk by influencing vascular neuropathology. The extent to which air pollution or noise exposures directly affect cognitive decline and incidence of dementia is less well understood.

Cognitive decline and dementia are major concerns for both older adults and communities. Estimates vary, but among adults over 65, the prevalence of mild cognitive impairment and of dementia is thought to be 30–40% and 10%, respectively. The incidence and prevalence of both strongly increase with age (3). In the coming decades, virtually all countries will face challenges related to the growth of aging populations and the subsequent economic and social burden of caring for those with dementia (88).

Significance

Possible modifiable risk factors for dementia and cognitive impairment identified thus far include early-life education, physical activity, smoking, social isolation, and a number of health-related factors, such as diabetes, hypertension, traumatic brain injury, and hearing loss (5, 7, 53). While these factors could all be targets for intervention and prevention, some are more amenable to medical or public health strategies than others. Ambient environmental exposures such as air pollution, ambient noise, or ambient pesticides represent potential risk factors that could be changed by public policy (53). Many of the dementia-related risk factors may be influenced by—or arise from—environmental pollution. In fact, we argue that modification of proximal individual-level risk factors [see Livingston (53)] may achieve limited success as long as the causative upstream environmental exposure remains in place.

Ambient environmental exposures are long term and often affect large populations. While these exposures may yield relatively modest risk increases, they nevertheless result in large numbers of cases. Reducing environmental pollution is clearly feasible, though lowering levels requires collective action and long-term policies such as standard setting, often at the national level as well as the local level.

Pathways from Environment to the Brain

Tau and β-amyloid (Aβ) deposited in the brain are thought to be the proximate pathological mechanisms underlying most nonvascular dementias and cognitive impairment. However, little to no research is available that assesses how pollutants affect the development of tau or Aβ protein aggregates. The dominant paradigm (and much of the evidence) presently frames cardiovascular risk factors and conditions as possible mediators of the association between pollutants and cognitive change/dementia incidence (71, 84). For example, increasing global cortical Aβ deposition has been linked with an increasing number of conventional cardiovascular disease (CVD)

risk factors at midlife such as obesity, smoking, hypertension, diabetes, and cholesterol (37), and an extensive literature links air pollution to stroke (8). Particles have been found to reduce heart rate variability; in addition, high levels of air pollution have been associated with chronic brain inflammation, which has in turn been linked to neurodegeneration in AD (9, 15, 16, 41, 58, 69, 76, 81). Animal studies have confirmed that ultrafine particles (<0.1 μm in aerodynamic diameter) can reach the brain, cause inflammation, and act as neurotoxins (33, 62, 89). Particles may access the brain directly from the nose: Olfactory bulb neurons have been found loaded with particles, impaired olfactory function is a precursor of AD (80), and pathogens may enter the brain via anterograde transport (42). In studies of autopsied brains from deceased residents of metropolitan areas with high particulate and ozone air pollution, investigators found the inflammatory mediator cyclo-oxygenase-2 to be more highly expressed in the frontal cortex and hippocampus and found more neuronal and astrocytic accumulation of AD-specific protein aggregates in neurons (13). Even more surprising is that tau hyperphosphorylation with pretangle-like material and diffuse Aβ plaques were found at younger ages in half of the exposed urbanites but in none of the unexposed urbanites (13).

Biologic pathways linking ambient noise exposure and dementia are less well studied. Some animal evidence indicates that long-term high-level noise exposure is associated with persistent tau pathology, accelerated overproduction of Aβ, and induction of abnormal auditory input to the brain, resulting in aberrant changes in the hippocampus and the cortex (22, 27–29, 56). A number of studies have found increased levels of neuronal oxidative stress in response to noise. Although evidence of neurodegenerative events from lower but chronic levels of noise exposure is generally lacking, epidemiologic studies have linked chronic noise to cardiovascular health, especially chronic hypertension (60, 61), and possibly to stroke occurrence as well (32).

STUDY REVIEWS

Cognitive Change and Dementia Incidence as Outcomes in Studies of Environmental Exposures

Most longitudinal studies of change in cognitive function report a decline in test scores over time and a more rapid decline with increasing age. Such studies have reported baseline differences with numerous risk factors, but far fewer risk factors have been firmly associated with longitudinal change in cognition. The English Longitudinal Study on Aging, an example of a well-executed longitudinal normative aging study, has suggested that such factors are age, gender, education, depression, alcohol, and physical exercise (99). While generally related to cognitive outcomes, these factors are not necessarily associated with environmental exposures, such that adjusting for them as potential confounders may not be necessary or appropriate. However, they may also be potential effect measure modifiers for environmental exposures. For a conceptual framework between environmental exposures and cognitive decline and dementia, see **Figure 1**.

Assessment of predictors of dementia incidence and cognitive change is most effective with longitudinal study designs that include high-quality, repeated measurements of both exposures and outcomes. Repeated measures of exposure allow investigators to observe time-dependent effects of environmental factors on cognitive decline. Most studies that attempt to link environmental exposures to cognitive change and dementia incidence to date, however, do not meet these criteria. This review highlights studies that are longitudinal with neuropsychological examination for cognitive outcomes, have adequate sample size, are population based, assess established cognitive risk factors for potential confounder control, and investigate incident dementia or change in cognitive function repeatedly (**Table 1**).

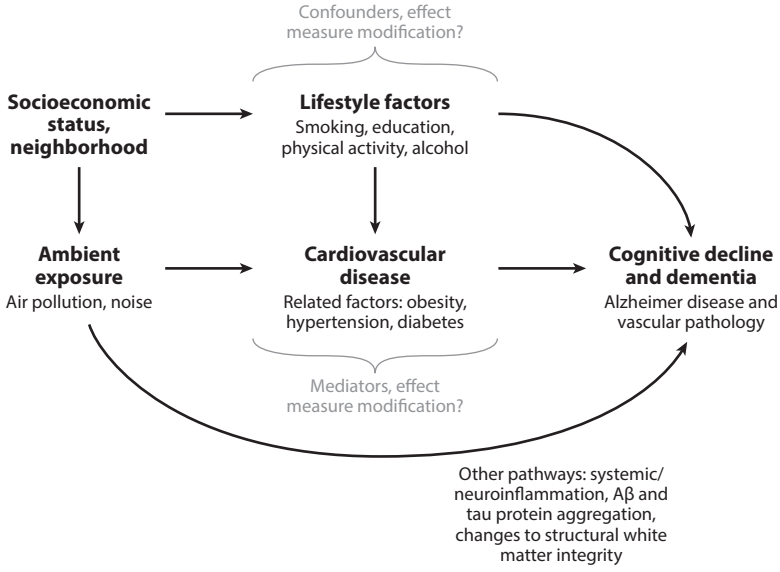

Figure 1

Ambient environmental exposures and cognition conceptual model. Proposed pathways between ambient environmental exposures and late-life cognitive decline: indirectly through cardiovascular disease (CVD) and health factors related to CVD, and directly through pathways such as systemic inflammation and neuroinflammation, beta amyloid (Aβ) and tau protein aggregation, or changes to structural white matter integrity. It should be noted, though, that the other pathways, such as systemic inflammation, may be related to cardiovascular health, as well.

Ambient Air Pollution

Air pollution is a complex mixture of compounds from different sources, including combustion, industrial, agricultural, or natural sources, and includes particulate matter (PM), ozone, carbon monoxide (CO), sulfur and nitrogen oxides, methane, volatile organic compounds (VOCs; e.g., benzene, toluene, and xylene), and metals (e.g., lead, manganese, vanadium, iron) (10). Certain exposures are more typical for urban environments, such as traffic-related air pollution (TRAP), whereas in rural communities much of the contributions to air pollution may originate from diesel equipment or burning of biological matter. The components of air pollution have also changed over time; for instance, the lead content in TRAP decreased drastically after the banning and phasing out of leaded gasoline in the United States between the 1980s and 1995. We do not know whether a most relevant exposure period exists for late-life cognitive function, but long-term exposures extending over decades or even the entire life course likely affect these outcomes.

Particulate matter (PM): delineated by <2.5 μm (fine), 2.5–10 μm (coarse), and <10 μm

CO: Carbon monoxide

NO_2: nitrogen dioxide

NO_x: nitrogen oxides

Air pollution is routinely monitored according to US Environmental Protection Agency (EPA) directions for pollutants referred to as criteria pollutants [CO, PM, SO_2, nitrogen dioxide (NO_2), lead] or as air toxics (such as benzene or other VOCs). More recently, researchers are developing complex spatiotemporal models that integrate such routine monitoring data with land use, emissions, and even satellite data and special research-driven monitoring protocols. Some pollutants are commonly thought of as surrogate markers for specific sources of air pollution. Common markers include particles of different sizes [aerodynamic diameter of <10 μm (PM_{10}) or <2.5 μm ($PM_{2.5}$)], carbon monoxide (CO), and nitric oxides (NO_2, NO_x), which have also been considered to represent TRAP in urban areas. This view may be oversimplified, however, as these pollutants often do not arise from a single source but from many. For example, PM_{10} or $PM_{2.5}$ may include

Table 1 Prospective, population-based studies, with adequate sample size, investigating the association between air pollution and late-life cognitive outcomes

Study	Country	Study type	Exposure measurement	Outcome measurement	Cognitive domains	Sample size	Outcome size	Summary	Outcomes
AD and dementia incidence									
Oudin et al. 2016 (63); Betula Study	Sweden	Longitudinal 1993–2010	Monitors and LUR; baseline year residential mean, NO_x	AD and VaD: clinical examination	NA	1,806	191 AD; 111 VaD	↑ Risk	NO_x quartile 4 versus 1: all-cause dementia HR = 1.43 (1.00, 2.05); AD HR = 1.38 (0.87, 2.19); VaD HR = 1.47 (0.83, 2.61)
Cacciottolo et al. 2017 (12); WHIMS	United States	Longitudinal 1995–2010	Spatiotemporal models and EPA AQS; $PM_{2.5}$	All-cause dementia: clinical examination	NA	3,647	173	↑ Risk	High $PM_{2.5}$ (versus low) HR = 1.92 (1.32, 2.80)
Cognitive impairment									
Loop et al. 2013 (54); REGARDS	United States	Longitudinal 2003–2007	Satellite sensing and EPA monitors/spatio-temporal model; $PM_{2.5}$	Six-item telephone screener ≤4	Short memory Orientation	20,150	1,633	Suggestive NS ↑ Risk	Per $PM_{2.5}$ 10 $\mu g/m^3$, OR = 1.26 (0.97, 1.64)
Cacciottolo et al. 2017 (12); WHIMS	United States	Longitudinal 1995–2010	Spatiotemporal models and AQS; $PM_{2.5}$	Eight-point 3MS decline	Global	3,647 women	329	↑ Risk	High $PM_{2.5}$ (versus low) HR = 1.81 (1.42, 2.32)
Cognitive decline									
Weuve et al. 2012 (93); NHS Cognitive Cohort	United States	Longitudinal 1995–2008	EPA monitors/ spatiotemporal model; $PM_{2.5}$ and $PM_{2.5-10}$	TICS and EBMT (telephone)	Global speed processing Verbal recall Memory	19,409 women	NA	Faster decline	Cognitive score change, per 10 $\mu g/m^3$: $PM_{2.5}$ $\beta = -0.018$ (−0.035, −0.002); $PM_{2.5-10}$ $\beta = -0.020$ (−0.032,−0.008)
Tonne et al. 2014 (85); Whitehall II	United Kingdom	Longitudinal 2002–2009	London monitors/ KCLurban dispersion model and postal code; $PM_{2.5}$ and PM_{10}	Cognitive tests: cognitive tests in person	Memory score Reasoning Verbal fluency	2,867	NA	Suggestive NS faster decline	Five-year standardized memory test decline, per IQR: $PM_{2.5}$ $\beta = -0.030$ (−0.062, 0.002); PM_{10} $\beta = -0.029$ (−0.065, 0.007)
Oudin et al. 2017 (64); Betula Study	Sweden	Longitudinal 1988–2010	Monitors and LUR; NO_x	Cognitive tests: episodic memory summary score in person	Memory score (episodic, semantic, working, attention, speed) Executive function	1,469	NA	No associa-tions	No association between five-year change on episodic memory measure and NO_x $\beta = 0.01$ (−0.02, 0.03)

Abbreviations: 3MS, Modified Mini-Mental State Exam; AD, Alzheimer's disease; AQS, EPA Air Quality System; EBMT, East Boston Memory Test; EPA, US Environmental Protection Agency; HR, hazard ratio; IQR, interquartile range; LUR, land use regression; NA, not applicable/outcome is a continuous measure of cognitive decline; NHS, Nurses' Health Study; NO_x, nitrogen oxides; NS, nonsignificant; OR, odds ratio; PM, particulate matter; REGARDS, Reasons for Geographic And Racial Differences in Stroke; TICS, Telephone Interview for Cognitive Status; VaD, vascular dementia; WHIMS, Women's Health Initiative Memory Study.

car and diesel emissions, as well as industry, power plant, and refinery emissions, depending on the region or area under study.

In recent years, several major epidemiologic studies have reported on associations between air pollutants and cognitive function. **Table 1** outlines the findings from the studies deemed of highest quality. For completeness, a summary of other air pollution and cognition studies, mostly record-based or cross-sectional, is included in **Supplemental Table 1**, but we do not discuss these in depth.

Supplemental Material >

Alzheimer's disease and related dementias. Two large cohorts, with long-term prospective follow-up and in-person clinical evaluations, have reported on air pollution and incident dementia. The Betula study in Northern Sweden enrolled and followed 1,806 participants for dementia incidence over a 15-year period, with 5 exams every 5 years between 1993 and 2014 (63). Over follow-up, 191 participants were diagnosed with AD and 111 with vascular dementia (VaD). The researchers modeled annual mean NO_x levels at the residential addresses at baseline using a land-use regression model trained on 4 weeklong measurements at 36 sites (November 2009 through June 2010). Participants living in homes that received the highest quartile NO_x exposure were at an increased risk of developing dementia relative to those in the lowest quartile [hazard ratio (HR) = 1.43; 95% confidence interval (CI): 1.00, 2.05] (**Table 1**). The analysis stratified by AD and VaD diagnosis yielded estimates of similar magnitude for both outcomes (AD HR = 1.38, 95% CI: 0.87, 2.19; VaD HR = 1.47, 95% CI: 0.83, 2.61). The researchers estimated the population attributable fraction of exposure to these dementias as 16% (95% CI: 4, 26) (63).

The risk of dementia from particulate air pollutants was examined in a US-wide cohort of 3,647 older, community-dwelling (>95% urban) women from the Women's Health Initiative Memory Study (WHIMS) (12). Ambient $PM_{2.5}$ concentration at all WHIMS residential locations from 1999 to 2010 was estimated using spatiotemporal chemical transport models derived from monitoring data provided by the US EPA Air Quality System (AQS). The time-varying three-year average exposure preceding either diagnosis or censoring date was used in analysis. Over an average of 9.9 years of follow-up, 173 participants were classified as incident cases of all-cause dementia at annual exams. Residing in locations with high $PM_{2.5}$, i.e., exceeding current National Ambient Air Quality Standards (NAAQS) standards, increased the risk for all-cause dementia by 92% (HR = 1.92, 95% CI:1.32, 2.80) (12). Similar to the results of the Betula study, this study estimated that ~21% of all-cause dementia documented by these researchers was attributable to residential exposure to high ambient $PM_{2.5}$.

Large sample size, long follow-up with clinical exams, collection of in-depth covariate data, and fine-scaled spatiotemporal exposure modeling are notable strengths of these studies. However, NO_x in the Betula study was measured (in 2009) 16 years after the first follow-up (in 1993), and baseline residential addresses were used for exposure assessment. While one could argue that relative levels of air pollution may be generally similar over a certain amount of time, population and traffic density or major roadway construction may have changed substantially, leading to some non-differential exposure misclassification. The WHIMS-constructed spatiotemporal chemical transport model exposure assessments may have established temporality more effectively in this cohort, but it allowed solely for the estimation of late-life exposure to $PM_{2.5}$ from 1999 to 2010. Exposures before 1999, when WHIMS participants were aged less than 65 years, could not be modeled well because nationwide monitoring data prior to this time did not have adequate quality or sufficient geographic coverage.

Cognitive decline and incident impairment. A small number of longitudinal studies with repeated cognitive exams have investigated the influence of air pollution using a variety of measures

(**Table 1**). Two studies of incident cognitive impairment provide some support for an adverse association with $PM_{2.5}$ exposure. A biracial US cohort study of 20,150 participants (REGARDS) measured incident cognitive impairment with a telephone six-item screener and integrated both EPA AQS monitoring data and satellite measurements of aerosol optical depth to estimate $PM_{2.5}$ concentration at the participants' baseline residence (2003–2007). A 10 $\mu g/m^3$ increase in 1-year mean baseline $PM_{2.5}$ concentration was associated with a 26% increase in risk [OR = 1.26 (0.97, 1.64)]. The risk was slightly stronger in participants living in urban areas [OR = 1.40 (1.06–1.85)], but the estimated effect sizes attenuated considerably after additional adjustments for demographic, behavioral, and health-related risk factors (54). In the same WHIMS cohort discussed above, high $PM_{2.5}$ was also associated with an 81% [HR = 1.81 (1.42, 2.32)] increased risk for incident cognitive impairment [8-point loss on the Modified Mini-Mental State Exam (3MS); $n = 329$] (12).

Three additional cohort studies examined cognitive decline over a period of follow-up. The Nurses' Health Study cognitive cohort ($n = 19{,}409$ older women) relied on three cognitive exams and assessed long-term PM exposure (7–14 years) at participants' residences using spatiotemporal models and AQS monitoring. Exposures to $PM_{2.5}$ and $PM_{2.5-10}$ were associated with faster cognitive decline, as measured by a composite global score [per 10 $\mu g/m^3$: $PM_{2.5}$ $\beta = -0.018$ (-0.035, -0.002); $PM_{2.5-10}$ $\beta = -0.020$ (-0.032, -0.008)] (93). A study in the United Kingdom (Whitehall II, $n = 2{,}867$) reports suggestive associations between a five-year decline on a standardized memory test and PM exposure, modeled at the baseline residence using a dispersion modeling approach and emissions data, but found no associations with reasoning or verbal fluency decline (85). In contrast, the Betula cohort from Northern Sweden, which observed an increased risk of NO_x exposure for incident dementia (discussed above) (63), did not see any association between NO_x and five-year change in episodic memory (64).

These studies expand beyond the WHIMS and Betula cohorts and somewhat corroborate the results for air pollution and incident all-cause dementia and AD. However, all air pollution measures were relatively short term and represented only exposures during middle to older age.

Other studies. Other published air pollution and cognition studies have a number of weaknesses (**Supplemental Table 1**). A series of four large, retrospective medical record–based studies in Taiwan and North America, using data from national air quality monitoring databases, all reported increased air pollution risks for dementia (19, 20, 44, 47). Medical record databases provide notable benefits, including large, representative, and often nationwide samples and the statistical power to detect weak to modest, but meaningful, effect sizes. However, dementia is not always documented well in medical records. For example, whether outpatient visits are recorded or dementia is diagnosed and recorded and at what stage varies widely by medical system. In addition, exposure assessment is generally limited to using the residential address or sometimes only the medical clinic address on file, limiting accurate or longer-term exposure assessment. Also, potential confounders beyond age, sex, and possibly some medical factors, including education, smoking, body mass index, and physical activity, are usually unavailable in record-based approaches. These should all be considered when researching cognitive outcomes, especially if socioeconomic status (SES) is related to air pollution in the areas under investigation.

Supplemental Material >

Analyzing cognitive performance of a geographically diverse sample of individuals from the National Alzheimer's Coordinating Center, researchers recently found that increased levels of ozone, but not $PM_{2.5}$, were associated with an increased rate of cognitive decline, as measured by both the Mini–Mental State Examination (MMSE) and the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) (25). However, the population was selected from patients of a number of neurologic clinics and was not representative of the general population.

To date, most studies examining the ambient environment and study participants' cognitive function were cross-sectional, based on prevalent cognitive function. Although most studies report at least one association between an air pollutant and a cognitive outcome, these findings are not necessarily seen in the primary analyses. For instance, positive associations may have been seen only in subanalyses, such as those restricted to urban populations or participants over 75 years of age. These studies are summarized in **Supplemental Table 1**.

Supplemental Material >

Neuroimaging. A series of studies with magnetic resonance imaging (MRI) scans have associated elevated air pollution exposure with smaller brain volume (**Table 2**). Analyzing MRIs from 943 participants of the Framingham Offspring Study (FOS), investigators associated increasing $PM_{2.5}$ exposure with lower cerebral brain volume, a marker of age-associated brain atrophy (96). Specifically, a 2 $\mu g/m^3$ increase in $PM_{2.5}$ exposure, modeled at the residential address with Moderate Resolution Imaging Spectroradiometer satellite-derived aerosol optical density measurements, was associated with smaller total cerebral brain volume [$\beta = -0.32\%$ (-0.59, -0.05)] and higher odds of covert brain infarcts [OR = 1.46 (1.10, 1.94)]. Living further away from a major roadway was also associated with greater log-transformed white matter hyperintensity (WMH) volume (96). However, in analyzing data from 236 participants in the Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort, researchers did not find any association between residential proximity to major roads or average $PM_{2.5}$, modeled in the same manner with satellite data as done for the FOS, and greater burden of small vessel disease or neurodegeneration. However, a 2-$\mu g/m^3$ increment in $PM_{2.5}$ in this cohort was associated with a -0.19 (-0.37, -0.005) lower natural log-transformed WMH volume (95).

Two studies from the WHIMS also reported on MRIs. Among 1,403 women without dementia at enrollment in the WHIMS, women who had greater $PM_{2.5}$ exposures had smaller white matter volume [per interquartile range (IQR), $\beta = 6.23$ cm^3 smaller (3.72, 8.74) in total brain and $\beta = 4.47$ cm^3 smaller (2.72, 6.67) in association areas], but not gray matter volumes (21). A recent follow-up to this study, analyzing MRIs from 1,365 WHIMS women using voxel-based morphometry, showed that higher $PM_{2.5}$ exposure was associated with smaller volumes in both cortical gray and subcortical white matter areas (17). And recent findings from the Atherosclerosis Risk in Communities (ARIC) study also suggest smaller brain volume with higher PM exposure (67). In the ARIC study, researchers modeled $PM_{2.5}$ and PM_{10} exposures at participants' residences over the 5–20 years prior to MRI using a spatiotemporal model and monitoring data (1990–2007). In a pooled analysis of four study sites, higher mean $PM_{2.5}$ and PM_{10} exposures were associated with smaller deep-gray regional brain volumes [e.g., for mean $PM_{2.5}$ from 1990 to 2007, $\beta = -0.03$ standard deviation (SD) units per 1 $\mu g/m^3$ higher exposure (-0.08, 0.00)]. Higher $PM_{2.5}$ exposures 5–14 years prior were marginally associated with smaller frontal lobe volumes [$\beta = -0.02$ SD units per 1–$\mu g/m^3$ higher exposure (-0.04, 0.00)] (67).

These studies provide important evidence that air pollution influences not only old age brain function but also brain structure. Yet, they also rely on relatively short-term air pollution exposure estimates from later in life, and there are currently no studies with repeated measurements to assess change over time.

Ambient Noise

Vehicular traffic, an important source of urban air pollution, also emits much of the ambient noise pollution found in urban areas. Thus, owing to their shared sources, air pollution and ambient noise often occur simultaneously. The association between chronic exposure to ambient noise and cognitive function has hardly been investigated. Most studies of ambient noise examined

Table 2 Studies investigating air pollution and brain structure[a]

Study	Country	Exposure measurement	Outcome measurement	Sample size	Summary	Outcomes
Chen et al. 2015 (21); WHIMS	United States	Spatiotemporal models and EPA AQS; $PM_{2.5}$	MRI (volumetric GM and WM)	1,403 women	↓ WM	Per $PM_{2.5}$ IQR: WM volume $\beta = 6.23$ cm^3 smaller (3.72, 8.74) in total brain; $\beta = 4.47$ cm^3 smaller (2.72, 6.67) in association areas
Wilker et al. 2015 (96); FOS	United States	Satellite sensing ($PM_{2.5}$) and distance to major roadways	MRI (TCBV, HV, WMHV, and CBI)	929 cognitively intact	↓ TCBV, ↑ CBI Risk	Per 2-$\mu g/m^3$ $PM_{2.5}$ increase: TCBV $\beta = -0.32$ (-0.59, -0.05) and CBI risk OR = 1.46 (1.10, 1.94). Living further from roadways: WMHV β per IQR = 0.10 (0.01, 0.19)
Wilker 2016 (95); MADRC	United States	Distance to major roadways; $PM_{2.5}$	MRI (BPF and WMHV)	236 cognitively impaired	↓ WMHV	No association between $PM_{2.5}$ and BPF or microbleeds. Per 2-$\mu g/m^3$ $PM_{2.5}$ increase, lower log transformed WMHV $\beta = -0.19$ (-0.37, -0.005)
Casanova 2016 (17); WHIMS	United States	Spatiotemporal models and EPA AQS; $PM_{2.5}$	MRI (volumetric GM and WM)	1,365 women	↓ WM and GM	Higher $PM_{2.5}$ associated with smaller GM and WM volume
Power 2018 (67); ARIC	United States	Spatiotemporal models and EPA AQS; $PM_{2.5}$ and PM_{10}	MRI (volumetric GM and WMH)	1,753	↓ Deep-gray brain volume	Higher mean $PM_{2.5}$ and PM_{10} exposures were associated with smaller deep-gray brain volumes; higher $PM_{2.5}$ exposures were associated with smaller total and regional brain volumes in Minnesota

Abbreviations: AQS, EPA Air Quality System; ARIC, Atherosclerosis Risk in Communities; BPF, brain parenchymal fraction; CBI, covert brain infarcts; EPA, US Environmental Protection Agency; FOS, Framingham Offspring Study; GM, gray matter; HV, hippocampal volume; IQR, interquartile range; MADRC, Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort; MRI, magnetic resonance imaging; OR, odds ratio; TCBV, total cerebral brain volume; WHIMS, Women's Health Initiative Memory Study; WM, white matter; WMHV, white matter hyperintensity volume.

[a]Note, all studies are cross-sectional (brain structure based on a single exam).

short-term effects and psychological outcomes, such as anxiety and annoyance. There is a long history of experimental studies associating administered noise with worse neuropsychiatric performance, and a few occupational studies have implicated high-noise occupations with cognitive deficits (6, 24, 36, 87). Only the Heinz Nixdorf Recall study has published observational findings on the relationship between traffic-related ambient noise at each participant's residence and cognitive performance. Among 4,086 community-dwelling participants in Germany, a 10-dB(A) (A-weighted decibels) elevation in traffic noise was associated with a lower global cognitive score (24-h noise measure $\beta = -0.32$, 95% CI: -0.62, -0.20) (86). Associations between ambient noise and global cognitive function were stronger in former and current smokers ($\beta = -0.57$, 95% CI: -0.95, -0.19) compared with nonsmokers ($\beta = -0.24$, 95% CI: -0.55, -0.07; p for interaction = 0.04). These cross-sectional findings are intriguing, but more high-quality studies are needed.

Susceptibility

Genetic susceptibility. Genetic risk factors represent a person's endogenous characteristics that may change susceptibility to environmental exposures and cognitive decline or dementia. Reported associations to date are based largely on outcomes of global functioning. Currently, the most salient genetic risk factor for cognitive impairment and dementia is apolipoprotein E4 (APOE). This genotype is present in about 25% of European ancestry populations and has been shown to influence (or modify) the associations between various risk factors and cognitive functioning and dementia (11, 38–40, 57, 78). Approximately 20 genes have been identified as increasing or decreasing risk for AD (30). However, as a group, these genetic variants have only a small effect on dementia/AD risk, and they remain largely unexplored in terms of modifying the effects of environmental exposures.

The WHIMS longitudinal cohort is the only study that met our criteria for a high-quality investigation that also reported on the role of APOE. Adverse $PM_{2.5}$ associations were exacerbated among the ε4 carriers for both incident all-cause dementia (ε3/3: HR = 1.68; ε3/4: HR = 1.91; ε4/4: HR = 2.95) and cognitive impairment (ε3/3: HR = 1.65; ε3/4: HR = 1.93; ε4/4: HR = 3.95) (12). These results are corroborated in a cross-sectional analysis of the SALIA (Study of the influence of Air pollution on Lung function, Inflammation and Aging) women's cohort, where cognitive function was affected by measures of traffic load and $PM_{2.5}$ absorbance only in those with at least one APOE ε4 risk allele (73).

More high-quality research is necessary to elucidate genetic susceptibility to ambient air pollution exposures. New understandings of environmental influences on DNA methylation and other epigenetic modes may also arise from future research and potentially even shed some light on the upstream environmental causes of cognitive impairment/dementia as well as elucidate transgenerational effects (23, 51, 65).

Social factors, life course, and social environment. Race/ethnicity, SES, and neighborhood physical and socioeconomic features are reported to co-vary with air pollution and/or other environmental exposures (4, 34, 66). Although abundant evidence supports race/ethnicity and neighborhood differential vulnerability to a wide array of diseases, little work has assessed the aging brain's vulnerability to toxins being enhanced by race, ethnicity, or low social status at the individual or neighborhood level.

The Americans' Changing Lives study ($n = 779$) recently reported cross-sectional adverse associations between $PM_{2.5}$ and cognitive function, and the estimated effect was stronger among adults living in what they considered high-stress neighborhoods [per 1 $\mu g/m^3$ increase, interaction incidence-rate ratio (IRR) = 1.09 (1.01, 1.18)] (1). The authors suggest that those living in

socioeconomically disadvantaged neighborhoods, where both social stressors and environmental hazards are more common, may be particularly susceptible to adverse health effects owing to both social and physical environmental exposures. Yet, this type of vulnerability has not been widely researched, let alone in a longitudinal design.

Important work has suggested that early childhood conditions, e.g., parental SES, food deprivation, stress in childhood, social and physical environment, may affect cognitive functioning in older ages (35, 55). In Mexico City, associations were reported between childhood brain pathology and air pollution (14), but long-term brain changes that start in childhood and extend to adulthood and older age have not yet been studied. The paucity of data obtained across the life course limits what one can say about upstream risk factors that may influence cognitive function and decline before adult middle age or older ages. There has been some scientific reluctance to studying exposure effects earlier in the life course owing to the belief that cognitive decline does not begin, or alternatively is not measurable, until late-middle to older age; i.e., detectable effects can be estimated only when a point is reached at which cognitive decline occurs more rapidly and can be measured with existing, often insensitive, tools. This position limits possibilities of identifying earlier upstream risk factors that could be useful for prevention. Any causal chain linking early-life exposures to late-life disease/function is inevitably long and influenced by a host of different factors. It may also be important to determine whether early life/midlife exposures to environmental toxicants contribute to cognitive decline later in life because this period constitutes sensitive or critical periods of brain development and maturation or because they simply represent a cumulative, long-term risk (26, 70, 82).

METHODOLOGICAL CHALLENGES

A critical first step in estimating effects of environmental exposures on cognitive decline and dementia incidence is to define the specific research question clearly and then to identify the appropriate statistical analysis to estimate the target parameter. This review is focused on whether environmental exposures have causal effects on cognitive decline and dementia incidence; thus, we focus on methodological challenges related to causal, rather than predictive, research questions. Major methodological challenges in research estimating the effects of environmental exposures on cognitive decline and dementia incidence include identifying the most relevant time of exposure for the outcome of interest; exposure assessment challenges, especially exposure measurement error due to spatial misalignment of monitoring data and study participants; challenges in measuring and modeling cognitive function and cognitive change; unmeasured confounding; and selection bias arising from selection into the sample and selective attrition. We briefly describe these challenges below but refer readers to more in-depth discussions elsewhere. On challenges in measuring cognitive outcomes, we refer the readers to a more detailed review of measurement, including uncertainty in diagnostic criteria and measurement error in neuropsychological assessments (92); on measuring air pollution and noise exposure, we refer readers to a review of confounding and exposure measurement error in air pollution epidemiology (77) and to work on measurement error methods corrections (72).

Timing of Exposure

Neuropathological challenges thought to be relevant to cognitive decline and dementia may begin 20 or more years prior to the onset of clinical symptoms (2). Thus, exposures in early life and midlife are probably quite relevant for the development of neuronal damage related to cognitive decline and dementia. Current evidence on environmental exposures and cognitive decline

and dementia incidence measures environmental exposures in late life. Nevertheless, information about the residential mobility among older adults in the study population of interest could provide insights into the extent to which residential environmental exposures measured in late life may represent exposure in midlife.

Exposure Measurement

One of the main challenges in estimating air pollution exposure from ambient stations is the spatial misalignment of monitoring data and study participants. Monitoring data are generally not available at the subject locations, and one must assume that a subject's ambient exposures are well represented by a monitoring station. Approaches to spatial prediction of pollutants vary across citywide or census-tract averages, to nearest monitor interpolation, to kriging, and land-use regression (LUR) (77). For pollutants with relatively homogeneous spatial structures (e.g., $PM_{2.5}$ or ozone), less refined spatial models may provide adequate estimates of exposure at residences or workplaces. However, for pollutants with a shorter range from the source (e.g., NO_x), city averages, nearest monitor, and even kriging will likely result in substantial exposure misclassification (46). LURs are designed to predict such spatially varying concentrations from sources such as traffic. Most methods integrate regulatory monitoring data. However, the number of fixed location monitors may be limited and may be preferentially sited close to or far from pollutant sources, leading to bias (31). Satellite-based chemical transport models of exposure are currently being developed to help alleviate this issue. Finally, there are trade-offs between using measures of ambient pollution exposure and using personal air pollution exposure measures. The latter remains very expensive to collect in terms of costs and subject burden, limiting the feasibility of measurement over longer periods of time. Ambient exposure measures have advantages in that they can serve as instrumental variables for personal exposures and thus are not impacted by confounders in the same manner that actual personal exposure measures might be (see 91).

Outcome Measurement

Major challenges in outcome measurement include validity and reliability of measuring cognitive function, cognitive change, and incident dementia. Distinguishing between true cognitive change and measurement error is critical for estimating the effects of exposures on cognitive decline. Cognitive measures with unequal interval scaling, including ceilings and floors, can either attenuate or inflate effect estimates in longitudinal studies (59, 68). Challenges in modeling cognitive decline to minimize biased estimates of the effect of exposures on the rate of cognitive decline include accounting for practice effects (90) and for nonlinear cognitive trajectories.

Confounding

Compared with studies examining the rate of cognitive decline, studies examining incident dementia are more susceptible to confounding by life course exposures that may influence environmental exposures and premorbid cognitive function, for example, childhood socioeconomic disadvantage or education. Thus, high-quality studies examining the rate of cognitive decline provide stronger evidence for causality of exposures. However, studies of cognitive decline are not immune to confounding. Environmental conditions correlated with the exposure of interest are an important potential source of confounding. For example, estimated daytime and nighttime noise tend to be higher for census block groups with lower SES in the United States (18).

Selection Bias

Selection bias arising from selection into the sample and selective attrition potentially induces spurious exposure–outcome associations if selection is a common effect of exposure and an unmeasured determinant of cognitive decline (and related causal structures) (43, 94). This selective loss to follow-up and survival is relevant particularly for air pollution studies because environmental exposures are linked with mortality, cognitive decline predicts mortality among older adults, and mortality rates are high in older adult populations (48, 49, 83, 97, 98). Selection into study participation among people who are alive is another potential source of selection bias (45, 50).

CONCLUSION

Research linking ambient air pollution and noise with cognitive decline and dementia is slowly accumulating. However, the current evidence is far from definitive, especially for chronic noise exposures. It is increasingly recognized that a life course perspective is likely relevant to identifying important determinants of cognitive decline that accompany aging. Thus, the evidence that environmental exposures play a role will be substantially strengthened by studies that measure exposures to environmental factors in early life and midlife and that record cognitive decline in a standardized and repeated fashion. Cheaper and noninvasive neuroimaging or blood-based biomarkers of neurodegeneration may be important future contributors to such research. Current longitudinal research is stymied both by the lack of address history prior to enrollment in many existing cohort studies as well as by a lack of dense enough air pollution monitoring networks before 1990. Continued follow-up of current adult cohorts into the coming decades for the assessment of late-life health, including cognition, will provide new opportunities for longer-term concomitant exposure assessment. Large, population-representative studies would help us gain a more complete picture of the potential link between environmental exposures and cognitive aging in diverse populations and settings, i.e., will help elucidate the burden of environmental factors for vulnerable aging populations in high-risk or high-pollution contexts. Reducing environmental pollution will require collective action and long-term policies at the national and local levels. Given the magnitude of exposure, there is great potential for prevention.

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The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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