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Particulate Air Pollutants, Brain Structure, and Neurocognitive Disorders in Older Women

Jiu-Chiuan Chen, Xinhui Wang, Marc Serre, Steven Cen, Meredith Franklin, and Mark Espeland

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with a Critique by the HEI Review Committee

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ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
- Competitively funds and oversees research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI's research and analyses to public and private decision makers.

HEI typically receives balanced funding from the U.S. Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 330 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 260 comprehensive reports published by HEI, as well as in more than 1,000 articles in the peer-reviewed literature.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Review Committee are widely disseminated through HEI's website (*www.healtheffects.org*), printed reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 193, *Particulate Air Pollutants, Brain Structure, and Neurocognitive Disorders in Older Women,* presents a research project funded by the Health Effects Institute and conducted by Dr. Jiu-Chiuan Chen, of the Department of Preventive Medicine and the Memory and Aging Center/Alzheimer's Disease Research Center, Keck School of Medicine, University of Southern California, Los Angeles, California, U.S.A., and his colleagues. This research was funded under HEI's Walter A. Rosenblith New Investigator Award Program, which provides support to promising scientists in the early stages of their careers. The report contains three main sections.

The HEI Statement, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Review Committee's comments on the study.

The Investigators' Report, prepared by Chen and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The Critique, prepared by members of the Review Committee with the assistance of HEI staff, places the study in a broader scientific context, points out its strengths and limitations, and discusses remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. This draft report is first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the Review Committee, an independent panel of distinguished scientists who have no involvement in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Critique reflects the information provided in the final version of the report.

HEI STATEMENT

Synopsis of Research Report 193

Air Pollution and Neurocognitive Effects in Older Women

INTRODUCTION

Dementia is relatively common in elderly people. Because there are no cures, there has been much interest in identifying modifiable risk factors. Recently, epidemiological studies have begun to explore the etiological role of exposures to common environmental pollutants, including air pollution. Yet to date, few epidemiological studies have investigated neurocognitive effects of long-term exposure to air pollution in older people. There are many methodological challenges involved in conducting such research, including the potential for selection bias, misclassification of the outcome, and uncertainties in the exposure estimation; many challenges also stem from the nature of dementia, which can have a decades-long incipient phase.

Dr. Jiu-Chiuan Chen of the University of Southern California, a recipient of HEI's Walter A. Rosenblith New Investigator Award, and colleagues examined the association between long-term outdoor particulate air pollution exposure and neurocognitive outcomes and brain volumes of older women in the United States. They also examined effect modification by factors that may increase susceptibility, such as a history of cardiovascular disease.

APPROACH

Dr. Chen used data from women enrolled in the U.S.-based Women's Health Initiative Memory Study (WHIMS), which consisted of two randomized clinical trials of postmenopausal hormone therapy. Both trials were terminated early because of side effects, though follow-up continued. In total, 7,479 women were included in the current study, all community dwellers (i.e., not living in nursing or medical facilities), 65 to 80 years old, and free of dementia at baseline (1996–1999). The study assessed neurocognitive outcomes, namely, mild cognitive impairment and dementia, and brain volume measures. The report analyzed neurocognitive outcomes measured annually by standardized protocols including neurological tests until 2007. Brain volume measures for certain brain regions were obtained from a single structural magnetic resonance imaging (MRI) assessment in a subset (~20%) of participants during 2005–2006.

Two PM exposure metrics were assessed: ambient $PM_{2.5}$ and diesel PM. Annual ambient $PM_{2.5}$ exposure was estimated at the residential address using a nationwide spatiotemporal model and U.S. EPA regulatory monitoring data for the years 1999–2007. Annual on-road diesel PM was obtained at the census-tract level from the U.S. EPA National-Scale Air Toxics Assessment database.

What This Study Adds

- Dr. Chen conducted a novel study examining the association between long-term exposure to ambient particulate air pollution and neurocognitive outcomes and brain volumes of older women in the United States.
- A high-quality neurocognitive outcome assessment, the inclusion of brain imaging data, and the availability of detailed individual-level covariate information were strengths of the study.
- The investigators observed that exposure to neither ambient fine particulate matter ($PM_{2.5}$) nor diesel particulate matter was associated with mild cognitive impairment and/or dementia in older women. Some positive and negative associations were reported between particulate air pollution and brain volumes, but the analyses were exploratory, their clinical significance remains unclear, and the findings differ from previous research.
- Evidence from the current study, along with results of previous studies, provides impetus for further research given the implications of the potential effects of ambient air pollution on dementia for our aging population.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Jiu-Chiuan Chen, Keck School of Medicine, University of Southern California, Los Angeles, California, and colleagues. Research Report 193 contains both the detailed Investigators' Report and a Critique of the study prepared by the Institute's Review Committee.

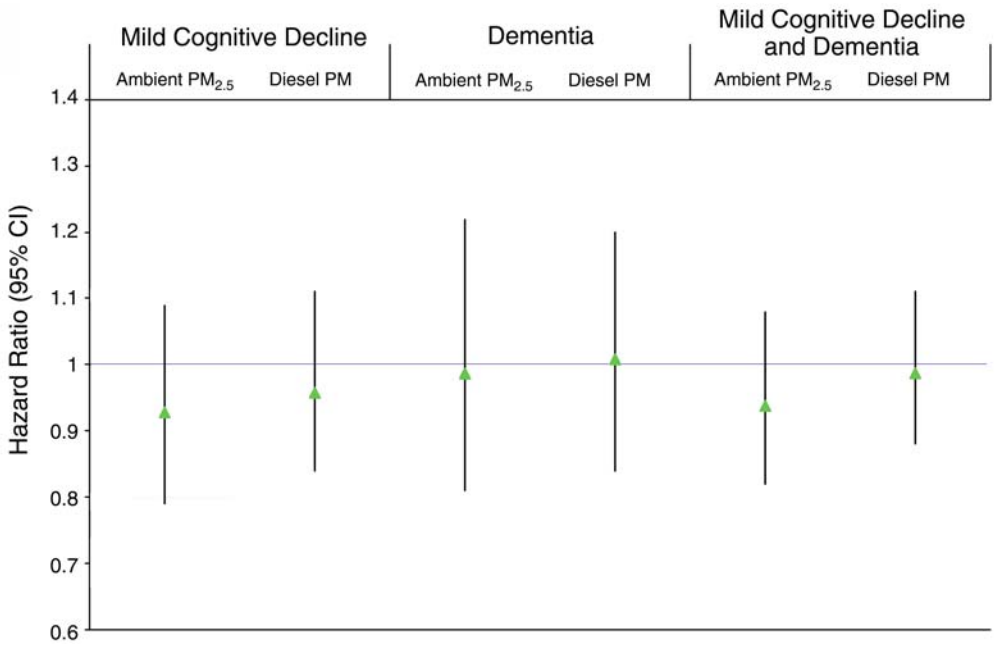
Neurocognitive and brain volume outcomes were first compared across exposure quartiles and then tested for significance using likelihood-ratio tests and analysis of covariance. Only statistically significant results were further investigated in Cox proportional hazard models (neurocognitive outcomes) and linear regression models (brain volumes) and adjusted for important confounders such as age, race, socioeconomic status, smoking, alcohol use, physical activity, body mass index, and some clinical characteristics.

MAIN RESULTS AND INTERPRETATION

In its independent review of the study, the HEI Review Committee concluded that Dr. Chen and colleagues conducted a novel study — one of the few to evaluate a potential relationship between long-term exposure to ambient particulate air pollution and neurocognitive outcomes and brain volumes. A high-quality neurocognitive outcome assessment, the inclusion of brain imaging data, and the availability of detailed individual-level covariate information were strengths of the study.

Chen and colleagues reported that exposure to neither ambient $PM_{2.5}$ nor diesel PM was associated with mild cognitive impairment and/or dementia in older women (see Statement Figure). Some positive and negative associations were reported between particulate air pollution and brain volumes, but the analyses were exploratory, their clinical significance remains unclear, and the findings differ from previous research.

The Committee had less confidence in the results for diesel PM than for ambient $PM_{2.5}$ because the exposure assessment was based on a screening tool that was considered less suitable for epidemiological studies and was likely prone to substantial measurement error. In addition, the effect modification analyses were hampered by lack of statistical power. Although the brain volume results were exploratory and the rationale for the statistical approach clearly described, the Committee questioned the emphasis on unadjusted findings in the report. Furthermore, it would have been useful to take additional steps to increase consistency in the brain volume analyses and reporting and to explore the potential for selection bias further. It should be noted that the number of air pollution studies on dementia-related outcomes remains small, and such studies are inherently difficult. Evidence from the current study, along with previous results, provides impetus for further research given the implications of the potential effects of ambient air pollution on dementia for our aging population.



Statement Figure. Association between neurocognitive outcomes and particulate air pollution in older women. Hazard ratio expressed per interquartile exposure range (3.9 µg/m³ for $PM_{2.5}$, 0.35 µg/m³ for diesel PM).

INVESTIGATORS' REPORT

Particulate Air Pollutants, Brain Structure, and Neurocognitive Disorders in Older Women

Jiu-Chiuan Chen[1,2], Xinhui Wang[1], Marc Serre[3], Steven Cen[4,5], Meredith Franklin[1], and Mark Espeland[6]

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ABSTRACT

An increasing number of studies have suggested that exposure to particulate matter (PM*) may represent a novel — and potentially amendable — environmental determinant of brain aging. The current longitudinal environmental epidemiological study addressed some important knowledge gaps in this emerging field, which combines the study of air pollution and neuroepidemiology. The investigators hypothesized that long-term PM exposure adversely influences global brain volume and brain regions (e.g., frontal lobe or hippocampus) that are critical to memory and complex cognitive processing or that are affected by neuropathological changes in dementia. It was also hypothesized that long-term PM exposure results in neurovascular damage and may increase the risk of mild cognitive impairment (MCI) and dementia. The investigators selected a well-characterized and geographically diverse population of older women (N = 7,479; average age = 71.0 ± 3.8 years at baseline) in the Women's Health Initiative (WHI) Memory Study (WHIMS) cohort (1996–2007), which included a subcohort (n = 1,403) enrolled in the WHIMS–Magnetic Resonance Imaging (WHIMS-MRI) study (2005–2006). Residence-specific yearly exposures to PM ≤ 2.5 µm in aerodynamic diameter ($PM_{2.5}$) were estimated using a Bayesian maximum entropy spatiotemporal model of annual monitoring data (1999–2007) recorded in the U.S. Environmental Protection Agency (U.S. EPA) Air Quality System (AQS). Annual exposures (1996–2005) to diesel PM (DPM) were assigned to each residential census tract in a nationwide spatiotemporal mapping, based on a generalized additive model (GAM), to conduct census tract–specific temporal interpolation of DPM on-road estimates given by the U.S. EPA National-Scale Air Toxics Assessment Program. Multiple linear regression and multicovariate-adjusted Cox models were used to examine the associations, with statistical adjustment for multiple potential confounders. The investigators found that participants had smaller brain volumes, especially in the normal-appearing white matter (WM), if they lived in locations with higher levels of cumulative exposure (1999–2006) to $PM_{2.5}$ before the brain MRI scans were performed. The associations were not explained by sociodemographic factors, socioeconomic status, lifestyle factors, or other clinical characteristics. Analyses showed that the adverse effect on brain structure in the participants was driven primarily by the smaller WM volumes associated with cumulative $PM_{2.5}$ exposures, which were present in the WM divisions of the

This Investigators' Report is one part of Health Effects Institute Research Report 193, which also includes a Critique by the Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Jiu-Chiuan Chen, Department of Preventive Medicine, University of Southern California, Keck School of Medicine, 2001 N. Soto Street, MC 9237, Los Angeles, CA 90089; e-mail: *jcchen@usc.edu*.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83467701 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

*A list of abbreviations and other terms appears at the end of this volume.

association brain area (frontal, parietal, and temporal lobes) and corpus callosum. Increased DPM exposures were associated with larger ventricular volume, suggesting an overall atrophic effect on the aging brains. The participants tended to have smaller gray matter (GM) volumes if they lived in areas with the highest (i.e., fourth quartile) estimated cumulative DPM exposure in the 10 years before the brain MRI scans, compared with women in the first to third quartiles. This observed association was present in the total brain GM and in the association brain cortices. The associations with normal-appearing WM varied by DPM exposure range. For women with estimated cumulative exposure below that of the fourth quartile, increased DPM estimates were associated with smaller WM volumes. However, for women with increased cumulative DPM exposures estimates in the fourth quartile, WM volumes were larger. This pattern of association was found consistently in the association brain area; no measurable difference was found in the volume of the corpus callosum. These observed adverse effects of cumulative exposure to $PM_{2.5}$ (linking exposure with smaller WM volumes) and to DPM (linking exposure in the highest quartile with smaller GM volumes) were not significantly modified by existing cardiovascular diseases, diabetes mellitus, obesity, or measured white blood cell (WBC) count. MRI measurements of the structural brain showed no differences in small-vessel ischemic diseases (SVID) in participants with varying levels of cumulative exposure to $PM_{2.5}$ (1999–2006) or DPM (1996–2005), and no associations between PM exposures and SVID volumes were noted for total brain, association brain area, GM, or WM. For neurocognitive outcomes followed until 2007, the investigators found no evidence for increased risk of MCI/dementia associated with long-term PM exposures. Although exploratory secondary analyses showed different patterns of associations linking PM exposures separately with MCI and dementia, none of the results was statistically significant. A similar lack of associations between PM exposures and MCI/dementia was found across the subgroups, with no strong indications for effect modification by cardiovascular diseases, diabetes mellitus, obesity, or WBC count. The investigators concluded that their study findings support the hypothesized brain-structure neurotoxicity associated with PM exposures, a result that is in line with emerging neurotoxicological data. However, the investigators found no evidence of increased risk of MCI/dementia associated with long-term PM exposures.

To better test the neurovascular effect hypothesis in PM-associated neurotoxic effects on the aging brain, the investigators recommend that future studies pay greater attention to selecting optimal populations with repeated measurements of cerebrovascular damage and address the possibility of selection biases accordingly. To further investigate the long-term consequence of brain-structure neurotoxicity on pathological brain aging, future researchers should take the pathobiologically heterogeneous neurocognitive outcomes into account and design adequately powered prospective cohort studies with improved exposure estimation and valid outcome ascertainment to assess whether PM-associated neurotoxicity increases the risks of pathological brain aging, including MCI and dementia.

INTRODUCTION

Exposure to PM has been recognized as a pervasive threat to cardiovascular health (Kaiser 2005; Nel 2005; Peters and Pope 2002). Over the last two decades, epidemiological studies have consistently shown that long-term exposure to particulate air pollutants, especially the fine particles ($PM_{2.5}$) from ambient sources, increases cardiovascular disease (CVD) risk and mortality (Brook et al. 2004, 2010). Previous studies have found that older people are more sensitive to these adverse health effects of particulate air pollutants (Shumake et al. 2013). Along with this mounting evidence in the epidemiological literature are intriguing findings from human exposure experiments and in vivo animal models, all pointing to the possibility that particulate air pollutants can induce systemic inflammation, perturb endothelial function, damage microvasculature, and cause the progression of atherosclerosis (Simkhovich et al. 2008). Although neuropathologic and epidemiological data have demonstrated the pivotal role of atherosclerosis and CVD risk factors in cognitive decline and dementia (Bowler and Gorelick 2007; Gorelick 2005; Hachinski 2007; Luchsinger et al. 2005; Mielke et al. 2007; Mosley et al. 2005; Prati et al. 2006), little attention has been directed to studying the adverse neurocognitive effects of exposures to ambient air pollution.

An increasing number of neurotoxicological studies have demonstrated that exposures to airborne PM induce oxidative stress, widespread neuroinflammation, and other neurotoxic reactions affecting multiple brain regions in animals (Block and Calderón-Garcidueñas 2009). Neuropathological examinations following autopsies of children and young adults living in urban areas with high levels of ambient air pollutants also revealed an increase in a biomarker of accelerated brain aging (Calderón-Garcidueñas et al. 2008). In the last few years, several cross-sectional studies have reported relatively low performance in various tests of cognitive functions among older people living in neighborhoods with higher levels of $PM_{2.5}$ (Ailshire and Clarke 2015; Ailshire and Crimmins 2014; Gatto et al. 2014) or in proximity to major roadways (Ranft et al. 2009; Wellenius

et al. 2012). Adverse PM effects on cognitive decline were reported in most longitudinal studies published so far, including the Nurses' Health Study Cognitive Cohort (Weuve et al. 2012) of older women (age 70 to 81 years), and more recently in older men and women (age 66 ± 6 years) of the Whitehall II subcohort living in Greater London (Tonne et al. 2014), but with no associations found in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort (Loop et al. 2013).

Despite a growing body of data supporting the concept that ambient air pollutants are novel — and potentially amendable — environmental determinants of brain aging (Block et al. 2012), there are substantial knowledge gaps in the emerging field that studies the role of ambient air pollution in the neuroepidemiology of neurocognitive impairment in the elderly. First, the affected brain structures and possible neuropathological damage underlying the PM-associated neurotoxic effects on cognitive decline remain unclear. Second, convincing cohort data linking PM exposures with increased risks of clinically significant cognitive impairment are still lacking. Third, there are very limited epidemiological data from studying effect modification by clinical characteristics, although such knowledge of individual susceptibility to neurotoxic effects of PM is essential both to help develop strategies for informed risk communication with high-risk patients and to inform toxicologists in selecting the appropriate animal models for future mechanistic studies.

SPECIFIC AIMS

The current study was proposed to address the above-mentioned knowledge gaps regarding whether and how exposure to ambient air pollution contributes to the neuroepidemiology of brain aging. Our research questions were based on two overarching hypotheses.

First, we hypothesized that long-term PM exposure adversely affects global brain volume and results in structural damage to brain regions (e.g., the association areas and hippocampus) that are critical for memory and complex cognitive processing or that are vulnerable to neuropathological changes in cognitive aging and dementia. This hypothesis was supported by numerous neurotoxicological studies reporting that exposures to airborne particles induce oxidative stress, widespread neuroinflammation, and other neurotoxic reactions affecting multiple brain regions (including the hippocampus and frontal lobes) in animals (Block and Calderón-Garcidueñas 2009).

Second, we hypothesized that long-term PM exposure results in neurovascular damages (e.g., cerebrovascular atherosclerosis and disruption of the blood–brain barrier), which may contribute both to cognitive aging (Gorelick and Pantoni 2013; Rincon and Wright 2013) and to neurodegeneration (Zlokovic 2005). This hypothesis was supported by the increasing amounts of evidence for neurovascular effects of PM exposures, including the elevated risk for ischemic stroke (Shin et al. 2014; Yang et al. 2014), impaired cerebrovascular perfusion (Wellenius et al. 2013), and damage to the blood–brain barrier (Hartz et al. 2008; Oppenheim et al. 2013).

These hypotheses were tested in a population of older women (aged ≥ 65 years). To test these hypotheses, we developed three specific aims (each with an illustrative hypothesized epidemiological association):

1. **To examine the anatomical measures of neuropathology associated with PM exposure.** (Exposure to high levels of particulate air pollutants is associated with smaller volumes of normal brain structures and larger ischemic lesion volumes, after adjustment for intracranial volume and multiple potential confounders.)
2. **To investigate whether PM exposure increases the risk for cognitive disorders.** (Living in places with high levels of particulate air pollutants is associated with increased risks for MCI or all-cause dementia, after adjustment for multiple potential confounders.)
3. **To identify the clinical determinants of susceptibility to neurotoxic effects of PM.** (Elderly women with indicators of population susceptibility [such as histories of cardiovascular diseases, including stroke, diabetes mellitus, obesity, and high WBC count] are more likely to be affected by the neurotoxic effects of ambient air pollution than those respectively without each indicated clinical characteristics.)

METHODS AND STUDY DESIGN

HUMAN STUDY APPROVAL

This project was approved by the Institutional Review Boards of the Keck School of Medicine of the University of Southern California and the Gillings School of Global Public Health of the University of North Carolina at Chapel Hill.

STUDY DESIGN AND POPULATION

We proposed a prospective study based in the geographically diverse and multiethnic WHIMS cohort. WHIMS was an ancillary study to the WHI trials of hormone therapy (WHI-HT) study, which consisted of two large,

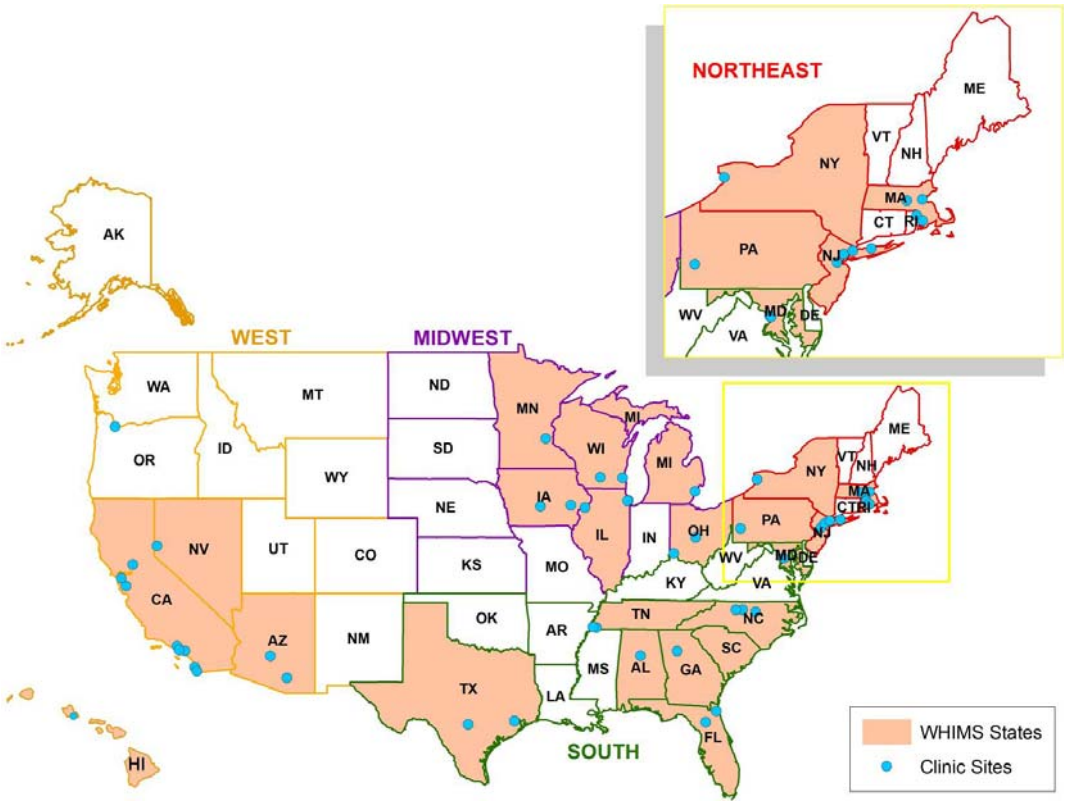

Figure 1. Geographic distributions of WHI Memory Study centers.

randomized, double-blind, placebo-controlled clinical trials of conjugated equine estrogen treatment alone (E-alone) for women with a prior hysterectomy or in combination with medroxyprogesterone acetate (E+P) for women without a prior hysterectomy (Additional Materials 1, Figure 1, available on the HEI website). The WHIMS study design, eligibility criteria, and recruitment procedures have been described elsewhere (Shumaker et al. 1998). After the discovery of an unfavorable risk-to-benefit ratio for its noncognitive endpoints, the E+P trial was discontinued in July 2002. The E-alone trial also ended earlier than planned, in February 2004, because of the discovery of a greater risk of stroke and a lack of benefit for coronary heart disease. These decisions also ended the WHIMS trial, but annual follow-ups continued into the WHIMS extension study (2005–2007). WHIMS included 7,479 participants who were community-dwelling older women, aged 65 to 80 years at baseline (1996–1999), appropriate candidates for hormonal therapy, enrolled from 38 (of 40) WHI clinical centers (Figure 1) in 24 states and Washington, D.C., and free of dementia as defined by WHIMS protocols (Espeland et al. 2004; Shumaker et al. 2003) at baseline. During the follow-up (2005–2006), 1,403 WHIMS participants were enrolled in the WHIMS-MRI study (Coker et al. 2009; Jaramillo et al. 2007), conducted at 14 WHIMS sites approximately 8 years after WHIMS enrollment and 2 to 4 years after the trials ended. The WHIMS-MRI study sites were selected to maximize geographic, racial, and ethnic diversity (Additional Materials 1, Figure 2, available on the HEI website).

STUDY OUTCOME DATA

The current study included two types of neurological health data: MRI-measured brain volumes (for Aim 1 and Aim 3), using data collected in the WHIMS-MRI study, and clinically defined neurocognitive outcomes (for Aim 2 and Aim 3), using data collected in the WHIMS main trials and extension study.

Neurocognitive Outcomes

Our study outcome variable was the incidence of MCI or probable dementia, as determined by the validated four-phase WHIMS protocols (Shumaker et al. 1998, 2004). In phase 1, trained, masked, and certified technicians administered the Modified Mini-Mental State Examination (Teng and Chui 1987) test at baseline and then annually. Women who screened positively for cognitive impairment, according to education-adjusted cut-points, proceeded to more extensive neuropsychological testing (phase 2), including a modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (Morris et al. 1989). Participants subsequently received a detailed clinical neurological and neuropsychiatric evaluation by physicians (i.e., neurologists, geriatricians, or geriatric psychiatrists) with experience in diagnosing dementia (phase 3). Each suspected case of dementia then underwent cranial CAT scan and a series of laboratory tests to rule out possible reversible causes of cognitive decline and dementia (phase 4). Following the accepted criteria (Shumaker et al. 2003) at WHIMS baseline, MCI was defined as poor performance ($\leq$ tenth percentile in CERAD norms) on at least one CERAD test, evidence of functional impairment (but not severe enough to interfere with activities of daily living), and absence of psychiatric or other medical disorders (including probable dementia) that could explain the cognitive impairment. All clinical and testing data were then transmitted to the central adjudication committee for final confirmation of dementia, based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association 1994).

Brain MRI Outcome Variables

The WHIMS-MRI Quality Control Center (Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania) developed scan acquisition (using 1.5-T scanners) and processing protocols for the WHIMS-MRI study (Coker et al. 2009; Lao et al. 2008; Resnick et al. 2009). Scanning pulse sequences were performed as follows:

- Series one: three-plane gradient echo localizer for positioning;
- Series two: sagittal T1-weighted spin echo midslice image to demonstrate anatomic location of the anterior commissure/posterior commissure (AC/PC) for slice angle and slice position;
- Series three: oblique axial spin density/T2-weighted spin echo (3200/0/30120/3) images from the vertex to skull base parallel to the AC/PC plane;
- Series four: oblique axial FLAIR T2-weighted spin echo (8000/2000/100/3) images matching the slice positions in series three; and
- Series five: oblique axial three-dimensional T1-weighted gradient echo (flip angle 30; 21/0/8/1.5) images from the vertex to the skull base parallel to the AC/PC plane. The field of view was 22 cm, and the acquisition matrix was 256×256 for series three, four, and five.

Standard T1-, T2-, proton density–weighted, and fluid-attenuated inversion recovery (FLAIR) scans were acquired. T1-weighted volumetric MRI scans were preprocessed to a standardized protocol for alignment, removal of extracranial material, and segmentation of brain into gray and white parenchyma and cerebrospinal fluid (CSF). Intracranial volume (ICV) was estimated as the total cerebral hemispheric volumes, including ventricular CSF and the CSF within the sulcal spaces. Regional volumetric measurements were obtained using an automated computer-based template warping method (Shen and Davatzikos 2002) that summed the number of respective voxels within each anatomical region of interest. This technique is based on a digital atlas labeled for brain lobes and individual structures, including the hippocampus. Atlas definitions were transferred to MRI scans via an image-warping algorithm performing pattern matching of anatomically corresponding brain regions. Supratentorial brain tissue was classified as GM or WM and assigned to one of 92 anatomic regions of interest in the cerebrum. The volumes of GM, WM, and CSF of each labeled brain region were obtained by summing the number of respective voxels within each region. Measures of regional volumes obtained by this approach showed high test–retest stability over time (Driscoll et al. 2009). The computer-assisted methodology was validated against manual segmentation used by other cohorts (Anbeek et al. 2004; Launer et al. 2011). In the current study, we performed region-of-interest analyses focused on the hippocampus and multimodal association brain area (i.e., the frontal, parietal, and temporal lobes), because these brain regions largely cover the most vulnerable neural networks affected by both aging and neurodegenerative disease (Jagust 2013; Squire and Zola-Morgan 1991). The determination of WM lesions was based on multimodal data, using the WM lesion segmentation (WMLS) algorithm (Lao et al. 2008; Zacharaki et al. 2008) to segment SVID on MRI images. After data preprocessing via histogram standardization and coregistration, the lesion segmentation component of the algorithm was applied to local features extracted from the coregistered multiparametric MRI sequences, specifically T1, T2, and FLAIR. The lesion segmentation component of WMLS

was based on a support vector machine classifier, which trains on expert-defined lesions and uses the training model to classify unseen voxels from the test image as SVID or normal tissue. By combining WMLS segmentation and tissue segmentation, estimates of the SVID-affected tissues (referred to as SVID volumes) in the total brain, GM, and WM were obtained.

ESTIMATION OF RESIDENTIAL PM EXPOSURES

Geocoded information about WHIMS participants' addresses was used to define the residential locations where exposures were estimated. Geocoding of the WHI address database followed a standardized protocol by a single geocoding vendor selected from four candidates on the basis of its accuracy. The results of studies of the reliability and validation of geocoding indicated a high level of accuracy in the geocoding of WHI addresses (Whitsel et al. 2004, 2006). Because WHI address data were collected prospectively at each clinical visit and updated at least biannually since WHI's inception in 1993, we were able to take into account residential mobility in the exposure assessment. High-quality geocodes of WHI participants have also been used in other environmental epidemiological studies (Griffin et al. 2013; Whitsel and Avery 2010).

Estimation of Annual $PM_{2.5}$ Exposure

At each geocoded residential location, annual $PM_{2.5}$ exposure was estimated using spatiotemporal modeling based on the Bayesian maximum entropy (BME) of nationwide yearly $PM_{2.5}$ monitoring data (1999 onward) recorded at the U.S. EPA AQS. The yearly $PM_{2.5}$ monitoring data were calculated based on hourly and daily $PM_{2.5}$ raw data downloaded from the AQS website and restricted to parameter code 88101 and 88502 (see part B, section 2.1, of Additional Materials 1, available on the HEI website, for more details). We were unable to estimate the $PM_{2.5}$ exposure data before 1999, because sufficiently extensive monitoring data were not available at that time.

However, given the BME spatiotemporal modeling results for yearly $PM_{2.5}$ exposures assigned to the longitudinal data on residential locations collected before and during WHIMS follow-up, we were able to construct subject-specific annual $PM_{2.5}$ exposure series for 1999–2007.

BME, a powerful stochastic modeling and mapping method (Christakos and Serre 2000a,b; Christakos et al. 2001; Serre et al. 2003, 2004), has been applied to estimate air pollution exposure in several epidemiological studies (Yu et al. 2007a,b) because it has several desirable features that better characterize environmental processes. First, BME jointly models the spatiotemporal interdependence of environmental data in terms of means structure and covariance functions varying across the spatiotemporal domains. Second, BME makes no distribution assumptions about the environmental processes, with the result that non-Gaussian data are automatically integrated into the estimation framework. Third, within its underlying Bayesian epistemic framework, the BME method provides the flexibility to overcome several analytic challenges inherent in ambient air pollution modeling and estimation (such as non-Gaussian distributions used to model the uncertainties associated with missing data). The classical spatial kriging method of linear geostatistics is obtained as a limiting case of BME when the analysis is restricted to the spatial domain and the uncertainty associated with the data is assumed to follow a Gaussian distribution. Hence, BME is a nonlinear estimation method that naturally extends the widely used linear kriging method. The fundamental BME and kriging equations are shown in Equations 3 and 4, respectively, in Additional Materials 1 (available on the website). Numerous previous works have already compared BME with its linear kriging limiting case (Christakos and Serre 2000a; Savelieva et al. 2004; Serre et al. 2004).

For our epidemiological study of the effects of air pollution, the implementation of BME-based spatiotemporal modeling followed three main stages. At the structural stage, a prior probability density function (PDF) for the distribution of $PM_{2.5}$ was constructed on the basis of its spatiotemporal covariance function (Equation 6 of Additional Materials 1, available on the website). At the specificatory stage, site-specific knowledge was organized by combining the data from the ambient monitoring system (which contained either hard data [complete observations] or soft data [incomplete observations; Equation 5 of Additional Materials 1, available on the website]). For each AQS monitoring site, we calculated the annual average concentration as the arithmetic mean of the recorded daily concentrations obtained from the AQS, which were classified as hard data if more than 75% of the intended daily samples were present for each quarter of the year or as soft data if otherwise. The selection of 75% data completeness as the cutoff was consistent with similar BME work published earlier (Akita et al. 2012; Reyes and Serre 2014); the resulting complete data were also used to determine the cross-validation data comparing the predicted exposures against the observed values. At the integration stage, an operational Bayesian conditionalization rule was used to assimilate the total knowledge base by updating the prior PDF with the combined data information from the second stage, leading to a posterior PDF that provided a statistical summary of air pollution concentrations at any space/time point of interest. In order to evaluate the implementation

of the BME approach, we compared its performance with that of two conventional approaches, the spatial nearest-neighbor approach (NNA) and the spatial inverse distance weighting (IDW) method, as well as with a third method consisting of BME's spatial linear limiting case, the spatial kriging method. We expected that a correct implementation of BME would result in model performance statistics exceeding those of the performance of either NNA or IDW but that would be similar to those of spatial kriging. A detailed description of this comparison is provided in Additional Materials 1 (available on the HEI website), where we showed that BME had better model performance statistics than NNA, IDW, and spatial kriging, indicating that our BME produces better predictions than the compared models. The better performance of BME over more naïve approaches is an expected result that is in line with all previous BME works. Therefore the fact that we obtained an expected result with BME provides evidence supporting that BME was correctly implemented. This comparison result was part of the QA/QC checks of our quality assurance plan.

Our empirical data showed that BME estimates of annual exposures were highly correlated (cross-validation Spearman's $R = 0.90$) with the yearly $PM_{2.5}$ concentrations recorded at the AQS monitoring sites (see Additional Materials 1, available on the HEI website). After we obtained the yearly exposure estimates, cumulative $PM_{2.5}$ exposures were calculated as time-weighted averages from 1999 to the WHIMS-MRI inception in 2005–2006.

Estimation of Annual DPM Exposure

The DPM exposure estimates came from the U.S. EPA National-Scale Air Toxics Assessment (NATA) Program (U.S. EPA 2011a,b), which was the only publicly accessible national database with information on traffic-related PM exposure at the time the current study was proposed.

Listed by U.S. EPA as a mobile-source air toxic, DPM is considered to best represent diesel exhaust in terms of its potential health risks. Previous applications of NATA-based exposure models to epidemiological research have included studies on autism in California (Windham et al. 2006), reproductive outcomes (Vassilev et al. 2001), mortality (Fox 2002), and pediatric cancer (Reynolds et al. 2003), all showing positive associations with modest effect sizes for selected hazardous air pollutants. Validation of NATA-based estimates for population exposures in health risk comparisons has also been published (Rosenbaum et al. 1999). The U.S. EPA's NATA program had estimated annual average DPM ambient concentrations (in $\mu g/m^3$) at the census-tract level for 1996, 1999, 2002, and 2005. These estimates are based on mobile-source spatial dispersion modeling of diesel emissions estimated from the National Mobile Inventory Model (U.S. EPA 2011c). This spatial dispersion model also takes into account both census-based demographics and meteorological measures. The specific DPM exposure estimates decomposed into on-road sources (e.g., cars and trucks) were extracted to represent the aggregated DPM estimates, which we considered to be proxy indicators of exposure to PM from roadway traffic. We did not consider the off-road DPM estimates also available in NATA. In order to estimate the ambient DPM concentrations in 1996–2005, which covered the intervening years with no validated models, we used the four-year wealth of NATA DPM data to conduct a nationwide census tract–specific ($i = 1, \ldots, 65{,}141$) multiyear interpolation using the GAMs. This analytic approach was justified by our earlier analyses (see Additional Materials 1, available on the website), based on a nationwide four-level hierarchical model to examine both temporal (64%) and spatial (36%) exposure variability, the latter of which was further decomposed into between-census-tract difference (43%) versus between-county/within-state (28%) or between-state difference (29%). Given the longitudinal data on residential geocodes, the resulting spatiotemporally interpolated GAM estimates without extrapolation allowed us to derive the annual DPM exposure from the inception of WHIMS (1996–1998) to 2005.

COVARIATES DATA

The comprehensive WHI covariates data offered a unique opportunity to assess the potential confounding of, and individual susceptibility to, PM neurotoxic effects.

Measurement of Covariates

Participants completed questionnaires to provide baseline information on demographics (age and race or ethnicity), socioeconomic status (SES; including education in years, family income, and employment status), lifestyle factors (smoking, alcohol consumption, and physical activity), and relevant clinical characteristics (use of menopausal HT, prior depression, and CVD and related risk factors). The women were grouped according to three body mass index (BMI, in kg/m^2) categories (<25.0 vs. 25.0–29.9 vs. ≥ 30.0). Hypertension was defined as taking an antihypertensive medication or having elevated blood pressure (systolic ≥ 140 or diastolic ≥ 90 mm Hg). Treated diabetes mellitus was defined as a physician diagnosis plus oral medications or insulin therapy. History of CVD included previous coronary heart disease (myocardial infarction, coronary angioplasty, or coronary artery bypass graft), stroke, or transient ischemic attack. Good reliability and validity of both the self-reported medical histories and the physical measures have been documented (Heckbert et

al. 2004; Langer et al. 2003). The Burnam screening algorithm (Burnam et al. 1988) was used to characterize the presence of prior depressive disorders, which increased the risk of MCI/dementia (Goveas et al. 2011) in WHIMS.

In our data analyses plan for the final analyses of brain MRI data and clinical endpoints (i.e., MCI or dementia), definition of these covariates followed the categorical specifications as described in the respective descriptive tables. The WHI's standard categorical age variables were used in our earlier analyses on both MRI data and incident MCI or dementia. In our subsequent work on the brain MRI data analyses, we computed a continuous age variable aligned to the individual age at the brain MRI scan. Because there were no major differences in the statistical results on brain MRI data analyses using the categorical age variable versus continuous age variable, we carried the final analyses on brain MRI data using the continuous age variable, which allowed us to construct more parsimonious models, in the relatively smaller WHIMS MRI subcohort.

Clinical Indicators of Increased Susceptibility

The proposed hypotheses about population susceptibility are consistent with the notion of disproportionately adverse health effects of PM exposure observed among vulnerable subpopulations with CVD (Bateson and Schwartz 2004; Chen 2007; Liao et al. 2004, 2005; Park et al. 2005; Pekkanen et al. 2002; Zeka et al. 2006), diabetes mellitus (Bateson and Schwartz 2004; Goldberg et al. 2000; Liao et al. 2005; O'Neill et al. 2005; Zanobetti and Schwartz 2002), obesity (Chen et al. 2007; Dubowsky et al. 2006; Miller et al. 2007), and the baseline level of WBC–neutrophil count (Dubowsky et al. 2006; Schwartz et al. 2005).

We used baseline data from medical histories and physical and laboratory measures to characterize each woman's susceptibility. These potential effect modifiers include histories of CVD (including stroke), diabetes mellitus, degree of obesity as defined by BMI (normal [<25.0], overweight [25.0–29.9], obese [≥30]), and WBC count. Previous studies have shown that information on these selected CVD entities reported by WHI participants agreed substantially (kappa = 0.64–0.84) with reviews by study physicians at clinical centers (Heckbert et al. 2004). At baseline, those women with physician-diagnosed non-pregnancy-related diabetes and receiving either oral medications or insulin were defined as having treated diabetes mellitus. Good test–retest reliability (as measured by intraclass correlation coefficient = 0.82) of this classification was previously documented (Langer et al. 2003). A similar definition for diabetes mellitus has been used in other WHI main analyses (Hsia et al. 2005; Margolis et al. 2004). The WBC count was derived from the hemogram testing sample collected in a tube containing the anticoagulant edetic acid. These samples were analyzed at local laboratories at each of the WHI clinical centers following standardized methods.

STATISTICAL METHODS AND DATA ANALYSIS

DESCRIPTIVE ANALYSES OF EXPOSURE DISTRIBUTION BY COVARIATES

We compared the distributions of estimated PM exposures across various population characteristics. For time-varying exposures, the distributions were based on the individual-specific summary measure aggregated from all relevant exposure estimates during the study follow-up. The exposure distributions were then given as the quartiles of the summarized PM exposure, stratified by various categories of population characteristics. Chi-square tests or Fisher's exact tests were used to compare the exposure distributions by population characteristics.

DISTRIBUTIONS OF BRAIN VOLUMES BY EXPOSURE CATEGORIES

The MRI-measured brain volumes were compared among subgroups defined by the quartiles of cumulative PM exposures before the WHIMS-MRI baseline in 2005–2006. Statistical significance was predetermined at the level of 0.01. Because volumetric measures may be partly attributable to individual differences in brain sizes, it is important to correct for ICV when analyzing the differences in regional brain volumes (O'Brien et al. 2006, 2011). Using analysis of covariance (ANCOVA) adjusting for ICV, the empirical associations were first explored by comparing brain volumes (normal brain and SVID volumes with log-transformation) across the exposure categories. Any observed differences in brain volumes were further tested for the presence of linear trend if indicated by the empirical comparison.

MULTIPLE LINEAR REGRESSION MODELS

Outcome variables with statistically significant associations in the ICV-adjusted ANCOVA were then further examined using multiple linear regression models to adjust for potential confounding by sociodemographic factors, SES, lifestyles, and clinical characteristics related to brain volume. In addition, we conducted two sets of sensitivity analyses. To evaluate possible residual confounding by race or ethnicity, the adjusted analyses were restricted

to non-Hispanic whites. To evaluate whether the results were sensitive to a missing-at-random (MAR) assumption in calculating the cumulative PM exposures before brain MRI scans, we also restricted the analyses to participants who had more complete yearly exposure estimates (with more than 60% complete data over the averaging period). To evaluate effect measure modification, we stratified the effect estimates by examining whether the putative neurotoxic effects differed by the presence of a prior history of CVD or diabetes mellitus, by BMI category, or by WBC count (dichotomized at median = 5,700/μL), using the likelihood-ratio test to evaluate the interaction. Statistical analyses (e.g., proc glm for ANCOVA and multiple linear regression) were performed using SAS System for Windows, Version 9.3 (SAS Institute, Cary, NC).

DISTRIBUTIONS OF MCI/DEMENTIA INCIDENCE BY EXPOSURE CATEGORIES

The associations of incident MCI/dementia with estimated long-term residential exposures to PM (Aim 2) were examined using the time-to-event analyses. Follow-up time for each woman was calculated from WHI randomization to the annual examination date that triggered the ultimate classification of defined cognitive impairment (MCI or dementia), or to the last date of the completion of an annual cognitive assessment, whichever came first. Statistical comparisons of the incidence rates across the defined PM exposure categories were conducted in robust Poisson regression, based on likelihood ratio tests.

COX PROPORTIONAL HAZARD MODELS

Cox models were used to estimate hazard ratios (HRs) for the neurocognitive outcomes associated with estimated PM exposures, adjusting for potential confounders. In our primary analyses, we pooled the data on the incidence of MCI and dementia in order to achieve sufficient statistical power (see Additional Materials 1, available on the HEI website). We used time on study as the time scale in the constructed Cox models because simulation studies have suggested that such an approach was less subject to potential biases in estimating the effects of environmental factors (e.g., PM exposures) with prominent secular trends (Griffin et al. 2012) compared with the alternatives (e.g., attained age and calendar time). Our secondary analyses also explored the putative adverse PM effects on MCI and on dementia, separately. For the MCI analyses, participants classified as having dementia without being classified as having MCI during the earlier follow-up were excluded, because MCI is considered a pre-dementia state and conceptually these dementia cases could not be at risk for developing MCI. The assumed proportional hazard was supported by the proportionality test.

To evaluate effect measure modification, we further stratified the effect estimates by examining whether neurocognitive outcomes differed by the presence of prior histories of CVD or diabetes mellitus, by BMI categories, or by WBC count (dichotomized at median = 5,500/μL), using the Wald test for evaluating interaction. Statistical analyses (e.g., proc phreg for the Cox proportional hazard model) were performed using the SAS System for Windows, Version 9.3 (SAS Institute).

RESULTS

$PM_{2.5}$ EXPOSURES

Population Characteristics and $PM_{2.5}$ Exposures in WHIMS-MRI Cohort

Table 1 shows the WHIMS-MRI population distribution of cumulative $PM_{2.5}$ exposures (1999–2006) in relation to selected baseline personal and clinical characteristics. Consider older women with cumulative exposures estimated in the upper two quartiles (>12.24 μg/m^3) as those residing in areas with relatively high $PM_{2.5}$ levels. A larger prevalence of living in high exposure categories was found in older women who were more likely to be a member of an ethnic minority (black or Hispanic white), to be less physically active (with no moderate or strenuous activity period ≥ 20 minutes/week), to currently smoke, or to have diabetes mellitus. WHIMS-MRI participants recruited from the South were the least likely to experience high exposure levels.

MRI-Measured Brain Volumes in Relation to $PM_{2.5}$ Exposures in WHIMS-MRI Cohort

ICV-adjusted ANCOVA comparing normal and ischemic brain volumes across the cumulative $PM_{2.5}$ exposures quartiles are summarized in Table 2. Participants in the lowest $PM_{2.5}$ exposure quartile (<10.67 μg/m^3) had the largest normal brain volume compared with those in the second to fourth exposure quartiles; this pattern persisted in the association brain areas. Differences in normal brain volumes associated with $PM_{2.5}$ exposures were largely limited to the normal-appearing WM; no statistically significant differences were observed in GM volumes. Across the quartile distribution of cumulative $PM_{2.5}$ exposures, the measured total WM volumes (mean ± SD in cm^3) decreased by 3.5% (from 410.71 ± 50.44 to 396.55 ± 49.30). Ventricular sizes and volumes of hippocampus or basal ganglia did not differ by $PM_{2.5}$ exposures. A consistent monotonic pattern of associations with decrements in WM volume across the $PM_{2.5}$ exposure quartiles was found in the association brain area and its three lobar divisions. SVID volumes did not differ by $PM_{2.5}$ exposures.

Table 1. Sociodemographic Factors, Lifestyle Factors, and Clinical Characteristics by $PM_{2.5}$ Exposure Quartiles in the WHIMS-MRI Cohort (1999–2006)

Population Characteristics[a]	N[b]	Cumulative Average Annual $PM_{2.5}$ (μg/m³) (quartile) 5.75–10.67 (N = 351)	10.67–12.24 (N = 351)	12.24–14.16 (N = 351)	14.16–22.18 (N = 350)	P value[c]
U.S. Region						<0.0001
Northeast	329	57 (17.3%)	74 (22.5%)	98 (29.8%)	100 (30.4%)	
South	207	64 (30.9%)	59 (28.5%)	69 (33.3%)	15 (7.2%)	
Midwest	486	137 (28.2%)	126 (25.9%)	84 (17.3%)	139 (28.6%)	
West	381	93 (24.4%)	92 (24.1%)	100 (26.2%)	96 (25.2%)	
Age at baseline (yr)						0.24
65–69	712	197 (27.7%)	169 (23.7%)	164 (23%)	182 (25.6%)	
70–74	495	111 (22.4%)	132 (26.7%)	135 (27.3%)	117 (23.6%)	
≥75	196	43 (21.9%)	50 (25.5%)	52 (26.5%)	51 (26%)	
Ethnicity						<0.0001
Black or African-American	64	7 (10.9%)	4 (6.3%)	27 (42.2%)	26 (40.6%)	
Hispanic White	21	1 (4.8%)	2 (9.5%)	10 (47.6%)	8 (38.1%)	
Non-Hispanic White	1,276	336 (26.3%)	336 (26.3%)	301 (23.6%)	303 (23.7%)	
Other or missing	42	7 (16.7%)	9 (21.4%)	13 (31%)	13 (31%)	
Participant's education level						0.79
<High school	63	20 (31.7%)	12 (19%)	15 (23.8%)	16 (25.4%)	
High school/GED	325	79 (24.3%)	86 (26.5%)	76 (23.4%)	84 (25.8%)	
>High school	1,012	252 (24.9%)	252 (24.9%)	260 (25.7%)	248 (24.5%)	
Family income						0.23
<$10,000	50	14 (28%)	13 (26%)	12 (24%)	11 (22%)	
$10,000 to $34,999	671	184 (27.4%)	158 (23.5%)	168 (25%)	161 (24%)	
$35,000 to $74,999	501	111 (22.2%)	133 (26.5%)	131 (26.1%)	126 (25.1%)	
≥$75,000	136	25 (18.4%)	40 (29.4%)	32 (23.5%)	39 (28.7%)	
Missing	45	17 (37.8%)	7 (15.6%)	8 (17.8%)	13 (28.9%)	
Employment						0.18
Currently employed	255	75 (29.4%)	60 (23.5%)	64 (25.1%)	56 (22%)	
Not working	146	29 (19.9%)	31 (21.2%)	40 (27.4%)	46 (31.5%)	
Retired	1,000	247 (24.7%)	260 (26%)	246 (24.6%)	247 (24.7%)	
Smoking status						0.0065
Never smoked	806	200 (24.8%)	199 (24.7%)	195 (24.2%)	212 (26.3%)	
Past smoker	526	136 (25.9%)	134 (25.5%)	145 (27.6%)	111 (21.1%)	
Current smoker	59	13 (22%)	12 (20.3%)	8 (13.6%)	26 (44.1%)	
Alcohol intake						0.10
Non-drinker	180	47 (26.1%)	30 (16.7%)	46 (25.6%)	57 (31.7%)	
Past drinker	232	62 (26.7%)	55 (23.7%)	53 (22.8%)	62 (26.7%)	
<1 drink per day	822	208 (25.3%)	218 (26.5%)	206 (25.1%)	190 (23.1%)	
>1 drink per day	158	31 (19.6%)	46 (29.1%)	43 (27.2%)	38 (24.1%)	

Table continues next page

[a] Shown as N (%) for each exposure quartile for the indicated subcategory of population characteristics. See Figure 1 for map showing regions of the United States.

[b] The total number of subjects summed up across each subcategory varies slightly because of missing values.

[c] Calculated by comparing the distribution of exposure quartiles across subcategories for each personal characteristic by chi-square or Fishers exact test.

[d] E-alone: conjugated equine estrogen alone; E+P: estrogen plus progestin (medroxyprogesterone acetate).

Table 1 (*continued*). Sociodemographic Factors, Lifestyle Factors, and Clinical Characteristics by $PM_{2.5}$ Exposure Quartiles in the WHIMS-MRI Cohort (1999–2006)

Population Characteristics[a]	N[b]	Cumulative Average Annual $PM_{2.5}$ (μg/m^3) (quartile) 5.75–10.67 (N = 351)	10.67–12.24 (N = 351)	12.24–14.16 (N = 351)	14.16–22.18 (N = 350)	P value[c]
Moderate or strenuous activity (≥20 min)						0.07
No activity	799	196 (24.5%)	188 (23.5%)	199 (24.9%)	216 (27%)	
Some activity	78	21 (26.9%)	17 (21.8%)	16 (20.5%)	24 (30.8%)	
2–4 episodes/wk	280	61 (21.8%)	78 (27.9%)	72 (25.7%)	69 (24.6%)	
≥4 episodes/wk	244	73 (29.9%)	67 (27.5%)	63 (25.8%)	41 (16.8%)	
BMI (kg/m^2)						0.90
<25	417	109 (26.1%)	106 (25.4%)	101 (24.2%)	101 (24.2%)	
25–29	527	130 (24.7%)	134 (25.4%)	138 (26.2%)	125 (23.7%)	
≥30	454	112 (24.7%)	109 (24%)	110 (24.2%)	123 (27.1%)	
HT ever						0.06
No	752	181 (24.1%)	201 (26.7%)	171 (22.7%)	199 (26.5%)	
Yes	651	170 (26.1%)	150 (23%)	180 (27.6%)	151 (23.2%)	
History of depression						0.79
No	1,291	321 (24.9%)	326 (25.3%)	320 (24.8%)	324 (25.1%)	
Yes	91	24 (26.4%)	20 (22%)	26 (28.6%)	21 (23.1%)	
Hypertension ever						0.23
No	889	229 (25.8%)	233 (26.2%)	209 (23.5%)	218 (24.5%)	
Yes	505	121 (24%)	115 (22.8%)	140 (27.7%)	129 (25.5%)	
Diabetes treated ever (pills or injections)						0.06
No	1,356	347 (25.6%)	338 (24.9%)	335 (24.7%)	336 (24.8%)	
Yes	46	4 (8.7%)	12 (26.1%)	16 (34.8%)	14 (30.4%)	
High cholesterol requiring pills ever						0.18
No	1,153	302 (26.2%)	284 (24.6%)	280 (24.3%)	287 (24.9%)	
Yes	223	43 (19.3%)	62 (27.8%)	60 (26.9%)	58 (26%)	
Cardiovascular disease ever						0.44
No	1,193	302 (25.3%)	307 (25.7%)	294 (24.6%)	290 (24.3%)	
Yes	193	45 (23.3%)	42 (21.8%)	51 (26.4%)	55 (28.5%)	
Subcohort membership[d]						0.97
E-alone control	263	69 (26.2%)	63 (24%)	64 (24.3%)	67 (25.5%)	
E-alone intervention	260	65 (25%)	62 (23.8%)	62 (23.8%)	71 (27.3%)	
						0.85
E+P control	447	113 (25.3%)	111 (24.8%)	118 (26.4%)	105 (23.5%)	
E+P intervention	433	104 (24%)	115 (26.6%)	107 (24.7%)	107 (24.7%)	

[a] Shown as N (%) for each exposure quartile for the indicated subcategory of population characteristics. See Figure 1 for map showing regions of the United States.

[b] The total number of subjects summed up across each subcategory varies slightly because of missing values.

[c] Calculated by comparing the distribution of exposure quartiles across subcategories for each personal characteristic by chi-square or Fishers exact test.

[d] E-alone: conjugated equine estrogen alone; E+P: estrogen plus progestin (medroxyprogesterone acetate).

Table 2. Brain Volume Outcomes by $PM_{2.5}$ Exposure Quartiles in the WHIMS-MRI Cohort (1999–2006)

MRI-Measured Brain Volume (mean ± SD [cm^3])	Cumulative Average Annual $PM_{2.5}$ ($\mu g/m^3$) (quartile) 5.75–10.67 ($N = 351$)	10.67–12.24 ($N = 351$)	12.24–14.16 ($N = 351$)	14.16–22.18 ($N = 350$)	*P* value[a]
Total brain volume	808.00 ± 74.17	799.41 ± 73.6	792.39 ± 78.68	799.22 ± 71.78	<0.0001[b]
Normal-Appearing Brain Structure					
Normal brain volume	798.99 ± 73.69	790.93 ± 73.06	783.51 ± 77.85	791.21 ± 71.1	<0.0001[b]
Association area	620.06 ± 58.65	613.20 ± 57.51	607.71 ± 60.9	614.54 ± 56.92	<0.0001[b]
Frontal lobe	284.25 ± 28.68	279.13 ± 27.75	277.94 ± 30.17	280.44 ± 27.72	<0.0001[b]
Parietal lobe	151.97 ± 15.79	151.11 ± 16.08	149.08 ± 16	151.33 ± 15.54	0.02[b]
Temporal lobe	183.84 ± 18.62	182.96 ± 18.45	180.68 ± 19.34	182.77 ± 17.77	0.009[b]
Ventricle	35.62 ± 15.02	37.73 ± 17.52	37.30 ± 15.73	37.80 ± 16.8	0.16[b]
GM					
Total GM	353.37 ± 40.06	350.72 ± 40.59	346.68 ± 45.49	359.64 ± 42.48	0.19[b]
Association cortex	268.40 ± 31.03	265.68 ± 32.31	261.96 ± 37.03	273.30 ± 34.57	0.24[b]
Frontal GM	118.61 ± 14.69	117.67 ± 15.17	116.53 ± 16.98	120.55 ± 16.56	0.30[b]
Parietal GM	62.43 ± 8.32	62.03 ± 9.15	60.56 ± 10.32	63.90 ± 9.25	0.25[b]
Temporal GM	87.36 ± 10.68	85.98 ± 10.61	84.87 ± 11.95	88.85 ± 10.96	0.28[b]
WM					
Total WM	410.71 ± 50.44	405.28 ± 54.38	402.03 ± 56.37	396.55 ± 49.3	<0.0001[b]
Association brain areas	351.65 ± 44.07	347.52 ± 46.81	345.75 ± 48.9	341.25 ± 42.73	<0.0001[b]
Frontal WM	165.64 ± 22.74	161.45 ± 22.7	161.41 ± 24.63	159.90 ± 21.68	<0.0001[b]
Parietal WM	89.54 ± 12.32	89.08 ± 13.24	88.52 ± 13.16	87.44 ± 12.24	0.0005[b]
Temporal WM	96.48 ± 12.13	96.98 ± 13.7	95.81 ± 13.47	93.92 ± 11.43	<0.0001[b]
Corpus callosum	9.21 ± 1.28	9.20 ± 1.3	9.14 ± 1.28	9.08 ± 1.37	0.03[b]
Hippocampus	5.68 ± 1.01	5.77 ± 1.04	5.77 ± 1.14	5.72 ± 1.03	0.76[b]
Basal ganglia	34.90 ± 3.41	34.93 ± 3.51	34.80 ± 3.58	35.02 ± 3.26	0.91[b]
Small-Vessel Ischemic Disease (SVID)					
Total brain SVID volume	9.01 ± 11.68	8.49 ± 10.16	8.88 ± 12.47	8.01 ± 10.35	0.06[c]
Association brain	7.25 ± 10.25	6.72 ± 8.84	7.32 ± 11.15	6.54 ± 9.08	0.22[c]
GM SVID	0.50 ± 1.43	0.36 ± 1.00	0.43 ± 1.23	0.34 ± 1.00	0.18[c]
WM SVID	7.63 ± 9.83	7.09 ± 8.56	7.55 ± 10.71	6.89 ± 8.87	0.14[c]

[a] *P* values calculated from ICV-adjusted ANCOVA, testing the difference or presence of linear trend in the indicated brain volumes or log-transformed SVID volumes across the exposure quartiles.

[b] *P* values from a linear trend test.

[c] *P* values from between-group comparisons by exposure categories.

Multiple Linear Regression Models

Main Effects of $PM_{2.5}$ Exposures Results of the linear regression models are summarized in Table 3, with adjustment for multiple potential confounders to estimate the putative adverse $PM_{2.5}$ effects on total WM and association brain area WM volumes. The volume of the corpus callosum, the largest WM tract that facilitates interhemispheric communication, was included as *post hoc* analyses. In order to estimate the $PM_{2.5}$ effect on each hierarchically organized WM volume while rigorously accounting for possible confounding by the other factors, we followed the step-by-step addition of multiple covariates (models I to VI in Table 3). $PM_{2.5}$ was analyzed as a continuous variable. Consistent with the patterns revealed by the ICV-adjusted ANCOVA, adverse $PM_{2.5}$ effects on WM volumes were present in the total

brain and also in the association brain area and across its divisions, although the precision in some effect estimates was lost for parietal WM. Multiple-covariate adjustment did not substantially change the effect estimates, suggesting that there was no strong evidence for significant confounding. Note that the number of observations differ in various adjusted models due to missing covariate data. For each interquartile (3.49 μg/m^3) increment of cumulative $PM_{2.5}$ exposure in the full models (model VI: including ICV, geographic region, sociodemographics, SES, lifestyles, HT use, depressive symptoms, BMI, and CVD and associated risk factors), WM volume (in cm^3) was lower by 4.47 ± 1.12 in the association brain area and by 6.23 ± 1.28 in the total brain. Except for the parietal lobe, the multiple-covariate-adjusted differences in WM volume all reached the predetermined level of significance ($P < 0.01$) for the comparisons in the frontal lobe (lower by 2.04 ± 0.59), temporal lobe (lower by 1.70 ± 0.33), and corpus callosum (lower by 0.12 ± 0.04) per interquartile increase of $PM_{2.5}$ exposure.

The adverse effects of long-term $PM_{2.5}$ exposures on WM volume remained in the sensitivity analyses (Table B.1 and Table B.2 in Appendix B, available on the HEI website). In these analyses, which were restricted to non-Hispanic white women, a consistent pattern of associations was found between $PM_{2.5}$ and smaller volumes of WM across the examined brain regions, with effect estimates comparable with those found in the full cohort. Despite a modest reduction in effect sizes among participants with more than 60% complete data on the yearly exposure estimates, the presumed association between $PM_{2.5}$ and associated neurotoxic effects with WM atrophy remained statistically significant ($P < 0.01$) for total WM, association brain area WM, temporal WM, and the corpus callosum.

Modification of $PM_{2.5}$ Effects on WM Volumes The relationship between $PM_{2.5}$ and WM volumes was fairly consistent across the subgroups defined by BMI, CVD history, diabetes mellitus, and WBC count (Table 4). Almost all tests of interactions did not reach statistical significance in the

Table 3. Linear Regression Modeling Results of $PM_{2.5}$ Exposure and Normal-Appearing WM Volumes[a] in the WHIMS-MRI Cohort (1999–2006)

Statistical Models[b]	WM Volume					Corpus Callosum
	Total	Association Brain	Frontal	Parietal	Temporal	
Crude (N = 1,403)	−4.95 ± 1.22 ($P < 0.01$)	−3.34 ± 1.08 ($P < 0.01$)	−1.37 ± 0.56 ($P = 0.01$)	−0.46 ± 0.33 ($P = 0.17$)	−1.51 ± 0.32 ($P < 0.01$)	−0.103 ± 0.037 ($P < 0.01$)
Model I (N = 1,403)	−5.52 ± 1.22 ($P < 0.01$)	−3.90 ± 1.08 ($P < 0.01$)	−1.74 ± 0.56 ($P < 0.01$)	−0.56 ± 0.33 ($P = 0.09$)	−1.60 ± 0.32 ($P < 0.01$)	−0.110 ± 0.037 ($P < 0.01$)
Model II (N = 1,399)	−5.52 ± 1.22 ($P < 0.01$)	−3.93 ± 1.08 ($P < 0.01$)	−1.75 ± 0.56 ($P < 0.01$)	−0.60 ± 0.33 ($P = 0.07$)	−1.57 ± 0.32 ($P < 0.01$)	−0.113 ± 0.038 ($P < 0.01$)
Model III (N = 1,377)	−5.90 ± 1.23 ($P < 0.01$)	−4.24 ± 1.08 ($P < 0.01$)	−1.90 ± 0.56 ($P < 0.01$)	−0.68 ± 0.33 ($P = 0.04$)	−1.66 ± 0.32 ($P < 0.01$)	−0.121 ± 0.038 ($P < 0.01$)
Model IV (N = 1,310)	−5.79 ± 1.25 ($P < 0.01$)	−4.13 ± 1.1 ($P < 0.01$)	−1.83 ± 0.57 ($P < 0.01$)	−0.68 ± 0.34 ($P = 0.04$)	−1.62 ± 0.33 ($P < 0.01$)	−0.113 ± 0.039 ($P < 0.01$)
Model V (N = 1,279)	−5.94 ± 1.27 ($P < 0.01$)	−4.26 ± 1.12 ($P < 0.01$)	−1.93 ± 0.58 ($P < 0.01$)	−0.70 ± 0.34 ($P = 0.04$)	−1.64 ± 0.33 ($P < 0.01$)	−0.110 ± 0.04 ($P < 0.01$)
Model VI (N = 1,272)	−6.23 ± 1.28 ($P < 0.01$)	−4.47 ± 1.12 ($P < 0.01$)	−2.04 ± 0.59 ($P < 0.01$)	−0.73 ± 0.34 ($P = 0.03$)	−1.70 ± 0.33 ($P < 0.01$)	−0.117 ± 0.04 ($P < 0.01$)

[a] Expressed as the regression coefficients (± standard error) per interquartile (3.49 μg/m^3) increase in cumulative yearly $PM_{2.5}$ (1999–2006). All analyses were adjusted for ICV.

[b] Model I: adjusted for geographic region, age, and race. Model II: adjusted for Model I covariates and SES (education, income, and employment status). Model III: adjusted for Model II covariates and lifestyle factors (smoking, alcohol use, and physical activity). Model IV: adjusted for Model III covariates, HT, depressive symptoms, and BMI. Model V: adjusted for Model IV covariates and conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia). Model VI: adjusted for Model V covariates and CVD histories.

Table 4. Linear Regression Modeling Results of $PM_{2.5}$ Exposure and Normal-Appearing WM Volumes[a] in the WHIMS-MRI Cohort (1999–2006) by BMI, CVD, Diabetes Mellitus, and WBC Count

Statistical Models	WM Volume					
	Total	Association Brain	Frontal	Parietal	Temporal	Corpus Callosum
Models by BMI						
Crude						
All (N = 1,398)	−4.89 ± 1.22 (P < 0.01)	−3.28 ± 1.08 (P < 0.01)	−1.32 ± 0.56 (P = 0.02)	−0.42 ± 0.33 (P = 0.20)	−1.54 ± 0.32 (P < 0.01)	−0.101 ± 0.037 (P < 0.01)
BMI < 25 (n = 417)	−1.79 ± 2.22 (P = 0.42)	−0.59 ± 1.96 (P = 0.76)	−0.08 ± 1.02 (P = 0.94)	0.89 ± 0.6 (P = 0.14)	−1.41 ± 0.57 (P = 0.01)	−0.054 ± 0.067 (P = 0.42)
BMI 25–29 (n = 527)	−5.39 ± 1.99 (P < 0.01)	−3.7 ± 1.75 (P = 0.03)	−1.73 ± 0.91 (P = 0.06)	−0.52 ± 0.53 (P = 0.33)	−1.45 ± 0.51 (P < 0.01)	−0.106 ± 0.06 (P = 0.08)
BMI ≥ 30 (n = 454)	−7.48 ± 2.14 (P < 0.01)	−5.56 ± 1.89 (P < 0.01)	−2.15 ± 0.98 (P = 0.03)	−1.64 ± 0.58 (P < 0.01)	−1.77 ± 0.55 (P < 0.01)	−0.143 ± 0.064 (P = 0.03)
Interaction test	P = 0.18	P = 0.18	P = 0.3	P < 0.01	P = 0.88	P = 0.63
Adjusted[b]						
All (N = 1,272)	−6.11 ± 1.28 (P < 0.01)	−4.35 ± 1.13 (P < 0.01)	−1.96 ± 0.59 (P < 0.01)	−0.69 ± 0.35 (P = 0.05)	−1.7 ± 0.34 (P < 0.01)	−0.114 ± 0.04 (P < 0.01)
BMI < 25 (n = 378)	−2.86 ± 2.32 (P = 0.22)	−1.39 ± 2.04 (P = 0.50)	−0.34 ± 1.06 (P = 0.75)	0.61 ± 0.63 (P = 0.33)	−1.66 ± 0.61 (P < 0.01)	−0.076 ± 0.073 (P = 0.3)
BMI 25–29 (n = 478)	−6.11 ± 2.04 (P < 0.01)	−4.49 ± 1.8 (P = 0.01)	−2.49 ± 0.94 (P < 0.01)	−0.47 ± 0.55 (P = 0.39)	−1.53 ± 0.53 (P < 0.01)	−0.153 ± 0.064 (P = 0.02)
BMI ≥ 30 (n = 416)	−9.35 ± 2.18 (P < 0.01)	−7.18 ± 1.92 (P < 0.01)	−3.04 ± 1 (P < 0.01)	−2.21 ± 0.59 (P < 0.01)	−1.92 ± 0.57 (P < 0.01)	−0.114 ± 0.068 (P = 0.09)
Interaction test	P = 0.12	P = 0.12	P = 0.15	P < 0.01	P = 0.87	P = 0.72
Models by CVD						
Crude						
All (N = 1,386)	−4.83 ± 1.8 (P < 0.01)	−3.44 ± 1.59 (P = 0.03)	−1.67 ± 0.82 (P = 0.04)	−0.44 ± 0.49 (P = 0.37)	−1.33 ± 0.47 (P < 0.01)	−0.134 ± 0.054 (P = 0.01)
No (n = 1,193)	−5.21 ± 1.33 (P < 0.01)	−3.44 ± 1.17 (P < 0.01)	−1.34 ± 0.61 (P = 0.03)	−0.48 ± 0.36 (P = 0.18)	−1.62 ± 0.34 (P < 0.01)	−0.097 ± 0.04 (P = 0.01)
Yes (n = 193)	−4.45 ± 3.35 (P = 0.18)	−3.44 ± 2.95 (P = 0.25)	−1.99 ± 1.53 (P = 0.19)	−0.39 ± 0.9 (P = 0.66)	−1.05 ± 0.87 (P = 0.23)	−0.171 ± 0.1 (P = 0.09)
Interaction test	P = 0.83	P = 1	P = 0.69	P = 0.93	P = 0.54	P = 0.49
Adjusted[b]						
All (N = 1,272)	−7.12 ± 1.85 (P < 0.01)	−5.45 ± 1.63 (P < 0.01)	−2.61 ± 0.85 (P < 0.01)	−1.06 ± 0.5 (P = 0.03)	−1.78 ± 0.48 (P < 0.01)	−0.165 ± 0.058 (P < 0.01)
No (n = 1,098)	−5.9 ± 1.37 (P < 0.01)	−4.11 ± 1.2 (P < 0.01)	−1.83 ± 0.63 (P < 0.01)	−0.61 ± 0.37 (P = 0.1)	−1.67 ± 0.36 (P < 0.01)	−0.1 ± 0.043 (P = 0.02)
Yes (n = 174)	−8.35 ± 3.42 (P = 0.01)	−6.8 ± 3.01 (P = 0.02)	−3.4 ± 1.57 (P = 0.03)	−1.51 ± 0.92 (P = 0.1)	−1.9 ± 0.89 (P = 0.03)	−0.23 ± 0.107 (P = 0.03)
Interaction test	P = 0.5	P = 0.4	P = 0.35	P = 0.36	P = 0.81	P = 0.26

Table continues next page

[a] Expressed as the regression coefficients per 3.49 μg/m^3 increase in cumulative yearly $PM_{2.5}$ (1999–2006); all analyses adjusted for the ICV.

[b] Using Model VI: adjusted for geographic region; age, race, or ethnicity; SES (education, income, and employment status); lifestyle factors (smoking, alcohol use, and physical activity); HT; depressive symptoms; BMI; conventional CVD risk factors (diabetes mellitus and hypercholesterolemia); and CVD histories.

WM regions we examined, except for stronger associations of parietal WM among participants who were obese (BMI > 30). For instance, the association of frontal WM atrophy with $PM_{2.5}$ was strongest (−3.04 ± 1.00) in obese participants, less strong (−2.49 ± 0.94) in the overweight group, and apparently null (−0.34 ± 1.06) in the normal group. When comparing participants with CVD with those without it, stronger associations of smaller WM volumes with $PM_{2.5}$ in the total brain (−8.35 ± 3.42 vs. −5.90 ± 1.37) and in the frontal lobe (−3.40 ± 1.57 vs. −1.83 ± 0.63) were noted.

Table 4 (*continued*). Linear Regression Modeling Results of $PM_{2.5}$ Exposure and Normal-Appearing WM Volumes[a] in the WHIMS-MRI Cohort (1999–2006) by BMI, CVD, Diabetes Mellitus, and WBC Count

	WM Volume					
Statistical Models	Total	Association Brain	Frontal	Parietal	Temporal	Corpus Callosum
Models by Diabetes Mellitus						
Crude						
All (N = 1,402)	−1.55 ± 4.89 (P = 0.75)	−0.57 ± 4.31 (P = 0.89)	−0.06 ± 2.24 (P = 0.98)	−0.33 ± 1.32 (P = 0.08)	−0.18 ± 1.26 (P = 0.88)	−0.157 ± 0.146} (P = 0.28)
No (n = 1,356)	−5.09 ± 1.23 (P < 0.01)	−3.46 ± 1.09 (P < 0.01)	−1.41 ± 0.57 (P = 0.01)	−0.47 ± 0.33 (P = 0.16)	−1.58 ± 0.32 (P < 0.01)	−0.1 ± 0.037 (P < 0.01)
Yes (n = 46)	1.99 ± 9.7 (P = 0.84)	2.32 ± 8.55 (P = 0.79)	1.3 ± 4.44 (P = 0.77)	−0.19 ± 2.61 (P = 0.94)	1.21 ± 2.5 (P = 0.63)	−0.214 ± 0.29 (P = 0.46)
Interaction test	P = 0.47	P = 0.5	P = 0.55	P = 0.92	P = 0.27	P = 0.7
Adjusted[b]						
All (N = 1,272)	−5.07 ± 5.58 (P = 0.36)	−4.21 ± 4.91 (P = 0.39)	−1.65 ± 2.56 (P = 0.52)	−1.7 ± 1.51 (P = 0.26)	−0.86 ± 1.46 (P = 0.56)	−0.136 ± 0.174 (P = 0.44)
No (n = 1,232)	−6.25 ± 1.28 (P < 0.01)	−4.47 ± 1.13 (P < 0.01)	−2.05 ± 0.59 (P < 0.01)	−0.71 ± 0.35 (P = 0.04)	−1.72 ± 0.34 (P < 0.01)	−0.117 ± 0.04 (P < 0.01)
Yes (n = 40)	−3.89 ± 11.07 (P = 0.73)	−3.94 ± 9.75 (P = 0.69)	−1.25 ± 5.08 (P = 0.81)	−2.69 ± 2.99 (P = 0.37)	0.01 ± 2.89 (P = 1)	−0.155 ± 0.346 (P = 0.65)
Interaction Test	P = 0.83	P = 0.96	P = 0.88	P = 0.51	P = 0.55	P = 0.91
Models by WBC Count						
Crude						
All (N = 1,403)	−4.82 ± 1.23 (P < 0.01)	−3.23 ± 1.09 (P < 0.01)	−1.36 ± 0.56 (P = 0.02)	−0.43 ± 0.33 (P = 0.2)	−1.44 ± 0.32 (P < 0.01)	−0.108 ± 0.037 (P < 0.01)
≥ Median (n = 670)	−4.44 ± 1.86 (P = 0.02)	−2.95 ± 1.64 (P = 0.07)	−1.57 ± 0.85 (P = 0.06)	−0.34 ± 0.5 (P = 0.5)	−1.04 ± 0.48 (P = 0.03)	−0.134 ± 0.056 (P = 0.02)
< Median (n = 733)	−5.19 ± 1.63 (P < 0.01)	−3.51 ± 1.44 (P = 0.01)	−1.16 ± 0.75 (P = 0.12)	−0.52 ± 0.44 (P = 0.24)	−1.84 ± 0.42 (P < 0.01)	−0.082 ± 0.049 (P = 0.09)
Interaction test	P = 0.76	P = 0.8	P = 0.71	P = 0.79	P = 0.21	P = 0.49
Adjusted[b]						
All (N = 1,272)	−6.21 ± 1.29 (P < 0.01)	−4.46 ± 1.13 (P < 0.01)	−2.06 ± 0.59 (P < 0.01)	−0.75 ± 0.35 (P = 0.03)	−1.65 ± 0.34 (P < 0.01)	−0.123 ± 0.04 (P < 0.01)
≥ Median (n = 614)	−6.44 ± 1.89 (P < 0.01)	−4.68 ± 1.67 (P < 0.01)	−2.39 ± 0.87 (P < 0.01)	−0.95 ± 0.51 (P = 0.06)	−1.35 ± 0.49 (P < 0.01)	−0.154 ± 0.059 (P < 0.01)
< Median (n = 658)	−5.99 ± 1.69 (P < 0.01)	−4.23 ± 1.49 (P < 0.01)	−1.73 ± 0.78 (P = 0.03)	−0.55 ± 0.46 (P = 0.23)	−1.95 ± 0.44 (P < 0.01)	−0.091 ± 0.053 (P = 0.08)
Interaction test	P = 0.86	P = 0.84	P = 0.57	P = 0.56	P = 0.36	P = 0.42

[a] Expressed as the regression coefficients per 3.49 μg/m^3 increase in cumulative yearly $PM_{2.5}$ (1999–2006); all analyses adjusted for the ICV.

[b] Using Model VI: adjusted for geographic region; age, race, or ethnicity; SES (education, income, and employment status); lifestyle factors (smoking, alcohol use, and physical activity); HT; depressive symptoms; BMI; conventional CVD risk factors (diabetes mellitus and hypercholesterolemia); and CVD histories.

DPM EXPOSURES

Population Characteristics and DPM Exposures in the WHIMS-MRI Cohort

Table 5 shows the population characteristics in relation to the quartiles of cumulative exposures (1996–2005) to on-road DPM in the WHIMS-MRI cohort. We found that older participants (≥70 years) tended to live in the census tracts with the higher DPM exposure categories. WHIMS-MRI participants recruited from the South were the least likely to live in census tracts with the highest exposure levels. Participants of racial/ethnic minorities (black or

Table 5. Sociodemographic Factors, Lifestyle Factors, and Clinical Characteristics by On-Road DPM Exposure[a] Quartiles in the WHIMS–MRI Cohort (1999–2006)

		On-Road DPM (μg/m^3) (quartile)				
Population Characteristics	N[b]	0.01–0.24 Median = 0.17 (N = 350)	0.24–0.35 Median = 0.29 (N = 351)	0.35–0.55 Median = 0.43 (N = 351)	0.55–3.93 Median = 0.78 (N = 351)	P value[c]
U. S. Region						<0.0001
Northeast	329	35 (10.6%)	109 (33.1%)	77 (23.4%)	108 (32.8%)	
South	207	101 (48.8%)	68 (32.9%)	32 (15.5%)	6 (2.9%)	
Midwest	486	122 (25.1%)	97 (20%)	139 (28.6%)	128 (26.3%)	
West	381	92 (24.1%)	77 (20.2%)	103 (27%)	109 (28.6%)	
Age at screening (yr)						<0.001
63–69	712	215 (30.2%)	171 (24%)	166 (23.3%)	160 (22.5%)	
70–74	495	103 (20.8%)	123 (24.8%)	125 (25.3%)	144 (29.1%)	
≥75	196	32 (16.3%)	57 (29.1%)	60 (30.6%)	47 (24%)	
Ethnicity						<0.0001
Black or African-American	64	3 (4.7%)	12 (18.8%)	8 (12.5%)	41 (64.1%)	
Hispanic White	21	1 (4.8%)	4 (19%)	6 (28.6%)	10 (47.6%)	
Non-Hispanic White	1,276	337 (26.4%)	328 (25.7%)	327 (25.6%)	284 (22.3%)	
Other or missing	42	9 (21.4%)	7 (16.7%)	10 (23.8%)	16 (38.1%)	
Participant's education level						0.02
< High school	63	15 (23.8%)	17 (27%)	10 (15.9%)	21 (33.3%)	
High school/GED	325	85 (26.2%)	94 (28.9%)	87 (26.8%)	58 (18.2%)	
> High school	1,012	250 (24.7%)	240 (23.7%)	251 (24.8%)	271 (26.8%)	
Family income						0.06
<$10,000	50	12 (24%)	11 (22%)	12 (24%)	15 (30%)	
$10,000 to $34,999	671	178 (26.5%)	188 (28%)	143 (21.3%)	162 (24.1%)	
$35,000 to $74,999	501	115 (23%)	116 (23.2%)	149 (29.7%)	121 (24.2%)	
≥$75,000	136	32 (23.5%)	30 (22.1%)	32 (23.5%)	42 (30.9%)	
Missing	45	13 (28.9%)	6 (13.3%)	15 (33.3%)	11 (24.4%)	
Employment						0.89
Currently employed	255	65 (25.5%)	61 (23.9%)	60 (23.5%)	69 (27.1%)	
Not working	146	40 (27.4%)	39 (26.7%)	36 (24.7%)	31 (21.2%)	
Retired	1,000	245 (24.5%)	251 (25.1%)	253 (25.3%)	251 (25.1%)	
Smoking status						0.18
Never smoked	806	213 (26.4%)	208 (25.8%)	199 (24.7%)	186 (23.1%)	
Past smoker	526	121 (23%)	126 (24%)	137 (26%)	142 (27%)	
Current smoker	59	12 (20.3%)	13 (22%)	12 (20.3%)	22 (37.3%)	

Table continues next page

[a] Shown as N (%) for each exposure quartile for the indicated subcategory of population characteristics.

[b] The total number of subjects summed up across each subcategory varies slightly because of missing values.

[c] Calculated by comparing the distribution of exposure quartiles across subcategories for each personal characteristic by chi-square or Fishers exact test.

[d] E-alone: conjugated equine estrogen alone; E+P: estrogen plus progestin (medroxyprogesterone acetate).

Table 5 (*continued*). Sociodemographic Factors, Lifestyle Factors, and Clinical Characteristics by On-Road DPM Exposure[a] Quartiles in the WHIMS–MRI Cohort (1999–2006)

		On-Road DPM (μg/m³) (quartile)				
		0.01–0.24	0.24–0.35	0.35–0.55	0.55–3.93	
Population Characteristics	N[b]	Median = 0.17 (N = 350)	Median = 0.29 (N = 351)	Median = 0.43 (N = 351)	Median = 0.78 (N = 351)	P value[c]
Alcohol intake						0.01
Non drinker	180	61 (33.9%)	53 (29.4%)	37 (20.6%)	29 (16.1%)	
Past drinker	232	60 (25.9%)	57 (24.6%)	58 (25%)	57 (24.6%)	
<1 drink per day	822	182 (22.1%)	211 (25.7%)	207 (25.2%)	222 (27%)	
>1 drink per day	158	43 (27.2%)	28 (17.7%)	46 (29.1%)	41 (25.9%)	
Moderate or strenuous activity (≥20 min)						0.68
No activity	799	204 (25.5%)	192 (24%)	197 (24.7%)	206 (25.8%)	
Some activity	78	19 (24.4%)	23 (29.5%)	14 (17.9%)	22 (28.2%)	
2–4 episodes/wk	280	63 (22.5%)	69 (24.6%)	77 (27.5%)	71 (25.4%)	
>4 episodes/wk	244	64 (26.2%)	67 (27.5%)	61 (25%)	52 (21.3%)	
BMI (kg/m²)						0.27
<25	417	102 (24.5%)	87 (20.9%)	116 (27.8%)	112 (26.9%)	
25–29	527	131 (24.9%)	138 (26.2%)	126 (23.9%)	132 (25%)	
≥30	454	115 (25.3%)	126 (27.8%)	107 (23.6%)	106 (23.3%)	
HT use ever						0.43
No	752	177 (23.5%)	190 (25.3%)	186 (24.7%)	199 (26.5%)	
Yes	651	173 (26.6%)	161 (24.7%)	165 (25.3%)	152 (23.3%)	
History of depression						0.60
No	1,291	318 (24.6%)	330 (25.6%)	326 (25.3%)	317 (24.6%)	
Yes	91	27 (29.7%)	19 (20.9%)	21 (23.1%)	24 (26.4%)	
Hypertension ever						0.01
No	889	244 (27.4%)	229 (25.8%)	216 (24.3%)	200 (22.5%)	
Yes	505	105 (20.8%)	121 (24%)	131 (25.9%)	148 (29.3%)	
Diabetes treated ever (pills or injections)						0.02
No	1,356	345 (25.4%)	340 (25.1%)	340 (25.1%)	331 (24.4%)	
Yes	46	5 (10.9%)	11 (23.9%)	10 (21.7%)	20 (43.5%)	
High cholesterol requiring pills ever						0.01
No	1,153	306 (26.5%)	285 (24.7%)	286 (24.8%)	276 (23.9%)	
Yes	223	38 (17%)	63 (28.3%)	54 (24.2%)	68 (30.5%)	
Cardiovascular disease ever						0.25
No	1,193	294 (24.6%)	312 (26.2%)	296 (24.8%)	291 (24.4%)	
Yes	193	51 (26.4%)	38 (19.7%)	49 (25.4%)	55 (28.5%)	
Subcohort membership[d]						0.56
E-alone control	263	75 (28.5%)	63 (24%)	62 (23.6%)	63 (24%)	
E-alone intervention	260	67 (25.8%)	74 (28.5%)	65 (25%)	54 (20.8%)	
						0.19
E+P control	447	102 (22.8%)	122 (27.3%)	106 (23.7%)	117 (26.2%)	
E+P intervention	433	106 (24.5%)	92 (21.2%)	118 (27.3%)	117 (27%)	

[a] Shown as N (%) for each exposure quartile for the indicated subcategory of population characteristics.

[b] The total number of subjects summed up across each subcategory varies slightly because of missing values.

[c] Calculated by comparing the distribution of exposure quartiles across subcategories for each personal characteristic by chi-square or Fishers exact test.

[d] E-alone: conjugated equine estrogen alone; E+P: estrogen plus progestin (medroxyprogesterone acetate).

Hispanic white) and those who received less than a high school education or never used alcohol, compared with their counterparts, were more likely to live in census tracts of the highest DPM exposure category. Participants who suffered from hypertension, high cholesterol, or diabetes were also more likely to live in these polluted neighborhoods compared with their counterparts.

MRI-Measured Brain Volumes in Relation to DPM Exposures in WHIMS-MRI Cohort

ICV-adjusted ANCOVA comparing normal and ischemic brain volumes across the cumulative DPM exposures quartiles are summarized in Table 6. We found no measurable differences in the normal brain volumes (total brain and association brain area). ICV-adjusted ANCOVA showed a

Table 6. Brain Volume Outcomes by On-Road DPM Exposure Quartiles in the WHIMS-MRI Cohort (1999–2006)

MRI-Measured Brain Volume (mean ± SD [cm^3])	DPM ($\mu g/m^3$) (quartile)				*P* value[a]	
	0.01–0.24	0.24–0.35	0.35–0.55	0.55–3.93		
	Median = 0.17 (*N* = 350)	Median = 0.29 (*N* = 351)	Median = 0.43 (*N* = 351)	Median = 0.78 (*N* = 351)	ANCOVA	GLM
Total brain volume	813.42 ± 74.16	801.70 ± 69.59	792.55 ± 75.92	791.39 ± 77.29	0.39	N/A
Normal-Appearing Brain Structure						
Normal brain volume	805.25 ± 73.44	793.05 ± 69.02	783.09 ± 75.03	783.29 ± 76.73	0.26	N/A
Association area	624.88 ± 58.18	615.93 ± 54.71	608.07 ± 59.39	606.66 ± 60.46	0.48	N/A
Frontal lobe	285.56 ± 28.22	281.51 ± 27.12	277.56 ± 29.36	277.13 ± 29.21	0.63	N/A
Parietal lobe	153.22 ± 15.81	152.31 ± 15.05	149.54 ± 15.96	149.44 ± 16.41	0.80	N/A
Temporal lobe	186.09 ± 18.46	183.11 ± 17.37	180.96 ± 18.5	180.09 ± 19.4	0.32	N/A
Ventricle	35.36 ± 15.22	36.97 ± 15.75	38.26 ± 17.45	37.86 ± 16.62	< 0.01	< 0.01[b]
GM						
Total GM	356.54 ± 39.68	362.83 ± 37.15	353.46 ± 41.97	337.58 ± 46.39	< 0.01	< 0.01[c]
Association cortex	270.49 ± 30.99	276.84 ± 28.83	268.65 ± 33.69	253.35 ± 37.63	< 0.01	< 0.01[c]
Frontal GM	119.68 ± 14.42	123.24 ± 13.77	119.70 ± 15.62	111.26 ± 17.27	< 0.01	< 0.01[c]
Parietal GM	62.79 ± 8.5	64.78 ± 8.02	62.83 ± 9.32	58.51 ± 10.30	< 0.01	< 0.01[c]
Temporal GM	88.01 ± 10.69	88.81 ± 9.7	86.66 ± 11.11	83.58 ± 12.28	< 0.01	< 0.01[c]
WM						
Total WM	413.64 ± 52.12	395.26 ± 49.3	394.81 ± 54.61	410.91 ± 52.78	< 0.01	< 0.01[d]
Association brain areas	354.39 ± 45.3	339.09 ± 42.57	339.41 ± 47.19	353.31 ± 45.85	< 0.01	< 0.01[d]
Frontal WM	165.88 ± 22.77	158.27 ± 21.43	158.40 ± 23.99	165.87 ± 22.76	< 0.01	< 0.01[d]
Parietal WM	90.43 ± 12.66	86.52 ± 12.04	86.71 ± 12.8	90.93 ± 12.93	< 0.01	< 0.01[d]
Temporal WM	98.08 ± 12.69	94.30 ± 11.83	94.31 ± 12.87	96.51 ± 13.24	< 0.01	< 0.01[d]
Corpus callosum	9.20 ± 1.33	9.23 ± 1.26	9.11 ± 1.26	9.10 ± 1.36	0.35	N/A
Hippocampus	5.81 ± 1.09	5.74 ± 0.99	5.62 ± 1.08	5.76 ± 1.06	0.25	N/A
Basal ganglia	35.07 ± 3.44	34.95 ± 3.34	34.83 ± 3.48	34.80 ± 3.50	0.30	N/A
Small-Vessel Ischemic Disease (SVID) Volumes						
Total Brain SVID	8.17 ± 10.30	8.65 ± 12.09	9.46 ± 12.45	8.10 ± 9.71	0.48	N/A
Association brain	6.55 ± 8.98	7.05 ± 10.74	7.68 ± 11.08	6.55 ± 8.41	0.45	N/A
GM SVID	0.42 ± 0.99	0.43 ± 1.52	0.40 ± 1.06	0.37 ± 1.08	0.86	N/A
WM SVID	6.90 ± 8.83	7.34 ± 10.15	8.03 ± 10.66	6.89 ± 8.25	0.41	N/A

[a] *P* values calculated from ICV-adjusted ANCOVA models with brain volumes or log-transformed SVID volumes.

[b] $P < 0.01$ calculated from ICV-adjusted linear trend models in GLM.

[c] *P* values < 0.01 calculated from ICV-adjusted brain volumes comparing the 4th quartile to the 1st–3rd quartiles in GLM.

[d] *P* values calculated from bivariate analyses comparing GLM with product term of both continuous and dichotomized exposure variables versus GLM with only dichotomized DPM variables (the 4th vs. the 1st–3rd quartiles).

linear increase in ventricular volume across the first three quartiles of DPM exposure (35 to 38 cm^3; ~ 9% increase) and no appreciable difference between the third and fourth quartiles. We also observed a consistent pattern of associations between DPM and normal GM volumes. Comparing participants in the fourth quartile of DPM exposure with those in the first to third quartiles, the MRI-measured association cortex was smaller ($P < 0.01$); this pattern was present in the GM of the three multi-modal association brain regions (all P values < 0.01). Normal-appearing total WM volume also differed significantly ($P < 0.01$) across the DPM exposure quartiles, but the pattern of associations appeared to be nonlinear. The ICV-adjusted average volumes of total WM decreased modestly from the first to the third exposure quartiles, followed by a noticeable increase in WM volume in the highest (fourth) exposure quartile, suggesting a reverse *J*-shaped association. These nonlinear associations were confirmed in a bivariate general linear model with statistically significant ($P < 0.01$) product terms of continuous exposure and dichotomized DPM categories (fourth vs. first to third quartiles), with better statistical fit than each exposure variable alone. Similar patterns with nonlinear effects of DPM across exposure quartiles were also present in the WM volumes of the association brain regions (frontal, parietal, and temporal), but not in the corpus callosum.

In the ICV-adjusted ANCOVA, we found no statistically significant differences in the volumes of basal ganglia or hippocampus across DPM exposure quartiles. In addition, no differences in the SVID volumes measured for, total brain, association brain, GM, and WM were found across the DPM exposure quartiles.

Multiple Linear Regression Models

Main Effects of DPM Exposures Linear regression modeling results are summarized in Table 7, with further adjustments for multiple potential confounders to examine the main effects of DPM exposures on ventricular sizes and GM volumes in the association cortices (Part A) and normal-appearing WM volumes in the association brain regions (Part B). Note that DPM exposure was analyzed as a continuous variable for the ventricle size analyses, as a dichotomous variable (the fourth quartile vs. first to third quartile) in the GM analyses, and as a continuous variable in the normal appearing WM, but stratified by exposure range (first to third quartile and fourth quartile).

In order to account rigorously for the influences of the listed covariates, we followed the step-by-step addition of multiple covariates (models I to model VI in Part A of Table 7). Consistent with the pattern revealed by the ICV-adjusted ANCOVA, smaller GM volumes associated with higher cumulative DPM exposures (fourth quartile vs. first to third quartiles) were found in all three association cortices (frontal, parietal, and temporal). The resulting effect estimates were reduced, but all remained statistically significant ($P < 0.01$), with multiple-covariate adjustment, suggesting that the associations could not be explained by the covariates included in the multiple linear regression models. For instance, comparing participants in the fourth quartile exposure with participants in the first to third quartiles of DPM exposures, the ICV-adjusted average volume of temporal GM (in cm^3) decreased by 3.24 ± 0.60. This decrease fell to -2.90 ± 0.60 after adjusting for geographic region, age, and race or ethnicity, but diminished only slightly (model VI: -2.23 ± 0.63) with further adjustment for the other covariates (SES, lifestyle, BMI, prior depression, and CVD-related clinical characteristics). The assumed linear increment of ventricular volume associated with increased DPM exposure remained robust in the multiple linear regression. For each interquartile (0.31 $\mu g/m^3$) increment of cumulative DPM exposure in the full models (model VI: including ICV, geographic region, sociodemographics, SES, lifestyle factors, HT use, prior depression, BMI, CVD and associated risk factors), the adjusted mean of ventricular size (in cm^3) increased by 0.96 ± 0.43 ($P = 0.03$).

The multiple-covariate-adjusted effects of DPM exposures on normal-appearing WM (part B of Table 7) varied by the estimated exposure range, as reflected by the statistically significant ($P < 0.01$) interaction term between the continuous exposure and the dichotomized DPM categories (fourth quartile vs. first to third quartiles). For women with estimated cumulative exposures between the first and third quartiles, increased DPM estimates were associated with smaller WM volumes in the association brain areas (frontal and temporal). However, association brain area WM volumes (frontal and parietal) became larger with increased cumulative DPM exposures when the exposure estimates were in the fourth quartile. Our sensitivity analyses revealed fairly consistent patterns of associations between DPM exposures and larger ventricles and smaller GM volumes. In the analyses restricted to non-Hispanic whites (Table B.3 in Appendix B, available on the HEI website) or to participants with more than 60% complete data on the yearly exposure estimates (Table B.4 in Appendix B), DPM exposure was associated with a modest increase in the ventricular volume. Likewise, we found that the association of smaller GM volumes with higher cumulative DPM exposures (fourth quartile vs. first to third DPM quartiles) remained in the sensitivity analyses.

Table 7. Linear Regression Modeling Results of On-Road DPM Exposure and Brain Volume Outcomes in the WHIMS-MRI Cohort (1999–2006)

Part A. Ventricle and GM[c]

Statistical Models[a]	Ventricle[b]	Association Brain GM	Frontal GM	Parietal GM	Temporal GM
Crude (N = 1,403)	1.67 ± 0.38 (P < 0.01)	−15.56 ± 1.79 (P < 0.01)	−8.05 ± 0.84 (P < 0.01)	−4.27 ± 0.52 (P < 0.01)	−3.24 ± 0.60 (P < 0.01)
Model I (N = 1,403)	1.28 ± 0.40 (P < 0.01)	−15.38 ± 1.78 (P < 0.01)	−8.04 ± 0.85 (P < 0.01)	−4.44 ± 0.51 (P < 0.01)	−2.90 ± 0.60 (P < 0.01)
Model II (N = 1,399)	1.28 ± 0.40 (P < 0.01)	−14.96 ± 1.79 (P < 0.01)	−7.84 ± 0.86 (P < 0.01)	−4.31 ± 0.52 (P < 0.01)	−2.81 ± 0.60 (P < 0.01)
Model III (N = 1,377)	1.33 ± 0.41 (P < 0.01)	−14.57 ± 1.8 (P < 0.01)	−7.60 ± 0.86 (P < 0.01)	−4.28 ± 0.52 (P < 0.01)	−2.7 ± 0.60 (P < 0.01)
Model IV (N = 1,310)	1.04 ± 0.42 (P = 0.01)	−13.51 ± 1.84 (P < 0.01)	−7.02 ± 0.89 (P < 0.01)	−4.07 ± 0.53 (P < 0.01)	−2.41 ± 0.62 (P < 0.01)
Model V (N = 1,279)	0.99 ± 0.43 (P = 0.02)	−12.96 ± 1.87 (P < 0.01)	−6.74 ± 0.91 (P < 0.01)	−3.93 ± 0.54 (P < 0.01)	−2.30 ± 0.63 (P < 0.01)
Model VI (N = 1,272)	0.96 ± 0.43 (P = 0.03)	−12.72 ± 1.88 (P < 0.01)	−6.64 ± 0.91 (P < 0.01)	−3.85 ± 0.55 (P < 0.01)	−2.23 ± 0.63 (P < 0.01)

Table continues next page

[a] Model I: adjusted for geographic region, age and race; Model II: adjusted for Model I covariates and SES (education, income, and employment status); Model III: adjusted for Model II covariates and lifestyle factors (smoking, alcohol use, and physical activity); Model IV: adjusted for Model III covariates, HT, depressive symptoms, and BMI; Model V: adjusted for Model IV covariates and conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia); Model VI: adjusted for Model V covariates and CVD histories.

[b] Difference in ventricular volume per DPM interquartile change (0.31 μg/m^3).

[c] Difference in brain volume comparing fourth quartile (median = 0.78 μg/m^3) versus first to third quartiles for DPM (median = 0.29 μg/m^3). All analyses were adjusted for ICV.

[d] Difference in WM volume per DPM interquartile change (0.31 μg/m^3), stratified by exposure range (first to third quartiles versus fourth quartile). All analyses were adjusted for ICV.

Modification of DPM Effects on Ventricles and GM Volumes The relationships between DPM exposures and brain volume were fairly consistent across the subgroups defined by BMI, CVD history, or WBC count (Table 8). The associations between DPM and smaller GM volumes were stronger in diabetic participants (vs. non-diabetic participants), with two- to threefold differences in the adjusted effect size, reaching statistical significance (interaction P = 0.03) for parietal GM only. The observed linear increment of ventricular volume associated with increased DPM did not vary substantially by CVD history, diabetes mellitus, or WBC count. Interestingly, increased ventricular size (2.41 ± 0.70 cm^3) associated with DPM was primarily observed in the overweight participants (BMI = 25–29), but the corresponding effect was not notable in the obese participants (0.02 ± 0.66 cm^3) or in those participants with BMI < 25 (0.54 ± 0.78 cm^3) in the fully adjusted model (interaction P value = 0.03; adjusting for ICV, geographic region, sociodemographics, SES, lifestyle factors, HT use, prior depression, CVD risk factors and CVD histories).

POPULATION CHARACTERISTICS AND $PM_{2.5}$ EXPOSURES IN WHIMS COHORT

Table 9 shows the results of WHIMS population characteristics in relation to the $PM_{2.5}$ exposure quartiles in 1999–2007. Participants who were recruited from the Midwest, self-identified as African-American, reported low household income (<$10,000) and low education attainment (< high school), less engaged in physical activities (with no moderate or strenuous activities ≥20 minutes/week), consumed less alcohol (non-drinker or past drinker), or were overweight/obese, were more likely to reside in locations where the cumulative $PM_{2.5}$ exposures were estimated in the highest quartile (15.01–27.08; median = 16.57 μg/m^3), compared with their counterparts (all P values < 0.05).

Table 7 (*continued*). Linear Regression Modeling Results of On-Road DPM Exposure and Brain Volume Outcomes in the WHIMS-MRI Cohort (1999–2006)

Part B. Normal-Appearing WM[d]

	First–Third Quartiles of DPM (median = 0.29 μg/m^3)				Fourth Quartile of DPM (median = 0.78 μg/m^3)				
Statistical Models[a]	Association Brain WM	Frontal WM	Parietal WM	Temporal WM	Association Brain WM	Frontal WM	Parietal WM	Temporal WM	Interaction
Crude (N = 1,403)	−6.32 (−10.97 to −1.67) P < 0.01	−3.22 (−5.62 to −0.81) P < 0.01	−1.22 (−2.64 to 0.2) P = 0.09	−1.88 (−3.27 to −0.48) P < 0.01	5.71 (2.88 to 8.55) P < 0.01	3.08 (1.62 to 4.55) P < 0.01	1.76 (0.9 to 2.63) P < 0.01	0.87 (0.02 to 1.72) P = 0.05	P < 0.01
Model I (N = 1,403)	−4.69 (−9.34 to −0.04) P = 0.05	−2.51 (−4.93 to −0.09) P = 0.04	−0.64 (−2.06 to 0.77) P = 0.37	−1.53 (−2.94 to −0.13) P = 0.03	5.29 (2.42 to 8.16) P < 0.01	2.77 (1.28 to 4.26) P < 0.01	1.60 (0.73 to 2.48) P < 0.01	0.92 (0.05 to 1.78) P = 0.04	P < 0.01
Model II (N = 1,399)	−5.18 (−9.85 to −0.52) P = 0.03	−2.75 (−5.18 to −0.32) P = 0.03	−0.86 (−2.28 to 0.56) P = 0.24	−1.57 (−2.98 to −0.16) P = 0.03	5.40 (2.54 to 8.27) P < 0.01	2.84 (1.35 to 4.33) P < 0.01	1.64 (0.76 to 2.51) P < 0.01	0.93 (0.06 to 1.79) P = 0.04	P < 0.01
Model III (N = 1,377)	−5.42 (−10.08 to −0.75) P = 0.02	−2.76 (−5.18 to −0.34) P = 0.03	−0.97 (−2.41 to 0.46) P = 0.18	−1.68 (−3.09 to −0.27) P = 0.02	5.43 (2.56 to 8.31) P < 0.01	2.93 (1.44 to 4.43) P < 0.01	1.62 (0.74 to 2.50) P < 0.01	0.88 (0.01 to 1.75) P = 0.05	P < 0.01
Model IV (N = 1,310)	−5.3 (−10.04 to −0.55) P = 0.03	−2.67 (−5.14 to −0.20) P = 0.03	−1.01 (−2.47 to 0.44) P = 0.17	−1.62 (−3.06 to −0.18) P = 0.03	5.92 (2.95 to 8.89) P < 0.01	3.21 (1.66 to 4.76) P < 0.01	1.84 (0.93 to 2.75) P < 0.01	0.86 (−0.04 to 1.76) P = 0.06	P < 0.01
Model V (N = 1,279)	−5.04 (−9.85 to −0.22) P = 0.04	−2.58 (−5.08 to −0.07) P = 0.04	−0.86 (−2.33 to 0.61) P = 0.25	−1.59 (−3.05 to −0.14) P = 0.03	5.70 (2.70 to 8.71) P < 0.01	3.13 (1.56 to 4.69) P < 0.01	1.78 (0.86 to 2.70) P < 0.01	0.79 (−0.12 to 1.7) P = 0.09	P < 0.01
Model VI (N = 1,272)	−5.16 (−9.99 to −0.33) P = 0.04	−2.60 (−5.11 to −0.08) P = 0.04	−0.91 (−2.38 to 0.57) P = 0.23	−1.66 (−3.12 to −0.19) P = 0.03	5.74 (2.73 to 8.75) P < 0.01	3.15 (1.59 to 4.72) P < 0.01	1.78 (0.86 to 2.70) P < 0.01	0.81 (−0.1 to 1.72) P = 0.08	P < 0.01

[a] Model I: adjusted for geographic region, age and race; Model II: adjusted for Model I covariates and SES (education, income, and employment status); Model III: adjusted for Model II covariates and lifestyle factors (smoking, alcohol use, and physical activity); Model IV: adjusted for Model III covariates, HT, depressive symptoms, and BMI; Model V: adjusted for Model IV covariates and conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia); Model VI: adjusted for Model V covariates and CVD histories.

[b] Difference in ventricular volume per DPM interquartile change (0.31 μg/m^3).

[c] Difference in brain volume comparing fourth quartile (median = 0.78 μg/m^3) versus first to third quartiles for DPM (median = 0.29 μg/m^3). All analyses were adjusted for ICV.

[d] Difference in WM volume per DPM interquartile change (0.31 μg/m^3), stratified by exposure range (first to third quartiles versus fourth quartile). All analyses were adjusted for ICV.

Table 8. Linear Regression Modeling Results of On-Road DPM Exposure and Brain Volume Outcomes in the WHIMS–MRI Cohort (1999–2006) by BMI, CVD, Diabetes Mellitus, and WBC Count

Statistical Models	Ventricle[b]	GM Volume[a]			
		Association Brain	Frontal	Parietal	Temporal
Models by BMI					
Crude					
All (N = 1,398)	1.69 ± 0.38 (P < 0.01)	−15.6 ± 1.80 (P < 0.01)	−8.09 ± 0.85 (P < 0.01)	−4.28 ± 0.52 (P < 0.01)	−3.26 ± 0.6 (P < 0.01)
BMI < 25 (n = 417)	1.15 ± 0.70 (P = 0.10)	−9.48 ± 3.21 (P < 0.01)	−4.97 ± 1.51 (P < 0.01)	−2.96 ± 0.93 (P < 0.01)	−1.55 ± 1.07 (P = 0.15)
BMI 25–29 (n = 527)	3.43 ± 0.65 (P < 0.01)	−18.70 ± 2.91 (P < 0.01)	−9.13 ± 1.37 (P < 0.01)	−5.50 ± 0.84 (P < 0.01)	−4.07 ± 0.97 (P < 0.01)
BMI ≥ 30 (n = 454)	0.50 ± 0.62 (P = 0.42)	−17.95 ± 3.22 (P < 0.01)	−9.83 ± 1.51 (P < 0.01)	−4.14 ± 0.93 (P < 0.01)	−3.99 ± 1.08 (P < 0.01)
Interaction test	P < 0.01	P = 0.07	P = 0.05	P = 0.13	P = 0.16
Adjusted[c]					
All (N = 1,272)	0.96 ± 0.43 (P = 0.03)	−12.72 ± 1.88 (P < 0.01)	−6.64 ± 0.91 (P < 0.01)	−3.85 ± 0.55 (P < 0.01)	−2.23 ± 0.63 (P < 0.01)
BMI < 25 (n = 378)	0.54 ± 0.78 (P = 0.48)	−8.69 ± 3.25 (P < 0.01)	−4.31 ± 1.57 (P < 0.01)	−2.95 ± 0.94 (P < 0.01)	−1.43 ± 1.09 (P = 0.19)
BMI 25–29 (n = 478)	2.41 ± 0.70 (P < 0.01)	−15.61 ± 2.97 (P < 0.01)	−7.68 ± 1.44 (P < 0.01)	−4.97 ± 0.86 (P < 0.01)	−2.96 ± 1.00 (P < 0.01)
BMI ≥ 30 (n = 416)	0.02 ± 0.66 (P = 0.97)	−13.33 ± 3.24 (P < 0.01)	−7.77 ± 1.57 (P < 0.01)	−3.42 ± 0.94 (P < 0.01)	−2.15 ± 1.08 (P = 0.05)
Interaction test	P = 0.03	P = 0.27	P = 0.19	P = 0.23	P = 0.58
Models by CVD					
Crude					
All (N = 1,386)	1.56 ± 0.38 (P < 0.01)	−15.58 ± 1.80 (P < 0.01)	−8.05 ± 0.85 (P < 0.01)	−4.28 ± 0.52 (P < 0.01)	−3.24 ± 0.60 (P < 0.01)
No (n = 1,193)	1.43 ± 0.42 (P < 0.01)	−14.98 ± 1.95 (P < 0.01)	−7.66 ± 0.92 (P < 0.01)	−4.10 ± 0.56 (P < 0.01)	−3.21 ± 0.65 (P < 0.01)
Yes (n = 193)	2.14 ± 0.88 (P = 0.01)	−18.95 ± 4.62 (P < 0.01)	−10.26 ± 2.18 (P < 0.01)	−5.26 ± 1.33 (P < 0.01)	−3.43 ± 1.55 (P = 0.03)
Interaction test	P = 0.46	P = 0.43	P = 0.27	P = 0.42	P = 0.90
Adjusted[c]					
All (N = 1,272)	0.96 ± 0.43 (P = 0.03)	−12.72 ± 1.88 (P < 0.01)	−6.64 ± 0.91 (P < 0.01)	−3.85 ± 0.55 (P < 0.01)	−2.23 ± 0.63 (P < 0.01)
No (n = 1,098)	0.91 ± 0.47 (P = 0.05)	−12.56 ± 2.01 (P < 0.01)	−6.47 ± 0.97 (P < 0.01)	−3.81 ± 0.58 (P < 0.01)	−2.28 ± 0.67 (P < 0.01)
Yes (n = 174)	1.22 ± 0.98 (P = 0.21)	−13.69 ± 4.77 (P < 0.01)	−7.66 ± 2.26 (P < 0.01)	−4.08 ± 1.35 (P < 0.01)	−1.94 ± 1.56 (P = 0.21)
Interaction test	P = 0.77	P = 0.82	P = 0.62	P = 0.85	P = 0.84

Table continues next page

[a] Difference in brain volume comparing fourth quartile (median = 0.78 μg/m^3) versus first to third quartiles for DPM (median = 0.29 μg/m^3). All analyses were adjusted for ICV.

[b] Difference in ventricular volume per DPM interquartile change (0.31 μg/m^3).

[c] Using Model VI: adjusted for geographic region; age, race, or ethnicity; SES (education, income, and employment status); lifestyle factors (smoking, alcohol use, and physical activity); HT; depressive symptoms; BMI; conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia); and CVD histories.

Table 8 (*continued*). Linear Regression Modeling Results of On-Road DPM Exposure and Brain Volume Outcomes in the WHIMS–MRI Cohort (1999–2006) by BMI, CVD, Diabetes Mellitus, and WBC Count

		GM Volume[a]			
Statistical Models	Ventricle[b]	Association Brain	Frontal	Parietal	Temporal
Models by Diabetes Mellitus					
Crude					
All (N = 1,402)	1.58 ± 0.38 (P < 0.01)	−14.89 ± 1.78 (P < 0.01)	−7.78 ± 0.84 (P < 0.01)	−4.08 ± 0.52 (P < 0.01)	−3.03 ± 0.60 (P < 0.01)
No (n = 1,356)	1.60 ± 0.39 (P < 0.01)	−14.50 ± 1.82 (P < 0.01)	−7.66 ± 0.86 (P < 0.01)	−3.93 ± 0.53 (P < 0.01)	−2.91 ± 0.61 (P < 0.01)
Yes (n = 46)	1.21 ± 1.58 (P = 0.44)	−23.76 ± 8.57 (P < 0.01)	−10.34 ± 4.05 (P = 0.01)	−7.59 ± 2.48 (P < 0.01)	−5.84 ± 2.87 (P = 0.04)
Interaction test	P = 0.81	P = 0.29	P = 0.52	P = 0.15	P = 0.32
Adjusted[c]					
All (N = 1,272)	0.96 ± 0.43 (P = 0.03)	−12.72 ± 1.88 (P < 0.01)	−6.64 ± 0.91 (P < 0.01)	−3.85 ± 0.55 (P < 0.01)	−2.23 ± 0.63 (P < 0.01)
No (n = 1,232)	1.03 ± 0.44 (P = 0.02)	−12.09 ± 1.91 (P < 0.01)	−6.40 ± 0.93 (P < 0.01)	−3.63 ± 0.55 (P < 0.01)	−2.05 ± 0.64 (P < 0.01)
Yes (n = 40)	−0.28 ± 1.65 (P = 0.87)	−28.16 ± 8.79 (P < 0.01)	−12.48 ± 4.26 (P < 0.01)	−9.20 ± 2.55 (P < 0.01)	−6.49 ± 2.94 (P = 0.03)
Interaction test	P = 0.44	P = 0.07	P = 0.16	P = 0.03	P = 0.14
Models by WBC Count					
Crude					
All (N = 1,364)	1.76 ± 0.39 (P < 0.01)	−15.51 ± 1.81 (P < 0.01)	−7.99 ± 0.85 (P < 0.01)	−4.24 ± 0.52 (P < 0.01)	−3.29 ± 0.61 (P < 0.01)
≥ Median (n = 706)	1.90 ± 0.57 (P < 0.01)	−15.45 ± 2.47 (P < 0.01)	−7.67 ± 1.16 (P < 0.01)	−4.24 ± 0.71 (P < 0.01)	−3.54 ± 0.83 (P < 0.01)
< Median (n = 658)	1.64 ± 0.53 (P < 0.01)	−15.58 ± 2.66 (P < 0.01)	−8.36 ± 1.25 (P < 0.01)	−4.23 ± 0.77 (P < 0.01)	−3.00 ± 0.89 (P < 0.01)
Interaction test	P = 0.74	P = 0.97	P = 0.69	P = 0.99	P = 0.66
Adjusted[c]					
All (N = 1,239)	1.02 ± 0.44 (P = 0.02)	−12.99 ± 1.92 (P < 0.01)	−6.69 ± 0.93 (P < 0.01)	−3.93 ± 0.56 (P < 0.01)	−2.36 ± 0.64 (P < 0.01)
≥ Median (n = 635)	1.04 ± 0.63 (P = 0.10)	−11.97 ± 2.59 (P < 0.01)	−5.83 ± 1.25 (P < 0.01)	−3.73 ± 0.75 (P < 0.01)	−2.41 ± 0.87 (P < 0.01)
< Median (n = 604)	1.00 ± 0.58 (P = 0.08)	−14.11 ± 2.71 (P < 0.01)	−7.64 ± 1.31 (P < 0.01)	−7.64 ± 1.31 (P < 0.01)	−2.31 ± 0.91 (P = 0.01)
Interaction test	P = 0.96	P = 0.56	P = 0.31	P = 0.68	P = 0.94

[a] Difference in brain volume comparing fourth quartile (median = 0.78 μg/m^3) versus first to third quartiles for DPM (median = 0.29 μg/m^3). All analyses were adjusted for ICV.

[b] Difference in ventricular volume per DPM interquartile change (0.31 μg/m^3).

[c] Using Model VI: adjusted for geographic region; age, race, or ethnicity; SES (education, income, and employment status); lifestyle factors (smoking, alcohol use, and physical activity); HT; depressive symptoms; BMI; conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia); and CVD histories.

Table 9. Sociodemographic Factors, Lifestyle Factors, and Clinical Characteristics by $PM_{2.5}$ Exposure Quartiles in the WHIMS Cohort (1999–2007)

Population Characteristics		Mean ± SD (μg/m³)	Cumulative Annual Average $PM_{2.5}$ (μg/m³) (quartile) 3.71–11.11 Median = 10.03	11.11–12.94 Median = 12.11	12.94–15.01 Median = 14.01	15.01–27.08 Median = 16.57	*P* value
All	*N* = 7,050	13.15 ± 3.22	*N* = 1,763	*N* = 1,762	*N* = 1,762	*N* = 1,763	
U.S. Region							<0.0001
Northeast	1,908	12.43 ± 1.70	385 (20.2%)	909 (47.6%)	432 (22.6%)	182 (9.5%)	
South	1,480	14.03 ± 2.29	235 (15.9%)	215 (14.5%)	596 (40.3%)	434 (29.3%)	
Midwest	1,705	13.65 ± 2.47	369 (21.6%)	397 (23.3%)	321 (18.9%)	618 (36.2%)	
West	1,957	12.74 ± 4.88	774 (39.6%)	241 (12.3%)	413 (21.1%)	529 (27%)	
Age at baseline (yr)							0.14
65–69	3,272	13.08 ± 3.17	839 (25.6%)	827 (25.3%)	794 (24.3%)	812 (24.8%)	
70–74	2,529	13.12 ± 3.23	644 (25.5%)	637 (25.2%)	633 (25.0%)	615 (24.3%)	
≥ 75	1,249	13.37 ± 3.32	280 (22.4%)	298 (23.9%)	335 (26.8%)	336 (26.9%)	
Ethnicity							<0.0001
Black or African-American	488	15 ± 2.51	31 (6.4%)	55 (11.3%)	161 (33%)	241 (49.4%)	
Hispanic White	159	13.16 ± 4.14	60 (37.7%)	25 (15.7%)	37 (23.3%)	37 (23.3%)	
Non-Hispanic White	6,147	13.05 ± 3.06	1,575 (25.6%)	1,646 (26.8%)	1,508 (24.5%)	1,418 (23.1%)	
Other or missing	256	11.78 ± 5.54	97 (37.9%)	36 (14.1%)	56 (21.9%)	67 (26.2%)	
Family income							<0.0001
< $10,000	380	13.21 ± 3.39	98 (25.8%)	68 (17.9%)	99 (26.1%)	115 (30.3%)	
$10,000–$34,999	3,405	13 ± 3.22	946 (27.8%)	822 (24.1%)	764 (22.4%)	873 (25.6%)	
$35,000–$74,999	2,307	13.28 ± 3.2	504 (21.8%)	630 (27.3%)	622 (27%)	551 (23.9%)	
≥$75,000	710	13.45 ± 3.29	146 (20.6%)	175 (24.6%)	215 (30.3%)	174 (24.5%)	
Missing	248	12.87 ± 2.91	69 (27.8%)	67 (27%)	62 (25%)	50 (20.2%)	
Participant's education level							0.0002
< High school	516	13.18 ± 3.32	123 (23.8%)	116 (22.5%)	121 (23.4%)	156 (30.2%)	
High school/GED	1,554	12.92 ± 3.16	432 (27.8%)	402 (25.9%)	331 (21.3%)	389 (25%)	
> High school	4,960	13.21 ± 3.23	1,202 (24.2%)	1,243 (25.1%)	1,304 (26.3%)	1,211 (24.4%)	
Employment							0.25
Currently employed	1,254	13.3 ± 3.17	301 (24%)	317 (25.3%)	317 (25.3%)	319 (25.4%)	
Not working	768	13.21 ± 3.37	193 (25.1%)	165 (21.5%)	200 (26%)	210 (27.3%)	
Retired	5,005	13.09 ± 3.21	1,265 (25.3%)	1,276 (25.5%)	1,238 (24.7%)	1,226 (24.5%)	

Table continues next page

Table 9 (*continued*). Population Distribution of Cumulative $PM_{2.5}$ Exposures in Relation to Sociodemographics, Lifestyle Factors, and Clinical Characteristics in the WHIMS Cohort (1999–2007)

Population Characteristics		Mean ± SD ($\mu g/m^3$)	Cumulative Annual Average $PM_{2.5}$ ($\mu g/m^3$) (quartile) 3.71–11.11 Median = 10.03	11.11–12.94 Median = 12.11	12.94–15.01 Median = 14.01	15.01–27.08 Median = 16.57	*P* value
Moderate or strenuous activity (≥20 min)							<0.0001
No activity	4,078	13.23 ± 3.22	988 (24.2%)	997 (24.4%)	992 (24.3%)	1101 (27%)	
Some activity	343	13.49 ± 3.22	73 (21.3%)	88 (25.7%)	88 (25.7%)	94 (27.4%)	
2–4 episodes	1,387	13.00 ± 3.26	355 (25.6%)	379 (27.3%)	350 (25.2%)	304 (21.9%)	
> 4 episodes	1,226	12.93 ± 3.18	345 (28.1%)	293 (23.9%)	328 (26.8%)	260 (21.2%)	
Smoking status							0.02
Never smoked	3,722	13.22 ± 3.3	929 (25%)	873 (23.5%)	943 (25.3%)	977 (26.2%)	
Past smoker	2,762	13.05 ± 3.12	695 (25.2%)	751 (27.2%)	670 (24.3%)	646 (23.4%)	
Current smoker	468	13.02 ± 3.16	118 (25.2%)	117 (25.0%)	115 (24.6%)	118 (25.2%)	
Alcohol intake							<0.0001
Non drinker	911	13.49 ± 3.64	227 (24.9%)	135 (14.8%)	237 (26%)	312 (34.2%)	
Past drinker	1,370	13.2 ± 3.27	371 (27.1%)	307 (22.4%)	296 (21.6%)	396 (28.9%)	
<1 drink/ day	3,857	13.07 ± 3.12	942 (24.4%)	1083 (28.1%)	971 (25.2%)	861 (22.3%)	
>1 drink/ day	847	13 ± 3.09	207 (24.4%)	227 (26.8%)	240 (28.3%)	173 (20.4%)	
HT use ever							<0.0001
No	3,834	13.18 ± 3.01	877 (22.9%)	1045 (27.3%)	965 (25.2%)	947 (24.7%)	
Yes	3,214	13.11 ± 3.46	885 (27.5%)	716 (22.3%)	797 (24.8%)	816 (25.4%)	
BMI (kg/m^2)							0.04
<25	2,048	13.07 ± 3.24	536 (26.2%)	505 (24.7%)	542 (26.5%)	465 (22.7%)	
25–29	2,546	13.15 ± 3.29	632 (24.8%)	648 (25.5%)	632 (24.8%)	634 (24.9%)	
≥ 30	2,418	13.20 ± 3.14	590 (24.4%)	598 (24.7%)	577 (23.9%)	653 (27%)	
History of depression							0.22
No	6,322	13.15 ± 3.21	1567 (24.8%)	1601 (25.3%)	1587 (25.1%)	1567 (24.8%)	
Yes	557	13.16 ± 3.3	144 (25.9%)	125 (22.4%)	133 (23.7%)	156 (28%)	
Diabetes treated ever (pills or injections)							0.23
No	6,604	13.15 ± 3.23	1659 (25.1%)	1659 (25.1%)	1633 (24.7%)	1653 (25%)	
Yes	434	13.12 ± 3.16	102 (23.5%)	99 (22.8%)	126 (29%)	107 (24.7%)	
High cholesterol requiring pills ever							0.49
No	5,692	13.11 ± 3.2	1433 (25.2%)	1440 (25.3%)	1417 (24.9%)	1402 (24.6%)	
Yes	1,264	13.25 ± 3.28	308 (24.4%)	305 (24.1%)	317 (25.1%)	335 (26.5%)	
Hypertension ever							0.05
No	4,257	13.11 ± 3.2	1070 (25.1%)	1089 (25.6%)	1082 (25.4%)	1016 (23.9%)	
Yes	2,714	13.2 ± 3.26	675 (24.9%)	660 (24.3%)	653 (24.1%)	726 (26.8%)	
Cardiovascular disease ever							0.17
No	5,746	13.13 ± 3.23	1440 (25.1%)	1458 (25.4%)	1442 (25.1%)	1406 (24.5%)	
Yes	1,197	13.19 ± 3.16	298 (24.9%)	284 (23.7%)	287 (24%)	328 (27.4%)	

POPULATION CHARACTERISTICS AND DPM EXPOSURES IN WHIMS COHORT

Table 10 shows the results of comparing the distributions of selected baseline personal and clinical characteristics with the exposure categories defined by the quartiles of cumulative yearly DPM exposures (1996–2005) in the WHIMS cohort. Participants recruited from the Northeast, were ≥70 years old, belonged to a minority group (black or Hispanic white), were current or past smokers, had current or past consumption of alcohol and did not use HT were more likely to live in a census tract with the highest (fourth quartile) DPM exposures compared with their counterparts (all P values < 0.05). The associations between DPM exposures and family income or education appeared to be nonlinear, with higher estimates of cumulative DPM exposures among participants with low income (<$10,000) and low educational attainment (<high school) or reporting high income (≥$75,000) and higher educational attainment (>high school).

Table 10. Sociodemographic Factors, Lifestyle Factors, and Clinical Characteristics by On-Road DPM Exposure Quartiles in the WHIMS Cohort (1996–2005)

			Cumulative Annual Average DPM (μg/m³) (quartile)				
Population Characteristics		Mean ± SD (μg/m³)	0–0.271 Median = 0.177	0.271–0.429 Median = 0.350	0.429–0.621 Median = 0.518	0.621–5.122 Median = 0.794	P value
All	N = 7,447	0.48 ± 0.3	N = 1,861	N = 1,862	N = 1,863	N = 1,861	
U.S. Region							<0.0001
Northeast	2,005	0.57 ± 0.4	255 (12.7%)	590 (29.4%)	541 (27%)	619 (30.9%)	
South	1,573	0.44 ± 0.2	416 (26.4%)	456 (29%)	384 (24.4%)	317 (20.2%)	
Midwest	1,787	0.44 ± 0.2	487 (27.3%)	438 (24.5%)	501 (28%)	361 (20.2%)	
West	2,082	0.47 ± 0.4	703 (33.8%)	378 (18.2%)	437 (21%)	564 (27.1%)	
Age at screening (yr)							0.0165
65–69	3,418	0.47 ± 0.3	894 (26.2%)	875 (25.6%)	842 (24.6%)	807 (23.6%)	
70–74	2,673	0.48 ± 0.3	664 (24.8%)	668 (25%)	664 (24.8%)	667 (25.3%)	
≥ 75	1,356	0.50 ± 0.3	303 (22.3%)	319 (23.5%)	357 (26.3%)	377 (27.8%)	
Ethnicity							<0.0001
Black or African-American	527	0.70 ± 0.4	35 (6.6%)	72 (13.7%)	150 (28.5%)	270 (51.2%)	
Hispanic White	177	0.60 ± 0.4	36 (20.3%)	26 (14.7%)	49 (27.7%)	66 (37.3%)	
Non-Hispanic White	6,472	0.46 ± 0.3	1,697 (26.2%)	1,726 (26.7%)	1,601 (24.7%)	1,448 (22.4%)	
Other or missing	271	0.47 ± 0.4	93 (34.3%)	38 (14%)	63 (23.2%)	77 (28.4%)	
Family income							<0.0001
< $10,000	418	0.52 ± 0.3	98 (23.4%)	87 (20.8%)	108 (25.8%)	125 (29.9%)	
$10,000–$34,999	3,619	0.46 ± 0.3	983 (27.2%)	958 (26.5%)	852 (23.5%)	826 (22.8%)	
$35,000–$74,999	2,406	0.49 ± 0.3	566 (23.5%)	583 (24.2%)	615 (25.6%)	642 (26.7%)	
≥$75,000	742	0.52 ± 0.3	150 (20.2%)	167 (22.5%)	221 (29.8%)	204 (27.5%)	
Missing	262	0.48 ± 0.3	64 (24.4%)	67 (25.6%)	67 (25.6%)	64 (24.4%)	
Participant's education level							0.0056
< High school	574	0.5 ± 0.4	144 (25.1%)	133 (23.2%)	143 (24.9%)	154 (26.8%)	
High school/GED	1,639	0.45 ± 0.3	442 (27%)	442 (27%)	405 (24.7%)	350 (21.4%)	
> High school	5,212	0.49 ± 0.3	1,271 (24.4%)	1,283 (24.6%)	1,307 (25.1%)	1,351 (25.9%)	

Table continues next page

Table 10 (*continued*). Sociodemographic Factors, Lifestyle Factors, and Clinical Characteristics by On-Road DPM Exposure Quartiles in the WHIMS Cohort (1996–2005)

Population Characteristics		Mean ± SD ($\mu g/m^3$)	Cumulative Annual Average DPM ($\mu g/m^3$) (quartile) 0–0.271 Median = 0.177	0.271–0.429 Median = 0.350	0.429–0.621 Median = 0.518	0.621–5.122 Median = 0.794	*P* value
Employment							0.094
Currently employed	1,317	0.49 ± 0.3	295 (22.4%)	311 (23.6%)	381 (28.9%)	330 (25.1%)	
Not working	815	0.49 ± 0.3	199 (24.4%)	202 (24.8%)	201 (24.7%)	213 (26.1%)	
Retired	5,290	0.48 ± 0.3	1,364 (25.8%)	1,341 (25.3%)	1,270 (24%)	1,315 (24.9%)	
Moderate or strenuous activity (≥20 min)							0.4708
No activity	4,338	0.49 ± 0.3	1,054 (24.3%)	1,079 (24.9%)	1,115 (25.7%)	1,090 (25.1%)	
Some activity	360	0.50 ± 0.4	81 (22.5%)	90 (25%)	93 (25.8%)	96 (26.7%)	
2–4 episodes	1,445	0.48 ± 0.3	382 (26.4%)	357 (24.7%)	341 (23.6%)	365 (25.3%)	
> 4 episodes	1,287	0.47 ± 0.3	342 (26.6%)	332 (25.8%)	308 (23.9%)	305 (23.7%)	
Smoking status							0.0054
Never smoked	3,893	0.46 ± 0.3	1,039 (26.7%)	977 (25.1%)	972 (25%)	905 (23.2%)	
Past smoker	2,915	0.50 ± 0.3	681 (23.4%)	724 (24.8%)	724 (24.8%)	786 (27%)	
Current smoker	528	0.51 ± 0.4	122 (23.1%)	129 (24.4%)	138 (26.1%)	139 (26.3%)	
Alcohol intake							0.0005
Non drinker	971	0.44 ± 0.3	287 (29.6%)	257 (26.5%)	239 (24.6%)	188 (19.4%)	
Past drinker	1,463	0.48 ± 0.3	382 (26.1%)	362 (24.7%)	357 (24.4%)	362 (24.7%)	
<1 drink/day	4,053	0.49 ± 0.3	964 (23.8%)	1,021 (25.2%)	1,005 (24.8%)	1,063 (26.2%)	
>1 drink/day	890	0.49 ± 0.3	212 (23.8%)	211 (23.7%)	237 (26.6%)	230 (25.8%)	
HT use ever							0.0053
No	4,056	0.48 ± 0.3	976 (24.1%)	987 (24.3%)	1,018 (25.1%)	1,075 (26.5%)	
Yes	3,389	0.47 ± 0.3	884 (26.1%)	874 (25.8%)	845 (24.9%)	786 (23.2%)	
BMI (kg/m^2)							0.5452
< 25	2,159	0.48 ± 0.3	564 (26.1%)	531 (24.6%)	540 (25%)	524 (24.3%)	
25–29	2,697	0.48 ± 0.3	679 (25.2%)	687 (25.5%)	673 (25%)	658 (24.4%)	
≥30	2,550	0.49 ± 0.3	607 (23.8%)	639 (25.1%)	639 (25.1%)	665 (26.1%)	
History of depression							0.9766
No	6,662	0.48 ± 0.3	1,664 (25%)	1,674 (25.1%)	1,676 (25.2%)	1,648 (24.7%)	
Yes	605	0.49 ± 0.4	150 (24.8%)	154 (25.5%)	148 (24.5%)	153 (25.3%)	
Diabetes treated ever (pills or injections)							0.1992
No	6,951	0.48 ± 0.3	1,733 (24.9%)	1,755 (25.2%)	1,741 (25%)	1,722 (24.8%)	
Yes	482	0.51 ± 0.3	123 (25.5%)	104 (21.6%)	119 (24.7%)	136 (28.2%)	
High cholesterol requiring pills ever							0.3797
No	6,010	0.48 ± 0.3	1,506 (25.1%)	1,512 (25.2%)	1,521 (25.3%)	1,471 (24.5%)	
Yes	1,336	0.50 ± 0.3	330 (24.7%)	326 (24.4%)	323 (24.2%)	357 (26.7%)	
Hypertension ever							0.3035
No	4,459	0.47 ± 0.3	1,129 (25.3%)	1,119 (25.1%)	1,131 (25.4%)	1,080 (24.2%)	
Yes	2,903	0.49 ± 0.3	715 (24.6%)	724 (24.9%)	706 (24.3%)	758 (26.1%)	
Cardiovascular disease ever							0.6988
No	6,049	0.48 ± 0.3	1,502 (24.8%)	1,528 (25.3%)	1,507 (24.9%)	1,512 (25%)	
Yes	1,283	0.48 ± 0.3	333 (26%)	307 (23.9%)	326 (25.4%)	317 (24.7%)	

FREQUENCIES OF MCI AND DEMENTIA BY $PM_{2.5}$ AND DPM EXPOSURES

In Table 11, we present the distribution of MCI and dementia incidence according to the population categories defined by the quartiles of exposures to $PM_{2.5}$ and DPM.

There were 232 subjects classified as having incident probable dementia and 360 as having incident MCI during an average of 7.7 years of follow-up, equivalent to estimated incidence rates of 4.00 per 1,000 person–years for dementia and 6.41 per 1,000 person–years for MCI. Among those with $PM_{2.5}$ exposure data, estimated incidence rates (3.72 and 6.34 per 1,000 person–years for dementia and MCI, respectively) were not substantially different from those of the entire WHIMS cohort. The total number of dementia and MCI cases available for the $PM_{2.5}$ analyses was 214 and 354, respectively. The observed overall differences in the frequency of dementia by $PM_{2.5}$ exposure categories reached marginal significance ($P = 0.05$), and there

Table 11. MCI and Dementia by $PM_{2.5}$ and On-Road DPM Exposure Quartiles in the WHIMS Cohort (1999–2007)

	All	Subjects with Exposures Not Missing	Cumulative Annual Average $PM_{2.5}$ (μg/m³) (quartile)				*P* Value[a]
			3.71–11.11	11.11–12.95	12.94–15.01	15.01–27.08	
$PM_{2.5}$ (μg/m³)							
MCI (*N*)	7,327	6,915	1,735	1,731	1,721	1,728	
Total person–year at risk	56,146.25	55,794.97	14,202.21	14,408.08	13,943.38	13,241.30	
Number of incident cases	360	354	91	61	102	100	
Event rate (cases per 1,000 person–year)	6.41	6.34	6.41	4.23	7.32	7.55	0.001
Dementia (*N*)	7,479	7,050	1,763	1,762	1,762	1,763	
Total person–year at risk	57,940.56	57,897.45	14,609.33	14,766.65	14,487.39	13,696.02	
Number of incident cases	232	214	43	46	62	63	
Event rate (cases per 1,000 person–years)	4.00	3.72	2.94	3.12	4.28	4.60	0.05

	All	Subjects with Exposures Not Missing	Cumulative Annual Average DPM (μg/m³) (quartile)				*P* Value[a]
			0–0.271	0.271–0.429	0.429–0.621	0.621–5.122	
DPM (μg/m³)							
MCI (*N*)	7,327	7,298	1,820	1,835	1,830	1,813	
Total person–year at risk	56,142	56,104	14,101	14,628	14,216	13,159	
Number of incident cases	360	358	69	92	99	98	
Event rate (cases per 1,000 person–years)	6.41	6.38	4.89	6.29	6.96	7.45	0.04
Dementia (*N*)	7,479	7,447	1,861	1,862	1,863	1,861	
Total person–year at risk	57,941	57,897	14,502	15,039	14,679	13,677	
Number of incident cases	232	229	61	45	61	62	
Event rate (cases per 1,000 person–year)	4.00	3.96	4.21	2.99	4.16	4.53	0.37

[a] Global *P* value testing the difference in incidence rate based on likelihood ratio tests in robust Poisson regression.

was a tendency for increased dementia incidence across the exposure quartiles ($P = 0.01$ for a linear trend test, data not shown), with an approximately 1.5-fold increase in the dementia incidence rate comparing the highest quartile (4.60 per 1,000 person–years) with the lowest quartile (2.94 per 1,000 person–years). The overall difference in MCI incidence rates by $PM_{2.5}$ exposure categories was greater ($P = 0.001$ by the likelihood-ratio test with robust Poisson regression), but the revealed association was nonlinear, with the lowest incidence rate found in the second exposure quartile (4.23 per 1,000 person–years) and the highest incidence rate found in the fourth quartile (7.55 per 1,000 person–years). Among participants with DPM exposure data, estimated incidence rates (3.96 and 6.38 per 1,000 person–years for dementia and MCI, respectively) were also very comparable to those estimated for the entire WHIMS cohort. Although the observed overall difference in the event rate of MCI by exposure categories was modest ($P = 0.04$), there was a gradual increase in the estimated MCI incidence rate across the quartiles of increased cumulative DPM exposure ($P = 0.03$ for a trend test). The event rate of dementia did not differ across the cumulative DPM exposure categories ($P = 0.37$).

COX MODELS FOR ADJUSTED ASSOCIATIONS WITH $PM_{2.5}$ EXPOSURES

In the crude Cox model, the HR for MCI/dementia increased modestly (crude HR = 1.05; 95% CI: 0.94–1.18, per interquartile increase [3.9-μg/m^3] in cumulative $PM_{2.5}$ exposures). Slightly increased HRs were also found in the secondary analyses separately for MCI (crude HR = 1.06; 95% CI: 0.93–1.21) and probable dementia (crude HR = 1.09; 95% CI: 0.92–1.29). However, none of these associations reached statistical significance. In subsequent Cox proportional hazard models (Table 12), no associations were reported between $PM_{2.5}$ and MCI and dementia.

MODIFICATIONS OF HYPOTHESIZED ADVERSE NEUROCOGNITIVE EFFECTS OF $PM_{2.5}$ EXPOSURES

Table 13 summarizes the results of Cox proportional hazard models assessing effect modifications by BMI categories, CVD histories, diabetes mellitus, or WBC count. No statistically significant associations were found between cumulative $PM_{2.5}$ exposures and the incidence of neurocognitive outcomes; a similar lack of statistically significant associations was found in the primary analyses for the

Table 12. Cox Proportional Hazard Modeling Results of $PM_{2.5}$ Exposure[a] and MCI and Dementia in the WHIMS Cohort (1999–2007)

Exposure Variable	Models[b]	MCI	Dementia	MCI/Dementia
Cumulative annual average $PM_{2.5}$ (lag0)	Crude	$N = 6{,}883$, $n = 322$ 1.06 (0.93 to 1.21), $P = 0.38$	$N = 7{,}050$, $n = 214$ 1.09 (0.92 to 1.29), $P = 0.32$	$N = 7{,}012$, $n = 451$ 1.05 (0.94 to 1.18), $P = 0.38$
	Model I	$N = 6{,}883$, $n = 32$ 0.95 (0.82 to 1.09), $P = 0.42$	$N = 7{,}050$, $n = 214$ 1.01 (0.85 to 1.20), $P = 0.92$	$N = 7{,}012$, $n = 451$ 0.95 (0.85 to 1.07), $P = 0.41$
	Model II	$N = 6{,}845$, $n = 317$ 0.95 (0.82 to 1.09), $P = 0.44$	$N = 7{,}011$, $n = 211$ 0.99 (0.83 to 1.18), $P = 0.92$	$N = 6{,}973$, $n = 445$ 0.95 (0.85 to 1.07), $P = 0.42$
	Model III	$N = 6{,}702$, $n = 306$ 0.94 (0.82 to 1.08), $P = 0.39$	$N = 6{,}862$, $n = 202$ 1.00 (0.83 to 1.20), $P = 1.00$	$N = 6{,}824$, $n = 428$ 0.96 (0.85 to 1.08), $P = 0.47$
	Model IV	$N = 6{,}308$, $n = 267$ 0.96 (0.82 to 1.12), $P = 0.59$	$N = 6{,}447$, $n = 171$ 1.00 (0.81 to 1.22), $P = 0.96$	$N = 6{,}413$, $n = 372$ 0.96 (0.84 to 1.10), $P = 0.56$
	Model V	$N = 6{,}185$, $n = 261$ 0.94 (0.80 to 1.11), $P = 0.47$	$N = 6{,}317$, $n = 168$ 1.00 (0.81 to 1.23), $P = 0.98$	$N = 6{,}287$, $n = 363$ 0.95 (0.83 to 1.09), $P = 0.46$
	Model VI	$N = 6{,}126$, $n = 256$ 0.93 (0.79 to 1.09), $P = 0.39$	$N = 6{,}258$, $n = 167$ 0.99 (0.81 to 1.22), $P = 0.95$	$N = 6{,}228$, $n = 358$ 0.94 (0.82 to 1.08), $P = 0.38$

[a] Expressed as the hazard ratios (95% confidence interval) associated with each interquartile increment (3.9 μg/m^3) of time-varying cumulative annual $PM_{2.5}$ exposures.

[b] Model I: adjusted for geographic region, age, and race or ethnicity. Model II: adjusted for Model I covariates and SES (education, income, and employment status). Model III: adjusted for Model II covariates and lifestyle factors (smoking, alcohol use, and physical activity). Model IV: adjusted for Model III covariates, HT, depressive symptoms, and BMI. Model V: adjusted for Model IV covariates and conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia). Model VI: adjusted for Model V covariates and CVD histories.

Table 13. Cox Proportional Hazard Modeling Results for $PM_{2.5}$ Exposure[a] and MCI and Dementia in the WHIMS Cohort (1999–2007) by BMI, CVD, Diabetes Mellitus, and WBC Count

Models	MCI	Dementia	Incident MCI or Dementia
Models by BMI			
Crude			
Main	*N* = 6,845, *n* = 320 1.06 (0.93 to 1.21), *P* = 0.38	*N* = 7,012, *n* = 213 1.09 (0.92 to 1.29), *P* = 0.31	*N* = 6,974, *n* = 449 1.05 (0.94 to 1.18), *P* = 0.38
BMI < 25 kg/m^2	*N* = 1,990, *n* = 110 1.02 (0.81 to 1.27), *P* = 0.90	*N* = 2,048, *n* = 80 1.13 (0.86 to 1.47), *P* = 0.37	*N* = 2,036, *n* = 156 1.02 (0.85 to 1.24), *P* = 0.81
BMI 25–29 kg/m^2	*N* = 2,482, *n* = 100 0.92 (0.73 to 1.16), *P* = 0.47	*N* = 2,546, *n* = 72 1.22 (0.92 to 1.6), *P* = 0.16	*N* = 2,532, *n* = 150 1.02 (0.84 to 1.24), *P* = 0.82
BMI ≥ 30 kg/m^2	*N* = 2,373, *n* = 110 1.28 (1.02 to 1.60), *P* = 0.03	*N* = 2,418, *n* = 61 0.89 (0.64 to 1.24), *P* = 0.49	*N* = 2,406, *n* = 143 1.12 (0.92 to 1.38), *P* = 0.26
Interaction *P* value	0.12	0.34	0.74
Adjusted[b]			
Main	*N* = 6,126, *n* = 256 0.94 (0.80 to 1.10), *P* = 0.43	*N* = 6,258, *n* = 167 1.00 (0.81 to 1.23), *P* = 0.98	*N* = 6,228, *n* = 358 0.95 (0.83 to 1.08), *P* = 0.43
BMI < 25 kg/m^2	*N* = 1,788, *n* = 86 0.93 (0.71 to 1.22), *P* = 0.61	*N* = 1,830, *n* = 55 1.06 (0.75 to 1.49), *P* = 0.74	*N* = 1,819, *n* = 117 0.96 (0.76 to 1.20), *P* = 0.70
BMI 25–29 kg/m^2	*N* = 2,225, *n* = 81 0.78 (0.60 to 1.03), *P* = 0.08	*N* = 2,277, *n* = 58 1.07 (0.77 to 1.48), *P* = 0.70	*N* = 2,267, *n* = 123 0.89 (0.71 to 1.10), *P* = 0.27
BMI ≥ 30 kg/m^2	*N* = 2,113, *n* = 89 1.12 (0.86 to 1.46), *P* = 0.38	*N* = 2,151, *n* = 54 0.85 (0.59 to 1.24), *P* = 0.40	*N* = 2,142, *n* = 118 1.01 (0.80 to 1.28), *P* = 0.91
Interaction *P* value	0.16	0.60	0.69
Models by CVD			
Crude			
Main	*N* = 6,778, *n* = 313 1.06 (0.93 to 1.21), *P* = 0.40	*N* = 6,943, *n* = 211 1.09 (0.92 to 1.29), *P* = 0.32	*N* = 6,906, *n* = 441, 1.05 (0.94 to 1.18), *P* = 0.41
No	*N* = 5,613, *n* = 243 1.03 (0.89 to 1.20), *P* = 0.69	*N* = 5,746, *n* = 167 1.09 (0.91 to 1.32), *P* = 0.34	*N* = 5,720, *n* = 350 1.04 (0.91 to 1.18), *P* = 0.58
Yes	*N* = 1,165, *n* = 70 1.17 (0.88 to 1.55), *P* = 0.29	*N* = 1,197, *n* = 44 1.06 (0.73 to 1.55), *P* = 0.75	*N* = 1,186, *n* = 91 1.10 (0.85 to 1.42), *P* = 0.46
Interaction *P* value	0.46	0.89	0.68
Adjusted[b]			
Main	*N* = 6,126, *n* = 256 0.94 (0.80 to 1.10), *P* = 0.43	*N* = 6,258, *n* = 167 1.00 (0.81 to 1.23), *P* = 0.98	*N* = 6,228, *n* = 358 0.95 (0.83 to 1.08), *P* = 0.43
No	*N* = 5,084, *n* = 194 0.92 (0.77 to 1.10), *P* = 0.36	*N* = 5,191, *n* = 130 1.02 (0.82 to 1.28), *P* = 0.84	*N* = 5,169, *n* = 279 0.94 (0.81 to 1.09), *P* = 0.43
Yes	*N* = 1,042, *n* = 62 1.00 (0.73 to 1.37), *P* = 0.99	*N* = 1,067, *n* = 37 0.90 (0.58 to 1.40), *P* = 0.64	*N* = 1,059, *n* = 79 0.97 (0.73 to 1.29), *P* = 0.83
Interaction *P* value	0.63	0.60	0.85

Table continues next page

[a] Expressed as the hazard ratios (95% confidence interval) associated with each interquartile increment (3.9 μg/m^3) of time-varying cumulative annual $PM_{2.5}$ exposures.

[b] Using Model VI: adjusted for geographic region, age, and race, or ethnicity; SES (education, income, and employment status); lifestyle factors (smoking, alcohol use, and physical activity); HT; depressive symptoms; BMI; conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia); and CVD histories.

Table 13 (*continued*). Cox Proportional Hazard Modeling Results for $PM_{2.5}$ Exposure[a] and MCI and Dementia in the WHIMS Cohort (1999–2007) by BMI, CVD, Diabetes Mellitus, and WBC Count

Models	MCI	Dementia	Incident MCI or Dementia
Models by Diabetes Mellitus			
Crude			
Main	*N* = 6,872, *n* = 321, 1.07 (0.94 to 1.22), *P* = 0.33	*N* = 7,038, *n* = 213 1.09 (0.93 to 1.29), *P* = 0.29	*N* = 7,001, *n* = 450 1.06 (0.94 to 1.18), *P* = 0.35
No	*N* = 6,448, *n* = 278 1.06 (0.92 to 1.22), *P* = 0.42	*N* = 6,604, *n* = 202 1.08 (0.91 to 1.28), *P* = 0.39	*N* = 6,574, *n* = 404 1.06 (0.94 to 1.19), *P* = 0.38
Yes	*N* = 424, *n* = 43 1.13 (0.78 to 1.64), *P* = 0.52	*N* = 434, *n* = 11 1.46 (0.70 to 3.02), *P* = 0.31	*N* = 427, *n* = 46 1.06 (0.74 to 1.53), *P* = 0.74
Interaction *P* value	0.75	0.43	0.97
Adjusted[b]			
Main	*N* = 6,126, *n* = 256 0.94 (0.80 to 1.10), *P* = 0.43	*N* = 6,258, *n* = 167 1.00 (0.81 to 1.23), *P* = 0.98	*N* = 6,228, *n* = 358 0.95 (0.83 to 1.08), *P* = 0.43
No	*N* = 5,763, *n* = 220 0.94 (0.79 to 1.11), *P* = 0.47	*N* = 5,887, *n* = 159 1.00 (0.81 to 1.23), *P* = 0.99	*N* = 5,863, *n* = 320 0.95 (0.83 to 1.10), *P* = 0.52
Yes	*N* = 363, *n* = 36 0.92 (0.60 to 1.41), *P* = 0.71	*N* = 371, *n* = 8 0.99 (0.39 to 2.53), *P* = 0.98	*N* = 365, *n* = 38 0.87 (0.58 to 1.31), *P* = 0.51
Interaction *P* value	0.94	0.98	0.67
Models by WBC Count			
Crude			
Main	*N* = 6,654, *n* = 303 1.05 (0.92 to 1.21), *P* = 0.47	*N* = 6,813, *n* = 203 1.06 (0.90 to 1.26), *P* = 0.48	*N* = 6,777, *n* = 426 1.04 (0.92 to 1.16), *P* = 0.55
WBC ≥5,000/μL	*N* = 3,233, *n* = 139 1.06 (0.87 to 1.30), *P* = 0.54	*N* = 3,318, *n* = 97 1.12 (0.87 to 1.42), *P* = 0.38	*N* = 3,296, *n* = 202 1.07 (0.90 to 1.26), *P* = 0.45
WBC < 5,000/μL	*N* = 3,421, *n* = 164 1.04 (0.86 to 1.25), *P* = 0.67	*N* = 3,495, *n* = 106 1.02 (0.80 to 1.29), *P* = 0.89	*N* = 3,481, *n* = 224 1.01 (0.86 to 1.19), *P* = 0.92
Interaction *P* value	0.88	0.60	0.63
Adjusted[b]			
Main	*N* = 5,929, *n* = 242 0.92 (0.78 to 1.08), *P* = 0.30	*N* = 6,053, *n* = 157 0.96 (0.78 to 1.19), *P* = 0.73	*N* = 6,025, *n* = 338 0.92 (0.80 to 1.06), *P* = 0.23
WBC ≥5,000/μL	*N* = 2,888, *n* = 109 0.94 (0.74 to 1.18), *P* = 0.57	*N* = 2,957, *n* = 80 1.01 (0.76 to 1.33), *P* = 0.96	*N* = 2,941, *n* = 162 0.94 (0.78 to 1.14), *P* = 0.52
WBC < 5,000/μL	*N* = 3,041, *n* = 133 0.90 (0.72 to 1.12), *P* = 0.34	*N* = 3,096, *n* = 77 0.91 (0.67 to 1.24), *P* = 0.56	*N* = 3,084, *n* = 176 0.89 (0.74 to 1.09), *P* = 0.26
Interaction *P* value	0.80	0.63	0.71

[a] Expressed as the hazard ratios (95% confidence interval) associated with each interquartile increment (3.9 μg/m^3) of time-varying cumulative annual $PM_{2.5}$ exposures.

[b] Using Model VI: adjusted for geographic region, age, and race, or ethnicity; SES (education, income, and employment status); lifestyle factors (smoking, alcohol use, and physical activity); HT; depressive symptoms; BMI; conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia); and CVD histories.

MCI/dementia outcome as well as in the secondary analyses for the specific incidence of MCI and dementia separately. Although the increased crude HR for MCI was statistically significant (crude HR = 1.28; 95% CI: 1.02–1.60) among participants who were obese (BMI ≥30 kg/m^2), this association became statistically nonsignificant (adjusted HR = 1.12; 95% CI: 0.86–1.46) after adjusting further for geographic region, age, race or ethnicity, SES, lifestyle factors, HT use, depressive symptoms, BMI, CVD risk factors, and CVD histories.

COX MODELS FOR ADJUSTED ASSOCIATIONS WITH DPM EXPOSURES

Table 14 presents the results of Cox proportional hazard models examining DPM exposure effects with statistical adjustment for multiple potential confounders. For cumulative average DPM (upper panel) in the crude Cox model, the HR for MCI or dementia was modestly elevated (crude HR = 1.07; 95% CI: 0.98–1.17, per interquartile increase [0.35 μg/m^3] in cumulative DPM exposures). A very modest increase in HR was also found in the secondary analyses separately for MCI (crude HR = 1.09; 95% CI: 0.98–1.2) and for dementia (crude HR = 1.03; 95% CI: 0.89–1.19); none of these differences reached the predetermined level of statistical significance ($P = 0.05$). The observed association between increased cumulative DPM exposure and elevated HR for MCI or dementia in the crude analyses went away after adjusting for geographic region, age, and race or ethnicity (adjusted HR = 0.96; 95% CI: 0.86–1.06; model I of Table 14, upper panel); the same lack of associations was found in the other Cox models after adjusting for the various potential confounders. Similarly, in the secondary analyses separately for MCI and dementia, our crude estimates with slightly increased HRs were greatly attenuated in the multiple-covariate-adjusted Cox models.

The HR for MCI or dementia associated with estimated DPM exposures at baseline (lower panel of Table 14) was modestly elevated (crude HR = 1.07; 95% CI: 0.96–1.2, per interquartile increase [0.35-μg/m^3] in baseline DPM exposures), but this association was not statistically significant ($P = 0.20$). In the secondary analyses, baseline DPM exposure was only associated with a modest increase in HR for MCI (crude HR = 1.08; 95% CI: 0.95–1.23); the association was not statistically significant ($P = 0.22$). Similar to the differences between the crude and adjusted analyses for cumulative DPM exposures, the observed modest associations between baseline DPM exposure and MCI/dementia and between baseline DPM exposure and MCI separately disappeared after adjusting for geographic region, age, and race or ethnicity (model I). In the multiple-covariate-adjusted Cox models for combined MCI/dementia or for MCI and dementia separately, no evidence was found for the hypothesized adverse effects of baseline DPM exposure on neurocognitive disorders. We found very similar results in the sensitivity analyses restricted to non-Hispanic whites or not adjusted for geographic region (Table B.5 in Appendix B, available on the HEI website). Note that the correlation between baseline DPM and cumulative DPM was very high (0.93) (Table A.1, Appendix A).

MODIFICATION OF HYPOTHESIZED ADVERSE NEUROCOGNITIVE EFFECTS OF DPM EXPOSURES

Table 15 summarizes the results from multiple-covariate-adjusted Cox models assessing effect modifications by BMI categories, CVD histories, diabetes mellitus, or WBC count. These effect-modification analyses revealed no statistically significant associations between cumulative DPM exposures and the incidence of neurocognitive outcomes. No statistical interactions were found in either the primary analyses with MCI/dementia combined or in the secondary analyses on the incidence of MCI and dementia separately.

Table 14. Cox Proportional Hazard Modeling Results of On-Road DPM Exposure[a] and MCI and Dementia in the WHIMS Cohort (1999–2007)

Exposure Variable /Models[b]	MCI	Dementia	Incident MCI or Dementia
DPM Cumulative Average (lag0)			
Crude	*N* = 7,295, *n* = 355 1.09 (0.98, 1.2), *P* = 0.12	*N* = 7,447, *n* = 229 1.03 (0.89, 1.19), *P* = 0.69	*N* = 7,437, *n* = 497 1.07 (0.98, 1.17), *P* = 0.12
Model I	*N* = 7,295, *n* = 355 0.94 (0.84, 1.07), *P* = 0.36	*N* = 7,447, *n* = 229 0.95 (0.81, 1.11), *P* = 0.53	*N* = 7,437, *n* = 497 0.96 (0.86, 1.06), *P* = 0.39
Model II	*N* = 7,253, *n* = 350 0.96 (0.85, 1.08), *P* = 0.47	*N* = 7,404, *n* = 226 0.96 (0.82, 1.13), *P* = 0.62	*N* = 7,394, *n* = 491 0.97 (0.87, 1.07), *P* = 0.53
Model III	*N* = 7,096, *n* = 339 0.96 (0.84, 1.09), *P* = 0.5	*N* = 7,239, *n* = 215 0.97 (0.82, 1.14), *P* = 0.69	*N* = 7,229, *n* = 472 0.97 (0.87, 1.08), *P* = 0.57
Model IV	*N* = 6,680, *n* = 298 0.98 (0.86, 1.11), *P* = 0.72	*N* = 6,803, *n* = 183 0.98 (0.81, 1.17), *P* = 0.79	*N* = 6,795, *n* = 413 0.99 (0.88, 1.1), *P* = 0.81
Model V	*N* = 6,546, *n* = 289 0.96 (0.84, 1.1), *P* = 0.57	*N* = 6,663, *n* = 178 1.00 (0.83, 1.20), *P* = 0.98	*N* = 6,656, *n* = 399 0.98 (0.87, 1.11), *P* = 0.78
Model VI	*N* = 6,485, *n* = 284 0.96 (0.84, 1.11), *P* = 0.60	*N* = 6,602, *n* = 177 1.01 (0.84, 1.2), *P* = 0.95	*N* = 6,595, *n* = 394 0.99 (0.88, 1.11), *P* = 0.81
DPM Baseline Average (lag0)			
Crude	*N* = 6,969, *n* = 340 1.08 (0.95, 1.23), *P* = 0.22	*N* = 7,112, *n* = 220 1.03 (0.87, 1.21), *P* = 0.75	*N* = 7,106, *n* = 477 1.07 (0.96, 1.2), *P* = 0.20
Model I	*N* = 6,969, *n* = 340 0.93 (0.81, 1.07), *P* = 0.33	*N* = 7,112, *n* = 220 0.95 (0.8, 1.14), *P* = 0.59	*N* = 7,106, *n* = 477 0.95 (0.85, 1.07), *P* = 0.40
Model II	*N* = 6,928, *n* = 335 0.96 (0.83, 1.10), *P* = 0.52	*N* = 7,071, *n* = 217 0.97 (0.82, 1.16), *P* = 0.77	*N* = 7,065, *n* = 471 0.97 (0.86, 1.09), *P* = 0.60
Model III	*N* = 6,780, *n* = 326 0.96 (0.83, 1.10), *P* = 0.53	*N* = 6,914, *n* = 206 0.98 (0.82, 1.18), *P* = 0.84	*N* = 6,908, *n* = 454 0.97 (0.86, 1.11), *P* = 0.64
Model IV	*N* = 6,387, *n* = 288 0.97 (0.84, 1.13), *P* = 0.73	*N* = 6,502, *n* = 174 0.97 (0.79, 1.18), *P* = 0.74	*N* = 6,497, *n* = 398 0.98 (0.86, 1.11), *P* = 0.71
Model V	*N* = 6,265, *n* = 279 0.95 (0.82, 1.11), *P* = 0.55	*N* = 6,366, *n* = 169 1.01 (0.83, 1.23), *P* = 0.93	*N* = 6,362, *n* = 384 0.98 (0.86, 1.11), *P* = 0.72
Model VI	*N* = 6,201, *n* = 274 0.95 (0.82, 1.11), *P* = 0.55	*N* = 6,310, *n* = 168 1.02 (0.83, 1.25), *P* = 0.84	*N* = 6,306, *n* = 379 0.98 (0.86, 1.12), *P* = 0.75

[a] Expressed as the hazard ratios (95% confidence interval) associated with each interquartile increment (0.35 μg/m^3) of time-varying cumulative annual or baseline exposures to DPM from on-road sources.

[b] Model I: adjusted for geographic region, age, and race or ethnicity. Model II: adjusted for Model I covariates and SES (education, income, and employment status). Model III: adjusted for Model II covariates and lifestyle factors (smoking, alcohol use, and physical activity). Model IV: adjusted for Model III covariates, HT, depressive symptoms, and BMI. Model V: adjusted for Model IV covariates and conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia). Model VI: adjusted for Model V covariates and CVD histories.

Table 15. Cox Proportional Hazard Modeling Results of On-Road DPM Exposure[a] and MCI and Dementia in the WHIMS Cohort (1999–2007) by BMI, CVD, Diabetes Mellitus, and WBC Count

Models	MCI	Dementia	Incident MCI or Dementia
Models by BMI			
Crude			
Main	*N* = 7,254, *n* = 353 1.08 (0.98, 1.20), *P* = 0.13	*N* = 7,406, *n* = 228 1.03 (0.89, 1.19), *P* = 0.72	*N* = 7,396, *n* = 495 1.07 (0.98, 1.17), *P* = 0.13
BMI < 25 kg/m^2	*N* = 2,100, *n* = 121 0.96 (0.78, 1.18), *P* = 0.69	*N* = 2,159, *n* = 90 1.08 (0.87, 1.34), *P* = 0.49	*N* = 2,155, *n* = 176 1.00 (0.84, 1.18), *P* = 0.96
BMI = 25–29 kg/m^2	*N* = 2,644, *n* = 112 1.15 (0.97, 1.36), *P* = 0.10	*N* = 2,697, *n* = 73 1.06 (0.83, 1.35), *P* = 0.64	*N* = 2,695, *n* = 163 1.15 (1.00, 1.32), *P* = 0.06
BMI ≥ 30 kg/m^2	*N* = 2,510, *n* = 120 1.12 (0.96, 1.31), *P* = 0.15	*N* = 2,550, *n* = 65 0.91 (0.67, 1.23), *P* = 0.55	*N* = 2,546, *n* = 156 1.07 (0.92, 1.25), *P* = 0.39
Interaction *P* value	0.37	0.65	0.45
Adjusted[b]			
Main	*N* = 6,485, *n* = 284 0.96 (0.84, 1.11), *P* = 0.58	*N* = 6,602, *n* = 177 1.01 (0.84, 1.20), *P* = 0.95	*N* = 6,595, *n* = 394 0.99 (0.88, 1.11), *P* = 0.82
BMI < 25 kg/m^2	*N* = 1,888, *n* = 96 0.86 (0.67, 1.11), *P* = 0.26	*N* = 1,928, *n* = 61 1.19 (0.90, 1.56), *P* = 0.22	*N* = 1,924, *n* = 132 0.95 (0.77, 1.17), *P* = 0.61
BMI = 25–29 kg/m^2	*N* = 2,365, *n* = 90 1.03 (0.85, 1.26), *P* = 0.74	*N* = 2,409, *n* = 59 0.96 (0.71, 1.29), *P* = 0.79	*N* = 2,408, *n* = 133 1.05 (0.89, 1.24), *P* = 0.59
BMI ≥ 30 kg/m^2	*N* = 2,232, *n* = 98 0.97 (0.78, 1.21), *P* = 0.79	*N* = 2,265, *n* = 57 0.87 (0.61, 1.24), *P* = 0.43	*N* = 2,263, *n* = 129 0.95 (0.77, 1.16), *P* = 0.60
Interaction *P* value	0.53	0.33	0.66
Models by CVD			
Crude			
Main	*N* = 7,182, *n* = 345 1.08 (0.97, 1.20), *P* = 0.15	*N* = 7,332, *n* = 225 1.04 (0.91, 1.20), *P* = 0.54	*N* = 7,322, *n* = 485 1.07 (0.98, 1.17), *P* = 0.13
No	*N* = 5,924, *n* = 266 1.06 (0.94, 1.20), *P* = 0.35	*N* = 6,049, *n* = 179 1.08 (0.93, 1.25), *P* = 0.32	*N* = 6,042, *n* = 384 1.06 (0.96, 1.18), *P* = 0.24
Yes	*N* = 1,258, *n* = 79 1.15 (0.93, 1.41), *P* = 0.19	*N* = 1,283, *n* = 46 0.90 (0.63, 1.29), *P* = 0.57	*N* = 1,280, *n* = 101 1.10 (0.91, 1.34), *P* = 0.31
Interaction *P* value	0.52	0.37	0.74
Adjusted[b]			
Main	*N* = 6,485, *n* = 284 0.96 (0.84, 1.11), *P* = 0.58	*N* = 6,602, *n* = 177 1.01 (0.84, 1.20), *P* = 0.95	*N* = 6,595, *n* = 394 0.99 (0.88, 1.11), *P* = 0.82
No	*N* = 5,358, *n* = 215 0.98 (0.84, 1.14), *P* = 0.80	*N* = 5,455, *n* = 138 1.06 (0.88, 1.27), *P* = 0.56	*N* = 5,450, *n* = 307 1.00 (0.88, 1.14), *P* = 0.94
Yes	*N* = 1,127, *n* = 69 0.91 (0.69, 1.19), *P* = 0.47	*N* = 1,147, *n* = 39 0.77 (0.49, 1.22), *P* = 0.27	*N* = 1,145, *n* = 87 0.92 (0.71, 1.18), *P* = 0.50
Interaction *P* value	0.60	0.21	0.51

Table continues next page

[a] Expressed as the hazard ratios (95% confidence intervals) for each interquartile increment (0.35 μg/m^3) of time-varying cumulative annual exposure to DPM from on-road sources.

[b] Using Model VI: adjusted for geographic region, age, race, or ethnicity; SES (education, income, and employment status); lifestyle factors (smoking, alcohol use, and physical activity); HT; depressive symptoms; BMI; conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia); and CVD histories.

Table 15 (*continued*). Cox Proportional Hazard Modeling Results of On-Road DPM Exposure[a] and MCI and Dementia in the WHIMS Cohort (1999–2007) by BMI, CVD, Diabetes Mellitus, and WBC Count

Models	MCI	Dementia	Incident MCI or Dementia
Models by Diabetes Mellitus			
Crude			
Main	*N* = 7,282, *n* = 353 1.09 (0.98, 1.20), *P* = 0.12	*N* = 7,433, *n* = 227, 1.04 (0.90, 1.19), *P* = 0.62	*N* = 7,423, *n* = 494 1.08 (0.98, 1.18), v = 0.11
No	*N* = 6,808, *n* = 306 1.08 (0.97, 1.21), *P* = 0.18	*N* = 6,951, *n* = 214 1.04 (0.90, 1.20), *P* = 0.58	*N* = 6,944, *n* = 442 1.08 (0.98, 1.18), *P* = 0.13
Yes	*N* = 474, *n* = 47 1.13 (0.85, 1.50), *P* = 0.41	*N* = 482, *n* = 13 0.94 (0.48, 1.84), *P* = 0.86	*N* = 479, *n* = 52 1.08 (0.81, 1.44), *P* = 0.58
Interaction *P* value	0.78	0.77	0.96
Adjusted[b]			
Main	*N* = 6,485, *n* = 284 0.96 (0.84, 1.11), *P* = 0.58	*N* = 6,602, *n* = 177 1.01 (0.84, 1.20), *P* = 0.95	*N* = 6,595, *n* = 394 0.99 (0.88, 1.11), *P* = 0.82
No	*N* = 6,079, *n* = 245 0.99 (0.86, 1.14), *P* = 0.87	*N* = 6,189, *n* = 167 1.03 (0.86, 1.23), *P* = 0.76	*N* = 6,185, *n* = 351 1.01 (0.90, 1.14), *P* = 0.88
Yes	*N* = 406, *n* = 39 0.80 (0.55, 1.16), *P* = 0.23	*N* = 413, *n* = 10 0.58 (0.23, 1.50), *P* = 0.26	*N* = 410, *n* = 43 0.79 (0.55, 1.15), *P* = 0.22
Interaction *P* value	0.28	0.24	0.21
Models by WBC Count			
Crude			
Main	*N* = 7,045, *n* = 334 1.08 (0.97, 1.20), *P* = 0.18	*N* = 7,191, *n* = 218 1.03 (0.89, 1.19), *P* = 0.72	*N* = 7,181, *n* = 470 1.07 (0.97, 1.17), *P* = 0.16
WBC ≥ 5,000/μL	*N* = 3,666, *n* = 179 1.05 (0.91, 1.21), *P* = 0.52	*N* = 3,737, *n* = 116 1.06 (0.89, 1.26), *P* = 0.50	*N* = 3,734, *n* = 247 1.05 (0.93, 1.18), *P* = 0.46
WBC < 5,000/μL	*N* = 3,379, *n* = 155 1.12 (0.95, 1.33), *P* = 0.18	*N* = 3,454, *n* = 102 0.97 (0.76, 1.24), *P* = 0.80	*N* = 3,447, *n* = 223 1.10 (0.95, 1.28), *P* = 0.19
Interaction *P* value	0.54	0.55	0.59
Adjusted[b]			
Main	*N* = 6,271, *n* = 268 0.97 (0.84, 1.11), *P* = 0.63	*N* = 6,382, *n* = 167 1.01 (0.84, 1.22), *P* = 0.91	*N* = 6,375, *n* = 372 0.99 (0.88, 1.12), *P* = 0.91
WBC ≥ 5,000/μL	*N* = 3,267, *n* = 146 0.96 (0.80, 1.15), *P* = 0.65	*N* = 3,318, *n* = 84 1.07 (0.85, 1.34), *P* = 0.57	*N* = 3,315, *n* = 194 1.00 (0.86, 1.17), *P* = 0.98
WBC < 5,000/μL	*N* = 3,004, *n* = 122 0.97 (0.79, 1.20), *P* = 0.81	*N* = 3,064, *n* = 83 0.94 (0.70, 1.25), *P* = 0.65	*N* = 3,060, *n* = 178 0.98 (0.83, 1.17), *P* = 0.85
Interaction *P* value	0.90	0.47	0.87

[a] Expressed as the hazard ratios (95% confidence intervals) for each interquartile increment (0.35 μg/m^3) of time-varying cumulative annual exposure to DPM from on-road sources.

[b] Using Model VI: adjusted for geographic region, age, race, or ethnicity; SES (education, income, and employment status); lifestyle factors (smoking, alcohol use, and physical activity); HT; depressive symptoms; BMI; conventional CVD risk factors (hypertension, diabetes mellitus, and hypercholesterolemia); and CVD histories.

DISCUSSION

NEUROTOXIC EFFECTS

Effects of $PM_{2.5}$ Exposure on Brain Structure

In this large-scale epidemiological study on residential exposure to fine particles and human brain structure, we found that healthy, cognitively intact participants had smaller brain volumes, especially in the normal-appearing WM, if they lived in locations with higher levels of long-term exposure to $PM_{2.5}$ before the brain MRI scans were performed. The observed associations were not explained by sociodemographic factors, SES, lifestyle factors, or other clinical characteristics. Our study findings add to the growing epidemiological evidence supporting the emerging concept that late-in-life exposures to ambient particulate air pollutants are a novel environmental determinant of brain aging.

Our analyses showed that the putative adverse effect on brain structure in participants was driven primarily by the smaller WM volumes associated with cumulative $PM_{2.5}$ exposures, which were present in the WM of association brain regions (frontal, parietal, and temporal) and the corpus callosum. In contrast, the brain volumes of normal GM tissues and the hippocampus did not differ by exposures. Although our observed lack of associations between GM volume and $PM_{2.5}$ exposures was consistent with current toxicology literature showing no strong evidence for neuronal death or synaptic loss in animals with inhaled exposures to fine particles, we could not exclude the possibility that smaller GM volumes might be found in the elderly exposed to other PM with different neurotoxic characteristics (e.g., ultrafine particles).

Our study did not provide evidence for the modification of adverse effects on smaller WM volume by cardiovascular risk factors. Although one can argue that stronger associations in participants with prior CVD suggested possible interactions of CVD-related neurovascular damage with an underlying neuropathology of smaller WM volumes associated with $PM_{2.5}$ exposures, the putative adverse effects on WM were still present in participants without CVD or diabetes mellitus.

Although we did not find that $PM_{2.5}$ exposure affected hippocampal volume, the consistent pattern of adverse effects on WM volumes in association brain regions (especially the frontal and temporal WM) points to the possible impairment of higher cortical control functions and memory with long-term $PM_{2.5}$ exposures. This projected memory loss was seen in two longitudinal studies (Tonne et al. 2014; Weuve et al. 2012). Using data from the Nurses' Health Study Cognitive Cohort, Weuve and colleagues reported that memory function declined in older women (70 to 81 years) living in locations with higher $PM_{2.5}$ exposures. Tonne and colleagues found an adverse $PM_{2.5}$ effect on memory decline among older men and women (N = 2,687; 66 ± 6 years old) in the Whitehall II cohort and living in Greater London. If our observed associations reflect some of the structural brain substrates linking $PM_{2.5}$ with cognitive aging, greater declines in executive functions, episodic memory, and information processing speed would be expected in the elderly with higher exposure. Although one longitudinal study of older women (Weuve et al. 2012) suggested that PM exposures adversely affected executive functions, such putatively neurotoxic effects on cognitive aging were not found in a longitudinal study of older men (Power et al. 2011) or in three cross-sectional analyses (Gatto et al. 2014; Ranft et al. 2009; Wellenius et al. 2012) that included men and women. Two studies, one cross-sectional (Ailshire and Crimmins 2014) and one longitudinal (Tonne et al. 2014), found associations between $PM_{2.5}$ exposure and diminished performance of episodic memory (Ailshire and Crimmins 2014), but two longitudinal studies (Power et al. 2011; Weuve et al. 2012) with instruments assessing episodic memory did not report such findings. We found no published data on $PM_{2.5}$ and information processing speed. This important knowledge gap in the emerging field that combines the study of air pollution and neuroepidemiology may be addressed by comprehensive analyses with longitudinal data on subdomain cognitive declines.

Our study findings add further evidence to the emerging field of environmental neurosciences by suggesting that WM architecture is a novel target of PM neurotoxicity. In an earlier study comparing regional brain volumes as measured by MRI, Calderón-Garcidueñas and colleagues (2011) found smaller WM volumes in the right parietal and bilateral temporal lobes of healthy children in Mexico City (n = 20) versus controls (n = 10). A recent cross-sectional study also showed that early-life $PM_{2.5}$ exposure may affect age-related WM maturation (Peterson et al. 2015). In a sample of 40 minority urban-dwelling school-age children, prenatal exposures to polycyclic aromatic hydrocarbons (measured from personal air samples of $PM_{2.5}$ during pregnancy) were associated with smaller local WM volume, as indicated by the reduction of surface areas. Neuroepidemiological studies have also linked ambient air pollution with the occurrence and relapse of multiple sclerosis (Oikonen et al. 2003), the most common WM disease characterized by extensive neuroinflammation. In mice exposed to concentrated particles (Allen et al. 2014b), more recent toxicological data showed persistent

glial activation in the corpus callosum. In addition to volumetric measures, future studies should use diffusion tensor imaging (Madden et al. 2009) to examine whether cerebral WM integrity is disrupted by PM exposure. To elucidate the neuropathology and mechanisms underlying the observed adverse $PM_{2.5}$ effects on WM volumes, we also need to understand whether exposures to airborne particles may cause myelination disturbance (Kohama et al. 2012) and age-related decrease of the oligodendrocytes in subcortical WM (Chen et al. 2011).

Effects of DPM Exposure on Brain Structure

In our analyses using aggregated DPM estimates at the census-tract level as a proxy indicator of exposure to PM from traffic sources in this nationwide cohort of older women, we found an association between increasing DPM exposure and larger ventricular volume, suggesting an overall atrophic effect on the aging brains. This association could not be explained by sociodemographic factors, SES, lifestyle, or other clinical characteristics. An overall atrophic effect on brain structure was also found in a recent toxicological study reporting ventriculomegaly (i.e., dilated lateral ventricle) following exposure to ultrafine (<100 nm) concentrated ambient particles (Allen et al. 2014a).

We also found that participants tended to have smaller GM volumes if they lived in areas with the highest estimate (i.e., in the fourth quartile) of cumulative DPM exposure in the 10 years prior to the brain MRI scans compared with the other women with lower estimates (i.e., in the first to third quartiles of exposures). This observed association was present for the total brain GM and in the association cortices (frontal, parietal, and temporal) and remained robust in the analyses adjusting for multiple potential confounders, including geographic region, sociodemographic features, SES, lifestyle factors, and other clinical characteristics. Under the assumptions (1) that NATA-derived DPM estimates were a reasonable ecological measure of PM exposure from traffic sources and (2) that there were no other major confounding in the association observed in this cohort of mostly cognitively intact older women, our study findings implied that the neuropathological changes underlying the neurotoxic effects in elderly women exposed to traffic-related air pollutants might involve damage to synapses. To the best of our knowledge, our study findings likely provide the first air pollution–epidemiological evidence for GM neurotoxicity associated with DPM, which is in line with previous reports demonstrating in vivo (Fonken et al. 2011) and in vitro (Davis et al. 2013) evidence for reduced synaptic plasticity in response to airborne particle exposures.

Unlike the fairly linear and consistent associations between $PM_{2.5}$ exposure and smaller WM volumes in the association brain and corpus callosum in the current study, our analyses suggested that the differences in WM volumes appeared to be nonlinear in participants with varying levels of DPM exposure, though such an association was not found for the corpus callosum. Although we rigorously adjusted for multiple potential confounders, we could not completely rule out the possibility that the nonlinear pattern of associations between DPM exposures and WM volumes might still be subject to other residual or unmeasured confounding. If any such confounding exists, it would suggest that the confounders would have to be more prevalent in the midrange of cumulative DPM exposure and that they would affect WM but not GM volumes. Alternatively, the nonlinear associations may imply the possibility of different pathological processes between participants who mostly lived in census tracts with lower exposure levels (the first to third quartiles) and those who lived with the highest exposure (the fourth quartile). However, it is unclear why the presumed exposure-associated complex pathological changes did not occur in the corpus callosum. Another possibility is that the observed nonlinear associations might be driven largely by the highly skewed exposure distribution (see Appendix A for the exposure distribution). In the high-exposure group (Table 7, Part B, right panel), the larger WM volumes associated with increased DPM were found in the association brain regions, where the corresponding comparisons revealed smaller GM volumes (Table 7, Part A), with no statistically significant influence on the volume of the corpus callosum (Table 6). Though results are surprising and interpretation of the DPM effects on both GM and WM in the high-exposure group is difficult, one speculated possibility is the presence of putative GM structural neurotoxicity with local compensatory WM hypertrophy. In a recent neuroimaging study (Yu et al. 2011), investigators used the support vector machine learning method to conduct a whole brain analysis with multivariate pattern classification between heavy smokers and controls. Regional brain-structure abnormalities with smaller GM volumes associated with larger volumes in adjacent WM were reported in the heavy smokers compared with the control subjects. Future studies may seek to apply similar approaches to replicate the observed smaller GM volumes with companion larger WM volumes associated with PM exposures from traffic sources.

NEUROVASCULAR EFFECTS OF LONG-TERM PM EXPOSURES

The hypothesized neurovascular effects of long-term PM exposures predict positive associations between structural

brain MRI-measured SVID volumes and greater PM exposure. However, our analyses did not reveal major differences in SVID volumes in participants with varying levels of cumulative exposure to $PM_{2.5}$ (1999–2006) or DPM (1996–2005), nor were statistically significant associations between PM exposures and SVID volumes found in our analyses for total brain, association brain areas, GM, or WM. Previous neuroimaging studies have not provided strong support for this hypothesized neurovascular link between air pollution and brain aging, although the hypothesized link is receiving great attention (Weuve 2014). For instance, structural-brain MRI data from two community-based cohorts (the Cardiovascular Health Study and the Framingham Offspring Study) showed inconsistent associations between PM exposure and WM hyperintensities versus silent cerebral infarcts (Semmens 2012; Wilker et al. 2015). One recent study (Wilker et al. 2016) in a clinical population (with concerns about memory loss) even reported negative associations between $PM_{2.5}$ exposure and cerebrovascular damage (with reduced WM hyperintensities and fewer cerebral microbleeds).

Long-term exposure to PM has been recognized as a pervasive threat to cardiovascular health (Kaiser 2005; Nel 2005; Peters and Pope 2002); resulting increases in both morbidities and mortalities associated with PM exposures (Brook et al. 2004, 2010) are present before age 65 or earlier. In the WHI Observational Study (Miller et al. 2007), increased incidence of CVD (including stroke) was found in postmenopausal women with higher $PM_{2.5}$ exposure during the follow-up, with much greater estimates of exposure-associated increases in CVD and cerebrovascular deaths than reported previously (Chen 2010; Dockery and Stone 2007). After the WHIMS enrollment in 1996–1998, at age 65 or older, all WHIMS-MRI participants had to survive and continue the follow-up through 2005–2006 for the brain MRI scans. Therefore, the lack of associations with SVID volumes in our study may reflect possible healthy survivor bias in the WHIMS and WHIMS-MRI cohorts. Longitudinal cohort studies with repeated brain MRI scans (e.g., starting in midlife) and well characterized for CVD and associated morbidities may be better positioned to address this potential bias.

NEURODEGENERATIVE EFFECTS OF PM EXPOSURES ON MCI/DEMENTIA RISK

In our large cohort of older women, we did not find evidence for increased MCI/dementia risks associated with PM exposures, although such putative neurodegenerative effects were suggested by previous reports of low performance in memory tests (Ailshire and Clarke 2015; Ailshire and Crimmins 2014; Ranft et al. 2009) or of declines in cognitive functions (Power et al. 2011; Tonne et al. 2014; Weuve et al. 2012; Weuve 2014). A large number of toxicological studies with inhalation exposures to concentrated airborne particles (Block and Calderón-Garcidueñas 2009) have documented widespread neuroinflammation and oxidative stress, which are implicated in the pathogenesis of dementia, including Alzheimer's disease (Block et al. 2012; Genc et al. 2012; Moulton and Yang 2012). However, whether such PM-induced neural responses translate to pathological brain aging (e.g., MCI or dementia) has not been convincingly demonstrated with high-quality data from prospective cohorts. Four studies have been published since 2014 (Chang et al. 2014; Jung et al. 2015; Kioumourtzoglou et al. 2016; Wu et al. 2015) that suggested a possible increase in dementia risk associated with PM exposure. Methodologic limitations of those studies include using claims data of uncertain validity to determine incident Alzheimer's disease and related disorders (Taylor et al. 2002), the inclusion of aggregated exposure estimates prone to ecological biases (Sheppard 2003), and the use of retrospective design subject to selection biases (Hayden and Farmer 2015).

Reflecting the growing interest in studying the effects of ultrafine particles from traffic sources, more recent experiments have reported evidence of hippocampal neurotoxicity (Win-Shwe et al. 2008, 2011), the elevated presence of early markers of neurodegeneration (Levesque et al. 2011), and compromised blood–brain barriers in animals exposed to nanoparticles and diesel-engine exhaust. Using aggregated DPM estimates at the census-tract level as a proxy indicator of exposure to PM from traffic sources for the nationwide WHIMS cohort of older women, we did not find statistically significant increases in the incidence of MCI or dementia associated with DPM exposure (Tables 14 and 15). In the only prospective cohort study to date (Oudin et al. 2015) of the neurodegenerative effects of exposure to gaseous pollutants from traffic, estimates of exposure were based on a spatial model toward the end of study follow-up, which obscured the temporality of the reported association. We are not aware of any published studies investigating the neurodegenerative effects of traffic-related PM exposure on MCI or dementia. Published studies attempting to link traffic-related PM with cognitive aging also yielded mixed results. Although an earlier report (Power et al. 2011) that used Normative Aging Study data suggested that exposure to black carbon was associated with decreased cognitive function in older men, such neurotoxic effects were not evident in the current analyses, which included more extended longitudinal data to investigate differential susceptibility to

cognitive effects of long-term exposure. Previously, two cross-sectional studies found low performance in cognitive function tests among older people living in close proximity to road traffic, but corresponding associations with the estimated PM exposure from the traffic sources were not apparent (Ranft et al. 2009; Wellenius et al. 2012). Findings from a recent longitudinal study on the Whitehall II cohort participants, who were residents of Greater London, did not support the hypothesis that particles from traffic sources are more strongly associated with cognitive function than are particles from all sources (Tonne et al. 2014).

In our main analyses, which combined MCI and dementia, the incidence rates of neurocognitive disorders did not differ significantly by the estimated level of cumulative exposure to $PM_{2.5}$ after adjusting for potential confounders. Our earlier decision to combine MCI and dementia in the proposed main analyses followed the same analytic strategy used by the WHIMS investigators (Espeland et al. 2004; Shumaker et al. 2003) in which MCI was considered to be a preclinical state of dementia. Our main analyses, which combined MCI and dementia, also assumed that PM exposures would increase the risk of MCI and dementia in a similar manner and that these neurocognitive disorders were perhaps derived from similar neuropathological processes. The calculated analytic gain in statistical power supported this earlier decision to use incident MCI or dementia as a composite outcome in our main analyses. However, we also conducted secondary analyses to explore the neurotoxic effects of PM on MCI and dementia separately (Tables 12 and 14). Our exploratory analyses showed that the PM exposure–response relationships with MCI and dementia differed (Table 11), which did not provide statistical support for a common neuropathology, as had been assumed in the main analyses. Because the neurobiological heterogeneity of MCI has increasingly been recognized, even among subjects who were clinically similar (Nettiksimmons et al. 2014), future studies on the neurodegenerative effects of PM exposure should separate MCI and dementia. In the present study, however, neither of the post hoc secondary analyses was adequately powered to examine the adverse $PM_{2.5}$ effects on MCI or dementia separately.

LIMITATIONS AND STRENGTHS

We recognize several limitations to our study. First, our analyses only included a one-time assessment of brain volumes, raising the possibility of reverse causation. However, given that our analyses already adjusted for SES and measured lifestyle and various health factors, it was unclear what the unmeasured factors could be that might have made participants with smaller WM volumes live and stay in locations with higher $PM_{2.5}$ exposures. It was also difficult to speculate on other factors that would make participants with smaller GM volumes live and stay in census-tract-level areas with the highest DPM concentrations in 1996–2005. Longitudinal studies with repeated brain MRI scans will be needed to address this limitation.

Second, because we only studied older women who had volunteered and were eligible for a clinical trial of HT, the reported findings may not be generalizable to other women or older men. However, it has been shown that sex has negligible effects on age-related changes in brain volume in a healthy population (Fjell et al. 2009).

Third, constrained by limited resources, we were only able to use geostatistical modeling for $PM_{2.5}$ and relied on the NATA dispersion modeling results for DPM. Given the results from our BME models, which were exclusively based on AQS data, our analyses only captured the exposure effects of $PM_{2.5}$ as a regional pollutant, with no information on emission sources, particle constituents, or interactions with other pollutant mixtures. One simulation study (Alexeeff et al. 2015) also showed that spatiotemporal models accounting for small-scale variation in air pollution (e.g., by using land-use regression models or incorporating numerical air quality models) would produce less biased estimates of chronic health effects compared with geostatistical approaches. For instance, a more advanced BME method has been developed by combining AQS data and chemical transportation model output to estimate the daily $PM_{2.5}$ exposures (Reyes et al. 2017). Applying this new method to a WHIMS subcohort of non-Hispanic whites with ApoE genetic data and extended follow-up to 2010, investigators recently reported an increased risk for all-cause dementia among older women historically residing in locations with high $PM_{2.5}$ levels exceeding the current EPA standard (Cacciottolo et al. 2017).

Although we considered the NATA-derived estimates to be reasonable surrogates for population exposure to PM from on-road sources, the DPM exposure data used in our analyses were still prone to substantial measurement errors that may explain some of the null associations observed (e.g., with MCI/dementia or SVID volumes) in this study. On the other hand, we could not rule out the possibility that the observed associations might be attributed to other constituents of neurotoxic pollutants also from traffic sources. Although researchers have begun to investigate these complexities of PM exposures in the context of cardiopulmonary endpoints, such data sources are both costly and limited for nationwide cohorts.

Fourth, our analyses did not include genetic determinants of brain structure and dementia. Although ApoE

allele frequencies vary by geographic region (Ward et al. 2012), there is no clear link between WM volume and ApoE polymorphism that determine hippocampal volume (Fouquet et al. 2014; Taylor et al. 2014) or GM atrophy (Wishart et al. 2006). Because our analyses did not reveal significant associations with hippocampal volumes, it was unlikely that the observed adverse $PM_{2.5}$ effects on smaller WM volumes were the result of confounding by ApoE. On the other hand, the ApoE allele may interact with PM exposure to increase the risk of MCI/dementia (Cacciottolo et al. 2017) or SVID volumes; this was not investigated in our analyses.

Fifth, as is the case for all community-based observational studies, our study was based on a selective sample (i.e., older women who were enrolled in the original WHIMS cohort). Therefore, we could not rule out the arguable possibility of selective attrition as the reason for not observing the association of increased risk of MCI/dementia with air pollution exposure in the current study. Had selective attrition played a major role in explaining our findings, a similar lack of associations would be expected from the results of studying other common risk factors for increased mortality and dementia risks in a cohort of elderly people. However, empirical data from WHIMS might suggest otherwise because common risk factors, such as sleep loss (Chen et al. 2015), symptoms of depressive disorders (Goveas et al. 2011), type 2 diabetes (Espeland et al. 2015), and CVD (Haring et al. 2013), all had increased risks for clinically significant cognitive decline or dementia.

Sixth, for this study, which focused on brain structures using anatomical MRI, we only conducted region-of-interest analyses, which aggregated the volumetric measures within predefined neuroanatomic regions but discarded local variations. Future research with more fine-grained analyses, such as voxel-based morphometric methods (Davatzikos et al. 2001), may provide a more powerful approach to uncovering local targets with small-area variations in other brain structures that may be associated with long-term PM exposure (Casanova et al. 2016).

Seventh, our sample sizes might not have been sufficient to detect statistically significant interactions between the PM exposure and the potential effect modifiers included in the study.

There were several notable strengths in our study. It included the largest neuroimaging study to examine the association between long-term PM exposures and the in vivo endophenotype of the aging brain. Our analyses included dementia cases that were ascertained by the well-validated WHIMS protocols. The WHIMS and WHIMS-MRI cohorts were geographically diverse and well characterized. The comprehensive and high-quality WHI covariate data enabled rigorous adjustment for multiple potential confounders in studying air pollution and brain aging.

CONCLUSIONS

Long-term exposure to $PM_{2.5}$ may contribute to WM loss in healthy older women. Our study findings, in line with emerging neurotoxicological data, suggest that WM architecture is an important target of PM-induced neurotoxicity in regions of the brain. Future studies are needed to determine whether PM exposures result in myelination disturbance, disruption of axonal integrity, damage to oligodendrocytes, or other WM neuropathologies. Findings from our cross-sectional analyses also support the hypothesized neurotoxic effects of traffic-related PM on association cortices. The observed smaller GM volume associated with DPM exposure was supported by the emerging data on synaptic neurotoxicity in animals with PM exposures near roadways. Our analyses did not provide evidence for an increased risk for MCI or dementia associated with either $PM_{2.5}$ or DPM exposures. Whether the neural responses to PM (both documented in the extensive neurotoxicological literature and supported by the adverse effects on brain structure shown in our study) translate to pathological brain aging remains to be demonstrated or refuted by high-quality prospective cohort studies with adequate statistical power, improved exposure estimation, and valid outcome ascertainment.

IMPLICATIONS OF FINDINGS

Our study findings suggest an association between long-term exposure to PM and WM loss in healthy older women and are in line with emerging neurotoxicological data. To better test the neurovascular-effect hypothesis in PM-associated neurotoxic effects on the aging brain, future studies may need to pay greater attention to selecting optimal populations with repeated measurements of cerebrovascular damage and to address the possibility of selection biases. Our analyses did not provide evidence for an increased risk for MCI or dementia associated with either $PM_{2.5}$ or DPM exposures. An adequately powered prospective cohort study with improved exposure estimation and high-quality outcome ascertainment will be needed to investigate whether long-term PM exposures increase the risk of pathobiologically heterogeneous neurocognitive outcomes, including MCI and dementia.

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REFERENCES

Ailshire JA, Clarke P. 2015. Fine particulate matter air pollution and cognitive function among U.S. older adults. J Gerontol B Psychol Sci Soc Sci 70(2):322–328; doi:10.1093/geronb/gbu064.

Ailshire JA, Crimmins EM. 2014. Fine particulate matter air pollution and cognitive function among older U.S. adults. Am J Epidemiol 180(4):359–366; doi: 10.1093/aje/kwu155.

Akita Y, Chen JC, Serre ML. 2012. The moving-window Bayesian maximum entropy framework: Estimation of $PM_{2.5}$ yearly average concentration across the contiguous United States. J Expo Sci Environ Epidemiol 22:496–501.

Alexeeff SE, Schwartz J, Kloog I, Chudnovsky A, Koutrakis P, Coull BA. 2015. Consequences of kriging and land use regression for $PM_{2.5}$ predictions in epidemiologic analyses: Insights into spatial variability using high-resolution satellite data. J Expo Sci Environ Epidemiol 25:138–144.

Allen JL, Liu X, Pelkowski S, Palmer B, Conrad K, Oberdörster G, et al. 2014a. Early postnatal exposure to ultrafine particulate matter air pollution: Persistent ventriculomegaly, neurochemical disruption, and glial activation preferentially in male mice. Environ Health Perspect 122:939–945.

Allen JL, Liu X, Weston D, Prince L, Oberdörster G, Finkelstein JN, et al. 2014b. Developmental exposure to concentrated ambient ultrafine particulate matter air pollution in mice results in persistent and sex-dependent behavioral neurotoxicity and glial activation. Toxicol Sci 140(1):160–178; doi: 10.1093/toxsci/kfu059.

American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders. Fourth ed. Washington, DC:American Psychiatric Association.

Anbeek P, Vincken KL, van Osch MJ, Bisschops RH, van der Grond J. 2004. Automatic segmentation of different-sized white matter lesions by voxel probability estimation. Med Image Anal 8:205–215.

Bateson TF, Schwartz J. 2004. Who is sensitive to the effects of particulate air pollution on mortality? A case-crossover analysis of effect modifiers. Epidemiology 15:143–149.

Block ML, Calderón-Garcidueñas L. 2009. Air pollution: Mechanisms of neuroinflammation and CNS disease. Trends Neurosci 32:506–516.

Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, et al. 2012. The outdoor air pollution and brain health workshop. Neurotoxicology 33:972–984.

Bowler JV, Gorelick PB. 2007. Advances in vascular cognitive impairment 2006. Stroke 38:241–244.

Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, et al. 2004. Air pollution and cardiovascular disease: A statement for healthcare professionals from the expert panel on population and prevention science of the American Heart Association. Circulation 109:2655–2671.

Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 121:2331–2378.

Burnam MA, Wells KB, Leake B, Landsverk J. 1988. Development of a brief screening instrument for detecting depressive disorders. Med Care 26:775–789.

Cacciottolo M, Wang X, Driscoll I, Woodward N, Saffari A, Reyes J, et al. 2017. Particulate air pollutants, ApoE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. Transl Psychiatry 7:e1022.

Calderón-Garcidueñas L, Engle R, Mora-Tiscareno A, Styner M, Gomez-Garza G, Zhu H, et al. 2011. Exposure to

severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. Brain Cogn 77:345–355.

Calderón-Garcidueñas L, Solt AC, Henriquez-Roldan C, Torres-Jardon R, Nuse B, Herritt L, et al. 2008. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol 36:289–310.

Casanova R, Wang X, Reyes J, Akita Y, Serre ML, Vizuete W, et al. 2016. A voxel-based morphometry study reveals local brain structural alterations associated with ambient fine particles in older women. Front Hum Neurosci 10:495.

Chang KH, Chang MY, Muo CH, Wu TN, Chen CY, Kao CH. 2014. Increased risk of dementia in patients exposed to nitrogen dioxide and carbon monoxide: A population-based retrospective cohort study. PLoS ONE 9:e103078.

Chen JC. 2007. Death stroked by dusty air: More mysteries to be solved. Occup Environ Med 64:3–4. [invited commentary]

Chen JC. 2010. Geographic determinants of disparities in stroke mortality: Role of ambient air pollution. Stroke 41:839–841. [editorial]

Chen JC, Cavallari JM, Stone PH, Christiani DC. 2007. Obesity is a modifier of autonomic cardiac responses to fine metal particulates. Environ Health Perspect 115:1002–1006.

Chen JC, Espeland MA, Brunner RL, Lovato LC, Wallace RB, Leng X, et al. 2015. Sleep duration, cognitive decline, and dementia risk in older women. Alzheimers Dement 12(1):21–33; doi: 10.1016/j.jalz.2015.03.004.

Chen L, Lu W, Yang Z, Yang S, Li C, Shi X, et al. 2011. Age-related changes of the oligodendrocytes in rat subcortical white matter. Anat Rec (Hoboken) 294:487–493.

Christakos G, Bogaert P, Serre ML. 2001. Temporal GIS: Advanced functions for field-based applications. New York:Springer.

Christakos G, Serre ML. 2000a. Spatiotemporal analysis of environmental exposure-health effect associations. J Expo Anal Environ Epidemiol 10:168–187.

Christakos G, Serre ML. 2000b. BME analysis of spatiotemporal particulate matter distributions in North Carolina. Atmos Environ 34:3393–3406.

Coker LH, Hogan PE, Bryan NR, Kuller LH, Margolis KL, Bettermann K, et al. 2009. Postmenopausal hormone therapy and subclinical cerebrovascular disease: The WHIMS-MRI study. Neurology 72:125–134.

Davatzikos C, Genc A, Xu D, Resnick SM. 2001. Voxel-based morphometry using the ravens maps: Methods and validation using simulated longitudinal atrophy. Neuroimage 14:1361–1369.

Davis DA, Akopian G, Walsh JP, Sioutas C, Morgan TE, Finch CE. 2013. Urban air pollutants reduce synaptic function of CA1 neurons via an NMDA/NO pathway in vitro. J Neurochem 127(4):509–519; doi: 10.1111/jnc.12395.

Dockery DW, Stone PH. 2007. Cardiovascular risks from fine particulate air pollution. N Engl J Med 356:511–513.

Driscoll I, Davatzikos C, An Y, Wu X, Shen D, Kraut M, et al. 2009. Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. Neurology 72:1906–1913.

Dubowsky SD, Suh H, Schwartz J, Coull BA, Gold DR. 2006. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. Environ Health Perspect 114:992–998.

Espeland MA, Brinton RD, Hugenschmidt C, Manson JE, Craft S, Yaffe K, et al. 2015. Impact of type 2 diabetes and postmenopausal hormone therapy on incidence of cognitive impairment in older women. Diabetes Care 38:2316–2324.

Espeland MA, Rapp SR, Shumaker SA, Brunner R, Manson JE, Sherwin BB, et al. 2004. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA 291: 2959–2968.

Fjell AM, Westlye LT, Amlien I, Espeseth T, Reinvang I, Raz N, et al. 2009. Minute effects of sex on the aging brain: A multisample magnetic resonance imaging study of healthy aging and Alzheimer's disease. J Neurosci 29:8774–8783.

Fonken LK, Xu X, Weil ZM, Chen G, Sun Q, Rajagopalan S, et al. 2011. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. Mol Psychiatry 16:987–995, 973.

Fouquet M, Besson FL, Gonneaud J, La Joie R, Chetelat G. 2014. Imaging brain effects of APOE4 in cognitively

normal individuals across the lifespan. Neuropsychol Rev 24:290–299.

Fox MA. 2002. Evaluating cumulative risk assessment for environmental justice: A community case study. Environ Health Perspect 110:203–209.

Gatto NM, Henderson VW, Hodis HN, St John JA, Lurmann F, Chen JC, et al. 2014. Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. Neurotoxicology 40:1–7.

Genc S, Zadeoglulari Z, Fuss SH, Genc K. 2012. The adverse effects of air pollution on the nervous system. J Toxicol 2012:782462.

Goldberg MS, Bailar JC III, Burnett RT, Brook JR, Tamblyn R, Bonvalot Y, et al. 2000. Identifying Subgroups of the General Population That May Be Susceptible to Short-Term Increases in Particulate Air Pollution: A Time-Series Study in Montreal, Quebec. Research Report 97. Cambridge, MA:Health Effects Institute.

Gorelick PB. 2005. William M. Feinberg Lecture: Cognitive vitality and the role of stroke and cardiovascular disease risk factors. Stroke 36:875–879.

Gorelick PB, Pantoni L. 2013. Advances in vascular cognitive impairment. Stroke 44:307–308.

Goveas JS, Espeland MA, Woods NF, Wassertheil-Smoller S, Kotchen JM. 2011. Depressive symptoms and incidence of mild cognitive impairment and probable dementia in elderly women: The Women's Health Initiative Memory Study. J Am Geriatr Soc 59:57–66.

Griffin BA, Anderson GL, Shih RA, Whitsel EA. 2012. Use of alternative time scales in Cox proportional hazard models: Implications for time-varying environmental exposures. Stat Med 31:3320–3327.

Griffin BA, Eibner C, Bird CE, Jewell A, Margolis K, Shih R, et al. 2013. The relationship between urban sprawl and coronary heart disease in women. Health & Place 20:51–61.

Hachinski V. 2007. The 2005 Thomas Willis Lecture: Stroke and vascular cognitive impairment: A transdisciplinary, translational and transactional approach. Stroke 38:1396.

Haring B, Leng X, Robinson J, Johnson KC, Jackson RD, Beyth R, et al. 2013. Cardiovascular disease and cognitive decline in postmenopausal women: Results from the Women's Health Initiative Memory Study. J Am Heart Assoc 2:e000369.

Hartz AM, Bauer B, Block ML, Hong JS, Miller DS. 2008. Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier. FASEB J 22:2723–2733.

Hayden KM, Farmer KM. 2015. Invited commentary: The importance of studying environmental risk factors for dementia. Alzheimer Dement (Amst) 1:268–269.

Heckbert SR, Kooperberg C, Safford MM, Psaty BM, Hsia J, McTiernan A, et al. 2004. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. Am J Epidemiol 160:1152–1158.

Hsia J, Wu L, Allen C, Oberman A, Lawson WE, Torrens J, et al. 2005. Physical activity and diabetes risk in postmenopausal women. Am J Prev Med 28:19–25.

Jagust W. 2013. Vulnerable neural systems and the borderland of brain aging and neurodegeneration. Neuron 77:219–234.

Jaramillo SA, Felton D, Andrews L, Desiderio L, Hallarn RK, Jackson SD, et al. 2007. Enrollment in a brain magnetic resonance study: Results from the Women's Health Initiative Memory Study Magnetic Resonance Imaging Study (WHIMS-MRI). Acad Radiol 14:603–612.

Jung CR, Lin YT, Hwang BF. 2015. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: A population-based cohort study in Taiwan. J Alzheimers Dis 44:573–584.

Kaiser J. 2005. Epidemiology. Mounting evidence indicts fine-particle pollution. Science 307:1858–1861.

Kioumourtzoglou MA, Schwartz JD, Weisskopf MG, Melly SJ, Wang Y, Dominici F, et al. 2016. Long-term $PM_{2.5}$ exposure and neurological hospital admissions in the northeastern United States. Environ Health Perspect 124:23–29.

Kohama SG, Rosene DL, Sherman LS. 2012. Age-related changes in human and non-human primate white matter: From myelination disturbances to cognitive decline. Age (Dordr) 34:1093–1110.

Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. 2003. The Women's Health Initiative Observational Study: Baseline characteristics of participants and reliability of baseline measures. Ann Epidemiol 13:S107–121.

Lao Z, Shen D, Liu D, Jawad AF, Melhem ER, Launer LJ, et al. 2008. Computer-assisted segmentation of white matter lesions in 3D MR images using support vector machine. Acad Radiol 15:300–313.

Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al. 2011. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): A randomised open-label substudy. Lancet Neurol 10:969–977.

Levesque S, Surace MJ, McDonald J, Block ML. 2011. Air pollution & the brain: Subchronic diesel exhaust exposure causes neuroinflammation and elevates early markers of neurodegenerative disease. J Neuroinflammation 8:105.

Liao D, Duan Y, Whitsel EA, Zheng ZJ, Heiss G, Chinchilli VM, et al. 2004. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: A population-based study. Am J Epidemiol 159:768–777.

Liao D, Heiss G, Chinchilli VM, Duan Y, Folsom AR, Lin HM, et al. 2005. Association of criteria pollutants with plasma hemostatic/inflammatory markers: A population-based study. J Expo Anal Environ Epidemiol 15:319–328.

Loop MS, Kent ST, Al-Hamdan MZ, Crosson WL, Estes SM, Estes MG Jr., et al. 2013. Fine particulate matter and incident cognitive impairment in the reasons for geographic and racial differences in stroke (REGARDS) cohort. PLoS ONE 8:e75001.

Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. 2005. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology 65:545–551.

Madden DJ, Bennett IJ, Song AW. 2009. Cerebral white matter integrity and cognitive aging: Contributions from diffusion tensor imaging. Neuropsychol Rev 19:415–435.

Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, et al. 2004. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: Results from the Women's Health Initiative Hormone Trial. Diabetologia 47:1175–1187.

Mielke MM, Rosenberg PB, Tschanz J, Cook L, Corcoran C, Hayden KM, et al. 2007. Vascular factors predict rate of progression in Alzheimer disease. Neurology 69:1850–1858.

Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. 2007. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 356:447–458.

Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, et al. 1989. The consortium to establish a registry for Alzheimer's disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 39:1159–1165.

Mosley TH Jr., Knopman DS, Catellier DJ, Bryan N, Hutchinson RG, Grothues CA, et al. 2005. Cerebral MRI findings and cognitive functioning: The Atherosclerosis Risk in Communities study. Neurology 64:2056–2062.

Moulton PV, Yang W. 2012. Air pollution, oxidative stress, and Alzheimer's disease. J Environ Public Health 2012: 472751.

Nel A. 2005. Atmosphere. Air pollution-related illness: Effects of particles. Science 308:804–806.

Nettiksimmons J, DeCarli C, Landau S, Beckett L. 2014. Biological heterogeneity in ADNI amnestic mild cognitive impairment. Alzheimers Dement 10:511–521.e1.

O'Brien LM, Ziegler DA, Deutsch CK, Frazier JA, Herbert MR, Locascio JJ. 2011. Statistical adjustments for brain size in volumetric neuroimaging studies: Some practical implications in methods. Psychiatry Res 193:113–122.

O'Brien LM, Ziegler DA, Deutsch CK, Kennedy DN, Goldstein JM, Seidman LJ, et al. 2006. Adjustment for whole brain and cranial size in volumetric brain studies: A review of common adjustment factors and statistical methods. Harv Rev Psychiatry 14:141–151.

Oikonen M, Laaksonen M, Laippala P, Oksaranta O, Lilius EM, Lindgren S, et al. 2003. Ambient air quality and occurrence of multiple sclerosis relapse. Neuroepidemiology 22:95–99.

O'Neill MS, Veves A, Zanobetti A, Sarnat JA, Gold DR, Economides PA, et al. 2005. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. Circulation 111:2913–2920.

Oppenheim HA, Lucero J, Guyot AC, Herbert LM, McDonald JD, Mabondzo A, et al. 2013. Exposure to vehicle emissions results in altered blood brain barrier permeability and expression of matrix metalloproteinases and tight junction proteins in mice. Part Fibre Toxicol 10:62.

Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, et al. 2015. Traffic-related air pollution and dementia incidence in northern Sweden: A longitudinal study. Environ Health Perspect 124(3):306–312.

Park SK, O'Neill MS, Vokonas PS, Sparrow D, Schwartz J. 2005. Effects of air pollution on heart rate variability: The VA Normative Aging Study. Environ Health Perspect 113:304–309.

Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, et al. 2002. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: The Exposure and Risk Assessment for Fine and Ultrafine

Particles in Ambient Air (ULTRA) study. Circulation 106:933–938.

Peters A, Pope CA 3rd. 2002. Cardiopulmonary mortality and air pollution. Lancet 360:1184–1185.

Peterson BS, Rauh VA, Bansal R, Hao X, Toth Z, Nati G, et al. 2015. Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood. JAMA Psychiatry 72:531–540.

Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A 3rd, Schwartz J. 2011. Traffic-related air pollution and cognitive function in a cohort of older men. Environ Health Perspect 119:682–687.

Prati P, Casaroli M, Bignamini A, Scotti S, Canciani L, Ruscio M, et al. 2006. Cognitive impairment and carotid atherosclerosis in a general Italian midlife and old population. Neuroepidemiology 27:33–38.

Ranft U, Schikowski T, Sugiri D, Krutmann J, Kramer U. 2009. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. Environ Res 109:1004–1011.

Resnick SM, Espeland MA, Jaramillo SA, Hirsch C, Stefanick ML, Murray AM, et al. 2009. Postmenopausal hormone therapy and regional brain volumes: The WHIMS-MRI study. Neurology 72:135–142.

Reyes JM, Serre ML. 2014. An LUR/BME framework to estimate $PM_{2.5}$ explained by on road mobile and stationary sources. Environ Sci Technol 48:1736–1744.

Reyes JM, Xu YD, Vizuete W, Serre ML. 2017. Regionalized $PM_{2.5}$ community multiscale air quality model performance evaluation across a continuous spatiotemporal domain. Atmos Environ 148:258–265.

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Smith DF. 2003. Childhood cancer incidence rate and hazardous air pollutants in California: an exploratory analysis. Environ Health Perspect 111:663–668.

Rincon F, Wright CB. 2013. Vascular cognitive impairment. Curr Opin Neurol 26:29–36.

Rosenbaum AS, Axelrad DA, Woodruff TJ, Wei YH, Ligocki MP, Cohen JP. 1999. National estimates of outdoor air toxics concentrations. J Air Waste Manag Assoc 49:1138–1152.

Savelieva E, Demyanov V, Kanevski M, Serre ML, Christakos G. 2004. BME application for uncertainty assessment of the Chernobyl fallouts. Geoderma 128:312–324.

Schwartz J, Park SK, O'Neill MS, Vokonas PS, Sparrow D, Weiss ST, et al. 2005. Glutathione-S-transferase M1, obesity, statins, and autonomic effects of particles. Am J Respir Crit Care Med 172(12):1529–1533.

Semmens EOB. 2012. Effects of traffic-related air pollution on cognitive function, dementia risk and brain MRI findings in the Cardiovascular Health Study [Ph.D.]. Ann Arbor:University of Washington.

Serre ML, Christakos G, Lee S-J. 2004. Soft data space/time mapping of coarse particulate matter annual arithmetic average over the U.S. In: Geoenv IV — Geostatistics for Environmental Applications, Vol. 1, (Sanchez-Vila X, Carrera J, Gomez-Hernandez JJ, eds). Dordrecht:Kluwer Academic Publishers, 115–126.

Serre ML, Kolovos A, Christakos G, Modis K. 2003. An application of the holistochastic human exposure methodology to naturally occurring arsenic in Bangladesh drinking water. Risk Anal 23:515–528.

Shen D, Davatzikos C. 2002. Hammer: Hierarchical attribute matching mechanism for elastic registration. IEEE Trans Med Imaging 21:1421–1439.

Sheppard L. 2003. Insights on bias and information in group-level studies. Biostatistics 4:265–278.

Shin HH, Fann N, Burnett RT, Cohen A, Hubbell BJ. 2014. Outdoor fine particles and nonfatal strokes: Systematic review and meta-analysis. Epidemiology 25:835–842.

Shumake KL, Sacks JD, Lee JS, Johns DO. 2013. Susceptibility of older adults to health effects induced by ambient air pollutants regulated by the European Union and the United States. Aging Clin Exp Res 25:3–8.

Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. 2004. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 291:2947–2958.

Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. 2003. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial. JAMA 289:2651–2662.

Shumaker SA, Reboussin BA, Espeland MA, Rapp SR, McBee WL, Dailey M, et al. 1998. The Women's Health Initiative Memory Study (WHIMS): A trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. Control Clin Trials 19:604–621.

Simkhovich BZ, Kleinman MT, Kloner RA. 2008. Air pollution and cardiovascular injury epidemiology, toxicology, and mechanisms. J Am Coll Cardiol 52:719–726.

Squire LR, Zola-Morgan S. 1991. The medial temporal lobe memory system. Science 253:1380–1386.

Taylor DH Jr, Fillenbaum GG, Ezell ME. 2002. The accuracy of Medicare claims data in identifying Alzheimer's disease. J Clin Epidemiol 55:929–937.

Taylor JL, Scanlon BK, Farrell M, Hernandez B, Adamson MM, Ashford JW, et al. 2014. APOE-epsilon4 and aging of medial temporal lobe gray matter in healthy adults older than 50 years. Neurobiol Aging 35:2479–2485.

Teng EL, Chui HC. 1987. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 48:314–318.

Tonne C, Elbaz A, Beevers S, Singh-Manoux A. 2014. Traffic-related air pollution in relation to cognitive function in older adults. Epidemiology 25:674–681.

U.S. EPA. 2011a. National air toxics assessments. Available: *www.epa.gov/nata/.*

U.S. EPA. 2011b. An overview of methods for EPA's national-scale air toxics assessment. Available: *www.epa.gov/ttn/atw/nata2005/05pdf/nata_tmd.pdf*.

U.S. EPA. 2011c. National mobile inventory model (NMIM). Available: *www.epa.gov/otaq/nmim.htm.*

Vassilev ZP, Robson MG, Klotz JB. 2001. Associations of polycyclic organic matter in outdoor air with decreased birth weight: A pilot cross-sectional analysis. J Toxicol Environ Health A 64:595–605.

Ward A, Crean S, Mercaldi CJ, Collins JM, Boyd D, Cook MN, et al. 2012. Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/4) among patients diagnosed with Alzheimer's disease: A systematic review and meta-analysis. Neuroepidemiology 38:1–17.

Wellenius GA, Boyle LD, Coull BA, Milberg WP, Gryparis A, Schwartz J, et al. 2012. Residential proximity to nearest major roadway and cognitive function in community-dwelling seniors: Results from the MOBILIZE Boston Study. J Am Geriatr Soc 60:2075–2080.

Wellenius GA, Boyle LD, Wilker EH, Sorond FA, Coull BA, Koutrakis P, et al. 2013. Ambient fine particulate matter alters cerebral hemodynamics in the elderly. Stroke 44:1532–1536.

Weuve J. 2014. Invited commentary: How exposure to air pollution may shape dementia risk, and what epidemiology can say about it. Am J Epidemiol 180:367–371.

Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. 2012. Exposure to particulate air pollution and cognitive decline in older women. Arch Intern Med 172:219–227.

Whitsel EA, Avery CL. 2010. The environmental epidemiology of atrial arrhythmogenesis. J Epidemiol Community Health 64:587–590.

Whitsel EA, Quibrera PM, Smith RL, Catellier DJ, Liao D, Henley AC, et al. 2006. Accuracy of commercial geocoding: Assessment and implications. Epidemiol Perspect Innov 3:8.

Whitsel EA, Rose KM, Wood JL, Henley AC, Liao D, Heiss G. 2004. Accuracy and repeatability of commercial geocoding. Am J Epidemiol 160:1023–1029.

Wilker EH, Martinez-Ramirez S, Kloog I, Schwartz J, Mostofsky E, Koutrakis P, et al. 2016. Fine particulate matter, residential proximity to major roads, and markers of small vessel disease in a memory study population. J Alzheimers Dis 53(4):1315–1323; doi: 10.3233/JAD-151143.

Wilker EH, Preis SR, Beiser AS, Wolf PA, Au R, Kloog I, et al. 2015. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. Stroke 46(5):1161–1166; doi: 10.1161/STROKEAHA.114.008348.

Win-Shwe TT, Yamamoto S, Fujitani Y, Hirano S, Fujimaki H. 2008. Spatial learning and memory function-related gene expression in the hippocampus of mouse exposed to nanoparticle-rich diesel exhaust. Neurotoxicology 29:940–947.

Win-Shwe TT, Yamamoto S, Fujitani Y, Hirano S, Fujimaki H. 2011. Nanoparticle-rich diesel exhaust affects hippocampal-dependent spatial learning and NMDA receptor subunit expression in female mice. Nanotoxicology 5:543–553. doi: 10.3109/17435390.2011.590904.

Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. 2006. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area. Environ Health Perspect 114:1438–1444.

Wishart HA, Saykin AJ, McAllister TW, Rabin LA, McDonald BC, Flashman LA, et al. 2006. Regional brain atrophy in cognitively intact adults with a single APOE epsilon4 allele. Neurology 67:1221–1224.

Wu Y-C, Lin Y-C, Yu H-L, Chen J-H, Chen T-F, Sun Y, et al. 2015. Association between air pollutants and dementia risk in the elderly. Alzheimers Dement (Amst) 1:220–228.

Yang WS, Wang X, Deng Q, Fan WY, Wang WY. 2014. An evidence-based appraisal of global association between air pollution and risk of stroke. Int J Cardiol 175:307–313.

Yu HL, Christakos G, Chen JC. 2007a. Spatiotemporal air pollution modeling and prediction in epidemiologic research. Hauppauge, NY: Nova Science Publishers, Inc.

Yu HL, Kolovos A, Christakos G, Chen JC, Warmerdam S, Dev B. 2007b. Interactive spatiotemporal modeling of health systems: The SEKS-GUI framework. Stochastic Environ Res Risk Assess 21:555–572.

Yu R, Zhao L, Lu L. 2011. Regional grey and white matter changes in heavy male smokers. PLoS ONE 6:e27440.

Zacharaki EI, Kanterakis S, Bryan RN, Davatzikos C. 2008. Measuring brain lesion progression with a supervised tissue classification system. Med Image Comput Comput Assist Interv 11:620–627.

Zanobetti A, Schwartz J. 2002. Cardiovascular damage by airborne particles: Are diabetics more susceptible? Epidemiology 13:588–592.

Zeka A, Zanobetti A, Schwartz J. 2006. Individual-level modifiers of the effects of particulate matter on daily mortality. Am J Epidemiol 163:849–859.

Zlokovic BV. 2005. Neurovascular mechanisms of Alzheimer's neurodegeneration. Trends Neurosci 28:202–208.

HEI QUALITY ASSURANCE STATEMENT

The conduct of this study was subjected to independent audits by RTI International staff members Dr. Linda Morris Brown, Mr. Larry C. Michael, and Dr. Prakash Doraiswamy. These staff members are experienced in quality assurance oversight for air quality monitoring and related epidemiological studies. Other participants on the RTI QA oversight team included Dr. Breda Munoz, a biostatistician who reviewed the statistical aspects.

The QA oversight program consisted of on-site audits at the University of North Carolina (UNC), Department of Environmental Sciences and Engineering, Chapel Hill, NC, and at the University of Southern California (USC), Department of Preventive Medicine, Keck School of Medicine of USC, Los Angeles, California; and a final review of the draft final report of the study. The UNC on-site audit was performed by Mr. Michael and Dr. Doraiswamy. The USC on-site audit was performed by Dr. Brown and Mr. Michael. The review of the draft final report was performed by Drs. Brown, Doraiswamy and Munoz, followed by a review of the revised final report by Drs. Munoz and Doraiswamy with feedback from Dr. Brown. Mr. Michael was no longer with RTI at the time the draft and revised final study reports were reviewed. The audits included review of study documentation and reports, and discussions with key project staff of study activities for conformance to the study protocol and standard operating procedures. The dates of the audits and reviews are listed below, along with a description of what was reviewed.

May 21, 2013 (Audit Phase 1, UNC)

The auditors conducted an on-site audit at the University of North Carolina, Department of Environmental Sciences and Engineering, Chapel Hill, NC, to verify data acquisition and processing procedures for the $PM_{2.5}$ data. The audit reviewed the following study components: progress reports; personnel and staff; adequacy of data security and storage; internal quality assurance procedures; and documentation of data processing procedures. A demonstration of system login and data processing was observed to verify that the described procedures had been followed. No significant errors were noted. Recommendations were made to (1) document use of method code in analysis, (2) include administrative signatures to the QA document, and (3) implement formal data archiving procedures.

June 24–25, 2013 (Audit Phase 1, USC)

The auditors conducted an on-site audit at the University of Southern California (USC) by the Department of Preventive Medicine, Keck School of Medicine of USC, Los Angeles, California. The audit reviewed the following study components: progress reports; personnel and staff; adequacy of equipment and facilities; internal quality assurance procedures; air quality sampling methodology; data processing procedures. Original and recoded data and program code for the WHIMS data were reviewed to verify the integrity of the database and that the described procedures had been followed. The audit also included review of the QA procedures for the exposure data, programming code, data storage, and data security procedures. No errors were noted, but more formal documentation of corrective actions was recommended.

March–April 2015 (Review of Draft Final Report)

The auditors reviewed the draft final report for the project. This audit of the report included reviewing the detailed description of procedures, the findings, and their

interpretation, and all the appendices. The review checked for detailed documentation of the methodology followed and the assumptions made, such that it allows for a third party to repeat the analysis. The review also ensured that the reported conclusions were consistent with the data presented in the tables and figures. No serious quality-related issues were identified during the review. A list of technical and editorial comments was provided to HEI.

November 2016–June 2017 (Review of Revised Final Report)

The auditors reviewed the revised final report for the project. The audit focused on similar aspects followed in the audit of the draft final report. Technical and editorial comments were provided, which were addressed by the authors. The responses were satisfactory. No serious quality-related issues were identified during the review. Minor recommendation was made to rephrase wording of descriptions of population characteristics.

Written reports of each activity were provided to HEI. These quality assurance oversight audits demonstrated that the study was conducted by a well-coordinated, experienced team according to the study protocol and standard operating procedures. Interviews with study personnel revealed a consistently high concern for data quality. The revised final report appears to be an accurate representation of the study.

Linda Morris Brown, M.P.H., Dr.P.H., Epidemiologist,
Quality Assurance auditor

Breda Munoz, Ph.D., Statistician,
Quality Assurance auditor

Prakash Doraiswamy, Ph.D., Air Quality Specialist,
Quality Assurance auditor

APPENDIX A.

Appendix Table A.1. Distributions and Correlations of PM Exposure Variables

Exposure Variables	*N*	Exposure Distributions: Mean	Standard Deviation	Minimum	Percentiles: 10th	25th	Median	75th	90th	Maximum
Fixed Cumulative Exposures in WHIMS–MRI										
Cumulative exposure to $PM_{2.5}$ (1999–2006)	1,403	12.64	2.78	5.75	10.11	10.67	12.24	14.16	16.22	22.2
Cumulative exposure to DPM (1996–2005)	1,403	0.44	0.33	0.01	0.14	0.24	0.35	0.55	0.83	3.93
Fixed Baseline Exposures in WHIMS										
Exposure to DPM at WHIMS baseline (1996–1998)	7,112	0.54	0.38	0	0.11	0.26	0.49	0.74	1	5.42
Time-Varying Exposures in WHIMS during Follow-up										
Time-varying cumulative $PM_{2.5}$ exposure (1999–2007)	7,050	13.15	3.22	3.71	9.45	11.11	12.95	15.01	16.93	27.1
Time-varying cumulative DPM exposure (1996–2005)	7,447	0.48	0.31	0	0.16	0.27	0.43	0.62	0.84	5.12

	Pearsons Correlations among PM Exposure Variables: (1)	(2)	(3)	(4)	(5)
Exposures Used in WHIMS–MRI					
(1) Baseline cumulative exposure to $PM_{2.5}$	1	0.45	0.42	0.99	0.45
(2) Baseline cumulative exposure to DPM	0.45	1	0.83	0.45	0.95
Exposures Used in WHIMS					
(3) Baseline exposure to DPM	0.42	0.83	1	0.4	0.93
(4) Summarized time-varying cumulative $PM_{2.5}$ exposure[a]	0.99	0.45	0.4	1	0.42
(5) Summarized time-varying cumulative DPM exposure[a]	0.45	0.95	0.93	0.42	1

[a] Individually summarized exposure aggregating all time-varying annual exposures before censoring for the analyses on dementia.

MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendix B and Additional Materials 1 contain supplemental material not included in the printed report. They are available on the HEI website, *www.healtheffects.org/publications.*

Appendix B. Additional Sensitivity Analyses

Additional Materials 1. Part A: Study Population, Design, and Outcome Ascertainment; Part B: Estimation of Residential Exposures; and Part C: Statistical Analyses

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OTHER PUBLICATION RESULTING FROM THIS RESEARCH

Chen J-C, Wang X, Wellenius GA, Serre ML, Driscoll I, Casanova R, et al. 2015. Ambient air pollution and neurotoxicity on brain structure: Evidence from Women's Health Initiative Memory Study. Ann Neurol 78:466–476.

CRITIQUE

Review Committee

Research Report 193, *Particulate Air Pollutants, Brain Structure, and Neurocognitive Disorders in Older Women*, J-C. Chen et al.

INTRODUCTION

Dementia, a decline in memory and other cognitive functions severe enough to interfere with daily life, is relatively common in elderly people and has a large social and economic impact on patients, families, and government programs (Hurd et al. 2013). The number of people with dementia in the United States and around the world is expected to triple by 2050, owing to the large increase in the elderly population (Prince et al. 2013). Little progress has been made to date in identifying effective treatments for most forms of dementia, and researchers have increasingly focused attention on prevention and identification of modifiable risk factors (Friedrich 2014). Research on risk factors for dementia has emphasized the potential contribution of individual behaviors, lifestyle factors, and other health conditions, such as subclinical and clinical cardiovascular disease. More recently, epidemiological studies have begun to explore the etiological role of exposures to common environmental pollutants, including air pollution (Power et al. 2016). Given its ubiquity, if exposure to air pollution is causally related to dementia, reductions in air pollution may reduce the population-level burden of dementia substantially.

To date, the associations of short-term and long-term air pollution exposure with cardiovascular and cerebrovascular morbidity and mortality have been well documented (Hoek et al. 2013; World Health Organization 2013). These associations may suggest a harmful impact on the brain and cognitive processes through vascular, inflammatory, and other mechanisms that have been implicated in cardiovascular disease (Langrish et al. 2012). Though poorly understood at present, several potential mechanisms involving oxidative stress, neuroinflammation, and direct neuronal and white matter injury have been postulated. Animal studies have shown deposition of engineered ultrafine particles containing metals in the olfactory bulb (from which the particles may travel directly to the brain) and in frontal cortical and subcortical areas, bypassing, for example, the so-called blood–brain barrier (Allen et al. 2016; Block et al. 2012). Yet to date, few epidemiological studies have investigated the neurocognitive effects of long-term exposure to air pollution in adults and the elderly (Power et al. 2016). There are many methodological challenges involved in conducting such research, including the potential for selection bias and/or limited generalizability (because study participants are typically healthier than nonparticipants), heterogeneity in the pathogenesis, misclassification of outcomes, and uncertainties in the exposure estimation; many challenges also stem from the nature of dementia, which can have a decades-long incipient phase (Weuve et al. 2015).

In response to HEI's RFA 08-2, the Walter A. Rosenblith New Investigator Award, Dr. Jiu-Chiuan Chen, then of the University of North Carolina, Chapel Hill, submitted an application for a three-year study, "Particulate Air Pollutants, Risk of Cognitive Disorders, and Neuropathology in the Elderly." Chen's study was designed to investigate the association between long-term outdoor particulate air pollution exposure and neurocognitive outcomes and brain volumes of older women. He also planned to investigate whether the health effects were modified by factors that may increase susceptibility, such as a history of cardiovascular disease, diabetes mellitus, or obesity (i.e., effect modification). The HEI Research Committee recommended Chen's application for funding because there had been few studies of air pollution and neurocognitive outcomes at that time and because they appreciated the proposed approach, which included standardized outcome ascertainment, assessment of mild cognitive impairment, and use of magnetic resonance imaging (MRI*) data.

This Critique provides the HEI Review Committee's evaluation of the study. It is intended to aid the sponsors of HEI and the public by highlighting both the strengths and the limitations of the study and by placing the Investigators' Report into scientific and regulatory perspective.

Dr. Chen's 3-year study, "Particulate Air Pollutants, Risk of Cognitive Disorders, and Neuropathology in the Elderly," began in December 2011. Total expenditures were $303,378. The draft Investigators' Report from Chen and colleagues was received for review in January 2015. A revised report, received in August 2016, was accepted for publication in October 2016. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Critique.

This document has not been reviewed by public or private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views of these parties, and no endorsements by them should be inferred.

* A list of abbreviations and other terms appears at the end of this volume.

APPROACH

SPECIFIC AIMS

The study's specific aims were twofold:

- To investigate the association between long-term outdoor particulate air pollution exposure and adverse neurocognitive outcomes and brain volumes of older women in the United States; and
- To examine effect modification by factors that may increase susceptibility, such as a history of cardiovascular disease, diabetes mellitus, or obesity.

Chen used data from women enrolled in the U.S.-based Women's Health Initiative Memory Study (WHIMS), which consisted of two randomized clinical trials of postmenopausal hormone therapy. The trials were terminated early due to side effects — not related to neurocognitive outcomes — but follow-up continued. At WHIMS baseline (1996–1999), all women were community dwelling (i.e., not living in nursing or medical facilities), aged 65 to 80 years, and free of dementia. In total, 8,094 participants were approached at 38 WHI clinical centers for enrollment in the trials, and 7,479 (92%) women were eventually included in the current study. Shumaker and colleagues (1998) published details of the WHIMS study design, eligibility criteria, and recruitment procedures.

Chen investigated two types of outcomes — neurocognitive outcomes and brain volume — using standardized neurological tests and structural MRI from the WHIMS cohort. He collaborated with Dr. Marc Serre at the University of North Carolina to develop exposure estimates for ambient $PM_{2.5}$ (particulate matter ≤ 2.5 µm in aerodynamic diameter) and diesel PM, and subsequently evaluated associations between the PM exposure estimates and the cognitive outcomes and brain volumes, respectively. The period covered by the current study was 1996–2007, though the exact study period differed per exposure–outcome pair.

METHODS

Neurocognitive outcomes, specifically mild cognitive impairment and dementia with clinically significant impairment, were measured yearly using standardized WHIMS protocols. Mild cognitive impairment is characterized by measurable cognitive deficits that do not interfere with everyday activities. Typically, people with mild cognitive impairment have an increased risk of developing dementia, though not all of them get worse and some eventually get better (Albert et al. 2011). In the current study, women who screened positively for cognitive impairment on the basis of an education-adjusted Modified Mini-Mental State Examination proceeded to more extensive neuropsychological testing and neurological evaluation. Moreover, each woman suspected to have dementia then underwent a series of laboratory tests to confirm the clinical diagnosis of dementia. A total of 167 women were classified as having incident dementia and 256 as having mild cognitive impairment.

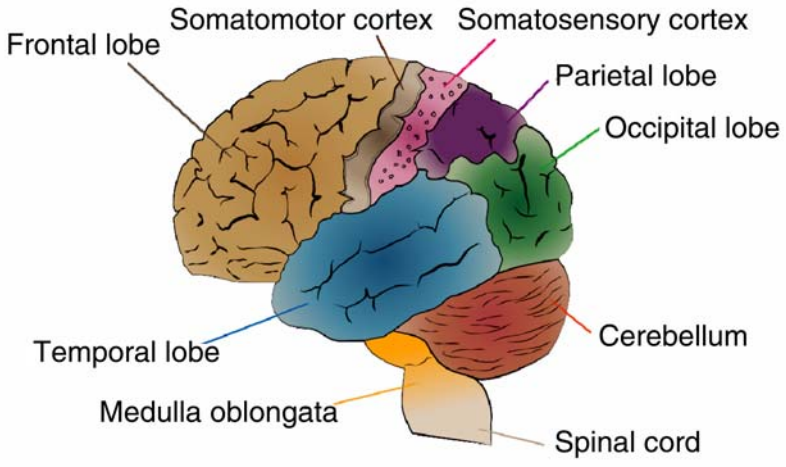
Brain volume measures were obtained from a single structural MRI assessment in a subset (n = 1,403) of the WHIMS participants (N = 7,479) obtained in the period 2005–2006. Only women from 14 of the 38 WHI clinical centers were eligible, and some exclusion criteria were formulated that would preclude an MRI, such as claustrophobia. Jamarillo and colleagues (2007) have provided additional details about the selection process. Brain volumes were only assessed in certain brain regions (specifically the hippocampus) and the multimodal association brain regions (frontal, parietal, and temporal lobes) because those brain regions were thought to be the most vulnerable to brain aging and neurodegenerative disease (see Critique Sidebar for description of brain structures). MRI data were analyzed centrally at the University of Pennsylvania to make sure the readings and interpretation were consistent.

Two PM exposure metrics were assessed: ambient $PM_{2.5}$ and diesel PM. Annual ambient $PM_{2.5}$ exposure was estimated at the residential address level with a nationwide Bayesian maximum entropy spatiotemporal model using U.S. Environmental Protection Agency (U.S. EPA) regulatory monitoring data for the years 1999–2007. The exposure assessment took changes in residence into account. The model was compared with other models including the nearest-neighbor approach, inverse distance weighting, and spatial kriging (see Additional Materials 1, available on the HEI website). In addition, annual on-road diesel PM was assessed at the census-tract level, using the U.S. EPA National-Scale Air Toxics Assessment (NATA) model for the years 1996, 1999, 2002, and 2005. A nonlinear interpolation approach was developed to fill in data for the missing years in order to obtain annual estimates for the full period (1996–2005).

Neurocognitive and brain volume outcomes were first compared across exposure quartiles and tested for significance using likelihood-ratio tests and analysis of covariance. Results for brain volume outcomes were adjusted for intracranial volume to account for individual differences in brain sizes but not for other important confounder variables. Only when statistically significant, results were further investigated in Cox proportional hazard models

CRITIQUE SIDEBAR: THE STRUCTURE OF THE HUMAN BRAIN

The brain can be divided into three basic structural units: the forebrain, the midbrain, and the hindbrain (see Critique Sidebar figure for details). The hindbrain includes the upper part of the spinal cord, the brainstem, and the cerebellum. The hindbrain controls the body's vital functions such as respiration and heart rate. The cerebellum coordinates movement, posture, and balance. The uppermost part of the brainstem is the midbrain, which controls some reflex actions and is part of the circuit involved in the control of eye movements and other voluntary movements. The forebrain is the largest part of the human brain and consists primarily of the cerebrum, the hypothalamus, thalamus, and hippocampus.



Critique Sidebar Figure. A diagram of the brain. Source: Wikimedia Commons 2017.

Cerebrum. The cerebrum is the largest brain structure in humans and accounts for about two-thirds of the brain's mass. It is divided into the left and right hemispheres. These two halves are connected by long neuron branches called the corpus callosum. The outer 3 millimeters of grey matter form the cerebral cortex, which consists of closely packed neurons that control most of the body functions, including the state of consciousness, the senses, motor skills, reasoning, and language. The cerebral cortex is grey because nerves in this area lack the insulation that makes most other parts of the brain appear to be white. The cerebrum is positioned over and around most other brain structures. The four lobes (frontal, temporal, parietal, and occipital) of the cerebrum are specialized by function but are richly interconnected:

1. The frontal lobe organizes responses to complex problems, plans steps to achieve an objective, searches memory for relevant experience, adapts strategies to accommodate new data, guides behavior with verbal skills, and houses working memory. It also controls emotional responses.
2. The temporal lobe controls long-term memory, emotions, hearing, and language.
3. The parietal lobe integrates sensory information and is the location for visual attention, touch perception, and manipulation of objects.
4. The occipital lobe processes visual data and routes it to other parts of the brain for identification and storage. The frontal, parietal and temporal lobes are sometimes called the "association brain area."

Thalamus. Located at the top of the brain stem, the thalamus acts as a two-way relay station, sorting, processing, and directing signals from the spinal cord and midbrain structures up to the cerebrum and, conversely, from the cerebrum down the spinal cord to the nervous system.

Basal ganglia. The basal ganglia are clusters of nerve cells surrounding the thalamus. They are responsible for initiating and integrating movements.

Hypothalamus. Located at the base of the brain where signals from the brain and the body's hormonal system interact, the hypothalamus maintains the body's status quo. It monitors numerous bodily functions, such as blood pressure and body temperature, and controls body weight and appetite.

Hippocampus. Located deep within the brain, the hippocampus processes new memories for long-term storage.

Ventricles. The ventricles of the brain are a communicating network of cavities filled with cerebrospinal fluid, which is formed there, and located in the core of the forebrain and brainstem.

(neurocognitive outcomes) and linear regression models (brain volumes) and adjusted for important confounders. In those analyses, results were adjusted for geographical region, age, race, socioeconomic status, smoking, alcohol use, physical activity, body mass index, and some clinical characteristics (including a history of cardiovascular disease, diabetes mellitus, obesity, depressive symptoms, and use of menopausal hormone therapy). Most covariate information was obtained from questionnaire data at baseline. The main estimates were expressed as hazard ratios and regression coefficients per interquartile range increase in exposure. In the adjusted analyses, ambient $PM_{2.5}$ was analyzed as a continuous variable; diesel PM was in some instances analyzed as a dichotomous outcome (for example, in the gray matter analyses) or as a continuous variable (in the white matter analyses) but stratified by exposure range (first–third quartile and fourth quartile).

The influence of potential effect modifiers (e.g., history of cardiovascular disease) was investigated in subgroup analyses and tested for statistical significance.

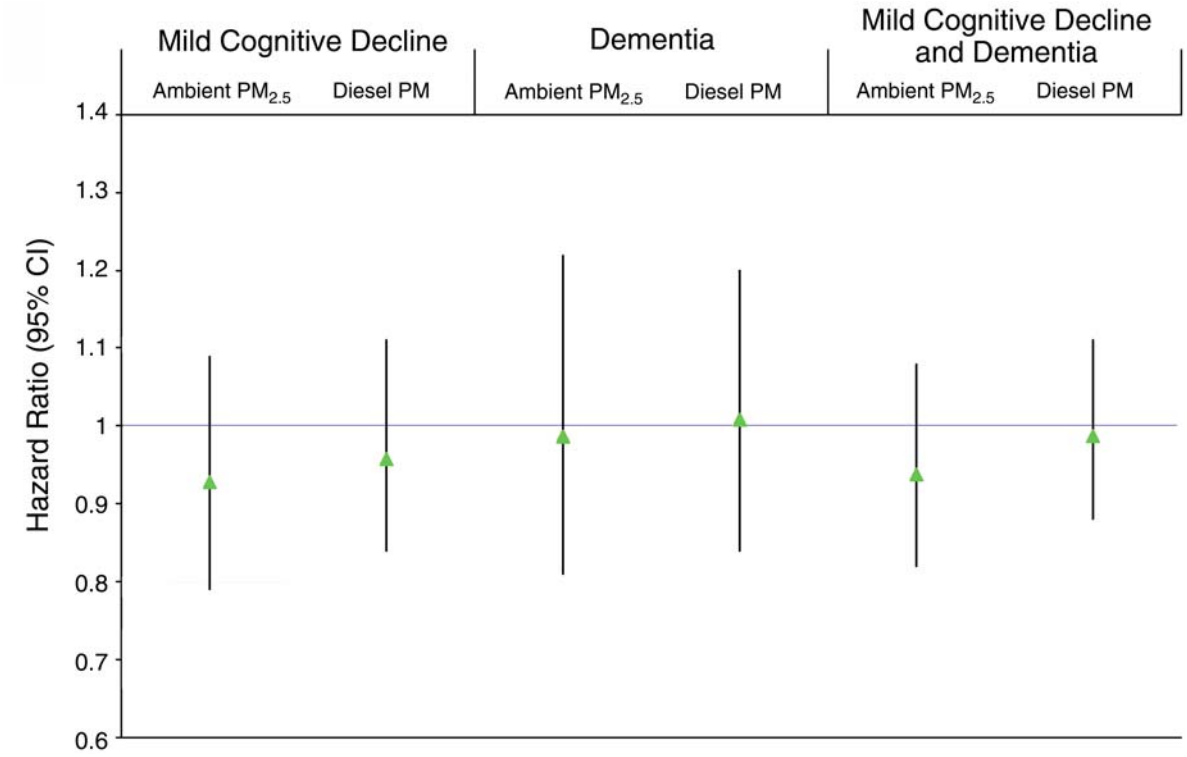
SUMMARY OF RESULTS

- Exposure to neither ambient $PM_{2.5}$ nor diesel PM was associated with mild cognitive impairment and/or dementia in older women (Critique Figure 1). Some positive and negative associations were reported between particulate air pollution and brain volumes.
- Associations of ambient $PM_{2.5}$ and brain volumes differed across brain regions and for white versus gray matter structures. An increase in ambient $PM_{2.5}$ was associated with a decrease in white matter volume in normal-appearing brain structures (Critique Figure 2). However, no such associations were reported for ambient $PM_{2.5}$ and gray matter volumes, ventricular volumes, hippocampal volumes, or volumes of the basal ganglia in models adjusted only for intracranial volume. To date, the investigators have published the $PM_{2.5}$ and brain volume results (Chen et al. 2015).
- In contrast, an increase in diesel PM was associated with a decrease in gray matter volumes. A puzzling nonlinear pattern was reported for white matter volumes, namely, a decrease in white matter volume at lower diesel PM exposure and an increase in white matter volume at higher exposures.
- For both types of outcomes, no significant effect modification was found of factors that may increase susceptibility.
- Results summarized are from fully adjusted models unless specified otherwise.

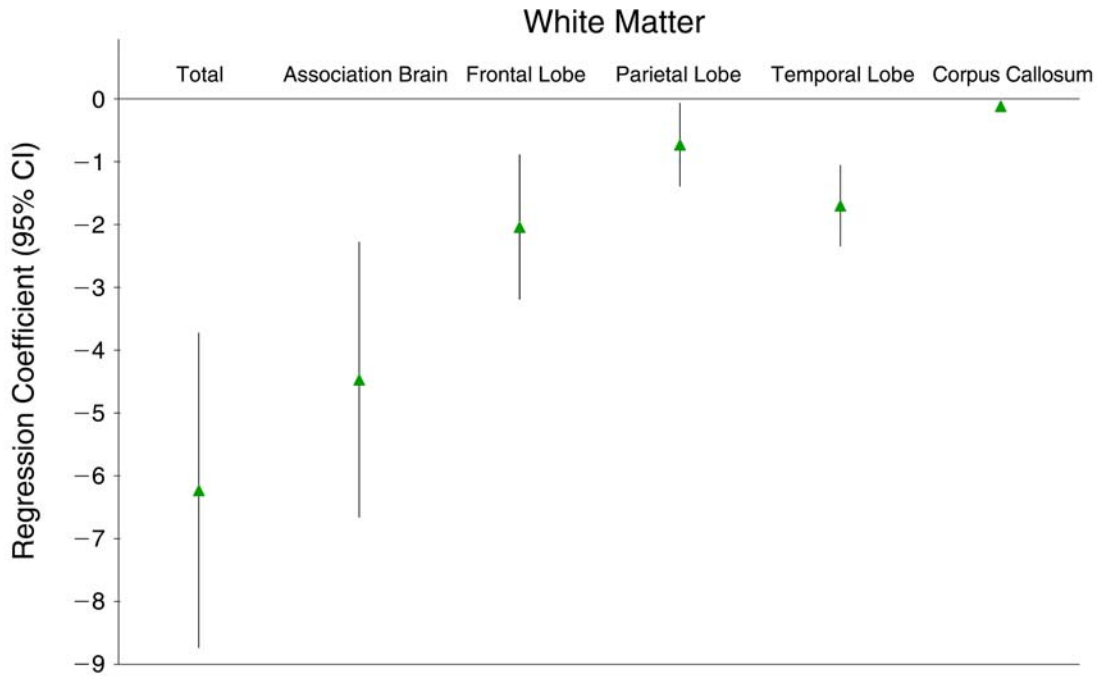
REVIEW COMMITTEE EVALUATION

In its independent review of the study, the HEI Review Committee concluded that Chen and colleagues conducted a novel study — one of the few to evaluate a potential relationship between long-term exposure to ambient particulate air pollution and neurocognitive outcomes and brain volumes. The Committee noted several strengths of the study: a high-quality assessment of neurocognitive outcomes, the inclusion of brain imaging data, and the availability of detailed individual-level covariate information. The neurocognitive outcome data were considered high quality because annual diagnostic assessments for dementia as well as mild cognitive impairment used standardized protocols and were available for all participants. Such data are more precise and accurate than dementia data from hospital records and/or death certificates, which are often hampered by substantial underreporting (Taylor et al. 2009). The inclusion of brain MRI data was considered another strength and a useful new resource for information that may provide insight into the underlying pathological processes. In addition, the availability of detailed individual covariate information at baseline, such as age, socioeconomic status, and smoking, allowed the results to be rigorously controlled for various important confounder variables.

Chen and colleagues report that exposure to neither ambient $PM_{2.5}$ nor diesel PM was associated with mild cognitive impairment and/or dementia in older women. Some positive and negative associations were reported between particulate air pollution and brain volumes; these results differed across brain areas, for white versus gray matter structures and for ambient $PM_{2.5}$ versus diesel PM. The results of the current study differ from those in previous research. A recent systematic review documented that almost all previous studies observed an association between at least one air pollutant and one dementia-related outcome (Power et al. 2016). However, only three studies to date have investigated dementia in relation to long-term exposure to air pollution. All three studies found an association with exposure to $PM_{2.5}$, ozone, and oxides of nitrogen as well as with living near major roads (Chen et al. 2017; Jung et al. 2015; Oudin et al. 2016). These results contrast with the current study's lack of associations with neurocognitive outcomes and its puzzling findings in brain volumes. Only one previous study examined long-term exposure to air pollution and brain volumes in older adults; it reported that higher $PM_{2.5}$ exposure was associated with smaller total cerebral brain volume and higher odds of covert brain infarcts but not with white matter hyperintensity volume or hippocampal



Critique Figure 1. Association between neurocognitive outcomes and particulate air pollution in older women. Hazard ratio expressed per interquartile exposure range (3.9 μg/m^3 for $PM_{2.5}$, 0.35 μg/m^3 for diesel PM).



Critique Figure 2. Associations between white matter brain volumes and ambient $PM_{2.5}$ exposure in older women. Regression coefficient expressed per interquartile exposure range (3.5 μg/m^3 for $PM_{2.5}$).

volume (Wilker et al. 2015). Also in the current study, no association was found between $PM_{2.5}$ and either hippocampal volume or small-vessel ischemic-disease–affected volume (the latter being a measure of cerebrovascular neuropathology equivalent to white matter hyperintensity volume).

It should be noted that the number of air pollution studies on dementia-related outcomes remains small. Evidence from the current study, along with previous results, provides impetus for further research, given the implications of the potential effects of ambient air pollution on dementia for our aging population. Below, the Review Committee summarizes several important analytical issues that should be considered when interpreting the results of this study.

The Committee had less confidence in the results for diesel PM than for ambient $PM_{2.5}$ because the exposure assessment was likely prone to substantial exposure measurement error. The impact of exposure measurement error on health effect estimations can be substantial, potentially distorting associations, reducing the power to detect effects, and leading to invalid inferences, depending on the context (Sheppard et al. 2012). The investigators obtained on-road diesel PM estimates at the census-tract level from the U.S. EPA NATA database, which is typically used as a screening tool to prioritize pollutants, emission sources, and locations of interest for further study (U.S. EPA 2011); NATA is less suitable for use in an epidemiological study. Moreover, the NATA methodology has been substantially updated over the years, which would prevent comparing absolute estimates across different model years. In addition to concerns about the use of NATA, the Committee thought that the diesel PM analyses were also hampered by a lack of contrast (an interquartile range of 0.31 $\mu g/m^3$ for diesel PM, compared with 3.9 $\mu g/m^3$ for ambient $PM_{2.5}$), and therefore some results were difficult to interpret. Diesel PM exposure contrast would likely have increased if off-road diesel PM, which is also available in the NATA database, had been assessed as well. However, this increase in exposure contrast would only be modest according to earlier analyses shown in Additional Materials 1, Part B (available on the HEI website, *www.healtheffects.org/publications*). The exposure assessment for ambient $PM_{2.5}$ was more sophisticated in that it used a nationwide Bayesian maximum entropy spatiotemporal model, which provided estimates at the residential address level. In addition, the $PM_{2.5}$ model was compared with other approaches and showed rather good performance (see Additional Materials 1, Part B). Yet the ambient $PM_{2.5}$ model did not include small-scale characteristics, such as land-use variables. Hence, both exposure approaches lack the level of detail needed to capture small-scale spatial variations in air pollution, which is especially important for an assessment of diesel PM because it exhibits higher spatial variation, largely related to traffic emissions (HEI 2010), than does ambient $PM_{2.5}$, which tends to have more uniform levels across large areas.

The Review Committee was also concerned that there may have been a lack of statistical power for the effect modification analyses in which none of the identified factors that may have increased susceptibility reached statistical significance. For the main analyses, the statistical power of the study was larger for neurocognitive outcomes, which were assessed yearly, than for brain volume measures, which were only assessed at one point in time and only in a subset (about 20%) of participants. Although this is understandable given the high cost of performing MRI, it was somewhat counterintuitive that some positive and negative associations were reported for brain volumes and no associations were found for the neurocognitive outcomes. The investigators did not evaluate whether participants with smaller white and gray matter volumes also showed higher incidence of mild cognitive impairment and/or dementia, in part because of the lack of statistical power. It would have been interesting to know whether this was the case, as it would have shed light on whether the puzzling brain volume findings are clinically relevant, which so far is not clear. From a clinical perspective, dementia is arguably the most important outcome of all the outcomes included in the current study. Therefore, it is noteworthy that the current study did not find associations between exposure to $PM_{2.5}$ and diesel PM and mild cognitive impairment and/or dementia. It is possible, however, that slight decrements in neurocognitive function may have been missed. In future analyses, the investigators may want to probe this issue further by, for example, analyzing actual test scores from the Modified Mini-Mental State Examination instead of deriving a dichotomous mild cognitive impairment outcome based on prespecified cutoffs. In general, the Committee had more confidence in the neurocognitive results than in the brain volume results because of the larger sample size, annual assessments, and standardized protocols.

Though the inclusion of MRI data to investigate brain volume outcomes was considered a strength and a novel contribution, the Review Committee noted several other issues in the statistical analyses of the brain volume outcomes that should be considered when interpreting the results. First, the Committee questioned the emphasis on unadjusted findings in the report. Typically, unadjusted estimates are a stepping stone to the more informative adjusted estimates. For example, the Committee felt that

all analyses should have been rigorously corrected for age, because age is a known risk factor for dementia-related outcomes, and the investigators alluded to a relation between age and exposure. Other research has shown that brain volume decreases by 0.5–1% per year after age 60, even in healthy (i.e., cognitively intact) people. Thus, a reduction in brain volume is a general feature of normal aging as well (Fjell et al. 2013), whether or not it is affected by air pollution exposure. Second, adjusted analyses for several brain volume measures, such as $PM_{2.5}$ and gray matter volumes, may have been revealing. The investigators conducted adjusted analyses only when an outcome was significantly different across exposure quartiles. The Committee noted, however, that this decision was based on crude unadjusted models and that this approach prevented a direct comparison of adjusted estimates across the outcomes. Third, the investigators analyzed ambient $PM_{2.5}$ as a continuous variable and diesel PM as a dichotomous variable in some of the brain volume analyses, which was also based on crude unadjusted models, and again, did not allow for a direct comparison in the adjusted analyses. The investigators did clearly lay out the rationale for the statistical approach that resulted in the brain volume outcomes; for example, they described how there may be differential vulnerability to brain aging and neurodegeneration across brain areas. In addition, they noted that the exposure–response functions across different brain volume outcomes and brain areas may vary. Finally, they discussed how the toxicity of $PM_{2.5}$ versus diesel PM may be different across brain areas. The Committee took note of these considerations and realized that this study was exploratory in many aspects, without much prior knowledge to build on. However, they thought that additional steps could have been taken in the brain volume analyses to allow for increased consistency in the analyses and reporting and for a direct comparison across different outcomes, brain areas, and pollutants.

In the discussion of the report, Chen and colleagues acknowledged the potential for selection bias, but it would have been useful to explore this further. Shumaker and colleagues (2008) and Jamarillo and colleagues (2007) have provided additional details regarding the selection process for including participants in the cohort and subcohort. Selection bias is a potential threat in any epidemiological study, but particularly in studies investigating dementia and related outcomes. Individuals who meet the eligibility criteria for a study of air pollution and a dementia-related outcome, enroll in that study, continue in it, and participate in additional substudies may differ in important ways from nonparticipants (Weuve et al. 2015). For example, studies with participants recruited at older ages may disproportionately represent "healthy survivors" because the probability of surviving and being free of severe disability — outcomes that may be associated with air pollution and cognitive status — diminishes with older age. As a result, associations of air pollution and dementia-related outcomes may be muted. The Committee thought that selection bias may have been likely, especially for brain volume measures, because those were only available in a subset (n = 1,403) of the WHIMS participants (N = 7,479). Moreover, of the 2,345 WHIMS participants who were approached for enrollment, the 61% who agreed to an MRI scan had significantly better cognitive function and less previous cognitive decline, on average, compared with those who did not receive an MRI for the study, highlighting that there may be sample and selection issues at play. In addition, the participants who received an MRI tended to be younger and more highly educated than those who did not (Jaramillo et al. 2007) — both characteristics that have been linked to exposure. The investigators could have explored the potential for selection bias further and could possibly have accounted for it using, for example, instrumental variables or inverse probability weighting methods (Weisskopf et al. 2015; Weuve et al. 2015).

The current study and air pollution–dementia research in general confront numerous other methodological and conceptual challenges, and such studies are inherently difficult. For example, dementia can have a decades-long incipient phase, and there are large uncertainties as to the timing of the exposure relative to when the disease manifests itself. Thus, the most relevant exposure period may be years to decades before the onset of the dementia, or the entire stretch of air pollution exposures from the distant past to the time of diagnosis may be relevant. There is an implicit assumption that "current" or "recent" exposure levels are adequate surrogates for past exposure levels. This may be reasonable if the induction time between exposure and health outcomes is relatively short, but its validity is unknown over longer intervals (Power et al. 2016).

SUMMARY AND CONCLUSION

Chen and colleagues have conducted a novel study, one of the few to evaluate a potential relationship between long-term exposure to particulate air pollution and neurocognitive outcomes and brain volumes. A high-quality neurocognitive outcomes assessment, the inclusion of brain imaging data, and the availability of detailed individual-level covariate information were considered to be the strengths of this study. The study found that exposure to neither ambient $PM_{2.5}$ nor diesel PM was associated with mild cognitive impairment and/or dementia in older women. Some positive and negative associations

were reported between particulate air pollution and brain volumes, but the analyses were exploratory, their clinical significance remains unclear, and the findings differ from previous research. The HEI Review Committee identified several important analytical issues that should be considered when interpreting the results. The Committee had less confidence in the results for diesel PM than those for ambient $PM_{2.5}$ because the exposure assessment was based on a screening tool that was considered less suitable for epidemiological studies and was likely prone to substantial measurement error. In addition, the effect modification analyses were hampered by a lack of statistical power. Although the brain volume results were exploratory and the rationale for the statistical approach was clearly described, the Committee questioned the emphasis on unadjusted findings in the report. Furthermore, it would have been useful to take additional steps to increase consistency in the brain volume analyses and reporting and to explore the potential for selection bias further. It should be noted again that the number of air pollution studies on dementia-related outcomes remains small, and such studies are inherently difficult. Evidence from the current study, along with previous results, provides impetus for further research given the implications of the potential effects of ambient air pollution on dementia for our aging population.

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REFERENCES

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:270–279.

Allen JL, Oberdörster G, Morris-Schafer K, Wong C, Klocke C, Sobolewski M, et al. 2016. Developmental neurotoxicity of inhaled ambient ultrafine particle air pollution: Parallels with neuropathological and behavioral features of autism and other neurodevelopmental disorders. Neurotoxicology. Available: *http://dx.doi.org/10.1016/j.neuro.2015.12.014* [online 22 December 2015].

Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, et al. 2012. The outdoor air pollution and brain health workshop. Neurotoxicology 33:972–984.

Chen H, Kwong JC, Copes R, Tu K, Villeneuve PJ, van Donkelaar A, et al. 2017. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: A population-based cohort study. Lancet 389:718–726.

Chen JC, Wang X, Wellenius GA, Serre ML, Driscoll I, Casanova R, et al. 2015. Ambient air pollution and neurotoxicity on brain structure: Evidence from Women's Health Initiative Memory Study. Ann Neurol 78:466–476.

Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB, Alzheimer's Disease Neuroimaging Initiative. 2013. Brain changes in older adults at very low risk for Alzheimer's disease. J Neurosci 33:8237–8242.

Friedrich MJ. 2014. Researchers test strategies to prevent Alzheimer disease. JAMA 311:1596–1598.

HEI Panel on the Health Effects of Traffic-Related Air Pollution. 2010. Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects. Special Report 17. Boston, MA:Health Effects Institute.

Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, et al. 2013. Long-term air pollution exposure and cardio-respiratory mortality: A review. Environ Health 12:43.

Hurd MD, Martorell P, Langa KM. 2013. Monetary costs of dementia in the United States. N Eng J Med 369:489–490.

Jaramillo SA, Felton D, Andrews L, Desiderio L, Hallarn RK, Jackson SD, et al. 2007. Enrollment in a brain magnetic resonance study: Results from the Women's Health Initiative Memory Study Magnetic Resonance Imaging Study (WHIMS-MRI). Acad Radiol 14:603–612.

Jung CR, Lin YT, Hwang BF. 2015. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: A population-based cohort study in Taiwan. J Alzheimers Dis 44:573–584.

Langrish JP, Bosson J, Unosson J, Muala A, Newby DE, Mills NL, et al. 2012. Cardiovascular effects of particulate

air pollution exposure: Time course and underlying mechanisms. J Intern Med 272:224–239.

Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, et al. 2016. Traffic-related air pollution and dementia incidence in northern Sweden: A longitudinal study. Environ Health Perspect 124:306–312.

Power MC, Adar SD, Yanosky JD, Weuve J. 2016. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic review of epidemiologic research. Neurotoxicology 56:235–253.

Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. 2013. The global prevalence of dementia: A systematic review and metaanalysis. Alzheimer's Dement 9:63–75 e2.

Sheppard L, Burnett RT, Szpiro AA, Kim SY, Jerrett M, Pope CA 3rd, et al. 2012. Confounding and exposure measurement error in air pollution epidemiology. Air Qual Atmos Health 5:203–216.

Shumaker SA, Reboussin BA, Espeland MA, Rapp SR, McBee WL, Dailey M, et al. 1998. The Women's Health Initiative Memory Study (WHIMS): A trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. Control Clin Trials 19:604–621.

Taylor DH Jr, Ostbye T, Langa KM, Weir D, Plassman BL. 2009. The accuracy of Medicare claims as an epidemiological tool: The case of dementia revisited. J Alzheimers Dis 17:807–815.

U.S. Environmental Protection Agency. 2011. An overview of methods for EPA's National-Scale Air Toxics Assessment. Available: *www.epa.gov/sites/production/files/2015-10/documents/2005-nata-tmd.pdf* [accessed 25 January 2017].

Weisskopf MG, Sparrow D, Hu H, Power MC. 2015. Biased exposure-health effect estimates from selection in cohort studies: Are environmental studies at particular risk? Environ Health Perspect 123:1113–1122.

Weuve J, Proust-Lima C, Power MC, Gross AL, Hofer SM, Thiebaut R, et al. 2015. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. Alzheimer's Dement 11:1098–1109.

Wilker EH, Preis SR, Beiser AS, Wolf PA, Au R, Kloog I, et al. 2015. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. Stroke 46:1161–1166.

World Health Organization. 2013 Review of Evidence on Health Aspects of Air Pollution — REVIHAAP Project: Final Technical Report. Available: *www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2013/review-of-evidence-on-health-aspects-of-air-pollution-revihaap-project-final-technical-report* [accessed 25 January 2017].

ABBREVIATIONS AND OTHER TERMS

AC/PC	anterior commissure/ posterior commissure
ANCOVA	analysis of covariance
AQS	Air Quality System (U.S. EPA)
BME	Bayesian maximum entropy
BMI	body mass index
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	confidence interval
CSF	cerebrospinal fluid
CVD	cardiovascular disease
DPM	diesel particulate matter
E-alone	estrogen treatment alone
E+P	medroxyprogesterone acetate
FLAIR	fluid-attenuated inversion recovery
GAM	generalized additive model
GM	gray matter
HR	hazard ratio
HT	hormone therapy
ICV	intracranial volume
IDW	inverse distance weighting
MAR	missing at random
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
NNA	nearest-neighbor approach
NATA	National-Scale Air Toxics Assessment
PDF	probability density function
PM	particulate matter
$PM_{2.5}$	particulate matter $\leq$ 2.5 μm in aerodynamic diameter
REGARDS	Reasons for Geographic and Racial Differences in Stroke (cohort)
SES	socioeconomic status
SVID	small vessel ischemic disease
U.S. EPA	United States Environmental Protection Agency
WBC	white blood cell
WHI	Women's Health Initiative
WHI-HT	WHI trials of hormone therapy
WHIMS	Women's Health Initiative Memory Study
WHIMS-MRI	WHIMS magnetic resonance imaging
WM	white matter
WMLS	white matter lesion segmentation

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