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Particulate matter and episodic memory decline mediated by early neuroanatomic biomarkers of Alzheimer's disease

Diana Younan,[1,*] Andrew J. Petkus,[1,*] Keith F. Widaman,[2] Xinhui Wang,[1] Ramon Casanova,[3] Mark A. Espeland,[3] Margaret Gatz,[1] Victor W. Henderson,[4] JoAnn E. Manson,[5] Stephen R. Rapp,[3] Bonnie C. Sachs,[3] Marc L. Serre,[6] Sarah A. Gaussoin,[3] Ryan Barnard,[3] Santiago Saldana,[3] William Vizuete,[6] Daniel P. Beavers,[3] Joel A. Salinas,[7] Helena C. Chui,[1] Susan M. Resnick,[8] Sally A. Shumaker[3] and Jiu-Chiuan Chen[1]

[*]These authors contributed equally to this work.

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Evidence suggests exposure to particulate matter with aerodynamic diameter <2.5 μm ($PM_{2.5}$) may increase the risk for Alzheimer's disease and related dementias. Whether $PM_{2.5}$ alters brain structure and accelerates the preclinical neuropsychological processes remains unknown. Early decline of episodic memory is detectable in preclinical Alzheimer's disease. Therefore, we conducted a longitudinal study to examine whether $PM_{2.5}$ affects the episodic memory decline, and also explored the potential mediating role of increased neuroanatomic risk of Alzheimer's disease associated with exposure. Participants included older females (n = 998; aged 73–87) enrolled in both the Women's Health Initiative Study of Cognitive Aging and the Women's Health Initiative Memory Study of Magnetic Resonance Imaging, with annual (1999–2010) episodic memory assessment by the California Verbal Learning Test, including measures of immediate free recall/new learning (List A Trials 1–3; List B) and delayed free recall (short- and long-delay), and up to two brain scans (MRI-1: 2005–06; MRI-2: 2009–10). Subjects were assigned Alzheimer's disease pattern similarity scores (a brain-MRI measured neuroanatomical risk for Alzheimer's disease), developed by supervised machine learning and validated with data from the Alzheimer's Disease Neuroimaging Initiative. Based on residential histories and environmental data on air monitoring and simulated atmospheric chemistry, we used a spatiotemporal model to estimate 3-year average $PM_{2.5}$ exposure preceding MRI-1. In multilevel structural equation models, $PM_{2.5}$ was associated with greater declines in immediate recall and new learning, but no association was found with decline in delayed-recall or composite scores. For each interquartile increment (2.81 μg/m^3) of $PM_{2.5}$, the annual decline rate was significantly accelerated by 19.3% [95% confidence interval (CI) = 1.9% to 36.2%] for Trials 1–3 and 14.8% (4.4% to 24.9%) for List B performance, adjusting for multiple potential confounders. Long-term $PM_{2.5}$ exposure was associated with increased Alzheimer's disease pattern similarity scores, which accounted for 22.6% (95% CI: 1% to 68.9%) and 10.7% (95% CI: 1.0% to 30.3%) of the total adverse $PM_{2.5}$ effects on Trials 1–3 and List B, respectively. The observed associations remained after excluding incident cases of dementia and stroke during the follow-up, or further adjusting for small-vessel ischaemic disease volumes. Our findings illustrate the continuum of $PM_{2.5}$ neurotoxicity that contributes to early decline of immediate free recall/new learning at the preclinical stage, which is mediated by progressive atrophy of grey matter indicative of increased Alzheimer's disease risk, independent of cerebrovascular damage.

1 University of Southern California, 2001 N Soto St, Los Angeles, CA 90032, USA
2 University of California at Riverside, 900 University Ave, Riverside, CA 92521, USA
3 Wake Forest School of Medicine, One Medical Center Blvd, Winston-Salem, NC 20157, USA

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4 Stanford University, 259 Campus Dr, Stanford, CA 94305, USA
5 Brigham and Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115, USA
6 University of North Carolina, 250 E Franklin S, Chapel Hill, NC 27514, USA
7 Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Boston, MA 02114, USA
8 Laboratory of Behavioral Neuroscience, National Institute on Aging, 251 Bayview Boulevard, Suite 100, Baltimore, MD 21224, USA

Correspondence to: Diana Younan
University of Southern California
2001 N Soto St, Los Angeles, CA, 90032, USA
E-mail: dyounan@usc.edu

Correspondence may also be addressed to: Jiu-Chiuan Chen
E-mail: jcchen@usc.edu

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Abbreviations: AD-PS = Alzheimer's disease pattern similarity; ADNI = Alzheimer's Disease Neuroimaging Initiative; CA = cornu ammonis; CVLT = California Verbal Learning Test; $PM_{2.5}$ = particulate matter with aerodynamic diameter <2.5 μm; SEM = structural equation model; SVID = small vessel ischaemic disease; WHI = Women's Health Initiative; WHIMS = Women's Health Initiative Memory Study; WHIMS-MRI = Women's Health Initiative Memory Study of Magnetic Resonance Imaging; WHISCA = Women's Health Initiative Study of Cognitive Aging

Introduction

Exposure to ambient air pollution represents a novel environmental risk factor of accelerated brain ageing (Underwood, 2017). In recent years, a growing number of epidemiological studies have shown that fine particulate matter with aerodynamic diameter <2.5 μm ($PM_{2.5}$) may increase the risk of dementia, including Alzheimer's disease (Jung *et al.*, 2015; Cacciottolo *et al.*, 2017; Chen *et al.*, 2017; Carey *et al.*, 2018; Oudin *et al.*, 2018). Toxicopathological studies suggest air pollution accelerates amyloid-β accumulation in mice (Bhatt *et al.*, 2015; Cacciottolo *et al.*, 2017) and neurofibrillary tangles in canines (Calderón-Garcidueñas *et al.*, 2003). Despite the increasing evidence supporting the neurological effects of $PM_{2.5}$ on Alzheimer's disease and related dementias, definitive conclusions on the causal association cannot be made because the underlying mechanisms remain unclear (The Lancet Neurology, 2018).

Declines in verbal episodic memory (e.g. the ability to remember details, with context, from daily and remote experiences) are the hallmark symptom of Alzheimer's disease detectable in the preclinical stage (Gallagher and Koh, 2011). Episodic memory is composed of distinct cognitive processes such as encoding the target information (learning) and subsequently retrieving the target information, each involving complex neural systems (Dickerson and Eichenbaum, 2010). Several animal studies have demonstrated that inhaled $PM_{2.5}$ exposures affect various neural systems thought to underlie these episodic memory processes (Fonken *et al.*, 2011; Cheng *et al.*, 2017; Ku *et al.*, 2017; Liu *et al.*, 2018). Few longitudinal epidemiological studies examined the association between $PM_{2.5}$ and episodic memory (Weuve *et al.*, 2012; Tonne *et al.*, 2014; Wurth *et al.*, 2018), and the majority of these studies used composite scores with mixed results. Importantly, no previous studies had directly linked air pollution exposures with cognitive decline and altered brain structure predictive of dementia risk. Therefore, we conducted a longitudinal study to examine the association between long-term exposure to $PM_{2.5}$ and decline in episodic memory (immediate recall/new learning; delayed-recall), and to investigate the extent to which the putative adverse $PM_{2.5}$ effects on declines were mediated by changes in neuroanatomic structure indicative of increased Alzheimer's disease risk.

Materials and methods

Study design and population

We conducted a prospective cohort study that included community-dwelling females who were initially enrolled in the Women's Health Initiative (WHI) Memory Study and subsequently participated in both the WHI Study of Cognitive Aging (WHISCA) and the WHI Memory Study of Magnetic Resonance Imaging (WHIMS-MRI) ancillary studies (Resnick *et al.*, 2009; Coker *et al.*, 2014). WHIMS participants (n = 7479) were postmenopausal females aged 65 years and older who were recruited from 1996 through 1999 across 48 states and free of dementia as determined by standardized study protocols, described elsewhere (Shumaker *et al.*, 2004) (Supplementary material). A subsample of cognitively-intact WHIMS participants (n = 2304) were followed in WHISCA with annual neurocognitive testing during the period of 1999–2010. Between April 2005 and January 2006, WHIMS participants (n = 1403) across 14 (of 38) active WHIMS sites were enrolled in the WHIMS-MRI study, yielding 1365 scans that met quality control standards. A total of 1050 females participated in both WHISCA and WHIMS-MRI. For the present study, we excluded subjects with missing data on relevant

covariates, resulting in a final analytic sample of 998 females (Fig. 1). A total of 531 females underwent a second MRI between 2009 and 2010.

Measures of episodic memory

Episodic memory was assessed using the California Verbal Learning Test (CVLT), focusing on immediate recall, new learning, and delayed-recall (Delis *et al.*, 1987). Participants were read a 16-item list of words (List A) from four semantically-related categories. Each time the list was read the participant was instructed to immediately repeat back as many words as she could remember. In WHISCA, participants were administered only three learning trials. After completion of the List A trials, a single learning/recall trial of the alternate List B items was administered. Promptly after the List B 'interference' trial, the participants were asked to freely recall all words from List A (short-delay free recall). After an approximate 20-min delay, the free recall trials were repeated (long-delay free recall). For the outcome variables, we used the total number of correct responses on each measure: (i) List A learning trials 1–3; (ii) List B learning/recall trial; (iii) List A short-delay free recall; and (iv) List A long-delay free recall. Each measure was *Z*-score standardized based on the mean and standard deviation (SD) at the initial WHISCA assessment. The *Z*-scores for these three List A measures were averaged to create the composite score of CVLT performance.

WHIMS-MRI acquisition and processing

MRI scans were performed using standardized scan acquisition protocols developed by the MRI Quality Control Center (Resnick *et al.*, 2009). Standard T_1-, T_2-, proton density-weighted, and fluid-attenuated inversion recovery (FLAIR) scans were acquired with a 22-cm field of view and a matrix of 256 × 256 in 1.5 T scanners at 14 sites. Included were oblique axial spin density/T_2-weighted spin echo (repetition time = 3200 ms, echo time = 30/120 ms, slice thickness = 3 mm), FLAIR T_2-weighted spin echo (repetition time = 8000 ms, inversion time = 2000 ms, echo time = 100 ms, slice thickness = 3 mm), and oblique axial 3D T_1-weighted gradient echo (flip angle = 30°, repetition time = 21 ms, echo time = 8 ms, slice thickness = 1.5 mm) images from the vertex to the skull base parallel to the anterior commissure–posterior commissure plane.

As part of the WHIMS-MRI protocol developed by the reading centre, a brain lesion segmentation algorithm was applied to T_1-, T_2-, and FLAIR scans to segment small-vessel ischaemic disease (SVID) (Lao *et al.*, 2008). By combining the tissue segmentation and lesion segmentation algorithm, each voxel was classified as either normal (not SVID-affect) or abnormal (SVID-affected). Normal-appearing brain volume and SVID volumes in grey and white matter regions were calculated, then abnormal brain volumes in these regions were combined to classify total SVID volume.

Joint brain MRI data processing across two populations

We used high-dimensional warping methods to process structural brain MRI images (T_1-weighted) from WHIMS-MRI participants. More details about the MRI data processing across dataset can be found in other reports (Tustison *et al.*, 2014; Casanova *et al.*, 2018). Here, we briefly describe the main steps. The Advanced Normalization Tools software was used to align the brain images from the WHIMS-MRI and the Alzheimer's Disease Neuroimaging Initiative (ADNI) into a common template. The images were submitted to N4 bias field correction (Tustison *et al.*, 2010), brain extraction, segmentation (Avants *et al.*, 2011), template construction and normalization. A script consisting of six stages (brain extraction, template registration, tissue segmentation, improved template registration, cortical thickness registration, and quality control and summary measurements) was used to generate the template based on a randomly selected sample of 50 cognitively normal Caucasian females (55–90 years old; mean age: 76.8) from ADNI. The brain MRI images (n = 2436) from both WHIMS-MRI and ADNI were segmented and warped to the template.

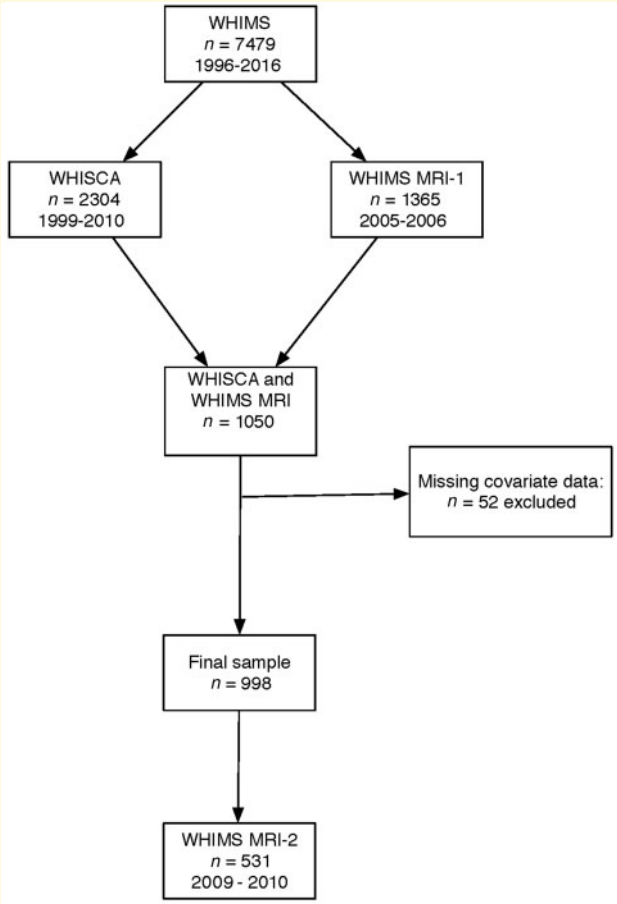

Figure 1 Flowchart for selection of final analytical sample.

Alzheimer's disease pattern similarity score

The Alzheimer's disease pattern similarity (AD-PS) score was derived using a high-dimensional (voxel-wise) supervised machine learning algorithm based on the elastic net regularized logistic regression (EN-RLR) to analyse structural brain MRI

data pattern at voxel level (Friedman *et al.*, 2010), comparing Alzheimer's disease cases and cognitively normal individuals (Casanova *et al.*, 2011). The EN-RLR is known to produce sparse models (Zou and Hastie, 2005), which translates in the context of our neuroimaging application into a variable selection mechanism able to identify voxels or brain areas relevant for classification that we call discriminative maps. The score formally is the class-conditional probability of membership to the Alzheimer's disease group as modelled by the EN-RLR model when discriminating cognitively normal from Alzheimer's disease participants in ADNI (Casanova *et al.*, 2013), interpreted as a measure of similarity of the brain spatial patterns found in one individual's MRI to those found in individuals diagnosed with Alzheimer's disease.

The AD-PS scores of WHIMS MRI participants were derived by two steps: (i) estimating the EN-RLR classifier based on grey matter probability maps from cognitively-normal and Alzheimer's disease participants in ADNI; and (ii) providing baseline and follow-up WHIMS-MRI grey matter probability maps as input to the EN-RLR classifier to generate the grey matter AD-PS score for WHIMS-MRI participants. The discriminative maps derived in step (i) revealed grey matter atrophies in areas (e.g. amygdala, hippocampus, para-hippocampal gyrus, thalamus, inferior temporal lobe areas and midbrain) where Alzheimer's disease neuropathologies are thought to first emerge (Brettschneider *et al.*, 2015). We had previously reported both cross-sectional and longitudinal relationships of higher AD-PS scores with increased age, poorer cognitive performance, and greater SVID volume in WHIMS-MRI participants (Casanova *et al.*, 2018). In a longitudinal analysis of global cognitive trajectories over 10 years, the groups of older females with relatively lower AD-PS scores were considered more resilient to cognitive decline (Espeland *et al.*, 2018). Our empirical data also showed that an SD (=0.23) increase in AD-PS scores over a 5-year period was associated with a 122% increase in dementia risk [hazard ratio = 2.22; 95% confidence interval (CI): 1.80 to 2.75] defined by DSM-IV criteria, adjusting for socio-demographics, region, lifestyle factors, and clinical characteristics.

Air pollution exposure assessment

Residential addresses of WHIMS participants were prospectively collected during each clinic visit and updated at least biannually. Residential histories were then sent to a single vendor that followed standardized protocols for geocoding (Whitsel *et al.*, 2004). Ambient concentration of $PM_{2.5}$ was estimated using the Bayesian maximum entropy (BME)-based spatiotemporal modelling approach, integrating nationwide monitoring data from both the US Environmental Protection Agency (EPA) Air Quality System (AQS) and the output of chemical transport models, entitled Community Multiscale Air Quality (Reyes *et al.*, 2017). Our empirical data showed that the BME estimates of daily $PM_{2.5}$ exposures correlated well with recorded concentrations from the AQS (average cross-validation Pearson's R^2 = 0.70). The statistically-validated BME model was then applied to each geocoded residential location, accounting for residential mobility in 1999–2010, and exposure estimates were then aggregated to represent the average $PM_{2.5}$ 3 years preceding the first MRI scan. See Supplementary material for further details.

Covariate data

A structured questionnaire was administered to participants at WHIMS enrolment to gather information on demographics [e.g. age; race/ethnicity (Black/African-American, Hispanic White, non-Hispanic White, other/missing)], socioeconomic factors [e.g. education (<high school, high school/GED, >high school); family income (<$10 000, $10 000–34 999, $35 000–74 999, ⩾$75 000); employment status (currently employed, not working, retired)], and lifestyle factors [e.g. smoking status (never smoked, past smoker, current smoker); alcohol intake (non-drinker, past drinker, <1 drink per day, >1 drink per day); physical activity (no activity, some activity, 2–4 episodes per week, >4 episodes per week)]. Additionally, clinical characteristics were ascertained including any postmenopausal hormone treatment ever, history of cardiovascular disease [including previous coronary heart disease (e.g. myocardial infarction, coronary angioplasty, or coronary artery bypass graft), stroke, or transient ischaemic attack, hypertension [defined as elevated blood pressure (systolic ⩾140 or diastolic ⩾90 mmHg), or use of antihypertensive medication], and diabetes mellitus (defined as physician diagnosis plus oral medications, or insulin therapy). Good reliability and validity of both the self-reported medical histories and the physical measures have been previously documented (Heckbert *et al.*, 2004; Johnson-Kozlow *et al.*, 2007; Margolis *et al.*, 2008).

Statistical analysis

We constructed multilevel structural equation models (SEM) to characterize the longitudinal trajectory of each CVLT measure and examined the respective association with $PM_{2.5}$ exposure. Years across repeated CVLT assessments were used as the time scale, centred on the individual-specific date of the first MRI (MRI-1). The average trajectories of CVLT performance were assumed to follow piecewise-linear declines joined at MRI-1. The multilevel SEM allowed for one random intercept (representing CVLT performance at MRI-1) and two random slopes (individual-specific linear changes before and after the MRI-1), while accounting for the practice effect and the use of two CVLT forms, as defined in the within-individual portion of SEM (Supplementary material, Equation 1). These individual-specific parameters of individual trajectories were entered into the between-individual portion of the multilevel SEM to assess the associations between $PM_{2.5}$ exposure and linear change in CVLT. To ensure the appropriate temporal relations between $PM_{2.5}$ and identified CVLT trajectories, the relevant exposure time window was defined as 3 years preceding the MRI-1, with the resulting effect on annual rate of CVLT change after MRI-1. The between-individual portion of the fully adjusted multilevel SEM is depicted in Fig. 2A and in the Supplementary material. Separate SEMs were run for each CVLT measure and composite score.

The estimated $PM_{2.5}$ exposure effects on CVLT performance at MRI-1 and change post MRI-1 were all adjusted for the following covariates: age at MRI-1, race/ethnicity, geographic region of residence, education, household income, employment status, lifestyle factors (smoking; alcohol use; physical activities), and clinical characteristics (any prior hormone use ever, hypercholesterolaemia, hypertension, diabetes, and history of cardiovascular disease).

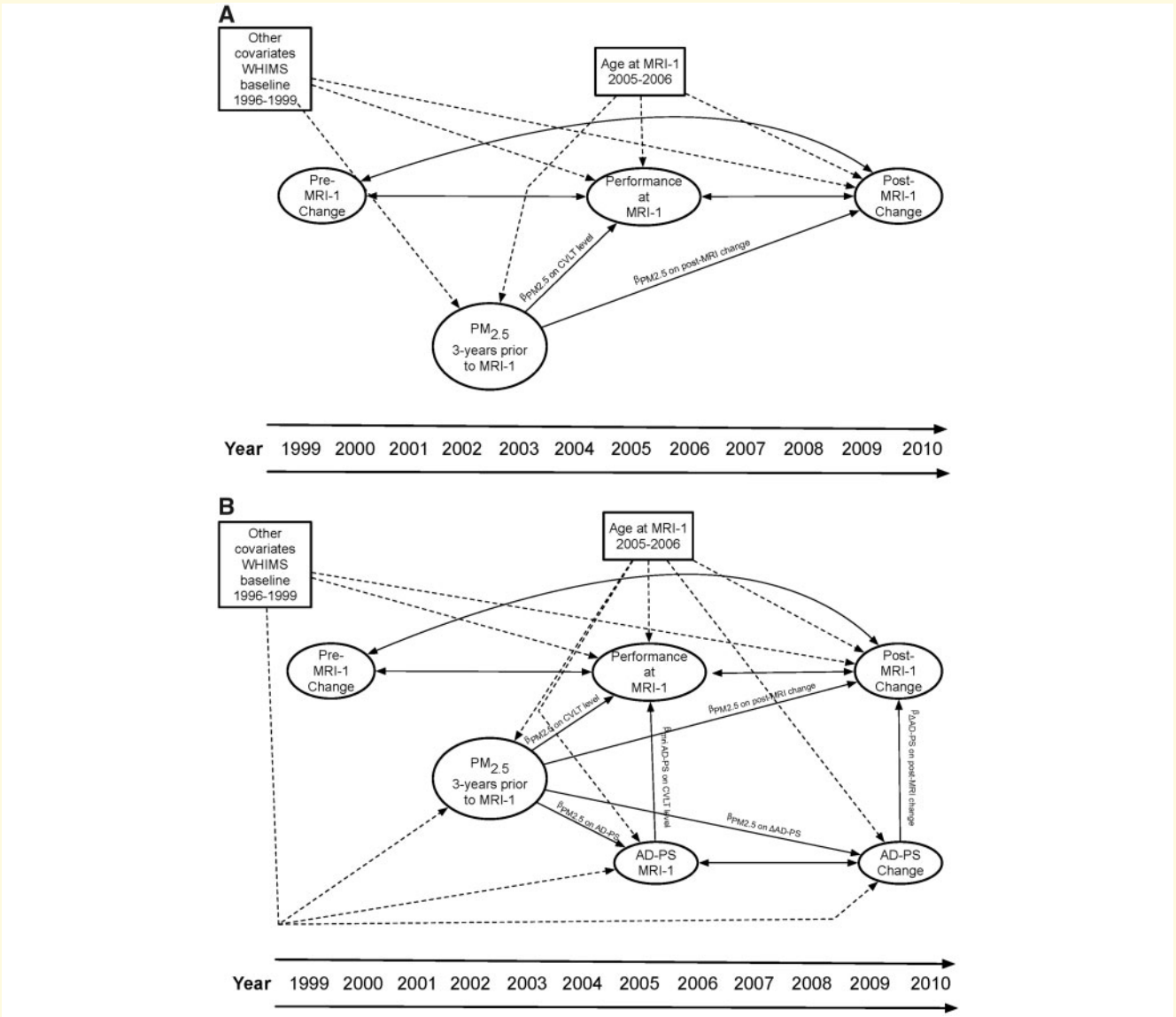

Figure 2 Depiction of the SEMs constructed. (**A**) Panel shows the portion of the fully adjusted multilevel SEM examining the associations between $PM_{2.5}$ exposure and level and change in CVLT performance. (**B**) Panel depicts parallel-process mediation SEM estimating the extent to which change in AD-PS score mediates the association between long-term fine particulate matter exposure and declines in episodic memory.

We used multilevel SEMs with parallel-process mediation (Cheong *et al.*, 2003) to assess whether increased AD-PS scores mediated the adverse $PM_{2.5}$ effects, if any observed on the post MRI-1 decline in CVLT performance. Figure 2B depicts the between-individual portion of the fully adjusted parallel process mediation SEM. AD-PS scores at MRI-1 and average annual changes in AD-PS [$(\text{AD-PS}_{\text{MRI2}} - \text{AD-PS}_{\text{MRI1}})$/years between MRI assessments] were added as variables to the between-individual portion of the multilevel model. The indirect effect, defined as the extent to which change in AD-PS score mediated the $PM_{2.5}$ effect on CVLT change, was estimated by multiplying the two SEM paths: (i) the effect of $PM_{2.5}$ on change in AD-PS score; and (ii) the effect of change in AD-PS score on change in CVLT. We then estimated the direct effect of $PM_{2.5}$ on CVLT change, defined as the $PM_{2.5}$ exposure effects on post MRI-1 change in CVLT performance, independent of change in AD-PS score. Using the approach described by Cheong *et al.* (2003) and MacKinnon *et al.* (2002), we estimated the proportion of the total $PM_{2.5}$ effect (the sum of the direct and indirect effect) on CVLT change that was mediated by changes in AD-PS score. In fully-adjusted multilevel parallel-process mediation SEMs, the $PM_{2.5}$ effects on the outcome variables (CVLT performance at MRI-1; annual change post MRI-1) and the putative mediators (AD-PS score at MRI-1 and subsequent change in AD-PS score) were all adjusted for the same set of covariates as described in the multilevel SEM models examining the $PM_{2.5}$ effect on CVLT trajectories.

Several additional analyses were conducted to examine the robustness of our findings. To assess the possible confounding by neighbourhood socioeconomic characteristics, the SEMs further adjusted for census track-level socioeconomic

characteristics of residential neighbourhood (Qi *et al.*, 2012) closest to MRI-1 (Supplementary material). To explore whether any observed associations between $PM_{2.5}$ and CVLT decline simply reflect the underlying dementia risk, we repeated our analyses after excluding incident dementia cases before the year 2010. To explore whether any observed associations could be explained by cerebrovascular disease and associated damage, we excluded incident stroke cases by 2010 (Supplementary material) and further adjusted for global SVID volume in the mediation analyses. We also conducted *ad hoc* mediation analyses by replacing the AD-PS score with global grey matter volume, to illustrate whether the associations between $PM_{2.5}$ and CVLT decline may be mediated by standard volumetric measures of global grey matter atrophy. To assess the possible unmeasured confounding by other factors that may operate through affecting the pre-MRI trajectories, we ran a sensitivity analysis allowing the correlation between exposure and the change in CVLT performance before MRI-1. Lastly, to ensure we were not overfitting the covariate structure, we constructed an alternative SEM where the estimated $PM_{2.5}$ effect on the post MRI-1 trajectory was only adjusted for the selected covariates significantly associated with changes in CVLT performance after MRI-1. All analyses were performed using MPLUS version 8 (Muthén and Muthén, 1998–2018) via the MPLUS automation package (Hallquist and Wiley, 2018) in R version 3.5.1.

Data availability

Access to all data elements used in this study may be made available following the established WHI policies.

Results

Population characteristics

The majority of the older females in our study population were Caucasian (92.0%) and had more than a high-school education (75.4%). Table 1 compares the distribution of the 3-year average $PM_{2.5}$ exposure prior to MRI-1, stratified by population characteristics. Participants exposed to higher levels of $PM_{2.5}$ were more likely to self-identify as African-American or Hispanic, reside in the West, and report higher household incomes ($\geqslant$\$75 000). Our study sample (n = 998) and the excluded subjects (n = 367) did not significantly differ by race/ethnicity, employment status, household income, smoking status, alcohol use, or selected clinical characteristics including hypertension, diabetes, or cardiovascular disease (Supplementary Table 1). Compared to females from the WHIMS-MRI cohort who were excluded from our final analytic sample, subjects included in our analyses were more likely to reside in the Midwest ($P < 0.01$), were more educated ($P < 0.01$), and reported more physical activities (P = 0.02), and also tended to have high cholesterol (P = 0.07) and use hormone treatment (P = 0.06). We also compared the population characteristics of our final sample (n = 998) by those who did (n = 531) and did not (n = 467) return for their second MRI scan (Supplementary Table 1). Compared to females who did not return, MRI-2 participants were more likely to reside in the Midwest and Northeast regions ($P < 0.01$) and self-identify as non-Hispanic White (P = 0.01), but were less likely to report having hypertension (P = 0.02).

Associations between $PM_{2.5}$ exposure and change in CVLT

Multilevel SEMs revealed significant linear declines in episodic memory before MRI-1 across all CVLT measures (Supplementary Table 2 with estimated population trajectories). Linear declines in CVLT performance were generally larger after the MRI-1 across all measures except for long-delay free recall. The observed between-individual variability was statistically significant for the level of CVLT performance at the MRI-1 and linear changes in individual-specific estimates of all CVLT trajectories before MRI-1. Between-individual variability in change was generally larger after the MRI-1 but not statistically significant.

Across all CVLT measures, $PM_{2.5}$ exposure was not associated with the estimated level of performance at MRI-1 (Table 2, top section). There was evidence for adverse $PM_{2.5}$ effects with greater declines in both CVLT measures of immediate recall and new learning (List A learning Trials 1–3 and List B learning/recall trial), but no statistically significant associations were found with delayed-recalls or composite measure (Table 2, bottom section). Across each interquartile increment of $PM_{2.5}$ (2.81 $\mu g/m^3$), the average rate of annual decline in immediate recall/new learning was significantly accelerated by 0.040 SDs (95% CI: −0.076 to −0.004) for Trials 1-3 and 0.057 SDs (−0.096 to −0.017) for List B. As compared with the effect of age at MRI-1 (β_{age} = −0.010; P = 0.017) in the same model on post MRI-1 change in CVLT Trials 1–3, the magnitude of the adverse exposure effect (per interquartile increment of $PM_{2.5}$) was equivalent to ∼4 years of accelerated decline in immediate recall/new learning performance. Overall, the multicovariate-adjusted average rate of change was significantly accelerated by 19.3% (95% CI: 1.9% to 36.2%) for Trials 1–3 and 14.8% (4.4% to 24.9%) for List B.

Mediation analyses involving AD-PS scores

The results of the multilevel SEMs with parallel process mediation are presented in Table 3. $PM_{2.5}$ exposure was associated with an increased AD-PS score ($\beta_{PM2.5 \text{ on } \Delta AD\text{-}PS}$ = 0.018; 95% CI: 0.001 to 0.034). Increases in the AD-PS score were also associated with greater declines on both Trials 1-3 ($\beta_{\Delta AD\text{-}PS \text{ on Trials 1-3 post-MRI change}}$ = −0.459; 95% CI: −0.804 to −0.115) and List B ($\beta_{\Delta AD\text{-}PS \text{ on List B post-MRI change}}$ = −0.347; 95% CI: −0.609 to −0.085) performance after MRI-1. The multicovariate-adjusted indirect

Table 1 Comparison of estimated $PM_{2.5}$ exposure measured at MRI-1 visit by baseline population characteristics (n = 998)

Population characteristics	*n* (%)	Distribution of 3-year average PM2.5[a]					*P*[b]
		Mean	SD	25th	Median	75th	
Overall	998	11.63	2.41	10.1	10.8	13.0	
Region of residence							<0.01
Northeast	174 (17.4)	11.62	1.36	10.7	11.2	12.6	
South	156 (15.6)	10.98	1.42	9.8	10.2	12.3	
Midwest	398 (39.9)	11.53	2.10	10.2	10.5	14.0	
West	270 (27.1)	12.16	3.47	10.1	10.8	14.5	
Race/ethnicity							<0.01
African-American	42 (4.2)	13.44	2.59	12.0	13.0	14.3	
Hispanic white	13 (1.3)	12.34	2.38	10.6	11.5	13.7	
Non-Hispanic white	918 (92)	11.52	2.33	10.1	10.7	12.6	
Other or missing	25 (2.5)	12.13	3.44	10.2	11.3	12.7	
Education							0.05
Less than high school	36 (3.6)	11.62	2.25	10.4	11.2	13.5	
High school	210 (21)	11.27	1.96	10.1	10.6	11.6	
More than high school	752 (75.4)	11.73	2.52	10.1	10.8	13.2	
Employment							0.28
Currently working	185 (18.5)	11.40	2.53	10.1	10.6	12.3	
Not working	99 (9.9)	11.84	2.33	10.2	10.9	13.4	
Retired	714 (71.5)	11.66	2.38	10.1	10.8	13.0	
Income, in USD							0.03
<9999	198 (19.8)	11.29	2.05	10.2	10.7	11.8	
10 000–34 999	299 (30)	11.59	2.38	10.0	10.7	13.0	
35 000–49 999	230 (23)	11.62	2.40	10.1	10.7	12.8	
50 000–74 999	141 (14.1)	11.77	2.64	10.2	10.9	13.2	
75 000 or more	100 (10)	12.28	2.71	10.4	11.0	14.5	
Don't know	30 (3)	11.59	2.41	10.1	11.1	13.2	
Lifestyle							
Smoking status							0.26
Never smoked	584 (58.5)	11.67	2.42	10.2	10.8	13.0	
Past smoker	376 (37.7)	11.52	2.34	10.1	10.7	12.6	
Current smoker	38 (3.8)	12.14	2.72	10.1	11.1	14.1	
Alcohol use							0.30
Non-drinker	131 (13.1)	11.85	2.46	10.1	11.0	13.5	
Past drinker	157 (15.7)	11.56	2.23	10.1	10.7	13.0	
Less than one drink per day	596 (59.7)	11.54	2.37	10.1	10.7	12.5	
More than one drink per day	114 (11.4)	11.92	2.73	10.3	11.0	13.2	
Moderate or strenuous activities ⩾20 min							0.15
No activity	547 (54.8)	11.66	2.44	10.1	10.8	13.2	
Some activity	57 (5.7)	12.01	2.35	10.4	10.8	14.3	
2–4 episodes/week	214 (21.4)	11.73	2.48	10.2	10.7	13.0	
⩾4 episodes/week	180 (18)	11.30	2.18	10.0	10.8	12.2	
Physical health							
Hypertension							0.78
No	644 (64.5)	11.61	2.44	10.1	10.8	13.0	
Yes	354 (35.5)	11.66	2.35	10.2	10.7	12.9	
High cholesterol							0.10
No	827 (82.9)	11.57	2.37	10.1	10.7	12.9	
Yes	171 (17.1)	11.91	2.58	10.3	10.9	13.3	
Diabetes mellitus							0.62
No	969 (97.1)	11.64	2.43	10.1	10.7	13.0	
Yes	29 (2.9)	11.41	1.33	10.6	10.9	12.3	
Cardiovascular disease							0.39
No	857 (85.9)	11.60	2.41	10.1	10.8	12.8	
Yes	141 (14.1)	11.79	2.40	10.2	10.7	13.7	
Hormone treatment ever							0.77
No	520 (52.1)	11.61	2.28	10.2	10.7	12.9	
Yes	478 (47.9)	11.65	2.53	10.1	10.8	13.0	

[a]$PM_{2.5}$ represents the 3-year exposures aggregated from the daily exposure levels estimated at each residential location prior MRI-1 visit time using the Bayesian maximum entropy spatiotemporal model.
[b]*P*-values estimated from ANOVA tests comparing average exposure.

Table 2 Associations between 3-year average $PM_{2.5}$ (per IQR of 2.81 μg/m^3) exposure and estimated trajectories of CVLT performance

CVLT measures	Unadjusted	Fully-adjusted
	β (95% CI)	β (95% CI)
Estimates[a] of $PM_{2.5}$ effects on CVLT performance at MRI-1[b]		
Trials 1–3	0.014 (−0.043, 0.070)	0.002 (−0.052, 0.057)
List B	0.045 (−0.002, 0.091)	0.041 (−0.003, 0.084)
Short-delay free recall	−0.011 (−0.067, 0.028)	−0.017 (−0.071, 0.038)
Long-delay free recall	−0.017 (−0.073, 0.038)	−0.026 (−0.080, 0.029)
Composite score	−0.008 (−0.063, 0.046)	−0.017 (−0.070, 0.036)
Estimates[a] of $PM_{2.5}$ effects on the annual change in CVLT performance after MRI-1[c])		
Trials 1–3	**−0.039 (−0.075, −0.004)**	**−0.040 (−0.076, −0.004)**
List B	**−0.053 (−0.093, −0.014)**	**−0.057 (−0.096, −0.017)**
Short-delay free recall	−0.009 (−0.046, 0.028)	−0.007 (−0.045, 0.031)
Long-delay free recall	−0.006 (−0.045, 0.033)	−0.002 (−0.041, 0.037)
Composite score	−0.020 (−0.052, 0.013)	−0.018 (−0.051, 0.015)

[a]All estimates derived from the multilevel structural equation model (SEM) as depicted in Fig. 2A.
[b]Estimates correspond to the $\beta_{PM2.5\ on\ CVLT\ level}$ parameter depicted in Fig. 2A. In fully adjusted models, the effect of $PM_{2.5}$ on CVLT performance at MRI-1 was adjusted for age at MRI-1, race/ethnicity, geographic region of residence, education, household income, employment status, lifestyle factors (smoking, alcohol use, physical activities) and clinical characteristics (use of hormone treatment; hypercholesterolaemia, hypertension, diabetes, and history of cardiovascular disease).
[c]Estimates correspond to the $\beta_{PM2.5\ on\ post\text{-}MRI\ change}$ parameter depicted in Fig. 2A. In fully-adjusted models, the effect of $PM_{2.5}$ on change in CVLT performance after MRI-1 was adjusted for age at MRI-1, race/ethnicity, geographic region of residence, education, household income, employment status, lifestyle factors (smoking, alcohol use, physical activities) and clinical characteristics (use of hormone treatment; hypercholesterolaemia, hypertension, diabetes, and history of cardiovascular disease).
Bolded estimates denote $PM_{2.5}$ effects that are statistically significant at $P < 0.05$.

$PM_{2.5}$ effects on post MRI-1 changes were statistically significant for both Trials 1-3 ($Indirect_{PM2.5\ on\ Trials\ 1\text{-}3\ post\text{-}MRI\ change}$ = −0.008; 95% CI: −0.0262 to −0.0002) and List B performance ($Indirect_{PM2.5\ on\ List\ B\ post\text{-}MRI\ change}$ = −0.006; 95% CI: −0.0170 to −0.0002). Together, the estimated change in AD-PS significantly mediated the observed association between $PM_{2.5}$ exposure and post MRI-1 declines of both Trials 1–3 and List B performance. In fully-adjusted models, the mediation path that linked $PM_{2.5}$ exposure with accelerated declines of episodic memory by increasing the AD-PS score explained 22.6% (95% CI: 1.0% to 68.9%) and 10.7% (1.0% to 30.3%) of the adverse effects on CVLT performance in Trials 1–3 and List B performance, respectively.

Sensitivity analyses

In the analysis further adjusting for census track-level socioeconomic characteristics of residential neighbourhood, the findings were robust (Supplementary Tables 3 and 4). After excluding 31 older females with incident dementia, the association with CVLT decline in Trials 1-3 was modestly attenuated and became marginally significant (P = 0.056), but the corresponding association with CVLT decline in List B performance remained statistically significant (Supplementary Table 5). Importantly, excluding the incident dementia cases only caused minimal changes to the results on mediation by increased AD-PS scores (Supplementary Table 6). Furthermore, the overall patterns of observed associations, including the estimates of adverse $PM_{2.5}$ effect and results of mediation analyses, were robust after excluding 17 females with incident clinical stroke by 2010 and further adjusting for global SVID (Supplementary Tables 7 and 8). When the change in total grey matter volume was assumed as a mediator of $PM_{2.5}$ effect on changes in CVLT performance, we found the direct $PM_{2.5}$ effects on decline of immediate recalls/new learning remained statistically significant, but global change in grey matter did not play any significant role in mediating the observed associations (Supplementary Table 9). Lastly, allowing CVLT change before MRI-1 to covary with $PM_{2.5}$ exposure (Supplementary Tables 10 and 11) or regressing change after MRI-1 only on selected covariates (age at MRI-1; geographic region of residence; household income) predictive of the post MRI-1 trajectories (Supplementary Tables 12 and 13) did not have any notable impacts on the results.

Discussion

In this prospective study on older females, our findings suggest that long-term exposure to ambient $PM_{2.5}$ at residential locations was associated with accelerated declines in episodic memory, specifically in the measures of immediate recall and new learning. Using a parallel-process SEM approach, we further demonstrated that the $PM_{2.5}$-associated greater decline in episodic memory (immediate recall and new learning) was partly (10–22%) mediated by increasing AD-PS scores (a structural brain MRI-based neuroanatomic biomarker reflecting high-dimensional grey matter atrophies in brain areas vulnerable to Alzheimer's disease neuropathology). These observed associations could not be explained by socio-demographic factors (age, geographic

Table 3 Multilevel SEMs with parallel process mediation to examine whether increased Alzheimer's disease pattern similarity scores mediate the adverse $PM_{2.5}$ effects (per IQR of 2.81 mg/m^3) on declines of immediate recall/new learning

	CVLT Trials 1–3		CVLT List B	
	Unadjusted β (95% CI)	Adjusted β (95% CI)	Unadjusted β (95% CI)	Adjusted β (95% CI)
Estimates[a] of direct effect				
Effect of $PM_{2.5}$ on annual change in CVLT performance after MRI-1, accounting for the indirect effect[b]	−0.024 (−0.059, 0.012)	**−0.030 (−0.089, −0.008)**	**−0.045 (−0.085, −0.006)**	**−0.049 (−0.089, −0.010)**
Estimates[a] of indirect effect				
Effects of $PM_{2.5}$ on the increase of in AD-PS scores[c]	**0.022 (0.006, 0.039)**	**0.018 (0.001, 0.034)**	**0.022 (0.006, 0.039)**	**0.018 (0.001, 0.034)**
Effects of increased AD-PS score on annual change in CVLT performance after MRI-1[d]	**−0.592 (−0.913, −0.271)**	**−0.459 (−0.804, −0.115)**	**−0.333 (−0.587, −0.079)**	**−0.347 (−0.609, −0.085)**
Proportion of total $PM_{2.5}$ effect mediated by increased AD-PS scores	**35.1% (6.2%, 78.1%)**	**22.6% (1%, 68.9%)**	**13.2% (1.3%, 35.1%)**	**10.7% (1%, 30.3%)**

Estimates bolded if statistically significant at $P < 0.05$. AD-PS was z-score standardized based on the mean and SD at WHIMS MRI-1.

[a]All estimates derived from the multilevel structural equation models with parallel process mediation as depicted in Fig. 2B. In fully-adjusted models, all the presented effect estimates on CVLT decline (direct $PM_{2.5}$ effects; indirect effect paths, including CVLT decline affected by increased AD-PS scores) were adjusted for age at MRI-1, race/ethnicity, attrition, geographic region of residence, education, household income, employment status, lifestyle factors (smoking, alcohol use, physical activities), and clinical characteristics (use of hormone treatment; hypercholesterolaemia, hypertension, diabetes, and history of cardiovascular disease).

[b]Estimate corresponds to the $\beta_{PM2.5\ on\ post\text{-}MRI\ change}$ parameter depicted in Fig. 2B.

[c]Estimate corresponds to the $\beta_{PM2.5\ on\ \Delta AD\text{-}PS}$ parameter depicted in Fig. 2B.

region, race/ethnicity, education, income), lifestyle (smoking, alcohol, physical activity), employment status, clinical characteristics (diabetes, high cholesterol, hypertension, cardiovascular diseases, hormone therapy), or MRI-measured cerebrovascular disease, and remained measurable after excluding incident cases of dementia and stroke. In contrast, we found no evidence of statistically significant associations between $PM_{2.5}$ exposure and the observed declines in delayed-recall or the composite measure of episodic memory. To our knowledge, this is the first study to suggest that long-term $PM_{2.5}$ exposure accelerates the early cognitive decline commonly seen before the dementia onset, and this putative neurotoxic effect in the preclinical stage is mediated by altered brain structure that predicts subsequent Alzheimer's disease risk.

Previous studies on air pollution and cognitive decline had yielded inconsistent results (Peters *et al.*, 2019), but our data provide the most compelling epidemiological evidence so far to support the adverse effect on the preclinical trajectories of episodic memory in older females affected by $PM_{2.5}$ exposure in late life, suggesting the long-term air pollution neurotoxicity across the Alzheimer's disease continuum. Episodic memory is one of the cognitive domains with early declines detectable in preclinical Alzheimer's disease (Aisen *et al.*, 2017). Three cohort studies had examined the association between $PM_{2.5}$ exposure and episodic memory decline, but their reported findings were mixed, including no significant association in the Nurses' Health Study (Weuve *et al.*, 2012), a positive association in the Boston Puerto Rican Health Study (Wurth *et al.*, 2018) and a negative association (with a single measure of immediate recall) in the Whitehall II study (Tonne *et al.*, 2014). These three reports were limited by only two to three cognitive assessments, and so far none of these cohort studies had examined the association between exposure and incident dementia or clinically significant cognitive impairment. Investigators in the Betula Project in Sweden possibly made the first attempt to establish the air pollution exposure effect continuum in dementia. They found nitrogen oxide exposure was associated with increased dementia risk (Oudin *et al.*, 2016), but not with episodic memory decline (Oudin *et al.*, 2017). The exact reasons for this discrepancy were unclear, because episodic memory measured 10 years prior to clinical diagnosis significantly predicted dementia in the Betula cohort (Boraxbekk *et al.*, 2015). One possible explanation is that the air pollution neurotoxicity observed in the Swedish cohort only accelerated the pathological brain ageing process during the clinical stage. However, this interesting hypothesis was not supported by the neurotoxicological data showing that diesel engine exhaust accelerated amyloid-β plaque formation, with no overt deficits in spatial memory (Hullmann *et al.*, 2017). In contrast, we have previously reported that residing in locations with high $PM_{2.5}$ exposure was associated with clinically significant cognitive impairment and dementia among non-Hispanic white older females from WHIMS (Cacciottolo

et al., 2017). In the current study using data from WHIMS participants who were tested with CVLT annually for the WHISCA, we further found that $PM_{2.5}$ exposure was associated with greater declines in episodic memory (immediate recall and new learning), equivalent to ~4 years of accelerated decline. These findings were observed even among cognitively intact older females without dementia. We also showed these observed adverse $PM_{2.5}$ effects on accelerated decline in episodic memory were partly mediated by the increased AD-PS score, an earlier biomarker reflecting the neuroanatomic risk associated with progressive grey matter atrophy in brain regions vulnerable to Alzheimer's disease neuropathology. Although our collective findings point to the possible continuum of $PM_{2.5}$ neurotoxicity across the early neuropsychological processes and altered brain structures predictive of subsequent dementia risk, we call for future studies to replicate our results in other populations and to further substantiate the scientific evidence of the continuum of air pollution neurotoxicity in the preclinical stage.

Our study illustrates the promise of new approaches to understanding the neuropsychological processes and altered brain structure associated with air pollution exposure.

First, to the best of our knowledge, this was the first air pollution epidemiological study to combine both longitudinal brain MRI and cognitive function data, allowing us to investigate the brain–behaviour relations affected by $PM_{2.5}$ neurotoxicity. Such combined neuroimaging-neuropsychological data analyses are important as they better inform our understanding of the brain determinants of the cognitive changes of Alzheimer's disease to address important clinical and scientific challenges presented by Alzheimer's disease (Mungas *et al.*, 2012). Second, using a sophisticated parallel-process SEM, our study represents the first application to air pollution epidemiology of brain ageing to simultaneously model level and change in both cognitive decline and longitudinal change in structural brain MRI measures and further examine the hypothesized mediation effects. This analytical approach is important because it allows researchers to directly examine complex questions about intra-individual changes in cognitive performance and neuroimaging data in a single statistical model. Lastly, we used the AD-PS scores as a more specific measure of altered brain structure in brain areas that are likely more vulnerable to the Alzheimer's disease neurodegenerative processes. In contrast, previous human studies using neuroimaging data to investigate $PM_{2.5}$ effects on altered brain structure used the region-of-interest approach (Chen *et al.*, 2015; Wilker *et al.*, 2015; Power *et al.*, 2018) or conducted whole-brain analyses (Casanova *et al.*, 2016), and none of these studies found a significant association with the volumes of hippocampus, which is not specific to Alzheimer's disease (Frisoni *et al.*, 2010). Also, the majority of these previous studies (Chen *et al.*, 2015; Wilker *et al.*, 2015; Casanova *et al.*, 2016) did not evaluate the possibility that $PM_{2.5}$ neurotoxicity may result in brain atrophy with unique spatial patterns, similar to the spreading of neurodegenerative proteins as shown in many neuropathological studies in Alzheimer's disease (Brettschneider *et al.*, 2015). Although Power *et al.* (2018) also studied grey matter volumes in brain regions vulnerable to Alzheimer's disease neuropathology, a few methodological differences were noteworthy. For instance, Power *et al.* investigated the putative neurotoxic effects of $PM_{2.5}$ on brain volumes measured at one time point, while we conducted a longitudinal study based on changes of AD-PS score across two time points (2005–06 and 2009–10). Additionally, the 'Alzheimer's disease signature regions' used by Power *et al.* were selected based on work by Dickerson *et al.* (2011) applying a hypothesis-driven region-of-interest approach. In contrast, to create the AD-PS score, we took a data-driven approach using supervised machine learning based on a large-scale regularization algorithm that analyses whole-brain grey matter tissue at the voxel-level and identifies the unique spatial patterns of localized grey matter atrophy in Alzheimer's disease.

Our empirical data pointed to the possibility that $PM_{2.5}$ neurotoxicity may have differential effects across the episodic memory processes, although the biological underpinnings of such observed differences are unclear. Published work on $PM_{2.5}$ and episodic memory decline had found an unexpected positive association in the Boston Puerto Rican Health Study (Wurth *et al.*, 2018) and no statistically significant association in the Nurses' Health Study (Weuve *et al.*, 2012), both using a composite measure, which ignores the important heterogeneity in the neuropsychological processes that comprise episodic memory performance. In the present study, we were able to show the differential effects of $PM_{2.5}$ exposure on episodic memory, with the exposure-associated decline predominantly affecting immediate recall and new learning and no significant association with delayed-recall ability or our composite measure of episodic memory. In the Baltimore Longitudinal Study of Aging, declines in CVLT immediate recall/encoding processes were observed first with Alzheimer's disease progression, followed by changes in long-delayed free recall scores, suggesting that changes in immediate recall/new learning may take place earlier during the preclinical stages of Alzheimer's disease (Bilgel *et al.*, 2014). Thus, the observation of differential exposure effects on CVLT measures reinforces the suggestion that our study was capturing the $PM_{2.5}$ neurotoxic effects on the early neuropsychological processes of episodic memory decline at the preclinical stage. The medial temporal lobe and the interactions of its structural components play a central role in the episodic memory (Dickerson and Eichenbaum, 2010). Early studies have documented the functional specification of the prefrontal cortex involved in different cognitive processes in episodic memory (Fletcher *et al.*, 1998*a*, *b*). More recent studies further demonstrated the distinctive roles of large-scale cortical networks contributing to the different cognitive processes of episodic memory in individuals with prodromal (Putcha *et al.*, 2019) and clinical Alzheimer's disease (Wolk *et al.*, 2011). Future studies

need to continue examining the possibly differential exposure effects on the episodic memory processes and further elucidate how these related neural networks are affected by $PM_{2.5}$ neurotoxicity.

Our study results, as well as the growing literature on air pollution neurotoxicity, point to several important directions for advancing the environmental neurosciences of brain ageing associated with exposure to ambient particles. We found that long-term $PM_{2.5}$ exposure was associated with increasing AD-PS scores, which only accounted for 10–22% the $PM_{2.5}$-associated greater decline in episodic memory, and the direct exposure effects remained statistically significant (Table 3). Other contributors to the observed episodic memory decline associated with $PM_{2.5}$ exposure may include the alteration of other brain structures, changes in neural networks, and specific neuropathological processes, not fully captured by the increased AD-PS scores. For example, hippocampal subfields may be critical targets of the air pollution neurotoxicity on the neuropsychological processes of episodic memory decline. The medial temporal lobe and its structural components (especially the hippocampus) play a central role in encoding (learning; recall) and retrieving (recall) details of events that compose episodic memories (Dickerson and Eichenbaum, 2010). Although the roles of hippocampal subfields [e.g. cornu ammonis (CA, CA2-3), CA4-denate gyrus, presubiculum, subiculum] on these distinct processes (encoding, retrieval) remain to be delineated, animal studies have demonstrated the adverse effects of particulate matter and its constituents on morphological and functional changes within hippocampal subfields. For instance, decreased apical dendritic spine density and dendritic branches in the CA1 and CA3 regions (Fonken *et al.*, 2011), reduced synaptic function (Ku *et al.*, 2017) in CA1 neurons (Davis *et al.*, 2013), and decreased myelin basic protein in white matter and increased atrophy of neurites in the CA1 region (Woodward *et al.*, 2017) have been observed. These neurotoxicological data collectively suggest that some hippocampal subfields may be more sensitive than others to the adverse particulate matter effects. Additionally, human imaging studies (Zhao *et al.*, 2019) have found that atrophy in hippocampal subfields imposed varying degrees of influences on different measures of episodic memory (immediate recalls; delayed-recalls; recognition). Previous research also suggests that the CA2, CA3, and dentate gyrus are responsible for encoding, while the CA1 and subiculum are responsible for retrieval (Zammit *et al.*, 2017). Our findings of significant declines predominantly in immediate recall/new learning imply that the adverse $PM_{2.5}$ effects on episodic memory processes may be more targeted towards hippocampal subfields related to encoding, such as the CA2, CA3, and dentate gyrus. High-resolution neuroimaging studies are needed to determine whether there is indeed a subfield neurotoxicity involved. Next, studies have shown that cerebrovascular disease, MRI measures of vascular brain injury (e.g. white matter hyperintensities; infarcts), and vascular risk factors are independently associated with cognitive decline (Marchant *et al.*, 2013; DeCarli *et al.*, 2019). Our exploratory analyses showed robust findings even after further adjustment for global SVID volume (a proxy for cerebrovascular damage) or excluding females with incident clinical stroke. Although these results suggest that the observed mediation by increased AD-PS score associated with late-life exposure to $PM_{2.5}$ may be independent of large-vessel diseases or global cerebrovascular damage, it is important not to rule out other measures of cerebral small-vessel diseases (e.g. microbleeds, cerebral amyloid angiopathy) for their potential contributions to the exposure effects on episodic memory declines. Lastly, other neuropathological processes underlying the observed mediation by increasing AD-PS scores are unclear. Meta-analyses of studies with PET scans of cognitively-normal individuals found that high amyloid-β status predicts subsequent decline in episodic memory (Baker *et al.*, 2017). PET studies have also shown that grey matter atrophy may be a consequence of tau neuropathological processes, which in turn may be driving the observed cognitive decline (Bejanin *et al.*, 2017; Jagust, 2018; Harrison *et al.*, 2019). Future neuroimaging studies are needed to determine whether specific neuropathological processes (e.g. aggregation of phosphorylated tau in neurofibrillary tangles; amyloid-β plaque deposition) drive the $PM_{2.5}$-associated greater decline in episodic memory.

We recognize several limitations of our study. First, although the BME spatiotemporal models were well cross-validated (average Pearson's R^2 = 0.70) to estimate $PM_{2.5}$ exposures, these resulting estimates were still subject to measurement errors because individual-level data on time-activity patterns of our study participants were not available. However, such estimation errors tend to be non-differential, most likely resulting in attenuation of the observed associations. Second, we were unable to estimate early- or mid-life $PM_{2.5}$ exposures, because nationwide $PM_{2.5}$ monitoring data were unavailable prior to 1999 and early-life residential location data were not collected in WHI. Since air pollution levels have been declining over the past two decades, early- or mid-life $PM_{2.5}$ exposure effects could have been greater than or different from what we observed in our study on late-life exposure. Third, our study focused on regional $PM_{2.5}$ only, and we did not investigate its chemical constituencies (e.g. black carbon; inorganic secondary aerosols), other exposure sources (e.g. from near roadways), or possible interactions with other pollutant mixtures (e.g. with photochemical reactions of gaseous pollutants). Fourth, although our sensitivity analyses suggest stroke and cerebrovascular disease damage could not explain the observed adverse $PM_{2.5}$ effects on episodic memory decline, we did not examine multiple mediation pathways involving longitudinal SVID changes. Extant literature on air pollution neuroimaging studies do not support the association between late-life exposure to air pollution and MRI-measured cerebrovascular damage (Chen *et al.*, 2015; Wilker *et al.*, 2015, 2016; Kulick

et al., 2017; Power *et al.*, 2018), but it remains possible that $PM_{2.5}$ exposures before late-life could impart adverse effects that we may have missed in the current study. Fifth, we could not completely rule out the possibility of unmeasured confounding by other environmental factors (e.g. outdoor noise; neighbourhood green space) that may be correlated with $PM_{2.5}$. However, the extant epidemiologic data do not provide strong evidence for these environmental factors to accelerate episodic memory decline at the preclinical stage; therefore, their role as potential confounders is not well-established. Lastly, our findings may not be generalizable to males or younger females.

This study also had several major strengths. First, females were prospectively followed over a long period of time (~11 years), with annual assessments of both their immediate- and delayed-recall, allowing us to examine whether of $PM_{2.5}$-exposure was differentially associated with these cognitive processes. Second, we used the sophisticated parallel-process mediation SEM approach, which allowed us to examine whether $PM_{2.5}$ effects level and change of episodic memory performance, while also investigating to what extent AD-PS scores may mediate this association. Third, our AD-PS scores were able to capture the spatial patterns of brain tissue atrophy more specific to Alzheimer's disease. Lastly, the rich, comprehensive data of the geographically diverse WHIMS cohort allowed us to adjust for potential confounding by multiple covariates and address other sources of biases.

In summary, this study provided the first epidemiological evidence suggesting long-term $PM_{2.5}$ exposure in late life is associated with accelerated decline of episodic memory, predominantly affecting immediate recall and new learning. Increases in neuroanatomical risk for Alzheimer's disease associated with $PM_{2.5}$ partially explained these negative associations. The adverse effects remained measurable even after excluding incident dementia, suggesting the possible continuum of $PM_{2.5}$ neurotoxicity that may contribute to early decline of immediate recall and new learning abilities at the preclinical stage. Because this is the first study of its kind combining both longitudinal data on cognitive decline and a neuroanatomic risk score for Alzheimer's disease, replication of our findings will be needed to substantiate the suggestion for continuum of air pollution neurotoxicity. Future neuroimaging studies are needed to further explore the links between episodic memory processes and altered brain structures, especially hippocampal subfields and other related neural networks, underpinning the observed association between $PM_{2.5}$ and dementia risk.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

References

Aisen PS, Cummings J, Jack CR, Morris JC, Sperling R, Frölich L, et al. On the path to 2025: understanding the Alzheimer's disease continuum. Alzheimers Res Ther 2017; 9: 60.

Avants BB, Tustison NJ, Wu J, Cook PA, Gee JC. An open source multivariate framework for n-tissue segmentation with evaluation on public data. Neuroinformatics 2011; 9: 381–400.

Baker JE, Lim YY, Pietrzak RH, Hassenstab J, Snyder PJ, Masters CL, et al. Cognitive impairment and decline in cognitively normal older adults with high amyloid-β: a meta-analysis. Alzheimers Dement (Amst) 2017; 6: 108–21.

Bejanin A, Schonhaut DR, La Joie R, Kramer JH, Baker SL, Sosa N, et al. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. Brain 2017; 140: 3286–300.

Bhatt DP, Puig KL, Gorr MW, Wold LE, Combs CK. A pilot study to assess effects of long-term inhalation of airborne particulate matter on early Alzheimer-like changes in the mouse brain. PLoS One 2015; 10: e0127102.

Bilgel M, An Y, Lang A, Prince J, Ferrucci L, Jedynak B, et al. Trajectories of Alzheimer disease-related cognitive measures in a longitudinal sample. Alzheimers Dement 2014; 10: 735–42.e4.

Boraxbekk CJ, Lundquist A, Nordin A, Nyberg L, Nilsson LG, Adolfsson R. Free recall episodic memory performance predicts dementia ten years prior to clinical diagnosis: findings from the Betula longitudinal study. Dement Geriatr Cogn Dis Extra 2015; 5: 191–202.

Brettschneider J, Del Tredici K, Lee VM, Trojanowski JQ. Spreading of pathology in neurodegenerative diseases: a focus on human studies. Nat Rev Neurosci 2015; 16: 109–20.

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

Calderón-Garcidueñas L, Maronpot RR, Torres-Jardon R, Henríquez-Roldán C, Schoonhoven R, Acuña-Ayala H, et al. DNA damage in nasal and brain tissues of canines exposed to air pollutants is associated with evidence of chronic brain inflammation and neurodegeneration. Toxicol Pathol 2003; 31: 524–38.

Carey IM, Anderson HR, Atkinson RW, Beevers SD, Cook DG, Strachan DP, et al. Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. BMJ Open 2018; 8: e022404.

Casanova R, Barnard RT, Gaussoin SA, Saldana S, Hayden KM, Manson JE, et al. Using high-dimensional machine learning methods to estimate an anatomical risk factor for Alzheimer's disease across imaging databases. Neuroimage 2018; 183: 401–11.

Casanova R, Hsu FC, Sink KM, Rapp SR, Williamson JD, Resnick SM, et al. Alzheimer's disease risk assessment using large-scale machine learning methods. PLoS One 2013; 8: e77949.

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

Casanova R, Whitlow CT, Wagner B, Williamson J, Shumaker SA, Maldjian JA, et al. High dimensional classification of structural MRI Alzheimer's disease data based on large scale regularization. Front Neuroinform 2011; 5: 22.

Chen H, Kwong JC, Copes R, Tu K, Villeneuve PJ, van Donkelaar A, et al. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. Lancet 2017; 389: 718–26.

Chen JC, Wang X, Wellenius GA, Serre ML, Driscoll I, Casanova R, et al. Ambient air pollution and neurotoxicity on brain structure: evidence from women's health initiative memory study. Ann Neurol 2015; 78: 466–76.

Cheng L, Lau WKW, Fung TKH, Lau BWM, Chau BKH, Liang Y, et al. PM2.5 Exposure suppresses dendritic maturation in subgranular zone in aged rats. Neurotox Res 2017; 32: 50–7.

Cheong J, Mackinnon DP, Khoo ST. Investigation of mediational processes using parallel process latent growth curve modeling. Struct Equ Modeling 2003; 10: 238.

Coker LH, Espeland MA, Hogan PE, Resnick SM, Bryan RN, Robinson JG, et al. Change in brain and lesion volumes after CEE therapies: the WHIMS-MRI studies. Neurology 2014; 82: 427–34.

Davis DA, Akopian G, Walsh JP, Sioutas C, Morgan TE, Finch CE. Urban air pollutants reduce synaptic function of CA1 neurons via an NMDA/NO pathway in vitro. J Neurochem 2013; 127: 509–19.

DeCarli C, Villeneuve S, Maillard P, Harvey D, Singh B, Carmichael O, et al. Vascular burden score impacts cognition independent of amyloid PET and MRI measures of Alzheimer's disease and vascular brain injury. J Alzheimers Dis 2019; 68: 187–96.

Delis DC, Kramer JH, Kaplan E, Ober BA. California verbal learning test–research edition. New York: The Psychological Corporation; 1987.

Dickerson BC, Eichenbaum H. The episodic memory system: neurocircuitry and disorders. Neuropsychopharmacology 2010; 35: 86–104.

Dickerson BC, Stoub TR, Shah RC, Sperling RA, Killiany RJ, Albert MS, et al. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. Neurology 2011; 76: 1395–402.

Espeland MA, Chen JC, Weitlauf J, Hayden KM, Rapp SR, Resnick SM, et al. Trajectories of relative performance with 2 measures of global cognitive function. J Am Geriatr Soc 2018; 66: 1575–80.

Fletcher PC, Shallice T, Dolan RJ. The functional roles of prefrontal cortex in episodic memory. I. Encoding. Brain 1998a; 121 (Pt 7): 1239–48.

Fletcher PC, Shallice T, Frith CD, Frackowiak RS, Dolan RJ. The functional roles of prefrontal cortex in episodic memory. II. Retrieval. Brain 1998b; 121 (Pt 7): 1249–56.

Fonken LK, Xu X, Weil ZM, Chen G, Sun Q, Rajagopalan S, et al. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. Mol Psychiatry 2011; 16: 987–95, 73.

Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. J Stat Softw 2010; 33: 1–22.

Frisoni GB, Fox NC, Jack CR, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 2010; 6: 67–77.

Gallagher M, Koh MT. Episodic memory on the path to Alzheimer's disease. Curr Opin Neurobiol 2011; 21: 929–34.

Hallquist MN, Wiley JF. MplusAutomation: an R package for facilitating large-scale latent variable analyses in Mplus. Struct Equ Modeling 2018; 25: 621–38.

Harrison TM, La Joie R, Maass A, Baker SL, Swinnerton K, Fenton L, et al. Longitudinal tau accumulation and atrophy in aging and Alzheimer disease. Ann Neurol 2019; 85: 229–40.

Heckbert SR, Kooperberg C, Safford MM, Psaty BM, Hsia J, McTiernan A, et al. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. Am J Epidemiol 2004; 160: 1152–8.

Hullmann M, Albrecht C, van Berlo D, Gerlofs-Nijland ME, Wahle T, Boots AW, et al. Diesel engine exhaust accelerates plaque formation in a mouse model of Alzheimer's disease. Part Fibre Toxicol 2017; 14: 35.

Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. Nat Rev Neurosci 2018; 19: 687–700.

Johnson-Kozlow M, Rock CL, Gilpin EA, Hollenbach KA, Pierce JP. Validation of the WHI brief physical activity questionnaire among women diagnosed with breast cancer. Am J Health Behav 2007; 31: 193–202.

Jung CR, Lin YT, Hwang BF. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. J Alzheimers Dis 2015; 44: 573–84.

Ku T, Li B, Gao R, Zhang Y, Yan W, Ji X, et al. NF-κB-regulated microRNA-574-5p underlies synaptic and cognitive impairment in response to atmospheric PM. Part Fibre Toxicol 2017; 14: 34.

Kulick ER, Wellenius GA, Kaufman JD, DeRosa JT, Kinney PL, Cheung YK, et al. Long-term exposure to ambient air pollution

and subclinical cerebrovascular disease in NOMAS (the Northern Manhattan Study). Stroke 2017; 48: 1966–8.
Lao Z, Shen D, Liu D, Jawad AF, Melhem ER, Launer LJ, et al. Computer-assisted segmentation of white matter lesions in 3D MR images using support vector machine. Acad Radiol 2008; 15: 300–13.
Liu X, Qian X, Xing J, Wang J, Sun Y, Wang Q, et al. Particulate matter triggers depressive-like response associated with modulation of inflammatory cytokine homeostasis and brain-derived neurotrophic factor signaling pathway in mice. Toxicol Sci 2018; 164: 278–88.
MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychol Methods 2002; 7: 83–104.
Marchant NL, Reed BR, Sanossian N, Madison CM, Kriger S, Dhada R, et al. The aging brain and cognition: contribution of vascular injury and aβ to mild cognitive dysfunction. JAMA Neurol 2013; 70: 488–95.
Margolis KL, Qi Lihong, Brzyski R, Bonds DE, Howard BV, Kempainen S, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. Clin Trials 2008; 5: 240–7.
Mungas D, Crane PK, Gibbons LE, Manly JJ, Glymour MM, Jones RN. Advanced psychometric analysis and the Alzheimer's Disease Neuroimaging Initiative: reports from the 2011 Friday Harbor conference. Brain Imaging Behav 2012; 6: 485–8.
Muthén LK, Muthén BO. Mplus user's guide. 8th edn. Los Angeles, CA: Muthén & Muthén; 1998–2018.
Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, et al. Traffic-related air pollution and dementia incidence in northern Sweden: a longitudinal study. Environ Health Perspect 2016; 124: 306–12.
Oudin A, Forsberg B, Lind N, Nordin S, Oudin Åström D, Sundström A, et al. Is long-term exposure to air pollution associated with episodic memory? A longitudinal study from Northern Sweden. Sci Rep 2017; 7: 12789.
Oudin A, Segersson D, Adolfsson R, Forsberg B. Association between air pollution from residential wood burning and dementia incidence in a longitudinal study in Northern Sweden. PLoS One 2018; 13: e0198283.
Peters R, Ee N, Peters J, Booth A, Mudway I, Anstey KJ. Air pollution and dementia: a systematic review. J Alzheimers Dis 2019; 70: S145–S163.
Power MC, Lamichhane AP, Liao D, Xu X, Jack CR, Gottesman RF, et al. The association of long-term exposure to particulate matter air pollution with brain MRI findings: the ARIC study. Environ Health Perspect 2018; 126: 027009.
Putcha D, Brickhouse M, Wolk DA, Dickerson BC; Alzheimer's Disease Neuroimaging Initiative. Fractionating the Rey auditory verbal learning test: distinct roles of large-scale cortical networks in prodromal Alzheimer's disease. Neuropsychologia 2019; 129: 83–92.
Qi L, Nassir R, Kosoy R, Garcia L, Curb JD, Tinker L, et al. Relationship between diabetes risk and admixture in postmenopausal African-American and Hispanic-American women. Diabetologia 2012; 55: 1329–37.
Resnick SM, Espeland MA, Jaramillo SA, Hirsch C, Stefanick ML, Murray AM, et al. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI study. Neurology 2009; 72: 135–42.
Reyes JM, Xu Y, Vizuete W, Serre ML. Regionalized PM2.5 Community Multiscale Air Quality model performance evaluation across a continuous spatiotemporal domain. Atmos Environ (1994) 2017; 148: 258–65.
Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004; 291: 2947–58.
The Lancet Neurology. Air pollution and brain health: an emerging issue. Lancet Neurol 2018; 17: 103.
Tonne C, Elbaz A, Beevers S, Singh-Manoux A. Traffic-related air pollution in relation to cognitive function in older adults. Epidemiology 2014; 25: 674–81.
Tustison NJ, Avants BB, Cook PA, Zheng Y, Egan A, Yushkevich PA, et al. N4ITK: improved N3 bias correction. IEEE Trans Med Imaging 2010; 29: 1310–20.
Tustison NJ, Cook PA, Klein A, Song G, Das SR, Duda JT, et al. Large-scale evaluation of ANTs and FreeSurfer cortical thickness measurements. NeuroImage 2014; 99: 166–79.
Underwood E. The polluted brain. Science 2017; 355: 342.
Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. Exposure to particulate air pollution and cognitive decline in older women. Arch Intern Med 2012; 172: 219–27.
Whitsel EA, Rose KM, Wood JL, Henley AC, Liao D, Heiss G. Accuracy and repeatability of commercial geocoding. Am J Epidemiol 2004; 160: 1023–9.
Wilker EH, Martinez-Ramirez S, Kloog I, Schwartz J, Mostofsky E, Koutrakis P, et al. Fine particulate matter, residential proximity to major roads, and markers of small vessel disease in a memory study population. J Alzheimers Dis 2016; 53: 1315–23.
Wilker EH, Preis SR, Beiser AS, Wolf PA, Au R, Kloog I, et al. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. Stroke 2015; 46: 1161–6.
Wolk DA, Dickerson BC, Initiative AsDN. Fractionating verbal episodic memory in Alzheimer's disease. Neuroimage 2011; 54: 1530–9.
Woodward NC, Pakbin P, Saffari A, Shirmohammadi F, Haghani A, Sioutas C, et al. Traffic-related air pollution impact on mouse brain accelerates myelin and neuritic aging changes with specificity for CA1 neurons. Neurobiol Aging 2017; 53: 48–58.
Wurth R, Kioumourtzoglou M-A, Tucker KL, Griffith J, Manjourides J, Suh H. Fine particle sources and cognitive function in an older Puerto Rican cohort in Greater Boston. Environ Epidemiol 2018; 2: e022.
Zammit AR, Ezzati A, Zimmerman ME, Lipton RB, Lipton ML, Katz MJ. Roles of hippocampal subfields in verbal and visual episodic memory. Behav Brain Res 2017; 317: 157–62.
Zhao W, Wang X, Yin C, He M, Li S, Han Y. Trajectories of the hippocampal subfields atrophy in the Alzheimer's disease: a structural imaging study. Front Neuroinform 2019; 13: 13.
Zou H, Hastie T. Regularization and variable selection via the elastic net. J R Statist Soc B 2005; 67: 301–20.