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Exposure to fine particulate matter and temporal dynamics of episodic memory and depressive symptoms in older women

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ABSTRACT

Background: Emerging data suggests $PM_{2.5}$ (particulate matter with aerodynamic diameter < 2.5 μm) may be associated with both earlier declines in episodic memory (EM) and increased depressive symptoms in older adults. Although late-life depressive symptoms are associated with EM, no longitudinal studies have examined the inter-relationship among $PM_{2.5}$, depressive symptoms and EM.

Methods: Older women (n = 2,202; aged 67–83 in 1999) enrolled in the Women's Health Initiative Study of Cognitive Aging completed up to eight annual assessments of depressive symptoms (15-item Geriatric Depression Scale) and EM (California Verbal Learning Test). A nationwide spatiotemporal model (1999–2010) was used to estimate ambient $PM_{2.5}$ exposure at residential locations. Univariate and bivariate structural equation models (SEMs) for latent-change scores were used to examine how 3-year average $PM_{2.5}$ preceding each assessment affects the temporal dynamics and bidirectional relations of annual changes in depressive symptoms and EM.

Results: In univariate SEMs, one inter-quartile (4.04 $\mu g/m^3$) increment of 3-year $PM_{2.5}$ was significantly ($p < 0.05$) associated with accelerated declines in verbal learning (List A trials 1–3: $\beta = -1.48$) and free-recall memory (short-delay: $\beta = -1.43$; long-delay: $\beta = -1.11$), but not with change in depressive symptoms ($\beta = 0.12$; $p = 0.71$). In bivariate SEMs, significant associations were observed between $PM_{2.5}$ and accelerated declines in EM measures ($\beta = -1.44$ to -0.99; $p < 0.05$) and between EM performance and changes in depressive symptoms ($\beta = -0.08$ to -0.05; $p < 0.05$), with significant indirect $PM_{2.5}$ effects on changes in depressive symptoms ($\beta = 0.08$–0.10; $p < 0.05$). These findings were robust with adjustment for multiple demographic, lifestyle, and clinical factors, and remained after excluding subjects with dementia or mild cognitive

Abbreviations: $PM_{2.5}$, particulate matter with aerodynamic diameter < 2.5 μm; ADRD, Alzheimer's disease and related dementias; WHISCA, Women's Health Initiative Study of Cognitive Aging; WHIMS, Women's Health Initiative Memory Study; WHI, Women's Health Initiative; GDS-15, 15-item Geriatric Depression Scale; CVLT, California Verbal Learning Test; BME, Bayesian Maximum Entropy; MCI, Mild Cognitive Impairment; DSM-4, Diagnostic and Statistical Manual of Mental Disorders – 4th edition; 3MS, Modified Mini-Mental State Exam; TICSm, Telephone Interview for Cognitive Status-modified; SEM, Structural Equation Modeling; LCS, latent change score; em, episodic memory; dep, depressive symptoms as measured by the 15-item Geriatric Depression Scale; lem, latent episodic memory score; ldep, latent depressive symptoms; res_{em}, error variance of episodic memory; res_{dep}, error variance of depressive symptoms; RMSEA, root mean square error of approximation

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impairment. No associations were found between $PM_{2.5}$ and change in depressive symptoms or depressive symptoms and subsequent EM decline.
Conclusions: Findings suggest that $PM_{2.5}$ neurotoxicity may damage brain areas implicated in EM, followed by manifestation of depressive symptoms. Our data did not support depressive symptoms as the neuropsychological mediator of accelerated brain aging associated with $PM_{2.5}$ exposure.

1. Introduction

Long-term exposure to particulate air pollutants represents a novel environmental risk factor of accelerated brain aging (The Lancet Neurology, 2018). An increasing number of epidemiologic studies have reported associations between late-life exposure to ambient $PM_{2.5}$ (particulate matter with aerodynamic diameter < 2.5 μm) and increased risks for cognitive decline (Cacciottolo et al., 2017; Tonne et al., 2014; Weuve et al., 2012) and dementia (Cacciottolo et al., 2017; Carey et al., 2018; Chen et al., 2017a, 2017b; Jung et al., 2015; Oudin et al., 2018). Recent longitudinal data also suggest $PM_{2.5}$ exposure may increase the risk of depression in adults (Kim et al., 2016). Biologically plausible mechanisms underlying these neurotoxic effects on brain aging may include particle-induced neuroinflammation, oxidative stress, cerebral vascular damage, and neurodegeneration via direct or indirect pathways. For instance, air pollution exposure can trigger systemic or peripheral inflammation that affects the central nervous system and neurobiology in the brain. Experimental data also showed that airborne engineered particles may translocate to the brain, possibly resulting in direct damage whereby astroglia, brain capillaries, and microglia respond with chronic activation, inflammation, and oxidative stress (Béjot et al., 2018; Block and Calderón-Garcidueñas, 2009).

A large body of literature has documented the close link between depressive symptoms, accelerated brain aging, and dementia (Byers and Yaffe, 2011). Earlier prospective cohort studies found an increased risk for cognitive impairment or dementia associated with prior depression or depressive symptoms in late-life (Barnes et al., 2006, 2012; Ownby et al., 2006; Saczynski et al., 2010; Wilson et al., 2002; Yaffe et al., 1999). More recent longitudinal analyses showed that late-life depressive symptoms are more likely to occur as the prodromal neuropsychiatric manifestation of Alzheimer's disease and related dementias (ADRD; Steffens, 2017). Even after accounting for neuropathological measures of ADRD (Wilson et al., 2014), depressive symptoms are still associated with cognitive decline in the elderly, although the exact directionality of this interrelation remains unclear. The same neural mechanisms may underlie both depressive symptoms and memory impairment (Disner et al., 2011). Depressive symptoms may lead to declines in episodic memory (Zahodne et al., 2014), which tends to decline with normal aging and represent one of the cognitive domains with early decline detectable in preclinical Alzheimer's disease (Gallagher and Koh, 2011). Neuroimaging studies have shown that hippocampal atrophy is elevated in individuals with untreated depression (Sheline et al., 2003), and the hippocampal networks play a key role in episodic memory. In contrast, other studies also found that poor episodic memory may actually lead to increased depressive symptoms over time (Jajodia and Borders, 2011; Vinkers et al., 2004), lending support for the opposite direction of coupling effect. An individual's self-awareness of their episodic memory impairment could lead to a psychological response of increased depression because they know their recollection of particular life experiences may fade or activities they used to enjoy (e.g., reading) become difficult (Ganguli, 2009). They also may experience increased concern about the future and developing dementia.

Extant knowledge of cognitive neurosciences of brain aging therefore raises at least two possibilities about the longitudinal associations linking air pollution exposure with these two phenotypes of brain aging. First, depressive symptoms in late life, if directly affected by air pollution (e.g., $PM_{2.5}$), may act as a neuropsychological mediator of exposure-associated cognitive impairment. Second, air pollution may indirectly lead to increased depressive symptoms via declines in episodic memory associated with exposure. To the best of our knowledge, no studies have examined whether and how air pollution exposure affects the temporal dynamics between depressive symptoms and episodic memory in late life. Understanding these complex associations is important from the public health perspectives, because each of the suggested pathways, if substantiated by empirical data, may point to different targets for primary prevention versus secondary interventions towards improving brain health of older people. Long-term studies with multiple assessments of these two phenotypes are needed to address whether air pollution exposures relate to the bidirectional changes in these two phenotypes of brain aging. In this longitudinal study we examined how exposure to $PM_{2.5}$ affects the temporal dynamics and possibly bidirectional relation between episodic memory and depressive symptoms over time in a community-dwelling cohort of older women assessed annually from 1999 to 2010.

2. Materials and methods

2.1. Study population

This longitudinal cohort study included 2,202 community-dwelling older women (baseline age 66–83 years old) without dementia in 1999 when enrolled in the Women's Health Initiative Study of Cognitive Aging (WHISCA; Resnick et al., 2004), an ancillary study to the Women's Health Initiative Memory Study (WHIMS; Shumaker et al., 1998). The WHIMS (N = 7,479) began in 1996 and was an ancillary study to the Women's Health Initiative (WHI) Clinical Trial of Hormone Therapy (The Women's Health Initiative Study Group, 1998). Between 1999 and 2010, WHISCA participants (n = 2304) completed annual neuropsychological assessments, including measures of depressive symptoms and episodic memory. Excluded from the present study were 102 women with missing data on relevant covariates, resulting in a final sample of 2,202.

2.2. Assessment of depressive symptoms

Depressive symptoms were assessed at baseline and at each annual follow-up (up to 8 assessments) using the 15-item Geriatric Depression Scale (GDS-15) (Yesavage and Sheikh, 1986). The GDS-15 is a reliable and valid instrument, commonly used to assess depressive symptoms in older adults (Mitchell et al., 2010). Scores were standardized on a T-score metric (Mean = 50; SD = 10), based on the baseline GDS-15 mean and standard deviation. Higher scores reflect greater depression symptoms.

2.3. Assessment of verbal episodic memory

Verbal episodic memory was assessed using a modified version of the California Verbal Learning Test (CVLT) (Delis et al., 1987). Participants were read a list of 16-words and instructed to repeat as many of the words from the list as they could. This procedure was repeated two more times. Only three learning trials were administered in WHISCA instead of the standard five trials. Learning/immediate recall ability was measured by the total number of words correctly recalled over the three learning trials (trials 1–3). The participant was then asked to freely recall all of the words that they could from the first list (short-delay free recall). Approximately 20-minutes after the short-delay free recall trial, the participants were asked again to freely recall as many words from the initial list of words (long-delay free recall). Performance on each measure was also standardized on a T-score metric based on the baseline mean and standard deviation.

2.4. Assessment of ambient $PM_{2.5}$

In this study, we focused on $PM_{2.5}$, because its associations with cognitive deficits in both human studies (Clifford et al., 2016) and animal models (Fonken et al., 2011; Ku et al., 2017) were more established than the other regional air pollutants. Briefly, participants residential addresses were prospectively collected at each annual WHISCA assessment and geocoded using standardized procedures (Whitsel et al., 2004). Using the Bayesian Maximum Entropy (BME) method (Christakos, 2000; Christakos et al., 2012), we constructed spatiotemporal models that are a function of space and time to generate individual-level, residence-specific $PM_{2.5}$ estimates. The BME integrates daily observed $PM_{2.5}$ data obtained from nationwide monitoring system of the U.S. Environmental Protection Agency Air Quality System, along with the output of chemical transport models that fully characterize the local emission sources, meteorology, chemicals transformations and transport of pollutants (Reyes et al., 2017). Estimates of daily $PM_{2.5}$ exposures were statistically cross-validated with a 10-fold estimations analysis. The results showed that the BME estimates of $PM_{2.5}$ exposure correlated well with EPA recorded concentrations (average Pearson's $R^2 = 0.70$). The resulting exposure estimates were then aggregated to represent the average $PM_{2.5}$ exposure 3-years preceding each WHISCA assessment. In all analyses $PM_{2.5}$ exposure was scaled to the interquartile range estimated for the baseline WHISCA assessment (4.04 μg/m^3).

2.5. Classification of mild cognitive impairment and dementia

Mild cognitive impairment (MCI) was classified using the Peterson's criteria (Petersen et al., 1994); and all-cause dementia was defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4) (American Psychiatric Association, 1994) criteria. From 1999 to 2008 annual screenings were conducted in 49 WHIMS sites (including satellite clinics) by centrally-trained and regularly-certified interviewers administering the Modified Mini-Mental State (3MS) (Teng and Chui, 1987). Women who screened positive according to age-/education-adjusted 3MS were administered extensive neuropsychological testing (Morris et al., 1989) and behavioral symptoms/function assessment. Beginning in 2008, a validated battery of tests was administered to participants annually by telephone using the Telephone Interview for Cognitive Status-modified (TICSm) (Rapp et al., 2012). For women who screened positive during telephone interviews (i.e., TICSm < 31), the standardized Dementia Questionnaire (Kawas et al., 1994) was administered by telephone to knowledgeable informants to assess the participant's dementia-related cognitive and behavioral changes and relevant medical history. All relevant assessments and information were submitted to a central adjudication committee for final classification, based on the DSM-IV. Data on MCI and dementia status were available up to December 2015.

2.6. Relevant covariate data

A structured questionnaire was administered at WHIMS baseline to gather information on the time independent covariates of demographics (age, race/ethnicity), geographic region of residence (Northeast, South, Midwest, and West), socioeconomic status (education; family income), lifestyle factors (smoking; alcohol use; physical activities), and clinical characteristics, including self-reported postmenopausal hormone treatment ever, history of cardiovascular disease (including previous coronary heart, stroke, or transient ischemic attack), hypertension (defined as elevated blood pressure or use of antihypertensive medication), and diabetes mellitus (defined as physician diagnosis plus oral medications, or insulin therapy). Good reliability and validity of the self-reported medical histories and the physical measures have been previously documented (Heckbert et al., 2004).

2.7. Statistical analysis

Structural equation models (SEMs) for latent change scores (LCSs) (McArdle, 2001) were constructed to examine the complex associations between $PM_{2.5}$ exposure and temporal changes in the two inter-related neuropsychological processes (episodic memory; depressive symptoms) over the WHISCA study period. The SEMs with LCS are advantageous because they allows for the modeling of dynamic change between two variables from one time point to the next. The LCS approach estimates dynamic annual change by combining features of latent growth curve models, which determine the systematic change over time (Meredith and Tisak, 1990), and autoregressive cross-lagged regressions, which estimate the proportional change over time (Selig and Little, 2012). Because women were assessed annually, we examined change over one-year intervals with the WHISCA inception time denoted as the baseline. The supplemental methods section provides a more detailed description of our analytic approaches.

2.7.1. Univariate latent change score models

To examine the association between $PM_{2.5}$ exposure and annual change in each neuropsychological process we first constructed univariate LCS models separately for episodic memory and depressive symptoms (see Fig. 1 for a depiction of the full univariate model). For episodic memory, individual-specific performance at baseline ($int_{em,i}$) was estimated along with between-individual variability in initial performance ($\sigma^2 int_{em}$). The equation to estimate annual individual-specific change in episodic memory for individual i at timepoint t was written as:

$$\Delta em_{i,t} = \alpha_{em} * slp_{em,i} + \beta_{em} * lem_{i,t} + \gamma_{PM2.5on\Delta em} * PM2.5_{i,t}. \cdots, \quad (1)$$

where $\Delta em_{i,t}$ denotes the estimated individual-specific annual change in episodic memory.

Individual-specific estimate of systematic linear change is represented by the $slp_{em,I}$ parameter. The effect estimate, denoted by α_{em}, linking the latent slope factor ($slp_{em,i}$) to annual change in episodic memory ($\Delta em_{i,t}$), was fixed to equal 1.0. Proportional change, denoted

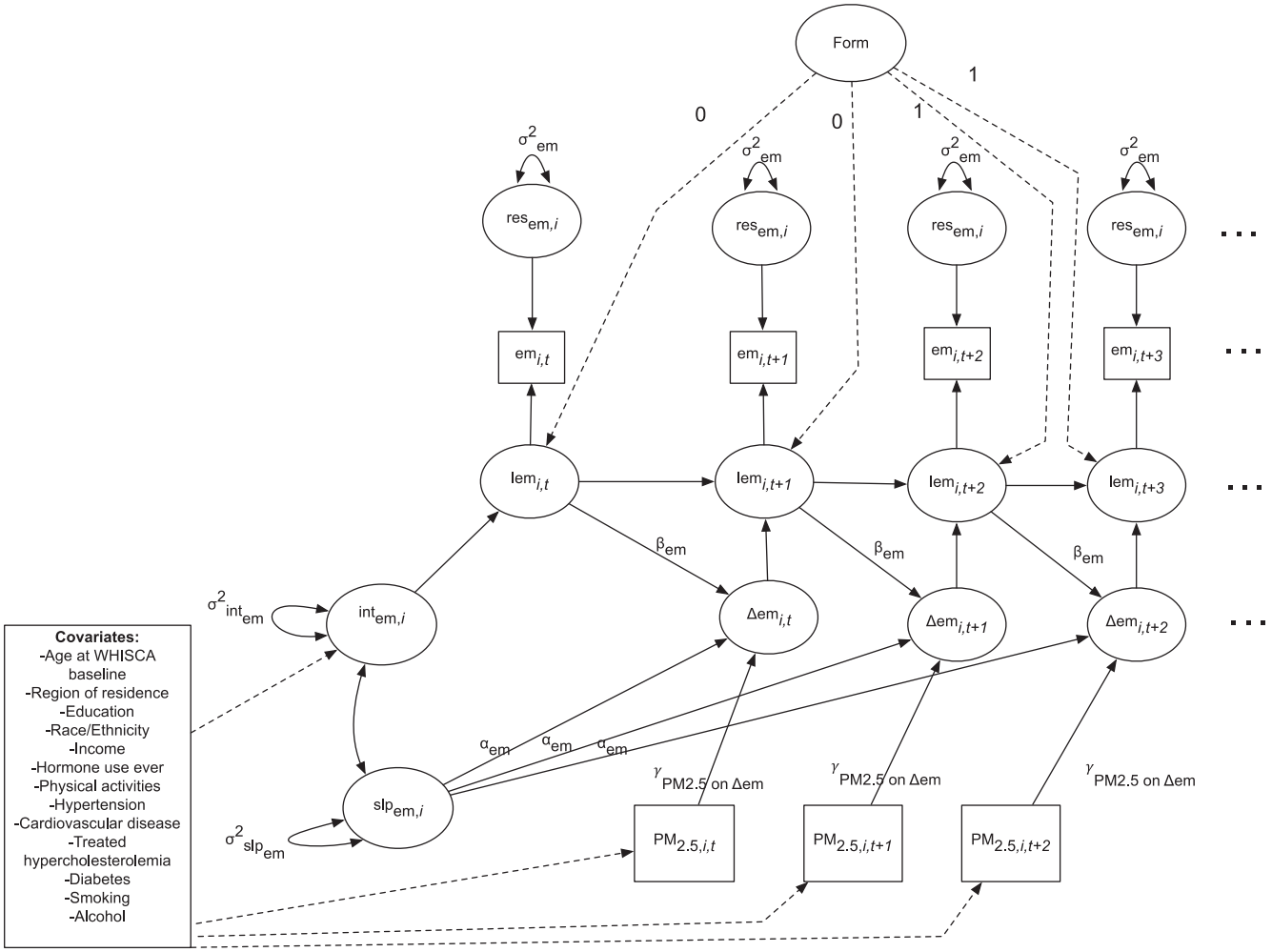
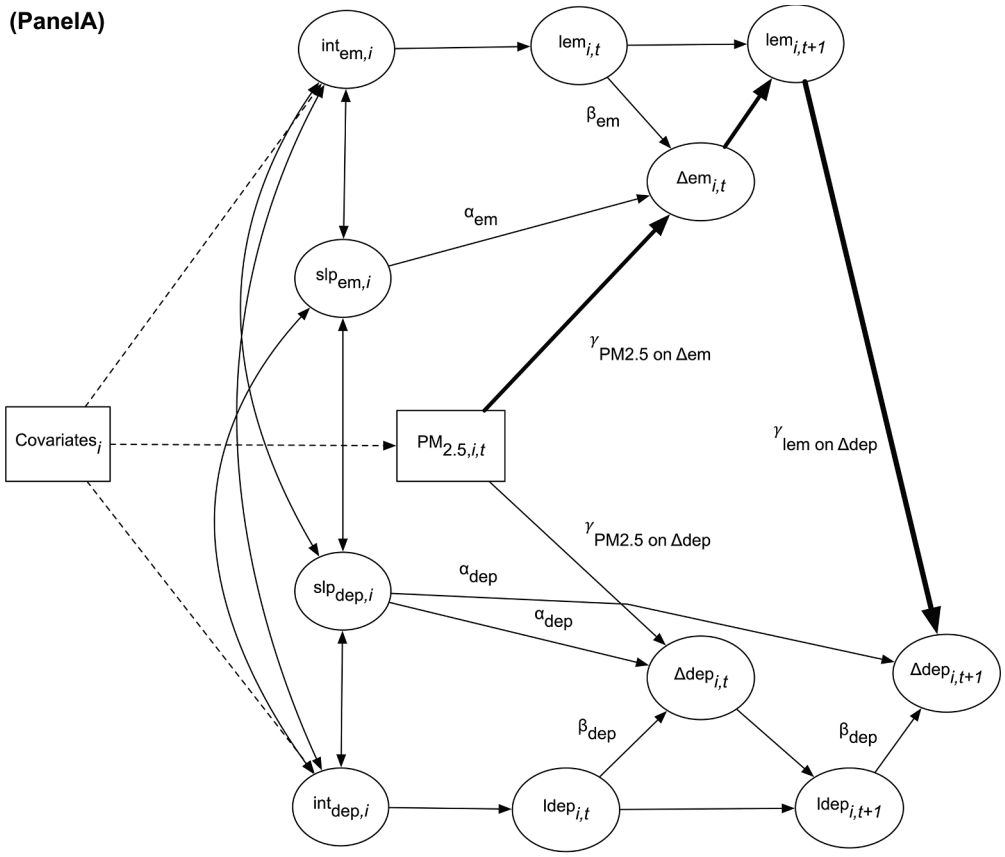


Fig. 1. Simplified depiction of the univariate latent change score structural equation model estimating the effect of preceding 3-year average $PM_{2.5}$ exposure on change in episodic memory performance. $Int_{em,i}$ = estimate of episodic memory (em) as measured by CVLT performance at WHISCA baseline for individual i. $slp_{em,i}$ = estimate of systematic linear change in episodic memory (em) for individual I as measured by CVLT performance. $PM_{2.5,i,t}$ = estimate of average daily particulate matter exposure for individual i, for the three-years prior to WHISCA assessment at time t. $lem_{i,t}$ = estimate of latent episodic memory (em) for individual i at time t as measured by CVLT performance. $\Delta em_{i,t}$ = estimate of latent change in episodic memory (em) for individual i at time t as measured by CVLT performance. Form = estimate of latent effect of the CVLT form. α_{em} = the path coefficient from estimate of systematic linear change to change in episodic memory latent variable. This coefficient was constrained to equal 1.0 in all models. β_{em} = the effect of proportional change in episodic memory. $\gamma_{PM2.5\ on\ \Delta em}$ = the effect of $PM_{2.5}$ exposure on change in episodic memory. $\sigma^2 int_{em}$ = the variance in individual specific estimates of CVLT performance at the WHISCA baseline. $\sigma^2 slp_{em}$ = the variance in individual specific estimates of linear change in CVLT performance. $res_{em,i}$ = the residual of CVLT performance for individual i. σ^2_{em} = the unexplained residual variance in CVLT performance. Bolded pathways represent the indirect effects estimated in each model. Only the baseline assessment ($lem_{i,t=0}$) is regressed onto the intercept factor ($INT_{em,i}$).

by β_{em}, is a fixed-effect estimate that quantifies the extent to which change from one time to the next is dependent on episodic memory performance at the previous year (denoted by $lem_{i,t}$). The term $\gamma_{PM2.5\ on\ \Delta em}$ denotes the effect of time-varying $PM_{2.5}$ exposure ($PM_{2.5,i,t}$) on change in episodic memory performance. Error variance in CVLT performance ($res_{em,i}$) was constrained to be equal across the study period. To account for the form effect due to the use of an alternative CVLT form at the second and third follow-up assessment (Resnick et al., 2009), we added a latent factor indicating the form effect, with the corresponding path set to 0 for the standard CVLT or 1 for the alternative form. To estimate the $PM_{2.5}$ exposure effect on each measure of episodic memory in univariate SEM, we adjusted for the following covariates: age at the WHISCA baseline, race/ethnicity, geographic region of residence, education, household income, lifestyle factors (smoking; alcohol use; physical activities), and clinical characteristics (any prior hormone use ever, hypercholesterolemia, hypertension, diabetes, and history of cardiovascular disease). Each measure of the CVLT (trials 1–3, short-delay free recall, long-delay free recall) was modeled separately. Analogous equations can be written for univariate SEM to estimate the $PM_{2.5}$ exposure effect on change of depressive symptoms. All covariates were assessed at the WHIMS baseline with the exception of age which was the baseline WHISCA age.



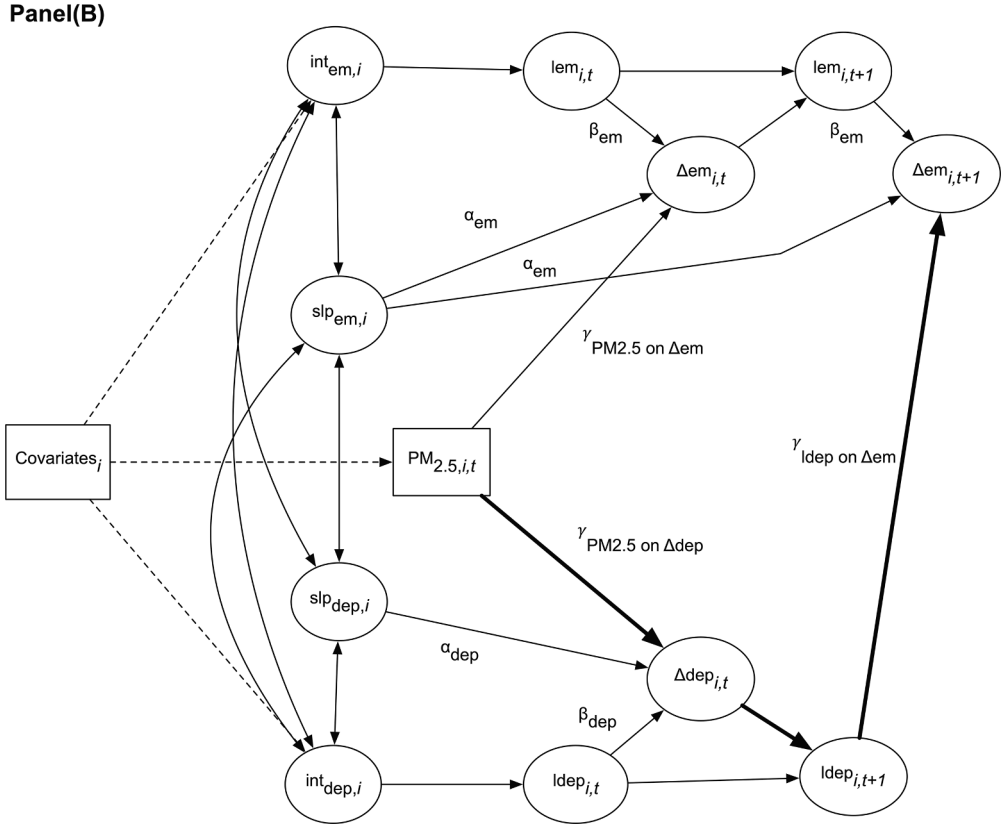


Fig. 2. (A). Simplified depiction of the bivariate latent score structural equation model estimating the indirect effect of $PM_{2.5}$ exposure on depressive symptoms. **(B).** Simplified depiction of the bivariate latent change score structural equation model estimating the indirect effect of $PM_{2.5}$ exposure on change in episodic memory performance. $Int_{em,i}$ = estimate of episodic memory (em) at WHISCA baseline for individual i as measured by CVLT performance. $slp_{em,i}$ = estimate of systematic linear change in episodic memory (em) for individual i as measured by CVLT performance. $PM_{2.5},_{i,t}$ = estimate of average daily particulate matter exposure for individual i, for the three-years prior to WHISCA assessment at time t. $lem_{i,t}$ = estimate of latent episodic memory performance for individual i at time t as measured by CVLT performance. $ldep_{i,t}$ = estimate of latent depressive symptoms for individual i at time t as measured by the GDS-15. $\Delta em_{i,t}$ = estimate of latent change in episodic memory (em) for individual i at time t as measured by CVLT performance. $\Delta dep_{i,t}$ = estimate of latent change in depressive symptoms for individual i at time t as measured by the GDS-15. Bolded pathways represent the indirect effects estimated in each model. Note: The full diagram is presented in Supplemental Materials, Figs. S2 and S3. Raw scores, residual variances, change parameter labels were omitted to simplify the diagram. One sided arrows without labels in the diagram are fixed to equal 1.0. Covariates include the following variables: age at WHISCA baseline, region of residence, education, race/ethnicity, income, hormone use ever, high cholesterol, diabetes, smoking, alcohol use. Only the baseline assessments ($lem_{i,t=0}$ or $ldep_{i,t=0}$) are regressed onto the intercept factors ($INT_{em,I}$ or $INT_{dep,i,t}$).

2.7.2. Bivariate latent change score models.

Bivariate LCS models allow us to examine how the level of one variable was associated with subsequent changes in a second variable. We employed bivariate LCS models to address two questions: (1) whether there was an indirect association between $PM_{2.5}$ exposure and changes in depressive symptoms that may be mediated by episodic memory decline; or (2) whether there was an indirect $PM_{2.5}$ exposure effect on declines in episodic memory mediated through increases in depressive symptoms associated with exposure.

Fig. 2 depicts a simplified depiction of the two bivariate hypotheses (Figs. S1 and S2 in Supplemental Materials present the full model estimated). These bivariate SEMs followed similar modeling structures as

Table 1
Comparison of estimated $PM_{2.5}$ exposure by baseline cohort characteristics (N = 2,202).

		Distribution of time-varying 3-year average$PM_{2.5}$[a]					
Population characteristics	N	Mean	SD	25th	Median	75th	p[b]
Overall	2202	12.63	2.60	10.74	12.07	14.23	
Region of residence							< 0.001
Northeast	462	12.25	1.36	11.14	12.20	13.27	
South	319	12.23	1.77	10.56	11.87	14.04	
Midwest	856	12.91	2.44	10.68	12.38	15.39	
West	565	12.75	3.70	10.46	11.70	14.32	
Race/ethnicity							< 0.001
African-American	136	15.05	2.38	13.58	14.69	16.38	
Hispanic white	26	13.29	2.89	11.11	12.29	14.36	
Non-hispanic white	1983	12.43	2.49	10.66	11.87	13.94	
Other or missing	57	13.56	3.28	11.38	12.84	15.52	
Education							0.027
Less than high school	107	12.67	2.58	10.89	11.96	14.31	
High school	469	12.34	2.28	10.63	11.75	13.63	
More than high school	1626	12.71	2.68	10.76	12.12	14.32	
Income (in USD)							0.004
< 9,999	483	12.38	2.56	10.61	11.73	14.21	
10,000–34,999	678	12.57	2.54	10.67	12.09	14.18	
35,000–49,999	469	12.59	2.56	10.68	11.96	14.01	
50,000–74,999	308	12.88	2.69	11.05	12.28	14.20	
75,000 or more	194	13.21	2.79	10.96	12.61	15.11	
Don't know	70	12.53	2.47	10.75	12.20	13.87	
Lifestyle							
Smoking status							0.276
Never smoked	1214	12.66	2.62	10.73	12.04	14.31	
Past smoker	862	12.65	2.55	10.82	12.16	14.15	
Current smoker	126	12.27	2.70	10.46	11.51	14.09	
Alcohol use							0.031
Non-drinker	271	13.07	2.75	10.66	12.50	15.07	
Past drinker	400	12.61	2.56	10.73	12.03	14.38	
Less than 1 drink per day	1263	12.55	2.56	10.73	12.00	14.01	
More than 1 drink per day	268	12.61	2.64	10.89	11.97	14.15	
Moderate or strenuous activities ≥ 20 min							0.294
No activity	1260	12.67	2.66	10.73	12.15	14.39	
Some activity	116	12.77	2.43	10.83	12.07	14.61	
2–4 episodes/week	446	12.68	2.53	10.82	12.04	14.23	
≥4 episodes/week	380	12.40	2.52	10.66	11.83	13.66	
Physical Health							
Hypertension							0.321
No	1385	12.59	2.59	10.69	12.01	14.22	
Yes	817	12.70	2.60	10.78	12.16	14.26	
Treated hypercholesterolemia							0.267
No	1817	12.60	2.60	10.73	12.06	14.22	
Yes	385	12.76	2.57	10.82	12.16	14.27	
Diabetes mellitus							0.593
No	2078	12.64	2.61	10.73	12.07	14.26	
Yes	124	12.51	2.44	10.87	12.12	13.60	
Cardiovascular disease							0.166
No	1847	12.60	2.59	10.73	12.03	14.19	
Yes	355	12.81	2.66	10.80	12.33	14.75	
Prior hormone therapy							0.500
No	1189	12.66	2.52	10.73	12.13	14.20	
Yes	1013	12.59	2.68	10.76	12.00	14.28	

[a] $PM_{2.5}$ represents the distribution of the individual-level summary of all time-varying 3-year exposures aggregated from the daily exposure levels estimated at each residential location using the spatiotemporal model.

[b] p values estimated from ANOVA F-tests or t-tests.

used in our previous work studying the directionality of the association between symptoms of anxiety and depression with cognitive performance (Petkus et al., 2019). In the first bivariate model the equation to estimate individual-specific change in depressive symptoms was written as:

$$\Delta dep_{i,t} = \alpha_{dep} * slp_{dep,i} + \beta_{dep} * ldep_{i,t} + \gamma_{PM2.5on\Delta dep} * PM2.5_{i,t} + \gamma_{lemon\Delta dep} * lem_{i,t}. \quad (2)$$

In bivariate models, the change in depressive symptoms ($\Delta dep_{i,t}$) was a function of linear systematic change ($slp_{dep,i}$), proportional change (β_{dep}), the effect of time-varying $PM_{2.5}$ exposure ($\gamma_{PM2.5\ on\ \Delta dem}$), and the effect of episodic memory performance on subsequent changes in depressive symptoms ($\gamma_{lem\ on\ \Delta dep}$).

Following SEM path tracing conventions, the specific indirect effect of $PM_{2.5}$ exposure on changes in depressive symptoms was estimated by multiplying the two estimated coupling parameters as depicted in the following equation:

$$Indirect_{PM2.5\,on\,\Delta dep} = \gamma_{PM2.5\,on\,\Delta em} * \gamma_{lem\backslash;\,on\,\Delta dep} \cdots\cdots\cdots \quad (3)$$

The significance of the indirect effect was estimated by bootstrap calculation of asymmetric confidence intervals (MacKinnon et al., 2002). The significant indirect effect was supported if the confidence interval did not include zero. All bivariate LCS models were adjusted for the same set of covariates as described in the univariate LCS models. Analogous equations can be written to examine whether there was an indirect effect of $PM_{2.5}$ exposure on changes in episodic memory that was mediated by changes in depressive symptoms.

We carried out additional analyses to evaluate the robustness of our findings. To explore whether any observed associations with $PM_{2.5}$ could be explained by the underlying risk for clinically significant neurocognitive disorders, we repeated the analyses after excluding individuals who developed incident dementia or mild cognitive impairment by 2015. When examining the indirect effect of $PM_{2.5}$ exposure on changes in CVLT Trials 1–3 performance, the SEMs would not converge after excluding individuals with either incident dementia or mild cognitive impairment by 2015. For this model we only examined individuals who had not developed dementia or mild cognitive impairment by the end of WHISCA in 2010. All LCS models were conducted using the SEM program MPLUS version 8 (Muthén and Muthén, 1998–2018) which was run via the MPLUS Automation package (Hallquist and Wiley, 2018) in R (Team, 2018).

3. Results

On average, participants completed near six (mean ± S.D. = 5.68 ± 2.02) assessments of episodic memory and depressive symptoms. Descriptive statistics for CVLT measures, GDS-15, and $PM_{2.5}$ exposure are presented in supplemental Tables S1 and S5. Bivariate correlations between respective CVLT measure, GDS-15, and $PM_{2.5}$ exposure are presented in supplemental Figs. S3–S5. Table 1 compares the distribution of the 3-year average $PM_{2.5}$ exposure prior to the WHISCA assessment by population characteristics. Participants with higher levels of $PM_{2.5}$ exposure estimates averaged over follow-up were more likely to be racial/ethnic minorities (African-American or Hispanic White), residing in the Midwest, a non-drinker or past-drinker, participating in some physical activity or 2–4 episodes/week, and reporting higher household incomes (≥$75,000).

Table 2
Univariate structural equation models examining the associations between 3-year average $PM_{2.5}$ exposure and change in verbal episodic memory and depressive symptoms (N = 2,202).

Outcome	Univariate Model 1 Estimates[a] of $PM_{2.5}$ effect on change	
	$\gamma_{PM2.5\ on\ \Delta em}$ or $\gamma_{PM2.5\ on\ \Delta dep}$	95% confidence interval
CVLT measures		
Trials 1–3	**−1.48**	**(−2.10, −0.85)**
Short-delay free recall	**−1.43**	**(−2.12, −0.73)**
Long-delay free recall	**−1.11**	**(−1.79, −0.42)**
Depressive symptoms		
GDS-15	0.12	(−0.51, 0.74)

Abbreviations: CVLT = California Verbal Learning Test; GDS-15 = 15 item Geriatric Depression Scale.
Estimates bolded if statistically significant at $p < 0.05$.
[a] All estimates derived from the latent change score structural equation model (SEM) as depicted in Fig. 1b, with $PM_{2.5}$ scaled by interquartile range (4.04 μg/m^3). In all models, the effect of time-varying $PM_{2.5}$ exposure on initial CVLT performance, and on initial GDS-15 were adjusted for age at WHISCA baseline, race/ethnicity, geographic region of residence, education, household income, lifestyle factors (smoking, alcohol use, physical activities) and clinical characteristics (use of hormone treatment; hypercholesterolemia, hypertension, diabetes, and history of cardiovascular disease).

All univariate LCS models fit data acceptably, with Root Mean Square Residual Approximations (RMSEA) meeting suggested cutoffs (Byrne, 2005) for a very close model fit (RMSEA's ranged from 0.048 to 0.055). See supplemental Table S6 for all model fit indices and supplemental Table S7 for growth parameter estimates from the univariate models. Supplemental Fig. S6 presents the estimated mean score on each outcome with 20 randomly selected individual trajectories to demonstrate variability around the average trajectory. 3-year average $PM_{2.5}$ exposure was negatively associated with change in all three CVLT measures, indicating the episodic memory declines were accelerated by increased exposures before each assessment (see Table 2 for parameter estimates). Although $PM_{2.5}$ exposure was associated with increasing depressive symptoms, this association was not statistically significant.

Fig. 3 depicts estimated trajectories of episodic memory or depressive symptoms associated with either relatively low (25th percentile), average (median), or relatively high (75th percentile) ambient $PM_{2.5}$ exposure for each WHISCA assessment, among women with the average levels of episodic memory performance or depressive symptoms at WHISCA baseline.

The results of bivariate LCS models examining the indirect effect of $PM_{2.5}$ on changes in depressive symptoms are presented in Table 3. All models exhibited good model fit (RMSEA < 0.05). Consistent with univariate models, increased $PM_{2.5}$ was associated with greater declines across all three CVLT measures. Women with worse performance on all three CVLT measures tended to have increasing depressive symptoms over the subsequent year. Significant indirect effects of $PM_{2.5}$ on increasing depressive symptoms were present across all three CVLT measures. These indirect effects suggest that $PM_{2.5}$ exposure was associated with greater declines in episodic memory which were then associated with increasing depressive symptoms over time. The direct

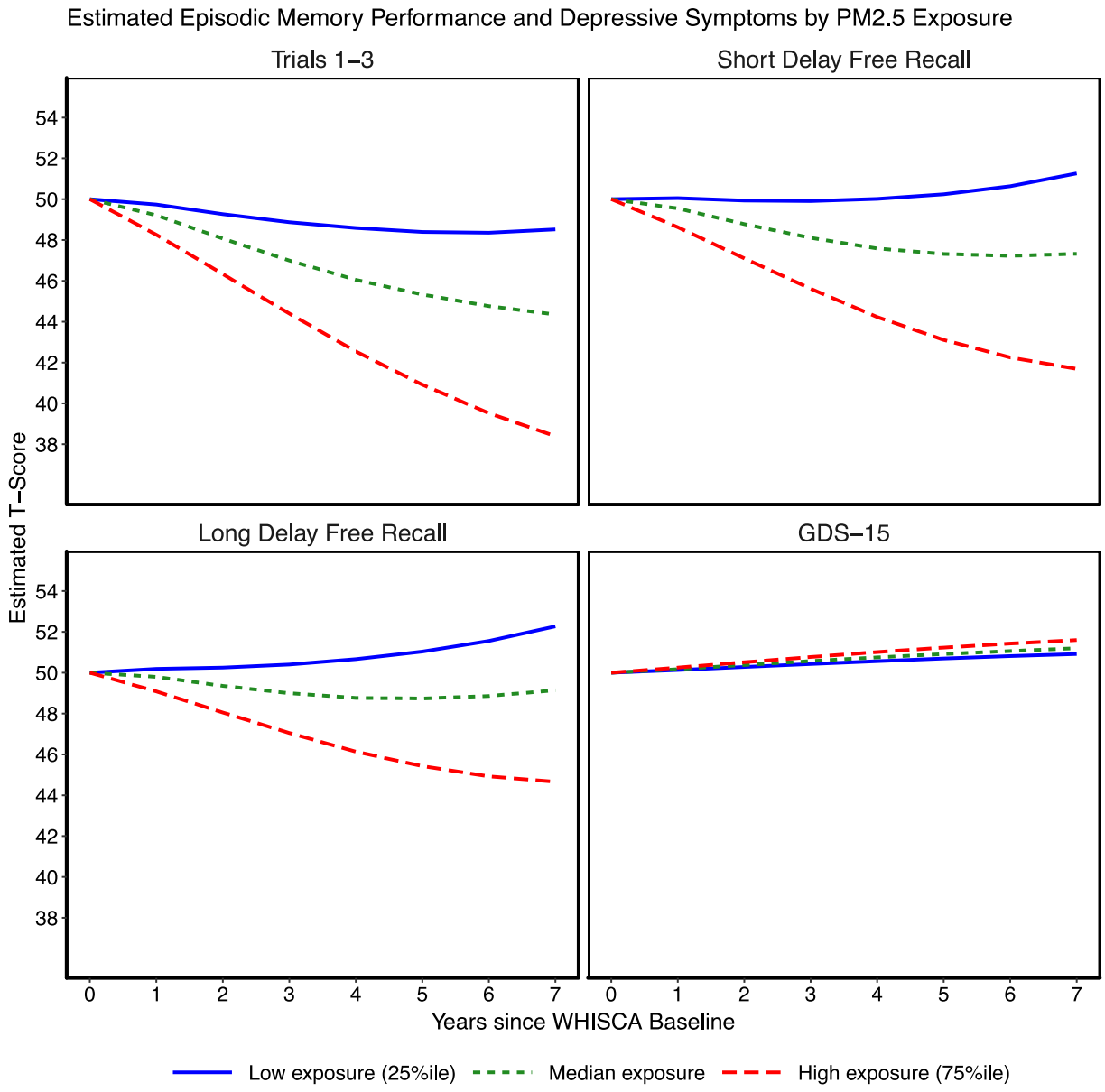


Fig. 3. Graphs of the estimated performance on the California Verbal Learning Test measures and depressive symptoms by low (25th percentile), median, and high (75th percentile) average daily $PM_{2.5}$ exposure.

effect of $PM_{2.5}$ exposure on changes in depressive symptoms was not significant.

Results of bivariate LCS models examining the indirect effect of $PM_{2.5}$ exposure on changes in episodic memory are presented in Table 4. All models exhibited acceptable model fit (RMSEA < 0.05). There were statistically significant direct effects of $PM_{2.5}$ exposure on declines in episodic memory, but no evidence supporting indirect effects of $PM_{2.5}$ exposure. $PM_{2.5}$ exposure was not directly associated with change in depressive symptoms, and depressive symptoms were not associated with subsequent changes in episodic memory.

Results from additional analyses excluding women with incident dementia by 2015 are similar (Supplemental Materials, Tables S8–S10). Although removing the incident dementia cases attenuated the parameter estimates of the $PM_{2.5}$ effects on changes in depressive symptoms, both the estimates of total effect (Table S8) and direct effect (Table S9) remained statistically non-significant. Additional analyses restricted to women without mild cognitive impairment or dementia by 2015 also revealed very similar results as the sensitivity analyses excluding women with incident dementia by 2015 (Supplemental Materials, Tables S11–S13).

Table 3
Bivariate latent change score structural equation models examining the direct effect of $PM_{2.5}$ exposure on changes in depressive symptoms and the indirect effects mediated by episodic memory declines (N = 2,202).

	CVLT measures		
	Trials 1–3 β (95% CI)	Short delay Free recall β (95% CI)	Long delay Free recall β (95% CI)
Estimates[a] of direct effect			
Effect of $PM_{2.5}$ on annual change in depressive ($\gamma_{PM2.5\ on\ \Delta dep}$)	0.07 (−0.53, 0.67)	0.07 (−0.53, 0.67)	0.01 (−0.58, 0.61)
Estimates[a] of indirect effect			
Effects of $PM_{2.5}$ on annual changes in CVLT variable ($\gamma_{PM2.5\ on\ \Delta em}$)	**−1.44** **(−2.08, −0.81)**	**−1.42** **(−2.11, −0.72)**	**−0.99** **(−1.68, −0.29)**
Effects of CVLT performance on annual change in depressive symptoms ($\gamma_{Lem\ on\ \Delta dep}$)	**−0.05** **(−0.10, −0.01)**	**−0.07** **(−0.11, −0.02)**	**−0.08** **(−0.13, −0.03)**
Indirect effect of $PM_{2.5}$ on annual change in depressive symptoms	**0.08** **(0.00, 0.19)**	**0.10** **(0.03, 0.17)**	**0.08** **(0.01, 0.15)**

Abbreviations: CVLT = California Verbal Learning Test.
Estimates bolded if statistically significant at $p < 0.05$.
[a] All estimates derived from the bivariate structural equation models (SEM) as depicted in Fig. 2 panel B, with $PM_{2.5}$ scaled by baseline interquartile range (4.04 μg/m^3). In all models, the initial level of $PM_{2.5}$, CVLT performance, and GDS-15 were adjusted for initial age, race/ethnicity, geographic region of residence, education, household income, lifestyle factors (smoking, alcohol use, physical activities), clinical characteristics (use of hormone treatment; hypercholesterolemia, hypertension, diabetes, and history of cardiovascular disease).

Table 4
Bivariate latent change score structural equation models examining the direct effect of $PM_{2.5}$ exposure on changes in episodic memory and the indirect effect mediated by depressive symptoms (N = 2,202).

	CVLT Measures		
	Trials 1–3 β (95% CI)	Short delay Free recall β (95% CI)	Long delay Free recall β (95% CI)
Estimates[a] of direct effect			
Effect of $PM_{2.5}$ on annual change in episodic memory ($\gamma_{PM2.5\ on\ \Delta em}$)	**−1.26** **(−1.90, −0.63)**	**−1.45** **(−2.45, −0.75)**	**−1.00** **(−1.70, −0.31)**
Estimates[a] of indirect effect			
Effects of $PM_{2.5}$ on annual changes in GDS-15 ($\gamma_{PM2.5\ on\ \Delta dep}$)	0.13 (−0.48, 0.64)	0.09 (−0.52, 0.70)	0.11 (−0.51, 0.72)
Effects of GDS-15 performance on annual change in episodic memory ($\gamma_{Ldep\ on\ \Delta em}$)	−0.01 (−0.07, 0.05)	0.04 (−0.01, 0.08)	0.02 (−0.02, 0.06)
Indirect effect of $PM_{2.5}$ on annual change in CVLT	− < 0.01 (−0.01, 0.01)	< 0.01 (−0.02, 0.03)	< 0.01 (−0.01, 0.02)

Abbreviations: CVLT = California Verbal Learning Test.
Estimates bolded if statistically significant at $p < 0.05$.
[a] All estimates derived from the bivariate structural equation models (SEM) as depicted in Fig. 2 panel B, with $PM_{2.5}$ scaled by baseline interquartile range (4.04 μg/m^3). In all models, the effect of time-varying $PM_{2.5}$ exposure on initial CVLT performance, and on initial GDS-15 were adjusted for initial age, race/ethnicity, geographic region of residence, education, household income, lifestyle factors (smoking, alcohol use, physical activities), clinical characteristics (use of hormone treatment; hypercholesterolemia, hypertension, diabetes, and history of cardiovascular disease).

4. Discussion

This is the first study to examine whether exposure to ambient air pollutants in late life affects the temporal dynamics and bidirectional relation of changes in depressive symptoms and episodic memory. In a geographically-diverse cohort of older women, long-term exposure to ambient $PM_{2.5}$ estimated at the residential locations was associated with accelerated declines in episodic memory over the 8-year study period. We did not find any significant direct association between $PM_{2.5}$ exposure and annual change in depressive symptoms. However, in bivariate models, we observed a significant indirect effect of $PM_{2.5}$ exposure on increasing depressive symptoms via declines in episodic memory. Our data did not support depressive symptoms as a neuropsychological mediator of brain aging associated with $PM_{2.5}$ exposure. These same associations were observed in older women who remained cognitively-intact during the follow-up, suggesting that neurocognitive disorders including dementia and its underlying neuropathological processes could not fully explain our findings. Taken together these results suggest that $PM_{2.5}$ exposure may exert a neurotoxic effect on brain areas implicated in episodic memory followed by a neuropsychological manifestation of depressive symptoms.

Our study demonstrates supporting evidence for accelerated decline in episodic memory associated with long-term $PM_{2.5}$ exposure. In univariate SEMs, higher $PM_{2.5}$ exposure was associated with greater annual declines in verbal learning as well as in short- and long-delay free recalls. This observation expanded the earlier report of $PM_{2.5}$-associated memory decline in a 5-year follow-up study which included only two repeated measures of verbal learning without assessing long-delay recall (Tonne et al., 2014). In our study, the putative adverse $PM_{2.5}$ effect sustained in the bivariate SEMs (Table 3), and the observed declines in episodic memory were further associated with subsequent increases in depressive symptoms, resulting in statistically significant indirect effects of $PM_{2.5}$ on increasing depressive symptoms (Table 3). It is noteworthy that the observed indirect association between $PM_{2.5}$

exposure and change in depressive symptoms was only modestly diminished after excluding incident cases of dementia or mild cognitive impairment. These findings lead to two possible interpretations. First, long-term air pollution exposure may accelerate declines in episodic memory, while increased depressive symptoms may be indicative of emotional reaction to self-awareness of cognitive declines (Ganguli, 2009) in the affected individuals or the psychological consequence, such as social and behavioral changes (e.g., changes in friendships and family relationships, ability to cope with stress, or engagement in positively reinforcing activities) associated with cognitive deficits. Second, the observed indirect effect on depressive symptoms suggests that $PM_{2.5}$ neurotoxicity may perpetuate some underlying brain aging processes, causing damage to brain regions and neural networks essential to maintain episodic memory and emotional health in late life.

Based on the bivariate LCS models, we found no statistically significant indirect effect of $PM_{2.5}$ on episodic memory decline mediated by changes in depressive symptoms (Table 4), while the direct association between exposure and episodic memory declines remained. These findings did not support the hypothesis that late-life depressive symptoms act as a neuropsychological mediator linking $PM_{2.5}$ exposure with accelerated cognitive decline. To the best of our knowledge, only one study (Tallon et al., 2017) attempted to test this hypothesis and suggested the possible mediation role of depressive symptoms. However, limited by only two repeated measures, Tallon et al., were unable to examine the change in either the hypothesized mediator or the cognitive outcome, and the direct exposure effect defined in their SEM was cross-sectional in nature. In the present study, we found no statistically significant evidence that the annual change in GDS-15 in older women was directly affected by $PM_{2.5}$ exposure, as shown in both univariate (Table 2) and bivariate SEMs (Table 4) adjusting for multiple potential confounders. Two previous studies, one conducted on community dwelling populations residing in Boston (aged ≥ 65 years) (Wang et al., 2014) and the other across the U.S. (aged 57–85 years) (Pun et al., 2017), reported null associations between long-term $PM_{2.5}$ exposure and change in depressive symptoms across two assessments. Collectively, these epidemiological data suggest that the neurotoxic effects of late-life $PM_{2.5}$ exposure on brain aging may not be primarily operated by aggravating the longitudinal change in depressive symptoms.

Our study results, as well as the growing literature on air pollution neurotoxicology, point to several important directions for future research in environmental neurosciences of brain aging associated with exposure to ambient air particles. Early decline of episodic memory is detectable in preclinical Alzheimer's disease. Episodic memory also declines with normal aging, related to volumetric reductions of the hippocampus and other medial temporal lobe structures (Dickerson and Eichenbaum, 2010). The indirect effects on increased depressive symptoms imply that part of the observed $PM_{2.5}$ neurotoxicity on episodic memory decline may also confer neural dysfunction in the fronto-striatal and limbic systems that is well-documented in late-life depression (Alexopoulos, 2002). Although animal studies (Fonken et al., 2011; Liu et al., 2018) suggested $PM_{2.5}$ exposure may alter brain structures including hippocampal subfields, extant cross-sectional data with regional brain MRI measures (Chen et al., 2015; Power et al., 2018; Wilker et al., 2015) did not show associations between $PM_{2.5}$ and hippocampal volumes. Longitudinal brain MRI studies are needed to examine whether air pollution neurotoxicity contributes to brain atrophy in hippocampus and other medial temporal lobe structures. In a whole-brain MRI analysis of using voxel-based morphometry of a subset of WHIMS participants, higher $PM_{2.5}$ exposure was associated with smaller volumes of prefrontal cortex, but not with hippocampal volumes (Casanova et al., 2016). Interestingly, we also found older women with elevated depressive symptoms had smaller gray matter volumes in frontal lobe subregions, but not in hippocampus or other medial temporal lobe structures (Goveas et al., 2011). These observations indicate the need to further examine the role of prefrontal cortex and related networks in mediating the episodic memory decline associated with $PM_{2.5}$ exposure. Also, an increasing number of studies suggest that white matter architecture may represent a novel target of airborne particle-induced neurotoxicity in laboratory animals (Allen et al., 2014; Woodward et al., 2017) and humans (Chenet al., 2015; Peterson et al., 2015). White matter abnormalities play an important role in late-life depression even in the absence of changes in gray matter (Sexton et al., 2012). In the above-mentioned whole-brain MRI analysis (Casanova et al., 2016), increased $PM_{2.5}$ exposure was also associated with smaller volumes of subcortical white matter including areas involved in salience network, and aberrant processing of this network has been linked to cortical dysfunction and apathy commonly seen in late-life depression (Uddin, 2015). Future research with diffusion tensor imaging can help elucidate whether $PM_{2.5}$ exposures disrupt white matter tracts in the fronto-striatal-limbic circuitry. Future studies also need to examine whether neurotoxic effects of ambient air particles compromise the functional connectivity, including the possible changes in resting-state (Fjell et al., 2015; Fjell et al., 2016), in the neural networks that modulate positive emotions and reward responses in late life. The inter-relation between memory decline and depressive symptoms has been overlooked in air pollution neurotoxicology. Carefully-designed experiments with late-life inhalation exposure and repeated multimodal behavioral assessments are much needed to clarify the temporal dynamics as well as the inter-relation of memory loss and depressive-like behaviors. Such animal models can also shed important lights on underlying mechanisms, no matter through common pathways or sequential neuropathological events that are driving these different phenotypes of brain aging in response to air pollution.

We recognize several limitations of our study. First, although the $PM_{2.5}$ spatiotemporal model was statistically cross-validated (average Pearson's $R^2 = 0.70$), (Cacciottolo et al., 2017; Reyes et al., 2017) the resulting exposure estimates were still subject to measurement errors. However, such estimation errors are likely non-differential and tend to attenuate the observed associations. Second, the present study focused on regional $PM_{2.5}$ only, so 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. Third, we examined only the inter-relation of neuropsychological processes related to emotion health and brain aging. Although our data did not support the hypothesis that depressive symptoms are a neuropsychological mediator of brain aging associated with $PM_{2.5}$ exposure, we could not rule out the possibility that increased $PM_{2.5}$ exposure may interfere with the regulation of emotions (e.g., emotional arousal) (Dolcos et al., 2014) and decline in other cognitive domains (e.g., working memory) in vulnerable populations. Fourth, although our analyses showed that the $PM_{2.5}$-associated episodic memory primarily resulted from the direct exposure effects (Tables 3 and 4), data on late-life depression were only collected on symptoms in this community-based sample. Therefore, we could not rule out the possibility that late-onset major depression, if affected by air pollution exposure and sustained over time, may still contribute to the progression of brain aging or ADRD with accelerated decline in episodic memory. Fifth, our modeling approach was based on the assumption that each neuropsychological process is homogeneous, which disregards the potential heterogeneities present in the longitudinal trajectories of brain aging phenotypes. Sixth, the bivariate SEM for LCS is not equipped to examine the possible exposure effects on concurrent neuropsychological processes of brain aging, including episodic memory decline and depressive symptoms that correlated with each other. However, the observed lack of direct exposure effect on change in depressive symptoms does not provide a strong support for this alternative hypothesis. Lastly, our findings may not be generalizable to men or younger women.

Our study has several strengths. First, women were prospectively followed over a long period of time (8 years), with annual assessments of both their EM and depressive symptoms, allowing us to closely

examine the temporal dynamics. Second, the use of sophisticated SEMs for latent change scores allowed us to examine the complex associations between $PM_{2.5}$ exposure and temporal changes in the two inter-related neuropsychological processes of EM and depressive symptoms. Third, the comprehensive data in the WHIMS cohort allowed us to account for a number of important covariates and reduce potential sources of biases.

5. Conclusions

Our study substantiates the epidemiologic evidence that long-term $PM_{2.5}$ exposure in late life may accelerate declines in episodic memory. Exposure was indirectly associated with increases in depressive symptoms through declines in episodic memory. Our data did not support depressive symptoms as the neuropsychological mediator of accelerated brain aging associated with $PM_{2.5}$ exposure, but suggested changes in depressive symptoms may result indirectly from episodic memory decline associated with exposure. These findings suggest that $PM_{2.5}$ neurotoxicity may damage brain areas implicated in episodic memory, possibly involving networks critical to emotion regulation in late life.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105196.

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