



# Air Pollution and the Dynamic Association Between Depressive Symptoms and Memory in Oldest-Old Women

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**BACKGROUND/OBJECTIVES:** Exposure to air pollution may contribute to both increasing depressive symptoms and decreasing episodic memory in older adulthood, but few studies have examined this hypothesis in a longitudinal context. Accordingly, we examined the association between air pollution and changes in depressive symptoms (DS) and episodic memory (EM) and their interrelationship in oldest-old (aged 80 and older) women.

**DESIGN:** Prospective cohort data from the Women's Health Initiative Memory Study-Epidemiology of Cognitive Health Outcomes.

**SETTING:** Geographically diverse community-dwelling population.

**PARTICIPANTS:** A total of 1,583 dementia-free women aged 80 and older.

**MEASUREMENTS:** Women completed up to six annual memory assessments (latent composite of East Boston Memory Test and Telephone Interview for Cognitive Status) and the 15-item Geriatric Depression Scale (GDS-15). We estimated 3-year average exposures to regional particulate matter with aerodynamic diameter below 2.5  $\mu\text{m}$  ( $\text{PM}_{2.5}$ ) (interquartile range [IQR] = 3.35  $\mu\text{g}/\text{m}^3$ ) and gaseous nitrogen dioxide ( $\text{NO}_2$ ) (IQR = 9.55 ppb) at baseline and during a remote period 10 years earlier, using regionalized national universal kriging.

**RESULTS:** Latent change structural equation models examined whether residing in areas with higher pollutant levels was associated with annual changes in standardized EM and DS while adjusting for potential confounders. Remote  $\text{NO}_2$  ( $\beta = .287$  per IQR;  $P = .002$ ) and  $\text{PM}_{2.5}$  ( $\beta = .170$  per IQR;  $P = .019$ ) exposure was significantly associated with larger increases in standardized DS, although the magnitude of the difference, less than 1 point on the GDS-15, is of questionable clinical significance. Higher DS were associated with accelerated EM declines ( $\beta = -.372$ ;  $P = .001$ ), with a significant indirect effect of remote  $\text{NO}_2$  and  $\text{PM}_{2.5}$  exposure on EM declines mediated by DS. There were no other significant indirect exposure effects.

**CONCLUSION:** These findings in oldest-old women point to potential adverse effects of late-life exposure to air pollution on subsequent interplay between DS and EM, highlighting air pollution as an environmental health risk factor for older women. *J Am Geriatr Soc* 00:1-11, 2020.

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People aged 80 and older, referred to hereafter as the oldest-old, represent the fastest growing segment of the U.S. population.<sup>1</sup> A U-shaped curve of depressive symptoms (DS) exists across older adulthood, with late-life DS decreasing during the early period of older adulthood with an uptick in the oldest-old.<sup>2</sup> Declines in episodic memory (EM)<sup>3</sup> become more pronounced after age 80 and typically co-occur with DS.<sup>4</sup> There is considerable environmental influence on the etiology of both DS<sup>5</sup> and EM.<sup>6,7</sup> However, in the oldest-old, the role of the physical environments has been understudied.

Exposure to air pollutants, such as ambient particulate matter with aerodynamic diameter below 2.5  $\mu\text{m}$  ( $\text{PM}_{2.5}$ ) and gaseous nitrogen dioxide ( $\text{NO}_2$ ), may represent novel environmental risk factors of accelerated brain aging.<sup>8</sup> Longitudinal studies have examined  $\text{PM}_{2.5}$  exposure as a risk factor for DS, EM decline, and dementia in older adulthood.<sup>9-13</sup> No longitudinal studies have examined associations between exposure to traffic-related pollutants with DS or depression in late life. Previous work has also focused on associations with exposures measured in recent years immediately before emotional or cognitive health assessment. It is unknown how remote exposure to air pollution is associated with trajectories of DS and EM performance in the oldest-old.

Research examining longitudinal interrelationships among  $\text{PM}_{2.5}$  exposure, DS, and EM suggests that memory decline related to air pollution may precede increases in DS.<sup>14</sup> Specifically,  $\text{PM}_{2.5}$  exposure that was averaged 3 years before annual neuropsychological assessments was associated with declining performance on EM tests, which were then associated with subsequent increases in DS. Although this report was the first demonstrating the temporal dynamics between DS and EM affected by air pollution exposure in late life, the average baseline age was 73 years, making it difficult to generalize the observed associations to the oldest-old. This previous work was further limited by studying only  $\text{PM}_{2.5}$ , whereas other studies had reported the associations of EM decline with  $\text{NO}_2$ .<sup>15,16</sup>

The purpose of this longitudinal study was to examine the associations of exposures to  $\text{NO}_2$  and  $\text{PM}_{2.5}$  with changes in EM and DS over a 5-year period in a geographically diverse community-dwelling cohort of women aged 80 and older. We also examined whether the observed associations might vary by pollutants ( $\text{NO}_2$  vs  $\text{PM}_{2.5}$ ) and exposure time period (in recent vs remote years).

## MATERIALS AND METHODS

### Study Population

This longitudinal cohort study included 1,583 community-dwelling older women aged 80 and older enrolled in the Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO)<sup>17</sup> who were dementia free (see Supplementary Methods for description of dementia ascertainment) at study baseline (aged 80–93 years). The WHIMS-ECHO began in 2008 and was an extension study to the Women's Health Initiative Memory Study (WHIMS)<sup>18</sup> that in turn was an ancillary study to the larger Women's Health Initiative (WHI) trial of postmenopausal hormone therapy<sup>19</sup> (Figure 1, panel A, shows a flowchart of this study sample; panel B presents a timeline of study assessments). Participants

completed annual phone-based neuropsychological assessments (up to six assessments) including measures of DS and EM. A more detailed description of the study population is included in the Supplementary Methods.

### Assessment of Depressive Symptoms

DS were assessed at WHIMS-ECHO baseline and at each annual follow-up using the 15-item Geriatric Depression Scale (GDS-15).<sup>20</sup> GDS-15 scores were positively skewed, so scores were transformed using a three-quantile spline transformation applied in our previous work.<sup>11</sup> Transformed scores were standardized on a T-score metric (mean = 50; standard deviation [SD] = 10), based on the baseline mean and SD. Higher scores reflect greater depression symptoms.

### Assessment of Verbal Episodic Memory

Verbal EM was assessed by the immediate recall (IR) and delayed recall (DR) measures from both the East Boston Memory Test (EBMT)<sup>21</sup> and word-list items of the Telephone Interview for Cognitive Status-modified (TICSm).<sup>22</sup> A higher score represents better performance on these four measures of EM. Performance on each measure was also standardized on a T-score metric based on the baseline mean and SD. To minimize the number of models that were fit, we combined the four measures of EM (EBMT-IR; EBMT-DR; TICSm-IR; and TICSm-DR) into a latent factor that captures the overall performance of EM (see Supplementary Methods for additional details).

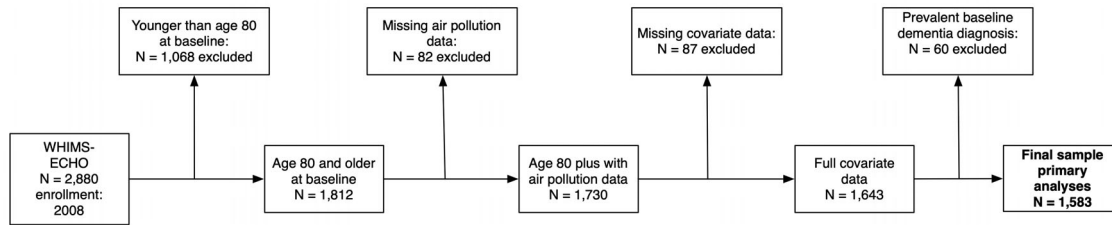
### Assessment of Ambient $\text{PM}_{2.5}$ and $\text{NO}_2$

Participants' addresses were collected prospectively at each WHI assessment and geocoded using standardized procedures.<sup>23,24</sup> Ambient annual mean concentrations of  $\text{PM}_{2.5}$  in micrograms per meter cubed ( $\mu\text{g}/\text{m}^3$ ) and  $\text{NO}_2$  in parts per billion (ppb) at each location were estimated using regionalized universal kriging models based on U.S. Environmental Protection Agency monitoring data.<sup>25-27</sup> Given the annual estimates, we calculated 3-year average exposures for each of these two pollutants both at WHIMS-ECHO baseline (referred to as recent exposures) and during the remote period 10 years earlier (referred to as remote exposures). Remote exposure corresponds to average annual exposure 10 to 13 years before the WHIMS-ECHO baseline (Figure 1B). Both exposure variables were scaled to the interquartile range (IQR) based on the remote exposure time period (remote  $\text{PM}_{2.5}$  IQR = 3.35  $\mu\text{g}/\text{m}^3$ ; remote  $\text{NO}_2$  IQR = 9.55 ppb).

### Relevant Covariate Data

A structured questionnaire was administered at WHIMS baseline to gather information on time-independent covariates: demographics (age, race/ethnicity), geographic region of residence (Northeast, South, Midwest, and West); socioeconomic status (education, family income, and employment status); lifestyle factors (smoking, alcohol use, and physical activities); and clinical characteristics including past or present self-reported postmenopausal hormone treatment, history of cardiovascular disease (including

(A) Flowchart of study participation



(B) Timeline of study assessments

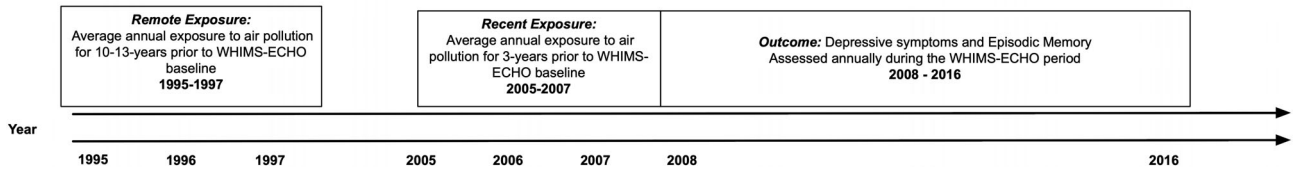


Figure 1. (A) Flowchart of study participation. (B) Timeline of study assessments. WHIMS-ECHO, Women’s Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes.

Table 1. Comparison of Estimated Remote PM<sub>2.5</sub> and NO<sub>2</sub> Exposures by Population Characteristics at Baseline (N = 1,583)

Population characteristics	N	Distribution of remote 3-y average <sup>a</sup> PM <sub>2.5</sub> exposure, µg/m <sup>3</sup>			Distribution of remote 3-y average <sup>a</sup> NO <sub>2</sub> exposure, ppb		
		Mean ± SD	(25th, median, 75th)	P <sup>b</sup>	Mean ± SD	(25th, median, 75th)	P <sup>b</sup>
Overall	1,583	13.34 ± 2.80	(11.7, 13.4, 15.0)		16.22 ± 7.28	(10.9, 15.3, 20.4)	
Region of residence				<.01			<.01
Northeast	498	12.95 ± 1.87	(11.7, 13.0, 14.0)		17.42 ± 7.75	(11.2, 16.0, 21.6)	
South	302	14.07 ± 2.04	(12.9, 14.3, 15.5)		13.95 ± 6.46	(8.7, 12.4, 18.7)	
Midwest	351	13.49 ± 2.13	(11.9, 13.4, 15.1)		13.98 ± 4.82	(10.3, 14.0, 17.6)	
West	432	13.17 ± 4.17	(9.6, 13.3, 15.8)		18.25 ± 7.97	(12.9, 17.8, 22.5)	
Race/Ethnicity				<.01			<.01
African American	68	15.16 ± 2.16	(14.0, 15.2, 16.0)		21.09 ± 8.43	(13.9, 21.1, 26.2)	
Hispanic White	18	14.59 ± 2.91	(13.1, 14.1, 16.4)		22.08 ± 7.06	(17.9, 21.9, 25.9)	
Non-Hispanic White	1,455	13.23 ± 2.78	(11.5, 13.3, 14.9)		15.82 ± 7.04	(10.6, 15.0, 19.7)	
Other or missing	42	13.89 ± 3.19	(12.3, 13.7, 15.4)		19.69 ± 8.71	(13.8, 19.1, 24.9)	
Education				.22			.02
Less than high school	70	13.72 ± 3.00	(11.9, 13.9, 15.7)		17.32 ± 8.57	(11.4, 16.4, 22.1)	
High school	330	13.14 ± 2.62	(11.4, 13.0, 14.8)		15.26 ± 6.69	(10.4, 14.5, 19.0)	
More than high school	1,183	13.38 ± 2.83	(11.8, 13.4, 15.1)		16.43 ± 7.33	(10.9, 15.6, 20.5)	
Employment				.56			<.01
Currently working	179	13.51 ± 2.86	(12.1, 13.4, 15.0)		17.83 ± 8.42	(11.2, 17.1, 22.7)	
Not working	151	13.18 ± 2.81	(11.7, 13.5, 14.9)		15.29 ± 6.37	(10.7, 14.2, 19.0)	
Retired	1,253	13.34 ± 2.78	(11.6, 13.4, 15.0)		16.11 ± 7.17	(10.7, 15.2, 20.2)	
Income, USD				.23			.20
<9,999	47	13.15 ± 3.56	(10.8, 13.7, 15.3)		16.01 ± 8.46	(9.7, 15.2, 20.1)	
10,000–34,999	232	13.22 ± 2.88	(11.6, 13.0, 15.0)		15.54 ± 7.31	(9.4, 15.1, 19.0)	
35,000–49,999	425	13.20 ± 2.87	(11.4, 13.3, 14.9)		15.96 ± 7.32	(10.6, 15.0, 19.8)	
50,000–74,999	296	13.48 ± 2.82	(11.7, 13.5, 15.4)		16.30 ± 7.21	(10.6, 15.5, 21.0)	
≥75,000	357	13.46 ± 2.48	(12.0, 13.5, 14.8)		16.86 ± 7.27	(11.4, 15.9, 21.0)	
Do not know	72	12.99 ± 2.50	(11.5, 13.0, 14.4)		15.72 ± 6.88	(11.3, 13.9, 19.3)	
Lifestyle				.23			<.01
Smoking status				.23			<.01
Never smoked	920	13.4 ± 2.79	(11.7, 13.4, 14.9)		15.74 ± 6.96	(10.4, 14.8, 19.7)	
Past smoker	600	13.26 ± 2.73	(11.6, 13.3, 15.1)		16.74 ± 7.50	(11.2, 16.2, 20.8)	
Current smoker	63	13.90 ± 3.38	(11.3, 14.2, 15.9)		18.29 ± 8.80	(11.2, 18.1, 23.0)	

(Continues)

Table 1 (Contd.)

Population characteristics	N	Distribution of remote 3-y average <sup>a</sup> PM <sub>2.5</sub> exposure, µg/m <sup>3</sup>			Distribution of remote 3-y average <sup>a</sup> NO <sub>2</sub> exposure, ppb		
		Mean ± SD	(25th, median, 75th)	P <sup>b</sup>	Mean ± SD	(25th, median, 75th)	P <sup>b</sup>
Alcohol use				.23			<.01
Nondrinker	190	13.40 ± 2.97	(11.7, 13.4, 15.1)		14.51 ± 7.93	(8.6, 12.3, 18.1)	
Past drinker	271	13.44 ± 2.96	(11.5, 13.5, 15.5)		15.80 ± 7.20	(10.5, 14.5, 19.8)	
<1 drink/d	916	13.39 ± 2.66	(11.7, 13.4, 14.9)		16.75 ± 7.14	(11.6, 16.1, 20.9)	
>1 drink/d	206	12.97 ± 2.96	(11.3, 13.2, 15.1)		16.00 ± 7.10	(10.7, 15.2, 20.2)	
Moderate or strenuous activities ≥20 min				.18			.10
No activity	852	13.38 ± 2.79	(11.8, 13.5, 15.0)		16.09 ± 7.40	(10.6, 15.3, 20.2)	
Some activity	84	13.80 ± 2.42	(12.2, 14.0, 15.5)		17.68 ± 6.73	(13.5, 17.9, 22.2)	
2–4 episodes/wk	347	13.36 ± 2.82	(11.7, 13.2, 15.0)		16.65 ± 7.31	(11.6, 15.3, 20.9)	
≥4 episodes/wk	300	13.09 ± 2.86	(11.3, 13.1, 14.9)		15.70 ± 7.00	(10.6, 14.5, 19.7)	
Physical health							
Hypertension				.71			.43
No	1,025	13.32 ± 2.84	(11.6, 13.4, 15.0)		16.12 ± 7.24	(10.7, 15.2, 20.1)	
Yes	558	13.38 ± 2.72	(11.8, 13.5, 15.0)		16.42 ± 7.33	(11.2, 15.6, 20.9)	
Treated hypercholesterolemia				.03			.90
No	1,302	13.27 ± 2.81	(11.6, 13.3, 15.0)		16.21 ± 7.24	(10.7, 15.4, 20.3)	
Yes	281	13.68 ± 2.71	(11.9, 13.7, 15.4)		16.27 ± 7.47	(11.2, 14.8, 20.7)	
Diabetes mellitus				.92			.77
No	1,513	13.34 ± 2.81	(11.7, 13.4, 15.0)		16.23 ± 7.30	(10.9, 15.4, 20.4)	
Yes	70	13.38 ± 2.48	(11.8, 13.7, 15.0)		15.97 ± 6.86	(10.8, 15.0, 19.7)	
Cardiovascular disease				.51			.26
No	1,343	13.36 ± 2.82	(11.7, 13.4, 15.0)		16.31 ± 7.30	(10.9, 15.4, 20.5)	
Yes	240	13.23 ± 2.64	(11.7, 13.4, 14.9)		15.74 ± 7.11	(10.5, 15.1, 19.8)	
Prior hormone therapy				.10			.06
No	886	13.45 ± 2.56	(11.9, 13.5, 14.9)		16.53 ± 7.37	(10.9, 15.6, 20.9)	
Yes	697	13.21 ± 3.07	(11.3, 13.3, 15.1)		15.83 ± 7.14	(10.7, 15.2, 19.7)	
Hormone therapy assignment				.11			.55
E-alone intervention	269	15.71 ± 7.47	(10.1, 14.2, 19.5)		13.23 ± 2.86	(11.5, 13.2, 15.3)	
E-alone control	295	16.74 ± 7.07	(11.7, 16.2, 20.6)		13.54 ± 3.02	(11.8, 13.7, 15.4)	
E + P intervention	486	15.78 ± 7.56	(10.3, 14.8, 19.7)		13.29 ± 2.81	(11.6, 13.2, 15.0)	
E + P control	553	16.60 ± 7.00	(11.3, 15.9, 20.9)		13.34 ± 2.62	(11.9, 13.5, 14.8)	

Abbreviations: E, estrogen; NO<sub>2</sub>, gaseous nitrogen dioxide; P, progesterone; PM<sub>2.5</sub>, particulate matter below 2.5 µm; SD, standard deviation.

<sup>a</sup>Three-year average of the annual exposure estimated before the remote period of 10 years before the WHIMS-ECHO baseline at each participant's location using the national spatiotemporal model.

<sup>b</sup>The *P* values are estimated from analysis of variance *F* tests or *t* tests comparing the mean exposures.

previous coronary heart, stroke, or transient ischemic attack), hypertension (defined as elevated blood pressure or use of antihypertensive medication), hypercholesterolemia, and diabetes mellitus (defined as physician diagnosis plus oral medications or insulin therapy). Reliability and validity of these self-reported medical histories and the physical measures were previously documented.<sup>28</sup> Neighborhood socioeconomic characteristics (nSES) were characterized using standard methods.<sup>29</sup>

### Statistical Analysis

Structural equation models (SEMs) for latent change scores (LCSs)<sup>30,31</sup> were constructed to characterize associations between air pollution exposure and temporal changes in the two interrelated neuropsychological processes (EM and DS) over the first 5 years of the WHIMS-ECHO study period.

We examined change over 1-year intervals because women completed annual assessments of both EM and DS. The Supplementary Methods provide a more detailed description of the analytic approach.

We first constructed univariate LCS models to examine the association between exposure and annual change in each of these two neuropsychological processes, separately for DS (Supplementary Figure S1) and EM (Supplementary Figure S2). For DS, the equation to estimate annual individual-specific change in DS for individual *i* at time point *t* ( $\Delta dep_{i,t}$ ) was written as:

$$\Delta dep_{i,t} = \alpha_{dep} * slp_{dep,i} + \beta_{dep} * ldep_{i,t} + \gamma_{exposure \text{ on } \Delta dep} * Exposure_i \quad (1)$$

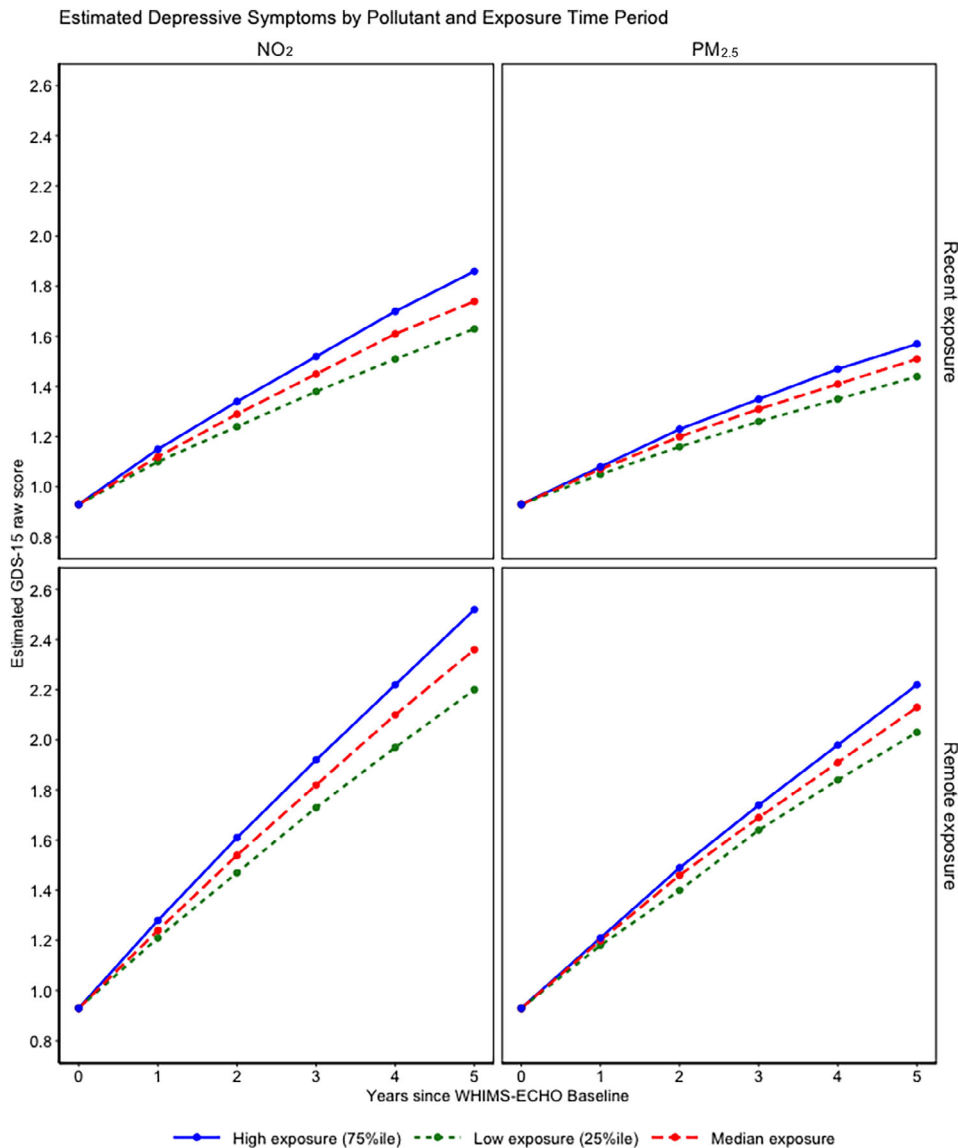
In the equation,  $\Delta dep_{i,t}$  denotes the estimated individual-specific annual change in DS and is a function of the

following effects: individual-specific constant linear change (denoted by  $\text{slp}_{\text{depi}}$ ), nonlinear proportional change capturing the extent to which magnitude of change depends on previous estimate of DS ( $\beta_{\text{dep}}$ ), and the effect of exposure ( $\gamma_{\text{exposure on } \Delta\text{dep}}$ ). Exposure effects and individual-specific estimates of initial symptoms and linear change were adjusted for these covariates: age at the WHIMS-ECHO baseline, race/ethnicity, employment status, geographic region of residence, education, household income, lifestyle factors (smoking, alcohol use, physical activities), nSES, and clinical characteristics (any prior hormone use ever, hypercholesterolemia, hypertension, diabetes mellitus, and history of cardiovascular disease). Analogous equations can be written for univariate SEM to estimate exposure effects on change in the EM latent factor. In univariate models for EM, a latent factor of EM performance consisting of the

four measures of EM (EBMT-IR, EBMT-DR, TICSm-IR, and TICSm-DR) was created at each time point (see Supplementary Methods). Separate models were run to examine how the defined neuropsychological process was influenced by ambient PM<sub>2.5</sub> or NO<sub>2</sub>, each including remote and recent exposures effects.

**Bivariate Latent Change Score Models**

Supplementary Figures S3 and S4 present the full bivariate models that were estimated. In the bivariate models, change in DS ( $\Delta\text{dep}_{i,t}$ ) was again a function of linear systematic change ( $\text{slp}_{\text{depi}}$ ), proportional change ( $\beta_{\text{dep}}$ ), and the effect of exposure ( $\gamma_{\text{exposure on } \Delta\text{dep}}$ ). The equation to estimate change in DS also contains a coupling parameter linking EM performance with subsequent change in DS ( $\gamma_{\text{lem on } \Delta\text{dep}}$ ).



**Figure 2.** Estimated depressive symptoms as measured by the 15-item Geriatric Depression Scale (GDS-15) by pollutants and exposure time period for low (25th percentile), median, and high (75th percentile) average 3-year exposure. The exposure effects are portrayed in a grid with the first row representing recent exposure and the second row representing remote exposure. The first column represents the NO<sub>2</sub> exposure effect; the second column is the PM<sub>2.5</sub> exposure effect. Therefore, the graph illustrated in the first row and first column represents the effect of recent NO<sub>2</sub> exposure. \*  $P < .05$ . \*\*  $P < .01$ . WHIMS-ECHO, Women’s Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes.

The specific indirect effect of exposure on changes in DS was estimated by multiplying the two estimated coupling parameters while deriving estimates of 95% confidence intervals (95% CIs) via Monte Carlo simulation.<sup>32</sup> 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 exposure on changes in EM mediated by exposure-related changes in DS. Again, separate models were run to examine effects of remote and recent exposure to both PM<sub>2.5</sub> and NO<sub>2</sub>.

We conducted three sensitivity analyses to examine the robustness of our study findings. We first excluded women (n = 137) with either prevalent stroke at the beginning of the study period or incident stroke by 2017, and we re-ran these analyses to examine whether our findings could be explained by stroke risk. Second, we excluded women (n = 289) who developed dementia (see Supplementary Methods for dementia ascertainment) by June 2018, to explore whether any observed associations remain among

the oldest-old who were cognitively intact during the entire study period. Last, we excluded women (n = 127) who self-reported a history of depression before the WHIMS baseline, to explore whether findings could be explained by a prior history of depression. All LCS models were conducted using the SEM program MPLUS v.8<sup>33</sup> that was run via the MPLUS Automation package<sup>34</sup> in R.

## RESULTS

On average, participants completed nearly five (mean ± SD = 4.25 ± 1.81) assessments of EM and DS. Table 1 compares the distribution of 3-year average exposures with regional PM<sub>2.5</sub> and NO<sub>2</sub> at the remote period 10 years before the WHIMS-ECHO baseline assessment by population characteristics. Participants exposed to higher concentrations of remote PM<sub>2.5</sub> were more likely to be racial/ethnic minorities (African American or Hispanic White), residing in the South, and have hypercholesterolemia. Participants with higher concentrations of remote NO<sub>2</sub> exposure were more likely to

**Table 2.** Bivariate Latent Change Score SEMs Examining Direct Effect of Recent and Remote Exposure to NO<sub>2</sub> and PM<sub>2.5</sub> on Changes in DS as Well as the Respective Indirect Exposure Effect Mediated by EM (N = 1,583)

	Exposure: NO <sub>2</sub>	
	Remote <sup>a</sup> exposure	Recent <sup>b</sup> exposure
	Est <sup>c</sup> (95% CI)	Est <sup>c</sup> (95% CI)
<b>Estimates of direct effect<sup>d</sup></b>		
Effect of NO <sub>2</sub> on annual change in DS ( $\gamma_{NO_2 \text{ on } \Delta dep}$ )	.221 (–.093 to .535)	.169 (–.185 to .523)
<b>Estimates of indirect effect<sup>d</sup></b>		
Effects of NO <sub>2</sub> on annual changes in EM ( $\gamma_{NO_2 \text{ on } \Delta em}$ )	–.074 (–.264 to .116)	–.163 (–.441 to .114)
Effects of EM performance on annual change in DS ( $\gamma_{Lem \text{ on } \Delta dep}$ )	.112 (–.276 to .500)	.094 (–.294 to .483)
Indirect effect of NO <sub>2</sub> on annual change in DS ( $\gamma_{NO_2 \text{ on } \Delta em} * \gamma_{Lem \text{ on } \Delta dep}$ )	–.008 (–.078 to .035) <sup>e</sup>	–.015 (–.140 to .059) <sup>e</sup>
<b>Exposure: PM<sub>2.5</sub></b>		
	Remote <sup>a</sup> exposure	Recent <sup>b</sup> exposure
	Est <sup>c</sup> (95% CI)	Est <sup>c</sup> (95% CI)
<b>Estimates of direct effect<sup>d</sup></b>		
Effect of PM <sub>2.5</sub> on annual change in DS ( $\gamma_{PM_{2.5} \text{ on } \Delta dep}$ )	.108 (–.158 to .373)	.115 (–.194 to .424)
<b>Estimates of indirect effect<sup>d</sup></b>		
Effects of PM <sub>2.5</sub> on annual changes in EM ( $\gamma_{PM_{2.5} \text{ on } \Delta em}$ )	–.095 (–.272 to .082)	–.026 (–.260 to .209)
Effects of EM performance on annual change in DS ( $\gamma_{Lem \text{ on } \Delta dep}$ )	.113 (–.278 to .503)	.085 (–.296 to .466)
Indirect effect of PM <sub>2.5</sub> on annual change in DS ( $\gamma_{PM_{2.5} \text{ on } \Delta em} * \gamma_{Lem \text{ on } \Delta dep}$ )	–.011 (–.088 to .041) <sup>e</sup>	–.002 (–.079 to .050) <sup>e</sup>

Abbreviations: CI, confidence interval; DS, depressive symptoms; EM, episodic memory; Est, parameter estimate; NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, particulate matter with <2.5 μm; SEM, structural equation model; episodic memory, latent factor consisting of the immediate and delayed recall from the East Boston Memory Test and the world list memory from the Telephone Interview for Cognitive Status; depressive symptoms, 15-item Geriatric Depression Scale.

<sup>a</sup>Remote represents the 3-year average exposures to regional PM<sub>2.5</sub> and NO<sub>2</sub> 10 years before study baseline.

<sup>b</sup>Recent represents the 3-year average exposures to regional PM<sub>2.5</sub> and NO<sub>2</sub> for the 3 years before study baseline.

<sup>c</sup>In all models, the effects were adjusted for initial age at WHIMS-ECHO, race/ethnicity, geographic region of residence, employment status, education, household income, lifestyle factors (smoking, alcohol use, physical activities), clinical characteristics (use of hormone treatment; hypercholesterolemia, hypertension, diabetes mellitus, and history of cardiovascular disease), and neighborhood socioeconomic characteristics.

<sup>d</sup>All effects below were derived from the bivariate SEMs as depicted in Figure 2A, with exposure scaled by interquartile range from the remote period (PM<sub>2.5</sub> scaled by 3.35 μg/m<sup>3</sup> and NO<sub>2</sub> scaled by 9.55 ppb).

<sup>e</sup>The 95% CI for the indirect effect is asymmetrical and estimated via Monte Carlo simulation.



have either more or less than a high school education, to reside in the West, and to be racial/ethnic minorities, current smokers, and nondrinkers (less than one drink per day).

All univariate LCS models fit data acceptably (Supplementary Table S1 for all model fit indices). Increased remote exposures were associated with greater annual increases in DS during the WHIMS-ECHO follow-up (Supplementary Table S2). For example, one interquartile increase in PM<sub>2.5</sub> (3.35 µg/m<sup>3</sup>) exposure was associated with a .170 larger annual increase in T-score standardized DS (95% CI = .027–.312). A similar putative adverse exposure effect was observed for NO<sub>2</sub> ( $\gamma_{\text{remote NO}_2 \text{ on } \Delta_{\text{dep}}} = .287$ ; 95% CI = .105–.470; per interquartile increment of 9.55 ppb). Although similar patterns of increased DS were also found in those residing in locations with higher exposures during the recent 3 years before WHIMS-ECHO baseline, the associations did not reach statistical significance ( $P = .090$  for NO<sub>2</sub>;  $P = .126$  for PM<sub>2.5</sub>). In contrast, there was no statistically significant association of EM decline with either PM<sub>2.5</sub> or NO<sub>2</sub>, regardless of exposure time periods.

Figure 2 presents the exposure effect parameter estimates and depicts estimated trajectories of EM and DS (transformed back to GDS-15 units to aid in clinical interpretation) associated with each pollutant at either relatively low (25th percentile), average (median), or relatively high (75th percentile) exposure concentrations among women with the average performance of EM or DS at WHIMS-ECHO baseline and average individual-specific linear change. Women residing in areas with high exposure to NO<sub>2</sub> experienced 24% larger increases in DS compared with women with low exposure; higher PM<sub>2.5</sub> exposure was associated with 17% larger increases. Applying recently published guidelines for effect size interpretation, our observed effect sizes of exposure on changes in DS are considered small yet potentially consequential.<sup>35</sup>

Table 2 presents the results of bivariate LCS models examining the direct and indirect effect of exposure on changes in DS. All models exhibited acceptable model fit (Supplementary Table S1). Consistent with univariate models, neither NO<sub>2</sub> nor PM<sub>2.5</sub> exposure over the remote

**Table 3. Bivariate Latent Change Score SEMs Examining the Direct Effect of Recent and Remote Exposure to NO<sub>2</sub> and PM<sub>2.5</sub> on Changes in EM as Well as the Respective Indirect Effect Mediated by DS (N = 1,583)**

	Exposure: NO <sub>2</sub>	
	Remote <sup>a</sup> exposure	Recent <sup>b</sup> exposure
	Est <sup>c</sup> (95% CI)	Est <sup>c</sup> (95% CI)
<b>Estimates of direct effect<sup>d</sup></b>		
Effect of NO <sub>2</sub> on annual change in EM ( $\gamma_{\text{NO}_2 \text{ on } \Delta_{\text{em}}}$ )	.179 (–.119 to .477)	–.024 (–.425 to .377)
<b>Estimates of indirect effect<sup>d</sup></b>		
Effects of NO <sub>2</sub> on annual changes in GDS-15 ( $\gamma_{\text{NO}_2 \text{ on } \Delta_{\text{dep}}}$ )	<b>.255 (.074 to .436)</b>	.203 (–.042 to .447)
Effects of GDS-15 performance on annual change in EM ( $\gamma_{\text{Ldep on } \Delta_{\text{em}}}$ )	<b>–.372 (–.594 to –.150)</b>	<b>–.384 (–.615 to –.154)</b>
Indirect effect of NO <sub>2</sub> on annual change in EM ( $\gamma_{\text{NO}_2 \text{ on } \Delta_{\text{dep}}} * \gamma_{\text{Ldep on } \Delta_{\text{em}}}$ )	<b>–.095 (–.171 to –.026)<sup>e</sup></b>	–.078 (–.184 to .018) <sup>e</sup>
	Exposure: PM <sub>2.5</sub>	
	Remote <sup>a</sup> exposure	Recent <sup>b</sup> exposure
	Est <sup>c</sup> (95% CI)	Est <sup>c</sup> (95% CI)
<b>Estimates of direct effect<sup>d</sup></b>		
Effect of PM <sub>2.5</sub> on annual change in EM ( $\gamma_{\text{PM}_{2.5} \text{ on } \Delta_{\text{em}}}$ )	.114 (–.149 to .377)	.154 (–.183 to .491)
<b>Estimates of indirect effect<sup>d</sup></b>		
Effects of PM <sub>2.5</sub> on annual changes in GDS-15 ( $\gamma_{\text{PM}_{2.5} \text{ on } \Delta_{\text{dep}}}$ )	.138 (–.004 to .280)	.123 (–.081 to .328)
Effects of GDS-15 performance on annual change in EM ( $\gamma_{\text{Ldep on } \Delta_{\text{em}}}$ )	<b>–.377 (–.608 to –.146)</b>	<b>–.380 (–.612 to –.148)</b>
Indirect effect of PM <sub>2.5</sub> on annual change in EM ( $\gamma_{\text{PM}_{2.5} \text{ on } \Delta_{\text{dep}}} * \gamma_{\text{Ldep on } \Delta_{\text{em}}}$ )	<b>–.052 (–.112 to –.001)<sup>e</sup></b>	–.047 (–.130 to .035) <sup>e</sup>

Abbreviations: CI, confidence interval; EM, episodic memory; Est, parameter estimate; NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, particulate matter with <2.5 µm; SEM, structural equation model; episodic memory, latent factor consisting of the immediate and delayed recall from the East Boston Memory Test and the world list memory from the Telephone Interview for Cognitive Status; depressive symptoms, 15-item Geriatric Depression Scale.

Estimates are bolded if statistically significant at  $P < .05$ .

<sup>a</sup>Remote represents the 3-year average exposures to regional PM<sub>2.5</sub> and NO<sub>2</sub> 10 years before study baseline.

<sup>b</sup>Recent represents the 3-year average exposures to regional PM<sub>2.5</sub> and NO<sub>2</sub> for the 3 years before study baseline.

<sup>c</sup>In all models, the effects were adjusted for initial age at WHIMS-ECHO, race/ethnicity, geographic region of residence, employment status, education, household income, lifestyle factors (smoking, alcohol use, physical activities), clinical characteristics (use of hormone treatment; hypercholesterolemia, hypertension, diabetes mellitus, and history of cardiovascular disease), and neighborhood socioeconomic characteristics.

<sup>d</sup>All effects below were derived from the bivariate SEMs as depicted in Figure 2A, with exposure scaled by interquartile range from the remote period (PM<sub>2.5</sub> scaled by 3.35 µg/m<sup>3</sup> and NO<sub>2</sub> scaled by 9.55 ppb).

<sup>e</sup>The 95% CI for the indirect effect is asymmetric and estimated via Monte Carlo simulation.

or recent period was associated with EM declines. Additionally, EM performance in the oldest-old women was not associated with subsequent changes in DS.

Results for the direct and indirect effects of exposure on changes in EM performance are presented in Table 3. Remote NO<sub>2</sub> and PM<sub>2.5</sub> exposures were both associated with increased DS over the follow-up period. For example, a one interquartile increment in remote NO<sub>2</sub> exposure was associated with .255 larger annual increases in T-score standardized DS. Oldest-old women with higher DS tended to have accelerated declines in EM during the subsequent year, with a one T-score increase in DS associated with .377 to .380 larger annual declines in EM performance. The resulting indirect effect of remote exposure on accelerating EM declines mediated by DS was present for both pollutants, with a larger effect estimate per IQR for NO<sub>2</sub> exposure. The magnitude of effects of recent exposures during the 3 years before the WHIMS-ECHO baseline was of similar magnitude as remote exposure although not statistically significant.

In our sensitivity analyses, the observed direct associations between exposures and increased DS (Supplementary Table S3), as well as the resulting indirect effects on EM decline mediated by increased DS (Supplementary Table S4), were largely the same after excluding women who experienced a stroke. After excluding oldest-old women who developed dementia by 2018, the associations of increased DS with remote exposures to NO<sub>2</sub> and PM<sub>2.5</sub> (Supplementary Table S5), as well as the indirect effects on EM decline (Supplementary Table S6), were substantially attenuated. The corresponding indirect effect of exposure on declines in EM mediated by DS was no longer statistically significant. After excluding oldest-old women who self-reported a history of depression before the WHIMS baseline, the associations between exposure to higher concentrations of PM<sub>2.5</sub> and NO<sub>2</sub> and annual changes in DS were significantly attenuated (Supplementary Table S7). The corresponding indirect effect of exposure to PM<sub>2.5</sub> on declines in EM mediated by DS was no longer statistically significant (Supplementary Table S8). The corresponding indirect effect of exposure to NO<sub>2</sub> on declines in EM mediated by DS was attenuated but remained statistically significant.

## DISCUSSION

In this geographically diverse cohort of women aged 80 and older, we found that living in locations with higher exposures to ambient air pollution was associated with increased DS, and this putatively adverse exposure effect may differ by pollutants. In univariate analyses, long-term exposure to ambient NO<sub>2</sub> or PM<sub>2.5</sub> was associated with increased DS, of small effect size, over the follow-up. Associations between exposure and changes in DS were slightly stronger and statistically significant for exposures of 10 to 13 years before the neuropsychological assessment. These observed associations were also stronger with NO<sub>2</sub> as compared with PM<sub>2.5</sub> exposure. The magnitude of these exposure effects on increases in DS were of questionable clinical significance corresponding to less than a one-unit increase in raw GDS-15 score per IQR increment of the exposure.

We did not find any statistically significant direct association of EM declines with remote or recent exposure to

NO<sub>2</sub> and PM<sub>2.5</sub>. In bivariate models, women with increasing DS tended to have larger declines in EM 1 year later, whereas EM was not associated with subsequent changes in DS. A statistically significant indirect effect of remote exposure to either NO<sub>2</sub> or PM<sub>2.5</sub> on declining EM via increased DS was present. This suggests DS might serve as a neuropsychological mediator of the association between long-term exposure and EM decline in the oldest-old women. Findings could not be explained by sociodemographic factors, lifestyle, individual SES, nSES characteristics, or clinical characteristics. To our knowledge, this is the first study to examine how air pollution exposures are associated with DS as well as the interrelationship between DS and EM in the oldest-old population.

Our study demonstrates evidence that living in areas with higher levels of ambient NO<sub>2</sub> and PM<sub>2.5</sub> are associated with increases in DS, of small magnitude, in the oldest-old. Previous longitudinal studies examining the association between air pollution and DS or major depression in late life have produced mixed results. For instance, PM<sub>2.5</sub> exposure might increase the risk of clinically significant depression across adulthood,<sup>36</sup> but such association was less consistent among middle-aged and older women.<sup>37</sup> Long-term PM<sub>2.5</sub> exposure has also been associated with more severe DS in some studies<sup>11,38</sup> but no direct associations in the others.<sup>14,39,40</sup> However, none of the prior studies focused on the oldest-old populations.

The magnitudes of the effect size of exposure on increases in DS were small and of questionable clinical significance. The modest size effect highlights the need for a larger sample to have adequate statistical power to detect effects of public health significance. Additionally, although we adjusted for important demographic, clinical, and lifestyle factors in our analyses, air quality might be a surrogate for other unmeasured social determinants of health. The statistically significant increases in DS were associated with remote exposures to PM<sub>2.5</sub> and NO<sub>2</sub>. Our data suggest that the neurotoxic insults resulting from air pollution exposures may accumulate over time, and the resulting neuropathological processes may continue up to 10 years or longer before the increases in DS become measurable in the oldest-old women. In our sensitivity analyses excluding older women with dementia, the observed exposure effect on increased in DS as well as its neurocognitive consequences was attenuated and no longer statistically significant. This suggests that the observed exposure effects on increased DS may coincide with neuropathological processes leading to dementia.

Findings of this study expand the results of our previous work,<sup>14</sup> suggesting the effect of living in areas with higher air pollution on the dynamic relation of DS and EM may vary by age in late life, although the exact reasons are unclear. In the present study on the oldest-old, we found that DS were a neuropsychological mediator of the association between exposure and declining EM. In our previous study among older women with an average age of 73 (SD = 3.8 years), we found EM was a neuropsychological mediator of the association between exposure and increased DS. Furthermore, we found no direct associations between time-varying PM<sub>2.5</sub> exposure on increased DS nor indirect effects on EM declines. Age differences in the perception of cognitive changes may be present. Declining EM



may be more distressing in earlier older adulthood compared with later older adulthood. It is possible that worse memory may be more distressing at younger ages. Therefore, we may see increases in DS as a reaction to worse EM at younger ages. During later older adulthood, worse memory may not be as distressing; therefore, there is no significant association between worse memory and subsequent increases in DS. Future studies should examine possible contributions to age differences in the association between DS and memory across older adulthood.

In the oldest-old women, the air pollution exposure effect on neuropsychological processes of brain aging may vary by pollutants. Specifically, we found that NO<sub>2</sub> exposure had a stronger association with changes in DS compared with PM<sub>2.5</sub> and DS. In the sensitivity analyses excluding dementia, the association between NO<sub>2</sub> exposure and DS was attenuated and no longer statistically significant. Previous studies showed that exposure to both PM<sub>2.5</sub> and NO<sub>2</sub> may increase risk of dementia.<sup>41</sup> The attenuation of the exposure effect after excluding women with incident dementia suggests that exposure to NO<sub>2</sub> and PM<sub>2.5</sub> may be contributing to a common neuropathological process contributing to both dementia risk and DS. Similarly, excluding prior depression attenuated the association between PM<sub>2.5</sub> and NO<sub>2</sub> on increases in DS. However, NO<sub>2</sub> was attenuated less than PM<sub>2.5</sub> after excluding women with a prior history of depression. This observation suggests that PM<sub>2.5</sub> may impact areas of the brain contributing to DS earlier in life. The observed differential exposure effects suggest that traffic-related air pollution, as compared with particulate matter from regional sources, may exert a greater neurotoxic effect on the brain areas important for emotional regulation and health of older people. Further research with animals and humans is needed to compare the adverse physiological effects of late-life exposures to NO<sub>2</sub> and PM<sub>2.5</sub>.

We recognize several limitations of our study. First, exposure estimates are still subject to measurement error, and we did not measure personal exposures directly. We compared average annual remote (10–13 years before WHIMS-ECHO baseline) and recent (0–3 years before WHIMS-ECHO baseline) exposure while not examining the magnitude or change in exposure for the years in between remote and recent exposure periods. Future studies need to examine how changes in exposure over time impact trajectories of DS and EM in the oldest-old. Second, although our data did not support the hypothesis that EM is a neuropsychological mediator of brain aging associated with exposure, we could not rule out the possibility that increased exposure may impact other cognitive abilities implicated with DS, specifically executive functioning. Third, the oldest-old women included in these analyses were mostly White, well educated, and generally in good health, whereas those excluded due to missing data on air pollution exposure or relevant covariates tended to have fewer years of schooling and were more likely to be African American, of lower socioeconomic status, and in poorer health. Although these factors were all accounted for in our analyses, differences in these population characteristics may limit the generalizability of our study findings. Lastly, our study did not include men or younger women.

Our study provides epidemiological evidence that living in areas with higher levels of PM<sub>2.5</sub> and NO<sub>2</sub> in late life

may contribute directly to increased DS, of small magnitude, and indirectly to declines in EM of the oldest-old women. These findings highlight that the adverse effect of air pollution on the interplay between DS and EM is heterogeneous, likely varying by pollutants and age.

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**Conflict of Interest:** The authors have declared no conflicts of interest for this article.

**Author Contributions:** Andrew J. Petkus has full access to all the data in the study and takes responsibility for the integrity and accuracy of the data analysis. *Study concept and design:* Petkus, Younan, Wang, Gruenewald, and Chen. *Data analysis:* Petkus. *Manuscript writing and revision:* All authors. *Obtained funding:* Chen and Chui.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

**Supplementary Figure S1:** Univariate latent change score structural equation model to estimate the effect of exposure to air pollution on changes in depressive symptoms (as measured by the Geriatric Depression Scale-15).

**Supplementary Figure S2:** Univariate latent change score structural equation model to estimate the effect of exposure to air pollution on changes in episodic memory (as measured by a latent factor consisting of immediate and delayed recall from the East Boston Memory Test and the word-list memory from the Telephone Interview of Cognitive Status-modified).

**Supplementary Figure S3:** Depiction of the full bivariate model constructed to estimate the indirect effect of exposure on changes in depressive symptoms.

**Supplementary Figure S4:** Depiction of the full bivariate model constructed to estimate the indirect effect of exposure on declines of episodic memory.

**Supplementary Table S1:** Model fit statistics of all univariate and bivariate latent change score models

**Supplementary Table S2:** Univariate structural equation models examining the associations between remote and recent exposure to PM<sub>2.5</sub> and NO<sub>2</sub> on change in depressive symptoms and episodic memory (N = 1,583).

**Supplementary Table S3:** Sensitivity analyses excluding women with incident stroke during the WHIMS-ECHO follow-up period (n = 137): to examine whether observed univariate associations between air pollution exposures and change in emotional distress could be confounded by stroke (N = 1,446).

**Supplementary Table S4:** Sensitivity analyses excluding women who experienced a stroke during the WHIMS-ECHO follow-up period (n = 137): to examine whether bivariate latent change score structural equation models examining the direct effect of remote exposure to NO<sub>2</sub> and PM<sub>2.5</sub> on changes in episodic memory as well as the respective indirect effect mediated by depressive symptoms were explained by stroke (N = 1,446).

**Supplementary Table S5:** Sensitivity analyses excluding women with dementia during the WHIMS-ECHO follow-up period ( $n = 289$ ): to examine whether observed univariate associations between air pollution exposures and change in emotional distress could be confounded by dementia risk ( $N = 1,294$ ).

**Supplementary Table S6:** Sensitivity analyses excluding women with dementia during the WHIMS-ECHO follow-up period ( $n = 289$ ): to examine whether bivariate latent change score structural equation models examining the direct effect of remote exposure to  $\text{NO}_2$  and  $\text{PM}_{2.5}$  on changes in episodic memory as well as the respective indirect effect mediated by depressive symptoms were explained by dementia risk ( $N = 1,294$ ).

**Supplementary Table S7:** Sensitivity analyses excluding women with self-reported prior history of depression before the WHIMS baseline ( $n = 127$ ): to examine whether observed univariate associations between air pollution exposures and change in depressive symptoms could be confounded by earlier life depression ( $N = 1,456$ ).

**Supplementary Table S8:** Sensitivity analyses excluding women with self-reported prior history of depression before the WHIMS baseline ( $n = 127$ ): to examine whether bivariate latent change score structural equation models examining the direct effect of remote exposure to  $\text{NO}_2$  and  $\text{PM}_{2.5}$  on changes in episodic memory as well as the respective indirect effect mediated by depressive symptoms were explained by early life depression ( $N = 1,456$ ).