Title

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

Journal

Journal of the American Geriatrics Society, 69(2)

ISSN

0002-8614

Authors

Petkus, Andrew J
Younan, Diana
Wang, Xinhui
et al.

Publication Date

2021-02-01

DOI

10.1111/jgs.16889

Peer reviewed

HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2022 February 01.

Published in final edited form as:

J Am Geriatr Soc. 2021 February ; 69(2): 474–484. doi:10.1111/jgs.16889.

Air pollution and the dynamic association between depressive symptoms and memory in oldest-old women

Andrew J. Petkus, Ph.D.[a], **Diana Younan, Ph.D.**[a], **Xinhui Wang, Ph.D.**[a], **Daniel P. Beavers, Ph.D.**[b], **Mark A. Espeland, Ph.D.**[b], **Margaret Gatz, Ph.D.**[a], **Tara Gruenewald, Ph.D.**[c], **Joel D. Kaufman, M.D.,M.P.H.**[d], **Helena C. Chui, M.D.**[a], **JoAnn E. Manson, M.D., DrPH**[e], **Susan M. Resnick, Ph.D.**[f], **Gregory A. Wellenius, ScD**[g], **Eric A. Whitsel, M.D.,M.P.H**[h], **Keith Widaman, Ph.D.**[I], **Jiu-Chiuan Chen, M.D.,ScD**[a]

[a]University of Southern California

[b]Wake Forest School of Medicine

[c]Chapman University

[d]University of Washington

[e]Brigham and Women's Hospital, Harvard Medical School

[f]Laboratory of Behavioral Neuroscience, National Institute on Aging

[g]Department of Environmental Health, Boston University, Boston, MA

[h]University of North Carolina

[I] University of California, Riverside

Abstract

Background/Objective: 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 and episodic memory and their interrelationship in oldest-old (aged ≥ 80 years) women.

Design: Prospective cohort data from the Women's Health Initiative Memory Study-Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO).

Corresponding Authors: Andrew J. Petkus, Ph.D., University of Southern California, Department of Neurology, 1520 San Pablo St., Suite 3000, Los Angeles, CA 90033, Phone: 323-442-8050, petkus@usc.edu, Jiu-Chiuan Chen, MD, ScD, Department of Preventive Medicine and Neurology, Keck School of Medicine, University of Southern California, SSB 225P 2001 N. Soto Street, Los Angeles, CA 90033, Phone: 323-442-2949, jcchen@usc.edu.

Author Contributions: 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: AJP, DY, XW, TG, J-CC

Data analysis: AJP

Manuscript writing and revisions: AJP, DY, XW, DPB, MAE, MG, TG, JDK, JEM, HCC, SMR, GAW, EAW, KW, J-CC

Obtained funding: J-CC, HCC

Conflicts of Interest: The authors have no conflicts

Academic conferences

This manuscript was submitted for presentation at the 2020 Annual Meeting of the International Society of Environmental Epidemiology in Washington D.C.

Setting: Geographically-diverse community-dwelling population.

Participants: 1,583 dementia-free women aged ≥ 80.

Measurements: Women completed up to 6-annual memory assessments (latent composite of East Boston Memory Test and Telephone Interview for Cognitive Status) and the 15-item Geriatric Depression Scale. We estimated 3-year average exposures to regional $PM_{2.5}$ (particulate matter with aerodynamic diameter <2.5 μm; interquartile range [IQR] = 3.35μg/m^3) and 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 episodic memory and depressive symptoms while adjusting for potential confounders. Remote NO_2 (β=.287 per IQR; p=.002) and $PM_{2.5}$ (β=.170 per IQR; p=.019) exposure was significantly associated with larger increases in standardized depressive symptoms, although the magnitude of the difference, less than 1 point on the GDS-15, is of questionable clinical significance. Higher depressive symptoms were associated with accelerated episodic memory declines (β=−.372; p=.001), with a significant indirect effect of remote NO_2 and $PM_{2.5}$ exposure on episodic memory declines mediated by depressive symptoms. There were no other significant indirect exposure effects.

Conclusions: These findings in oldest-old women point to potential adverse effects of late-life exposure to air pollution on subsequent interplay between depressive symptoms and episodic memory, highlighting air pollution as an environmental health risk factor for older women.

Keywords

Depressive symptoms; episodic memory; air pollution; oldest-old

1. Introduction

People age 80 year and older, referred to hereafter as the oldest-old, represent the fastest growing segment of the US population[1]. 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[2]. Declines in episodic memory (EM)[3], become more pronounced after age 80 and typically co-occur with DS[4]. There is considerable environmental influence on the etiology of both DS[5] and EM[6, 7]; however, in the oldest-old, the role of the physical environments has been understudied.

Exposure to air pollutants, such as ambient $PM_{2.5}$ (particulate matter with aerodynamic diameter <2.5 μm) and gaseous NO_2 (nitrogen dioxide), may represent novel environmental risk factors of accelerated brain aging[8]. Longitudinal studies have examined $PM_{2.5}$ exposure as a risk factor for DS, EM decline, and dementia in older adulthood[9–13]. No longitudinal studies have examined associations between exposure to traffic-related pollutants with DS or depression in late life. Previous work on has also focused on associations with exposures measured in recent years immediately prior to the 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 $PM_{2.5}$ exposure, DS, and EM suggests that air pollution-related memory decline may precede increases in DS[14]. Specifically, $PM_{2.5}$ exposure averaged 3-years prior to 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 old, making it difficult to generalize the observed associations to the oldest-old. This previous work was further limited by studying only $PM_{2.5}$, whereas other studies had reported the associations of EM decline with NO_2[15, 16].

The purpose of this longitudinal study was to examine the associations of exposures to NO_2 and $PM_{2.5}$ with changes in EM and DS over a 5-year period in a geographically-diverse community-dwelling cohort of women aged 80 years and older. We also examined whether the observed associations, might vary by pollutants (NO_2 vs. $PM_{2.5}$) and exposure time period (in recent vs. remote years).

2. Materials and Methods

2.1 Study Population

This longitudinal cohort study included 1,583 community-dwelling older women age 80 years or older enrolled in the Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO)[17] who were dementia-free (see Supplemental Methods for description of dementia ascertainment) at study baseline (aged 80–93 years old). The WHIMS-ECHO began in 2008, and was an extension study to the Women's Health Initiative Memory Study (WHIMS)[18] which itself was an ancillary study to the larger Women's Health Initiative (WHI) trial of postmenopausal hormone therapy[19] (see Supplementary Figure 1 for a panel A for a flowchart of this study sample while panel B presents a timeline of study assessments). Participants completed annual phone-based neuropsychological assessments (up to 6 assessments), including measures of DS and EM. A more detailed description of the study population is included in the Supplemental methods.

2.2 Assessment of DS

DS were assessed at WHIMS-ECHO baseline and at each annual follow-up using the 15-item Geriatric Depression Scale (GDS-15)[20]. GDS-15 scores were positively skewed, so scores were transformed using a 3-quantile spline transformation applied in our previous work[11]. Transformed scores were standardized on a T-score metric (Mean = 50; SD = 10), based on the baseline mean and standard deviation. Higher scores reflect greater depression symptoms.

2.3 Assessment of verbal EM

Verbal EM was assessed by the immediate (IR) and delayed recall (DR) measures from both the East Boston Memory Test (EBMT)[21] and word-list items of the Telephone Interview for Cognitive Status-modified (TICSm)[22]. 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 standard deviation. In order 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 Supplemental methods for additional details).

2.4 Assessment of ambient $PM_{2.5}$ and NO_2

Participants' addresses were prospectively collected at each WHI assessment and geocoded using standardized procedures[23, 24]. Ambient annual mean concentrations of $PM_{2.5}$ in ug/m^3 and NO_2 in ppb at each location were estimated using regionalized universal kriging models, which were based on US Environmental Protection Agency (EPA) monitoring data[25–27]. 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 10–13 years prior to the WHIMS-ECHO baseline (see Figure 1 panel B). Both exposure variables were scaled to the interquartile range (IQR) based on the remote exposure time period (remote $PM_{2.5}$ IQR = 3.35 μg/m^3; remote NO_2 IQR = 9.55 ppb).

2.5 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; employment status); lifestyle factors (smoking; alcohol use; physical activities); and clinical characteristics, including past or present self-reported postmenopausal hormone treatment, history of cardiovascular disease (including 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 have been previously documented[28]. Neighborhood socioeconomic characteristics (nSES) were characterized using standard methods[29].

2.6 Statistical Analysis

Structural equation models (SEMs) for latent change scores (LCSs)[30, 31] were constructed to characterize associations between air pollution exposure and temporal changes in the two inter-related neuropsychological processes (EM; DS) over the first five years of the WHIMS-ECHO study period. We examined change over one-year intervals because women completed annual assessments of both EM and DS. The Supplemental 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 (Supplemental Figure S1) and EM (Supplemental Figure S2). For DS, the equation to estimate annual individual-specific change in DS for individual i at timepoint t ($\Delta dep_{i,t}$) was written as:

$$\Delta \text{dep}_{i,t} = \alpha_{dep} * \text{slp}_{dep,i} + \beta_{dep} * \text{ldep}_{i,t} + \gamma_{\text{exposure on } \Delta \text{dep}} * Exposure_i \quad \text{(Equation 1)}$$

In the above equation, $\Delta\text{dep}_{i,t}$ denotes the estimated individual-specific annual change in DS and is a function of the following effects: individual-specific constant linear change (denoted by $\text{slp}_{\text{dep}i}$), non-linear proportional change capturing the extent to which magnitude of change is dependent on previous estimate of DS (β_{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 the following 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, 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 timepoint (see Supplemental methods). Separate models were run to examine how the defined neuropsychological process was influenced by ambient $PM_{2.5}$ or NO_2, each including remote and recent exposures effects.

2.6.3 Bivariate latent change score models.—Figures S3 and S4 in Supplemental materials 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 ($\text{slp}_{\text{dep}i}$), proportional change (β_{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 ($\gamma_{\text{lem on }\Delta\text{dep}}$).

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% CI) via Monte Carlo simulation[32]. 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 $PM_{2.5}$ and NO_2.

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 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 Supplemental 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 prior to the WHIMS baseline, to explore whether findings could be explained by prior history of depression. All LCS models were conducted using the SEM program MPLUS version 8[33] which was run via the MPLUS Automation package[34] in R.

3. Results

On average, participants completed nearly five (mean±S.D.= 4.25±1.81) assessments of EM and DS. Table 1 compares the distribution of 3-year average exposures to regional $PM_{2.5}$ and NO_2 at the remote period 10 years before the WHIMS-ECHO baseline assessment by population characteristics. Participants exposed to higher concentrations of remote $PM_{2.5}$ 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_2 exposure were more likely to have either more or less than a high school education, to reside in the West, and to be racial/ethnic minorities, current smokers, and non-drinkers (less than one drink per day).

All univariate LCS models fit data acceptably (Supplemental Table S1 for all model fit indices). Increased remote exposures were associated with greater annual increases in DS during the WHIMS-ECHO follow-up (Supplemental Table S2). For example, one inter-quartile increment increase in $PM_{2.5}$ (3.35 μg/m^3) exposure was associated with a .170 larger annual increase in T-score standardized DS (95% confidence interval (CI) = .027-.312). A similar putative adverse exposure effect was observed for NO_2 ($\gamma_{\text{remote NO2 on }\Delta\text{dep}}$ = .287; 95% CI = .105-.470; per inter-quartile 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 NO2; p=.126 for $PM_{2.5}$). In contrast, there was no statistically significant association of EM decline with either $PM_{2.5}$ or NO_2, 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 (25^{th} percentile), average (median), or relatively high (75^{th} 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_2 experienced 24% larger increases in DS compared to women with low exposure while higher $PM_{2.5}$ exposure was associated with 17% larger increases. Applying recently published guidelines for effect size interpretation our observed effect sizes of exposure on changes in depressive symptoms are considered small yet potentially consequential[35].

In Table 2, the results of bivariate LCS models examining the direct and indirect effect of exposure on changes in DS are presented. All models exhibited acceptable model fit (see Supplemental Table S1). Consistent with univariate models, neither NO_2 nor $PM_{2.5}$ exposure over the remote 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_2 and $PM_{2.5}$ exposures were both associated with increased DS over the follow-up period. For example, a one inter-quartile increment in remote NO_2 exposure was associated with a .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 being associated with .377-.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 interquartile range for NO_2 exposure. The magnitude of effects of recent exposures during the 3 years before the WHIMS-ECHO baseline were of similar magnitude as remote exposure although not statistically significant.

In our sensitivity analyses, the observed direct associations between exposures and increased DS (Table S3), as well as the resulting indirect effects on EM decline mediated by increased DS (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_2 and $PM_{2.5}$ (Supplement Table S5), as well as the indirect effects on EM decline (Supplement 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 prior to the WHIMS baseline, the associations between exposure to higher concentrations of $PM_{2.5}$ and NO_2 and annual changes in DS were significantly attenuated (Supplement Table S7). The corresponding indirect effect of exposure to $PM_{2.5}$ on declines in EM mediated by DS was no longer statistically significant (Supplement Table S8). The corresponding indirect effect of exposure to NO_2 on declines in EM mediated by DS was attenuated but remained statistically significant.

4. Discussion

In this geographically-diverse cohort of women aged 80 years 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_2 or $PM_{2.5}$ 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 10–13 years before the neuropsychological assessment. These observed associations were also stronger with NO_2, as compared to $PM_{2.5}$ 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_2 and $PM_{2.5}$. In bivariate models, women with increasing DS tended to have larger declines in EM one year later, whereas EM was not associated with subsequent changes in DS. A statistically significant indirect effect of remote exposure to either NO_2 or $PM_{2.5}$ 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 socio-demographic factors, lifestyle, individual SES, neighborhood socioeconomic 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_2 and $PM_{2.5}$ 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, $PM_{2.5}$ exposure might increase the risk of clinically significant depression across adulthood[36], but such association was less consistent among middle-aged and older women[37]. Long-term $PM_{2.5}$ exposure has also been associated with more severe DS in some studies[11, 38] , but no direct associations in the others[14, 39, 40]. 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-sized 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 associated with remote exposures to $PM_{2.5}$ and NO_2, 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[14], 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 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 $PM_{2.5}$ 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 to later older adulthood. It is possible that worse memory may be more distressing at younger ages. Therefore, we may see increases in DS being 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_2 exposure had a stronger association with changes in DS compared to $PM_{2.5}$ and DS. In the sensitivity analyses excluding dementia, the association between NO_2 exposure and DS was attenuated and no longer statistically significant. Previous studies have shown that exposure to both $PM_{2.5}$ and NO_2 may increase risk of dementia[41]. The attenuation of the exposure effect after excluding women with incident dementia suggests that exposure to NO_2 and $PM_{2.5}$ may be

contributing to a common neuropathological process contributing to both dementia risk and DS. Similarly, excluding prior depression attenuated the association between $PM_{2.5}$ and NO_2 on increases in DS. However, NO_2 was attenuated less than $PM_{2.5}$ after excluding women with a prior history of depression. This observation suggests that $PM_{2.5}$ 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 to 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_2 and $PM_{2.5}$.

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 prior to WHIMS-ECHO baseline) and recent (0–3 years prior to 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 Caucasian 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 and were more likely be African-American and 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 epidemiologic evidence that living in areas with higher levels of $PM_{2.5}$ and NO_2 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 heterogenous, likely varying by pollutants and age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The corresponding authors, Chen and Petkus, affirm that all of the authors have contributed significantly to the work and has obtained consent from all contributors.

Funding sources

The WHIMS was funded by Wyeth Pharmaceuticals, St Davids, PA,USA, and Wake Forest University. This study and related research are supported by the National Institute of Environmental Health Sciences (R01ES025888; 5P30ES007048), the National Institute on Aging (R01AG033078) and The Alzheimer's Disease Research Center at USC (P50AG005142). Petkus and Chen are supported in part by the RF1AG054068. Younan and Chen are also supported by the P01AG055367. The Women's Health Initiative Study of Cognitive Aging was supported by the Department of Health and Human Services and the National

Institute on Aging (N01-AG-1-2106), The WHI program is funded by the National Heart, Lung, and Blood Institute (NIH) through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C and HHSN271201100004C. The air pollution models were developed under a STAR research assistance agreement, No. RD831697 (MESA Air) and RD-83830001 (MESA Air Next Stage), awarded by the US Environmental Protection Agency (EPA).

Financial Disclosure: This study and related research are supported by the National Institute of Environmental Health Sciences (R01ES025888; 5P30ES007048), the National Institute on Aging (R01AG033078) and The Alzheimer's Disease Research Center at USC (P50AG005142). Petkus and Chen are supported in part by the RF1AG054068. Younan and Chen are also supported by the P01AG055367. The WHIMS was funded by Wyeth Pharmaceuticals, St Davids, PA,USA, and Wake Forest University. The Women's Health Initiative Study of Cognitive Aging was supported by the Department of Health and Human Services and the National Institute on Aging (N01-AG-1-2106), The WHI program is funded by the National Heart, Lung, and Blood Institute (NIH) through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C and HHSN271201100004C. The air pollution models were developed under a STAR research assistance agreement, No. RD831697 (MESA Air) and RD-83830001 (MESA Air Next Stage), awarded by the US Environmental Protection Agency (EPA)

Sponsors Role: Representatives from the NIH serving on the WHI Publications and Presentations Committee reviewed this manuscript before submission but had no direct role in its development and final submission.

References

[1]. Ortman JM, Velkoff VA, Hogan H. An aging nation: The older population in the United States population estimates and projections. 2014, pp. 1140.

[2]. Sutin AR, Terracciano A, Milaneschi Y, An Y, Ferrucci L, Zonderman AB. The trajectory of depressive symptoms across the adult life span. JAMA Psychiatry. 2013;70: 803–811. [PubMed: 23760442]

[3]. Tulving E Episodic memory: from mind to brain. Annu Rev Psychol. 2002;53: 1–25. [PubMed: 11752477]

[4]. Byers AL, Yaffe K. Depression and risk of developing dementia. Nat Rev Neurol. 2011;7: 323–331. [PubMed: 21537355]

[5]. Petkus AJ, Beam CR, Johnson W, et al. Gene-environment interplay in depressive symptoms: moderation by age, sex, and physical illness. Psychol Med. 2017;47: 1836–1847. [PubMed: 28202098]

[6]. Swan GE, Reed T, Jack LM, et al. Differential genetic influence for components of memory in aging adult twins. Arch Neurol. 1999;56: 1127–1132. [PubMed: 10488814]

[7]. McClearn GE, Johansson B, Berg S, et al. Substantial genetic influence on cognitive abilities in twins 80 or more years old. Science. 1997;276: 1560–1563. [PubMed: 9171059]

[8]. The Lancet N Air pollution and brain health: an emerging issue. Lancet Neurol. 2018;17: 103. [PubMed: 29413304]

[9]. Cacciottolo M, Wang X, Driscoll I, et al. Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. Transl Psychiatry. 2017;7: e1022. [PubMed: 28140404]

[10]. Younan D, Petkus AJ, Widaman KF, et al. Particulate matter and episodic memory decline mediated by early neuroanatomic biomarkers of Alzheimer's disease. Brain. 2020;143: 289–302. [PubMed: 31746986]

[11]. Petkus AJ, Younan D, Wang X, et al. Particulate Air Pollutants and Trajectories of Depressive Symptoms in Older Women. Am J Geriatr Psychiatry. 2019;27: 1083–1096. [PubMed: 31311712]

[12]. Lim YH, Kim H, Kim JH, Bae S, Park HY, Hong YC. Air pollution and symptoms of depression in elderly adults. Environ Health Perspect. 2012;120: 1023–1028. [PubMed: 22514209]

[13]. Chen H, Kwong JC, Copes R, et al. Exposure to ambient air pollution and the incidence of dementia: A population-based cohort study. Environment international. 2017;108: 271–277. [PubMed: 28917207]

[14]. Petkus AJ, Younan D, Widaman K, et al. Exposure to fine particulate matter and temporal dynamics of episodic memory and depressive symptoms in older women. Environ Int. 2020;135: 105196. [PubMed: 31881430]

[15]. Kulick ER, Wellenius GA, Boehme AK, et al. Long-term exposure to air pollution and trajectories of cognitive decline among older adults. Neurology. 2020.

[16]. Kulick ER, Elkind MSV, Boehme AK, et al. Long-term exposure to ambient air pollution, APOE-ε4 status, and cognitive decline in a cohort of older adults in northern Manhattan. Environ Int. 2020;136: 105440. [PubMed: 31926436]

[17]. Espeland MA, Rapp SR, Manson JE, et al. Long-term Effects on Cognitive Trajectories of Postmenopausal Hormone Therapy in Two Age Groups. J Gerontol A Biol Sci Med Sci. 2017;72: 838–845. [PubMed: 27506836]

[18]. Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. Control Clin Trials. 1998;19: 604–621. [PubMed: 9875839]

[19]. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials. 1998;19: 61–109. [PubMed: 9492970]

[20]. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17: 37–49. [PubMed: 7183759]

[21]. Scherr PA, Albert MS, Funkenstein HH, et al. Correlates of cognitive function in an elderly community population. Am J Epidemiol. 1988;128: 1084–1101. [PubMed: 3189282]

[22]. Welsh KA, Breitner JC, Magruder-Habib KM. Detection of dementia in the elderly using telephone screening of cognitive status. Neuropsychiatry, Neuropsychology, & Behavioral Neurology. 1993;6: 103–110.

[23]. Whitsel EA, Rose KM, Wood JL, Henley AC, Liao D, Heiss G. Accuracy and repeatability of commercial geocoding. Am J Epidemiol. 2004;160: 1023–1029. [PubMed: 15522859]

[24]. Whitsel EA, Quibrera PM, Smith RL, et al. Accuracy of commercial geocoding: assessment and implications. Epidemiol Perspect Innov. 2006;3: 8. [PubMed: 16857050]

[25]. Bergen S, Sheppard L, Sampson PD, et al. A national prediction model for PM2.5 component exposures and measurement error-corrected health effect inference. Environ Health Perspect. 2013;121: 1017–1025. [PubMed: 23757600]

[26]. Sampson PD, Richards M, Szpiro AA, et al. A regionalized national universal kriging model using Partial Least Squares regression for estimating annual PM2.5 concentrations in epidemiology. Atmos Environ (1994). 2013;75: 383–392. [PubMed: 24015108]

[27]. Young MT, Bechle MJ, Sampson PD, et al. Satellite-Based NO2 and Model Validation in a National Prediction Model Based on Universal Kriging and Land-Use Regression. Environ Sci Technol. 2016;50: 3686–3694. [PubMed: 26927327]

[28]. Heckbert SR, Kooperberg C, Safford MM, et al. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. Am J Epidemiol. 2004;160: 1152–1158. [PubMed: 15583367]

[29]. Chi GC, Hajat A, Bird CE, et al. Individual and Neighborhood Socioeconomic Status and the Association between Air Pollution and Cardiovascular Disease. Environ Health Perspect. 2016;124: 1840–1847. [PubMed: 27138533]

[30]. McArdle JJ. A latent difference score approach to longitudinal dynamic structural analyses. Structural Equation Model: Present Future, 2001, pp. 342–380.

[31]. Kievit RA, Brandmaier AM, Ziegler G, et al. Developmental cognitive neuroscience using latent change score models: A tutorial and applications. Dev Cogn Neurosci. 2018;33: 99–117. [PubMed: 29325701]

[32]. Selig JP, Preacher KJ. Monte Carlo method for assessing mediation: An interactive tool for creating confidence intervals for indirect effets. http://quantpsy.org, 2008.

[33]. Muthen LK, Muthen BO. Mplus User's Guide. Sixth Edition ed. Los Angeles, CA, 2010.

[34]. Hallquist MN, Wiley JF. MplusAutomation: An R Package for Facilitating Large-Scale Latent Variable Analyses in Mplus. Struct Equ Modeling. 2018;25: 621–638. [PubMed: 30083048]

[35]. Funder DC, Ozer DJ. Evaluating effect size in psychological research: Sense and nonsense. Advances in Methods and Practices in Psychological Science. 2019;2: 156–168.

[36]. Kim KN, Lim YH, Bae HJ, Kim M, Jung K, Hong YC. Long-Term Fine Particulate Matter Exposure and Major Depressive Disorder in a Community-Based Urban Cohort. Environ Health Perspect. 2016;124: 1547–1553. [PubMed: 27129131]

[37]. Kioumourtzoglou MA, Power MC, Hart JE, et al. The Association Between Air Pollution and Onset of Depression Among Middle-Aged and Older Women. Am J Epidemiol. 2017;185: 801–809. [PubMed: 28369173]

[38]. Wang R, Yang B, Liu P, et al. The longitudinal relationship between exposure to air pollution and depression in older adults. Int J Geriatr Psychiatry. 2020.

[39]. Wang Y, Eliot MN, Koutrakis P, et al. Ambient air pollution and depressive symptoms in older adults: results from the MOBILIZE Boston study. Environ Health Perspect. 2014;122: 553–558. [PubMed: 24610154]

[40]. Pun VC, Manjourides J, Suh H. Association of Ambient Air Pollution with Depressive and Anxiety Symptoms in Older Adults: Results from the NSHAP Study. Environ Health Perspect. 2017;125: 342–348. [PubMed: 27517877]

[41]. Peters R, Ee N, Peters J, Booth A, Mudway I, Anstey KJ. Air Pollution and Dementia: A Systematic Review. J Alzheimers Dis. 2019;70: S145–S163. [PubMed: 30775976]

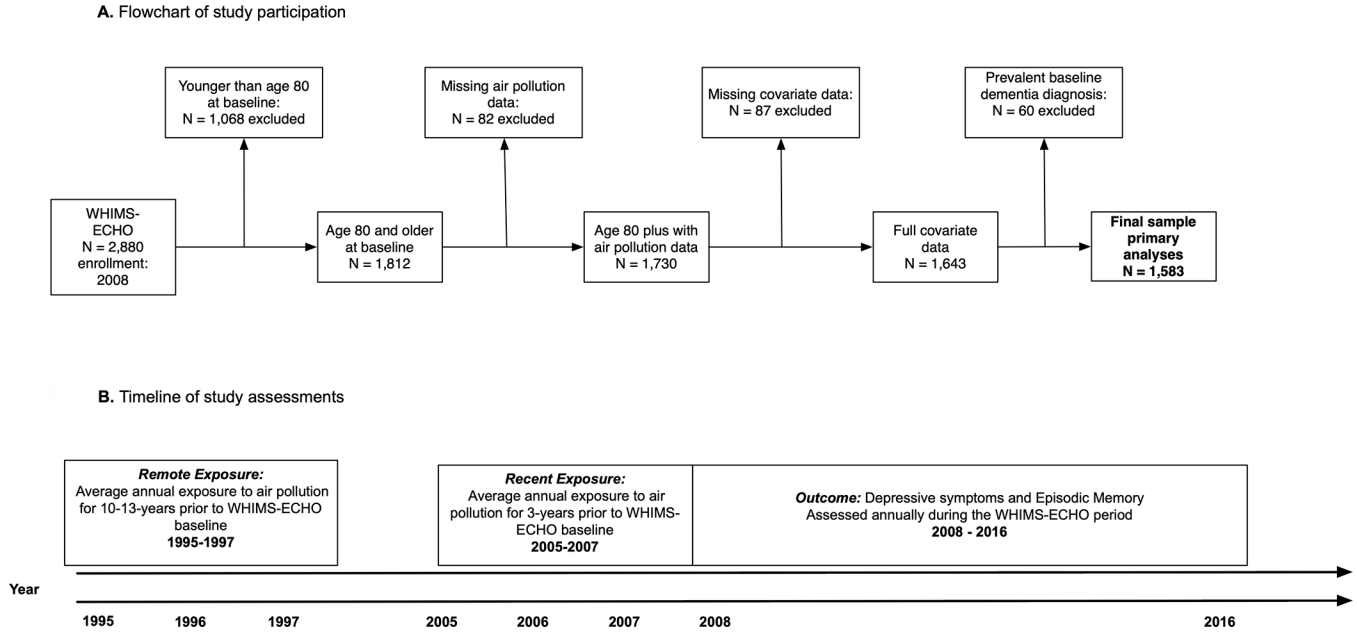

Figure 1.

(A). Flowchart of study participation. **(B).** Timeline of study assessments

WHIMS-EHCHO = Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes

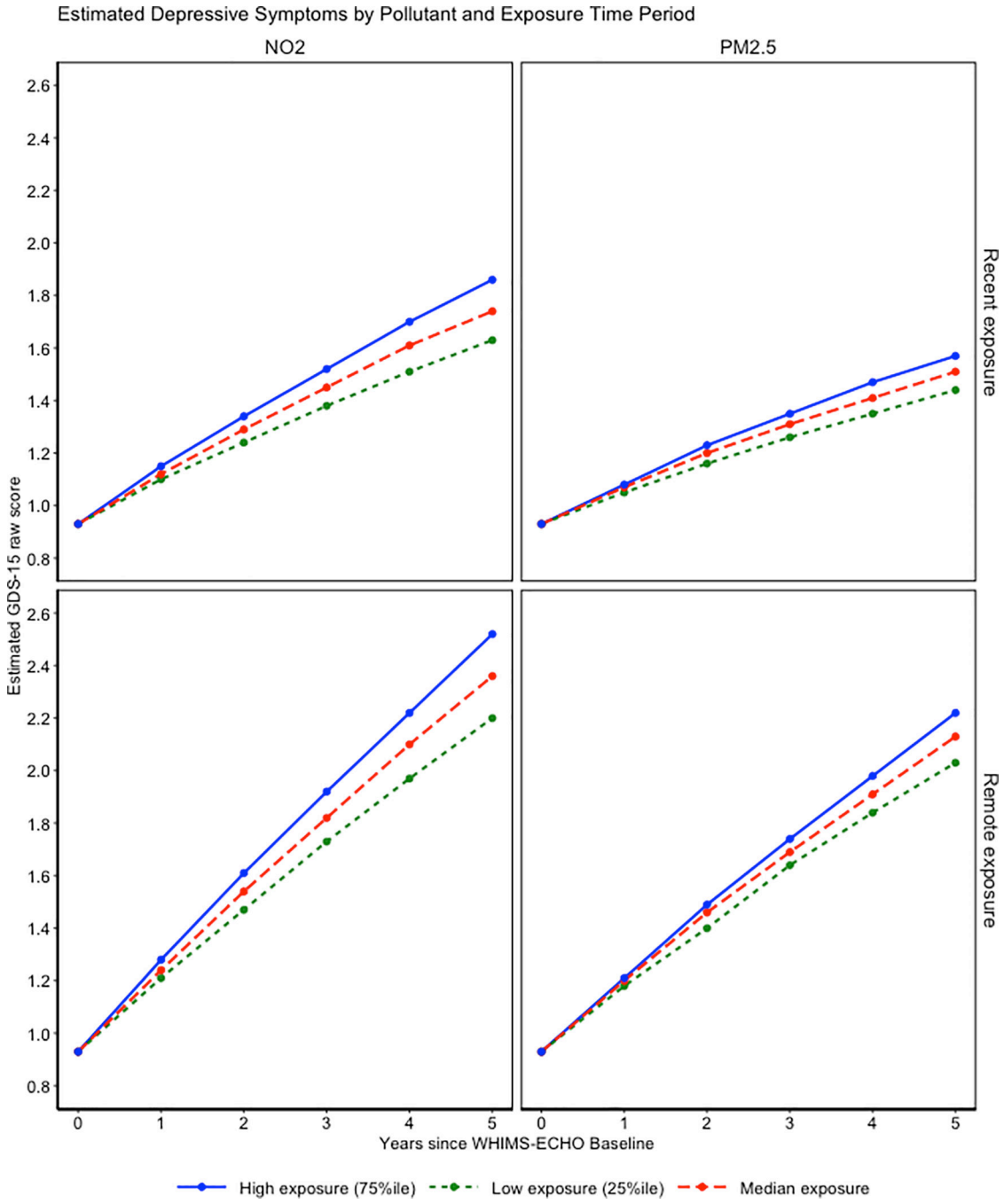

Figure 2.

Estimated depressive symptoms as measured by the 15-item Geriatric Depression Scale 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_2 exposure effect while the second column is the $PM_{2.5}$ exposure effect. Therefore, the graph illustrated in the first row and first column represents the effect of recent NO_2 exposure.

* Denotes p <.05
** Denotes p<.01

Table 1.

Comparison of Estimated Remote $PM_{2.5}$ and NO_2 Exposures by Population Characteristics at Baseline (N = 1,583).

		Distribution of remote 3-year average[a] $PM_{2.5}$ exposure($\mu g/m^3$)			Distribution of remote 3-year average[a] NO_2 exposure (ppb)		
Population Characteristics	**N**	**Mean ± SD**	**(25th, Median, 75th)**	**p[b]**	**Mean ± SD**	**(25th, Median, 75th)**	**p[b]**
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	1455	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	1253	13.34 ± 2.78	(11.6, 13.4, 15.0)		16.11 ± 7.17	(10.7, 15.2, 20.2)	
Income (in 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 or more	357	13.46 ± 2.48	(12.0, 13.5, 14.8)		16.86 ± 7.27	(11.4, 15.9, 21.0)	
Don’t know	72	12.99 ± 2.50	(11.5, 13.0, 14.4)		15.72 ± 6.88	(11.3, 13.9, 19.3)	
Lifestyle							
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)	
Alcohol use				.23			<.01
Non-drinker	190	13.40 ± 2.97	(11.7, 13.4,15.1)		14.51 ± 7.93	(8.6, 12.3, 18.1)	

		Distribution of remote 3-year average[a] $PM_{2.5}$ exposure(μg/m^3)			Distribution of remote 3-year average[a] NO_2 exposure (ppb)		
Population Characteristics	**N**	**Mean ± SD**	**(25th, Median, 75th)**	**p[b]**	**Mean ± SD**	**(25th, Median, 75th)**	**p[b]**
Past drinker	271	13.44 ± 2.96	(11.5, 13.5, 15.5)		15.80 ± 7.20	(10.5, 14.5, 19.8)	
Less than 1 drink/ day	916	13.39 ± 2.66	(11.7, 13.4, 14.9)		16.75 ± 7.14	(11.6, 16.1, 20.9)	
More than 1 drink/ day	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 minutes				.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/week	347	13.36 ± 2.82	(11.7, 13.2, 15.0)		16.65 ± 7.31	(11.6, 15.3, 20.9)	
≥4 episodes/week	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	1025	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	1302	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	1513	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	1343	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)	

Note

[a] 3-year average of the annual exposure estimated before the remote period of 10-years prior to the WHIMS-ECHO baseline at each participant's location using the national spatiotemporal model

[b] p values estimated from ANOVA F-tests or t-tests comparing the mean exposures.

Table 2.

Bivariate latent change score structural equation models examining the direct effect of recent and remote exposure to NO_2 and $PM_{2.5}$ on changes in depressive symptoms as well as the respective indirect exposure effect mediated by episodic memory (N = 1,583).

	Exposure: NO_2	
	Remote[a] Exposure	Recent[b] Exposure
	Est[d] (95% CI)	Est[d] (95% CI)
Estimates of Direct Effect[c]		
Effect of NO_2 on annual change in depressive symptoms ($\gamma_{NO2\ on\ \Delta dep}$)	.221 (−.093; .535)	.169 (−.185; .523)
Estimates of Indirect Effect[c]		
Effects of NO_2 on annual changes in episodic memory ($\gamma_{NO2on\ \Delta em}$)	−.074 (−.264; .116)	−.163 (−.441; .114)
Effects of episodic memory performance on annual change in depressive symptoms ($\gamma_{Lem\ on\ \Delta dep}$)	.112 (−.276; .500)	.094 (−.294; .483)
Indirect effect of NO_2 on annual change in depressive symptoms ($\gamma_{NO2on\ \Delta em} * \gamma_{Lem\ on\ \Delta dep}$)	−.008 (−.078; .035)[e]	−.015 (−.140; .059)[e]
	Exposure: $PM_{2.5}$	
	Remote[a] Exposure	Recent[b] Exposure
	Est[d] (95% CI)	Est[d] (95% CI)
Estimates of Direct Effect[c]		
Effect of $PM_{2.5}$ on annual change in depressive symptoms ($\gamma_{PM2.5\ on\ \Delta dep}$)	.108 (−.158; .373)	.115 (−.194; .424)
Estimates of Indirect Effect[c]		
Effects of $PM_{2.5}$ on annual changes in episodic memory ($\gamma_{PM2.5\ on\ \Delta em}$)	−.095 (−.272; .082)	−.026 (−.260; .209)
Effects of episodic memory performance on annual change in depressive symptoms ($\gamma_{Lem\ on\ \Delta dep}$)	.113 (−.278; .503)	.085 (−.296; .466)
Indirect effect of $PM_{2.5}$ on annual change in depressive symptoms ($\gamma_{PM2.5\ on\ \Delta em} * \gamma_{Lem\ on\ \Delta dep}$)	−.011 (−.088; .041)[e]	−.002 (−.079; .050)[e]

Abbreviations: NO_2 = nitrogen dioxide; $PM_{2.5}$ = particulate matter with <2.5 μm; 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, CI = Confidence interval, Est = parameter estimate

Estimates bolded if statistically significant at p<0.05

[a] Remote represents the 3-year average exposures to regional $PM_{2.5}$ and NO_2 10 years prior to study baseline

[b] Recent represents the 3-year average exposures to regional $PM_{2.5}$ and NO_2 for the 3 years prior to study baseline

[c] All effects below were derived from the bivariate structural equation models (SEM) as depicted in figure 2 panel A, with exposure scaled by interquartile range from the remote period ($PM_{2.5}$ scaled by 3.35 μg/m^3 and NO_2 scaled by 9.55 ppb).

[d] 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, and history of cardiovascular disease), and neighborhood socioeconomic characteristics.

[e] 95% confidence interval for the indirect effect is asymmetric and estimated via Monte Carlo Simulation

Table 3.

Bivariate latent change score structural equation models examining the direct effect of recent and remote exposure to NO_2 and $PM_{2.5}$ on changes in episodic memory as well as the respective indirect effect mediated by depressive symptoms (N = 1,583).

	Exposure: NO_2	
	Remote[a] Exposure	Recent[b] Exposure
	Est[d] (95% CI)	Est[d] (95% CI)
Estimates of Direct Effect[c]		
Effect of NO_2 on annual change in episodic memory ($\gamma_{NO2\ on\ \Delta em}$)	.179 (−.119; .477)	−.024 (−.425; .377)
Estimates of Indirect Effect[c]		
Effects of NO_2 on annual changes in GDS-15 ($\gamma_{NO2\ on\ \Delta dep}$)	**.255 (.074; .436)**	.203 (−.042; .447)
Effects of GDS-15 performance on annual change in episodic memory ($\gamma_{Ldep\ on\ \Delta em}$)	**−.372 (−.594; −.150)**	**−.384 (−.615; −.154)**
Indirect effect of NO_2 on annual change in episodic memory ($\gamma_{NO2\ on\ \Delta dep} * \gamma_{Ldep\ on\ \Delta em}$)	**−.095 (−.171; −.026)** [e]	−.078 (−.184; .018)[e]
	Exposure: $PM_{2.5}$	
	Remote[a] Exposure	Recent[b] Exposure
	Est[d] (95% CI)	Est[d] (95% CI)
Estimates of Direct Effect[c]		
Effect of $PM_{2.5}$ on annual change in episodic memory ($\gamma_{PM2.5\ on\ \Delta em}$)	.114 (−.149; .377)	.154 (−.183; .491)
Estimates of Indirect Effect[c]		
Effects of $PM_{2.5}$ on annual changes in GDS-15 ($\gamma_{PM2.5\ on\ \Delta dep}$)	.138 (−.004; .280)	.123 (−.081; .328)
Effects of GDS-15 performance on annual change in episodic memory ($\gamma_{Ldep\ on\ \Delta em}$)	**−.377 (−.608; −.146)**	**−.380 (−.612; −.148)**
Indirect effect of $PM_{2.5}$ on annual change in episodic memory ($\gamma_{PM2.5\ on\ \Delta dep} * \gamma_{Ldep\ on\ \Delta em}$)	**−.052 (−.112; −.001)** [e]	−.047 (−.130; .035)[e]

Abbreviations: NO_2 = nitrogen dioxide; $PM_{2.5}$ = particulate matter with <2.5 μm; 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, CI = Confidence interval, Est = parameter estimate

Estimates bolded if statistically significant at p<0.05

[a] Remote represents the 3-year average exposures to regional $PM_{2.5}$ and NO_2 10 years prior to study baseline

[b] Recent represents the 3-year average exposures to regional $PM_{2.5}$ and NO_2 for the 3 years prior to study baseline

[c] All effects below were derived from the bivariate structural equation models (SEM) as depicted in figure 2 panel A, with exposure scaled by interquartile range from the remote period ($PM_{2.5}$ scaled by 3.35 μg/m^3 and NO_2 scaled by 9.55 ppb).

[d] 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, and history of cardiovascular disease), and neighborhood socioeconomic characteristics.

[e] 95% confidence interval for the indirect effect is asymmetric and estimated via Monte Carlo Simulation