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Associations Between Air Pollution Exposure and Empirically Derived Profiles of Cognitive Performance in Older Women

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Abstract

Background: Elucidating associations between exposures to ambient air pollutants and profiles of cognitive performance may provide insight into neurotoxic effects on the aging brain.

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SUPPLEMENTARY MATERIAL

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Objective: We examined associations between empirically derived profiles of cognitive performance and residential concentrations of particulate matter of aerodynamic diameter < 2.5 (PM_{2.5}) and nitrogen dioxide (NO₂) in older women.

Method: Women ($N = 2,142$) from the Women's Health Initiative Study of Cognitive Aging completed a neuropsychological assessment measuring attention, visuospatial, language, and episodic memory abilities. Average yearly concentrations of PM_{2.5} and NO₂ were estimated at the participant's addresses for the 3 years prior to the assessment. Latent profile structural equation models identified subgroups of women exhibiting similar profiles across tests. Multinomial regressions examined associations between exposures and latent profile classification, controlling for covariates.

Result: Five latent profiles were identified: low performance across multiple domains (poor multi-domain; $n = 282$; 13%), relatively poor verbal episodic memory (poor memory; $n = 216$; 10%), average performance across all domains (average multi-domain; $n = 974$; 45%), superior memory ($n = 381$; 18%), and superior attention ($n = 332$; 15%). Using women with average cognitive ability as the referent, higher PM_{2.5} (per interquartile range [IQR] = 3.64 $\mu\text{g}/\text{m}^3$) was associated with greater odds of being classified in the poor memory (OR = 1.29; 95% Confidence Interval [CI] = 1.10–1.52) or superior attention (OR = 1.30; 95% CI = 1.10–1.53) profiles. NO₂ (per IQR = 9.86 ppb) was associated with higher odds of being classified in the poor memory (OR = 1.38; 95% CI = 1.17–1.63) and lower odds of being classified with superior memory (OR = 0.81; 95% CI = 0.67–0.97).

Conclusion: Exposure to PM_{2.5} and NO₂ are associated with patterns of cognitive performance characterized by worse verbal episodic memory relative to performance in other domains.

Keywords

Cognitive aging; latent class analysis; nitrogen dioxide; particulate matter; women

INTRODUCTION

More than 47 million people worldwide are living with Alzheimer's disease and related dementias (ADRD), with that number expected to triple by 2050 [1]. Exposure to ambient air pollutants in later life may be a modifiable risk factor for developing ADRD [2]. A growing body of literature suggests that fine particulate matter with aerodynamic diameter < 2.5 μm (PM_{2.5}) and nitrogen dioxide (NO₂) may increase the risk of dementia, including Alzheimer's disease (AD) [3, 4]. Despite the increasing evidence of negative impacts of air pollution across the ADRD continuum, studies examining associations between ambient air pollution and domain-specific cognitive performance in older adults have produced mixed findings [5]. Some studies reported significant adverse cross-sectional associations between exposure to PM_{2.5} or NO₂ and worse episodic memory [6–8], processing speed/attention [8, 9], semantic fluency [7], phonemic fluency [10], visuospatial ability [11], and aspects of executive function [7, 11, 12], whereas other studies fail to show adverse associations across these domains [6, 10–13]. All these studies examined associations between exposure and performance independently without considering possible heterogeneous patterns of performance across domains.

A growing number of studies using general mixture modeling clustering approaches, such as latent profile analysis (LPA), highlight the presence of heterogeneous patterns of performance across multiple cognitive domains in older adulthood [14–19]. For example, recent studies with two community-based cohorts identify five latent profiles of performance [20, 21]. The latent profiles identified by these studies included three latent profiles of participants who had similar performance across all domains (e.g., “Multiple-Domain Impairment”, “Average”, and “Superior cognition”). Two additional latent profiles with heterogeneous patterns across domains were identified including a “Memory-Specific Impairment” and “Frontal Impairment” latent profiles. Heterogeneous profiles of cognitive performance are clinically meaningful as they are likely manifestations of different underlying neuropathological factors [14–19]. For example, processing speed, attention/working memory, and executive function are disproportionately impacted in cerebrovascular disease, whereas declines in verbal episodic memory and language with relative sparing of basic attention and executive function may be more indicative of AD.

To our knowledge, no research has examined associations between exposure to air pollution and empirically derived profiles of cognitive performance. Prior studies linking air pollution and multiple domains of cognitive performance have only examined exposure and cognitive performance independently across domains. This approach may be overly simplistic, as it does not consider the joint performance across domains. Clarifying associations between air pollution exposure and cognitive profiles may elucidate the neurotoxic effects of air pollution on the brain while also potentially providing insight into the mixed findings reported by previous studies.

To address these knowledge gaps, we conducted the present study with a geographically diverse sample of community dwelling older women without dementia at the time of cognitive testing. The first objective of this study was to identify subgroups of women who exhibited similar patterns of cognitive performance across multiple domains using LPA. We hypothesized that we would identify subgroups of women who exhibited similar patterns of performance. Second, we examined whether residing in areas with higher concentrations of ambient air pollution was associated with empirically derived profiles of cognitive performance. We hypothesized that residing in locations with increased concentrations of ambient air pollution would be associated with increased odds of being classified in empirically derived profiles of performance characterized by worse performance across domains.

METHODS

Study population

We conducted a cross-sectional study that included 2,142 community-dwelling women without dementia who were enrolled in the Women’s Health Initiative Study of Cognitive Aging (WHISCA; $n = 2,304$) [22]. WHISCA was an ancillary study to the Women’s Health Initiative Memory Study (WHIMS) [23], which itself was an ancillary study to the larger Women’s Health Initiative (WHI) hormone therapy trial [24]. Women were enrolled in WHIMS between the years 1996–1998, included a subsample of cognitively intact WHIMS participants who completed additional annual (1999–2010) neuropsychological assessments

through participation in WHISCA. For the present study, we analyzed data from the baseline WHISCA assessment. We excluded 12 women who had either missing air pollution or cognitive performance data. An additional 107 women were excluded due to missing covariate data, while 43 were excluded due to being right censored for dementia diagnosis prior to the WHISCA baseline. Figure 1A presents a flowchart of study participation, while Fig. 1B presents a timeline of estimated air pollution concentrations in relation to neuropsychological assessment. All participants and procedures were in compliance with protocols approved by local Institutional Review Boards.

Three-year average annual exposure to ambient PM_{2.5} and NO₂

Geocoding procedures were first applied to each participant's residential addresses [25] at the day of the WHISCA assessment and for the 3 years prior. A regionalized universal kriging model [25–28] was then applied to estimate annual mean concentrations of ambient PM_{2.5} (in µg/m³) and NO₂ (in ppb) at each participant's residential addresses, accounting for residential mobility. The regionalized universal kriging models are based on US Environmental Protection Agency (EPA) monitoring data and geographic covariates [26, 28]. For PM_{2.5} estimation, over 300 geographic covariates were used to estimate concentrations, including population density, distance to roads, and vegetation in the vicinity. For NO₂ estimation, the model included satellite data and over 400 geographic covariates that covered proximity and buffer measures [28]. The models were cross-validated and had acceptable R² of 0.88 for PM_{2.5} and 0.85 for NO₂. The concentration estimates were then averaged over the 3 years prior to the WHISCA baseline. This approach to estimate both PM_{2.5} and NO₂ have been utilized in previous research in the Women's Health Initiative [29–31].

Assessment of cognitive performance

The WHISCA neurocognitive batteries assessed multiple cognitive domains including attention, verbal episodic memory, figural memory, language, and spatial ability. The forward and backward Digit Span subtest of the Wechsler Adult Intelligence Scale [32] was administered to measure attention. The Card Rotations Test [33] was administered to measure spatial ability. Phonemic (F-A-S) [34] and semantic verbal fluency (vegetables, fruits) [35] were used to measure language ability. The number of errors on the Benton Visual Retention Test (BVRT) [36] was used to measure figural memory. The BVRT was transformed so a higher score represented better performance. Verbal episodic memory was measured using a modified version of the California Verbal Learning Test [37]. Specifically, the total number of words successfully recalled across the three immediate recall trials (CVLT IR) and the total number of words freely recalled after a long delay (CVLT LDR) were used. In WHISCA only three CVLT immediate recall trials were administered instead of the standard five trials.

Dementia ascertainment

Through participation in WHIMS women were screened annually for all-cause dementia defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4). Between 1996 to 2008, women completed the Modified Mini Mental State (3MS) examination each year. Women who screened positive using age-/education-adjusted

3MS scores were administered an extensive neuropsychological evaluation and functional assessment. Beginning in 2008, annual cognitive screenings were conducted by telephone through participation in the WHIMS-Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO) study. The data from these telephone assessments were then used to adjudicate dementia diagnosis. A committee of experts assigned diagnosis and data was available up to June 2018.

Covariates

Demographic characteristics (age, race/ethnicity), US Census tract-level region of residence (northeast, south, Midwest, and west), socioeconomic status (education; family income; employment status), lifestyle factors (smoking; alcohol use; physical activity), and clinical characteristics (self-reported postmenopausal hormone treatment use ever, history of cardiovascular disease, hypertension, hypercholesterolemia, and diabetes mellitus [defined as physician diagnosis plus oral medications, or insulin therapy]) were collected at the WHI baseline via a structured questionnaire. Good reliability and validity of the self-reported medical histories and the physical measures have been previously documented [38]. Depressive symptom severity was measured with the 15-item Geriatric Depression Scale (GDS-15) [39], a reliable and valid measure of depressive symptom severity with scores ranging from 0–15 (higher scores mean greater severity). US Census tract-level data was used to create a composite score of neighborhood socioeconomic characteristics (nSES), including: the natural log of median household income (in dollars), the natural log of median value of owner-occupied housing units, percentage of households receiving interest, dividends or net rental income, the percentage of adults aged 25 + with a college degree, and percentage of civilian population aged 16 + with professional, managerial, or executive occupations [40]. A more detailed description of the nSES composite variable is provided in the Supplementary Methods.

Statistical analysis

LPA is a data-driven approach using general mixture modeling techniques to identify subpopulations, called latent profiles, within a population that exhibit similar patterns of performance across indicator variables. The manual Bolck, Croon, and Hagnaars (BCH) [41] approach to LPA with covariates was followed [42]. A more detailed description of our analytic approach is provided in the Supplementary Methods. The first step of the manual BCH approach was to construct a measurement model to identify the number of latent profiles to extract. Here we included all eight of the adjusted cognitive variables as indicator variables into the LPA measurement model. Because the objective of the paper was to use latent profile analysis to identify subgroups of women with similar patterns of cognitive performance across multiple domains, we examined each respective score instead of creating either composite scores within a domain or a global composite score. We also included age, race/ethnicity, and education as covariate predictors in the LPA model because these demographic variables are associated with cognitive performance in older adulthood and including these covariates will improve fit and model estimation [43]. All LPA analyses were run with 100 random starting values with 10 optimizations to ensure the model was reaching the global maximum. Models with one to six latent profiles were evaluated in a stepwise, iterative fashion. The number of latent profiles to extract was determined

by examining multiple indicators of model fit. First, the Bayesian Information Criterion (BIC) was examined with smaller values indicating better-fitting models. We compared models with k latent profiles with $k-1$ latent profiles using both the Vuon-Lo-Mendell-Rubin adjusted likelihood ratio test (VLMR-LRT) and the Bootstrapped Likelihood Ratio Test (BLRT). The classification accuracy of each model was evaluated with the entropy index (range: 0–1; higher scores indicating more precise assignment to latent profile) and the average posterior probabilities for each extracted latent profile. Finally, when determining the number of latent profiles to extract, we evaluated model parsimony and clinical meaningfulness of the latent profiles.

The second step in the BCH approach entails calculating individual-specific classification error for the modal latent profile assignment and generating BCH weights from the inverse logits of the individual-specific classification errors. These weights were then utilized in the third step, which included constructing a structural equation model (SEM) that included a multinomial logistic regression to estimate associations between living in locations with higher air pollution and membership within latent profile, controlling for covariates. Figure 2 presents a diagram of the SEM constructed in this third step. The BCH weights are incorporated in the SEM to ensure that latent profile membership does not shift with the inclusion of covariates in the model while also accounting for error in latent profile classification [42]. All air pollution effects on latent profile membership were adjusted for the following covariates: age at the WHISCA baseline, race/ethnicity, employment status, geographic region of residence, education, household income, lifestyle factors (smoking; alcohol use; physical activities), composite of global nSES, depressive symptoms, and clinical characteristics (any prior hormone use ever, hypercholesterolemia, hypertension, diabetes mellitus, and history of cardiovascular disease). Separate models were constructed for PM_{2.5} and NO₂ exposure.

Two sensitivity analyses were conducted. In the first sensitivity analysis, we examined potential effects of spatial confounding while adding WHISCA site as a cluster variable. In the second sensitivity analyses, we examined the potential effect of inaccurate covariate assessment due to the fact that clinical and lifestyle covariates were assessed at the WHI baseline and not at the time of the cognitive assessment. In these sensitivity analyses we updated hypertension, history of cardiovascular disease, and smoking covariate data prior between the WHI baseline and the WHISCA baseline using data from WHI follow-up assessments. All SEMs were conducted using the program MPLUS version 8 [44].

RESULTS

Descriptive statistics

Table 1 compares the distribution of average annual concentrations of regional PM_{2.5} ($M = 13.10 \pm 2.80$; Range = 2.89–22.93) and NO₂ ($M = 15.60 \pm 8.20$; Range = 2.97–42.58) for the 3-years prior to WHISCA baseline by population characteristics. The distribution of both PM_{2.5} and NO₂ are provided in Supplementary Figure 1. Women residing in locations with higher concentrations of PM_{2.5} were more likely to be racial/ethnic minorities (Black, non-Hispanic, and Hispanic/Latino), reside in the West, report some physical activity, and be treated for hypercholesterolemia. Women residing in locations with higher concentrations of

NO₂ were more likely to be racial/ethnic minorities, reside in the Northeast, have less than a high school education, report lower income, be past smokers, consume alcohol, and report little or no physical activity.

Identification of latent profiles

The LPA identified five significant latent profiles of cognitive performance (see Supplementary Table 1 for model comparisons). The five-profile model was able to classify women into latent profiles with acceptable precision, as indicated by the entropy (0.75) and mean posterior probabilities (greater than or equal to 0.79). The Vuon-Lo-Mendell-Rubin adjusted likelihood ratio test also suggested that extracting five latent profiles provided a significantly better fit to the data compared to the four-profile solution ($p < 0.001$). Figure 3 depicts the estimated mean performance on each test with 95% confidence interval for each identified latent profile. Latent profiles included a subgroup who performed poorly on all cognitive tests (poor multi-domain 13%), a subgroup who performed poorly on episodic verbal memory tests and significantly worse on semantic compared to phonemic fluency (poor memory 10%), a subgroup with average performance across all tests (average multi-domain 45%), a subgroup with superior attentional ability (superior attention 15%), and a subgroup with superior episodic verbal memory (superior memory 17%).

Population characteristics of latent profiles

Table 2 compares population characteristics by each latent profile. Women in the poor multi-domain profile were older, more likely to reside in the South, identify as either Black, non-Hispanic or Hispanic/Latino, have less than a high school education, be a past-drinker, report no moderate to strenuous physical activity, have a history of cardiovascular disease, endorsed significantly more depressive symptoms on the GDS-15, report an annual household income of less than 10,000 dollars, and reside in locations with lower neighborhood socioeconomic characteristics compared to women in the other latent profiles. Women in the superior memory profile were more likely to reside in the Northeast, and either never smoked or were past smokers, while women in the superior attention profile were more likely to reside in the Midwest. Lastly, women with a hysterectomy were more likely to be classified into the poor multi-domain profile while women without a hysterectomy were more likely to be classified as having superior attention.

Latent profile membership and dementia incidence rate

We calculated the dementia incidence rate until the year 2018 for each latent profile. The poor multi-domain profile had the highest incidence rate ($N = 42$ cases or 15.32%). The poor memory latent profile had an incidence rate of 14.22% ($N = 31$), followed by the superior attention profile (10.60%; $N = 34$), and the average performance profile (9.85%; $N = 96$). Lastly the superior memory profile had the lowest rate of incident dementia (8.17%; $N = 29$).

Associations between PM_{2.5} and latent profile membership

The results of the SEM with multinomial regression estimating associations between concentrations of PM_{2.5} and latent profile classification are presented in Table 3. Relative

to women with average cognitive ability, higher PM_{2.5} (per interquartile range [IQR] = 3.64 µg/m³) was associated increased odds of being classified as having poor verbal memory (OR = 1.29; 95% Confidence Interval [CI] = 1.10, 1.52) or having superior attention (OR = 1.30; 95% CI = 1.10, 1.53). The odds of classification into the poor multi-domain profile with PM_{2.5} were of smaller magnitude and not statistically significant. Living in locations with higher concentrations of PM_{2.5} was associated with lower odds of being classified with superior memory, although this was not statistically significant. When attempting to constrain the effect of PM_{2.5} on latent profile to be equal across the four exposure effects, the model fit was significantly worse (Wald Test, $z(3) = 11.69$, $p < 0.01$), providing further evidence that these associations between PM_{2.5} exposure and defined profile memberships were quantitatively different from each other.

Associations between NO₂ and latent profile membership

The results from SEMs with multinomial regression estimating the association between NO₂ on latent profile assignment are presented in Table 4. Using women with average cognitive ability as the referent, residing in locations with elevated concentrations of NO₂ (per IQR = 9.86 ppb) was associated with significantly increased odds of being classified with poor verbal memory (OR = 1.38; 95% CI = 1.17, 1.63) and decreased odds of being classified with superior memory (OR = 0.86; 95% CI = 0.74, 0.99). Residing in locations with elevated NO₂, however, did not significantly increase the odds of being classified as in the poor multi-domain or superior attention profile, relative to the referent. The NO₂ concentration effects on profile membership were quantitatively different from each other as evidence of significantly worse model fit when we constrained the effects to be equal (Wald Test, $z(3) = 14.85$, $p < 0.01$).

Sensitivity analysis

Results of the first sensitivity analysis when adding WHISCA site as a cluster variable the effect were essentially unchanged; however, parameter estimates were less precise (Supplementary Tables 2 and 3). Results of the second sensitivity analysis where covariate data on hypertension, cardiovascular disease, and smoking were updated are presented in Supplementary Tables 4 and 5. The pattern of results was essentially unchanged after updating these covariates.

DISCUSSION

In this cross-sectional study of a geographically diverse cohort of older women, we used latent profile SEMs to identify five subgroups of women who exhibited similar profiles of cognitive performance. We found that older women residing in locations with higher ambient levels of PM_{2.5} or NO₂ were more likely to have an empirically derived profile characterized by poor memory. Across the domains assessed, these women with similar profiles of poor memory had cognitive performance notable for lower episodic verbal memory relative to performance in other domains as well as significantly worse semantic verbal fluency compared to letter fluency. The observed associations between concentrations of air pollution and latent profiles do not appear to be explained by between-participant differences in socio-demographic factors (age; geographic region; race/ethnicity; education;

income; employment status; neighborhood socioeconomic characteristics), lifestyle factors (smoking; alcohol; physical activity), depressive symptoms, and clinical characteristics (diabetes; hypercholesterolemia; hypertension; cardiovascular disease; hormone therapy use). Living in locations with higher concentrations of PM_{2.5} or NO₂ did not increase the odds of being classified as having poor performance across all domains (multi-domain).

Findings in the context of previous research using latent profile analysis

Our study adds novel epidemiologic data to support the presence of heterogeneous patterns of performance across domains of verbal and figural episodic memory, language, attention/working memory, and visuospatial ability in cognitively healthy older adults. Using LPA, we identified five significant latent profiles of cognitive performance, which are consistent with previous studies applying a similar approach with cognitively healthy older adults [20, 21]. Consistent with these studies, we identified latent profiles of performance characterized by poor performance across all domains (multi-domain), poor episodic verbal memory, and average performance across all domains. In contrast to these previous studies, we identified two latent profiles characterized by superior cognitive ability, one with superior attentional ability and a second profile with superior memory. Consistent with previous research [20, 21], we also observed differences in latent profile memberships with Black, non-Hispanic and Hispanic/Latino women being more likely to be classified in the poor multi-domain performance while non-Hispanic White women were more likely to be classified in the superior attention or memory latent profiles. Lastly, also consistent with these previous studies we found that women in the multi-domain impairment group were more likely to have a history of cardiovascular disease compared to the other latent profiles.

Findings in the context of previous research examining air pollution and domain-specific cognitive performance

Prior studies examining associations between air pollution and domain-specific cognitive performance in older adulthood have yielded inconsistent results [5]. Starting with episodic memory, some studies report cross-sectional associations between NO₂ and PM_{2.5} exposure with worse episodic memory [6–8]; whereas others fail to observe significant associations with NO₂ [11, 13] or PM_{2.5} [7, 10, 11]. These previous studies did not account for concurrent performance across other domains as they only examined associations between NO₂ or PM_{2.5} with episodic memory independently. By illustrating those different patterns of performance across multiple domains present in cognitively healthy older women, our study results raise the possibility that prior studies examining associations between exposure air pollution exposures and episodic memory separately without considering its joint performance with other domains may be overly simplistic. For example, we identified two subgroups of older women with poor episodic memory performance (poor memory and poor multi-domain profiles). Even though these two empirically derived subtypes were not significantly different from each other in terms of mean episodic memory performance, living in locations with higher concentrations of PM_{2.5} or NO₂ were only associated with significantly higher odds of classification into the poor memory latent profile (and not multi-domain impairment). Differences in cognitive performance across other domains were what distinguished these profiles. Women in the poor memory profile largely had average performance across the other cognitive domains. In contrast, the women in the

poor multi-domain profile had poor performance across all other domains. PM_{2.5} and NO₂ were associated with worse episodic memory performance relative to other domains and other latent classes. Women classified in the profile characterized by superior attention, on average, performed worse on tests of episodic verbal memory, relative to forward and backwards digit span. Despite performing better on tests of episodic memory relative to women with average performance, there was a marginally significant association between both NO₂ and PM_{2.5} with greater odds of having superior attention compared to average ability. Again, performance across the other cognitive tests is what differentiated older women in the superior attention group from those with average performance. Our finding that exposure to air pollution may be associated with a profile of performance characterized by worse episodic memory, relative to other domains, is consistent with one cross-sectional study examining associations between exposure and subtypes of mild cognitive impairment [45]. This study found that living in locations with elevated PM_{2.5} was associated with increased risk of amnesic mild cognitive impairment but not non-amnesic MCI.

Prior studies examining associations between exposure to PM_{2.5} or NO₂ and performance across other domains have also provided mixed findings. Some studies reported significant adverse associations between exposure to PM_{2.5} or NO₂ and processing speed/attention [8, 9], semantic fluency [7], phonemic fluency [10], visuospatial ability [11], and aspects of executive function [7, 11, 12]; however, other studies failed to show adverse associations across these domains [6, 10–13]. Several factors may contribute to these mixed findings including differences in exposure estimation or cognitive tests, sampling methods and characteristics, and analytic approaches. Findings from the current study again raise the possibility that concurrently comparing profiles of performance across domains is important and failing to do so in prior studies may have contributed to the mixed findings reported. For instance, in terms of verbal fluency ability, some studies do not observe significant associations [11, 12], while others report significant adverse effects of air pollution exposures [10]. In the present study, we found that it may be important to examine discrepancies between phonemic and semantic fluency in relation to air pollution exposure. Women classified in the latent profile most strongly associated with exposure to PM_{2.5} and NO₂ (poor memory) was the only latent class where women performed significantly worse on semantic fluency compared to phonemic fluency.

Link between pollution and dementia

There is an increasing number of epidemiologic studies showing an increased risk of ADRD and declines in cognitive function associated with late-life exposures to PM_{2.5} [46–59]. Not only does PM_{2.5} show the most consistent relationship with ADRD, but these epidemiologic data are further supported by inhalation neurotoxicological data in animal models demonstrating increased levels of early markers of neurodegenerative disease (e.g., accumulation of amyloid-β; phosphorylation of tau), structural changes in hippocampal neuronal morphology, and increased cognitive deficits associated with inhaled exposure to particles [60–66]. There is also evidence from longitudinal cohort studies pointing towards an association between greater exposure to gaseous pollutants (e.g., NO₂; NO_x) and increased risk of ADRD [49, 50, 53, 55–57, 67, 68]; however, the relationship between cognitive decline with NO_x and NO₂ is less clear [69]. For the epidemiology studies

reporting an association between NO₂ and dementia, it is possible that NO₂ most likely represented the gaseous surrogate of the traffic-related air pollutants mixture.

Neuropathological processes underlying air pollution and cognitive ability

By providing further speculation into the neuropathological processes underlying the associations between air pollution and profiles of cognitive ability in older adulthood, our study adds novel data to the emerging field of environmental neurosciences of air pollution and brain aging. In previous work, individuals classified as having multi-domain impairments or memory-specific impairment may have more amyloid- β and tau tangle accumulation compared to their counterparts with average cognition [14]. Other studies suggest that adults with memory-specific MCI may have greater atrophy in the medial temporal lobe compared to other subtypes of MCI [16]. Our finding of association between increased odds of poor memory and residing in locations with higher concentrations of air pollution therefore supports the possibility that air pollution may exert neurotoxic effects on the medial temporal lobe. The possible link between air pollution and medial temporal lobe atrophy is also consistent with previous reports showing associations between PM_{2.5} and NO₂ with greater atrophy to grey matter in areas vulnerable to AD [70–72], which includes the medial temporal lobe. In addition to relatively poor performance on tests of episodic verbal memory, women in poor memory latent profile also performed significantly worse on a test semantic fluency compared to phonemic fluency. Throughout aging, most individuals perform better on tests of semantic compared to phonemic fluency [73]. Worse semantic fluency compared to phonemic fluency is associated with AD neuropathology [74] and increased likelihood of developing AD [75].

Study limitations

We recognize several limitations of our study. First, the cross-sectional nature of the study limits our ability to make causal inferences or examine changes in cognitive performance over time. Second, we only studied associations between empirically derived cognitive profiles and ambient levels of air pollutants without measuring personal exposures directly or measuring exposures before later-life. The exposure estimates are not without measurement errors. Although our air pollution estimates accounted for residential mobility during the three-year exposure period, we were unable to capture exposure from commuting or indoor air quality. This may have resulted in non-differential exposure misclassification that likely attenuated our associations. Third, the cognitive battery administered in WHISCA did not include measures of executive function which prevents inferences relating to how exposure is related to this important cognitive domain. Fourth, participants were all women, mostly well-educated and Caucasian, and generally in good physical and cognitive health which limit the potential generalizability of our findings to men and more racially/ethnically diverse populations of older adults.

CONCLUSIONS

In summary, the present study of older women provides epidemiologic evidence that air pollution exposure in older adulthood is associated with specific profiles of cognitive performance across multiple domains. Our data demonstrate that exposure to PM_{2.5} or

NO₂ may significantly increase the probability of having a profile of cognitive ability characterized by worse verbal episodic memory performance in relation to other cognitive domains. Future studies are needed to better understand the neuropathological processes underlying these cognitive profiles and the longitudinal stability of this finding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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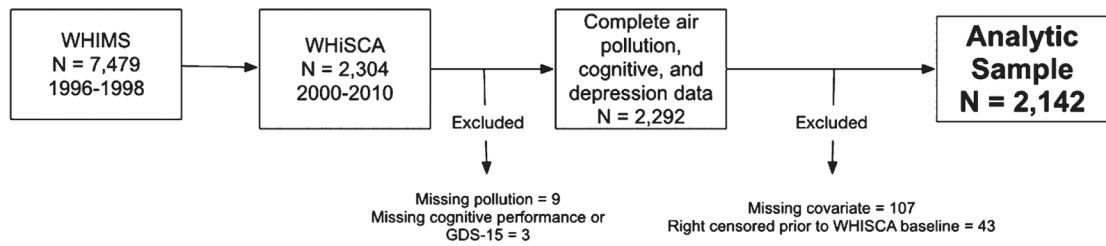
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Panel A. Flowchart of study participation



Panel B. Timeline of study assessments

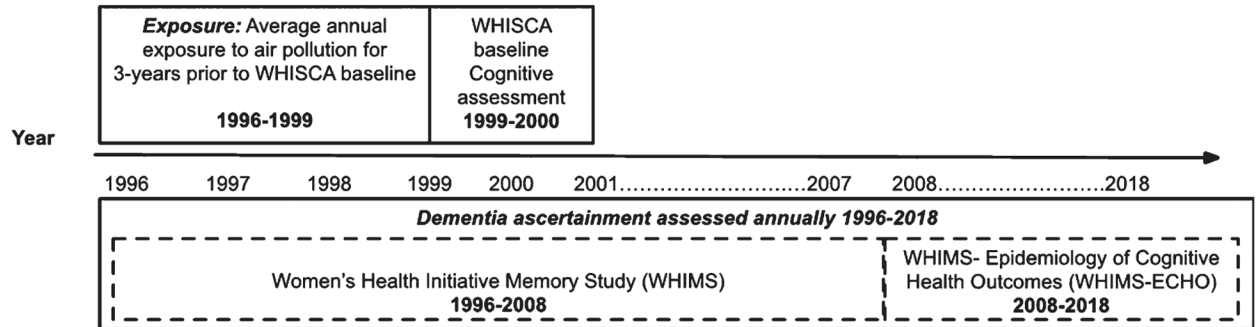


Fig. 1. Flowchart of study participation (A) and timeline of study assessments (B). WHIMS, Women’s Health Initiative Memory Study; WHISCA, Women’s Health Initiative Study of Cognitive Aging.

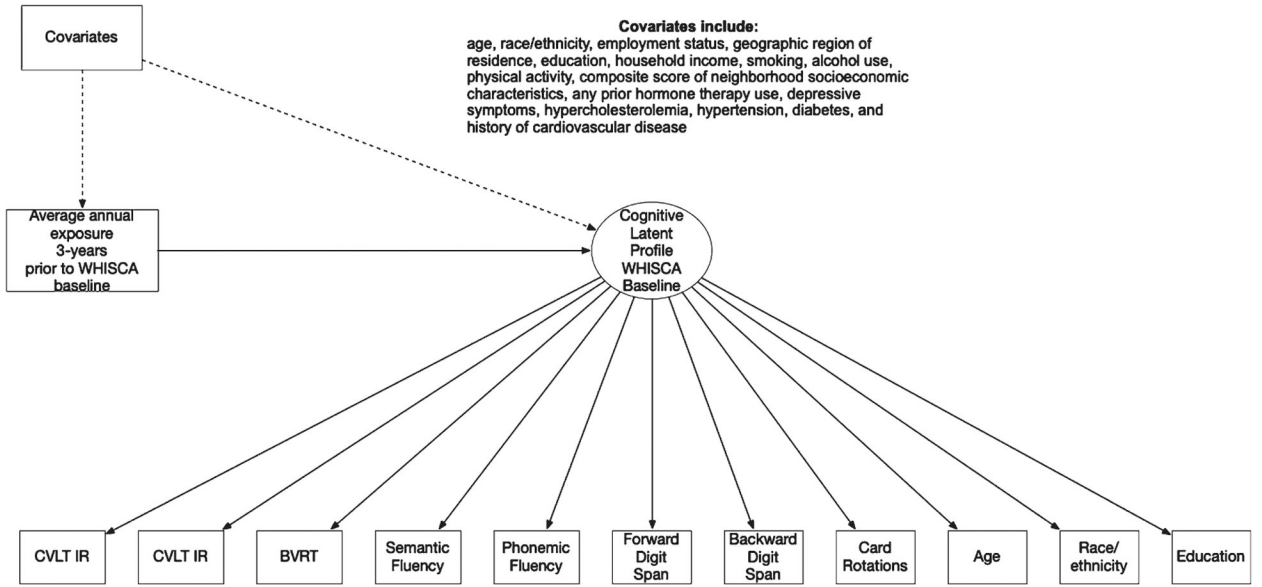


Fig. 2. Illustration of the structural equation model constructed to estimate associations between latent profile classification at the Women’s Health Initiative Study of Cognitive Aging baseline assessment with residing in locations with higher concentrations of air pollution ($N = 2,142$). CVLT IR, California Verbal Learning Test immediate recall; CVLT LDR, California Verbal Learning Test long delay free recall; BVRT, Benton Visual Recognition Test. Covariates are a vector of variables including age, race/ethnicity, employment status, geographic region of residence, education, household income, smoking, alcohol use, physical activity, composite score of neighborhood socioeconomic characteristics, any prior hormone therapy use, hypercholesterolemia, hypertension, diabetes, history of cardiovascular disease, and depressive symptoms.

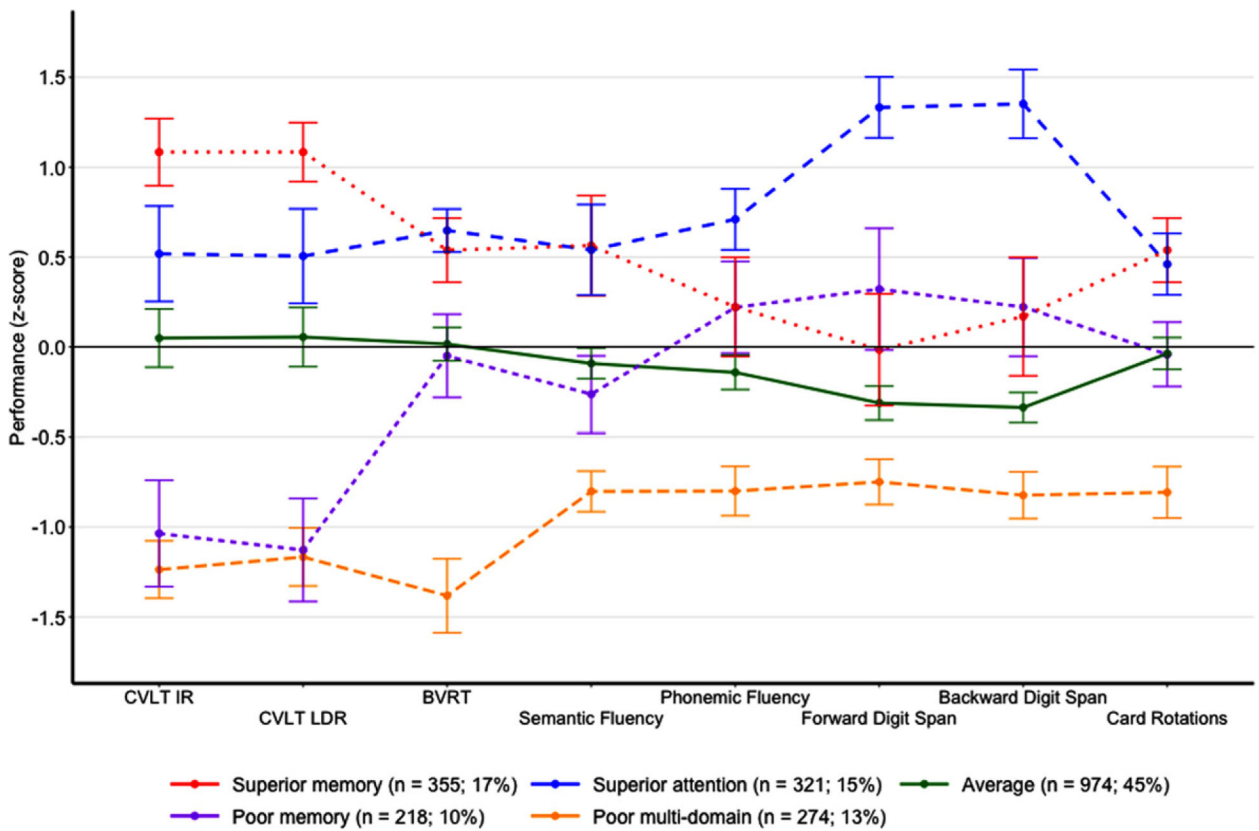


Fig. 3. Estimated mean standardized cognitive test performance with 95% confidence intervals for identified latent profiles of cognitive performance at the Women’s Health Initiative Study of Cognitive Aging baseline assessment ($N = 2,142$). CVLT IR, California Verbal Learning Test immediate recall; CVLT LDR, California Verbal Learning Test long delay free recall; BVRT, Benton Visual Recognition Test.

Table 1
 Comparison of estimated concentrations of PM_{2.5} and NO₂ for the 3 years prior to the Women’s Health Initiative Study of Cognitive Aging baseline by population characteristics (N= 2,142)

Population Characteristics	Distribution of 3-year average ^a PM _{2.5} exposure (µg/m ³)			Distribution of 3-year average ^a NO ₂ exposure (ppb)		
	N	Mean±SD	(25 th , Median, 75 th) ^b p ^b	Mean±SD	(25 th , Median, 75 th) ^b p ^b	
Overall	2,142	13.1 ± 2.8	(11.3, 13.0, 14.9)	15.6 ± 8.2	(9.3, 14.1, 19.6)	< 0.01
Region of Residence						
Northeast	451	13.1 ± 2.8	(11.2, 12.5, 13.6)	19.7 ± 9.7	(11.2, 17.0, 27.5)	
South	308	12.5 ± 1.8	(10.9, 12.7, 14.0)	8.4 ± 3.0	(6.0, 7.9, 10.8)	
Midwest	838	12.5 ± 1.7	(11.6, 13.0, 15.0)	14.1 ± 5.4	(9.7, 13.8, 18.1)	
West	545	13.1 ± 2.3	(11.0, 14.7, 16.5)	18.5 ± 9.0	(12.1, 17.9, 22.9)	
Race/Ethnicity						
Black, non-Hispanic	132	15.5 ± 2.4	(14.0, 15.5, 16.4)	23.9 ± 9.5	(16.5, 25.7, 31.3)	< 0.01
Hispanic/Latina	54	14.7 ± 3.5	(12.7, 14.3, 16.5)	20.8 ± 9.7	(13.0, 19.2, 31.0)	
Non-Hispanic White	1,930	12.9 ± 2.7	(11.1, 12.7, 14.7)	14.8 ± 7.6	(9.0, 13.5, 18.8)	
Other or Missing	26	14.8 ± 3.0	(13.2, 14.9, 16.5)	22.3 ± 9.7	(15.1, 20.6, 27.8)	
Education						
Less than high school	104	13.2 ± 2.7	(11.2, 12.8, 15.4)	17.2 ± 9.9	(9.5, 14.5, 23.8)	< 0.01
High school	458	12.8 ± 2.4	(11.2, 12.6, 14.3)	14.6 ± 7.3	(9.0, 13.6, 18.0)	
More than high school	1,580	13.2 ± 2.9	(11.3, 13.1, 15.1)	15.7 ± 8.3	(9.3, 14.2, 19.9)	
Employment						
Currently working	278	13.1 ± 2.9	(11.3, 13.0, 14.8)	16.3 ± 8.7	(9.6, 14.6, 21.6)	0.25
Not working	165	13.2 ± 2.8	(11.4, 13.1, 15.0)	15.9 ± 8.6	(8.8, 14.2, 20.0)	
Retired	1,699	13.1 ± 2.8	(11.3, 13.0, 14.9)	15.4 ± 8.1	(9.2, 13.9, 19.4)	
Income (in USD)						
<9,999	98	13.4 ± 3.2	(11.4, 13.4, 15.5)	16.9 ± 9.7	(9.3, 15.4, 21.7)	< 0.01
10,000–34,999	1,031	13.0 ± 2.9	(11.0, 12.9, 14.8)	14.8 ± 8.1	(8.7, 13.1, 18.9)	
35,000–74,999	758	13.4 ± 2.7	(11.4, 13.1, 14.9)	16.9 ± 8.6	(10.1, 15.1, 22.0)	
75,000 or more	140	13.1 ± 2.6	(11.3, 13.1, 14.7)	16.4 ± 8.3	(10.8, 14.2, 21.0)	
Don’t know	115	13.3 ± 2.7	(11.5, 13.1, 15.1)	16.0 ± 8.0	(10.1, 14.8, 19.9)	< 0.01

Composite neighborhood socioeconomic characteristics

Population Characteristics	Distribution of 3-year average ^a PM _{2.5} exposure (µg/m ³)			Distribution of 3-year average ^a NO ₂ exposure (ppb)			
	N	Mean±SD	(25 th , Median, 75 th)	<i>p</i> ^b	Mean±SD	(25 th , Median, 75 th)	<i>p</i> ^b
Low (first tertial)	547	13.4 ± 3.0	(11.2, 13.3, 15.3)		15.4 ± 9.4	(7.8, 13.1, 19.6)	
Average (middle tertial)	1,091	12.7 ± 2.8	(10.8, 12.5, 14.3)		14.4 ± 7.6	(8.6, 12.9, 18.2)	
High (third tertial)	547	13.8 ± 2.5	(11.9, 13.6, 15.6)		18.1 ± 7.2	(12.4, 17.6, 22.4)	
Lifestyle							
Smoking status				0.30			0.01
Never smoked	1,177	13.2 ± 2.8	(11.3, 13.0, 15.0)		15.1 ± 7.9	(9.0, 13.6, 19.2)	
Past smoker	842	13.1 ± 2.7	(11.3, 13.0, 14.9)		16.2 ± 8.4	(10.0, 14.8, 20.2)	
Current Smoker	123	12.8 ± 3.0	(10.9, 12.3, 14.9)		15.4 ± 8.8	(9.2, 12.4, 19.1)	
Alcohol use				0.70			0.02
Non-drinker	264	13.3 ± 3.0	(11.2, 13.1, 15.0)		14.1 ± 8.7	(7.9, 11.2, 17.4)	
Past drinker	388	13.1 ± 2.8	(11.2, 13.0, 15.1)		15.4 ± 8.2	(9.2, 13.9, 19.7)	
< 1 drink/ day	1,288	13.1 ± 2.8	(11.3, 13.0, 14.8)		15.9 ± 8.1	(9.8, 14.5, 20.0)	
1 drink/ day	262	13.1 ± 2.8	(11.4, 13.1, 14.9)		15.7 ± 7.9	(10.0, 14.3, 19.3)	
Moderate or strenuous activities 20 min				0.03			0.06
No activity	1,226	13.1 ± 2.9	(11.3, 13.0, 15.0)		15.8 ± 8.4	(9.3, 14.2, 20.0)	
Some activity	113	13.5 ± 2.6	(11.7, 13.4, 15.4)		15.9 ± 8.0	(10.2, 14.8, 19.1)	
2-4 episodes/week	435	13.3 ± 2.7	(11.5, 13.2, 15.1)		15.7 ± 7.9	(9.6, 14.2, 19.7)	
> 4 episodes/week	368	12.8 ± 2.6	(11.0, 12.6, 14.4)		14.5 ± 7.7	(8.7, 13.0, 18.5)	
Physical Health							
Hypertension				0.14			0.06
No	1,353	13.1 ± 2.8	(11.2, 12.9, 14.8)		15.3 ± 8.1	(9.1, 13.7, 19.4)	
Yes	789	13.3 ± 2.8	(11.4, 13.1, 15.1)		16.0 ± 8.3	(9.5, 14.4, 20.0)	
Hypercholesterolemia				0.07			0.22
No	1,775	13.1 ± 2.8	(11.2, 13.0, 15.9)		15.5 ± 8.1	(9.1, 14.0, 19.5)	
Yes	367	13.4 ± 2.7	(11.5, 13.1, 15.1)		16.0 ± 8.5	(9.8, 14.4, 20.1)	
Diabetes Mellitus				0.68			0.13
No	2,024	13.1 ± 2.8	(11.3, 13.0, 14.9)		15.5 ± 8.2	(9.2, 14.0, 19.5)	
Yes	118	13.2 ± 2.6	(11.5, 13.1, 14.9)		16.7 ± 8.5	(10.3, 14.8, 20.9)	
Cardiovascular disease				0.95			0.11
No	1,798	13.1 ± 2.8	(11.3, 13.0, 14.8)		15.4 ± 8.0	(9.3, 14.0, 19.4)	

Population Characteristics	Distribution of 3-year average ^a PM _{2.5} exposure (µg/m ³)			Distribution of 3-year average ^a NO ₂ exposure (ppb)			
	N	Mean±SD	(25 th , Median, 75 th)	<i>b</i> <i>p</i>	Mean±SD	(25 th , Median, 75 th)	<i>b</i> <i>p</i>
Prior hormone therapy				0.45			0.10
Yes	344	13.1 ± 3.0	(11.2, 13.0, 15.3)		16.2 ± 9.1	(9.1, 14.5, 20.2)	
No	1,155	13.1 ± 2.6	(11.3, 13.0, 14.8)		15.8 ± 8.2	(9.2, 14.2, 20.3)	
Hormone therapy assignment				0.75			0.91
E-alone intervention	413	13.2 ± 2.9	(11.4, 13.1, 15.1)		15.8 ± 8.6	(9.2, 14.0, 19.9)	
E-alone control	411	13.1 ± 2.9	(11.3, 13.0, 15.0)		15.4 ± 7.9	(9.5, 14.0, 19.4)	
E + P intervention	640	13.1 ± 2.8	(11.3, 12.9, 14.8)		15.6 ± 8.2	(9.4, 14.0, 19.8)	
E + P control	678	13.2 ± 2.7	(11.2, 13.0, 14.9)		15.5 ± 8.0	(9.1, 14.2, 19.5)	

^a 3-year average of the annual exposure prior to the Women’s Health Initiative Study of Cognitive Aging baseline at each participant’s address using the regionalized national universal kriging model.

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

Table 2

Comparison of baseline population characteristics by latent profile of cognitive performance^a in the Women's Health Initiative Study of Cognitive Aging (N = 2,142)

Population Characteristics	Poor multi-domain N = 274 Mean (sd) or % ^b (N)	Poor Memory N = 218 Mean (sd) or % ^b (N)	Average N = 974 Mean (sd) or % ^b (N)	Superior Attention N = 355 Mean (sd) or % ^b (N)	Superior memory N = 321 Mean (sd) or % ^b (N)	p ^c
Age (y)	75.12 (4.22)	74.63 (3.95)	73.16 (3.54)	72.34 (3.29)	72.48 (3.59)	< 0.01
GDS-15	2.47 (2.83)	1.66 (2.08)	1.36 (1.99)	1.26 (1.92)	1.16 (1.70)	< 0.01
Region						< 0.01
Northeast	13% (57)	11% (49)	42% (190)	15% (66)	20% (89)	
South	16% (50)	11% (34)	49% (151)	11% (34)	13% (39)	
Midwest	12% (99)	9% (77)	47% (393)	19% (161)	13% (108)	
West	13% (68)	11% (58)	44% (240)	17% (94)	16% (85)	
Ethnicity						< 0.01
Black, non-Hispanic	49% (65)	9% (12)	38% (50)	2% (2)	2% (3)	
Hispanic/Latina	19% (5)	15% (4)	54% (14)	12% (3)	0% (0)	
White (not Hispanic)	10% (191)	10% (194)	46% (889)	18% (342)	16% (314)	
Other or Missing	24% (13)	15% (8)	39% (21)	15% (8)	7% (4)	
Education						< 0.01
Less than high school	53% (55)	0% (0)	42% (44)	2% (2)	3% (3)	
High school	14% (62)	7% (30)	55% (254)	13% (60)	11% (52)	
More than high school	10% (157)	12% (188)	43% (676)	19% (293)	17% (266)	
Employment						0.86
Currently working	10% (29)	10% (29)	48% (132)	17% (46)	15% (42)	
Not working	12% (20)	12% (19)	49% (81)	15% (25)	12% (20)	
Retired	13% (225)	10% (170)	45% (761)	17% (284)	15% (259)	
Annual income (dollars)						< 0.01
< 9,999	31% (30)	9% (9)	40% (39)	14% (14)	6% (6)	
10,000–34,999	16% (160)	10% (101)	49% (501)	15% (154)	11% (119)	
35,000–74,999	5% (7)	14% (19)	41% (57)	16% (22)	25% (36)	
75,000 or more	18% (21)	10% (11)	42% (48)	16% (18)	15% (18)	
Don't know	7% (56)	10% (78)	43% (329)	19% (147)	20% (153)	

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Population Characteristics	Poor multi-domain $N = 274$ Mean (sd) or % ^a (N)	Poor Memory $N = 218$ Mean (sd) or % ^a (N)	Average $N = 974$ Mean (sd) or % ^a (N)	Superior Attention $N = 355$ Mean (sd) or % ^a (N)	Superior memory $N = 321$ Mean (sd) or % ^a (N)	p^c
Composite neighborhood socioeconomic characteristics	-2.07 (5.22)	0.14 (5.41)	-0.10 (5.00)	0.68 (5.15)	1.22 (5.27)	< 0.01
Lifestyle						
Smoking status						< 0.01
Never smoked	12% (100)	10% (87)	42% (352)	19% (160)	17% (143)	
Past smoker	12% (15)	8% (10)	44% (54)	12% (15)	24% (29)	
Current Smoker	14% (159)	10% (121)	48% (568)	15% (180)	13% (149)	
Alcohol use						< 0.01
Non-drinker	16% (42)	8% (22)	53% (140)	11% (30)	11% (30)	
Past drinker	20% (76)	9% (36)	47% (181)	14% (53)	11% (42)	
< 1 drink / day	11% (137)	10% (128)	44% (539)	18% (226)	16% (198)	
1 drink / day	7% (19)	12% (32)	44% (114)	18% (46)	20% (51)	
Moderate or strenuous activities > 20 min						0.01
No activity	15% (183)	9% (108)	47% (574)	16% (194)	14% (167)	
Some activity	9% (10)	7% (8)	47% (53)	19% (21)	19% (21)	
2-4 episodes/week	11% (48)	10% (46)	46% (202)	16% (68)	16% (71)	
> 4 episodes/week	9% (33)	15% (56)	39% (145)	20% (72)	17% (62)	
Physical Health						
Hypertension						0.45
No	12% (159)	10% (139)	46% (620)	17% (227)	15% (208)	
Yes	15% (115)	10% (79)	45% (354)	16% (128)	14% (113)	
Hypercholesterolemia						0.82
No	13% (223)	10% (177)	46% (813)	17% (292)	15% (270)	
Yes	14% (51)	11% (41)	44% (161)	17% (63)	14% (51)	
Diabetes						0.10
No	12% (250)	10% (207)	46% (924)	17% (341)	15% (302)	
Yes	20% (24)	9% (11)	42% (50)	12% (14)	16% (19)	
Cardiovascular disease						0.02
No	12% (212)	10% (179)	46% (828)	17% (303)	15% (276)	
Yes	18% (62)	11% (39)	42% (146)	15% (52)	13% (45)	

Population Characteristics	Poor multi-domain N = 274 Mean (sd) or % ^a (N)	Poor Memory N = 218 Mean (sd) or % ^a (N)	Average N = 974 Mean (sd) or % ^a (N)	Superior Attention N = 355 Mean (sd) or % ^a (N)	Superior memory N = 321 Mean (sd) or % ^a (N)	p ^c
Hormone treatment ever						0.36
No	12% (143)	9% (108)	46% (532)	18% (204)	15% (168)	
Yes	13% (131)	11% (110)	45% (442)	15% (153)	16% (153)	
Hormone therapy assignment						<0.01
E-alone intervention	18% (75)	12% (51)	45% (187)	13% (52)	12% (48)	
E-alone control	15% (61)	11% (44)	46% (188)	14% (56)	15% (62)	
E + P intervention	11% (69)	8% (50)	48% (307)	18% (113)	16% (101)	
E + P control	10% (69)	11% (73)	43% (292)	20% (134)	16% (110)	

^a latent profile classification derived from the latent profile analysis extracting five latent profiles. Participants were assigned to latent profile based on highest posterior probabilities.

^b percentages represent the row percentages.

^c p values estimated from ANOVA F-tests for continuous variables or chi-square tests for categorical variables, comparing the population characteristics by latent profile.

Multinomial regression SEMs to examine the effect of residing in locations with higher concentrations of PM_{2.5} on probability of being classified into respective latent profile of cognitive performance at the Women’s Health Initiative Study of Cognitive Aging baseline assessment (N = 2,142)

Table 3

Outcome: Latent profile ^a classification	N	PM _{2.5} ^b	PM _{2.5} Per 3.64 µg/m ³	95% Confidence Interval		p
				Lower	Upper	
Average	974	13.04 (2.83)	0	1	Ref	Ref
Poor multi-domain	274	13.67 (2.90)	0.121	1.13	0.936	1.360 0.205
Poor memory	218	13.46 (2.76)	0.253	1.29	1.096	1.515 0.002
Superior attention	321	13.21 (2.68)	0.260	1.30	1.099	1.530 0.002
Superior memory	355	12.81 (2.69)	-0.079	0.92	0.812	1.052 0.235

^a latent profile classification derived from the latent profile analysis with five latent profiles. Bolck, Croon, Hagenaars (BCH) weights were included in each model to account for uncertainty in latent profile assignment.

^b PM_{2.5} is the 3-year average concentrations prior to the WHISCA baseline at each participant’s address using the regionalized national universal kriging model.

^c parameter estimates were adjusted for age, race/ethnicity, employment status, geographic region of residence, education, household income, smoking, alcohol use, physical activity, composite score of neighborhood socioeconomic characteristics, any prior hormone therapy use, hypercholesterolemia, hypertension, diabetes, and history of cardiovascular disease.

PM_{2.5}, fine particulate matter with aerodynamic diameter < 2.5 µm; OR, Odds ratio. Bolded terms denote *p* < 0.05.

Multinomial regression SEMs to examine the effect of residing in locations with higher concentrations of NO₂ on probability of being classified into respective latent profile of cognitive performance at the Women's Health Initiative Study of Cognitive Aging baseline assessment ($N = 2,142$)

Table 4

Outcome: Latent profile classification	N	NO ₂ ^b	95% Confidence Interval				p
			Mean (SD)	β^c	OR	Lower	
Average	974	15.04 (7.54)	0	1	Ref	Ref	Ref
Poor Multi-domain	282	17.26 (8.71)	0.149	1.16	0.951	1.415	0.143
Poor memory	216	16.64 (7.87)	0.321	1.38	1.165	1.633	<0.001
Superior attention	332	15.43 (7.30)	0.133	1.14	0.962	1.355	0.130
Superior memory	381	14.37 (6.44)	-0.153	0.86	0.739	0.997	0.045

^a latent profile classification derived from the latent profile analysis with five latent profiles. Bolck, Croon, Hagenaars (BCH) weights were included in each model to account for uncertainty in latent profile assignment.

^b NO₂ is the 3-year average exposure prior to the WHISCA baseline at each participant's address using the regionalized national universal kriging model.

^c parameter estimates were adjusted for age, race/ethnicity, employment status, geographic region of residence, education, household income, smoking, alcohol use, physical activity, composite score of neighborhood socioeconomic characteristics, any prior hormone therapy use, hypercholesterolemia, hypertension, diabetes, and history of cardiovascular disease.

NO₂ = nitrogen dioxide; OR = Odds ratio. Bolded terms denote $p < 0.05$.