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Associations between ambient air pollution and cognitive abilities from midlife to early old age: Modification by *APOE* genotype

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Abstract

Background.—Fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) measures of ambient air pollution are associated with accelerated age-related cognitive impairment, and Alzheimer's disease and related dementias (ADRD).

Objective.—We examined associations between air pollution, 4 cognitive factors, and the moderating role of apolipoprotein E *(APOE)* genotype in the understudied period of midlife.

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Conflict of Interest

The authors have no conflicts of interest to report.

Methods.—Participants were ~1100 men in the Vietnam Era Twin Study of Aging. Baseline cognitive assessments were from 2003 to 2007. Measures included past (1993–1999) and recent (3 years prior to baseline assessment) $PM_{2.5}$ and NO_2 exposure, in-person assessment of episodic memory, executive function, verbal fluency, and processing speed, and *APOE* genotype. Average baseline age was 56 years with a 12-year follow-up. Analyses adjusted for health and lifestyle covariates.

Results.—Performance in all cognitive domains declined from age 56 to 68. Higher $PM_{2.5}$ exposures were associated with worse general verbal fluency. We found significant exposure-by-*APOE* genotype interactions for specific cognitive domains: $PM_{2.5}$ with executive function and NO_2 with episodic memory. Higher $PM_{2.5}$ exposure was related to worse executive function in *APOE*-ε4 carriers, but not in non-carriers. There were no associations with processing speed.

Conclusion.—These results indicate negative effects of ambient air pollution exposure on fluency alongside intriguing differential modifications of cognitive performance by *APOE* genotype. *APOE*-ε4 carriers appeared more sensitive to environmental differences. The process by which air pollution and its interaction with genetic risk for ADRD affects risk for later life cognitive decline or progression to dementia may begin in midlife.

Keywords

air pollution; $PM_{2.5}$; Nitrogen dioxide (NO_2); cognition; aging; midlife; *APOE* genotype

INTRODUCTION

A 2020 Lancet commission report concluded that modification of 12 risk factors—including ambient air pollution—could reduce dementia incidence by as much as 40% [1]. Ambient air pollution (e.g., pollution coming from sources that use combustible fuels such as automobiles, power plants, and industries) acts as a notable public health hazard, especially in urban settings [2–5]. The World Health Organization estimated that 92% of the world population experiences excess exposure to fine particulate matter (PM) [5]; fine PM (particles with aerodynamic diameters less 2.5 microns) are considered particularly harmful to health. Although the Lancet commission's estimated relative risk for dementia related to air pollution was relatively low (relative risk=1.1; 95% CI: [1.1–1.1]), the weighted population attributable fraction—the burden of air pollution accounting for other health risks—was higher (2.3%) due in part to the high prevalence of air pollution (75%). This places ambient air pollution above other Alzheimer's disease and related dementia (ADRD) risk factors such as diabetes, physical inactivity, hypertension, alcohol consumption, and obesity. Of note, in regard to the present study, the Lancet report listed air pollution as a later life risk factor (age > 65) for ADRD, despite evidence that neurotoxicants such as those found in air pollution affect cognitive and brain health in childhood [6, 7].

Long-term exposure to air pollutants such as $PM_{2.5}$ and nitrogen dioxide (NO_2), increases risk for cardiovascular disease, stroke, inflammation, and neurotoxic reactions [6, 8–16]. $PM_{2.5}$ exposure may accelerate brain-aging indicative of increased risk for AD [6, 9, 11, 17]. Air pollution levels are also associated with socioeconomic risk factors that predict poorer health and cognitive outcomes, increased stress, and higher risk for AD [3, 18]. There is not

yet an identified threshold at the low end of the concentration range at which the effects disappear. Because these factors all have implications for cognitive functioning and AD, it is important to identify potentially modifiable risk factors as early in the life course as possible that may help to reduce risk of ADRD and thereby lighten its burden on the individual and society.

Small but consistent associations are found between ambient air pollution, ADRD, mild cognitive impairment (MCI), and accelerated cognitive decline; these associations are more likely found in studies of older women, adults over 65 years old, and in studies with higher levels of ambient air pollution [4, 19–29]. Studies focusing on specific cognitive abilities have not shown consistent patterns of association with air pollutants [3, 4, 8, 28], though some have found evidence for associations between some specific cognitive abilities and some air pollution components. In our review of the literature, we focused on adult cohorts with measures of specific cognitive abilities and fine particulate matter ($PM_{2.5}$, PM_{10}) and nitrogen oxides (NO_2, NO_x). Because of the relatively few studies examining air pollution and specific cognitive abilities, we included some older studies that used traffic density or distance from roadways as a proxy.

The most frequently researched cognitive ability is episodic memory (i.e., list learning tasks, story recall, visuospatial memory), presumably because episodic memory impairment is a prominent diagnostic feature of ADRD in older adults. Fewer than half of the samples found poorer memory associated with higher levels of air pollution [30–35], two reported better memory [33, 36], and 10 reported null or inconsistent associations [30, 32, 37–44]. Although research on ADRD has typically focused on memory, there is growing recognition of the importance of early deficits in executive function (EF)—a heterogeneous group of cognitive abilities that are very susceptible to aging and appear early in ADRD and MCI [45–48]—as a risk indicator. With regard to air pollution and EF, the heterogeneity of the abilities—encompassing working memory, set-shifting, and cognitive inhibition—and the tests used to assess EF make comparisons among studies challenging [45–48]. Among different samples evaluated, 4 found worse EF performance under conditions of higher air pollution [30, 34, 41, 49], 2 found better performance [38, 44], and 3 reported non-significant effects [30, 39, 50]. Most studies only measured one aspect of EF, often with only one test, or failed to adjust for related abilities (e.g., not adjusting for processing speed in Trails switching tests) [30, 32, 33, 37, 39, 40, 42]. Findings for verbal fluency and ambient air pollution are also mixed: associations range from worse [34, 35, 37, 42], to non-significant [32, 36, 39, 40, 44], to better performance [37, 41]. Other cognitive abilities such as processing speed and visuospatial ability are underrepresented in the air pollution literature. A few studies showed poorer processing speed [42, 44], but the majority found no association [30, 36, 39, 42, 51], while very few studies examined visuospatial ability [32, 34]. Most studies used only a single measure.

The opportunity for direct comparisons among studies is limited due to the widely varying assessments of air pollution and cognitive measures, and many cognitive measures were brief, screening, or global in nature. Sample characteristics such as age, sex, and socioeconomic status also vary widely. Finally, few studies of adults examine air pollution and cognitive abilities prior to old age with the majority being conducted in adults over

65 [3]. Despite recognition of the importance of the neurobiology of middle age [52], studies of ambient air pollution and cognitive functions in middle age—when interventions may crucially affect later ADRD outcomes—still constitute a major knowledge gap in this research.

Another knowledge gap in the air pollution/cognition literature is the extent to which genetic influences may moderate air pollution-cognition relationships [53]. Genetic factors such as *APOE* are non-modifiable risk factors that may influence the effect of modifiable risk factors such as air pollution. Thus, understanding the interacting effect of the genetic and environmental influences can highlight the importance of reducing the effect of air pollution in those who are genetically susceptible. Some research suggests that the apolipoprotein E (*APOE*) genotype affects ADRD risk by modifying susceptibility to environmental and health factors [53–57]. In a small autopsy study of children and young adults living in heavily polluted areas of Mexico City, *APOE*-ε4 allele carriers had accelerated beta amyloid 42 accumulation in the frontal cortex and hippocampus [6]. The authors proposed that older *APOE*-ε4 carriers might have additionally increased risk for developing ADRD if they resided in polluted environments [6]. In studies of older adults, however, 5 found no significant ambient air pollution-by-*APOE* genotype interaction [21, 58–61], and 1 found a significant interaction effect only on a measure of motor planning and execution [32]. One study reported significant moderation of the association between cognitive change and ambient air pollution (NO_2, $PM_{2.5}$, and PM_{10}); *APOE*-ε4 carriers exposed to higher air pollution levels showed more pronounced cognitive decline, but cross-sectional findings were not addressed [59]. Mouse models of air pollution show more consistent adverse impact on carriers of human ApoE4 transgenes than ApoE3 [58, 62–67]. Because of their younger ages, these experimental studies suggest earlier/younger human ages should be examined where possible. Few air pollution studies examine the effects of *APOE* during midlife.

The *APOE*-ε4 allele is consistently associated with increased risk for accelerated cognitive aging, and ADRD in older adults [20, 68–71]. However, studies of ε4 carriers have found both preserved executive functioning and accelerated decline depending on life stage [20, 68, 72–76]. Whether *APOE* status modulates the effects of air pollution exposure on cognition in middle age remains unclear. We previously showed that *APOE* genotype was associated with significant decline in EF from middle to early old age [77]. In the present study, we examined whether effects of ambient air pollution on cognition—in particular on EF—from middle to old age are moderated by *APOE* genotype.

By using detailed residential $PM_{2.5}$ and NO_2 concentrations covering both past and recent air pollution exposures combined with in-depth cognitive assessments conducted from midlife to early old age, as well as *APOE* genotyping, this study provides a unique opportunity to address significant knowledge gaps in the ambient air pollution/cognition literature. VETSA's extensive in-person evaluations, with multiple indicators of each cognitive domain in its day-long clinical neuropsychological protocol, allows us to replicate and extend previous research on specific cognitive domains. We first examined the extent to which specific cognitive factors—representing 4 cognitive domains of episodic memory, executive function, verbal fluency, and processing speed—were sensitive to the effect of past

or recent ambient air pollution in midlife. In particular, we focused on episodic memory and executive functions as abilities most relevant to later ADRD. Second, we examined whether *APOE* genotype moderated the effects air pollution on cognitive functioning.

METHODS

Participants.

The Vietnam Era Twin Study of Aging (VETSA) is a longitudinal behavioral genetic study of cognitive and brain aging and risk for MCI and AD [78]. We randomly recruited participants from the Vietnam Era Twin Registry (VETR), a large nationally distributed registry of male-male twin pairs who served in the United States military at some point between 1965 and 1975 [79, 80]. All participants previously participated in the Harvard Twin Study of Substance Abuse [81], which included no exclusion criteria based on substance abuse or any diagnostic or other personal characteristic. At the baseline assessment (VETSA 1, data collection: 2003–2007; average age 56, range 51–61), inclusion criteria were that both members of a twin pair agreed to participate and were 50–59 years old at recruitment [82]. Follow-up inclusion criteria did not require participation of the cotwin (VETSA 3; 2016–2019; average age 68, range 61–73). Details of the sample ascertainment and data collections are described in detail elsewhere [78, 82]. Participants have comparable health, education, and lifestyle characteristics to American men in their age range [83]. Although all participants are veterans, most (80%) did not experience combat. From hereon we refer to the cognitive assessment waves as age 56 or age 68.

Procedures.

VETSA in-person assessments at both time points involved self-report questionnaires, medical history interviews, and in-depth neuropsychological testing. Assessments using identical protocols occurred at University of California, San Diego (UCSD) and Boston University (BU). The studies were approved by human subjects' research protections review boards at the participating institutions. Participants provided written informed consent.

Measures.

Cognitive measures.—At mean ages 56 and 68, participants were administered the same extensive clinical neuropsychological battery comprising 16 standard cognitive tests comprising 24 subtests representing multiple cognitive domains. We used factor scores calculated for four cognitive domains (episodic memory, executive function, processing speed, and verbal fluency) based on our prior work which validated these latent variables [84–88]; factor scores comprising multiple tests are more robust than individual tests. Cognitive scores at age 68 were adjusted for practice effects prior to factor analysis; this approach adjusts for the expected improvement in performance among longitudinal research participants with previous exposure to the same tests [84–89].

Episodic memory factor. The episodic memory factor comprises 7 scores [84]: the total of the five learning trials, the short-delay free recall, and the long-delay free recall conditions from the Delis-Kaplan Executive Function System (D-KEFS) California Verbal Learning Test version 2 (CVLT) [90], and the immediate and delayed recall conditions from Visual

Reproductions and Logical Memory subtests from the Wechsler Memory Scale (WMS)-III [91].

Executive function factor. An influential model of executive function—the unity/diversity model—has identified a robust common factor underlying executive function measures representing response inhibition, task-set switching, and working memory by modeling it as a common executive function latent factor [46, 47]. The common executive function factor reflects goal management abilities necessary for initiating and completing a task and to pursuing goal-directed actions despite distractions [77, 86].

The VETSA common executive function factor comprises scores from 6 measures that represent the 3 subdomains of executive function. Inhibition was assessed with the Stroop task [92, 93]. Set-shifting was assessed using the D-KEFS Trail Making Test switching trial adjusted for performance (i.e., speed) on the letter and number sequencing conditions and the D-KEFS category-switching subtest for verbal fluency adjusted for number of correct boys' names and animals [94]. Working memory subdomain included 3 measures: the letter number sequencing, forward and backward digit span subtests from the Wechsler Memory Scale-III [91] and the reading span test [95].

In these analyses, we focus on the common executive function factor (EF). However, because a number of studies have examined working memory, we also created an additional working memory factor that allows more direct comparison with other studies that only assessed working memory based on previous research [77, 86, 96]. The working memory factor (WM) is based only on the 3 working memory tasks. Importantly, the working memory factor score used here reflects a contribution of common EF and working memory-specific abilities. It is thus highly correlated with common EF but still distinct because the 3 working memory measures all involve the ability to temporarily hold and manipulate information in one's brain.

Verbal Fluency factor. The verbal fluency factor is based on our factor analysis of abilities in common across the multiple verbal fluency tests administered in VETSA (phonemic fluency & semantic fluency) [85]. The general verbal fluency factor (VF) [85] captured common variance on the D-KEFS verbal fluency phonemic (3 letters) and semantic conditions (3 categories, including the number of items generated in the switching task ignoring the number of switches) [94]. Because some air pollution studies only examined semantic fluency, we also created a separate semantic fluency factor score based on just the three D-KEFS semantic conditions. The semantic fluency factor has high overlap with the general fluency factor.

Processing speed factor. The processing speed factor comprises six processing speed indices [88]: the D-KEFS Trail Making number and letter sequencing conditions [94], word and color conditions of the Stroop task [92, 93], and a computerized version of simple reaction time [97]. Scores are coded so that high scores indicate better performance.

Air Pollution Exposure Assessment.—Address histories/geocoding. We combined 3 sources of residential addresses to create detailed address histories from 1993–2017:

addresses provided to the study as part of ongoing study recruitment and retention, a mailed survey requesting addresses lived at between 1993 and 2018 for 6 months or longer, and LexisNexis. After we created detailed residential address histories, all geocodes were provided to the University of Washington Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESAAir) group. Geocodes data did not include dates or identification numbers and a large number of random geocodes were included to retain anonymity. MESAAir provided the VETR with $PM_{2.5}$ and NO_2 concentration levels at each geocode from 1993 to 2017. VETR staff then created individualized $PM_{2.5}$ and NO_2 histories for each participant by month. Since $PM_{2.5}$ prior to 1999 was provided as an annual exposure, if an individual lived in different locations across a particular year, the air pollutant value for each location was time-weighted to the address history.

Creation of exposure concentration scores. For the data analyses, we created individualized past and recent exposure concentration scores for each participant for $PM_{2.5}$ and/or NO_2 exposure. The past score averaged pollutant data from 1993–1999. The recent score averaged pollutant data from the 36 months prior to a participant's baseline cognitive testing date. We excluded participants if more than 20% of their pollution data were missing for the designated period. Out of the 1237 VETSA 1 participants, 1124 had usable exposure histories (91%); 112 (9%) did not have enough usable geocodes to create address histories or lived outside of the continental United States. Comparisons of the characteristics of participants with usable air pollution data with those who did not have usable data found only one significant difference for variables listed in Table 1; participants were more likely to be heavy drinkers in the group with more missing air pollution data [X^2 (2, 1234) = 7.38, p=.025].

Air pollution level concentrations: $PM_{2.5}$ and NO_2. The MESAAir statistical prediction of air pollution concentrations uses pollutant measurements from monitored locations in conjunction with multiple types of geographic, atmospheric, and physiochemical information as covariates in statistical models to predict the concentration of pollutants at a much larger number of unmonitored locations over a given timeframe[104]. The MESAAir fine scale national spatiotemporal model is an extension of universal kriging. Kriging, a Gaussian process regression, is a method by which data from a limited sampling of geographic data (e.g., a pollutant such as $PM_{2.5}$ measured at a specific monitor) are interpolated to provide estimates of the value of that pollutant over a continuous spatial field. The universal kriging approach combines land-use regression (LUR) techniques with simple kriging methods tapping into the strengths of both. The model makes use of up to 400 geographic covariates based on geographic information systems (GIS) data. More specifically, the model combines information such as seasonal and systematic trends in emission sources, population, land use and near-source concentrations (i.e., the LUR construct; constant time-averaged spatial field) that vary over space and generates predicted concentration values. NO_2 models may also include satellite data. The modeling is based on the assumption that pollutant concentrations exhibit systematic seasonal and secular trends that vary over space that can be used to predict other concentrations. The MESA Air model is unique because it is based on spatially-varying temporal pollution processes [98].

Initially the MESAAir models were developed for specific communities but have been extended to predict across the continental United States. By using spatial smoothing methods, the model also provides more realistic pollution surfaces, even in areas without adequate monitor coverage. Information from data-rich areas combined with other data can be interpolated to produce estimates even for sparsely populated regions with less monitoring infrastructure. To facilitate the extended models, MESAAir investigators divided the country into 9 climatic/topographic regions (for $PM_{2.5}$ model) or three regions (for NO_2) in order to account for subnational region-specific pollution processes and ensure each region contained supplemental monitors. Overall, the model reliably yields accurate predictions at specific geolocations; for $PM_{2.5}$ the results prior to 1999 were predicted on an annual scale and after 1999, on a monthly scale. For NO_2, results from 1993–2017 were predicted on a monthly scale. Values have been cross-validated with an R^2 of 0.89 for $PM_{2.5}$ and 0.87 for NO_2 [98]. For regions with little or no monitor coverage, the R^2 was 0.77. Given that the Environmental Protection Agency's extensive monitoring system was only established in 1999, data prior to that period relied on ground-based data from 1999–2010 which was run through a spatiotemporal historical prediction model and back-extrapolated, resulting in R^2 values ranging from 0.55 to 0.87 [98].

APOE.: At a participant's first assessment certified phlebotomists drew blood that was used to determine *APOE* genotype; detailed methods were described previously [99]. In brief, *APOE* genotype was determined using polymerase chain reaction conditions and the HhaI restriction digest method in the laboratory at the Puget Sound VA Healthcare System. All genotypes were determined independently twice by laboratory personnel blind to initial genotype. We divided the sample into two groups: ε4 positive (individuals with 1 or 2 ε4 alleles) and ε4 negative (no ε4 alleles).

Covariates.: Covariates were chosen based on prior research and included time (age 56, age 68 assessment), location, age, lifetime education, race/ethnicity, household income, smoking status, alcohol consumption status, depressive symptoms, self-reported physician diagnosis of cardiovascular disease, diabetes, high cholesterol, and/or stroke. Location was coded based on rural-urban continuum (RUC) codes that use zip code to categorize location by counties and recoded as: metropolitan (1= ≥ 1 million), urban/suburban (2= ≥ 50,000 to < 1 million), 3= rural (< 50,000) [100]. Education is a continuous measure reflecting years of formal education completed (i.e., completed high school = 12; completed college = 16; PhD/MD = 20). Race/ethnicity is categorized as 1 = White non-Hispanic versus 0 = Other. Cigarette smoking status is coded as 0 = never, 1 = former, 2 = current. Alcohol is coded as the extent in the past 2 weeks a person consumed beer, wine, and/or hard liquor: 0 = no alcohol; 1 = > 0 to ≤ 2 drinks per day, and 3 = > 2 drinks per day. Health information on cardiovascular conditions, stroke, diabetes, hypertension was self-reported in a medical history interview on the same day as cognitive testing (1 = present/0 = absent). Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D) [101]. Education, household income, and depressive symptoms are modeled as continuous measures. Familial and adult socioeconomic status (SES) measures are a weighted combination of education and occupation.

Statistical analyses.

In preliminary analyses we divided $PM_{2.5}$ and NO_2 measures into quartiles and examined quartile differences in demographic measures and covariates to ascertain whether associations might be non-linear. There was little evidence of non-linearity (Supplemental Table S1 & S2) so we conducted analyses using continuous air pollution measures. In particular, *APOE* status did not differ by quartile.

Multivariate analyses were conducted with continuous $PM_{2.5}$, NO_2, and the 4 cognitive factors. We used generalized estimating equations implemented in SAS PROC GEE. GEE provides improved efficiency over mixed models and fits a marginal model to longitudinal data. The correlations between twins were taken into account in the working matrix, and the time effects (repeated measures at the age 56 and age 68 assessments) were estimated as a fixed effect in the output. In Model 1, we first examined the main effects of past and current $PM_{2.5}$ or NO_2 and *APOE*-ε4 status. Covariates included time, location, age, lifetime education, race/ethnicity, household income, smoking status, alcohol consumption status, depressive symptoms, and self-reported physician diagnosis of cardiovascular disease, diabetes, high cholesterol, and/or stroke. Models were conducted separately for past and recent $PM_{2.5}$ and NO_2. Tests of main effects in Model 1 test whether pollution exposure is related to cognitive function essentially averaged over both timepoints.

Second, in Model 2 we added air pollutant-by-*APOE* status and air pollutant-by-time interactions to Model 1. Model 2 tests whether pollution exposure effects differ as a function of *APOE* genotype, and whether the magnitude of pollution-cognition associations differed over time. For categorical moderators such as *APOE* in the current study, the concept of moderation is consistent with analytic interaction [102]. Although the participants are twins, these were non-twin analyses. Because these analyses treat the twins as individuals, GEE models control for the non-independence of the twins and address nested correlations (i.e., twins and age). In follow-up/sensitivity analyses, we also examined the working memory and semantic fluency sub-factors. To address the potential increased likelihood of multicollinearity in the models with interactions, we centered all the independent variables that formed the interaction terms in the models with *APOE*-by-pollutant interactions and calculated variance inflation factors (VIFs). VIFs for all the independent variables for each cognitive outcome were all less than 2, indicating no serious multicollinearity for any models.

RESULTS.

Descriptive analyses.

$PM_{2.5}$ and NO_2 declined steadily from 1993 to 2017 (Figure 1; Table 1). At past and recent timepoints, average $PM_{2.5}$ levels were 13.37 $\mu g/m^3$ (range 4.90–24.33) and 11.15 $\mu g/m^3$ (range 2.58–24.37), respectively. These $PM_{2.5}$ levels are below the 1997 Environmental Protection Agency (EPA) standards of 15 $\mu g/m^3$. Average past NO_2 was 11.14 ppb (range 1.60–44.74); average recent NO_2 was 9.28 ppb (range 1.72–37.37); these NO_2 levels were lower than EPA standard of annual average 53 ppb set in 1971. Paired t-tests indicate both PM2.5 and NO_2 declined significantly within participant. Mean change from past to recent

for $PM_{2.5}$ was an average decrease of 2.12 μg/m^3 (SD 1.73) [t (1070) = 41.99, p<0.0001] and for NO_2 an average decrease of 1.18 ppb (SD 3.36) [t (1071) = 17.67, p<0.0001]. All of the cognitive factors showed significant effects of time indicating change (declines) in cognitive performance from mean age 56 to 68 (see Supplemental Tables S3–S6).

The majority of participants (90.8%) were non-Hispanic White, with average lifetime education of 13.9 years. See Table 1 for descriptive statistics. Past and recent $PM_{2.5}$ were correlated r=0.81 (p<.0001); past and recent NO_2 were correlated r=0.86 (p<.0001). Within time correlations between the two air pollutants ranged from r=0.60 (p<.0001; past) to 0.46 (p<.0001; recent). In the GEE models, age, education, and depressive symptoms were consistently significantly associated with the cognitive factors, with the exception of the correlation between age and working memory (see Tables S3–S6).

Participants who did not return for the age 68 assessment included 78 deceased (6.3%) and 208 non-returnees for other reasons (16.8%). Comparisons of returnees with non-returnees of any type showed that non-returnees were significantly more likely to have been smokers, have cardiovascular conditions, had a stroke, lower education, and lower income at age 56 (all ps<.05 2-tailed). Non-returnees did not differ from returnees in $PM_{2.5}$ or NO_2 exposure, ethnicity, *APOE* genotype, BMI, respiratory problems, depressive symptoms, or urban/rural location. Past and/or recent air pollution exposure was no different for deceased participants compared with returnees.

We examined correlations of $PM_{2.5}$ and NO_2 with sociodemographic characteristics; associations varied by characteristic and pollutant (see Table 2). Parental SES was associated with men having higher $PM_{2.5}$ but not NO_2 concentrations in midlife. Living in a more urban setting at age 20 and having non-White race/ethnicity were both significantly associated with higher $PM_{2.5}$ and NO_2 in midlife. Living in a more urban setting at age 20 was also significantly associated with higher parental SES, adult SES, and adult income. At midlife, participants with more years of education and higher own SES lived in settings with significantly higher NO_2 but not $PM_{2.5}$. Thus, these air pollutants at midlife showed complex associations with earlier and midlife demographic factors.

Model testing.

Model 1: Associations between ambient air pollution, *APOE*-ε4 status, and cognitive functions adjusting for time, location, age, lifetime education, race/ethnicity, household income, smoking status, alcohol consumption status, depressive symptoms, and self-reported physician diagnosis of cardiovascular disease, diabetes, high cholesterol, and stroke. In Model 1, both past $PM_{2.5}$ and recent $PM_{2.5}$ were significantly associated with the general verbal fluency factor (β = −0.03, 95% CI [−0.05, −0.01]; β = −0.03, 95% CI [−0.05, −0.00] respectively; S3, S4). There were no significant main effects of recent or past $PM_{2.5}$ or NO_2 levels on the other three cognitive factors and no main effect of *APOE* genotype (see Supplemental tables S3–S6).

We also examined associations with the working memory and semantic fluency sub-factors. Associations for $PM_{2.5}$ were not significant. Both past NO_2 and recent NO_2 levels were significantly associated with the semantic fluency factor (β= −0.01, 95% CI [−0.03, −0.00];

β = −0.02, 95% CI [−0.03, −0.01], respectively; Supplemental Tables S5, S6). However, examination of confidence intervals suggests there is no strong evidence supporting a major difference between the general fluency and semantic fluency factors for $PM_{2.5}$ versus NO_2 exposures. Neither past NO_2 nor recent NO_2 was associated with the working memory sub-factor.

Model 2: Model 1 plus air pollutant-by-*APOE* genotype and air pollutant-by-time interactions. The interactions of *APOE* genotype with both past and the recent $PM_{2.5}$ were significant for executive function (past $PM_{2.5}$-by-*APOE*: β= −0.06, 95% CI [−.10, −0.02]; recent $PM_{2.5}$-by-*APOE:* β= −0.05, 95% CI [−.09, −0.01]; Table 3).

Compared to *APOE*-ε4 non-carriers, ε4 carriers had steeper and more negative slopes indicating poorer executive function with increasing $PM_{2.5}$ levels (Figure 2). In contrast, ε4 non-carriers had relatively flat slopes that were not significantly different from zero with regard to $PM_{2.5}$. Interestingly, examining the confidence intervals (see Figure 3), *APOE*-ε4 carriers had significantly better executive functioning than the non-carriers when $PM_{2.5}$ levels were low. Results were similar for working memory (past $PM_{2.5}$-by-*APOE:* β= −0.05, 95% CI [−.09, −0.01]; recent $PM_{2.5}$-by-*APOE:* β= −0.05, 95% CI [−.09, −0.01] Figure 3; Table 3). The $PM_{2.5}$-by-*APOE* interactions were not significant for the other cognitive domains. There were no significant air pollutant-by-time interactions (see Table S7).

Past and recent NO_2-by-*APOE* interactions for episodic memory were significant (past NO_2-by-*APOE*: β = 0.02, 95% CI [.004, 0.04]; recent NO_2 -by-*APOE*: β = 0.03, 95% CI [.001, 0.05], respectively; Table 3, Figure 4). Compared to *APOE*-ε4 non-carriers, ε4 carriers had positive slopes indicating better episodic memory with increasing NO_2 levels. Among non-carriers, there were no associations between exposures and cognition. The NO_2-by-*APOE* interactions were not significant for the other cognitive domains. There were no other significant NO_2-by-*APOE* interactions (see Table S7).

CONCLUSIONS

These findings from the VETSA sample demonstrate associations of $PM_{2.5}$ and NO_2 with certain cognitive functions from midlife to early old age, with certain associations differing as a function of *APOE* genotype. The only main effect was that individuals exposed to higher ambient air pollution had lower verbal fluency—general verbal fluency for $PM_{2.5}$ and semantic fluency for NO_2. These results are partially consistent with 4 studies of primarily older adults [34, 35, 37, 42], but 2 of those 4 studies only examined semantic fluency.

We found significant interactions between *APOE* genotype and air pollution in relation to executive function and episodic memory domains, suggesting the importance of examining complex modifiers that may begin to explain variability of previous findings in the literature. Although *APOE*-ε4 is the major risk allele for Alzheimer's disease and *APOE*-ε4 may increase susceptibility to environmental and health factors [53–57, 71, 103], it also shows variability across the life course [20, 104]. Here, the interaction effect was such that as either past or recent as $PM_{2.5}$ levels increased, executive function and working memory worsened in ε4 carriers, but not non-carriers. However, at very low levels of $PM_{2.5}$ ε4 carriers actually

had significantly better performance than non-carriers (Figure 2). While all participants had similar episodic memory performance at past lower levels of NO_2, somewhat surprisingly, ε4 carriers had significantly better episodic memory at the highest levels of NO_2. The steeper slopes of the ε4 carriers is consistent with evidence for *APOE* being a variability gene i.e., that it has variable sensitivity to environmental influences and that the ε4 allele is not always associated with more negative outcomes [54]. We do not know of other evidence that higher NO_2 improves cognition. Previous literature has, for example, found that *APOE* ε4 carriers show either preserved functioning or accelerated decline in executive function depending on life stage [20, 68, 72–75, 105].

The complexity of these associations with ambient air pollution is evident in our finding that although the slopes were steeper for ε4 carriers, it remains unclear what could account for the opposite direction of these two sets of interaction effects. One possible explanation may lie in the different associations between NO_2 and demographic factors. Participants with higher education and higher income experienced higher NO_2 but not $PM_{2.5}$ exposures in midlife, and also had better episodic memory. Men with higher education and income, as well as familial SES, were more likely to live in urban settings even at age 20. Given that $PM_{2.5}$ exposures tend to be "flatter" across a metropolitan area and NO_2—as a marker of traffic-related air pollution—has more fine area contrasts, NO_2 may be more sensitive to SES gradients than $PM_{2.5}$. These associations suggest there may be some spatial confounding as evidenced by associations between the air pollution measures and demographics. Although our statistical models adjusted for urban/rural location, education and income, it may be there are other differences not captured by our covariates that are associated with who resides in areas with higher pollution. In addition, while average levels of $PM_{2.5}$ were relatively close to national EPA standards, average levels of NO_2 were relatively low and well within the "good" range compared with EPA standards.

Limitations of this paper are that the sample is all male and mostly White non-Hispanic, so the results may not generalize to women and other ethnicities. Estimates of differences between white and non-white participants are based on a small subsample. We calculated air pollution measures based on residential address; however, at age 56 the majority of the men worked full-time, and many were still working at age 68. We did not have access to work geocodes. Thus, the residential addresses may not accurately reflect full exposures. Furthermore, the sample was a nationwide sample with about one-third residing in relatively rural areas where traffic-related ambient air pollution may be low and also less accurately assessed due to distances between pollution monitors. We also were limited to past and recent $PM_{2.5}$ and NO_2 and did not have pollution estimates at age 68. Finally, although we examined whether *APOE* genotype moderates the effects of air pollution, we did not examine other biological mechanisms. Different mechanisms have been proposed for why air pollution may be associated with risk for ADRD including vascular risk factors, other biological vulnerabilities, stress, behavioral and socioeconomic risks that may link residing in more polluted areas with poorer cognitive performance [3, 22, 53, 71, 106, 107].

Despite its limitations, this study has many strengths. Unlike many previous studies examining air pollution and cognition, VETSA administered an in-depth in-person cognitive battery at 2 time points from midlife to early old age. There were multiple measures for each

cognitive domain. In addition, we were able to calculate both past and recent air pollutant concentrations during midlife for 2 key air pollutants. The sample's narrow age range at VETSA 1 (10 years) starting in midlife provides insights into an understudied age group. Effects of *APOE* genotype are complex, especially when taking the life course into account, so having a large sample in a narrow age range allowed us to focus on effects from midlife to early-old age. VETSA is also a nationwide sample providing heterogeneous exposures from very rural to very urban areas. Finally, our examination of the common executive function factor and its working memory sub-factor provide a more thorough investigation of executive function than in most prior studies.

In summary, these results reflect the complex interplay among *APOE* genotype, different air pollutants, cognitive abilities, and demographic factors across the life course. Also of import are the findings that the main contributors to cognitive function in midlife and later life were covariates reflecting influences such as education and depression, as well as age and time. Both education and depression are modifiable risk factors for ADRD and may interact with other risks such as air pollution [108, 109]; however, the possibility of meaningful modification of education will most likely be much earlier in life. Finally, it is important to consider the possibility of other modifiers, including other genes in the *APOE* cluster [110, 111]. Like prior studies, effect sizes in the present study were small. However, although research has found only small effects of air pollution on Alzheimer's disease and mixed results for effects on cognition, as Livingston et al. point out [1], when taken in the context of the large proportion of the population exposed to high air pollution, the overall impact is increased.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

The data supporting the findings of this study are available on request from the corresponding author. The data are not available on a public website due to privacy or ethical restrictions established by the Vietnam Era Twin Registry (VETR). A data request form is available on the VETSA website (https://psychiatry.ucsd.edu/research/programs-centers/

vetsa/index.html). Data requests can also be made at the VETR; the access process is described at: https://www.seattle.eric.research.va.gov/VETR/Investigator_Access.asp.

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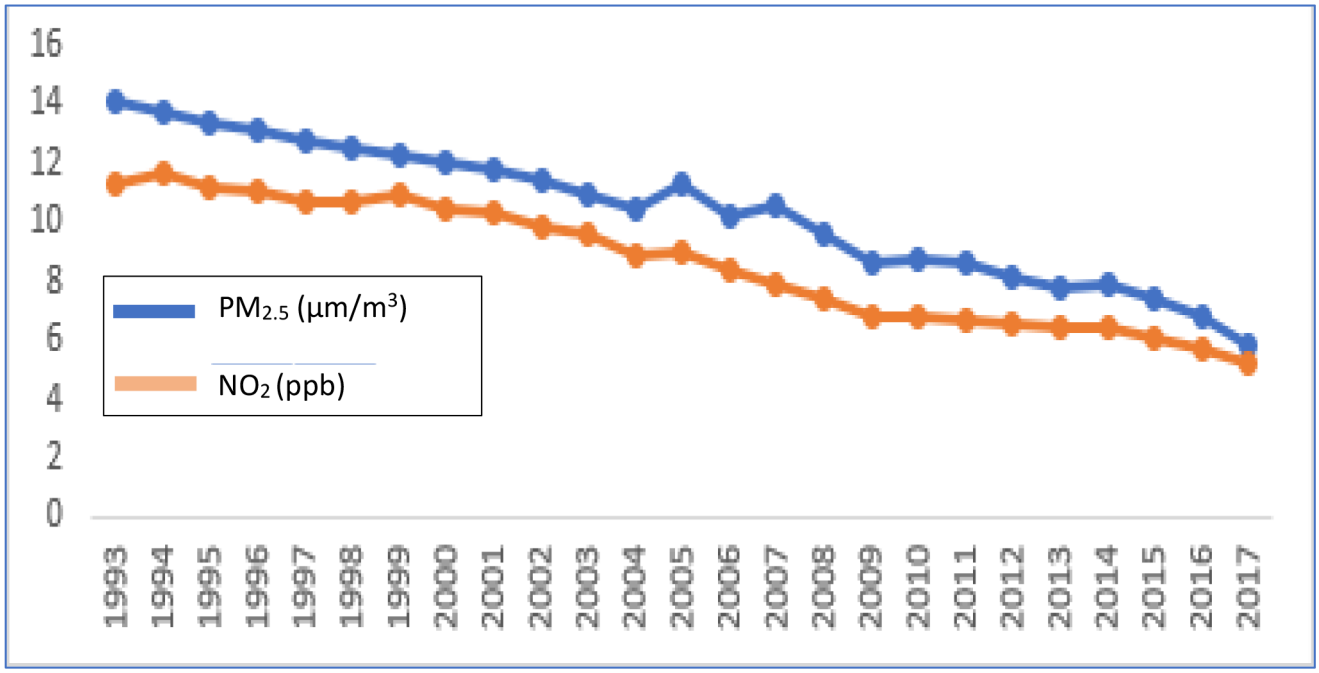

Figure 1.
Average $PM_{2.5}$ and NO_2 by Year: 1993–2017.

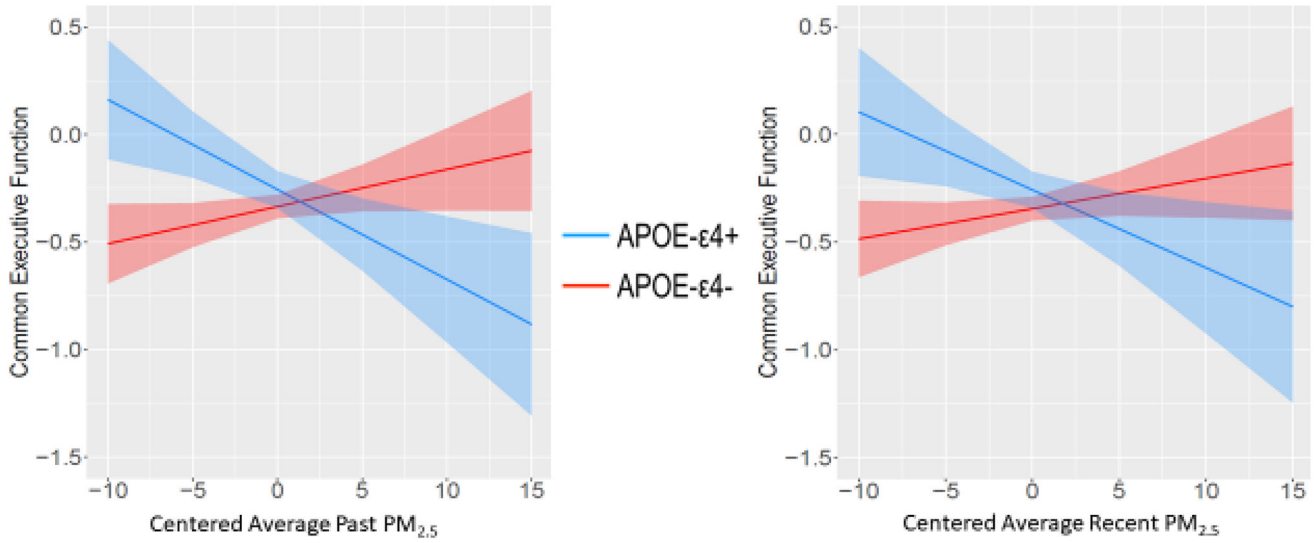

Figure 2.
Executive Function Factor and $PM_{2.5}$-by-*APOE* interaction

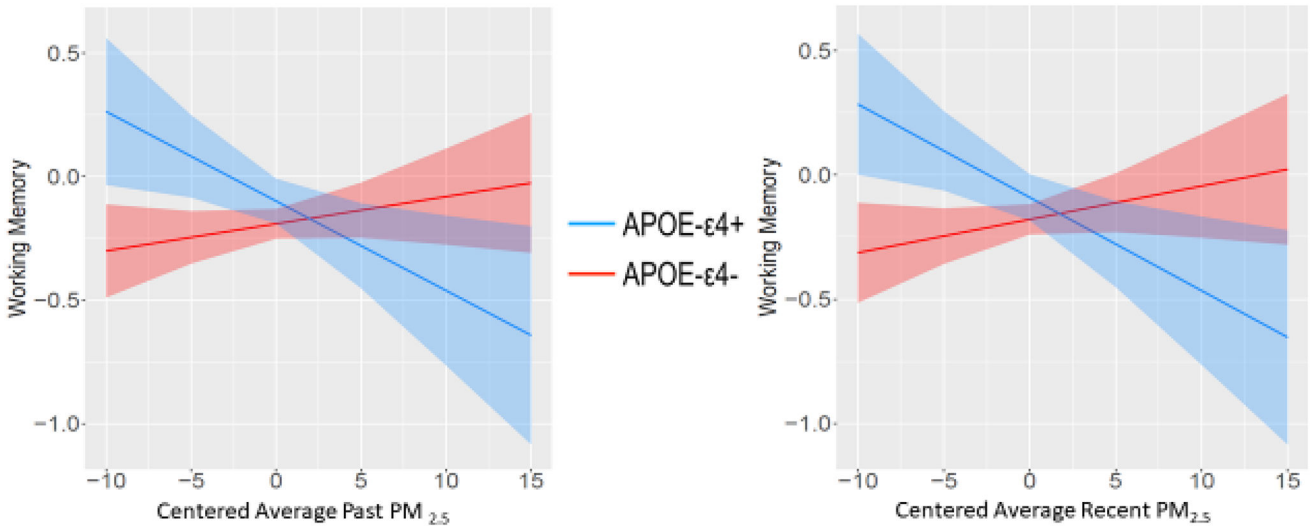

Figure 3.
Working Memory Factor and $PM_{2.5}$-by-*APOE* interaction

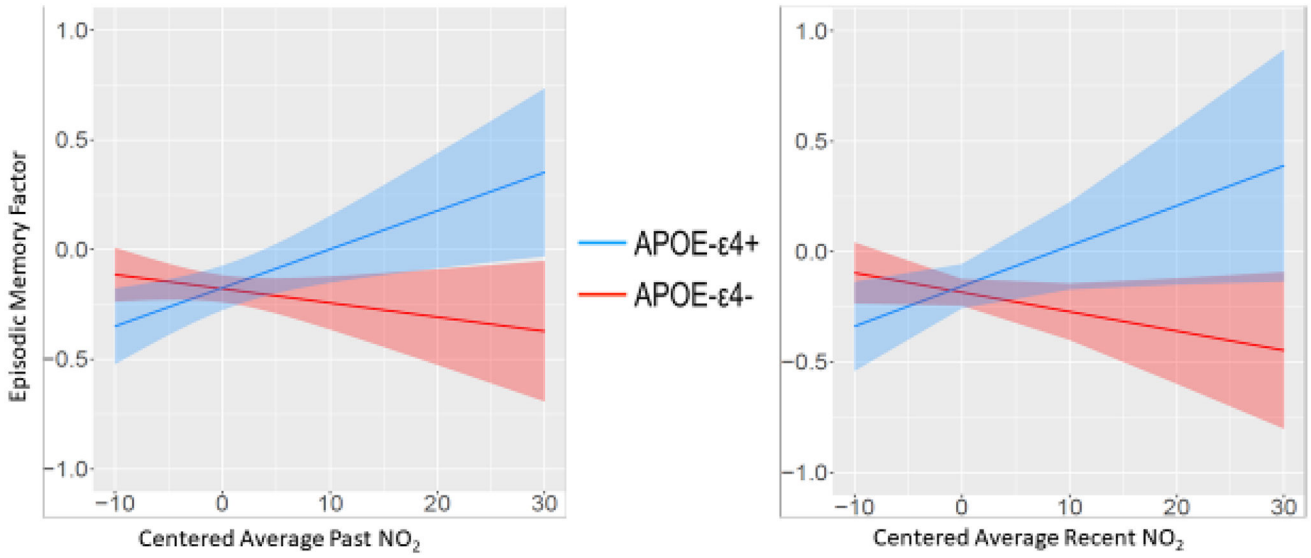

Figure 4.
Episodic Memory Factor and NO_2-by-*APOE* interaction

Table 1.

Descriptive statistics

	1993–1999		VETSA 1		VETSA 3	
	Total N	**Mean (STD)/N(%)**	**Total N**	**Mean (STD)/N(%)**	**Total N**	**Mean (STD)/N(%)**
Age Mean (STD)			1123	55.9 (2.5)	838	67.6 (2.4)
Ethnicity N (%)	1144		1123		838	
White non-Hispanic		1053 (92.1)		1036 (92.3)		770 (91.9)
Others		91 (8)		87 (7.8)		68 (8.1)
Location (Urban/Rural) Mean N (%)	1084	2.5 (1.9)	1113	2.5 (1.9)	831	2.6 (1.9)
Education Mean (STD)	1144	13.9 (2.1)	1123	13.9 (2.1)	838	14 (2.1)
Family_income Mean (STD)	1121	7.7 (3.2)	1100	7.6 (3.2)	827	7.8 (3.2)
APOE N (%)	1136		1117		834	
APOE 4 non-carrier		792 (69.7)		786 (70.4)		593 (71.1)
APOE 4 carrier		344 (30.3)		331 (29.6)		241 (28.9)
$PM_{2.5}$ (μm/m^3) Mean (STD)	1144	13.3 (2.8)	1123	11.1 (2.8)	838	11.1 (2.9)
NO^2 (ppb) Mean (STD)	1144	11.1 (6.4)	1123	9.3 (5.2)	824	9.3 (5.2)
Smoke Status			1123		836	
Never				358 (31.9)		279 (33.4)
Former				507 (45.2)		446 (53.4)
Current				258 (23)		111 (13.3)
History of high cholesterol N (%)			1121	337 (30.1)	838	587 (70)
Hstory of Hypertension N (%)			1121	643 (57.4)	838	633 (75.5)
History of cardio/vascular event N (%)			1121	131 (11.7)	838	242 (28.9)
History of respiratory illness N (%)			1121	96 (8.6)	838	144 (17.2)
Drug abuse N (%)			1120	14 (1.3)	838	7 (0.8)
Alcohol use N (%)			1121		837	
No alcohol use in past 2 weeks				386 (34.4)		331 (39.6)
>0 and <= 2 drinks per day				581 (51.8)		404 (48.3)
> 2 drinks per day				154 (13.7)		102 (12.2)
History of Stroke N (%)			1121	22 (2)	838	50 (6)
BMI Mean (STD)			1119	29.3 (4.9)	809	30 (5.4)

	1993–1999		VETSA 1		VETSA 3	
	Total N	Mean (STD)/N(%)	Total N	Mean (STD)/N(%)	Total N	Mean (STD)/N(%)
Depression Mean (STD)			1115	8.2 (8.1)	834	6.9 (7.5)

Table 2.

Demographic measures: Correlations with $PM_{2.5}$ AND NO_2

	Past $PM_{2.5}$ (93–99)	Recent $PM_{2.5}$ (3 yrs prior to VETSA 1)	Past NO_2 (93–99)	Recent NO_2 (3 yrs prior to VETSA 1)
Family of Origin Socioeconomic Status	**−0.11**	**−0.10**	−0.01	−0.02
Ethnicity (1= White non-Hispanic/0=other)	**−0.12**	−0.06	**−0.19**	**−0.16**
Age 20 Location (0=rural to 9=most urban; ~1969)	**0.16**	**0.11**	**0.30**	**0.32**
Education-Years of formal education	0.00	−0.02	**0.10**	**0.12**
Age 20 General Cognitive Ability	**−0.07**	−0.02	−0.01	0.04
Own Socioeconomic Status (age 56)	−0.01	−0.03	**0.07**	**0.08**
Own Income (age 56)	0.04	0.04	0.05	0.04
Own occupation (age 56)	−0.01	0.00	0.06	0.06

*Items in bold are significant at than p<.05, two-tailed. With the exception of ethnicity, all measures are continuous variables.

Table 3.

Summary of Results from Model 2 With Significant $PM_{2.5}$ or NO_2 by *APOE* Genotype Associations: Shown are Main Effects of Pollutant, *APOE* and Pollutant by *APOE* Interaction for the Significant Cognitive Factor

Model 2 summary	beta	Estimate	se	95% CI	Chi^2	p-value
Past $PM_{2.5}$ *APOE and Executive Functions Factor						
Past $PM_{2.5}$	0.02		(0.01)	−0.0050, 0.0417	1.00	0.317
APOE (REF ε4-)	0.08		(0.07)	−0.0464, 0.2128	1.57	0.209
Past $PM_{2.5}$*APOE	**−0.06**		**(0.02)**	**−0.0993,−0.0200**	**7.95**	**0.005**
Recent $PM_{2.5}$ *APOE and Executive Functions Factor						
Recent $PM_{2.5}$	0.01		(0.01)	−0.0070, 0.0365	0.83	0.362
APOE (REF ε4-)	0.09		(0.07)	−0.0360, 0.2187	1.96	0.161
Recent $PM_{2.5}$*APOE	**−0.05**		**(0.02)**	**−0.0918,−0.0090**	**5.54**	**0.019**
Past $PM_{2.5}$ *APOE and Working Memory Sub-factor						
Past $PM_{2.5}$ 93–99	0.01		(0.01)	−0.0108, 0.0404	0.84	0.360
APOE (REF ε4-)	0.09		(0.07)	−0.0507, 0.2347	1.59	0.208
Past $PM_{2.5}$*APOE	**−0.05**		**(0.02)**	**−0.0927,−0.0111**	**5.82**	**0.016**
Recent $PM_{2.5}$ *APOE and Working Memory Sub-factor						
Recent $PM_{2.5}$	0.01		(0.01)	−0.0118, 0.0359	0.94	0.331
APOE (REF ε4-)	0.10		(0.07)	−0.0440, 0.2350	1.79	0.181
Recent $PM_{2.5}$*APOE	**−0.05**		**(0.02)**	**−0.0896,−0.0053**	**4.73**	**0.030**
Past NO_2 *APOE and Episodic Memory Factor						
Past NO_2 93–99	−0.01		(0.01)	−0.0200, 0.0067	−0.98	0.329
APOE (REF ε4-)	0.01		(0.08)	−0.1433, 0.1622	0.12	0.904
Past NO_2*APOE	**0.02**		**(0.01)**	**0.0043, 0.0422**	**2.41**	**0.016**
Recent NO_2 *APOE and Episodic Memory Factor						
Recent NO_2	−0.01		(0.01)	−0.0235, 0.0063	−1.13	0.259
APOE (REF ε4-)	0.03		(0.08)	−0.1174, 0.1841	0.43	0.665
Recent NO_2*APOE	**0.03**		**(0.01)**	**0.0019, 0.0499**	**2.12**	**0.034**

Notes. Summary results are from Model 2. Shown are the results for the pollutant, APOE ε4 status, and the pollutant by APOE interaction when the interaction is significant. Model 2 is run separately for the 4 pollutant measures predicting cognitive factors. Model 2 included the air pollutant, APOE ε4- status, the air pollutant by APOE ε4 interaction, air pollutant by time interaction covariates of time, location, age, lifetime education, race/ethnicity, household income, smoking status, alcohol consumption status, depressive symptoms, self-reported physician diagnosis of cardiovascular disease, diabetes, high cholesterol, and/or stroke. Full results for all Model 2 analyses (showing all variables in models) are in Supplemental Table 7.