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Long-term exposure to ambient air pollution, APOE-ε4 status, and cognitive decline in a cohort of older adults in northern Manhattan

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ABSTRACT

Background: There is mounting evidence that long-term exposure to air pollution is related to accelerated cognitive decline in aging populations. Factors that influence individual susceptibility remain largely unknown, but may involve the apolipoprotein E genotype E4 (APOE-ε4) allele.

Objectives: We assessed whether the association between long-term exposure to ambient air pollution and cognitive decline differed by APOE-ε4 status and cognitive risk factors.

Methods: The Washington Heights Inwood Community Aging Project (WHICAP) is a prospective study of aging and dementia. Neuropsychological testing and medical examinations occur every 18–24 months. We used mixed-effects models to evaluate whether the association between markers of ambient air pollution (nitrogen dioxide [NO_2]), fine [$PM_{2.5}$], and coarse [PM_{10}] particulate matter) and the rate of decline in global and domain-specific cognition differed across strata defined by APOE-ε4 genotypes and cognitive risk factors, adjusting for socio-demographic factors and temporal trends.

Results: Among 4821 participants with an average of 6 years follow-up, higher concentrations of ambient air pollution were associated with more rapid cognitive decline. This association was more pronounced among APOE-ε4 carriers ($p < 0.001$). A one interquartile range increase in NO_2 was associated with an additional decline of 0.09 standard deviations (SD) (95%CI −0.1, −0.06) in global cognition across biennial visits among APOE-ε4 positive individuals and a 0.07 SD (95%CI −0.09, −0.05) decline among APOE-ε4 negative individuals. Results for $PM_{2.5}$, PM_{10} and cognitive domains were similar. The association between air pollutants and rate of cognitive decline also varied across strata of race-ethnicity with the association strongest among White non-Hispanic participants.

Conclusions: These results add to the body of evidence on the adverse impact of ambient air pollution on cognitive aging and brain health and provide new insights into the genetic and behavioral factors that may impact individual susceptibility.

1. Introduction

Age-related cognitive decline is a growing public health concern as increases in life expectancy and the aging of the population are expected to substantially increase the prevalence of cognitive impairment and dementia (Ferri et al., 2005; Prince et al., 2013). Approximately 5.8 million Americans live with dementia (Alzheimer's Association, 2019; Plassman et al., 2007), with the prevalence expected to rise to almost 14 million by 2050 (Hebert et al., 2013; Prince et al., 2015). The most common cause of dementia in older adults is Alzheimer disease (AD), accounting for between 60 and 70% of all dementia cases, but most patients have a mix of pathologies including AD, vascular dementia,

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and dementia with Lewy bodies (National Institute on Aging, 2017; World Health Organization, 2017; Alzheimer's Research UK, 2019). Poor cognitive function is the sixth leading cause of death in the United States and a key cause of disability among older adults and can have profound social, economic, and health implications (Alzheimer's Association, 2019; Sosa-Ortiz et al., 2012). Global healthcare expenditures for cognitive impairment reached $818 billion in 2015 and are expected to reach a staggering two trillion dollars by 2030 (Prince et al., 2015).

The causes of dementia in the aging population are multi-faceted and are likely a combination of lifestyle, genetic, and environmental risk factors. Risk of accelerated cognitive decline increases with age, cerebrovascular disease, and the presence of traditional cardiovascular risk factors, but these factors do not fully account for risk of cognitive decline in the population. Currently, the strongest known genetic risk factor for AD and related dementias (ADRD) is the presence of the Apolipoprotein E genotype E4 (APOE-ε4) allele. There are multiple underlying mechanisms through which APOE-ε4 may impact cognitive function including neuroinflammation, amyloid-β (Aβ) plaque aggregation, and decreased vascular function (Liu et al., 2013; Dwyer et al., 2013; Sun et al., 2015; Daviglus et al., 2011; Daviglus et al., 2010; Poirier et al., 1993).

There is mounting evidence that environmental exposures including long-term exposure to ambient air pollution may have a detrimental effect on cognitive function in aging populations (Power et al., 2011; Weuve et al., 2012; Wellenius et al., 2012; Kioumourtzoglou et al., 2016; Tzivian et al., 2017; Ailshire and Clarke, 2015). In a previous publication we showed that estimates of ambient levels of nitrogen dioxide [NO_2), fine [$PM_{2.5}$], and coarse [PM_{10}] particulate matter outside the residence were associated with cognitive decline in an older, multi-ethnic cohort of participants in northern Manhattan, New York City (NYC) (Kulick et al., 2020). As concern regarding the deleterious health effects of ambient air pollution grows, several biological mechanisms have been hypothesized to underlie the adverse effects of pollutants on the brain and cerebral vasculature, with the strongest evidence surrounding pathways of systemic inflammation and oxidative stress (Campbell et al., 2005; Levesque et al., 2011; Calderón-Garcidueñas et al., 2008; Calderón-Garcidueñas et al., 2016; Calderón-Garcidueñas et al., 2012).

Due to a shared inflammatory mechanism, a series of both animal and human studies have suggested that the effect of ambient air pollution on cognitive function may be more pronounced among individuals with the APOE-ε4 allele (Calderón-Garcidueñas et al., 2008; Cacciottolo et al., 2017; Schikowski et al., 2015). To date, only two population-based studies have evaluated whether the association between residential air pollution and cognitive function differs by APOE-ε4, with both studies finding a stronger association among APOE-ε4 carriers (Cacciottolo et al., 2017; Schikowski et al., 2015). We investigated this relationship in a large, multi-ethnic cohort based in northern Manhattan, examining whether the previously observed association between ambient air pollution and rate of cognitive decline was stronger among individuals with at least one APOE-ε4 allele. We additionally examined whether the effects of ambient air pollution on rate of cognitive decline varied across strata of other established risk factors for accelerated cognitive decline.

2. Materials and methods

2.1. Study sample

The Washington Heights-Inwood Community Aging Project (WHICAP) is an ongoing, prospective, population-based study of aging and dementia. Established in three recruitment waves, the first wave of participants was recruited in 1992 from a random sample of Medicare-eligible adults (age ≥ 65 years) residing in the neighborhoods of Washington-Hamilton Heights and Inwood in northern Manhattan. The second and third waves were recruited from the same communities in 1999 and 2010, with a goal to recruit a cohort of ethnically and educationally diverse non-demented elderly based on the following goals: (1) the final sample would be equally divided among Hispanics, non-Hispanic blacks, and non-Hispanic whites, (2) the cohort would represent equal proportions of those 65–74 and ≥75 years old at enrollment, and (3) individuals would be excluded from participation if they had substantial cognitive problems, had been diagnosed with dementia, or did not speak English or Spanish. Participants are evaluated longitudinally every 18–24 months, with a comprehensive neuropsychological battery, medical and neurological examination, and survey about health-related behaviors, medication, comorbidities, and cardiovascular risk factors. A sub-sample of participants consented to a blood draw at enrollment and underwent genotyping to identify APOE status. The sampling strategies, recruitment outcomes, and examination methodology used in WHICAP have been published previously (Manly et al., 2005; Tang et al., 2001).

To date, at least one neuropsychological examination has been collected on 6261 older adults. The primary analytical sample for this study was comprised of individuals that, additionally: (1) consented to blood draw at enrollment for APOE genotyping, (2) had primary addresses in NYC, allowing for assessment of ambient air pollution levels at the residence, and (3) had no missing data for any of the confounding variables. These exclusion criteria resulted in a sample size of 4821 individuals. Secondary analyses utilized individuals in the full WHICAP cohort (n = 6077), which included individuals with and without blood draw at enrollment.

All activities pertaining to WHICAP were approved by the Institutional Review Board at Columbia University Medical Center. Written informed consent was provided by each participant at enrollment.

2.2. Assessment of residential ambient air pollution

Participants' residential addresses at the time of the first neuropsychological evaluation (henceforth referred to as "enrollment") were geocoded using Geosupport Batch Address Translator Desktop Edition (NYC Department of City Planning, NY, NY) (Fig. 1).

We ascertained estimates of residential ambient air pollution levels in the calendar year prior to enrollment at each geocoded address using regionalized universal kriging models for nitrogen dioxide (NO_2; ppb), fine particulate matter less than 2.5 μm in diameter ($PM_{2.5}$; $\mu g/m^3$), and respirable particulate matter (PM_{10}; $\mu g/m^3$), as previously described (Sampson et al., 1994; Young et al., 2016). Measurements of NO_2, $PM_{2.5}$, and PM_{10} were obtained from the U.S. Environmental Protection Agency (EPA) Air Quality System and annual average values were used in a universal kriging regression framework to predict concentrations at individual addresses. Partial least square methods were used to include geographic covariates (roadway density, population density, urban land, agricultural land, forests, bodies of water), land use, and roadway proximity to improve predictions. Additionally, the NO_2 model incorporated satellite data to improve predictions (Young et al., 2016).

2.3. Outcome ascertainment

Neuropsychological test batteries used in WHICAP were designed to capture key cognitive domains in both English-speaking and Spanish-speaking older adults and developed to permit the calculation of domain-specific z-scores. A complete list of tests included is shown in Supplementary Table 1. As in previous studies (Kulick et al., 2020) we constructed a composite global cognitive score by standardizing raw scores from all available neuropsychological tests into z-scores using cohort-specific means and standard deviations from enrollment wave. Z-scores for individual tests were then averaged to create an overall z-score. The primary outcome of this study was the change in global cognitive scores over time. We then considered the change over time in

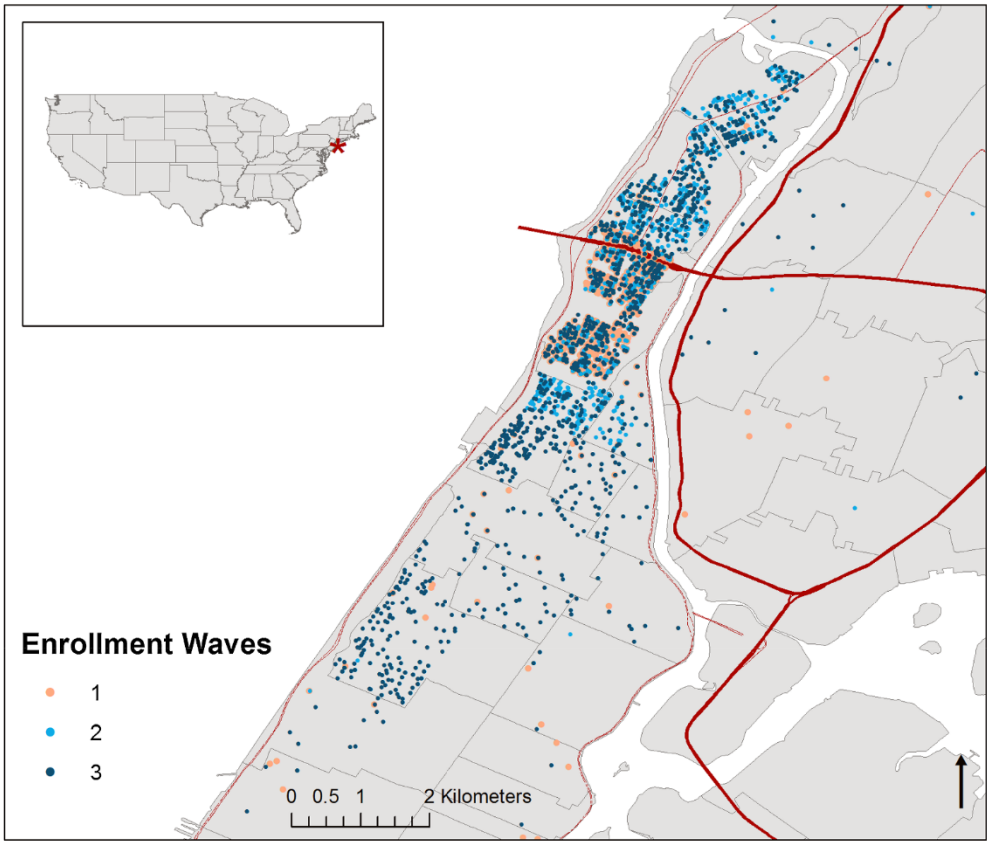

Fig. 1. Residential Location at Enrollment of WHICAP Participants throughout Northern Manhattan, New York City.

each of three individual functional domains (memory, executive function, and language), identified through factor analyses performed previously in the WHICAP Cohort (Manly et al., 2005). We expressed domain-specific scores as the mean of the individual test z-scores loading into each domain. We were unable to analyze the processing score domain as an individual functional domain because of model instability due to low response rate in tests which loaded into that domain. To enhance interpretability of the results, the global cognitive score and domain-specific scores were standard-normal transformed using means and standard deviations at enrollment, such that results reflect a change in outcome over time relative to the standard deviation of each outcome at enrollment. While some participants in this cohort had up to 13 neuropsychological examinations, given that recruitment spanned multiple waves over approximately 20 years, fewer than 10% of participants had data available from more than 6 exams. To ensure model stability, we limited our analyses to data from exams 1–6.

2.4. Covariates

At time of enrollment, participants underwent in-person interviews in their primary language (English or Spanish) conducted by trained interviewers to assess sociodemographic characteristics, health status and risk factors using validated data collection instruments, physical, and neurological examinations.

Race-ethnicity was collected through self-identification using the format of the 2000 US Census. All individuals were first asked to report their racial group and then, in a second question, were asked whether they were of Hispanic origin. For the purpose of analysis, individuals were categorized into White non-Hispanic, Black non-Hispanic, Hispanic, and other. Education was collected through self-report as total years of education completed. Age was self-reported at time of neuropsychological assessment. We derived a summary z-score for socioeconomic status (SES) at the census tract level as a marker of neighborhood wealth, education, and occupation (Diez Roux et al., 2001).

DNA was extracted from blood samples taken at enrollment and the pattern of each individual's APOE-ε4 isoforms was identified using the method of Hixson and Vernier, with slight modification (Hixson, 1991.; Mayeux et al., 1995). Individuals with one or more copies of the APOE-ε4 allele were considered to be APOE-ε4 positive, as in prior studies (Cosentino et al., 2008; Tsapanou et al., 2015). Smoking status was obtained through self-report and dichotomized into never smokers versus former or current smokers for analysis.

2.5. Statistical analysis

Distributions of sociodemographic characteristics and cardiovascular risk factors were calculated as mean (± SD) for continuous variables and proportions (n (%)) for categorical variables. Estimates of pollutant exposure were presented as mean [interquartile range (IQR)].

We used a series of stabilized inverse probability weights (IPW) to account for possible selection bias due to both non-random selection into the sub-cohort of participants who opted in to genotyping and non-random loss to follow-up over time (Howe et al., 2016; Hernán et al., 2009). To estimate IPW, we fit logistic regression models modeling selection from the full WHICAP cohort into the sub-cohort with APOE genotyping, predicting the probability that an individual would be selected into the sub-cohort. We regressed a binary indicator for study membership on a series of available time-invariant sociodemographic and health-related covariates (age, race-ethnicity, wave, dementia status at enrollment, neighborhood SES, diabetes, history of cardiac disease, and hypertension) that may have influenced an individual's decision to undergo a blood draw at enrollment.

Stabilized inverse probability of censoring weights (IPCW) further

accounted for non-random loss to follow-up in the sub-cohort over time. To estimate the IPCW, we fit pooled logistic models at each time point predicting the probability that an individual remained in the study up until that time point. At each time point we regressed a binary indicator for censorship on pollutant levels at enrollment as well as a series of available time-invariant sociodemographic covariates (sex, race-ethnicity, education, and neighborhood socioeconomic status) and a set of time-varying covariates that included age at the time of assessment and cognitive function at previous visit. The stabilized IPCW were calculated as the marginal probability of each individuals' censorship status (yes or no) divided by the probability of each individual's censorship status conditional on the set of time-invariant and time-varying covariates. We weighted the final analytical sample by the product of the IPW and IPCW weights. Using this method, individuals with a larger probability of not receiving genotyping and being lost to follow up would be weighted more heavily in the final analysis. The use of inverse probability weights results in a pseudo-population in which the censorship is marginally independent of treatment. IPW were created for each exposure and outcome combination to create a series of pseudo-populations for analysis. Secondary analyses completed in the full cohort were adjusted only by IPCW weights.

We used weighted linear mixed models for repeated measures to study the relationship of ambient air pollution to cognitive decline (Laird and Ware, 1982). We first fit separate models to estimate the associations of $PM_{2.5}$, PM_{10}, NO_2, and APOE-ε4 status with longitudinal change in global cognition, memory domain scores, language domain scores, and executive function scores. All models were adjusted for visit number, visit by pollutant interaction, age, sex, race-ethnicity, education, neighborhood socioeconomic status, and an indicator for cohort wave to account for secular trends. The models, analyzed using PROC MIXED procedures, fitted participants as a random effect and used a compound symmetry covariance matrix.

To assess whether the association between ambient air pollution and cognitive decline differed across subgroups defined by APOE-ε4 status, we included three-way interaction terms between APOE-ε4 status, exposure measures, and visit number in a series of fully adjusted models for each of the four outcomes of interest. Interaction terms with a p-value < 0.15 were considered potentially statistically significant. We calculated stratum-specific estimates to look at differences in the association between ambient air pollution and cognitive decline between APOE-ε4 positive and APOE-ε4 negative individuals. We further assessed whether the rate of cognitive change due to air pollution varied across subgroups of known risk factors for cognition (age, smoking status, race-ethnicity, and sex) using the same method as above. In secondary analyses, we repeated these analyses using the full WHICAP sample (n = 6077).

Previous studies have shown that the effect of the APOE-ε4 allele on the rate of cognitive decline differs by race-ethnicity (Tang et al., 1996). Since air pollution levels may also vary by race-ethnicity, in sensitivity analyses we further stratified the air pollution-cognition models by APOE-ε4 status within the race-ethnicity groups.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

Participants in the APOE cohort were predominately women (68%) with a median age of 76.3 (± 6.6) years. Mean follow-up time for the cohort was 5.9 ± 3.5 years. Half of participants self-identified as Hispanic (49%) and there was a high prevalence of traditional cardiovascular risk factors among participants. More than a quarter of participants (27.5%) of those genotyped carried an APOE-ε4 allele, with the prevalence of the allele highest in Black non-Hispanic participants. At the end of six follow up visits, 1743 (36%) of the cohort had died and 2279 (47%) were censored for other reasons (Supplemental Table 2). Mean [IQR] annual estimates of ambient air pollution were 13.5 [4.42] μg/m^3 for $PM_{2.5}$, 21.8 [7.95] μg/m^3 PM_{10}, and 33.0 [11.2] ppb NO_2 (Table 1). There were no substantial differences in characteristics of participants of the APOE cohort and the full cohort (Supplemental Table 3). Residential air pollution levels did not vary across categories of potential effect modifiers (Supplemental Fig. 1).

Table 1
Characteristics of the WHICAP APOE cohort at enrollment, stratified by APOE-ε4 status.

	APOE Cohort[a] (n = 4821)	APOE-ε4 Positive[b] (n = 1327)	APOE-ε4 Negative (n = 3494)
Sociodemographic Characteristics	**Mean [SD] or n (%)**		
Age, y	76.3 [6.6]	75.9 [6.4]	76.4 [6.7]
Men	1555 (32.3)	913 (31.2)	1141 (32.7)
Race-ethnicity			
White non-Hispanic	1055 (21.9)	240 (18.1)	815 (23.3)
Black non-Hispanic	1375 (28.5)	485 (36.6)	890 (25.5)
Hispanic	2339 (48.5)	590 (44.5)	1749 (50.1)
Years of Education	9.30 [4.95]	9.29 [4.93]	9.30 [4.96]
Census Z-Score	−3.21 [3.26]	−3.32 [3.17]	−3.17 [3.30]
Recruitment Wave			
Wave 1 (1992)	1457 (30.2)	423 (31.9)	1034 (29.6)
Wave 2 (1999)	1877 (38.9)	516 (38.9)	1361 (39.0)
Wave 3 (2010)	1487 (30.8)	388 (29.2)	1099 (31.5)
Cardiovascular Risk Factors			
Smoking Status			
Current or Former	2006 (41.6)	583 (43.9)	1423 (40.7)
Never	2815 (58.4)	744 (56.1)	2071 (59.3)
Hypertension[c]	3868 (80.2)	1072 (80.8)	2796 (80.0)
Diabetes[d]	1399 (29.0)	331 (24.9)	1068 (30.6)
History of Cardiac Disease	1824 (37.8)	508 (38.3)	1316 (37.7)
APOE-ε4 positive	1327 (27.5)	1327 (100)	0 (0)
Diagnosis of Dementia	509 (10.6)	178 (13.4)	331 (9.5)
Residential Pollutant Levels	**Mean [IQR]**		
NO_2 (ppb)	33.0 [11.2]	33.4 [10.5]	32.9 [11.4]
$PM_{2.5}$ (μg/m^3)	13.5 [4.42]	13.6 [4.10]	13.4 [4.51]
PM_{10} (μg/m^3)	21.8 [7.95]	22.2 [8.00]	21.7 [7.97]

IQR indicates interquartile range.
[a] Individuals who consented to blood draw at enrollment.
[b] Individuals with at least one copy of the APOE-ε4 allele considered positive.
[c] Hypertension = systolic blood pressure > 140 mm/Hg, diastolic blood pressure recording > 90 mm/Hg (based on the average of two measurements), physician diagnosis, or self-report.
[d] Diabetes = fasting blood glucose ≥ 126 mg/dL, self-report, insulin, or hypoglycemic use.

As expected, both ambient air pollution and APOE-ε4 status were associated with faster rates of cognitive decline over time (Table 2), with similar results across pollutants and cognitive domains. The association between air pollution and cognitive decline were similar in the APOE and full cohorts (Supplemental Table 4).

We assessed whether the association between air pollution and cognitive decline varied across levels of APOE-ε4 status and found that NO_2, $PM_{2.5}$, and PM_{10} were each associated with a statistically significantly faster rate of cognitive decline among APOE-ε4 positive versus negative individuals (Fig. 2, Table 3). For example, an IQR shift in NO_2 was associated with a decline of −0.09 SD (95% CI −0.11, −0.06) in global cognitive score across biennial visits among APOE-ε4 positive individuals and a −0.07 SD (95% CI −0.09, −0.05) decline among APOE-ε4 negative individuals (p-value for interaction: < 0.001). This pattern was consistent across all measures of ambient air pollution and all cognitive function domains.

We examined whether the association between residential air pollution and cognitive function differed across subgroups of participants

Table 2
Associations between Residential Levels of Ambient Air Pollutants and APOE-ε4 Status on Cognitive Decline.

	NO_2		$PM_{2.5}$		PM_{10}		APOE-ε4	
	Change in Cognitive Scores[a]	95% CI	Change in Cognitive Scores[a]	95% CI	Change in Cognitive Scores[a]	95% CI	Change in Cognitive Scores[b]	95% CI
Global Cognition	−0.075	−0.10, −0.05	−0.093	−0.12, −0.07	−0.046	−0.06, −0.03	−0.048	−0.07, −0.03
Memory Domain	−0.037	−0.06, −0.01	−0.047	−0.08, −0.02	−0.022	−0.04, −0.003	−0.049	−0.05, −0.05
Language Domain	−0.055	−0.08, −0.03	−0.066	−0.10, −0.03	−0.025	−0.04, −0.01	−0.059	−0.08, −0.03
Executive Function	−0.031	−0.06, −0.01	−0.051	−0.08, −0.02	−0.023	−0.04, −0.01	−0.040	−0.06, −0.02

All models adjusted for individual (age, education, sex, race/ethnicity), neighborhood sociodemographic variables (Census based SES z-score), and a cohort indicator to adjust for secular trends. All models weighted by the product of the IPW and IPCW weights.

[a] Expressed as a standard deviation change in the rate of decline in cognitive score associated with an IQR change in pollutant.

[b] Expressed as a standard deviation change in the rate of decline in cognitive score associated with being APOE-ε4 positive.

with other risk factors of cognitive decline, specifically age at baseline, race-ethnicity, sex, and smoking status (Table 4). Of these risk factors, the association between ambient air pollution and rate of decline in global cognitive score differed only across strata of race-ethnicity, with less rapid pollution-associated decline in global cognitive function observed among Hispanics as compared to White non-Hispanic and Black non-Hispanic participants (p-value for interaction 0.02). Results were similar across pollutants. Results were similar when considering individual functional domains, where the associations between ambient air pollution and memory and language domain-specific declines were stronger among non-Hispanic individuals. In addition, the associations between pollution and memory and language domain-specific decline were stronger among participants greater than 75 years of age. There were no significant variations across sub-groups in effect modification in the executive function domain (Supplemental Table 5). In the full WHICAP cohort, we also saw effect measure modification by age across all cognitive domains, but saw no differences in association between ambient air pollution and cognitive decline across racial-ethnic groups (Supplemental Table 6).

In sensitivity analyses where the air pollution-cognition models were stratified by APOE-ε4 status within race-ethnic groups, we found these relationships were consistent in direction overall, but varied slightly by race-ethnicity. In contrast to relationships in the overall population, we saw no effect modification between APOE-ε4 and individual pollutants among non-Hispanic Black participants (Supplemental Table 7).

4. Discussion

In a multiethnic prospective cohort of older residents in an urban environment, we found that residential ambient air pollution was associated with a faster rate of cognitive decline among individuals with at least one copy of the APOE-ε4 allele. Results were similar across pollutants considered and across functional domains of cognition. We also saw more rapid pollution-associated cognitive decline among non-Hispanic individuals as compared to Hispanic participants.

Several biological mechanisms behind the adverse effects of air pollution on the brain and cerebral vasculature have been proposed, with the strongest evidence surrounding pathways of systemic inflammation and oxidative stress. A series of experimental animal studies indicate that ambient Particles may affect the central nervous system either through a systemic response via the circulatory system, or intra-nasally by direct translocation to the brain through the olfactory bulb (Oberdörster et al., 2004; Oberdörster and Utell, 2002; Peters et al., 2006). Once in the nervous system pollutant particles activate a series of systemic inflammatory pathways leading to vascular inflammation (Campbell et al., 2005; Levesque et al., 2011; Calderón-Garcidueñas et al., 2008), impaired microvascular reactivity (Adar et al., 2010), and changes in cerebral hemodynamics (Wellenius et al., 2013). Further evidence of these mechanisms comes from a series of studies done in Mexico City where strong histological evidence of cerebral microvascular damage, systemic inflammatory markers, and brain pathology has been observed in autopsied brains of dogs and children residing in high versus low pollutant areas (Calderón-Garcidueñas et al., 2016; Calderón-Garcidueñas et al., 2012).

Currently, the strongest known genetic risk factor for cognitive decline and dementia is the presence of the APOE-ε4 allele. There are multiple underlying mechanisms through which APOE-ε4 may affect cognitive function. APOE-ε4 has been shown to increase the risk of atherosclerosis and stroke due to a build-up of cholesterol in the vessels, making it a risk factor for vascular impairment and dementia (Liu et al., 2013; Dwyer et al., 2013; Sun et al., 2015). Inside the brain, the APOE-ε4 protein has been shown to be less effective than APOE-ε2 and APOE-ε3 in clearing amyloid-β (Aβ) plaques, leading to Aβ aggregation and tangle formation, brain atrophy, neuroinflammation, and decreased vascular function (Liu et al., 2013; Dwyer et al., 2013; Sun et al., 2015;

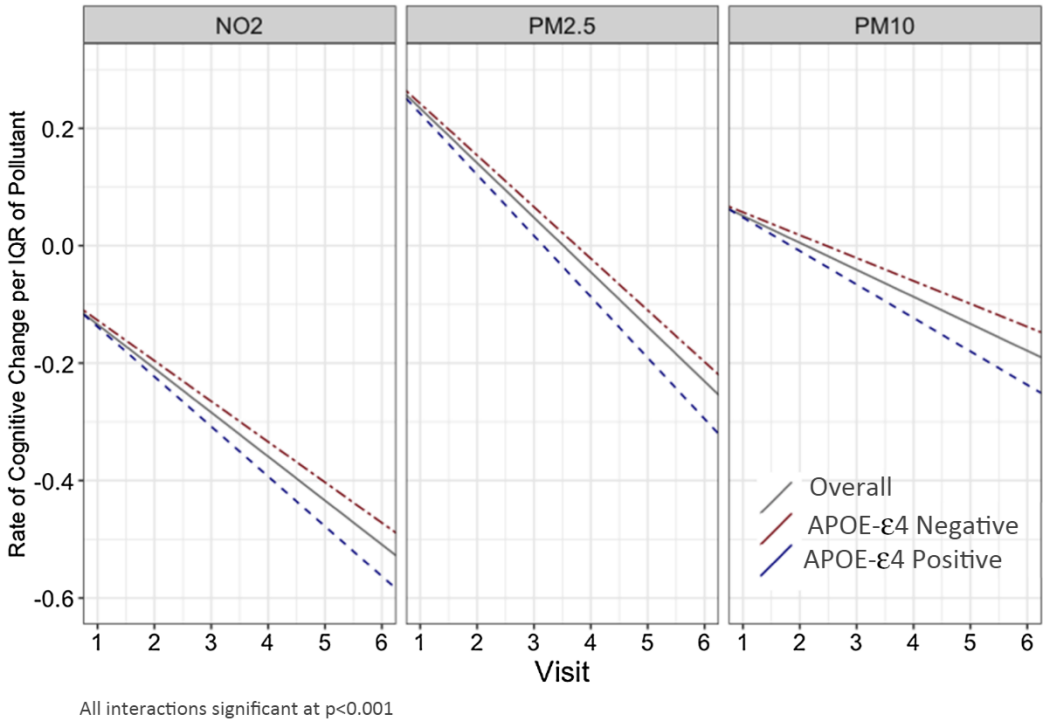

Fig. 2. Associations between Ambient Air Pollution and Global Cognitive Decline by APOE-ε4 Status.

Daviglus et al., 2011; Daviglus et al., 2010; Poirier et al., 1993). Due to a shared inflammatory mechanism between air pollution and APOE-ε4, a series of both animal and human studies have suggested that APOE-ε4 genotypes modify the association between ambient air pollution and cognitive function. An earlier study of autopsied brains suggested that APOE-ε4 carriers could be at higher risk for developing AD if they are exposed to higher levels of air pollutants by showing that APOE-ε4 carriers living in highly polluted areas of Mexico City had accelerated amyloid plaque accumulation as compared to non-carriers (Calderón-Garcidueñas et al., 2008). Cacciottolo et al. found evidence that the detrimental effect of air pollution on both neurodegenerative changes in mice and cognitive decline in older women was stronger among carriers of the APOE-ε4 allele (Cacciottolo et al., 2017). Similar results were found in a study of older women in Germany, where exposure to air pollution was associated with poorer cognition only among APOE-ε4 carriers (Schikowski et al., 2015). Consistent with the results of earlier studies, we observed evidence of a differential association between air pollution and cognitive decline in models stratified by APOE-ε4 status.

Additionally, earlier work done in the WHICAP cohort indicated that the effect of the APOE-ε4 allele on cognition varied by racial-ethnic groups (Tang et al., 1996). We further stratified our analyses by race-ethnicity, acknowledging we may have had limited power to detect effects, and saw no effect modification between APOE-ε4 and individual pollutants among non-Hispanic Black participants. This is consistent with prior research which showed that differences in the APOE-ε4 genotype more strongly influenced the risk of AD in non-Hispanic White and Hispanic individuals. In addition, the overall effects of air pollution on cognitive decline were different by race-ethnicity, where the associations were strongest among non-Hispanic white participants.

Differential cognitive function by race-ethnicity is not unique to this study, earlier cross-sectional studies have shown that lower mean global cognitive scores in may reflect inequalities such as educational experience, occupational opportunities, and racism that may lead to late-life differences in cognition (Zahodne et al., 2016; Melrose et al., 2015; Sisco et al., 2015; Schwartz et al., 2004; Liu et al., 2017). Similarly, in the WHICAP cohort, we saw that at baseline, white non-Hispanics had the highest global cognitive scores, followed by black non-Hispanics and Hispanics (data not shown). Consensus around the impacts of these early life experiences on cognitive decline are more heterogenous, however, with some studies showing little impact on overall cognitive function over time (Sisco et al., 2015; Weuve et al., 2018) and others showing substantial influences on trajectories of cognitive decline (Melrose et al., 2015). While we saw significant differences on the impact of ambient air pollution on cognitive decline across racial-ethnic groups, further studies should be done to assess the impact of air pollution in the broader context of these other experiences.

In addition to genetic factors like the presence of the APOE-ε4 allele, age is one of the most well known risk factors for cognitive decline (Alzheimer's Association., 2019; Daviglus et al., 2011; Daviglus et al., 2010). In our study, age also acted as an effect modifier with the association between air pollution and cognitive decline stronger among individuals greater than 75 years old at enrollment. Our results are contrary to the results of an earlier study, which found that living 50 m from a high traffic road was associated with lower Consortium to Establish a Registry for Alzheimer's Disease (CERAD-plus) scores only in women < 74 years old, with no association in those older than 74 years old (Ranft et al., 2009). A limitation of that study, however, is the sample size of women older than 74 years old living within 50 m of a high traffic roadway was very small (n = 7) and may have been due to selection bias of cognitively impaired women leaving the study (Ranft et al., 2009). While our study attempted to address these limitations by using IPW weighting to adjust for selection bias, it is clear more research is needed to address whether the association between air pollution and cognitive function differs by age.

We did not find differential associations by sex or smoking status. These results are in contrast to what was found in the Health and Retirement study, in which current smokers were found to have worse cognitive function than non-smokers in specific quartiles of exposure (Ailshire and Crimmins, 2014). There are several substantial differences between the two studies, however, including definition and categorization of exposure and type of neuropsychological testing used that

Table 3
Association between Ambient Air Pollution and Cognitive Decline by APOE-ε4 status.

	NO_2			$PM_{2.5}$			PM_{10}		
	Change in Cognitive Scores[a]	95% CI	p-value[b]	Change in Cognitive Scores[a]	95% CI	p-value[b]	Change in Cognitive Scores[a]	95% CI	p-value[b]
Global Cognitive Score									
APOE-ε4 -	−0.069	−0.09, −0.05	< 0.001	−0.088	−0.12, −0.06	< 0.001	−0.039	−0.06, −0.02	< 0.001
APOE-ε4 +	−0.085	−0.11, −0.06		−0.104	−0.13, −0.08		−0.057	−0.07, −0.04	
Memory Domain									
APOE-ε4 -	−0.033	−0.06, −0.01	0.03	−0.043	−0.07, −0.01	0.02	−0.018	−0.04, 0.001	0.02
APOE-ε4 +	−0.043	−0.07, −0.02		−0.053	−0.09, −0.02		−0.029	−0.05, −0.01	
Executive Function Domain									
APOE-ε4 -	−0.025	−0.05, 0.001	< 0.001	−0.047	−0.08, −0.02	< 0.01	−0.018	−0.04, 0.003	< 0.001
APOE-ε4 +	−0.040	−0.07, −0.01		−0.061	−0.09, −0.03		−0.033	−0.05, −0.01	
Language Domain									
APOE-ε4 -	−0.046	−0.07, −0.02	< 0.001	−0.059	−0.09, −0.03	< 0.001	−0.017	−0.04, 0.001	< 0.001
APOE-ε4 +	−0.066	−0.09, −0.04		−0.078	−0.11, −0.05		−0.038	−0.06, −0.02	

All models adjusted for individual (age, education, sex, race/ethnicity), neighborhood sociodemographic variables (Census based SES z-score), and a cohort indicator to adjust for secular trends. All models weighted by the product of the IPW and IPCW weights.

[a] Expressed as a standard deviation change in the rate of decline in cognitive score associated with an IQR change in pollutant.

[b] p-values for cross-product terms for interaction in the association of air pollutants and cognition.

Table 4
Association between Ambient Air Pollution and Global Cognitive Decline Across Strata of Risk Factors for Cognitive Decline.

	NO_2			$PM_{2.5}$			PM_{10}		
	Change in Cognitive Scores[a]	95% CI	p-value[b]	Change in Cognitive Scores[a]	95% CI	p-value[b]	Change in Cognitive Scores[a]	95% CI	p-value[b]
Age									
< 75 yrs old	−0.080	−0.11, −0.05	0.42	−0.115	−0.15, −0.08	0.62	−0.038	−0.06, −0.02	0.22
≥ 75 yrs old	−0.083	−0.11, −0.06		−0.117	−0.15, −0.09		−0.043	−0.06, −0.02	
Smoking Status									
Never Smoker	−0.076	−0.10, −0.05	0.32	−0.094	−0.12, −0.07	0.61	−0.048	−0.07, −0.03	0.13
Former/Current Smoker	−0.072	−0.10, −0.05		−0.092	−0.12, −0.06		−0.042	−0.06, −0.03	
Race-ethnicity									
White non-Hispanic	−0.144	−0.19,-0.09	—	−0.171	−0.23, −0.11	—	−0.087	−0.13, −0.05	—
Black non-Hispanic	−0.110	−0.16, −0.06	0.14	−0.136	−0.20, −0.08	0.33	−0.058	−0.09, −0.02	0.26
Hispanic	−0.045	−0.08, −0.01	0.02	−0.050	−0.09, −0.01	0.08	−0.029	−0.05, −0.01	0.04
Sex									
Male	−0.08	−0.10, −0.05	0.27	−0.091	−0.12, −0.07	0.39	−0.047	−0.06, −0.03	0.22
Female	−0.07	−0.10, −0.05		−0.094	−0.12, −0.06		−0.042	−0.06. −0.02	

All models adjusted for individual (age, education, sex, race/ethnicity), neighborhood sociodemographic variables (Census based SES z-score), and a cohort indicator to adjust for secular trends. All models weighted by the product of the IPW and IPCW weights.

[a] Expressed as a standard deviation change in the rate of decline in cognitive score associated with an IQR change in pollutant.

[b] p-values for cross-product terms for interaction in the association of air pollutants and cognition.

may be causing the inconsistent results. An earlier study found that smoking acted as an effect modifier between residential distance to roadway and incident ischemic stroke in the Northern Manhattan Stroke Study, where the association between proximity to roadways and ischemic stroke was significantly stronger among non-smokers (Kulick et al., 2018). Air pollution has been shown to be associated with many known shared risk factors for both stroke and cognitive decline such as cardiovascular diseases (Hart et al., 2015; Hoffmann et al., 2015; Hoffmann et al., 2006; Tonne et al., 2016; Van Hee et al., 2009; Dominici et al., 2006), greater carotid atherosclerotic burden (Adar et al., 2013; Kaufman et al., 2012), and vascular risk factors (Samet and Krewski, 2007; Park et al., 2015). It may also be possible that the association of air pollution and cognition are mediated through these cardiovascular mechanisms and future studies should begin to examine whether these risk factors are mediating both diseases through a similar pathway.

Our study had several important limitations. First, the study area may have limited variability in pollutant levels across the study area or across time, potentially limiting our statistical power to detect meaningful associations of smaller magnitude. In addition, we utilized regional models developed for the eastern United States and not optimized for our smaller study area. On the other hand, the urban study area is also a strength since this is one of the few studies to focus primarily on intra-urban variation in measures of ambient air pollution, perhaps reducing confounding by factors that vary between cities. In addition, although we adjusted for neighborhood and individual-level measures of SES in our analysis, we were unable to adjust for individual income levels. Second, the estimates of residential air pollution did not include data on time spent in locations outside the home or measure lifetime or occupational exposure. While the majority of participants were retired at the time of the study, there is limited data on lifetime workplace pollution exposures. Occupational exposures seem unlikely to be associated with residential outdoor levels of air pollutants, and thus unlikely to confound the analyses.

Third, similar to the prevalence in the overall population, the percentage of individuals with homozygous ε4 alleles is very low in the WHICAP cohort and therefore individuals heterozygous and homozygous for the ε4 allele were combined into a single group for the purpose of analysis, as done in prior studies (Cosentino et al., 2008; Tsapanou et al., 2015). The odds of developing ADRD among heterozygous and homozygous carriers is substantially different; individuals heterozygous for the ε4 allele have between 2 and 4 fold increased odds of developing ADRD, while homozygous individuals have been shown to have a 5 to 34 fold increased odds of developing the disease (Farrer et al., 1997; Kukull et al., 1996). Within the group of APOE-ε4 positive individuals in this study, there may be heterogenous effects of the association of air pollution and cognitive function due to the differences in odds of developing dementia between individuals heterozygous and homozygous for the ε4 allele. In addition, this study analyzed the association between air pollution and cognitive decline, without including data on pathological causes of decline. Future studies should examine etiologies of dementia to further understand mechanisms of action. A final limitation is the potential for unmeasured confounders in the association between ambient air pollution and cognitive decline. We have consistently shown a stronger association between air pollution and cognitive decline in the APOE cohort as compared to the full WHICAP population despite using IPW to mitigate selection bias. We have looked extensively at potential differences between the populations and have found no substantial differences suggesting we still haven't fully accounted for the probability of consenting to a blood draw at enrollment.

A key strength of this study is the user of a large, prospective cohort which allowed for the evaluation of multi-dimensional neuropsychological data in a diverse population in northern Manhattan as well as the use of individual assignment of air pollution measures to participants' residential address. To our knowledge, this is the first study to test whether APOE genotypes interact with air pollution on cognition in a large, multi-ethnic population. Earlier studies have shown that prevalence of cognitive decline and dementia vary by sex and race-ethnic group (Plassman et al., 2007; Manly and Mayeux, 2004), therefore it is important to have a racially and ethnically diverse population of older adults that is not limited by sex to be able to ascertain differences in higher risk segments of the population.

These results further support the current evidence on the role of air pollution on accelerated cognitive aging and brain health; however, the evidence behind effect modification of the relationship between air pollution and cognition is still very limited. Future studies should pay special attention to potential effect modifiers largely to identify potentially vulnerable populations that may be at highest risk for harmful health effects due to air pollution.

CRediT authorship contribution statement

Erin R. Kulick: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft. **Mitchell S.V. Elkind:** Conceptualization, Writing - review & editing, Supervision. **Amelia K. Boehme:** Methodology, Software, Writing - review & editing. **Nina R. Joyce:** Methodology, Writing - review & editing. **Nicole Schupf:** Writing - review & editing. **Joel D. Kaufman:** Resources, Writing - review & editing. **Richard Mayeux:** Resources, Funding acquisition, Writing - review & editing. **Jennifer J. Manly:** Writing - review & editing. **Gregory A. Wellenius:** Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

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