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Long-term exposure to ambient air pollution and cognitive function in older US adults

The Multi-Ethnic Study of Atherosclerosis

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Background: Air pollution effects on cognitive function have been increasingly recognized. Little is known about the impact of different sources of fine particulate ($PM_{2.5}$). We aim to evaluate the associations between long-term air pollution exposure, including source-specific components in $PM_{2.5}$, and cognition in older adults.

Methods: Cognitive assessment, including the Cognitive Abilities Screening Instrument (CASI), Digit Symbol Coding (DSC), and Digit Span (DS), was completed in 4392 older participants in the United States during 2010–2012. Residence-specific air pollution exposures (i.e., oxides of nitrogen [NO_2/NOx], $PM_{2.5}$ and its components: elemental carbon [EC], organic carbon [OC], sulfur [S], and silicon [Si]) were estimated by geo-statistical models. Linear and logistic regression models were used to estimate the associations between each air pollutants metric and cognitive function.

Results: An interquartile range (IQR) increase in EC (0.8 μg/m^3) and Si (23.1 ng/m^3) was associated with –1.27 (95% confidence interval [CI]: –0.09, –2.45) and –0.88 (95% CI: –0.21, –1.54) lower CASI scores in global cognitive function. For each IQR increase in Si, the odds of low cognitive function (LCF) across domains was 1.29 times higher (95% CI: 1.04, 1.60). For other tests, NO_x was associated with slower processing speed (DSC: –2.01, 95% CI: –3.50, –0.52) and worse working memory (total DS: –0.4, 95% CI: –0.78, –0.01). No associations were found for $PM_{2.5}$ and two $PM_{2.5}$ components (OC and S) with any cognitive function outcomes.

Conclusion: Higher exposure to traffic-related air pollutants including both tailpipe (EC and NO_x) and non-tailpipe (Si) species were associated with lower cognitive function in older adults.

Keywords: Air pollution; PM2.5 components; Cognitive function; Older adults

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Introduction

Brain health is a public health priority of the United States. Dementia is a common neurodegenerative disease that is preceded by a protracted period of cognitive decline.[1] As the US population rapidly ages, more than 131.5 million people are expected to be affected by dementia in 2050, which inflicts a substantial burden and expense for the patients, their families and society.[2] In the absence of effective dementia treatment, recent research has focused on identifying modifiable risk factors for disease prevention.[3,4]

Ambient air pollution is a complex mixture of particles and gases that has been shown to have a wide range of respiratory and cardiovascular health effects.[5] Fine particulate matter with a diameter ≤ 2.5 μm ($PM_{2.5}$) and traffic-related pollutants are thought to have important neurotoxic effects since small particles may enter the circulation from the lungs, the olfactory system and cross the blood–brain barrier.[6,7] Nitrogen oxides (NO_2/NO_X) is an important indicator of traffic-related air pollutants which is highly correlated with ultrafine particles in urban

What this study adds

Although studies on air pollution exposure and cognitive function have been expanded recently, few of them provided insight into the sources and components of fine particulate matters ($PM_{2.5}$) that are more likely to explain the associations. Using a well-characterized cohort across six U.S. sites, we assessed the associations between air pollution, including source-specific components in $PM_{2.5}$, and of cognitive function in older adults. Our finding adds to the limited epidemiological literature demonstrating that higher exposure to traffic-related air pollutants including both tailpipe and non-tailpipe species are associated with lower cognitive function in a multi-ethnic population.

areas.[8] Recent reviews of epidemiologic research on brain health has provided supportive evidences of chronic effects of exposure to $PM_{2.5}$ and traffic-related pollutants on cognitive impairment and dysfunction in older adults.[3,4,9,10] Ambient $PM_{2.5}$ represents a heterogeneous mixture of constituents from diverse sources such as fossil fuel combustion, biomass burning, and human activity where the contribution of a single component may vary differently by geographical locations.[11] However, little is known about which specific components of $PM_{2.5}$ may be implicated in the toxic effects on cognitive function. Elemental carbon (EC), also known as black carbon (BC), is a carcinogenic toxin in $PM_{2.5}$ generated primarily from diesel engine exhaust, is the only component that has been examined in association with a series of cognitive function tests in two studies.[12,13] Understanding the role that specific components of $PM_{2.5}$ play in contributing to cognitive function may provide important implications for air pollution regulation and air pollution-induced neuropathology, which may ultimately may improve brain health.

Using the well-characterized cohort of the Multi-Ethnic Study of Atherosclerosis (MESA), we aim to examine the independent association of long-term exposure to ambient air pollution, including $PM_{2.5}$ components, and results of a battery of cognitive performance tests in older adults.

Methods

Study population

MESA is a population-based cohort study that enrolled 6814 participants aged 45–84 years old without a clinical history of cardiovascular disease (CVD) in six cities of the United States (Baltimore, MD; Chicago, IL; Los Angeles County, CA; New York City, NY; St. Paul, MN; and Winston-Salem, NC). Recruitment was initiated in 2000. The primary aim of MESA is to identify characteristics related to progression of subclinical to clinical CVD in middle-aged and older adults.[14] Participants were recruited to obtain a balance of more than one self-identified race/ethnicity categories (Black, Hispanic/Latino, Asian, White) within each site, although not every site recruited each of the self-identified categories. Written informed consent was obtained from all participants. The study was approved by the institutional review boards of all of the field and reading centers in MESA. The present study involved the participants who returned for MESA exam 5 (2010–2012) and completed cognitive testing.

Cognitive assessment

Cognitive function was assessed during the fifth follow-up examination of MESA in 2010-2012 using standardized and validated tests including the following: (1) Cognitive Abilities Screening Instrument (CASI, version 2), as measure of global cognitive functioning; (2) Digit Symbol Coding (DSC), a test of processing speed; and (3) Digit Span (DS, forward and backward), a test of working memory. Details of the cognitive testing has been described elsewhere.[15] In brief, the CASI is a battery of 25 items that represent nine cognitive domains with an overall score ranging from 0 to 100. This test was selected to measure global cognitive function because it was explicitly developed for cross-cultural use. Given the lack of an acceptable threshold for cognitive impairment based on CASI,[15] we defined a threshold for low cognitive function (LCF) as the lowest 10th percentile of CASI score distribution. The DSC (range 0–133) and DS (range 0–28) are subsets of the Wechsler Adult Intelligence Scale-III, with lower scores indicating worse performance. In the present study, the DS and DSC scores were accumulated to create a DS total score. The cognitive tests were completed by 4591 participants across the six MESA study areas, resulting in a completion rate of 96.8% among the participants at exam 5. We excluded participants with invalid tests, pre-existing dementia or memory medication history, resulting in 4392 individuals with qualified cognitive data.

Exposure assessment of air pollution

MESA Air Pollution Study (MESA Air) is an ancillary study of MESA with the main focus on understanding the potential health effects of air pollution. MESA Air has established advanced region-specific spatiotemporal exposure models to estimate long-term outdoor residence-specific concentrations for NO_2, NO_X, and $PM_{2.5}$. Detailed description of the methodology for model development has been published elsewhere.[16] In brief, the spatiotemporal models were developed based upon continuous long-term measurements (1999–2013) from the Air Quality System (AQS) of the US Environmental Protection Agency (EPA) (N = 2 to 45) and spatially dense supplementary data specific to the MESA study to capture spatial variations of the air pollutants, including home monitoring for a subsample of participants (N = 86 to 136). City-specific models incorporated a large number of geographical variables covering a wide diversity of geographic features, such as traffic, industrial emissions, population density and land use. The performance of these models ranged from moderate to excellent as assessed by the overall cross-validation (CV) R^2 evaluated at participant residence locations (range: 0.45 in Chicago, IL, to 0.90 in Baltimore, MD, for NO_2, 0.50 in New York, NY, to 0.92 in Baltimore, MD for NO*x*, 0.54 in New York, NY, to 0.85 in Winston-Salem, NC for $PM_{2.5}$). We refer to these three pollutants (NO_2, NO_x, $PM_{2.5}$) as our primary pollutants in this analysis.

In addition to the primary pollutants, we focused on four $PM_{2.5}$ components: EC, organic carbon (OC), sulfur (S), and silicon (Si) as roughly reflecting combustion-related traffic emissions (EC), primary and secondary organic aerosol (OC), secondary inorganic aerosol (S), and airborne crustal matter (Si), respectively. The $PM_{2.5}$ component models applied the same modeling approach as that of NO_2, NO_X, and $PM_{2.5}$ but only relied on the MESA Air monitoring data between 2005 and 2009 due to different sampling approaches used by the AQS and MESA Air sites.[17] The CV R^2s of the models varied from 0.61 (for Si) to 0.92 (for S).

We estimated annual average concentrations for the years 2010–2012 (concurrent with exam 5) for NO_2, NO_X, $PM_{2.5}$ and for the years 2007–2008 for $PM_{2.5}$ components at the participants' homes when all data were available, and consider these as the primary exposure concentrations in our analyses. Change of locations was weighted by time period at each location within the MESA cities. Otherwise, we assigned missing values for those who moved outside the MESA cities.

Estimation of the ApoE ε4 allele

Two polymorphisms (rs429358 and rs7412) have been described to define the major ApoE isoforms ε2, ε3, and ε4. In particular, the isoform ε4 allele of the ApoE gene is a strong risk factor for Alzheimer's disease and impaired cognitive function, and this allele has been genotyped in all MESA participants.[18] ApoE isoforms were defined as having at least one ApoE e4 allele versus none in the model.

Statistical analyses

We used multiple linear regression models to assess the relationships between long-term exposure to ambient air pollution

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including $PM_{2.5}$ components and cognitive functions (i.e., CASI, DSC, and DS total scores). The models were developed by stages. The basic model included adjustment for basic demographic factors, such as age, gender, and race/ethnicity. The primary model further adjusted for several important risk factors (e.g., height, weight, body mass index [BMI], smoking [status and pack-years], secondhand smoke exposure, alcohol consumption, physical activity) and social economic factors (e.g., education levels including high school or less, some colleges, college or graduate levels; and socioeconomic status (SES) index derived from data of census on wealth, income, education, employment, and occupation with higher value indicating more socioeconomic disadvantage).[19] Furthermore, the primary models also included adjustment for systolic and diastolic blood pressure (BP) as they are important risk factors for cognitive functions in MESA.[20,21] We examined overall effects based on the estimates of the primary models as well as within-city effects with additional adjustment for sites.

For LCF, logistic regression models were used to estimate the odds ratio (OR) of associations between long-term air pollution exposure and prevalence of LCF with adjustment for the same covariates in the staged models as those for the continuous cognitive variables.

We evaluated potential effect modification by age, gender, race, obesity, smoking status, SES, and the presence of ApoE ε4 allele. To assess the concentration–response relationship of a specific air pollutant that may be associated with any of the cognitive outcomes, we refitted the model using a natural spline with 4 degrees of freedom. In sensitivity analyses, we included addition of co-pollutants, that is, $PM_{2.5}$ in the NO_2, NO_X, or $PM_{2.5}$ component models, or NO_X in the $PM_{2.5}$ model, if a significant association was found with any of the air pollutants. We also assessed the impact of BP on the associations between air pollutants and cognitive function by excluding these variables in the model. Interquartile range increases in each of the air pollutants were used to express the model parameter estimates. All analyses were performed using SAS 9.4 (SAS Institute; Cary, NC).

Results

Of the 4392 participants with valid cognitive tests, a total of 4,208 had estimated outdoor residential exposure concentrations for the year of exam 5. Table 1 summarizes participant characteristics by study regions. Participants were an average of 70 years old (standard deviation: 9.5 years) at exam 5 with slightly fewer men (46%) than women. Over half were lifelong nonsmokers (52%), one third was non-Hispanic white (41%) and two thirds had at least a college education (68%). The cognitive function scores were normally distributed, with average values of approximately 87, 50, and 15 for the CASI, DSC, and total DS, respectively. Correlations between the scores of the cognitive tests were low to moderate (Table S2; http://links.lww.com/EE/A216).

Table 1.

Descriptive statistics of the MESA participants at exam 5.

	All cities	Winston-Salem	New York	Baltimore	St. Paul	Chicago	Los Angeles
Demographics							
N	4,208	703	696	616	717	772	704
Age	69.7 (9.4)	70.1 (9)	69.5 (9.5)	70.5 (9.1)	68.4 (9.6)	69.9 (9.4)	70 (9.8)
Male (%)	46.4	45.4	39.9	46.8	49.1	46.8	50.4
Race/ethnicity (%)							
White	41.3	52.2	22.3	53.2	57.9	50.9	11.6
Chinese	10.9	0.0	0.1	0.0	0.0	24.7	37.9
Black	26.5	47.8	31.5	46.8	0.0	24.4	12.1
Hispanic	21.3	0.0	46.1	0.0	42.1	0.0	38.4
Education (%)							
High school or less	31.7	28.1	40.8	25.0	38.2	12.4	46.6
Some college/technical	29.2	31.2	28.3	31.0	35.4	22.8	27.4
College or graduate	39.1	40.7	30.9	44.0	26.4	64.8	26.0
Risk factors							
BMI	28.5 (5.7)	29.1 (5.7)	29 (5.7)	29.6 (5.8)	29.7 (5.6)	26.7 (5.1)	27.2 (5.4)
Smoking status (%)							
Never	52.6	46.0	52.6	46.6	47.6	54.0	67.8
Former	40.0	45.1	40.4	44.5	43.2	40.6	27.0
Current	7.4	8.9	7.0	8.9	9.2	5.4	5.2
Pack-year	11.1 (20.9)	14.2 (25)	9.7 (18.4)	13.9 (21.6)	11.5 (19.8)	12 (23.6)	5.7 (13.7)
Environment smoking (%)	51.1	61.1	45.5	52.5	62.3	53.9	31.1
Alcohol use (%)	43.6	40.9	32.3	51.7	53.4	55.8	27.0
Social disadvantage[a]	–1.4 (6.3)	–0.9 (4.7)	0.1 (8.1)	–0.9 (4.6)	0.2 (3.3)	–6.6 (6.7)	0 (6)
Systolic BP (mm Hg)	124.0 (20.7)	126.2 (21.5)	126.7 (20.4)	124.9 (20.2)	120.7 (19.4)	122.1 (20.2)	123.9 (21.8)
Diastolic BP (mm Hg)	68.2 (10.0)	68.1 (10.7)	70.2 (9.9)	67.5 (9.7)	67.6 (9.7)	68.5 (9.9)	67 (10.1)
ApoE ε4 carrier (%)	26.8	28.9	27.2	29.1	22.4	30.6	23.3
Cognitive function							
CASI score	87.2 (10.9)	89.0 (9.6)	84.3 (11.2)	88.1 (8.4)	87.9 (10.8)	89.3 (9.4)	84.1 (13.9)
Digit symbol coding	50.3 (18.6)	50.1 (16.9)	43.4 (19.2)	48.3 (16.2)	52.4 (18.6)	55 (17.1)	51.8 (20.1)
Total digit span	15.3 (4.6)	14.3 (3.6)	14.5 (4.5)	16.8 (4.4)	14.4 (4.3)	16.3 (4.1)	15.5 (5.6)
Long-term exposures							
NO_2 (ppb)	14.6 (7.8)	5.5 (2)	26.1 (4.5)	10.9 (3.5)	9.4 (2.3)	14.1 (2.9)	21.3 (3.6)
NO_X (ppb)	25.7 (15.8)	9.5 (4)	52.8 (10.5)	19.2 (7)	16.4 (4.6)	22.2 (5)	33.9 (8.5)
$PM_{2.5}$ (μg/m^3)	11.0 (1.4)	10.4 (0.4)	12.4 (1.7)	10.2 (0.9)	9.7 (1.1)	11.7 (0.8)	11.7 (1.1)
EC (μg/m^3)	1.5 (0.6)	1.1 (0.1)	2.4 (0.4)	1.3 (0.2)	0.8 (0.1)	1.4 (0.2)	2 (0.3)
OC (μg/m^3)	2.2 (0.4)	2.6 (0.2)	2.2 (0.4)	2.2 (0.4)	1.7 (0.1)	1.9 (0.3)	2.3 (0.3)
S (μg/m^3)	1.3 (0.3)	1.7 (0.1)	1.5 (0.1)	1.7 (0.1)	0.8 (0)	1.2 (0.1)	1.1 (0)
Si (ng/m^3)	110.0 (20.0)	97.9 (5.9)	117.6 (9.8)	85 (12.5)	98.6 (6.1)	107.9 (9.1)	141.7 (17.2)

[a]Social disadvantage is a SES index [continuous variable constructed by factor analysis of six indicators of neighborhood-level SES, that is, wealth, income, education, employment, and occupation, with higher value indicating more socioeconomic disadvantage].

Annual average air pollution concentrations varied substantially across and within the study areas, with the highest mean concentrations in New York for primary pollutants (NO_2, NO_X, $PM_{2.5}$, and EC) and in Winston-Salem for secondary pollutants (OC and S) and the lowest concentrations in Winston-Salem and St. Paul (Table 1 and Table S1; http://links.lww.com/EE/A216). For Si, the highest and the lowest concentrations were found in Los Angeles and Baltimore, respectively. Correlations of predictions of the primary pollutants were positive and relatively high with each other, but were low with the secondary pollutants (Table S3; http://links.lww.com/EE/A216).

Air pollution and global cognitive function

We found negative associations of most exposures with overall CASI across the study regions. For instance, an IQR increase in NO_2, NO_X, $PM_{2.5}$, EC, and Si in $PM_{2.5}$ was significantly associated with lower CASI values, with effect estimates ranging from 0.57 (95% CI: 0.11, 1.03) for $PM_{2.5}$ to 1.31 (95% CI: 0.70, 1.93) for EC in $PM_{2.5}$ (Table 2). Within-city associations remain significant with wide CIs for EC and Si, 1.27 (95% CI: 0.09, 2.45) and 0.88 (95% CI: 0.21, 1.54) respectively, after site adjustment, but were attenuated for the other pollutants. We observed no association between the CASI score and OC or S in $PM_{2.5}$ in any of the staged models (Table S4; http://links.lww.com/EE/A216). Similarly, LCF was positively associated with NO_2, NO*x*, $PM_{2.5}$, and EC across the study regions although none remained significant when the cognitive effects were compared among the residences within the same study region. For Si, we found 29% higher odds of LCF associated with increased exposure level of 23.1 ng/m^3 (OR: 1.29, 95% CI: 1.04, 1.60) within the same study region. The associations remained robust without controlling for BP variables (Table S5; http://links.lww.com/EE/A216). Addition of $PM_{2.5}$ as covariates did not change the associations with exposure to EC or Si (Table S6; http://links.lww.com/EE/A216). There is little evidence of a non-linear relationship between EC or Si concentrations and differences in global cognitive function (Figure 1). we found suggestive evidence that socioeconomic disadvantage modified the effect of EC and Si exposure on CASI scores, with stronger associations among those with greater disadvantage (Table 3).

Air pollution and specific cognitive subscales

Among the pollutants across the specific cognitive outcomes, increased level of exposure to NO_X was consistently associated with both slower processing speed and worse working memory represented by lower DSC (−2.01, 95% CI: −3.50, −0.52) and total DS (−0.4, 95% CI: −0.78, −0.01), after adjustment for study regions (Table S4; http://links.lww.com/EE/A216). Adding $PM_{2.5}$ as an additional covariate did not alter the significance of the models (Table S6; http://links.lww.com/EE/A216). We found the associations between NO_X exposure and DSC was greater among females [−2.70 (95% CI: −4.31, −1.08) vs. males: −1.32 (95% CI: −2.94, 0.29)] (Table S7; http://links.lww.com/EE/A216). Associations of the other pollutants were inconsistent with DSC and total DS when the effects were estimated across the study regions (Table S4; http://links.lww.com/EE/A216).

Discussion

In this cross-sectional study of a well-characterized cohort, in which we have fine spatial-scale exposure information for air pollutants including components of $PM_{2.5}$, we found higher levels of annual average exposure to air pollutants (i.e., NO_2, NO_X, $PM_{2.5}$, EC and Si) associated with lower scores in global cognition function (CASI) and subscales including processing speed (DSC). The associations remain significant for exposures to EC, Si in $PM_{2.5}$ with CASI and for NO_X with DSC within the same study region. The associations were robust in co-pollutant models with addition of $PM_{2.5}$. Strengths of the study include its relatively large sample size, use of advanced methods for estimating individual-level outdoor concentrations and high-quality individual information on the outcome measures and potential confounding factors.

Air pollutants such as NO*x*, and EC, Si in $PM_{2.5}$ are commonly generated from direct emissions of engine exhausts or indirectly generated from traffic-related sources such as road dust, resuspensions, and so forth. Exposure to traffic-related pollutants may be important for brain health as people living close to heavy traffics have shown a higher risk of dementia onset.[22] Although direct comparison of the effect estimates with our study is challenging due to inherent difference in cognitive testing, a growing number of studies have accumulated with evidence of adverse effects of exposure to NO_2/NO_X and $PM_{2.5}$ on cognitive functions of global evaluation or its specific domains.[3,4,9] In a cross-sectional study in Los Angeles, ambient exposure to NO_2 and $PM_{2.5}$ was associated with lower ability in tests of logical memory and verbal learning respectively in older adults.[23] In elderly women, Shikowski et al observed consistent associations between exposures to NO_2 and $PM_{2.5}$ with visuospatial deficits, a measure of functioning domain associated with both Alzheimer and Parkinsons.[24] In a national study of adults in the United States, long-term exposure to $PM_{2.5}$ was associated with worse episodic memory, albeit the relationship was not linear.[25] Our study contributes to the small number of studies that assess the effects of air pollution on the difference of global cognitive function and related specific domains simultaneously.[4,13,26,27] Because of the larger between-city variability of air pollutants than within-city variability in the predictions, we eliminated much of the exposure variability when adjusting

Table 2.

Difference in CASI score and OR of LCF (95% CI) associated with an interquartile range increase in air pollutant levels over the preceding year.

	CASI Score (95% CI)		LCF (95% CI)	
Pollutant[a]	Overall[b]	Within-city[b]	Overall[b]	Within-city[b]
NO_2	−1.31 (−1.93, −0.70)	−0.07 (−1.43, 1.29)	1.40 (1.12, 1.74)	0.97 (0.60, 1.58)
NO_X	−0.89 (−1.36, −0.42)	0.25 (−0.77, 1.26)	1.26 (1.08, 1.48)	0.83 (0.59, 1.17)
$PM_{2.5}$	−0.57 (−1.03, −0.11)	−0.10 (−0.70, 0.50)	1.22 (1.04, 1.44)	1.06 (0.86, 1.31)
EC	−1.18 (−1.72, −0.64)	−1.27 (−2.45, −0.09)	1.28 (1.05, 1.56)	1.24 (0.82, 1.87)
OC	−0.09 (−0.69, 0.52)	−0.22 (−1.07, 0.62)	1.01 (0.80, 1.27)	1.26 (0.93, 1.71)
S	0.00 (−0.63, 0.63)	−0.10 (−2.60, 2.41)	1.17 (0.89, 1.54)	0.94 (0.38, 2.31)
Si	−0.80 (−1.22, −0.37)	−0.88 (−1.54, −0.21)	1.06 (0.91, 1.24)	1.29 (1.04, 1.60)

[a]IQR: 12.1 ppb for NO_2, 19.4 ppb for NO_X, 1.8 μg/m^3 for $PM_{2.5}$, 0.8 μg/m^3 for EC, 0.7 μg/m^3 for OC, 0.5 μg/m^3 for S, and 23.1 ng/m^3 for Si.

[b]Overall associations (model 2) adjusted for age, gender, race, height, weight, BMI, smoking status, pack-year, environment smoking, alcohol uses, physical activity, education, social economic index, systolic and diastolic blood pressure; within-city associations additionally adjusted for site.

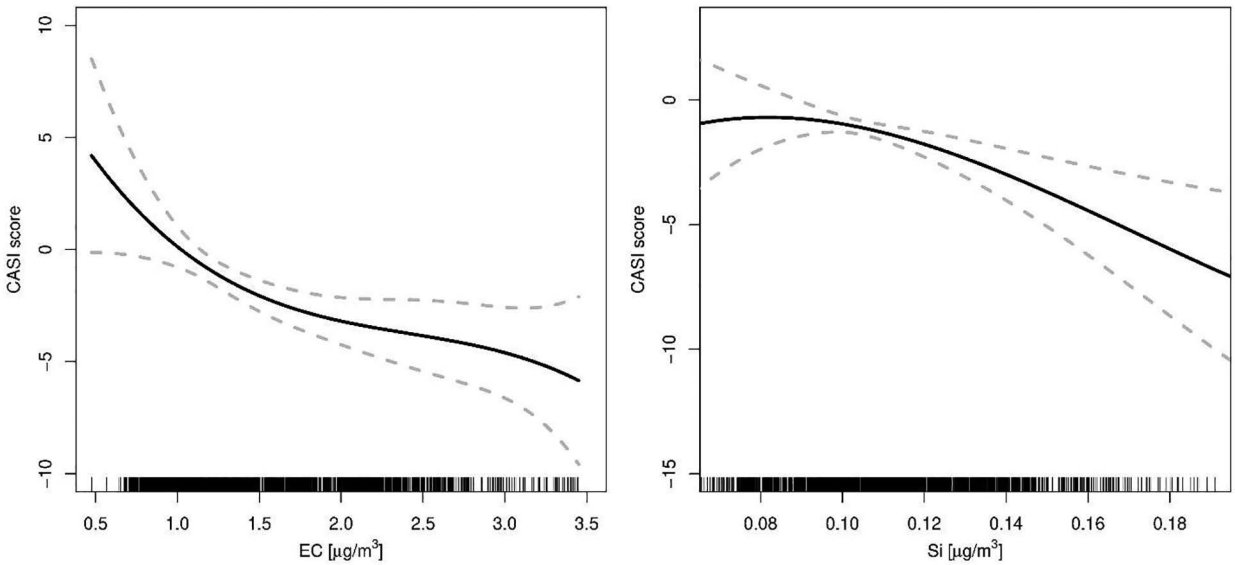

Figure 1. Concentration–response relationships for difference in CASI score associated with EC and Si exposure in $PM_{2.5}$ over the preceding year using natural spline with 4 degrees of freedom.

Table 3.

Difference in CASI score and OR of LCF (95% CI) associated with an interquartile range increase in EC and Si in $PM_{2.5}$[a] over the preceding year: modification by participant characteristics.

	CASI score				ORs of LCF	
	EC (95% CI)	*P*[b]	Si (95% CI)	*P*[b]	Si (95% CI)	*P*[b]
Age		0.17		0.12		0.34
<70	−1.04 (−2.27, 0.19)		−0.73 (−1.42, −0.04)		1.50 (0.93, 2.43)	
≥70	−1.45 (−2.66, −0.24)		−0.94 (−1.60, −0.27)		1.28 (1.00, 1.64)	
Gender		0.39		0.24		0.65
Female	−1.51 (−2.81, −0.21)		−1.11 (−1.87, −0.34)		1.32 (0.95, 1.82)	
Male	−1.07 (−2.34, 0.20)		−0.66 (−1.42, 0.10)		1.25 (0.93, 1.68)	
BMI		0.94		0.25		0.44
<30	−1.23 (−2.46, 0.00)		−0.72 (−1.43, −0.02)		1.22 (0.94, 1.58)	
≥30	−1.27 (−2.65, 0.10)		−1.20 (−2.09, −0.32)		1.87 (1.19, 2.93)	
Smoking		0.83		0.27		0.38
Never	−1.37 (−2.62, −0.11)		−1.09 (−1.85, −0.34)		1.17 (0.86, 1.58)	
Former	−1.23 (−2.59, 0.13)		−0.66 (−1.45, 0.13)		1.43 (1.03, 1.99)	
Current	−0.72 (−3.04, 1.60)		0.32 (−1.75, 2.40)		0.73 (0.06, 9.33)	
SES index[c]		0.04		<0.01		0.16
Advantage	−0.87 (−2.11, 0.37)		−0.71 (−1.38, −0.04)		1.02 (0.70, 1.49)	
Disadvantage	−1.48 (−2.68, −0.28)		−1.09 (−1.76, −0.41)		1.59 (1.13, 2.23)	
ApoE		0.90		0.71		0.54
Non-ε4	−1.26 (−2.44, −0.07)		−0.96 (−1.66, −0.27)		1.23 (0.97, 1.57)	
ε4	−1.50 (−5.28, 2.28)		−0.78 (−1.85, 0.29)		2.00 (1.06, 3.80)	

[a]IQR: 0.8 μg/m^3 for EC and 23.1 ng/m^3 for Si.

[b]*P* value shows the interaction term between individual air pollutants and the effect modifiers.

[c]Advantage indicates that SES index is less than or equal to zero; disadvantage indicates that SES index is greater than zero.

for study regions, resulting in attenuated and/or more uncertain measures of association.[28]

Compared with studies focusing on $PM_{2.5}$, few studies have investigated associations between exposure to EC and decreased global cognition within a city,[12,13] and no study has reported cognitive effects from direct exposure to Si in $PM_{2.5}$. BC particles are generated from direct combustion, including motorized road traffic and biomass burning. It is considered a better indicator than $PM_{2.5}$ to evaluate health risk of exposure to combustion-related air pollution as it is more source-specific and toxic, and shows larger health benefit from pollution reduction than $PM_{2.5}$.[29] Si particles were dominated by traffic predictor variables (e.g., road networks) in our exposure model. Thus, Si particles serve as an indicator for road dust or a proxy for exposures to traffic-related pollutants with toxicity effects found in several studies.[30,31] In multi-city study like MESA, heterogeneity exists regarding the contributions of predominant components to $PM_{2.5}$ due to different combination of emission sources between the study regions. Moreover, $PM_{2.5}$ exposure was weakly or moderately correlated with its components. Thus, the health effects of exposure to $PM_{2.5}$ may be attenuated if the pathological pathway of neurotoxicity is affected by the toxic particle components that were related to traffic rather than other sources.

Several biological mechanisms have been proposed to better understand the observed adverse effects of traffic-related pollutants on cognitive function, including neuroinflammation, oxidative stress, cerebral vascular damage, and neurodegenerative

pathways.[32] In one animal study, BC-rich particles activated brain microglia, a production of proinflammatory and reactive oxygen species, and subsequently initiated neuroinflammation and oxidative stress in male mice.[33] Inhalation exposure to diesel exhaust increased the levels of potential indicators of preclinical neurodegenerative disease (e.g., αβ42, phosphorylated tau and α synuclein) in rat brains.[32] In one human study, telomere length in DNA and C-reactive protein modified the relationship between BC and cognitive impairment in older men.[34] Furthermore, air pollution may have an indirect effect on cognitive function through the effects of cardiovascular health. In MESA, subclinical atherosclerosis was associated with both air pollution and cognitive function.[21,35] Future studies including mediation analysis are needed to better understand the role of atherosclerosis on the air pollution-cognition effect.

We found stronger associations between EC and Si and global cognitive function among subjects at greater socioeconomic disadvantage. A recent study has suggested that those living in lower socioeconomic neighborhoods were more susceptible to the adverse effects of social stressors and air pollution exposures.[36] Chronic exposure to social stressors can increase susceptibility to toxicants such as air pollution[37] and/or accelerate respiration,[38] which jointly resulted in cognitive impairment and decline. Moreover, we observed no difference in associations of the pollutants with any cognitive domains by presence of ApoE ε4 allele, which is in line with the finding of a recent study on genetic modifications.[24] It is possible that the cognitive function relationships are not via Alzheimer's disease, which pathway through susceptible genes may not be critical in our study. Furthermore, we cannot rule out exposure misclassifications due to imperfect predictions.

Our study has some limitations that could affect the findings. First, although we employed advanced statistical modeling methods to produce accurate air pollution predictions at the outdoor location of each residence, exposure misclassification remains a concern: (1) exposure models showed moderate performances in some cities; (2) outdoor air pollutant concentrations do not fully represent individual exposure; (3) the prediction period for $PM_{2.5}$ components does not concurrent with the period of cognitive testing. Such misclassifications were nondifferential which may attenuate our associations toward null.[39] Second, the older adults enrolled in MESA Air tended to be healthier than the general population as they have been followed up to more than 10 years since an average age of 62. Thus, there may be potential selection bias in effect estimates and the generalizability of our finding needs to be considered with caution. Third, we investigated several air pollutants that may jointly affect cognitive function. Future study will be conducted on overall mixture effects of cognitive function in this population. Fourth, this is cross-sectional study cannot be used to infer causality of our findings. Fifth, we cannot rule out biases due to unmeasured confounders. We minimized this concern owing to very extensive data on potential confounding variables in MESA and the robustness of our findings across the several confounder models. Finally, multiple testing issue may occur in our study given several different exposure and outcome combinations.

In conclusion, higher exposure to traffic-related air pollutants including both tailpipe (EC and NO_x) and non-tailpipe (Si) species were associated with lower cognitive function in older adults. Since many people in the United States are exposed in similar levels of the pollutants as those in the six MESA cities, if the relationships in our study is causal and confirmed in other research, intervention to reduce exposure to traffic-related emissions may lead to substantial benefits for brain health.

Conflict of interest statement

The authors declares that they have no conflicts of interest with regard to the content of this report.

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