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Full Length Article

Association between exposure to air pollution and hippocampal volume in adults in the UK Biobank

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ABSTRACT

Background: The hippocampus is important for memory processing. Several neuropsychiatric diseases including Alzheimer's disease are associated with reduced hippocampal volume, and further the hippocampus appears vulnerable to environmental insult. Air pollution has been associated with cardiovascular disease, abnormal brain structure, and cognitive deficits.

Objective: Because of hippocampal vulnerability to environmental insults and based on the association between exposure to air pollution and cognitive function and brain structure, we evaluated the association between exposure to toxins in air pollution and left and right hippocampal volume using brain-imaging and air-pollution data from the UK Biobank, a large community-based dataset.

Methods: We used regression modelling to evaluate the association between exposure to nitrogen dioxide, nitrogen oxides, $PM_{2.5}$, $PM_{2.5\text{-}10}$, and $PM_{10.}$ and left and right hippocampal volume controlling for age, sex, body-mass index, overall health, alcohol use, smoking, educational attainment, socioeconomic status, inverse distance from the nearest major road, and a measure of total brain volume.

Results: In these models, $PM_{2.5}$ concentration was associated with smaller left hippocampal volume. None of the other measures of air pollution was associated with either left or right hippocampal volume, although interaction models provided some evidence that sex might moderate the relationship between air pollution and hippocampal volume. In adjusted models, age, sex, educational attainment, income, overall health, current smoking, alcohol intake, and body-mass index were associated with hippocampal volume.

Conclusions: $PM_{2.5}$ at levels found in the United Kingdom was associated with smaller left hippocampal volume. Additional associations between several covariates and hippocampal volumes indicate that hippocampal volume might be associated with several potentially modifiable variables.

1. Introduction

The hippocampus is essential to learning and memory (Eichenbaum, 2017), and memory deficits and smaller hippocampal volume are associated with cognitive aging (Raz and Rodrigue, 2006), dementia (Moodley and Chan, 2014), and several neuropsychiatric diseases (Adriano et al., 2012; Nelson and Tumpap, 2017; Videbech and Ravnkilde, 2004). Further, the hippocampus appears to be particularly vulnerable to insult from different sources including hypoxia (Gale and Hopkins, 2004), carbon-monoxide poisoning (Gale et al., 1999), traumatic brain injury (Bigler et al., 1997), and socioeconomic stressors (Elbejjani et al., 2017), possibly due to its significant plasticity (Bartsch and Wulff, 2015; McEwen, 1994). In this regard, air pollution is a major public-health problem (D'Angiulli, 2018) associated with cardiovascular (Brook et al., 2010) and pulmonary disease (Yang et al., 2019) that prior work has suggested could affect the hippocampus, including studies reporting possible associations between air pollution and cognitive function (Ailshire and Crimmins, 2014; Khan et al., 2019; Tallon et al., 2017), possibly dementia (Chen et al., 2017), and brain structure (de Prado Bert et al., 2018; Sram et al., 2017). Although previous work has not found associations between air pollution and hippocampal volume (Calderón-Garcidueñas et al., 2011; Chen et al., 2015; Wilker et al., 2015), the neuroinflammation and oxidative stress associated with air pollution provide a plausible mechanism by which air pollution

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Table 1
Descriptive statistics of study variables.
Source: UK Biobank.

	Mean	Standard Deviation	Minimum	Maximum
Hippocampal volume (mm^3)				
Left	3810.38	476.44	1212.00	5952.00
Right	3920.36	490.31	1390.00	6160.00
Total brain volume (mm^3)	1504427.91	72550.79	1151700.00	1793910.00
Air pollution (ug/m^3)				
Particulate $matter_{2.5}$	9.90	1.01	8.17	19.65
Particulate $matter_{2.5\text{-}10}$	6.36	.88	5.57	10.25
Particulate $matter_{10}$	16.01	1.85	11.78	25.21
Nitrogen dioxide	25.61	6.86	12.93	89.55
Nitrogen oxides	42.33	14.02	19.74	231.89
Inverse distance to major road	.01	.01	.00	.91
Age	62.15	7.44	44	80
Female	.52		.00	1.00
Race				
White	.97		.00	1.00
Black	.01		.00	1.00
Asian	.01		.00	1.00
Other	.01		.00	1.00
College degree	.05		.00	1.00
Household income (in pounds)				
< 18k	.12		.00	1.00
18k - 30,999	.28		.00	1.00
31k - 51,999	.31		.00	1.00
52k - 100k	.23		.00	1.00
> 100k	.06		.00	1.00
Overall health	2.99	.66	1.00	4.00
Body-mass index	26.59	4.42	13.39	58.70
Smoking status				
Non-smoker	.63		.00	1.00
Past	.33		.00	1.00
Current	.04		.00	1.00
Drinking frequency				
Daily or almost daily	.17		.00	1.00
3-4 times/week	.28		.00	1.00
Once or twice/week	.27		.00	1.00
1-3 times/month	.12		.00	1.00
Special occasions	.10		.00	1.00
Never	.06		.00	1.00

Note: N = 18,278.

could affect hippocampal volume (Costa et al., 2017). Given the potential vulnerability of the hippocampus to environmental insult and considering the need to identify potentially modifiable causes of cognitive decline and dementia, we sought to investigate further the association between air pollution and hippocampal volume using a cross-sectional sample from the large UK Biobank database of well characterized participants who had measures of brain volume including the hippocampus and estimates of exposure to air pollution. The large sample size from the UK Biobank had sufficient power to detect small differences and enabled the inclusion of several relevant covariates to control for confounding.

2. Materials and methods

2.1. Study sample

After obtaining the required approval from the UK Biobank for our research proposal, we used data for all our analyses from the UK Biobank, a study of approximately 500,000 community-dwelling adults living in the United Kingdom that sampled subjects via population-based registries. Participants in the UK Biobank came from all over the United Kingdom, with data collected at 22 centers (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200). From 2006 to 2010, the UK Biobank enrolled participants ages 40 to 69 years and obtained demographic, medical, and cognitive data from questionnaires and physical assessments (http://www.ukbiobank.ac.uk; (Sudlow et al., 2015). After initial data collection, a subset of participants completed brain imaging (UK Biobank Brain Imaging Documentation, http://www.ukbiobank.ac.uk). Among the 21,390 with MRI data, there were 18,278 participants who had complete data for exposure to air pollution, left and right hippocampal volume, and the selected covariates included in our analyses.

2.2. Hippocampal volume

We obtained volumetric imaging data was from the UK Biobank (Alfaro-Almagro et al., 2018; Miller et al., 2016). For dependent variables, we used pre-processed three-dimensional magnetization prepared for rapid gradient-echo (3D MP-RAGE) T1-weighted structural magnetic-resonance imaging image-derived phenotypes containing numerical volume data for the right and left hippocampus obtained from UK Biobank imaging-processing pipelines. To correct for head size and total brain volume, we also used pre-processed (3D MP-RAGE) T1-weighted image-derived phenotype numerical volume data from the UK Biobank for total white and gray matter normalized for head size. For all brain imaging, the UK Biobank used a standard Siemens Skyra 3 T magnetic-resonance imaging scanner with a 32-channel RF receiver head coil (Siemens Medical Solutions, Germany). Resolution was 1 × 1 × 1 mm with a field of view of 208 × 256 × 256. Full scanning information is available at UK Biobank Brain Imaging Documentation (biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf), Miller et al. (2016), and Alfaro-Almagro et al. (2018). We investigated left and right hippocampal volumes separately rather than sum the two measures because prior studies have found lateralized differences in brain structures in healthy participants, and a meta-analysis in dementia found lateralized differences in hippocampal volumes by disease severity (Shi et al., 2009). Similarly, previous work also has found greater left than right hippocampal atrophy following traumatic brain injury (Bigler et al., 1996).

2.3. Air pollution measures

For the independent variables of interest, we used estimates for exposure to nitrogen dioxide, nitrogen dioxides, $PM_{2.5}$, $PM_{2.5\text{-}10}$, and PM_{10} obtained from the UK Biobank (http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=114). The UK Biobank uses air-pollution estimates from the Small Area Health Statistics Unit (http://www.sahsu.org), which is in conjunction with the BioSHaRE-EU Environmental Determinants of Health Project (http://bioshare.eu). Estimates of exposure to nitrogen dioxide, nitrogen dioxides, $PM_{2.5}$, $PM_{2.5\text{-}10}$, and PM_{10} at the address level for mean annual concentration in 2010 were from a land-use regression model developed from the European Study of Cohorts for Air Pollution Effects (http:/www.escapeproject.eu/) and traffic data for 2008 from land-use regression modeling from Eurostreets (biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=114). The UK

Table 2a
Relationship between Particulate Matter 2.5 (ug/m^3) and Left Hippocampal Volume (mm^3) Unstandardized Coefficients from Linear Regression. Source: UK Biobank. * $p < .05$. ** $p < .01$. *** $p < .001$.

	Bivariate	Controlled	Interactions with $PM_{2.5}$			
			Age	Sex	Education	Health
Particulate matter$_{2.5}$	−7.20*	−10.78**	−14.54	−4.91	−10.79*	−30.25*
Total brain volume (mm^3)		.00***	.00***	.00***	.00***	.00***
Inverse distance to major road		341.52	339.57	367.41	341.55	322.91
Age		−8.88***	−9.48*	−8.84***	−8.88***	−8.89***
Female		−240.33***	−240.35***	−127.21*	−240.33***	−240.36***
Race						
White		.00	.00	.00	.00	.00
Black		−180.54***	−180.37***	−180.07***	−180.54***	−179.45***
Asian		−108.16***	−108.09***	−108.28***	−108.16***	−107.67***
Other		−28.33	−28.30	−28.23	−28.33	−27.91
College degree		44.44***	44.45***	44.69***	44.15	44.37***
Household income (pounds)						
< 18k		.00	.00	.00	.00	.00
18k - 30,999		9.27	9.32	8.99	9.27	8.77
31k - 51,999		13.05	13.11	12.88	13.05	12.56
52k - 100k		35.71**	35.74**	35.69**	35.71**	35.19**
> 100k		36.32*	36.26*	36.14*	36.32*	36.15*
Overall health		17.34**	17.33**	17.39**	17.34**	−47.65
Body-mass index		.74	.74	.76	.74	.74
Smoking status						
Non-smoker		.00	.00	.00	.00	.00
Past		.72	.73	.78	.72	.74
Current		−44.94**	−44.93*	−44.75*	−44.94**	−44.44*
Drinking frequency						
Daily or almost daily		.00	.00	.00	.00	.00
3-4 times/week		24.37*	24.36*	24.62*	24.38*	24.34*
Once or twice/week		9.28	9.25	9.51	9.28	9.18
1-3 times/month		22.21	22.20	22.57	22.21	22.18
Special occasions		10.97	10.97	11.42	10.97	11.05
Never		10.14	10.10	10.06	10.14	9.86
Interactions						
$PM_{2.5}$ x Age			.06			
$PM_{2.5}$ x Female				−11.42		
$PM_{2.5}$ x College degree					.03	
$PM_{2.5}$ x Overall health						6.54
Constant	3881.62***	2521.53***	2558.93***	2458.73***	2521.69***	2716.44***

Note: N = 18,278.

Biobank considers estimates of exposure to air pollution valid for 400 km from Greater London but not beyond, and as such, the UK Biobank did not include estimates for addresses more than 400 km from Greater London, resulting in 33,935 missing addresses (biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=114).

2.4. Covariates

We included covariates that could potentially confound the association between exposure to air pollution and hippocampal volume. In particular, we included age, sex, body-mass index, overall health, alcohol use, smoking, educational attainment, and socioeconomic status because these have been associated with cognitive decline (Baumgart et al., 2015; Marden et al., 2017), and we anticipated similar confounding for hippocampal volume. We also included inverse distance from the nearest major road (Khan et al., 2018) because noise pollution from transportation is associated with adverse health outcomes, such as ischemic heart disease (Vienneau et al., 2015) and diabetes (Clark et al., 2017), and because in a murine model exposure to traffic noise resulted in brain changes including a reduction in hippocampal volume (Jafari et al., 2018). To control for head size and total brain volume, we included a measure of total brain volume (white matter plus gray matter normalized for head size) (Alfaro-Almagro et al., 2018). We dichotomized the variables for educational attainment as having graduated from college or not, similar to previous studies that have used data from the UK Biobank (Lyall et al., 2016). For the overall health measure, the UK Biobank asked participants to rate their overall health as excellent (1), good (2), fair (3), poor (4), don't know, or prefer not to answer (https://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2178).

Table 2b
Relationship between Particulate Matter 2.5 (ug/m^3) and Right Hippocampal Volume (mm^3) Unstandardized Coefficients from Linear Regression. Source: UK Biobank. * $p < .05$. ** $p < .01$. *** $p < .001$

	Bivariate	Controlled	Interactions with $PM_{2.5}$			
			Age	Sex	Education	Health
Particulate matter$_{2.5}$	−.39	−2.28	10.88	2.00	−.99	10.93
Total brain volume (mm^3)		.00***	.00***	.00***	.00***	.00***
Inverse distance to major road		24.49	31.30	43.35	22.60	37.12
Age		−8.51***	−6.40	−8.48***	−8.51***	−8.50***
Female		−265.84***	−265.76***	−183.43**	−265.78***	−265.82***
Race						
White		.00	.00	.00	.00	.00
Black		−224.73***	−225.32***	−224.38***	−224.79***	−225.47***
Asian		−125.96***	−126.21***	−126.05***	−125.89***	−126.29***
Other		−51.71	−51.80	−51.63	−51.45	−51.99
College degree		58.69***	58.66***	58.86***	82.66	58.73***
Household income (pounds)						
< 18k		.00	.00	.00	.00	.00
18k - 30,999		22.29	22.14	22.09	22.39	22.64
31k - 51,999		23.93*	23.72*	23.80*	24.01*	24.26*
52k - 100k		35.47**	35.36**	35.45**	35.57**	35.82**
>100k		52.06**	52.25**	51.93**	52.09**	52.18**
Overall health		22.55***	22.60***	22.58***	22.58***	66.65
Body-mass index		2.71***	2.71***	2.73***	2.71***	2.71***
Smoking status						
Non-smoker		.00	.00	.00	.00	.00
Past		−6.94	−6.95	−6.91	−6.96	−6.96
Current		−28.06	−28.12	−27.91	−28.00	−28.39
Drinking frequency						
Daily or almost daily		.00	.00	.00	.00	.00
3-4 times/week		21.28*	21.32*	21.45*	21.22*	21.30*
Once or twice/week		14.57	14.65	14.74	14.51	14.63
1-3 times/month		35.08**	35.12**	35.35**	35.01**	35.11**
Special occasions		2.42	2.45	2.75	2.33	2.37
Never		6.85	6.99	6.80	6.84	7.04
Interactions						
$PM_{2.5}$ x Age			−.21			
$PM_{2.5}$ x Female				−8.32		
$PM_{2.5}$ x College degree					−2.42	
$PM_{2.5}$ x Overall health						−4.43
Constant	3924.19***	2536.88***	2406.11***	2491.13***	2524.05***	2404.65***

Note: N = 18,278.

2.5. Statistical analyses

We used linear regression models to examine associations between left and right hippocampal volumes and exposure to air pollution, adjusting for possible confounding variables. Linear regression is an appropriate method for these analyses because hippocampal volume is a normally distributed continuous variable. This is a similar approach to other research that examines changes in hippocampal volumes (Elbejjani et al., 2017; Guxens et al., 2018). We also tested for interactions between each of the measures of air pollution and age, sex, educational status, and the estimate of overall health in predicting left and right hippocampal volumes. We used Stata 15.1 for all analyses (StataCorp, Stata Statistical Software, Release 15. College Station, Texas).

3. Results

The sample size was 18,278, of whom 52 percent were women. The mean age was 62.15 years (standard deviation: 7.44; range: 44.–80 years). Ninety-seven percent of the sample was White. The mean left hippocampal volume was 3810.38 mm^3 (standard deviation: 476.44), and the mean right hippocampal volume was 3920.36 mm^3 (standard deviation: 490.31). The mean $PM_{2.5}$ concentration was 9.90 $\mu g/m^3$ (standard deviation: 1.01; range: 8.17–19.65) (Table 1). Table 1 also shows additional demographic information, such as educational attainment, income findings, and air-pollution data, as well as estimates of overall health, body-mass index, smoking, and alcohol-use.

$PM_{2.5}$ concentration was inversely associated with left hippocampal volume in both the bivariate model (coefficient = −7.20, $p < 05$) and the adjusted model that included all of the covariates (coefficient = −10.78, $p < .01$, Table 2a). There were no associations between $PM_{2.5}$ and right hippocampal volume (Table 2b) or between left and right

Table 3a
Relationship between Particulate Matter 2.5 to 10 (ug/m^3) and Left Hippocampal Volume (mm^3) Unstandardized Coefficients from Linear Regression. Source: UK Biobank. * $p < .05$. ** $p < .01$. *** $p < .001$.

	Bivariate	Controlled	Interactions with $PM_{2.5-10}$			
			Age	Sex	Education	Health
Particulate matter$_{2.5-10}$	−6.13	−6.75	36.34	−7.43	−5.64	−23.68
Total brain volume (mm^3)		.00***	.00***	.00***	.00***	.00***
Inverse distance to major road		246.05	251.08	244.37	249.25	239.99
Age		−8.73***	−4.31	−8.73***	−8.72***	−8.73***
Female		−240.02***	−240.07***	−248.53***	−240.04***	−239.95***
Race						
White		.00	.00	.00	.00	.00
Black		−186.55***	−187.35***	−186.50***	−186.53***	−186.33***
Asian		−109.44***	−109.51***	−109.43***	−109.44***	−109.27***
Other		−30.45	−31.09	−30.49	−30.46	−30.21
College degree		43.39***	43.48***	43.40***	59.09	43.37***
Household income (pounds)						
< 18k		.00	.00	.00	.00	.00
18k - 30,999		11.27	11.43	11.28	11.27	11.15
31k - 51,999		15.90	15.87	15.91	15.89	15.94
52k - 100k		39.64**	39.83**	39.64**	39.63**	39.66**
> 100k		41.71*	42.00*	41.70*	41.69*	41.88*
Overall health		17.65***	17.71***	17.65***	17.66***	−18.44
Body-mass index		.75	.75	.75	.75	.76
Smoking status						
Non-smoker		.00	.00	.00	.00	.00
Past		−.48	−.37	−.49	−.50	−.54
Current		−47.05**	−47.36**	−47.05**	−47.09**	−47.05**
Drinking frequency						
Daily or almost daily		.00	.00	.00	.00	.00
3-4 times/week		24.38*	24.49*	24.39*	24.34*	24.47*
Once or twice/week		9.14	9.26	9.15	9.18	9.21
1-3 times/month		21.67	21.91	21.68	21.68	21.82
Special occasions		10.08	10.40	10.08	10.09	10.22
Never		9.12	9.24	9.13	9.15	9.15
Interactions						
$PM_{2.5-10}$ x Age			−.69			
$PM_{2.5-10}$ x Female				1.34		
$PM_{2.5-10}$ x College degree					−2.47	
$PM_{2.5-10}$ x Overall health						5.66
Constant	3849.37***	2442.08***	2167.15***	2446.42***	2434.70***	2550.14***

Note: N = 18,278.

hippocampal volumes and $PM_{2.5-10}$ (Tables 3a and 3b), PM_{10} (Tables 4a and 4b), nitrogen dioxide (Tables 5a and 5b), and nitrogen oxides (Tables 6a and 6b) in either the bivariate or multivariate models.

There were no interactions between $PM_{2.5}$ (Tables 2a and 2b) and age, sex, overall estimated health, or having obtained a college degree in predicting left and right hippocampal volumes. Similarly, there were no interactions between $PM_{2.5-10}$ (Tables 3a and 3b) or PM_{10} (Tables 4a and 4b) and age, sex, having obtained a college degree, and estimated overall health in predicting left and right hippocampal volumes. An interaction between nitrogen dioxide and sex predicted left hippocampal volume (Table 5a), although there were no interactions between concentration of nitrogen dioxide and age, sex, having obtained a college degree, and estimated overall health in predicting right hippocampal volume (Table 5b). There was an interaction with sex and nitrogen oxides in predicting left hippocampal volume but no interactions with age, estimated overall health, and having obtained a college degree (Table 6a). Finally, an interaction between sex and nitrogen oxide predicted right hippocampal volume, but there were no interactions between nitrogen oxides and age, having obtained a college degree, and estimated overall health in predicting right hippocampal volume (Table 6b).

In addition to the association between PM $_{2.5}$ concentration and smaller left hippocampal volume, several of the covariates were associated with hippocampal volumes in the adjusted models. Increasing age, female sex, ethnic background, and current smoking were associated with smaller hippocampal volumes, whereas educational attainment, income, overall health, and drinking frequencies of three to four times a week and one to three times a month compared to daily or almost daily drinking were associated with larger hippocampal volumes. While current smoking was associated with decreased hippocampal volume, past smoking in most models was not (Tables 1a and 6b). There were no associations between inverse distance to the nearest major road and hippocampal volume.

Table 3b
Relationship between Particulate Matter 2.5 to 10 (ug/m^3) and Right Hippocampal Volume (mm^3) Unstandardized Coefficients from Linear Regression. Source: UK Biobank. * $p < .05$. ** $p < .01$. *** $p < .001$.

	Bivariate	Controlled	Interactions with $PM_{2.5\text{-}10}$			
			Age	Sex	Education	Health
Particulate matter$_{2.5\text{-}10}$	−5.49	−5.61	34.41	−4.87	−3.72	12.39
Total brain volume (mm^3)		.00***	.00***	.00***	.00***	.00***
Inverse distance to major road		63.82	68.50	65.68	69.28	70.27
Age		−8.48***	−4.38	−8.48***	−8.48***	−8.48***
Female		−265.90***	−265.94***	−256.51***	−265.92***	−265.97***
Race						
White		.00	.00	.00	.00	.00
Black		−226.17***	−226.92***	−226.23***	−226.14***	−226.40***
Asian		−125.97***	−126.03***	−125.98***	−125.97***	−126.15***
Other		−51.37	−51.96	−51.32	−51.39	−51.63
College degree		58.15***	58.23***	58.14***	84.92	58.17***
Household income (pounds)						
< 18k		.00	.00	.00	.00	.00
18k - 30,999		22.73	22.88	22.73	22.74	22.86
31k - 51,999		24.45*	24.42*	24.45*	24.42*	24.41*
52k - 100k		36.06**	36.23**	36.06**	36.04**	36.03**
>100k		52.95**	53.22**	52.96**	52.93**	52.76**
Overall health		22.66***	22.72***	22.66***	22.69***	61.06
Body-mass index		2.75***	2.75***	2.75***	2.76***	2.74***
Smoking status						
Non-smoker		.00	.00	.00	.00	.00
Past		−7.22	−7.12	−7.20	−7.26	−7.15
Current		−28.36	−28.65	−28.37	−28.42	−28.36
Drinking frequency						
Daily or almost daily		.00	.00	.00	.00	.00
3-4 times/week		21.27*	21.37*	21.25*	21.21*	21.17*
Once or twice/week		14.59	14.71	14.58	14.66	14.52
1-3 times/month		35.09**	35.30**	35.08**	35.09**	34.93**
Special occasions		2.56	2.85	2.56	2.58	2.41
Never		6.67	6.78	6.67	6.72	6.65
Interactions						
$PM_{2.5\text{-}10}$ x Age			−.64			
$PM_{2.5\text{-}10}$ x Female				−1.48		
$PM_{2.5\text{-}10}$ x College degree					−4.21	
$PM_{2.5\text{-}10}$ x Overall health						−6.02
Constant	3955.23***	2546.76***	2291.35***	2541.96***	2534.17***	2431.79***

Note: N = 18,278.

4. Discussion

In this study of 18,278 adult participants in the United Kingdom, there was an association between $PM_{2.5}$ concentration and smaller left but not right hippocampal volume. Further, there were no associations between $PM_{2.5\text{-}10}$, PM_{10}, nitrogen dioxide, and nitrogen oxides concentrations and either left or right hippocampal volumes in models adjusted for brain volume, age, sex, ethnic background, educational attainment, household income, the inverse of the distance to major roads, an overall health score, body-mass index, frequency of alcohol use, and smoking status. Further, we found no associations between left and right hippocampal volumes and the inverse of the distance from major roads.

These findings are broadly consistent with the results of previous studies that have found associations between exposure to air pollution and brain volume (Chen et al., 2015; D'Angiulli, 2018; Power et al., 2018). In contrast to our findings, several previous studies have not found associations between air pollution and hippocampal volumes neither in children (Calderón-Garcidueñas et al., 2011) nor adults (Chen et al., 2015; Power et al., 2018; Wilker et al., 2015), dissimilarities that could be due to differences in sample size, age, and included covariates.

We found that for every one-unit increase in $PM_{2.5}$ concentration, left hippocampal volume decreases by 10.78 mm^3 while controlling for all of the covariates we included in the models, including age. This translates into a 0.28 percent decrease in left-hippocampal volume for every one-unit increase in $PM_{2.5}$ concentration or a 1.4 percent decrease in left-hippocampal volume for every five-unit increase in $PM_{2.5}$ concentration. To put this into perspective, prior work has estimated age-related hippocampal atrophy to be approximately 1.2 percent per year, with a rate of less than 1 percent for healthy young adults and 1.7 percent for the elderly (Raz and Rodrigue, 2006).

We found the association between $PM_{2.5}$ and smaller left hippocampal volume in a sample from the United Kingdom, a region where levels of exposure to air pollutants are lower than in many other regions. In India, for example, the mean population-weighted exposure of

Table 4a
Relationship between Particulate Matter 10 (ug/m³) and Left Hippocampal Volume (mm³) Unstandardized Coefficients from Linear Regression. Source: UK Biobank. * $p < .05$. ** $p < .01$. *** $p < .001$.

	Bivariate	Controlled	Interactions with PM_{10}			
			Age	Sex	Education	Health
Particulate matter$_{10}$	−2.73	−2.71	20.90	−2.33	−2.30	−5.05
Total brain volume (mm³)		.00***	.00***	.00***	.00***	.00***
Inverse distance to major road		229.95	232.27	231.36	231.05	229.39
Age		−8.75***	−2.66	−8.74***	−8.74***	−8.75***
Female		−240.04***	−239.98***	−227.73***	−240.03***	−240.01***
Race						
White		.00	.00	.00	.00	.00
Black		−185.45***	−186.52***	−185.47***	−185.41***	−185.35***
Asian		−108.87***	−109.27***	−108.88***	−108.86***	−108.78***
Other		−30.53	−30.91	−30.49	−30.48	−30.48
College degree		43.63***	43.66***	43.63***	57.22	43.60***
Household income (pounds)						
<18k		.00	.00	.00	.00	.00
18k - 30,999		11.05	11.04	11.03	11.06	10.99
31k - 51,999		15.58	15.28	15.57	15.59	15.54
52k - 100k		39.09**	39.07**	39.08**	39.10**	39.06**
>100k		40.81*	41.36*	40.80*	40.79*	40.86*
Overall health		17.56***	17.65***	17.55***	17.58***	5.00
Body-mass index		.74	.73	.74	.74	.74
Smoking status						
Non-smoker		.00	.00	.00	.00	.00
Past		−.28	−.23	−.27	−.30	−.29
Current		−46.83**	−47.30**	−46.83**	−46.84**	−46.82**
Drinking frequency						
Daily or almost daily		.00	.00	.00	.00	.00
3-4 times/week		24.44*	24.55*	24.43*	24.41*	24.44*
Once or twice/week		9.22	9.28	9.22	9.23	9.23
1-3 times/month		21.78	22.00	21.78	21.75	21.81
Special occasions		10.22	10.39	10.25	10.21	10.25
Never		9.31	9.45	9.31	9.32	9.28
Interactions						
PM_{10} x Age			−.38			
PM_{10} x Female				−.77		
PM_{10} x College degree					−.85	
PM_{10} x Overall health						.78
Constant	3854.17***	2445.68***	2065.38***	2439.29***	2438.93***	2483.34***

Note: N = 18,278.

$PM_{2.5}$ concentration in 2017 was 89.9 µg/m³ (Collaborators, 2019), far higher than the average $PM_{2.5}$ of 9.9 µg/m³ in our UK sample. For additional context, the World Health Organization's recommended upper limit for exposure to ambient $PM_{2.5}$ is 10 µg/m (WHO, 2018). Numerous other world regions exceed the average of 9.9 µg/m³ that we found in the UK Biobank sample (Costa et al., 2017). In contrast to our findings, there were no associations between $PM_{2.5}$ concentrations and a measure of brain atrophy in a sample of subjects attending a memory clinic in a region where mean ambient $PM_{2.5}$ concentrations were 11.0 µg/m³ (Wilker et al., 2016). Nonetheless, if replicated, our findings suggesting the possibility of smaller left-hippocampal volume with exposure to comparatively low concentrations of air pollution are concerning given the widespread distribution of air pollution. Additional studies need to address associations between hippocampal volume and air pollution in regions that have higher concentrations of air pollutants than the ones in our study.

It remains unclear why there was an association between $PM_{2.5}$ concentration and left hippocampal volume but not right hippocampal volume. If replicated, this would suggest differential left-right hippocampal vulnerability to $PM_{2.5,}$ although we did not design our study to investigate molecular mechanisms underlying potential differences in vulnerability between the left and right hippocampus. However, Topiwala et al. (2017) found different right-left hippocampal vulnerability to alcohol exposure, again suggesting differential vulnerability between the right and left hippocampus to certain exposures. Similarly, prior studies in groups with other types of injury or disease such as traumatic brain injury, diabetes, and dementia also have found asymmetrical effects on hippocampal volumes (Bigler et al., 1996; Milne et al., 2018; Shi et al., 2009). In addition to potential asymmetrical hippocampal volume loss associate with injury, prior work has also suggested hippocampal asymmetry in healthy subjects, typically with the right hippocampus having greater volume than the left (Pedraza et al., 2004; Woolard and Heckers, 2012). Our study confirms this finding. Questions for future study include why data from the UK Biobank suggested an asymmetrical effect of $PM_{2.5}$ on hippocampal volume and whether higher concentrations of $PM_{2.5}$ than were present in

Table 4b
Relationship between Particulate Matter 10 (ug/m^3) and Right Hippocampal Volume (mm^3) Unstandardized Coefficients from Linear Regression. Source: UK Biobank. * $p < .05$. ** $p < .01$. *** $p < .001$.

	Bivariate	Controlled	Interactions with PM_{10}			
			Age	Sex	Education	Health
Particulate matter$_{10}$	−1.22	−.82	18.46	1.48	.43	12.38
Total brain volume (mm^3)		.00***	.00***	.00***	.00***	.00***
Inverse distance to major road		8.02	9.92	16.43	11.36	11.21
Age		−8.48***	−3.51	−8.47***	−8.48***	−8.48***
Female		−265.80***	−265.75***	−192.46**	−265.78***	−265.93***
Race						
White		.00	.00	.00	.00	.00
Black		−225.69***	−226.56***	−225.77***	−225.57***	−226.29***
Asian		−126.02***	−126.35***	−126.08***	−125.98***	−126.49***
Other		−52.07	−52.38	−51.85	−51.92	−52.33
College degree		58.49***	58.51***	58.54***	99.80	58.64***
Household income (pounds)						
< 18k		.00	.00	.00	.00	.00
18k - 30,999		22.65	22.64	22.54	22.69	23.00*
31k - 51,999		24.42*	24.18*	24.37*	24.45*	24.65*
52k - 100k		36.10**	36.08**	36.00**	36.11**	36.30**
> 100k		52.90**	53.35**	52.84**	52.86**	52.61**
Overall health		22.59***	22.67***	22.54***	22.66***	93.34*
Body-mass index		2.72***	2.71***	2.73***	2.73***	2.70***
Smoking status						
Non-smoker		.00	.00	.00	.00	.00
Past		−7.14	−7.10	−7.09	−7.20	−7.10
Current		−28.42	−28.80	−28.37	−28.44	−28.49
Drinking frequency						
Daily or almost daily		.00	.00	.00	.00	.00
3-4 times/week		21.30*	21.38*	21.24*	21.19*	21.30*
Once or twice/week		14.57	14.62	14.60	14.61	14.53
1-3 times/month		35.02**	35.20**	35.00**	34.93**	34.88**
Special occasions		2.32	2.46	2.49	2.31	2.15
Never		6.70	6.82	6.73	6.73	6.83
Interactions						
PM_{10} x Age			−.31			
PM_{10} x Female				−4.58		
PM_{10} x College degree					−2.58	
PM_{10} x Overall health						−4.41
Constant	3939.92***	2525.00***	2214.50***	2486.97***	2504.50***	2312.74***

Note: N = 18,278.

this UK sample also would affect right hippocampal volume.

Investigating potential interaction between measures of air pollution and our covariates, we found few interactions overall. However, interactions between nitrogen dioxide and sex (Table 5a) and between nitrogen oxides and sex predicted left hippocampal volume (Table 6a), and an interaction between nitrogen oxides and sex predicted right hippocampal volume (Table 6b). As such, sex might moderate associations between air pollution and hippocampal volumes, the mechanisms of which require further research.

While we did not design our study to investigate mechanisms by which air pollution could affect hippocampal volume, several plausible mechanisms exist. Neurotoxins in air pollution are associated with proinflammatory effects (Babadjouni et al., 2017), neuroinflammation, oxidative stress (Costa et al., 2017), and gene expression (Solaimani et al., 2017), all of which plausibly could affect hippocampal volume. There is also evidence that air pollution may affect the immune system and may be associated with autoimmune diseases (Zhao et al., 2019). Furthermore, animal models suggest that $PM_{2.5}$is associated with structural changes to the hippocampus including decreased hippocampal dendritic spine density and pathology that is typically associated with Alzheimer's disease (Bhatt et al., 2015; Fonken et al., 2011). As stated by Kilian and Kitazawa (2018), there is evidence to suggest associations between air pollution and cognitive impairment, including dementia, and that these associations are supported by animal studies that suggest potential mechanisms. Overall our findings are consistent with these observations.

In addition to the association between $PM_{2.5}$ and smaller left hippocampal volume, several of the covariates we included as controls were associated with hippocampal volume. While a full discussion of all of these associations is beyond the scope of this paper, we found that age, sex, educational attainment, income, overall health, current smoking, alcohol intake, and body-mass index were associated with hippocampal volume, indicating that hippocampal volume might be susceptible to a variety of demographic and medical variables. Because

Table 5a
Relationship between Nitrogen dioxide (NO_2 ug/m ^{3}) and Left Hippocampal Volume (mm^3) Unstandardized Coefficients from Linear Regression. Source: UK Biobank. * $p < .05$. ** $p < .01$. *** $p < .001$.

	Bivariate	Controlled	Interactions with NO_2			
			Age	Sex	Education	Health
NO_2	.02	−.74	−3.60	.60	−1.27	−1.73
Total brain volume (mm^3)		.00***	.00***	.00***	.00***	.00***
Inverse distance to major road		224.41	223.01	223.53	234.34	227.24
Age		−8.80***	−9.98***	−8.74***	−8.80***	−8.80***
Female		−240.05***	−240.20***	−173.83***	−240.20***	−240.02***
Race						
White		.00	.00	.00	.00	.00
Black		−182.25***	−180.86***	−181.38***	−182.18***	−181.73***
Asian		−107.58***	−106.65***	−108.90***	−107.76***	−107.21***
Other		−29.40	−29.06	−29.36	−30.13	−29.31
College degree		44.27***	44.30***	44.63***	19.67	44.23***
Household income (pounds)						
<18k		.00	.00	.00	.00	.00
18k - 30,999		10.34	10.56	9.97	10.09	10.16
31k - 51,999		14.71	15.00	14.51	14.44	14.53
52k - 100k		38.22**	38.32**	38.16**	37.86**	38.02**
> 100k		39.64*	39.32*	39.48*	39.41*	39.52*
Overall health		17.44***	17.37**	17.32**	17.36**	8.87
Body-mass index		.71	.71	.73	.72	.71
Smoking status						
Non-smoker		.00	.00	.00	.00	.00
Past		.18	.22	.18	.20	.19
Current		−45.97**	−45.79**	−45.75**	−46.11**	−45.80**
Drinking frequency						
Daily or almost daily		.00	.00	.00	.00	.00
3-4 times/week		24.33*	24.30*	24.70*	24.36*	24.33*
Once or twice/week		9.10	9.00	9.42	9.16	9.06
1-3 times/month		21.68	21.69	22.22	21.79	21.63
Special occasions		10.19	10.17	10.73	10.34	10.20
Never		9.59	9.51	9.55	9.60	9.47
Interactions						
NO_2 x Age			.05			
NO_2 x Female				−2.58**		
NO_2 x College degree					.96	
NO_2 x Overall health						.33
Constant	3809.85***	2426.16***	2500.39***	2384.74***	2439.34***	2452.38***

Note: N = 18,278.

97 percent of the sample was White, any estimates regarding ethnic background are likely unreliable.

A previous study found that socioeconomic status is associated with hippocampal volume in children but not in young adults ages 18–25 years (Yu et al., 2018), in contrast to our findings of positive associations between income and educational attainment and hippocampal volume in adults. Possible reasons for these different findings include sample size (64 versus 18,278) and age differences in that the adult subjects in our study were older than were the young adults in the Yu et al. (2018) study. Consistent with our findings were those of Elbejjani et al. (2017), who found an association between socioeconomic status in midlife and subsequent lower hippocampal volume in older age.

Several of our models showed that compared to daily or near-daily alcohol use, less frequent use was associated with larger hippocampal volume. In this regard, Topiwala et al. (2017) found a dose-response relationship between moderate alcohol intake and reduced hippocampal volume.

We also found that cigarette smoking was associated with decreased hippocampal volume, consistent with previous findings (Durazzo et al., 2013). The decreased hippocampal volume associated with cigarette smoking we found is also consistent with findings showing associations between cigarette smoking and processing speed, working memory, and problem solving (Vermeulen et al., 2018) in that hippocampal volume reduction associated with cigarette smoking could mediate some of the associations between cigarette smoking and cognition. Further, in older adults, cigarette smoking is associated with cognitive decline (Anstey et al., 2007). We also found that the decreases in hippocampal volume associated with cigarette smoking might be at least somewhat reversible after smoking cessation, as hippocampal volume in former smokers did not differ from hippocampal volume in never smokers. Finally, we note that the associations between current smoking and hippocampal volume were only present for the left hippocampus, again suggesting the possibility of differential left-right hippocampal vulnerability to certain exposures.

Table 5b
Relationship between Nitrogen dioxide (NO_2 ug/m ^{3}) and Right Hippocampal Volume (mm^3) Unstandardized Coefficients from Linear Regression. Source: UK Biobank. * $p < .05$. ** $p < .01$. *** $p < .001$.

	Bivariate	Controlled	Interactions with NO_2			
			Age	Sex	Education	Health
NO_2	.81	.29	−2.30	1.18	−.08	2.13
Total brain volume (mm^3)		.00***	.00***	.00***	.00***	.00***
Inverse distance to major road		−44.74	−46.00	−45.33	−37.83	−50.05
Age		−8.44***	−9.51***	−8.40***	−8.44***	−8.43***
Female		−265.65***	−265.79***	−221.55***	−265.75***	−265.70***
Race						
White		.00	.00	.00	.00	.00
Black		−227.49***	−226.24***	−226.91***	−227.45***	−228.47***
Asian		−127.20***	−126.36***	−128.08***	−127.32***	−127.90***
Other		−53.33	−53.02	−53.30	−53.84	−53.48
College degree		58.43***	58.46***	58.67***	41.31	58.49***
Household income (pounds)						
< 18k		.00	.00	.00	.00	.00
18k - 30,999		23.06*	23.26*	22.81	22.89	23.39*
31k - 51,999		25.07*	25.33*	24.94*	24.89*	25.42*
52k - 100k		37.08**	37.17**	37.04**	36.83**	37.44**
>100k		54.25**	53.96**	54.14**	54.09**	54.47**
Overall health		22.65***	22.58***	22.56***	22.59***	38.72
Body-mass index		2.70***	2.70***	2.72***	2.71***	2.70***
Smoking status						
Non-smoker		.00	.00	.00	.00	.00
Past		−7.43	−7.40	−7.43	−7.41	−7.45
Current		−29.06	−28.89	−28.91	−29.15	−29.36
Drinking frequency						
Daily or almost daily		.00	.00	.00	.00	.00
3-4 times/week		21.30*	21.27*	21.55*	21.32*	21.30*
Once or twice/week		14.50	14.41	14.72	14.55	14.58
1-3 times/month		34.86**	34.87**	35.22**	34.94**	34.94**
Special occasions		1.88	1.86	2.24	1.99	1.85
Never		6.42	6.35	6.39	6.43	6.65
Interactions						
NO_2 x Age			.04			
NO_2 x Female				−1.72		
NO_2 x College degree					.67	
NO_2 x Overall health						−.62
Constant	3899.63***	2500.50***	2567.54***	2472.92***	2509.67***	2451.35***

Note: N = 18,278.

We also found associations between the estimate of overall health and hippocampal volume and between body-mass index and hippocampal volume, suggesting that health status might be an important and potentially modifiable factor associated with hippocampal volume. Somewhat surprisingly, we found some evidence of an association between body-mass index and increased hippocampal volume, in contrast to previous work that found an inverse association between increased body weight and hippocampal volume (Cherbuin et al., 2015).

While genetic factors are involved with hippocampal volume (Janowitz et al., 2014), the associations between several of the covariates we used and hippocampal volume suggest that several potentially modifiable environmental variables, such as educational attainment, income, overall health, current smoking, alcohol intake, and body-mass index could influence hippocampal volume. In that hippocampal volume is associated with Alzheimer's disease (Moodley and Chan, 2014), environmental factors that might influence hippocampal volume could potentially modify risk for Alzheimer's disease.

Strengths of this study include its large, community-based sample size, inclusion of multiple control variables including health and sociodemographic indicators, and use of objective measures of the outcome variable. Several limitations, however, require consideration when interpreting the findings. The estimates of exposure to air pollution we used were based on one year of exposure rather than cumulative exposure over the lifetime of a participant, and we used cross-sectional hippocampal volume as the outcome variable. As a result, our study design was cross sectional, precluding causal determination between $PM_{2.5}$ concentration and smaller left hippocampal volume and the associations we found between several covariates and hippocampal volumes. Perhaps a more important consideration regarding causality in this case is the potential for unmeasured and thus uncontrolled for confounding. While we included multiple covariates into our models to control for potential confounding, other variables too might be relevant

Table 6a
Relationship between Nitrogen Oxides (ug/m 3) and Left Hippocampal Volume (mm^3)Unstandardized Coefficients from Linear Regression. Source: UK Biobank. * $p < .05$. ** $p < .01$. *** $p < .001$.

	Bivariate	Controlled	Interactions with Nitrogen Oxides			
			Age	Sex	Education	Health
Nitrogen oxides	−.14	−.45	−1.85	.24	−.72*	−.74
Total brain volume (mm^3)		.00***	.00***	.00***	.00***	.00***
Inverse distance to major road		290.05	287.35	294.57	300.04	290.91
Age		−8.81***	−9.77***	−8.75***	−8.81***	−8.81***
Female		−240.07***	−240.19***	−183.71***	−240.19***	−240.05***
Race						
White		.00	.00	.00	.00	.00
Black		−182.35***	−181.16***	−181.08***	−182.57***	−182.10***
Asian		−107.63***	−106.92***	−108.73***	−107.78***	−107.45***
Other		−29.43	−29.25	−29.61	−30.09	−29.42
College degree		44.22***	44.25***	44.56***	22.94	44.20***
Household income (pounds)						
<18k		.00	.00	.00	.00	.00
18k - 30,999		10.17	10.43	9.59	9.96	10.08
31k - 51,999		14.39	14.70	14.07	14.17	14.30
52k - 100k		37.74**	37.91**	37.61**	37.43**	37.64**
> 100k		38.89*	38.64*	38.65*	38.86*	38.87*
Overall health		17.36**	17.27**	17.27**	17.27**	13.09
Body-mass index		.72	.72	.75	.72	.72
Smoking status						
Non-smoker		.00	.00	.00	.00	.00
Past		.23	.24	.26	.23	.23
Current		−45.92**	−45.79**	−45.53**	−46.03**	−45.82**
Drinking frequency						
Daily or almost daily		.00	.00	.00	.00	.00
3-4 times/week		24.33*	24.27*	24.83*	24.35*	24.34*
Once or twice/week		9.13	8.97	9.44	9.16	9.11
1-3 times/month		21.74	21.70	22.35	21.86	21.72
Special occasions		10.32	10.21	11.01	10.47	10.32
Never		9.71	9.56	9.75	9.71	9.65
Interactions						
Nitrogen oxides x Age			.02			
Nitrogen oxides x Female				−1.33**		
Nitrogen oxides x College degree					.50	
Nitrogen oxides x Overall health						.10
Constant	3816.45***	2426.55***	2487.00***	2390.47***	2438.11***	2439.36***

Note: N = 18,278.

for the associations we found, resulting in the potential for residual confounding. Because only a minority of the original UK Biobank sample underwent brain imaging, there is some risk of selection bias. Further, exact ascertainment of exposure to air pollution is likely problematic in that numerous factors might influence a person's exposure in addition to concentrations of air pollutants at a particular address, such as exposure to air pollution at place of occupation and time spent away from home. We also did not take into account indoor air pollution. There are also limitations inherent in quantitative neuroimaging given that between study variability can be related to many factors including but not limited to differences in imaging parameters, preprocessing, segmentation, post-processing, and age of the subjects and which covariates to include. Finally, our sample was comprised solely of adults, precluding generalization to children and adolescents.

In conclusion, in this study based on UK Biobank data, there was an association between $PM_{2.5}$ concentration and smaller left hippocampal volume but no associations between $PM_{2.5–10}$, PM_{10}, nitrogen dioxide, and nitrogen oxides concentrations and either left or right hippocampal volumes in adults, although sex might interact with air pollution to affect hippocampal volume. An important consideration, though, is that the sample in this study was from the United Kingdom, where concentrations of air pollution are lower than in some other regions of the world, suggesting that even comparatively low concentrations of $PM_{2.5}$ might affect left hippocampal volume. There were also multiple associations between hippocampal volume and the potentially modifiable environmental factors educational attainment, income, overall health, current smoking, and alcohol intake, indicating the potential for a complex interplay between genetic and environmental influences in determining adult hippocampal volume.

Table 6b
Relationship between Nitrogen Oxides (ug/m ^{3}) and Right Hippocampal Volume (mm^3) Unstandardized Coefficients from Linear Regression.
Source: UK Biobank. * $p < .05$. ** $p < .01$. *** $p < .001$.

	Bivariate	Controlled	Interactions with Nitrogen Oxides			
			Age	Sex	Education	Health
	(1)	(2)	(3)	(4)	(5)	(6)
Nitrogen oxides	.24	.10	−1.31	.61	−.11	.94
Total brain volume (mm^3)		.00***	.00***	.00***	.00***	.00***
Inverse distance to major road		−47.19	−49.92	−43.85	−39.40	−49.66
Age		−8.45***	−9.42***	−8.41***	−8.45***	−8.44***
Female		−265.68***	−265.81***	−223.97***	−265.77***	−265.72***
Race						
White		.00	.00	.00	.00	.00
Black		−226.81***	−225.61***	−225.87***	−226.98***	−227.53***
Asian		−126.82***	−126.09***	−127.63***	−126.93***	−127.35***
Other		−52.94	−52.75	−53.06	−53.45	−52.96
College degree		58.50***	58.53***	58.74***	41.89	58.57***
Household income (pounds)						
< 18k		.00	.00	.00	.00	.00
18k - 30,999		22.95*	23.21*	22.51	22.78	23.21*
31k - 51,999		24.93*	25.24*	24.69*	24.75*	25.21*
52k - 100k		36.89**	37.06**	36.80**	36.65**	37.16**
>100k		54.01**	53.76**	53.84**	53.99**	54.06**
Overall health		22.64***	22.55***	22.58***	22.57***	34.97*
Body-mass index		2.70***	2.70***	2.73***	2.70***	2.70***
Smoking status						
Non-smoker		.00	.00	.00	.00	.00
Past		−7.34	−7.34	−7.32	−7.34	−7.32
Current		−28.85	−28.71	−28.56	−28.93	−29.14
Drinking frequency						
Daily or almost daily		.00	.00	.00	.00	.00
3-4 times/week		21.29*	21.23*	21.66*	21.31*	21.27*
Once or twice/week		14.51	14.34	14.73	14.53	14.58
1-3 times/month		34.88**	34.84**	35.33**	34.97**	34.92**
Special occasions		1.95	1.84	2.47	2.07	1.95
Never		6.48	6.34	6.52	6.49	6.65
Interactions						
Nitrogen oxides x Age			.02			
Nitrogen oxides x Female				−.98*		
Nitrogen oxides x College degree					.39	
Nitrogen oxides x Overall health						−.29
Constant	3910.10***	2504.86***	2565.96***	2478.16***	2513.88***	2467.87***

Note: N = 18,278.

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