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Original Contribution

Association of Black Carbon with Cognition among Children in a Prospective Birth Cohort Study

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While studies show that ultrafine and fine particles can be translocated from the lungs to the central nervous system, the possible neurodegenerative effect of air pollution remains largely unexplored. The authors examined the relation between black carbon, a marker for traffic particles, and cognition among 202 Boston, Massachusetts, children (mean age = 9.7 years (standard deviation, 1.7)) in a prospective birth cohort study (1986–2001). Local black carbon levels were estimated using a validated spatiotemporal land-use regression model (mean predicted annual black carbon level, 0.56 $\mu g/m^3$ (standard deviation, 0.13)). The Wide Range Assessment of Memory and Learning and the Kaufman Brief Intelligence Test were administered for assessment of cognitive constructs. In analysis adjusting for sociodemographic factors, birth weight, blood lead level, and tobacco smoke exposure, black carbon (per interquartile-range increase) was associated with decreases in the vocabulary (−2.2, 95% confidence interval (CI): −5.5, 1.1), matrices (−4.0, 95% CI: −7.6, −0.5), and composite intelligence quotient (−3.4, 95% CI: −6.6, −0.3) scores of the Kaufman Brief Intelligence Test and with decreases on the visual subscale (−5.4, 95% CI: −8.9, −1.9) and general index (−3.9, 95% CI: −7.5, −0.3) of the Wide Range Assessment of Memory and Learning. Higher levels of black carbon predicted decreased cognitive function across assessments of verbal and nonverbal intelligence and memory constructs.

air pollution; child; cognition; intelligence; neurotoxicity syndromes; particulate matter; soot; vehicle emissions

Abbreviations: CI, confidence interval; IQ, intelligence quotient; K-BIT, Kaufman Brief Intelligence Test; SD, standard deviation; WRAML, Wide Range Assessment of Memory and Learning.

It is well documented that air pollution is associated with a number of adverse respiratory and cardiovascular health effects (1–3). Many of these effects seem to be more strongly associated with particles from traffic (1), which are rich in elemental carbon and are the principal source of ultrafine particle exposure. However, the possible neurodegenerative effect of air pollution remains largely unexplored. The potential effect of translocation of particles from the lung to other organs has been documented. Researchers have shown that ultrafine and fine particles can be translocated from the lungs when they penetrate pulmonary tissue and enter the capillaries, reaching other organs (i.e., liver, spleen, kidneys, heart, brain) through circulation (4). In addition, fine and coarse particles can be phagocytized by macrophages and dendritic cells carrying the particles to the lymph nodes (5).

Animal studies have shown that inhaled particles can be translocated from the respiratory system directly to the central nervous system. In rats, Oberdorster et al. (6) found ultrafine carbon-13 particles in the olfactory bulb and the

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cerebrum and cerebellum after inhalation exposure of ultrafine elemental carbon-13 particles. More recently, Elder et al. (4) confirmed that ultrafine particles can reach the brain, either through circulation or directly translocated to the olfactory nerve from the nose to the brain. This raises the question of whether traffic particles can have neurotoxic effects.

The few studies that have focused on the potentially neurotoxic effects of particulate matter have focused on pathologic lesions that are generally present in neurodegenerative diseases (i.e., Parkinson's disease and Alzheimer's disease). Researchers have proposed that damage mediated by the particles is probably related to the oxidative stress pathway. Calderon-Garciduenas et al. (7) presented histologic evidence of chronic brain inflammation (i.e., nuclear factor-κB activation and inducible nitric oxide synthase production) and an acceleration of Alzheimer-like pathology (i.e., apoptotic glial white matter cells, nonneuritic plaques, neurofibrillary tangles) among canines chronically exposed to high levels of air pollutants in Mexico City. Levels of proinflammatory cytokines, including interleukin-1α and tumor necrosis factor-α, were higher in the brain tissues of mice exposed to particulate matter than in mice that were not exposed (8). In humans, exposure to severe air pollution has been associated with increased levels of cyclooxygenase-2, an inflammatory mediator, and accumulation of the 42-amino-acid form of β-amyloid, a cause of neuronal dysfunction (9). Changes in brain cytokine and chemokine expression in mice have been directly linked to intranasal exposure to ultrafine black carbon, suggesting a more general inflammatory response (10). Changes in cognitive function have been shown to be associated with relatively low doses of heavy metal exposure (11), which in high doses can produce some of the lesions cited above. Those low doses have also been associated with increased inflammation and oxidative stress.

Taken together, these results suggested that further examination of possible associations between markers of traffic particles and cognitive function would be worthwhile. Thus, we examined the relation between black carbon from traffic sources, a component of particulate matter, and cognition among children followed in a prospective birth cohort study. This provided us with the opportunity to adjust for markers of socioeconomic status and other environmental factors known to affect cognitive development.

MATERIALS AND METHODS

Study population

The sample for these analyses was drawn from participants in the Maternal-Infant Smoking Study of East Boston, a prospective cohort study designed to evaluate the effects of pre- and postnatal tobacco smoke exposure on childhood lung growth and development and respiratory health. The study has been described in detail previously (12). In brief, pregnant women receiving prenatal care (<20th week of gestation) at an urban community health center in Boston, Massachusetts, between March 1986 and October 1992 were eligible for enrollment. Women who did not speak either English or Spanish, who did not plan to have pediatric follow-up at the clinic, and who were less than 18 years of age at the time were excluded. One thousand women were eligible and enrolled, of whom 848 continued participation and delivered a live infant. In November 1996, new study initiatives were implemented, including the assessment of social stressors and neurocognitive assessment, at which time 500 women and their children continued active follow-up. All active subjects were approached to participate in the cognitive battery, and 218 children completed the neurocognitive assessment. Notably, there were no significant differences between those who participated in the cognitive assessment and those who did not with regard to sociodemographic factors, birth weight, blood lead level, or tobacco smoke exposure. The study was approved by the human studies committees at the Harvard School of Public Health, Brigham and Women's Hospital, and the Beth Israel Deaconess Medical Center.

In the longitudinal study, detailed data on race/ethnicity and socioeconomic position (based on maternal educational level) had been ascertained through standardized questionnaires administered at baseline and clinic follow-up visits, as previously described (12).

Black carbon

Exposure to black carbon was estimated on the basis of the children's residence during study follow-up. In order to estimate residential black carbon level, we used a validated spatiotemporal land-use regression model to predict 24-hour measures of traffic exposure using data from more than 80 locations in the Greater Boston area. Three quarters of the monitoring sites were residential; the rest were commercial or government facilities. The data consisted of over 6,021 pollution measurements from 2,127 unique exposure days. A detailed description of all sources of exposure data is provided elsewhere (13). Predictors included in the regression analysis were the black carbon level at a central stationary monitor (to capture average concentrations in the area on that day), meteorologic conditions and other characteristics (e.g., weekday/weekend) of a particular day, and measures of the amount of traffic activity (e.g., geographic-information-system-based measures of cumulative traffic density within 100 m, population density, distance to the nearest major roadway, percentage of urbanization) at a given location. A cumulative traffic density measure was recorded once per location. We used spline regression methods to allow these factors to affect exposure levels in a potentially nonlinear way. Finally, we used thin-plate splines, a two-dimensional extension of regression splines, to model longitude and latitude and capture additional spatial variability that was unaccounted for after we included our deterministic spatial predictors in the model. This approach is a form of universal kriging (i.e., kriging extended to incorporate covariates) or a geoadditive model (14) for daily concentrations of particle levels. We had complete information on all of these factors for 2,114 of the 2,127 unique exposure days. Separate models were fitted for the warm (May–October) and cold (November–April) seasons. The R^2 value for the model (over both seasons) was 0.82, and the cross-validated R^2 between the daily measurements

taken outside the residential locations and corresponding predictions obtained from fitting the model to the data after excluding data from a particular residential location was 0.36. For the purposes of these analyses, we used the average of the two seasons as a measure of average lifetime black carbon exposure. If children moved during the study period ($n = 12$), an average black carbon measure for all addresses was calculated.

Cognitive measures

When the children were aged 8–11 years, a battery of cognitive tests was administered, including the Kaufman Brief Intelligence Test (K-BIT) and the Wide Range Assessment of Memory and Learning (WRAML). The K-BIT is an individually administered test of verbal and nonverbal intelligence (15). Two subscales, vocabulary and matrices, comprise the test, as well as a composite intelligence quotient (IQ) score. The K-BIT has acceptable correlation with the widely used Wechsler verbal performance and full-scale IQ scores (16); validation studies have been conducted for children less than 7 years of age with normative data available (17). The WRAML is a well-standardized psychometric instrument that allows evaluation of a child's ability to actively learn and memorize a variety of information (18, 19). The WRAML includes subscales on verbal memory, visual memory, and learning and an overall general index scale. It has been normed for children aged 5–17 years among racially diverse groups, including minorities. All measures are expressed as standardized scores, which represent the score of the individual taking the test relative to scores obtained by children of the same age and gender in the standardization sample. All scores have a mean of 100 and a standard deviation of 15.

Tobacco smoke exposure

At each clinic visit during pregnancy, mothers were asked about their smoking status and the smoking habits of members of their households. A urine specimen was obtained for determination of a creatinine-corrected cotinine level, as previously detailed (12). A mother was classified as never smoking during her pregnancy if she always reported that she had never smoked on the standardized questionnaire and each of her urinary cotinine levels was less than 200 ng/mg creatinine (12). At any visit, if the report of nonsmoking by the mother was contradicted by the urinary cotinine measure, the mother was classified as a current smoker for that interval. Maternally reported postnatal exposure of the child to secondhand smoke was assessed by questionnaire (monthly through age 26 months, every 6 months between ages 26 months and 4 years, and annually thereafter). Children were considered to have been exposed to secondhand smoke in a particular follow-up interval if the mother reported personal active smoking or active smoking by any other person living in the household. Postnatal secondhand smoke was categorized as early (occurring from birth through 25 months of age) or late (26 months of age or older). The late secondhand smoke exposure category included children exposed both early and late (54 children) and late only (13 children), given that there were relatively few children in the latter category. Children's exposure to maternal smoking during pregnancy was highly correlated with postnatal secondhand smoke exposure. Forty-two children were exposed to prenatal tobacco smoke; among these children, only two were not exposed to secondhand smoke after birth.

Blood lead level

Children in Massachusetts are mandated by law to have blood lead testing annually, starting at 9 months of age, until age 4 years, unless they are considered to be at high risk (living in pre-1978 housing that is deteriorated or undergoing construction or having a sibling with lead poisoning), in which case they are tested annually until age 6 years. Results are incorporated into the medical records at the community health centers where the children obtain pediatric follow-up. Using a standardized instrument, blood lead levels were extracted from medical records at these health centers by a physician blinded to the study aims. Because the children had varying numbers of blood lead measurements which were dependent on their lead exposure (children with higher lead exposure had more follow-up tests than children with lower lead concentrations), we used the highest blood lead level recorded up to age 6 years for each child, referred to hereafter as the ''peak blood lead level.''

Statistical analyses

A total of 218 children completed the cognitive assessment, of whom 214 were successfully geocoded and assigned a black carbon measure. Eleven children were removed from the data set before analysis because they had black carbon values considered to be outliers according to the extreme studentized deviation model (20); in addition, one child was missing information on socioeconomic status. This left 202 children for our analyses. Multiple imputation was used to impute missing data on birth weight (seven children) and blood lead level (12 children). Since black carbon was being used as a surrogate for traffic particle exposure, which includes more than just carbon particles, it did not make sense for us to report results on a unit mass basis. Instead, we report estimated effects of predicted black carbon level per interquartile-range increase. We conducted bivariate analyses to determine the association between cognitive outcomes and demographic and environmental measures of interest. We also tested for associations between black carbon and environmental and sociodemographic markers. The effect of predicted black carbon on cognition was estimated by linear regression while adjusting for child's age at cognitive assessment, gender, race/ethnicity, and maternal education (as a marker of socioeconomic status) (model 1). To assess the potential for confounding, we examined the sensitivity of those results to further adjustment for in-utero and postnatal secondhand tobacco smoke exposure (model 2), birth weight (model 3), and blood lead level (model 4). All analyses were conducted in SAS, version 9.0 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Among the 202 children in this study, 52 percent were female and 57 percent spoke Spanish as their primary language. Maternal educational level was less than high school graduation for 42 percent of the mothers (table 1). The mean age was 9.7 years (standard deviation (SD), 1.7), and the mean peak blood lead level was 8.5 μg/dl (SD, 6.1). Mean scores on the K-BIT subscales were as follows: composite, 94.9 (SD, 13.9); vocabulary, 89.5 (SD, 16.3); and matrices, 101.4 (SD, 14.0). WRAML mean subscale scores were: verbal memory index, 84.7 (SD, 15.1); visual memory index, 93.3 (SD, 13.8); learning index, 101.1 (SD, 15.0); and general index, 91.1 (SD, 14.5). The mean annual predicted black carbon level was 0.56 $\mu g/m^3$ (SD, 0.13).

In bivariate analyses (data not shown) of black carbon and cognitive measures, black carbon was associated with the vocabulary, matrices, and composite subscales of the K-BIT and the visual and verbal subscales and the general index of the WRAML. Primary language spoken at home and maternal education were associated with the cognitive measures and black carbon. Children who primarily spoke Spanish at home and children whose parents had a high school education or less scored lower on the composite, vocabulary, verbal, and general memory subscales of the WRAML and K-BIT. In addition, they had higher predicted black carbon levels than children who primarily spoke English at home and whose parents had more than a high school education. Marital status was not associated with any of the cognitive measures or with black carbon. Thus, in multivariate analyses, we adjusted for both parental education and primary language spoken at home, as well as birth weight, blood lead level, and in-utero and postnatal secondhand tobacco smoke exposure.

In multiple linear regression analyses (tables 2 and 3), an interquartile-range increase in log black carbon predicted a 2-point decrease (95 percent confidence interval (CI): −5.3, 1.3) on the vocabulary scale, a 4.2-point decrease (95 percent CI: −7.7, −0.7) on the matrices scale, and a 3.4-point decrease (95 percent CI: −6.6, −0.3) on the composite subscale of the K-BIT. Black carbon level also predicted a 1.1-point decrease (95 percent CI: −4.6, 2.3) on the verbal learning scale, a 5.2-point decrease (95 percent CI: −8.6, 1.7) on the visual learning scale, a 2.7-point decrease (95 percent CI: −6.5, 1.1) on the learning scale, and a 3.7-point decrease (95 percent CI: −7.2, −0.2) on the general index scale of the WRAML. Further adjustment for tobacco smoke exposure, birth weight, and blood lead level did not attenuate these effect estimates.

TABLE 1. Demographic characteristics, environmental exposures, and scores on cognitive subscale measures ($n = 202$) in the Maternal-Infant Smoking Study of East Boston, 1986–2001

	No.	%	Mean (SD*)
Demographic characteristics			
Child's age (years)			9.7 (1.7)
Child's gender			
Male	97	48.0	
Female	105	52.0	
Primary language spoken at home			
English	87	43.1	
Spanish	115	56.9	
Mother's educational level			
Some college	37	18.3	
High school graduation/technical school	81	40.1	
Less than high school/no graduation	84	41.6	
Marital status			
Married/living with someone	155	76.7	
Separated/divorced/single	47	23.3	
Medical history and environmental exposures			
Tobacco exposure			
Nonsmoker	70	34.7	
In-utero and SHS* exposure	42	20.8	
Early SHS exposure†	23	11.4	
Late SHS exposure‡	67	33.2	
Birth weight (kg)			3.35 (0.5)
Peak blood lead level (μg/dl)			8.5 (6.1)
Black carbon ($\mu g/m^3$)			0.56 (0.13)
Cognitive subscales			
Kaufman Brief Intelligence Test			
Composite			94.9 (13.9)
Matrices			101.4 (14.0)
Vocabulary			89.5 (16.3)
Wide Range Assessment of Memory and Learning			
Verbal			84.7 (15.1)
Learning			101.1 (15.0)
Visual			93.3 (13.8)
General index			91.1 (14.5)

* SD, standard deviation; SHS, secondhand smoke.
† SHS exposure before 26 months of age.
‡ SHS exposure at 26 months of age or older.

DISCUSSION

In this prospective urban birth cohort study, long-term concentration of black carbon particles from mobile sources was associated with decreases in cognitive test scores, even after adjustment for socioeconomic status, birth weight, tobacco smoke exposure, and blood lead level. Although our linear regression-based analyses do not establish causation, only associations, a number of features strengthen our findings. Decreases in cognitive functioning were seen in verbal and nonverbal intelligence constructs as well as memory constructs. Moreover, our results are consistent in that we noted decreases across all subscales, though not all associations between black carbon and cognitive subscales were statistically significant.

TABLE 2. Relation of predicted black carbon levels (average of summer and winter) at children's residences to scores on subscales of the Kaufman Brief Intelligence Test in linear regression models ($n = 202$), Maternal Infant Smoking Study of East Boston, 1986–2001†

Black carbon model	Vocabulary		Matrices		Composite	
	Estimate	95% CI‡	Estimate	95% CI	Estimate	95% CI
Adjusted for demographic factors§	−2.0	−5.3, 1.3	−4.2	−7.7, −0.7*	−3.4	−6.6, −0.3*
Adjusted for above factors + in-utero tobacco smoke + secondhand smoke	−2.0	−5.3, 1.4	−4.0	−7.5, −0.4*	−3.3	−6.4, −0.1*
Adjusted for above factors + birth weight	−2.0	−5.4, 1.3	−4.0	−7.6, −0.5*	−3.3	−6.5, −0.2*
Adjusted for above factors + blood lead level	−2.2	−5.5, 1.1	−4.0	−7.6, −0.5*	−3.4	−6.6, −0.3*

* $p < 0.05$.
† Change in subscale score per interquartile-range (0.4-μg/m^3) increase in log black carbon level.
‡ CI, confidence interval.
§ Adjusted for age, gender, primary language spoken at home, and mother's education.

These results are of comparable magnitude to results found for other environmental neurotoxicants. For example, among children, a 10-μg/dl increase in blood lead level has been associated with a loss of 1–5 IQ points (21). Children born to mothers who smoke 10 or more cigarettes per day during pregnancy have an average decrease of 4 IQ points (22). In our cohort, an interquartile-range (0.4-μg/m^3) increase in log black carbon predicted a 3-point decrease in IQ (K-BIT composite subscale).

There are several potential mechanisms that could be contributing to the associations found in this study. First, since black carbon comes almost entirely from traffic, these particles are surrogates for all traffic particles, and other components of traffic particles may play a role. For example, there is evidence that ultrafine particles are translocated up the olfactory nerve to the brain without entering the lung (6). Ultrafine particles in the brain are probably associated with increased oxidative stress, since that has been seen in other tissues (23). The carbon particles themselves are rarely pure carbon; they generally have transition metals adsorbed on the surface. These metals have been shown to induce oxidative stress in the lung (24–28). Other studies have also implicated traffic exposure in oxidative stress (29–31). There is evidence that the oxidative stress and inflammation induced by particles translates systemically (30). For example, exposure of rodents to concentrated air particles collected from a busily trafficked roadway resulted in increased oxidative stress in the heart as well as the lung (31). Other studies comparing animal brains in areas of Mexico City that are heavily influenced by traffic have reported histologic evidence of chronic brain inflammation and an acceleration of Alzheimer-like pathology (7). Taken together, the current body of knowledge suggests that inflammatory processes and increased oxidative stress (7) may play a role in the mechanism by which particles can have an impact on the nervous system; however, additional work in this area of research remains to be done.

While, to our knowledge, no other studies have examined an association between air pollution and cognition, a few have examined the role of traffic noise in cognition among children (32, 33). In the RANCH project, a cross-sectional study of 2,000 children from three European cities (Madrid, London, and Amsterdam), aircraft noise at home and at school was associated with impaired reading comprehension (32). Road traffic noise, however, was not associated with reading comprehension. It is possible that the associations found in our study could be attributable to traffic and/or aircraft noise and not to black carbon; conversely, it is also possible that the associations previously found between road and aircraft noise and cognition are actually due to air

TABLE 3. Relation of predicted black carbon levels (average of summer and winter) at children's residences to scores on subscales of the Wide Range Assessment of Memory and Learning in linear regression models ($n = 202$), Maternal Infant Smoking Study of East Boston, 1986–2001†

Black carbon model	Verbal		Visual		Learning		General	
	Estimate	95% CI‡	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Adjusted for demographic factors§	−1.1	−4.6, 2.3	−5.2	−8.6, −1.7*	−2.7	−6.5, 1.1	−3.7	−7.2, −0.2*
Adjusted for above factors + in-utero tobacco smoke + secondhand smoke	−1.2	−4.7, 2.3	−5.3	−8.8, −1.8*	−2.6	−6.5, 1.2	−3.7	−7.3, −0.1*
Adjusted for above factors + birth weight	−1.3	−4.7, 2.2	−5.3	−8.8, −1.8*	−2.6	−6.5, 1.3	−3.8	−7.4, −0.2*
Adjusted for above factors + blood lead level	−1.3	−4.8, 2.2	−5.4	−8.9, −1.9*	−2.8	−6.6, 1.1	−3.9	−7.5, −0.3*

* $p < 0.05$.
† Change in subscale score per interquartile-range (0.4-μg/m^3) increase in log black carbon level.
‡ CI, confidence interval.
§ Adjusted for age, gender, primary language spoken at home, and mother's education.

pollutants, such as black carbon. Future studies may be designed to distinguish traffic effects due to noise from those due to pollution.

The current study had a number of limitations. As is typical with longitudinal studies, there was a significant reduction in the sample available from the original cohort over time. The nonparticipation of some subjects from the longitudinal study may be seen as a limitation, although there were no differences based on race/ethnicity, maternal education, smoking status, birth weight, or blood lead level when we compared children who had cognition assessed with those who did not among the participants who remained in follow-up. Thus, this is unlikely to have influenced our findings. While we were able to adjust for a number of factors associated with cognition and air pollution, it is still possible that the associations found in this study could be attributable to unmeasured or residual confounding, perhaps most notably from socioeconomic status. Socioeconomic status has been shown to be a determinant of cognitive ability and achievement from early childhood through young adulthood (34, 35). Furthermore, socioeconomic status can determine whether a family lives in close proximity to roadways (36). In addition to adjusting for mother's educational level, the present study was somewhat restricted regarding socioeconomic status, given that all families were recruited from one neighborhood health center in Boston. This restricted the variability of income in this population, thereby reducing the potential for confounding.

Our measure of exposure was also subject to limitations. While we attempted to capture black carbon exposure from all residential addresses, it is possible that we potentially missed exposures incurred at school and/or other locations where children spend portions of their time. However, this potential misclassification of exposure was nondifferential with respect to the outcome, and thus it is unlikely to account for the associations found. Furthermore, compared with adults who work, children spend considerably longer periods of time at home or in the vicinity of their home. Furthermore, exposure studies using personal monitors indicate that home exposures are the most important in predicting personal exposure (37). While demonstrated in adults, time activity studies indicate that children spend more time at home and near home, making the finding relevant (38). Other studies (39) have shown that residential indoor concentrations of particulate matter of outdoor origin are highly correlated with outdoor concentrations. In another study (40), the personal exposures of the working spouses of persons with chronic illnesses have been shown to be highly correlated with their spouses' personal exposures. Taken together, we believe these studies indicate that personal exposures to ambient particles are driven primarily by exposures incurred at home. Moreover, we attempted to capture black carbon exposure from all residential addresses when children moved.

Another limitation of this study is the use of predicted exposure, rather than observed measurements taken outside the residences of the study participants. Since the latter approach is not practical in a large community-based study, we decided to use all available exposure data and advanced modeling approaches to predict the missing exposure at the residences of the participants. This is an approach that has become very popular in recent years. A potential statistical issue that arises when using spatial-temporal predictions of exposure rather than measured quantities is that predicted quantities are uncertain, and this could bias the resulting health effect estimates. In a previous study, Gryparis et al. (41) found that the use of predictions from spatial exposure models induces a Berkson-type measurement error. This results in unbiased parameter estimates for the association between the predicted exposure and the observed health outcome. However, the standard errors for the parameter of interest might be incorrect. In such a case, we would expect larger standard errors for the parameter of interest.

In summary, this is the first study to have found a consistent relation between exposure to black carbon and reduced neurocognitive functioning across a number of domains in urban, community-dwelling school-aged children. More studies are needed to explore the potentially neurotoxic effects of particulate matter, both to determine the possible impact on cognitive development among children and cognitive decline across the life cycle and to determine the potential contribution of air pollutants to the development and exacerbation of neurodegenerative diseases (i.e., Parkinson's disease, Alzheimer's disease).

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