Prenatal air pollution and childhood IQ: preliminary evidence of effect modification by folate

Christine T Loftus[a], **Marnie F Hazlehurst**[b], **Adam A Szpiro**[c], **Yu Ni**[b], **Frances A Tylavsky**[d], **Nicole R Bush**[e,f], **Sheela Sathyanarayana**[a,g,i], **Kecia N Carroll**[h], **Catherine J Karr**[a,b,i], **Kaja Z LeWinn**[e]

[a]Department of Environmental and Occupational Health Sciences, 4225 Roosevelt Way NE, University of Washington (UW), Seattle WA 95105

[b]Department of Epidemiology, 1959 NE Pacific Street, Box 357236, UW, Seattle WA 98195

[c]Department of Biostatistics, UW, Box 357232, Seattle WA 98195

[d]Department of Biostatistics and Epidemiology, 462 Doctors Office Building, 66 N Pauline St, University of Tennessee Health Science Center, Memphis TN 38163

[e]Department of Psychiatry, University of California (UC) 401 Parnassus Ave, San Francisco, CA 94143

[f]Department of Pediatrics, 550 16th Street, Box 0110 UC San Francisco CA 94143

[g]Seattle Children's Research Institute, 1900 9th Ave, Seattle, WA 98101

[h]Division of General Pediatrics, 2200 Children's Way, Vanderbilt University Medical Center, Nashville TN 27232

[i]Department of Pediatrics, 1959 NE Pacific St, UW Seattle, WA 98195

Abstract

Objectives: Animal studies suggest that air pollution is neurotoxic to a developing fetus, but evidence in humans is limited. We tested the hypothesis that higher air pollution is associated with lower child IQ and that effects vary by maternal and child characteristics, including prenatal nutrition.

Methods: We used prospective data collected from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood study. Outdoor pollutant exposure during pregnancy was predicted at geocoded home addresses using a validated national universal kriging

Corresponding author: Christine T. Loftus, Department of Environmental and Occupational Health Sciences, 4225 Roosevelt Way NE, Seattle WA 98105, cloftus@uw.edu. Phone: 206-616-3697. Fax number: 206-685-7031.

model that combines ground-based monitoring data with an extensive database of land-use covariates. Distance to nearest major roadway was also used as a proxy for traffic-related pollution. Our primary outcome was full-scale IQ measured at age 4–6. In regression models, we adjusted for multiple determinants of child neurodevelopment and assessed interactions between air pollutants and child sex, race, socioeconomic status, reported nutrition, and maternal plasma folate in second trimester.

Results: In our analytic sample (N=1005) full-scale IQ averaged 2.5 points (95% CI: 0.1, 4.8) lower per 5 $\mu g/m^3$ higher prenatal PM_{10}, while no associations with nitrogen dioxide or road proximity were observed. Associations between PM_{10} and IQ were modified by maternal plasma folate ($p_{interaction} = 0.07$). In the lowest folate quartile, IQ decreased 6.8 points (95% CI: 1.4, 12.3) per 5-unit increase in PM_{10}; no associations were observed in higher quartiles.

Conclusions: Our findings strengthen evidence that air pollution impairs fetal neurodevelopment and suggest a potentially important role of maternal folate in modifying these effects.

Keywords

Air pollution; pediatric health; neurodevelopment; prenatal folate; particulate matter

Introduction

Recent epidemiologic studies have linked prenatal and early-life air pollution exposure to poorer neurodevelopmental outcomes in children, including impaired cognitive development,[1–7] poorer emotional regulation,[8] increased risk of behavioral problems,[9–12] and diagnosis of autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD) and other disorders.[13–15] Toxicologic research describes plausible biological mechanisms for neurodevelopmental toxicity of air pollution, including by increased microglial activation, oxidative stress, and neuroinflammation, and dysregulation of epigenetic programming.[16–21] Because air pollution exposure is pervasive and increasing in several regions of the world, potential public health implications of a true effect on neurodevelopment are vast.[22–23]

The strength of existing epidemiological evidence is limited, in part, by the possibility of residual or unmeasured confounding. Several determinants of pediatric neurodevelopment relate to socioeconomic status (SES) and poverty, both of which are highly correlated with outdoor air pollution in several regions of the United States (US).[24–27] Disentangling the effect of air pollution from the effects of individual- and neighborhood-level disadvantage on neurodevelopment is therefore challenging. Furthermore, several studies have examined whether potential associations are modified by maternal or child characteristics, but evidence is inconclusive. Animal experiments indicate that male fetuses are more susceptible to neurotoxic effects of air pollution,[16,17,28–30] but epidemiologic evidence is mixed.[2,5,31–32] Poverty or material hardship may increase susceptibility to air pollution.[33–34] Other investigators have hypothesized that maternal nutrition during pregnancy may moderate neurotoxic effects of air pollution. A maternal diet rich in antioxidants, for example, may counteract oxidative stress induced by air pollution exposure.[18,35] Insufficient prenatal

folate, a major methyl donor,[36–37] may increase susceptibility to epigenetic dysregulation caused by air pollution exposure.[38–41] However, rigorous tests of effect modification by these factors have been limited because most studies are underpowered to detect interaction and additionally lack well-characterized exposure data across social, nutritional, and chemical domains.

We contribute to this area of research by examining associations between prenatal air pollution and child cognitive development in the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) cohort, a longitudinal study of 1503 mother-child dyads in Shelby County, TN. We applied well-developed air pollution models with high spatial resolution to estimate exposures to NO_2 and PM_{10}[42,43] and further evaluated distance to roadway as a proxy for traffic-related air pollution. (We did not evaluate the effect of $PM_{2.5}$ exposure since our models predicted insufficient spatial variability in $PM_{2.5}$ concentrations across the study region [data not shown].) We hypothesized that prenatal exposure to ambient air pollution would be associated with poorer cognitive ability in early childhood, and that associations would vary by child sex, SES, maternal race and prenatal nutrition. To our knowledge, we are the first to examine whether relationships between environmental exposures and child neurodevelopment are modified by nutrition using a biomarker of maternal folate.

Methods

Study design and population

A detailed description of the CANDLE study and cohort is available elsewhere.[44–45] In brief, CANDLE is a prospective pregnancy cohort study set in Shelby County, TN, originally established to identify early-life determinants of neurocognitive development. Between 2006 and 2011, CANDLE enrolled 1503 women with uncomplicated pregnancies between 16 and 28 weeks gestation and intent to deliver at one of four participating hospitals. All research activities were approved by the Institutional Review Board (IRB) of the University of Tennessee Health Sciences Center. These analyses were conducted as part of the ECHO PATHWAYS study, and were approved by the University of Washington IRB.

Clinic visits were conducted twice during pregnancy and at approximately yearly intervals throughout childhood. Other points of data collection were two home visits in early childhood, and multiple phone visits per year. Visits involved physical and neurodevelopmental assessments of mother and child, biospecimen collection, direct observation of care-taking environment with the Home Observation Measurement of the Environment (HOME) inventory,[46] and extensive survey-based data collection. Specific measures included in statistical analyses (below) include the Brief Symptom Inventory (BSI),[47] the Block 2005 Food Frequency Questionnaire (FFQ),[48] Knowledge of Infant Development Inventory (KIDI),[49] and the Children's Sleep Habits Questionnaire (CSHQ).[50] Maternal IQ was measured using the Weschler Abbreviated Scale of Intelligence (WASI) short form.[51] Maternal blood was collected in the second trimester and analyzed for plasma folate concentrations, as described elsewhere.[52]

IQ outcome assessment

Child IQ was assessed at the CANDLE 4–6 year clinic visit using the Stanford Binet Intelligence Scales, edition 5 (SB-5), widely used to assess early childhood IQ and validated and normed in large, diverse populations.[53] The SB-5 yields composite, standardized scores for Full Scale (FSIQ), Verbal (VIQ), and Nonverbal IQ (NVIQ) as well as five standardized subtest scores for Fluid Reasoning, Knowledge, Quantitative Reasoning, Working Memory, and Visual-spatial skills (all with mean=100; SD=15). In analyses, FSIQ was our primary outcome metric, and VIQ, NVIQ and the five subtest scores were secondary outcomes.

Air pollution exposures and other spatial measures

CANDLE collected residential addresses from mothers at enrollment and then updated addresses at each subsequent contact. We geocoded addresses using Census TIGER line files in ArcGIS, Texas A&M geocoder, or manual matching. If a move date was not provided, it was assumed to be the midpoint between the date of the last reported address and the date of the new reported address.

Estimates of outdoor NO_2 and PM_{10} at each participant's address were determined using universal kriging models (land-use regression with spatial smoothing) for the contiguous US; details in Sampson et al. (2013) and Young et al. (2016).[42,43] These models utilize air quality monitoring data from AQS and IMPROVE networks and incorporate more than 200 geographic covariates to calculate annual average pollutant concentrations. The NO_2 model was further enhanced with satellite data.[43] The 10-fold cross-validated R^2 for NO_2 and PM_{10} exposure models ranged from 0.79 to 0.89 and 0.40 to 0.63, respectively. For participants who moved at least once during the prenatal period, we calculated time-weighted averages of NO_2 and PM_{10} across all addresses. Prenatal NO_2 and PM_{10} were calculated using one year of exposure predictions, 2006, for the entire cohort in order to minimize potential confounding by long-term temporal trends. We additionally characterized early childhood NO_2 and PM_{10} exposures (birth to time of assessment) as potential confounders of associations between prenatal exposure and neurodevelopment.

As a proxy measure of exposure to traffic-related air pollution, we also estimated distance between the residential address and nearest major roadway. For our primary road proximity metric, we defined near road proximity as living within 150 m of an A1, A2 or A3 road. If a woman lived at multiple addresses during pregnancy, we assigned road proximity based on the single location at which she lived the longest. In sensitivity analysis, we tested additional thresholds as low as 50 m, and repeated analyses of road proximity with exclusion of women who moved during pregnancy.

Neighborhood SES was estimated with the Childhood Opportunity Index (COI), a spatial measure of relative childhood neighborhood opportunity.[54] Specifically, we used two of the three "opportunity domains" comprising the COI to capture distinct aspects of neighborhood quality supportive of healthy child development: *educational opportunity*, calculated using adult educational attainment rate (college and above), school poverty rate, reading proficiency rate, math proficiency rate, preschool/nursery school attendance rate, high school graduation rate, proximity to accredited early education centers, and proximity to

early childhood education centers of any type; and *social and economic opportunity*, calculated using neighborhood foreclosure rate, poverty rate, unemployment rate, public assistance rate, and proximity to employment. For each mother, the address at which the she lived the longest during pregnancy was linked to COI data by census tract.

Statistical Analyses

We conducted descriptive analyses to characterize the cohort overall and by high vs. low exposure. Spearman rank correlation coefficients were calculated to assess pairwise correlations among pollutants and continuous distances to each class of roadway.

Epidemiologic associations were measured using multivariate linear regression with robust standard errors. To address potential confounding, we controlled for several covariates in a staged approach, with "minimal", "full" and "expanded" models established *a priori*. We included potential confounders that are established risk factors for pediatric neurodevelopmental problems and are likely to be correlated with exposure to one or more pollutant. Our minimal models were adjusted for child sex, age at the time of assessment, and child date of birth as cubic splines with 4 degrees of freedom per year. The full models included additional confounders and precision variables: individual-level SES measures (maternal education at baseline [high school degree/GED or less, college degree or technical school, graduate or professional degree] and insurance status at baseline [Medicaid/Medicare only or no insurance versus other]), neighborhood-level SES measures (recruitment site and two domains of the COI [economic opportunity and educational opportunity] in census tract of prenatal residence modeled as cubic splines with 3 degrees of freedom), maternal demographics (maternal age at birth [16–18, 19–21, 22–29, and 30 and over years] and maternal race [African American or other]), measures of maternal health during pregnancy (reported smoking [any or none], maternal depression (BSI t-score for depression above 60), maternal cognitive ability (full scale IQ score), birth order (first child or not), and two aspects of early childhood health (breastfeeding [never, <6 months,   6 months], and sleep survey score at time of assessment [continuous score]). Expanded models included all covariates in the full models, plus reported prenatal vitamin use (yes or no), maternal marital status at baseline, paternal education at baseline (same categories as maternal education, plus unknown), maternal pre-pregnancy body mass index (underweight, normal, overweight, obese), and total score on the KIDI survey. In NO_2 and PM_{10} models, we additionally controlled for postnatal pollutant exposure in sensitivity analyses.

To assess robustness of results to method of estimating prenatal NO_2 and PM_{10}, we repeated all analyses using year prior to birth for the averaging period instead of the fixed year for all participants (2006). The results did not change meaningfully (results not shown). We also conducted sensitivity analyses to evaluate potential bias due to residual confounding or missing covariates. Specifically, we conducted multiple imputation of missing covariates and outcome variables in our fully-adjusted models and additionally imputed two potential confounders not selected for full models due to nonrandom missingness greater than 10%: reported household income at enrollment and HOME inventory score. All imputation was conducted using chained equations, and the imputation models included all exposures, outcomes and covariates, as well as some variables not in epidemiologic models that may

predict missing values. N=10 datasets were generated and combined in regression analyses using Rubin's rules.[78] Finally, we repeated analysis with exclusion of postnatal covariates (breastfeeding and child sleep at assessment), which could be on the causal pathway between air pollution and health outcomes, but we observed no change in associations (results not shown).

We additionally assessed evidence for effect modification of associations between prenatal air pollution and FSIQ by child sex, insurance status (Medicaid/Medicare only or no insurance versus other), maternal race (African American or other), and two measures of prenatal nutrition. Maternal reported dietary intake was assessed using the FFQ administered in the second trimester. We excluded participants who reported less than 1000 kcal or over 5000 kcal total daily intake, and summed total daily servings of vegetables and fruit. This value was split at the median to identify mothers with relatively low reported vegetable and fruit intake versus high intake. We also assessed effect modification by quartiles of maternal plasma folate, a biomarker measure of maternal nutrition. P-values for interaction were estimated using a Wald test with robust standard errors.

All analyses were conducted in Stata version 15 (StataCorp LLC, College Station, Texas) or R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

We included N=1005 mother-child dyads with address histories and FSIQ at the outcome visit. Figure 1 illustrates cohort retention from enrollment to the time of outcome assessments and sizes of analytic samples. Compared to women who enrolled in CANDLE but were excluded from the current analysis (N=498), participants in our analytic sample were more likely to be African American, reported slightly more child sleep problems, had first-born children, and lived in a census tract of slightly lower COI economic index. The two groups were otherwise similar with respect to other characteristics and all exposure measures (Supplemental Table 1).

Mothers predominantly identified as African American (64.5%), were covered by Medicaid/ Medicare or had no insurance (57%), and had a high school education or less at time of enrollment (60%) (Table 1). Few mothers reported smoking (9.0%) during pregnancy and the majority breastfed their children (63.4%). Children were an average of 4.4 (SD=0.6) years at the time of neurodevelopmental assessments. Compared to those with lower levels of pollution exposures, mothers with higher exposure to NO_2 and busy road proximity were more likely to be African American and experience sociodemographic disadvantage, including lower individual and neighborhood SES, higher rates of single parenthood, and Medicaid insurance (Table 1).

There were fewer differences in participant characteristics for high vs. low PM_{10} exposure categories, though participants were somewhat more likely to be African American, have a higher BMI, have lower plasma folate, and to have not breastfed (Table 1). Table 2 summarizes IQ results at the outcome visit.

Median prenatal exposures to PM_{10} and NO_2 were 20.79 ug/m3(IQR = 2.76) and 11.96 ppb (IQR = 3.81), respectively (Table 3). N=279 (27.8%) of participants lived within 150 m of a busy road for the majority of their pregnancy. Prenatal NO_2 and PM_{10} were poorly correlated (rho = − 0.0358; Supplemental Table 2). Participants living within 150 m of an A1, A2 or A3 road had higher NO_2 exposures but similar PM_{10} concentrations as those living further from major roads (Supplemental Figure 1). Postnatal exposures were highly correlated with prenatal exposures (rho = 0.79 and 0.74 for NO_2 and PM_{10}, respectively and smaller in magnitude than prenatal levels. Estimated NO_2 is highest around major roadways and concentrated in the Memphis urban center, while PM_{10} is highest in some regions of downtown and in the southeast, the location of several industrial sources of air pollution (Supplemental Figure 2). The predicted annual NO_2 exposures were lower than US Environmental Protection Agency (EPA) annual average standard of 53 ppb; there is no PM_{10} annual average standard for comparison.

Prenatal air pollution and cognitive ability (IQ)

Prenatal NO_2 and residential proximity to road traffic were both associated with significantly lower IQ at age 4–6 years in minimally-adjusted models but not in fully adjusted models, indicating that minimally-adjusted models may have been confounded (Figure 2). A 5 ug/m3 increase in PM_{10} was associated with 2.47 points lower full-scale IQ (95% CI: 0.14, 4.79) in fully-adjusted models, which was attenuated only slightly by additional adjustment in the expanded model (2.46 decrease in IQ points [95% CI: 0.14, 4.79] per 5 unit increase). This association was robust to sensitivity analyses aimed at assessing bias due to missing covariates or residual confounding (Supplemental Table 3). We further controlled for reported household income at baseline and HOME inventory score in main adjustment models, variables that were not included in our main models due to substantial missingness. We observed that associations between PM_{10} and IQ were attenuated and less precise in complete case analyses with addition of income and/or HOME score, but after multiple imputation of missing values the associations were very similar to the main results without inclusion of household income or HOME inventory score. In imputed datasets with control for income and HOME score, a 5 unit increase in PM_{10} was associated with 2.58 lower IQ points (95% CI: 0.41, 4.76). In addition, results did not change meaningfully with additional control for postnatal PM_{10} exposures: a 5 ug/m3 increase in prenatal PM_{10} was associated with a difference of −2.85 IQ points (95%CI: −6.06, −0.36) with additional control for postnatal PM10. In sensitivity analyses, we varied the threshold applied to define proximity and observe no evidence for health effects at any distance cut-off: the effect estimates varied in direction and magnitude, and none were statistically significant (Supplemental Table 4). Road proximity findings did not change meaningfully after exclusion of N=142 women who moved during pregnancy (results not shown).

In secondary analyses, we explored associations with subtests and subscales of the SB-5 (Supplemental Table 5). Verbal IQ and nonverbal IQ were both negatively associated with PM_{10}, though associations with verbal IQ were stronger and more precise (−2.67 [95% CI: −5.01,−0.34] versus −1.86 [95% CI: −4.25, 0.53] point difference per 5 unit higher PM_{10} for verbal and nonverbal IQ, respectively). Of five subtests, all were lower with higher PM_{10}

exposure, while fluid reasoning and quantitative reasoning exhibited the largest and most precise associations with PM_{10}.

Effect modification

We observed little evidence that any associations varied by child sex, reported prenatal fruit and vegetable intake, maternal race, or individual-level SES (Figure 3). Associations between PM_{10} and FSIQ were stronger among children whose mothers had lower plasma folate, and the test of interaction by quartiles of maternal folate was borderline significant (p=0.07). For the lowest folate quartile, FSIQ decreased 6.8 points (95%CI: 1.4, 12.3) per 5 units increase in PM_{10}, over twice the magnitude of effect in the overall population (Figure 2). No association between PM_{10} and FSIQ was observed for those in the highest quartiles of folate exposure.

Discussion

We found that children in the CANDLE cohort exposed to higher ambient PM_{10} *in utero* had lower IQ in early childhood. These findings were robust to adjustment for a number of potential confounders and in several sensitivity analyses. We did not observe any associations with road proximity or ambient NO_2, and no evidence that any associations varied by child sex, SES, maternal race or reported fruit and vegetable intake during pregnancy. However, we found that the association between PM_{10} and FSIQ might be modified by maternal folate in the second trimester. A strong, negative association between PM_{10} and FSIQ was observed for those in the lowest quartile of prenatal folate, whereas no association with IQ was observed among those in higher folate quartiles, suggesting that maternal folate levels may modify the impact of prenatal air pollution exposure on child cognition. These exploratory findings are novel and may have important public health implications if replicated in future studies.

A few pregnancy cohort studies have examined prenatal particulate matter and pediatric cognitive development, but findings are inconsistent. $PM_{2.5}$ has been associated with poorer cognitive outcomes in a Boston cohort of relatively high socioeconomic adversity[31] but not in a larger study in the same city with a study population of relatively high SES.[1] Notably, no associations with $PM_{2.5}$ have been observed in settings of much higher $PM_{2.5}$ exposures. [3,4,55] Pregnancy cohorts in New York[6,56] and Poland[57] consistently reported associations between cognitive outcomes and prenatal PAH, a component of ambient PM. Studies of larger PM size fractions (PM_{coarse} and PM_{10}) were not associated with cognitive development in European settings,[3,4] but prenatal PM_{10} was linked to impaired early life cognitive ability in a Korean population.[58] These between-study inconsistencies in particulate matter associations could be due to variations between regions in particulate composition, difference in underlying susceptibility of study populations, or methodological limitations, such as exposure measurement error, confounding, selection bias, or small sample size.

We observed no evidence that IQ is associated with markers of prenatal exposure to traffic-related air pollution (i.e., NO_2 or road proximity), in contrast to other birth cohort findings. [1,4,55,59] Our lack of findings with NO_2 could be due to relatively low NO_2 levels compared

to studies reporting associations.[4,55,59] Therefore, our null findings constitute relatively weak evidence that prenatal exposure to traffic-related air pollution is not neurotoxic. By contrast, PM_{10} is not correlated with NO_2 and road proximity in this region, likely a reflection of numerous PM sources not related to roadway. Shelby County emissions inventories indicate that the largest sources of PM in the Memphis region include a coal-fired power plant, multiple metal manufacturing plants, a petrochemical refinery, and food processing plants. Other major contributors of PM pollution are the largest cargo airport in the world and the third-largest US rail center. To our knowledge there have been no comprehensive evaluations of the chemical composition or particle size fractions comprising PM_{10} in the Memphis region.

Mounting evidence suggests biologically plausible mechanisms linking air pollution to child neurodevelopmental outcomes. Air pollution may cause systemic inflammation,[60] which, during pregnancy, may impact fetal brain development via placental transfer.[61] There is also evidence that particulate matter could be transmitted to the fetus via the placenta, resulting in direct effects on neuronal development.[62] A neuroimaging study demonstrated associations between prenatal air pollution exposure and global reductions in white matter surface area in the left hemisphere that were linked to slower information processing speed and behavioral problems.[63] While animal model work shows some evidence of impacts on learning, more consistent evidence is for short term memory.[17] However, despite these suggestive findings, more work is needed to better understand specific mechanisms linking prenatal air pollution exposure and child neurodevelopment.[17]

Our results suggest that prenatal folate may attenuate neurotoxic effects of prenatal air pollution. This finding aligns with current knowledge about the biochemical role of folate in neuronal growth and development as well as proposed mechanisms for neurotoxicity of prenatal air pollution. The importance of folate in healthy neurodevelopment has been well-documented.[64] Folate is a major methyl-donor,[36–37,65] and maternal folate levels have been linked to altered DNA methylation-related programming in the placenta,[66] including in specific genes implicated in neurodevelopment.[67] Various health effects of air pollution, including neurotoxic effects, may be mediated by altered DNA methylation.[38–41] Prenatal exposure has been associated with global placental hypomethylation[40] as well as gene-specific changes in placental DNA methylation,[68–69] including in the leptin (LEP) promotor, which may play an important role in pediatric neurodevelopmental health.[70] In addition, folate has anti-oxidant properties[71] and may counteract oxidative stress caused by prenatal air pollution exposure, promoting resilience. Our evidence adds to two studies reporting stronger associations between prenatal chemical exposure and pediatric neurodevelopment with lower maternal folic acid intake in pregnancy.[72–73] However, these studies estimated folic acid intake based on maternal report of diet and vitamin supplementation, susceptible to recall error and bias. By contrast, we utilized an objective, biologically based measure of maternal folate.

Our study has important strengths. CANDLE is a large, prospective birth cohort study with 92% retention and rich longitudinal data collection on several predictors of pediatric neurodevelopment with low data missingness, increasing opportunities to mitigate confounding and conduct well-powered analyses of effect modification. Observational

studies of ambient air pollution and neurodevelopment are vulnerable to residual confounding by individual and neighborhood level SES. Disparities in exposure by income and race/ethnicity have been well-documented in the US[24–27,74] and in Memphis specifically.[75–76] Missing data in this analysis were rare, and we found that multiple imputation of missing potential confounders did not affect our findings. We estimated spatially-resolved air pollution exposures using well-validated national models[42,43] reducing exposure measurement error, which can bias results towards or away from the null. Another strength is the uniqueness of our population. The few existing studies of this research question in diverse populations with high levels of socioeconomic adversity have much smaller sample sizes.[2,6,31]

At the same time, we cannot rule out the possibility that PM_{10}-IQ associations are biased towards or away from the null by unmeasured confounding (e.g., by exposure to greenspace or noise) or mismeasurement in influential confounders. Also, it is difficult to distinguish any true effects of prenatal versus postnatal exposures. Recent research has suggested that recent, short-term exposure to air pollution affects performance on neurodevelopment assessments.[77] In sensitivity analyses, we additionally controlled for postnatal pollutants; associations between IQ and PM_{10} were not attenuated but did lose precision. The lack of specificity of PM_{10} exposure, as mentioned above, is another limitation of our study, as PM_{10} encompasses a wide variety of particle sizes and chemical composition. We modeled annual $PM_{2.5}$ but did not examine associations with IQ due to very low variability; future work will include spatio-temporal modeling of $PM_{2.5}$, in order to leverage temporal variability and address this limitation of the current analysis. Additional weaknesses related to exposure assessment include measurement error, due to lack of information about participants' time-activity patterns and/or model-associated errors.

Finally, while use of a folate biomarker is a strength of our study, there are uncertainties inherent this measure. We quantified folate in maternal plasma, which is a relatively short-lived biomarker that reflects short-term tissue folate levels.[79] Red blood cell folate is a more stable measure of tissue folate, indicating levels over the past three months, and is therefore less influenced by recent dietary intake. Red blood cell folate was not measured in the CANDLE cohort. However, plasma folate is considered to be an objective marker of folate status [79, 80] and has been utilized as a functional component in long-term metabolic indices. [67] Furthermore, repeated measures of prenatal plasma folate in this cohort show moderately high correlation between second and third trimester measures, indicating that one measure of plasma folate should be a good measure of pregnancy-average levels.[52]

Conclusions

Our study expands upon existing evidence of air pollutant neurodevelopmental toxicity and suggests that prenatal folate may modify these effects. Notably, adverse associations were observed at fairly low concentrations of ambient air pollution: the study region has not exceeded the EPA 24-hour PM_{10} standard in the past 20 years. If causal, our results indicate that current national ambient air quality standards are not adequately protective of pediatric health in this community. Furthermore, the suggestive evidence that prenatal folate modifies neurotoxic effects of air pollution exposure in pregnancy warrant additional investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Glossary

ADHD	Attention Deficit Disorder
ASD	Autism Spectrum Disorder
BSI	Brief Symptom Inventory
CANDLE	Conditions Affecting Neurocognitive Development and Learning in Early Childhood
CI	Confidence Intervals
COI	Childhood Opportunity Index
CSHQ	Children's Sleep Habits Questionnaire
DNA	Deoxyribonucleic Acid
ECHO	Environmental Influences on Child Health Outcomes
EPA	Environmental Protection Agency
FFQ	Food Frequency Questionnaire
FSIQ	Full Scale Intelligence Quotient
HOME	Home Observation Measurement of the Environment
IQ	Intelligence Quotient
IRB	Institutional Review Board
KIDI	Knowledge of Infant Development Inventory
LEP	Leptin
NO2	Nitrogen Dioxide
NVIQ	Nonverbal Intelligence Quotient
PM	Particulate Matter

PM10	Particulate Matter of 10 Microns or Less in Aerodynamic Diameter
PM2.5	Particulate Matter of 2.5 Microns or Less in Aerodynamic Diameter
SB-5	Stanford-Binet Version 5
SD	Standard Deviation
SES	Socioeconomic Status
TN	Tennessee
US	United States
VIQ	Verbal Intelligence Quotient
WASI	Weschler Abbreviated Scale of Intelligence

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HIGHLIGHTS

- Air pollution may impair fetal neurodevelopment; little is known about modifying factors

- In this study, prenatal particulate matter was associated with lower childhood IQ

- Associations were strongest with lower prenatal plasma folate levels

- This is the first evidence that maternal folate may affect susceptibility

Full Scale IQ
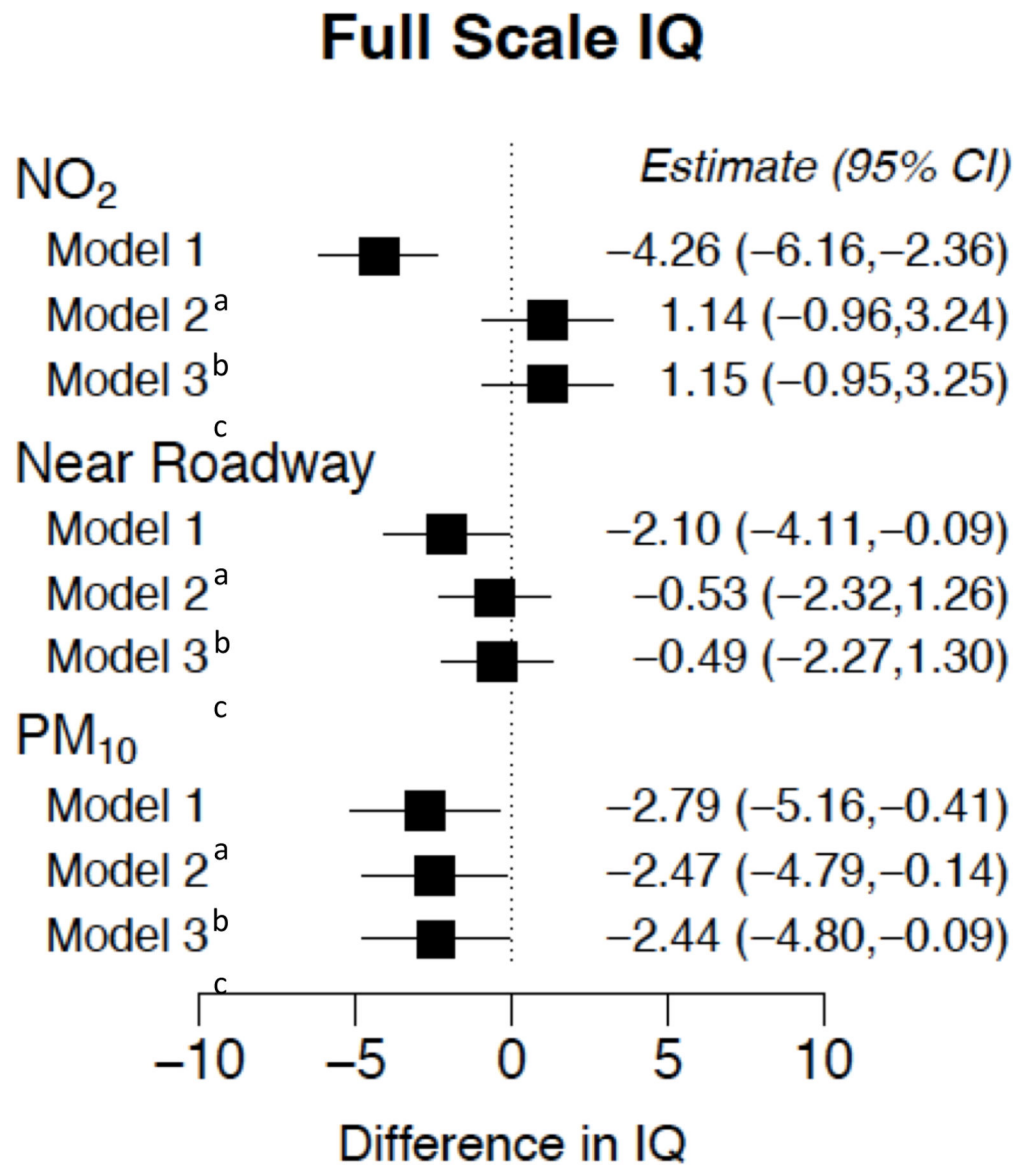
Figure 1. Inclusion Flowchart

Of N=1503 mothers enrolled in CANDLE, up to N=1005 were included in analyses. Outcome (IQ) was not available for children who did a phone visit only or who were uncooperative or otherwise unable to complete the assessment. Geocodes were not available if mothers opted out of sharing of identifiable information.

(a) Model 1 (minimal) adjusted for child age and sex, and date of birth

(b) Model 2 (main) additionally adjusted for maternal education, insurance status, Childhood Opportunity Index subscales, maternal age, race, and IQ, prenatal depression, prenatal smoking, birth order, breastfeeding, and child sleep.

(c) Model 3 (expanded) additionally adjusted for prenatal vitamin use, marital status, paternal education, maternal pre-pregnancy body mass index, and Knowledge of Infant Development survey score.
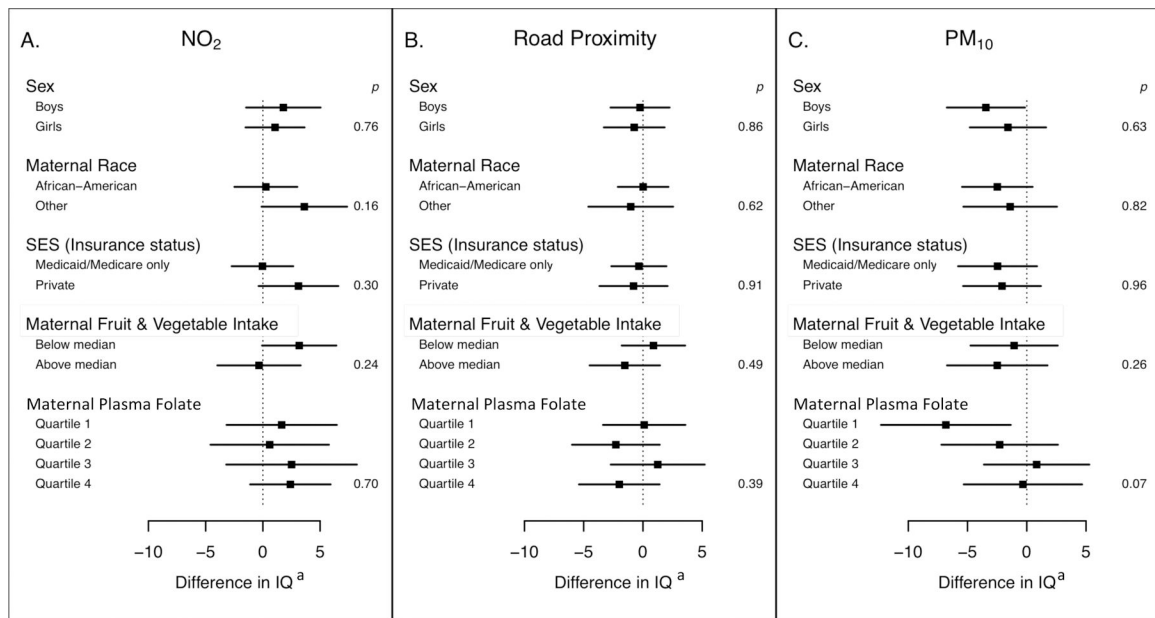
Figure 2. Prenatal Air Pollution and Full-scale IQ at Outcome Assessment

Associations between prenatal air pollution and child full-scale IQ. For NO_2 or PM_{10}, effect estimates are adjusted for covariates (see footnotes) and scaled to a 5 unit increase in pollutant. Near roadway is defined as residence within 150 meters of a busy roadway.

(a) Associations adjusted for child age and sex, date of birth, maternal education, insurance status, Childhood Opportunity Index subscales, maternal age, race, and IQ, prenatal depression, prenatal smoking, birth order, breastfeeding, and child sleep.

Abbreviations: NO_2 = nitrogen dioxide; PM_{10} = particulate matter of 10 microns or less in aerodynamic diameter; CI = confidence interval
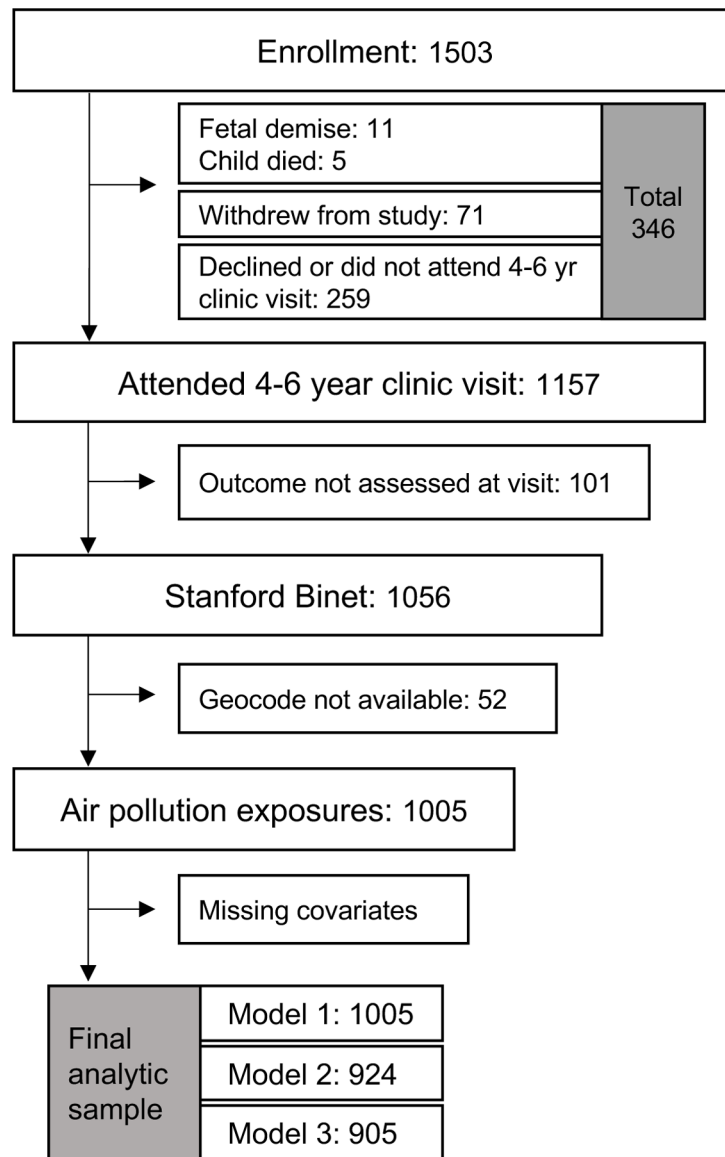
Figure 3. Associations Prenatal Air Pollution and Full-scale IQ by Child and Maternal Characteristics

Strata-specific associations between prenatal air pollution and child full-scale IQ. All associations adjusted for the main model covariates (see footnote). P-values for interaction were estimated using a Wald test with robust standard errors.

Table 1:

Characteristics of Study Population, Overall and with Stratification by Air Pollution Exposure

	Overall	Roadway proximity		NO2 exposure		PM10 exposure	
	N=1,005 Mean(SD) / N(%)	>= 150 m N=726 Mean(SD) / N(%)	< 150 m N=279 Mean(SD) / N(%)	<=12 ppb N=503 Mean(SD) / N(%)	>12 ppb N=502 Mean(SD) / N(%)	<=21 ug/m3 N=507 Mean(SD) / N(%)	>21 ug/m3 N=498 Mean(SD) / N(%)
Child age at assessment (years)[c]	4.4 (0.6)	4.4 (0.6)	4.4 (0.6)	4.3 (0.5)	4.4 (0.6)	4.4 (0.6)	4.4 (0.5)
Child sex							
Male	503 (50.1%)	357 (49.2%)	146 (52.3%)	250 (49.7%)	253 (50.4%)	257 (50.7%)	246 (49.4%)
Female	502 (50.0%)	369 (50.8%)	133 (47.7%)	253 (50.3%)	249 (49.6%)	250 (49.3%)	252 (50.6%)
Maternal age at birth (years)[c]	26.6 (5.5)	26.7 (5.5)	26.3 (5.6)	27.1 (5.6)	26.1 (5.4)	26.5 (5.5)	26.6 (5.6)
Maternal race[c,d]							
African American	648 (64.5%)	448 (61.7%)	200 (71.7%)	283 (56.3%)	365 (72.7%)	310 (61.1%)	338 (67.9%)
White	291 (29%)	227 (31.3%)	64 (22.9%)	188 (37.4%)	103 (20.5%)	158 (31.2%)	133 (26.7%)
Asian	9 (0.9%)	7 (1.0%)	2 (0.7%)	6 (1.2%)	3 (0.6%)	5 (1.0%)	4 (0.8%)
Other	3 (0.3%)	2 (0.3%)	1 (0.4%)	3 (0.6%)	0 (0%)	0 (0%)	3 (0.6%)
Multiple	54 (5.4%)	42 (5.8%)	12 (4.3%)	23 (4.6%)	31 (6.2%)	34 (6.7%)	20 (4.0%)
Maternal education[a,b,c]							
< High school	122 (12.1%)	87 (12.0%)	35 (12.5%)	44 (8.8%)	78 (15.5%)	72 (14.2%)	50 (10.0%)
High school/GED	480 (47.8%)	326 (44.9%)	154 (55.2%)	219 (43.5%)	261 (52%)	233 (46.0%)	247 (49.6%)
Technical school	97 (9.7%)	74 (10.2%)	23 (8.2%)	52 (10.3%)	45 (9%)	44 (8.7%)	53 (10.6%)
College degree	194 (19.3%)	155 (21.4%)	39 (14.0%)	117 (23.3%)	77 (15.3%)	95 (18.7%)	99 (19.9%)
Grad/Prof degree	111 (11.0%)	83 (11.4%)	28 (10.0%)	71 (14.1%)	40 (8%)	63 (12.4%)	48 (9.6%)
Maternal IQ score[c]	94.6 (16.2)	95.1 (16.5)	93.3 (15.5)	97.5 (16.0)	91.7 (15.9)	94.4 (16.9)	94.8 (15.5)
Maternal marital status[a,b,c]							
Never Married	417 (41.5%)	284 (39.1%)	133 (47.7%)	180 (35.8%)	237 (47.2%)	215 (42.4%)	202 (40.6%)
Married	376 (37.4%)	294 (40.5%)	82 (29.4%)	236 (46.9%)	140 (27.9%)	192 (37.9%)	184 (37.0%)
Living with partner	183 (18.2%)	130 (17.9%)	53 (19.0%)	74 (14.7%)	109 (21.7%)	89 (17.6%)	94 (18.9%)
Divorced	18 (1.8%)	11 (1.5%)	7 (2.5%)	8 (1.6%)	10 (2.0%)	7 (1.4%)	11 (2.2%)
Separated	9 (0.9%)	5 (0.7%)	4 (1.4%)	4 (0.8%)	5 (1.0%)	3 (0.6%)	6 (1.2%)

	Overall N=1,005 Mean(SD)/N(%)	Roadway proximity >=150 m N=726 Mean(SD)/N(%)	<150 m N=279 Mean(SD)/N(%)	NO2 exposure <=12 ppb N=503 Mean(SD)/N(%)	>12 ppb N=502 Mean(SD)/N(%)	PM10 exposure <=21 ug/m3 N=507 Mean(SD)/N(%)	>21 ug/m3 N=498 Mean(SD)/N(%)
Widowed	1 (0.1%)	1 (0.1%)	0 (0%)	1 (0.2%)	0 (0%)	1 (0.2%)	0 (0%)
Household income [a] [b,c]							
0–10k	203 (20.2%)	135 (18.6%)	68 (24.4%)	70 (13.9%)	133 (26.5%)	100 (19.7%)	103 (20.7%)
10–20k	139 (13.8%)	98 (13.5%)	41 (14.7%)	50 (9.9%)	89 (17.7%)	76 (15.0%)	63 (12.7%)
20–35k	187 (18.6%)	121 (16.7%)	66 (23.7%)	86 (17.1%)	101 (20.1%)	88 (17.4%)	99 (19.9%)
35–55k	133 (13.2%)	104 (14.3%)	29 (10.4%)	80 (15.9%)	53 (10.6%)	70 (13.8%)	63 (12.7%)
55–75k	110 (11.0%)	87 (12.0%)	23 (8.2%)	80 (15.9%)	30 (6.0%)	52 (10.3%)	58 (11.7%)
75k+	154 (15.3%)	128 (17.6%)	26 (9.3%)	107 (21.3%)	47 (9.4%)	74 (14.6%)	80 (16.1%)
missing	79 (7.9%)	53 (7.3%)	26 (9.3%)	30 (6%)	49 (9.8%)	47 (9.3%)	32 (6.4%)
Health insurance status [a,c]							
Medicaid or Medicare only	572 (56.9%)	396 (54.6%)	176 (63.1%)	238 (47.3%)	334 (66.5%)	298 (58.8%)	274 (55.0%)
Private insurance only	395 (39.3%)	300 (41.3%)	95 (34.1%)	248 (49.3%)	147 (29.3%)	188 (37.1%)	207 (41.6%)
Medicaid/Medicare and private insurance	36 (3.6%)	29 (4.0%)	7 (2.5%)	16 (3.2%)	20 (4.0%)	20 (3.9%)	16 (3.2%)
No insurance	2 (0.2%)	1 (0.1%)	1 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Prenatal smoking							
No	913 (90.9%)	667 (91.9%)	246 (88.2%)	465 (92.5%)	448 (89.2%)	455 (89.7%)	458 (92.0%)
Yes	91 (9.1%)	59 (8.1%)	32 (11.5%)	38 (7.6%)	53 (10.6%)	52 (10.3%)	39 (7.8%)
Prenatal depression (BSI Sub-scale T-score)	48.4 (7.9)	48.1 (7.7)	49.0 (8.4)	48.0 (7.8)	48.7 (8.0)	48.2 (7.7)	48.5 (8.1)
Maternal BMI category							
Underweight	44 (4.4%)	34 (4.7%)	10 (3.6%)	22 (4.4%)	22 (4.4%)	27 (5.3%)	17 (3.4%)
Normal	389 (38.7%)	283 (39.0%)	106 (38.0%)	196 (39.0%)	193 (38.5%)	206 (40.6%)	183 (36.8%)
Overweight	237 (23.6%)	174 (24.0%)	63 (22.6%)	126 (25.1%)	111 (22.1%)	116 (22.9%)	121 (24.3%)
Obese	332 (33%)	234 (32.2%)	98 (35.1%)	159 (31.6%)	173 (34.5%)	156 (30.8%)	176 (35.3%)
Child birth order							
First-born	608 (60.5%)	431 (59.4%)	177 (63.4%)	292 (58.1%)	316 (63%)	312 (61.5%)	296 (59.4%)
Not first-born	397 (39.5%)	295 (40.6%)	102 (36.6%)	211 (42.0%)	186 (37.1%)	195 (38.5%)	202 (40.6%)
Breastfeeding [c]							
Never	359 (35.7%)	252 (34.7%)	107 (38.4%)	152 (30.2%)	207 (41.2%)	172 (33.9%)	187 (37.6%)

	Overall	Roadway proximity		NO2 exposure		PM10 exposure	
	N=1,005 Mean(SD) / N(%)	>= 150 m N=726 Mean(SD) / N(%)	< 150 m N=279 Mean(SD) / N(%)	<=12 ppb N=503 Mean(SD) / N(%)	>12 ppb N=502 Mean(SD) / N(%)	<=21 ug/m3 N=507 Mean(SD) / N(%)	>21 ug/m3 N=498 Mean(SD) / N(%)
< 6 months	299 (29.8%)	226 (31.1%)	73 (26.2%)	159 (31.6%)	140 (27.9%)	154 (30.4%)	145 (29.1%)
>= 6 months	339 (33.7%)	242 (33.3%)	97 (34.8%)	186 (37.0%)	153 (30.5%)	175 (34.5%)	164 (32.9%)
Maternal plasma folate [c,d]							
Q1 (3.7 to 14.62 nmol/L)	250 (24.9%)	175 (24.1%)	75 (26.9%)	102 (20.3%)	148 (29.5%)	124 (24.5%)	126 (25.3%)
Q2 (14.63 to 21.74 nmol/L)	250 (24.9%)	181 (24.9%)	69 (24.7%)	127 (25.3%)	123 (24.5%)	109 (21.5%)	141 (28.3%)
Q3 (21.8 to 29.33 nmol/L)	250 (24.9%)	176 (24.2%)	74 (26.5%)	129 (25.7%)	121 (24.1%)	132 (26%)	118 (23.7%)
Q4 (29.4 to 109.14 nmol/L)	250 (24.9%)	191 (26.3%)	59 (21.2%)	143 (28.4%)	107 (21.3%)	139 (27.4%)	111 (22.3%)
missing	5 (0.5%)	3 (0.4%)	2 (0.7%)	2 (0.4%)	3 (0.6%)	3 (0.6%)	2 (0.4%)
Childhood opportunity index: educational index [b,c,d]	0.003 (0.6)	0.03 (0.6)	−0.1 (0.5)	0.2 (0.6)	−0.2 (0.4)	−0.05 (0.5)	0.1 (0.6)
Childhood opportunity index: economic index [c]	−0.1 (0.6)	−0.1 (0.6)	−0.1 (0.6)	0.02 (0.6)	−0.2 (0.7)	−0.1 (0.7)	−0.1 (0.6)
Child sleep score at assessment	44.1 (7.0)	44.1 (7.0)	44.0 (6.8)	43.9 (7.1)	44.3 (6.8)	(7.1)	44.1 (6.8)

[a] Reported at enrollment

[b] Difference in characteristic by road proximity is statistically significant (p<0.05)

[c] Difference in characteristic by low versus high NO2 exposure is statistically significant (p<0.05)

[d] Difference in characteristic by low versus high PM10 exposure is statistically significant (p<0.05)

ABBREVIATIONS: ppb = parts per billion; m = meters; ug/m3 = micrograms per cubic meters; SD = standard deviation; BSI = brief symptom inventory; kg = kilograms; nmol/L = nanomoles per liter

Table 2:

Stanford Binet-5 IQ Results at 4–6 Year Assessment

Measure	N	Mean	SD	Min	Max
Full-scale IQ	1,005	99.67	14.93	40	138
Verbal IQ[a]	1,004	98.86	15.16	47	140
Nonverbal IQ	1,005	100.89	14.74	42	139
Fluid reasoning	1,005	101.63	15.36	53	147
Knowledge	1,004	98.78	11.78	49	134
Quantitative reasoning	1,004	102.87	16.98	50	138
Working memory	1,004	98.91	15.28	48	141
Visual-spatial	1,004	97.57	16.30	48	149

[a] One participant had insufficient data to permit calculation of Verbal IQ and four of the five subscales. Exclusion of this participant in sensitivity analyses resulted in no meaningful changes to findings.

Table 3:

Summary of air pollution exposure in study population

Air pollution metric	N	Mean	SD	Median	Min	Max	IQR
NO2, 2006 annual average (ppb)	1,005	12.06	2.34	11.96	5.71	16.81	3.81
PM10, 2006 annual average (ug/m3)	1,005	20.88	2.01	20.79	16.14	27.83	2.76
Distance to A1 roadway (m)	1,005	2552.19	1860.41	2096	45	11399	2362
Distance to A2 roadway (m)	1,005	1998.92	1648.23	1518	9	8658	2425
Distance to A3 roadway (m)	1,005	450.70	534.51	304	9	6219	398