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Journal
Environmental Health Perspectives, 130(6)

ISSN
1542-4359

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Publication Date
2022-06-01

DOI
10.1289/ehp10248

Peer reviewed

A Section 508–conformant HTML version of this article
is available at https://doi.org/10.1289/EHP10248.

Associations of Pre- and Postnatal Air Pollution Exposures with Child Behavioral Problems and Cognitive Performance: A U.S. Multi-Cohort Study

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BACKGROUND: Population studies support the adverse associations of air pollution exposures with child behavioral functioning and cognitive performance, but few studies have used spatiotemporally resolved pollutant assessments.

OBJECTIVES: We investigated these associations using more refined exposure assessments in 1,967 mother–child dyads from three U.S. pregnancy cohorts in six cities in the ECHO-PATHWAYS Consortium.

METHODS: Pre- and postnatal nitrogen dioxide (NO_2) and particulate matter (PM) ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) exposures were derived from an advanced spatiotemporal model. Child behavior was reported as Total Problems raw score using the Child Behavior Checklist at age 4–6 y. Child cognition was assessed using cohort-specific cognitive performance scales and quantified as the Full-Scale Intelligence Quotient (IQ). We fitted multivariate linear regression models that were adjusted for sociodemographic, behavioral, and psychological factors to estimate associations per 2-unit increase in pollutant in each exposure window and examined modification by child sex. Identified critical windows were further verified by distributed lag models (DLMs).

RESULTS: Mean NO_2 and $PM_{2.5}$ ranged from 8.4 to 9.0 ppb and 8.4 to 9.1 $\mu g/m^3$, respectively, across pre- and postnatal windows. Average child Total Problems score and IQ were 22.7 [standard deviation (SD): 18.5] and 102.6 (SD: 15.3), respectively. Children with higher prenatal NO_2 exposures were likely to have more behavioral problems [β: 1.24; 95% confidence interval (CI): 0.39, 2.08; per 2 ppb NO_2], particularly NO_2 in the first and second trimester. Each 2-$\mu g/m^3$ increase in $PM_{2.5}$ at age 2–4 y was associated with a 3.59 unit (95% CI: 0.35, 6.84) higher Total Problems score and a 2.63 point (95% CI: −5.08, −0.17) lower IQ. The associations between $PM_{2.5}$ and Total Problems score were generally stronger in girls. Most predefined windows identified were not confirmed by DLMs.

DISCUSSION: Our study extends earlier findings that have raised concerns about impaired behavioral functioning and cognitive performance in children exposed to NO_2 and $PM_{2.5}$ *in utero* and in early life. https://doi.org/10.1289/EHP10248

Introduction

Early brain morphology in humans begins in the third week post conception and rapidly develops by midgestation.[1–3] Ongoing structural change and functional development continue for an extended period postnatally until early adulthood.[1,4,5] Subtle disturbances in early life may interfere with the normal trajectory of brain development and cause subsequent functional impairment.[2] Children with behavioral and cognitive impairment early in life may have persistent problems, including increased risk of substance abuse, violent behavior, and depression in adolescence and/or adulthood,[6] as well as diminished academic performance and economic productivity over their life span.[7,8] Therefore, identifying modifiable factors on which to intervene is a research priority. In recent decades, growing evidence has demonstrated the human neurodevelopmental toxicity of common air pollutants, including nitrogen oxides (NO_2), particulate matter (PM) ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$), and polycyclic aromatic hydrocarbons (PAHs), on the central nervous system (CNS) with subsequent behavioral and cognitive impacts.[9–11]

Air pollutants can invade deep in the lungs, trigger oxidative stress, and induce systemic inflammation in pregnant women.[12–14] Circulating markers pass the maternal–fetal blood barrier and promote chronic inflammation and neurodegeneration in the fetus,[15–17] with evidence of longer-term impact on offspring neurodevelopmental outcomes.[18–20] Postnatal air pollution exposures may affect children's CNS more directly. Besides penetrating into the lungs, inhaled pollutants may also translocate along the olfactory nerve into the olfactory bulb, promote diffusion of oxidative stress and inflammatory markers across the impaired blood brain barrier, and induce microglial activation on entering the CNS.[21–24] Previous population studies in the United States,[25–28] Europe,[29–31] and Asia[32–34] have consistently linked air pollution exposures in both pre- and postnatal windows to poorer neurodevelopmental outcomes during early to late childhood. Nevertheless, exposure data at a small scale are scarce and available in only a few studies,[28,32,35–38] four of which estimated trimester specific associations.[28,32,36,37] In these previous studies, various pollutants (mainly NO_2 and PM)

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Supplemental Material is available online (https://doi.org/10.1289/EHP10248).

A.A.S. has been a consultant for the Health Effects Institute on the traffic-related air pollution panel. E.B. was a consultant for the California Environmental Protection Agency in 2020. Their freedom to design, conduct, interpret and publish research is not compromised by the institutes. The other authors declare they have no actual or potential competing financial interests.

Received 2 September 2021; Revised 26 May 2022; Accepted 6 June 2022; Published 23 June 2022.

were estimated from a number of exposure assessment methods, including conventional geographic information system-based methods (e.g., land use regression), direct measurements from residential ambient monitors, and biomarkers of exposure.[10] The use of spatiotemporally resolved air pollution assessment across different developmental windows in a multiregion sample is limited. Other methodological limitations in prior studies include inadequate assessment of confounding, failure to consider outcomes across neurodevelopmental domains, and inability to disentangle the associations from distinct exposure windows due to limited statistical power and/or air pollution predictions with a low temporal resolution.

In this study, we further the current body of literature and our own recent analyses[27,39] of NO_2 and PM_{10} with child behavioral problems and intelligence quotient (IQ). Specifically, here we expand the study population to include three pregnancy cohorts in the United States, use spatiotemporally resolved predictions of NO_2 and $PM_{2.5}$, and evaluate several sensitive developmental periods in both pre- and postnatal windows. We hypothesized that children with higher pre- and/or postnatal exposures to NO_2 and $PM_{2.5}$ would have more behavioral problems and a lower IQ. In addition, research has identified several sex differences in neurodevelopment, including morphological, physiological, and chemical differences.[40] Several lines of evidence suggest that the air pollution–child neurodevelopment association may be sex-specific, possibly with a more pronounced relationship in boys.[25,30,35,41–43] However, heterogeneities in study design of previous studies, including varied exposure and outcome assessments, have hampered the ability to draw firm conclusions regarding differential vulnerability by sex. Hence, we also examined whether the associations of interest differed by child sex in the current study.

Methods

Study Population

As part of the Environmental Influences on Child Health Outcomes (ECHO) study, we aimed to maximize power in the current analysis to estimate effects from air pollution exposures on child behavioral and cognitive outcomes and explore nuanced research questions of effect modification by child sex by pooling all three U.S. pregnancy cohorts that compose the ECHO-PATHWAYS Consortium: the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study, the Infant Development and Environment Study (TIDES), and the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS). Based in Shelby County, Tennessee, the CANDLE study initially aimed to identify risk factors for child neurodevelopment.[44] Women were considered eligible if they were 16–40 y old, had medically low-risk singleton pregnancies, and planned to deliver at a participating study hospital. From 2006 to 2011, 1,503 women were recruited in their second trimester from either the general community or affiliated medical group clinics. More than three quarters of the enrolled participants ($n = 1,143$) completed a clinic visit when the resulting children were age 4–6 y. The TIDES study was designed to examine the impacts of exposure to endocrine disrupting chemicals, notably phthalates, on child health and development.[45] From 2010 to 2012, recruitment commenced in academic medical centers in four cities: San Francisco, California; Rochester, New York; Minneapolis, Minnesota; and Seattle, Washington. Pregnant women in their first trimester were considered eligible if they were age 18 y or older, were English-speaking, had singleton pregnancies without any serious threat, and planned to deliver at a participating study hospital. There were 749 women who were retained in the study throughout the pregnancy and delivered a live birth, and 551 mother–child dyads completed the 6-y visit. Last, the GAPPS study was established to inform evidence-based treatments and interventions to reduce preterm birth and stillbirth through development of a biorepository (www.gapps.org). Families who had participated in the GAPPS study and met eligibility criteria (consented to contact for future study; had prenatal questionnaire data and biospecimens available; child age was eligible for the 4–6-y visit) were invited to participate in the ECHO-PATHWAYS Consortium. From July 2017 to April 2020, 439 mother–child dyads from Seattle and Yakima, Washington, were enrolled and completed the follow-up visit at child age 4–6 y.

The current study included 1,967 CANDLE, TIDES, and GAPPS children who completed behavioral and cognitive assessments at clinical visits at 4–6 y of age and had valid residential addresses in the pre- and/or postnatal windows reported by parents. Each woman provided informed consent upon enrollment in original cohorts. This analysis uses previously collected data from the three cohorts and was approved by the Human Subjects Division at the University of Washington.

Child Cognitive and Behavioral Measurements

Child behaviors were assessed using the Child Behavior Checklist (CBCL), administered at a visit that occurred at age 4–6 y. The CBCL involves caregiver reporting of a wide range of emotional and behavior problems in children and is broadly used in both research and clinical settings.[46,47] One of two CBCL versions were administered, depending on the child's age: the CBCL preschool form (ages 1.5–5 y)[48] or the CBCL school-age form (ages 6–18 y).[49] All CANDLE participants completed the preschool form, all TIDES participants completed the school-age forms, and GAPPS families completed a mix of both forms. The preschool form includes report of the frequency of 99 child behaviors in the past 2 months, whereas the school-age form includes 112 behaviors in the past 6 months. Caregivers rate these items on a scale of *Not True (0)*, *Somewhat or Sometimes True (1)*, to *Very True or Often True (2)*. Although additional behaviors appropriate for children up to age 18 y are added in the school-age form, given that the children in our study were essentially in the same developmental stage, caregivers reported similar types and counts of behaviors across forms. Therefore, we combined the data collected by two CBCL forms. Because the standardized t-scores estimated from these two CBCL forms differ in whether child sex was adjusted,[50] we computed the raw score for the Total Problems scale as the primary outcome and further calculated the standardized z-score using all ECHO-PATHWAYS participants with behavioral problems measured by either CBCL form as the reference to verify our findings.

Child cognitive performance was examined at the same visit as the behavior measurement. The IQs of the CANDLE, TIDES, and GAPPS children were assessed using the Stanford-Binet Intelligence Scales, Fifth Edition (SB-5),[51,52] the abbreviated five-subtest version of the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V),[53,54] and the Wechsler Preschool & Primary Scale of Intelligence, Fourth Edition (WPPSI-IV, age 4:0–7:7 version),[55,56] respectively. The three IQ batteries are examiner-administered, highly reliable, and valid measures of intellectual and cognitive abilities in childhood. All examiners were trained on the administration and scoring by licensed psychologists. They participated in didactic instruction and guided practice, interrater reliability exercises, as well as weekly supervision by psychologists post training. Considering that Full-Scale IQ is less frequently included in large population studies due to its heavy burden on examiners and participants, we aimed to maximize use of these data as others have before us.[57–59] In CANDLE, full-scale IQ was derived from the 10 subtests in the SB-5 addressing five cognitive factors with verbal and nonverbal tests for each factor: knowledge, fluid reasoning, quantitative reasoning, visual-spatial processing, and working memory. In TIDES, Full-Scale IQ was estimated using the Tellegen and Briggs formula,[60] incorporating five WISC-V domains—verbal comprehension, visual spatial, fluid reasoning, working memory, and processing speed. The calculation of Full-Scale IQ from the WPPSI-IV in GAPPS included scores in the five cognitive domains, similar to the five WISC-V domains in TIDES. Although the specific tests used to capture different domains of cognitive performance may vary across the IQ instruments, full-scale IQ provides a standardized metric of overall performance across all the subtests, with a high correlation across instruments.[61]

Air Pollution Assessments

Detailed residential addresses were collected from CANDLE participants at enrollment and updated at each subsequent point of contact. The availability of address data varied by site in the TIDES study: all participants reported residential addresses at enrollment, at the age 4 y visit, and at the age 6 y visit; participants in Rochester and San Francisco were contacted for one more update between enrollment and the age 4 y visit. GAPPS participants were asked to provide comprehensive address histories at the age 4–6 y visit retrospectively from enrollment to present. Point-based NO_2 and $PM_{2.5}$ exposures were estimated from a spatiotemporal model on a 2-wk scale.[62] This model used monitoring data from regulatory networks, further enhanced with air pollution measurements from intensive research cohort-specific monitors. A geographic information system was used to identify covariates representing land use characteristics that could reflect spatial variability in air pollution distributions, and the dimension-reduced regression covariates were obtained using partial least squares from more than 400 geographic variables. The space–time features of pollution concentrations were decomposed into spatially varying long-term averages, spatially varying seasonal and long-term trends, and spatially correlated but temporally independent residuals, and these components were fitted jointly in a likelihood-based spatiotemporal extension of universal kriging. We estimated biweekly NO_2 and $PM_{2.5}$ predictions from region-specific models (three regions for the NO_2 models and nine regions for the $PM_{2.5}$ models), and averaged the exposure concentrations over each trimester, the whole pregnancy, and the two postnatal windows from childbirth to 2 y old and from 2 to 4 y old. The 2–4-y $PM_{2.5}$ estimates were missing in 150 participants whose 4-y-old birthday was beyond the prediction window of the spatiotemporal model (30 December 1998 to 4 July 2017). Moving was accounted for by calculating the time-weighted averages of NO_2 and $PM_{2.5}$ in the relevant windows based on the reported move date. For families who moved between two points of contact and did not report a move date, we estimated the move date as the midpoint of the two contact dates. We refer readers to a recent paper by Kirwa et al. (2021)[63] for a thorough discussion of different air pollution prediction models.

Covariates

Several indicators for maternal, child, and family characteristics, including multilevel social determinants, were harmonized across cohorts. Maternal characteristics included age at enrollment; region- and inflation-adjusted household annual income[64]; household members (2–3 vs. 4 vs. 5 vs. ≥ 6); education level (<high school vs. high school/Graduate Equivalency Diploma vs. college/technical school vs. graduate or professional degree); marital status (married/living as married vs. single/living as single); pregnancy smoking (smoker vs. nonsmoker); pregnancy alcohol consumption (ever vs. never); pregnancy vitamin supplement intake (ever vs. never); prepregnancy body mass index (BMI); IQ measured by Wechsler Abbreviated Scale of Intelligence [the composite score of four subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning) from the first edition[65] in CANDLE, the composite score of two subtests (Vocabulary and Matrix Reasoning) from the second edition[66,67] in TIDES and GAPPS]; depression, assessed at the visit when child outcome assessments were taken, by either the Center for Epidemiologic Studies Depression Scale (CES-D)[68] or the Patient-Reported Outcomes Measurement Information System (PROMIS)[69] and quantified as *t*-scores; and breastfeeding practice (ever vs. never). Child characteristics included age at cognitive and behavioral assessments; sex (male vs. female); birth order (first born vs. not first born); birth year; and secondhand smoking exposure (anyone living in the child's home smoked vs. no one smoked). The indices in two of the three domains of the Childhood Opportunity Index (COI) were calculated based on the residential address history in pre- and postnatal windows: A larger index in the social and economic subscale reflected higher neighborhood-level socioeconomic status (SES), and a larger index in the educational subscale indicated better early childhood education quality.[70] We also included parent-reported child race (White vs. Black, vs. others) as a confounder, given that race is not only a proxy for racial residential segregation, which directly associates with air pollution exposures, but also a strong predictor of socioeconomic position that results in health disparities.[71] American Indian/Alaska Native, Asian, and Native Hawaiian/other Pacific Islanders were grouped together to improve statistical power and enhance the data harmonizability across cohorts.

Statistical Analyses

We conducted descriptive analyses in the entire sample and by cohort to summarize the characteristics of the participants, the air pollution exposures, and the child cognitive and behavioral assessments. Linear regressions with robust standard errors were performed to estimate the associations of individual exposures ($PM_{2.5}$ or NO_2) in each window with child Total Problems score and IQ based on observations with complete data pooled from three cohorts. To enable comparisons with studies with relatively low air pollution levels and variabilities, effect estimates were rescaled to a 2-unit incremental increase, which approximates the interquartile ranges (IQRs) for long-term exposures in the six study sites. Based on substantive knowledge from existing literature, we developed a staged adjustment approach comprising three models, allowing us to explore the influence of increasing levels of adjustment on results. We further created a directed acyclic graph (DAG; Figure S1) to help visualize the relationships. Model 1 (the minimal model) controlled for basic demographics—child sex, child age at outcome assessments, and study site. An indicator of CBCL form was additionally included in the analysis of Total Problems score. We defined Model 2 as the primary model, which was further adjusted for major confounders or precision variables, including child race, maternal education, log-transformed region- and inflation-adjusted household income, household members, an interaction between household members and income to account for nonproportional financial needs of a household grow with additional members,[72] marital status, maternal age at enrollment, birth order, pregnancy smoking, pregnancy alcohol consumption, maternal depression, maternal IQ, child secondhand smoking exposure, and COI subscales (economics and education). Adjustment for covariates that are only associated with the outcomes (i.e., precision variables) in a linear setting is desirable, because it will improve the precision of the effect estimates by reducing residual variance.[73] Model 3, an extended model, included additional adjustments for four covariates that may be proxies for unmeasured confounders[74]: Prepregnancy BMI, prenatal vitamin supplement intake, and breastfeeding may serve as proxies for maternal preventative behaviors, and child year of birth may act as a surrogate for birth cohort effects.

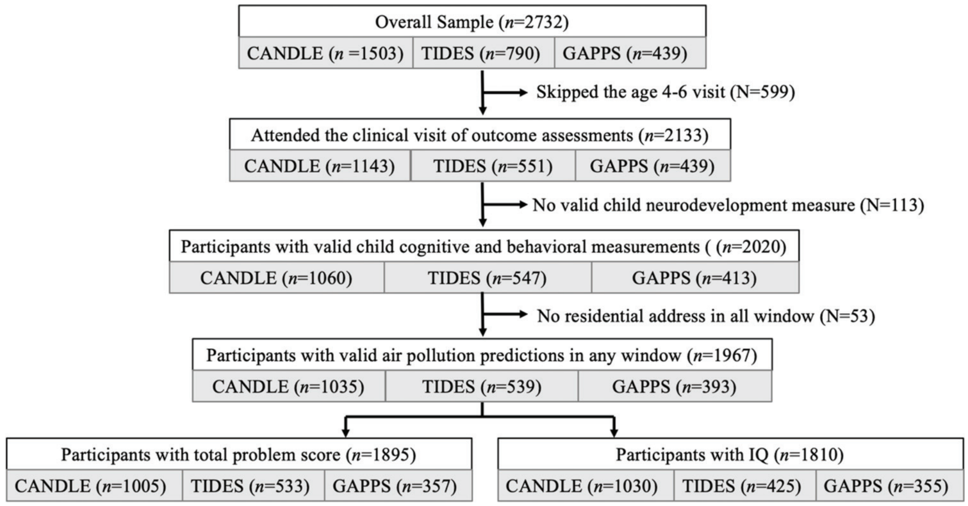

Figure 1. Shown are the inclusion of the three U.S. pregnancy cohorts in the ECHO-PATHWAYS Consortium (the CANDLE, TIDES, and GAPPS study) from enrollment to the visit of child cognitive and behavioral assessments, as well as the analytic sample sizes remaining from the implementation of each exclusion criterion. Note: CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; ECHO, Environmental Influences on Child Health Outcomes; GAPPS, Global Alliance to Prevent Prematurity and Stillbirth; IQ, intelligence quotient; TIDES, The Infant Development and Environment Study.

In a secondary analysis, we introduced cross product terms of child sex and individual air pollution exposures in each window in separate primary models (i.e., Model 2) and estimated the interaction *p*-values as well as sex-specific associations. Several sensitivity analyses were performed to verify the robustness of our main findings. First, we implemented complete case analysis as the primary approach. Although the data for most covariates were nearly complete in the analytic data set, 16.2% of the women did not have IQ measurement, and more than half of the missingness in this covariate came from the GAPPS study. To address the issue of missing data in maternal IQ and other covariates, we began by verifying the assumption that the chance of being a complete case solely depends on the observed covariates, where data were missing at random (MAR).[75] We constructed the Receiver Operating Characteristic (ROC) curve by computing the metrics of sensitivity and specificity at various threshold settings via 5-fold cross-validation[76] and further estimated the area under the ROC curve—a measure indicating the probability of models with the observed covariates to correctly distinguish complete cases from noncomplete cases.[77] The area under the ROC curve indicated that this MAR assumption was plausible, and both complete case analysis and multiple imputation would give unbiased results. We thus employed multiple imputation by chained equations (MICE) in the minimal, primary, and extended models.[75,78] Each missing value was imputed 10 times with 100 iterations between each round of imputation using predictive mean matching.[79]

Second, to investigate the validity of combining data of behavioral outcomes measured by different CBCL forms, we replaced the raw Total Problems score with the standardized *z*-score. Third, considering that children born earlier than 34 wk are at higher risks of substantially lower IQ, attention, and executive function in comparison with those with a gestational week 37 and above,[80] we restricted the sample to those born at gestational week 34 or later. Fourth, to investigate whether the associations of interest were confounded by the exposures in the other windows, we simultaneously included NO_2 or $PM_{2.5}$ estimates in all three trimesters in the primary models and further controlled for postnatal exposures. In addition, we mutually adjusted for exposures over the whole pregnancy and postnatal pollution estimates. Fifth, to further confirm the identified critical exposure windows, we fit fully adjusted constrained distributed lag models (DLM) of biweekly air pollution predictions with varied degrees of freedom (df) from 4 to 9. The prenatal windows were restricted to 38 wk, and those born prior to gestational week 36 were imputed with the measurements in the latest available biweekly window. The prenatal and postnatal biweekly exposures were modeled separately with adjustments for average exposures in the other period(s), considering the different biological mechanisms linking child neurodevelopment with air pollution exposures *in utero* and after birth. Sixth, to assess the linearity of the relationships between air pollution exposures and outcomes, we conducted generalized additive models with full adjustments in the overall sample, as well as in strata by child sex. Finally, to better understand the impacts of inherent heterogeneity across the cohorts and sites and potential modified confounding by site on the findings, we implemented three additional analyses: a leave-one-cohort-out analysis, a leave-one-site-out analysis, and a set of three models compared to the results of fixed effects models (i.e., the primary analysis), including fixed effects models with site–covariate interactions, mixed-effects models with a fixed intercept and random slopes by site, and mixed-effects models with site–covariate interactions. All analyses were conducted in R (version 3.6.5; R Development Core Team).

Results

Characteristics of the Study Participants

The inclusion of participants from enrollment to outcome assessment as well as the analytic sample sizes are illustrated in Figure 1. Among the total analytic sample of 1,967 mother–child dyads, the CANDLE, TIDES, and GAPPS studies contributed 53%, 27%, and 20% of the population, respectively (Table 1). Children were on average 5.2 y of age (SD: 1.0) at outcome measurements, and there was an approximately equal number of boys and girls. Nearly half (48%) were identified as White by their parents and 39% as Black. One-fifth of the children were living with at least one relative who smoked. Mothers had an average age of 28.5 y (SD: 6.0) at enrollment, 56% had a college degree and above, and 70% were married or living as married. The median region- and inflation-adjusted household income was $55,800 USD (IQR: 62,500). Maternal IQ was normally distributed, with a mean of 100 (SD: 17.4). The average *t*-score of CES-D or PROMIS was 48.5 (SD: 7.4), indicating a typical level of maternal depression on average. Compared across

Table 1. Characteristics of participants from the three U.S. pregnancy cohorts in the ECHO-PATHWAYS consortium (the CANDLE, TIDES, and GAPPS study) included in analysis.

	Total	Cohort		
		CANDLE	TIDES	GAPPS
	($n=1{,}967$)	($n=1{,}035$)	($n=539$)	($n=393$)
Child characteristics				
Child age at outcome assessment (y)	5.2 (±1.0)	4.4 (±0.6)	6.4 (±0.4)	5.6 (±0.7)
Missing	47	2	3	42
Child sex				
Male	963 (49%)	517 (50%)	251 (47%)	195 (50%)
Female	1,003 (51%)	518 (50%)	287 (53%)	198 (50%)
Missing	1	0	1	0
Child race				
White	917 (48%)	264 (26%)	354 (68%)	299 (78%)
Black	752 (39%)	679 (67%)	64 (12%)	9 (2%)
Others	246 (13%)	68 (7%)	101 (19%)	77 (20%)
Missing	52	24	20	8
Birth order				
Not firstborn	1,134 (58%)	629 (61%)	244 (46%)	261 (67%)
Firstborn	819 (42%)	406 (39%)	282 (54%)	131 (33%)
Missing	14	0	13	1
Year of birth				
2007	85 (4%)	85 (8%)	0 (0%)	0 (0%)
2008	201 (10%)	201 (19%)	0 (0%)	0 (0%)
2009	246 (13%)	246 (24%)	0 (0%)	0 (0%)
2010	283 (14%)	283 (27%)	0 (0%)	0 (0%)
2011	468 (24%)	220 (21%)	197 (37%)	51 (13%)
2012	417 (21%)	0 (0%)	304 (56%)	113 (29%)
2013	175 (9%)	0 (0%)	38 (7%)	137 (35%)
2014	86 (4%)	0 (0%)	0 (0%)	86 (22%)
2015	6 (0%)	0 (0%)	0 (0%)	6 (2%)
Secondhand smoking exposure				
No	1,523 (80%)	704 (68%)	465 (96%)	354 (91%)
Yes	378 (20%)	324 (32%)	19 (4%)	35 (9%)
Missing	66	7	55	4
Maternal characteristics				
Maternal age at enrollment (y)	28.5 (±6.0)	26.3 (±5.6)	31.0 (±5.5)	31.0 (±5.5)
Missing	12	0	0	12
Region-, inflation-adjusted household income ($1,000)	55.8 [62.5]	31.8 [50.9]	101.7 [107.7]	86.0 [67.1]
Missing	77	46	24	7
Household members				
2–3	410 (21%)	220 (21%)	124 (24%)	66 (17%)
4	767 (40%)	361 (35%)	247 (48%)	159 (42%)
5	435 (23%)	248 (24%)	95 (19%)	92 (24%)
≥ 6	311 (16%)	200 (19%)	47 (9%)	64 (17%)
Missing	44	6	26	12
Maternal education				
Less than high school	167 (9%)	123 (12%)	32 (6%)	12 (3%)
High school/GED	683 (35%)	495 (48%)	88 (16%)	100 (26%)
College/technical school	644 (33%)	304 (29%)	169 (32%)	171 (45%)
Graduate or Professional degree	458 (23%)	112 (11%)	246 (46%)	100 (26%)
Missing	15	1	4	10
Marital status				
Married/living as married	1,365 (70%)	572 (55%)	456 (85%)	337 (88%)
Single/living as single	589 (30%)	462 (45%)	82 (15%)	45 (12%)
Missing	13	1	1	11
Pregnancy smoking				
Nonsmoker	1,828 (94%)	942 (91%)	514 (96%)	372 (97%)
Smoker	122 (6%)	92 (9%)	19 (4%)	11 (3%)
Missing	17	1	6	10
Pregnancy alcohol consumption				
No alcohol consumption	1,760 (90%)	947 (92%)	472 (88%)	341 (90%)
Alcohol consumption	188 (10%)	87 (8%)	65 (12%)	36 (10%)
Missing	19	1	2	16
Pregnancy supplement intake				
Never	260 (13%)	57 (6%)	181 (34%)	22 (6%)
Ever	1,675 (87%)	958 (94%)	356 (66%)	361 (94%)
Missing	32	20	2	10
Breastfeeding practice				
Never	443 (23%)	375 (36%)	46 (9%)	22 (6%)
Ever	1,512 (77%)	658 (64%)	485 (91%)	369 (94%)
Missing	12	2	8	2

Table 1. (*Continued.*)

	Total	Cohort		
		CANDLE	TIDES	GAPPS
	($n = 1{,}967$)	($n = 1{,}035$)	($n = 539$)	($n = 393$)
Prepregnancy BMI (kg/m^2)	27.1 (±7.43)	28.0 (±7.88)	25.5 (±6.23)	27.0 (±7.36)
Missing	45	3	14	28
Maternal IQ[a]	100 (±17.4)	94.6 (±16.3)	109 (±16.3)	108 (±13.3)
Missing	328	12	111	205
Maternal depression[b]	48.5 (±7.4)	48.6 (±6.9)	48.3 (±8.2)	48.9 (±7.8)
Missing	28	9	14	5
Child Opportunity Educational Index (Prenatal)	−0.022 (±0.073)	−0.049 (±0.064)	0.019 (±0.072)	−0.006 (±0.067)
Missing	28	5	6	17
Child Opportunity Educational Index (0–2 y)	−0.022 (±0.073)	−0.049 (±0.063)	0.020 (±0.073)	−0.007 (±0.066)
Missing	8	0	4	4
Child Opportunity Educational Index (2–4 y)	−0.019 (±0.074)	−0.048 (±0.065)	0.026 (±0.070)	−0.0028 (±0.064)
Missing	16	2	9	5
Child Opportunity Economics Index (Prenatal)	−0.045 (±0.257)	−0.133 (±0.266)	0.057 (±0.233)	0.051 (±0.160)
Missing	28	5	6	17
Child Opportunity Economics Index (0–2 y)	−0.042 (±0.249)	−0.131 (±0.252)	0.060 (±0.231)	0.054 (±0.156)
Missing	8	0	4	4
Child Opportunity Economics Index (2–4 y)	−0.034 (±0.246)	−0.126 (±0.253)	0.073 (±0.218)	0.063 (±0.147)
Missing	16	2	9	5
Recruitment site				
Memphis	1,035 (53%)	1,035 (100%)	0 (0%)	0 (0%)
San Francisco	135 (7%)	0 (0%)	135 (25%)	0 (0%)
Minneapolis	151 (8%)	0 (0%)	151 (28%)	0 (0%)
Rochester	135 (7%)	0 (0%)	135 (25%)	0 (0%)
Seattle TIDES	118 (6%)	0 (0%)	118 (22%)	0 (0%)
Seattle GAPPS	199 (10%)	0 (0%)	0 (0%)	199 (51%)
Yakima	194 (10%)	0 (0%)	0 (0%)	194 (49%)

Note: Shown in the table are mean (±SD), counts (percentage), and median (interquartile range); proportions were calculated in complete cases. BMI, body mass index; CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; ECHO, Environmental Influences on Child Health Outcomes; GAPPS, Global Alliance to Prevent Prematurity and Stillbirth; GED, general equivalency diploma; IQ, intelligence quotient; SD, standard deviation; TIDES, The Infant Development and Environment Study.
[a]Maternal IQ was measured by Wechsler Abbreviated Scale of Intelligence [the composite score of four subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning) from the first edition in CANDLE, the composite score of two subtests (Vocabulary and Matrix Reasoning) from the second edition in TIDES and GAPPS].
[b]Maternal depression was quantified using the *t*-scores at the visit of child outcome assessments by either the Center for Epidemiologic Studies Depression Scale (CES-D) or the Patient-Reported Outcomes Measurement Information System (PROMIS).

cohorts, the CANDLE cohort comprised a larger proportion of Black participants and low-income families, whereas the TIDES participants were relatively more educated, with a higher household income. The analytic sample was similar to the overall sample of participants at enrollment (Table S1). The distribution of child Total Problems score was slightly right skewed (Figure S2) with a median of 18 (IQR: 22), whereas child IQ was relatively normally distributed with a mean of 102.6 (SD: 15.3). Variations in the distribution of child outcomes by cohort were observed (Table 2).

Air Pollution Exposures

NO_2 levels were relatively stable and did not show a clear pattern over time, with a mean ranging from 8.4 (SD: 3.8) to 9.0 (SD: 3.9) ppb in different pre- and postnatal windows (Table 3). The correlation between NO_2 in nonoverlapping windows was highest between overall pregnancy and age 0–2 y (Spearman correlation: 0.84) and lowest between the first and third trimester (Spearman correlation: 0.32) (Table S2). Prenatal $PM_{2.5}$ was marginally higher than the exposures in the two postnatal windows. The concentrations were 9.0 (SD: 2.3) $\mu g/m^3$, 8.8 (SD: 2.0) $\mu g/m^3$, and 8.4 (SD: 1.8) $\mu g/m^3$ averaged over the pregnancy, 0–2 y, and 2–4 y, respectively. $PM_{2.5}$ aggregated in shorter windows had a greater variation than the exposures in the longer windows. There was a medium to high correlation of $PM_{2.5}$ across windows (Spearman correlation: 0.50–0.89), mainly driven by between-cohort correlations. The variation in $PM_{2.5}$ was lower than that in NO_2, and $PM_{2.5}$ and NO_2 in the same period were moderately correlated (Spearman correlation: 0.01–0.47). The NO_2 concentrations in Seattle, San Francisco, and Minneapolis were greater than those in Memphis, Rochester, and Yakima (Figure S3). In contrast, Memphis had the highest $PM_{2.5}$ level, followed by San Francisco, Minneapolis, and Rochester. Seattle and Yakima in Washington state had the lowest $PM_{2.5}$ level.

Associations of Air Pollution Exposures with Child Total Problems Score and IQ

***NO_2*.** Higher exposures to NO_2 in the first trimester [β: 0.70; (95% confidence interval (CI): 0.13, 1.27) per 2 ppb NO_2], the second trimester [β: 0.92 (95% CI: 0.31, 1.53) per 2 ppb NO_2], and averaged over the whole pregnancy [β: 1.24 (95% CI: 0.39, 2.08) per 2 ppb NO_2] were associated with more behavioral problems in children (Table 4). There was no significant association between prenatal NO_2 and child IQ, and we found no significant association between postnatal NO_2 and either outcome.

***$PM_{2.5}$*.** We found an adverse association between $PM_{2.5}$ in the first trimester and behavioral functioning [β: 1.32 (95% CI: 0.12, 2.52)], but an insignificantly positive association with child IQ [β: 0.80 (95% CI: −0.01, 1.62)]. For postnatal exposures, each 2-$\mu g/m^3$ increase in $PM_{2.5}$ at age 2–4 y was associated with a 3.59 unit (95% CI: 0.35, 6.84) higher Total Problems score and a 2.63 point (95% CI: −5.08, −0.17) lower child IQ. Additionally, children with higher $PM_{2.5}$ exposures at age 0–2 y were estimated to have a 2.55-unit (95% CI: −0.16, 5.27) higher Total Problems score, and a 1.47-point (95% CI: −3.40, 0.46) lower IQ on average, in comparison with their counterparts with a 2-$\mu g/m^3$ lower exposure; however, these results had larger statistical uncertainty.

Sex Modification

From the interaction models with child sex, we found a stratum-specific association between higher second trimester $PM_{2.5}$ and

Table 2. Distributions of child total problems score and IQ in participants from the three U.S. pregnancy cohorts in the ECHO-PATHWAYS consortium (the CANDLE, TIDES, and GAPPS study).

Outcomes	Cohort	*n*	Min	1st quartile	Median	Mean (SD)	3rd quartile	Max
Total problem score	Overall	1,895	0	9	18	22.66 (18.52)	31	132
	CANDLE[a]	1,005	0	10	19	23.72 (19.37)	33	132
	TIDES[b]	533	0	9	18	21.82 (17.13)	29	96
	GAPPS preschool form	262	0	9	15.5	20.96 (17.71)	28	110
	GAPPS school-age form	95	0	9	14	20.93 (18.6)	27.5	94
IQ	Overall	1,810	40	93	104	102.57 (15.27)	113	149
	CANDLE	1,030	40	90	100	99.7 (14.85)	110	138
	TIDES	425	55	97	107	105.96 (16.37)	118	149
	GAPPS	355	52	99	108	106.86 (13.19)	115	136

Note: CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; ECHO, Environmental Influences on Child Health Outcomes; GAPPS, Global Alliance to Prevent Prematurity and Stillbirth; min, minimum; max, maximum; SD, standard deviation; TIDES, The Infant Development and Environment Study.
[a]All CANDLE participants completed the preschool form.
[b]All TIDES participants completed the school-age forms.

more behavioral problems in girls [β: 1.50 (95% CI: 0.19, 2.81) in girls, β: −0.35 (95% CI: −1.89, 1.18) in boys, $P_{\text{interaction}}$: 0.026], and a stratum-specific association between higher second trimester $PM_{2.5}$ and a lower IQ in boys [β: −0.07 (95% CI: −0.92, 0.79) in girls, β: −1.19 (95% CI: −2.18, −0.2) in boys, $P_{\text{interaction}}$: 0.040], although the results were null from the primary analysis (Figure 2; Table S3). In both postnatal windows, there was suggestive evidence of stronger estimated effects of $PM_{2.5}$ on Total Problems score in girls than in boys; nevertheless, the insignificant interaction terms indicated that the effect difference between groups might be due to chance [0–2 y: β: 3.50 (95% CI: 0.61, 6.39) in girls, β: 1.72 (95% CI: −1.25, 4.70) in boys, $P_{\text{interaction}}$: 0.101; 2–4 y: β: 4.80 (95% CI: 1.25, 8.36) in girls, β: 2.74 (95% CI: −0.74, 6.23) in boys, $P_{\text{interaction}}$: 0.121]. No sex difference in other associations was detected.

Sensitivity Analyses

First, to handle the missing data in all covariates in the primary model, we constructed the ROC curve to verify the plausibility of the MAR assumption. An average area under curve of 0.891 (95% CI: 0.868, 0.914) was calculated, suggesting that we had an 89.1% chance of correctly distinguishing a complete case from one with missing data using the model with only covariates (Figure S4). We then implemented MICE to impute the missingness and show the results in Table S4. In comparison with the primary results, the point estimates obtained from MICE for the associations with child Total Problems score were mostly attenuated with a higher precision, whereas there was no clear pattern for the changes in associations with child IQ. The positive associations between NO_2 in the first trimester, the second trimester, and the whole pregnancy and Total Problems score achieved statistical significance in both the complete case analysis and MICE [first trimester: β: 0.51 (95% CI: 0.03, 0.98); second trimester: β: 0.61 (95% CI: 0.11, 1.11); whole pregnancy: β: 0.81 (95% CI: 0.17, 1.45)]. The positive association between first trimester $PM_{2.5}$ and IQ also gained a higher precision in MICE [β: 0.70 (95% CI: 0.05, 1.35)]. Second, we estimated a correlation of 0.99 between the raw Total Problems score and the standardized z-score, and the conclusions remained the same after we replaced the standardized *z*-score as the outcome (Table S5). Third, when restricting the analytic sample to participants born at gestational week 34 or later, the estimated direct effects of air pollution exposures on both outcomes were very similar to the findings from the primary analysis except for a slightly larger association with significance between first trimester $PM_{2.5}$ and IQ [β: 0.88 (95% CI: 0.06, 1.70)] (Table S6). Fourth, after simultaneously adjusting for exposures across windows, we derived significant associations between second trimester NO_2 and Total Problems score with smaller effect sizes than those from single exposure models [adjustments for NO_2 in other trimesters: β: 0.77 (95% CI: 0.01, 1.53); adjustments for NO_2 in other trimesters and postnatal windows: β: 0.79 (95% CI: 0.04, 1.54)] (Table S7). Stronger positive associations between first trimester $PM_{2.5}$ and IQ were also detected when $PM_{2.5}$ in other windows were included [adjustments for $PM_{2.5}$ in other trimesters: β: 0.84 (95% CI: 0.02, 1.66); adjustments for $PM_{2.5}$ in other trimesters and postnatal windows: β: 1.29 (95% CI: 0.30, 2.29)]. Other significant associations in the primary analysis were attenuated to null. Constrained DLM results depended on the df and were generally not consistent with our primary findings. The DLM with a df of 8 identified a critical window of gestational week 4–5 where higher $PM_{2.5}$ exposures were related to more behavioral problems (Figure S5), which agreed with the significantly positive association found in the first trimester. DLMs using a df of 4 to 9 also indicated positive associations between $PM_{2.5}$ and IQ in slightly different windows

Table 3. Distributions of NO_2 and $PM_{2.5}$ in each pre- and postnatal window in the overall analytic sample from the three U.S. pregnancy cohorts in the ECHO-PATHWAYS consortium (the CANDLE, TIDES, and GAPPS study).

Exposures	Window	*n*	Min	1st quartile	Median	Mean (SD)	3rd quartile	Max
NO_2 (ppb)	1st trimester	1,935	1.59	6.01	8.62	8.96 (3.92)	11.49	33.74
	2nd trimester	1,934	1.44	5.66	7.97	8.45 (3.77)	10.82	29.15
	3rd trimester	1,920	1.19	5.56	7.91	8.36 (3.82)	10.56	33.53
	Overall pregnancy	1,932	1.74	6.36	8.35	8.62 (3.17)	10.65	27.29
	0–2 y	1,894	1.63	6.79	8.78	8.71 (2.93)	10.53	26.37
	2–4 y	1,894	1.61	6.46	8.68	8.59 (3.03)	10.50	25.93
$PM_{2.5}$ ($\mu g/m^3$)	1st trimester	1,935	1.82	7.33	9.43	8.95 (2.7)	10.63	21.32
	2nd trimester	1,934	2.14	7.41	9.56	8.99 (2.74)	10.68	18.65
	3rd trimester	1,920	2.26	7.41	9.51	9.09 (2.93)	10.97	20.33
	Overall pregnancy	1,932	2.14	7.69	9.56	9 (2.32)	10.84	13.77
	0–2 y	1,894	3.03	7.41	9.54	8.75 (2.01)	10.28	12.04
	2–4 y	1,763	2.61	7.15	9.14	8.38 (1.79)	9.62	11.61

Note: CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; ECHO, Environmental Influences on Child Health Outcomes; GAPPS, Global Alliance to Prevent Prematurity and Stillbirth; min, minimum; max, maximum; SD, standard deviation; TIDES, The Infant Development and Environment Study.

Table 4. Associations of NO_2 and $PM_{2.5}$ in each pre- and postnatal window with child total problems score and IQ estimated from multivariable linear regressions in the overall analytic sample from the three U.S. pregnancy cohorts in the ECHO-PATHWAYS consortium (the CANDLE, TIDES, and GAPPS study).

	NO_2[a]				$PM_{2.5}$[a]			
	Total problems score		IQ		Total problems score		IQ	
Model[b]	n[c]	β (95% CI)	n[c]	β (95% CI)	n[c]	β (95% CI)	n[c]	β (95% CI)
1st trimester								
Model 1	1,823	0.8 (0.32, 1.28)	1,776	−0.8 (−1.17, −0.42)	1,823	1.07 (0.1, 2.04)	1,776	−0.67 (−1.45, 0.11)
Model 2	1,376	0.7 (0.13, 1.27)	1,423	0.28 (−0.1, 0.66)	1,376	1.32 (0.12, 2.52)	1,423	0.8 (−0.01, 1.62)
Model 3	1,347	0.58 (−0.02, 1.17)	1,391	0.37 (−0.03, 0.77)	1,347	1.28 (0.08, 2.48)	1,391	0.89 (0.05, 1.73)
2nd trimester								
Model 1	1,822	0.94 (0.4, 1.48)	1,775	−0.95 (−1.33, −0.56)	1,822	0.58 (−0.36, 1.52)	1,775	−1.22 (−1.9, −0.53)
Model 2	1,376	0.92 (0.31, 1.53)	1,423	0.15 (−0.24, 0.54)	1,376	0.55 (−0.6, 1.71)	1,423	−0.62 (−1.36, 0.12)
Model 3	1,347	0.94 (0.3, 1.59)	1,391	0.16 (−0.25, 0.57)	1,347	0.41 (−0.83, 1.65)	1,391	−0.48 (−1.27, 0.31)
3rd trimester								
Model 1	1,811	0.34 (−0.15, 0.82)	1,764	−1.31 (−1.71, −0.91)	1,811	0.25 (−0.64, 1.15)	1,764	−1.76 (−2.42, −1.1)
Model 2	1,368	0.27 (−0.31, 0.84)	1,415	−0.25 (−0.64, 0.14)	1,368	−0.54 (−1.48, 0.41)	1,415	−0.33 (−0.98, 0.32)
Model 3	1,339	0.3 (−0.29, 0.9)	1,383	−0.27 (−0.67, 0.13)	1,339	−0.99 (−2.05, 0.08)	1,383	−0.17 (−0.88, 0.54)
Overall pregnancy								
Model 1	1,821	1.22 (0.54, 1.9)	1,774	−1.59 (−2.08, −1.1)	1,821	1.81 (0.25, 3.37)	1,774	−3.52 (−4.72, −2.32)
Model 2	1,376	1.24 (0.39, 2.08)	1,423	0.13 (−0.37, 0.63)	1,376	1.38 (−0.6, 3.35)	1,423	−0.26 (−1.53, 1.01)
Model 3	1,347	1.22 (0.34, 2.09)	1,391	0.17 (−0.35, 0.7)	1,347	1.03 (−1.27, 3.34)	1,391	0.18 (−1.25, 1.62)
0–2 y								
Model 1	1,792	0.7 (−0.03, 1.43)	1,741	−1.55 (−2.14, −0.96)	1,792	2.09 (0.01, 4.16)	1,741	−6.03 (−7.8, −4.25)
Model 2	1,363	0.41 (−0.53, 1.34)	1,407	0.37 (−0.21, 0.95)	1,363	2.55 (−0.16, 5.27)	1,407	−1.47 (−3.4, 0.46)
Model 3	1,334	0.67 (−0.28, 1.62)	1,375	0.25 (−0.35, 0.85)	1,334	1.62 (−1.29, 4.53)	1,375	−0.8 (−3, 1.41)
2–4 y								
Model 1	1,783	0.63 (−0.07, 1.34)	1,741	−1.51 (−2.07, −0.94)	1,691	3.45 (1.24, 5.67)	1,622	−8.31 (−10.33, −6.29)
Model 2	1,347	0.32 (−0.57, 1.21)	1,393	0.06 (−0.49, 0.61)	1,287	3.59 (0.35, 6.84)	1,311	−2.63 (−5.08, −0.17)
Model 3	1,318	0.44 (−0.46, 1.34)	1,361	0 (−0.56, 0.57)	1,262	2.55 (−0.82, 5.92)	1,284	−2.18 (−5, 0.64)

Note: BMI, body mass index; CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CBCL, Child Behavior Checklist; CI, confidence interval; ECHO, Environmental Influences on Child Health Outcomes; GAPPS, Global Alliance to Prevent Prematurity and Stillbirth; IQ, intelligence quotient; TIDES, The Infant Development and Environment Study.

[a]NO_2 and $PM_{2.5}$ in each window were rescaled to 2-unit increments.

[b]Multivariable linear regressions were performed. Model 1 (the minimal model) minimally controlled for child sex, child age at outcome assessments, and study site. An indicator of CBCL forms was additionally included in the analysis of Total Problems score. Model 2 (the primary model) was further adjusted for child race, maternal education, log-transformed region- and inflation-adjusted household income, household members, an interaction between household members and income, marital status, maternal age at delivery, birth order, pregnancy smoking, pregnancy alcohol consumption, maternal depression, maternal IQ, child secondhand smoking exposure, and Child Opportunity Index (the domains of educational and economic opportunity) in corresponding windows with $PM_{2.5}$ and NO_2 exposures. Model 3 (the extended model) included additional adjustments for prepregnancy BMI, pregnancy supplement intakes, breastfeeding, and child year of birth.

[c]*n* is the analytic sample size for each model.

within the range of gestation week 6–13, and a similar relationship has been evident in the analysis with the exposure in the first trimester, although the results are insignificant. Apart from these findings, DLMs either showed associations that contradicted our hypotheses and the primary results or displayed associations that were null in our primary analysis, particularly in DLMs with a high df. In addition, the smooth effect curves generated from GAMs in the overall sample (Figure 3) and in each sex stratum (Figure S6) generally did not indicate significant departures from the conclusions of the primary and secondary analyses, although the association between first trimester $PM_{2.5}$ and Total Problems score appeared to be predominantly driven by the exposure outliers in the high end. Last, leaving out the CANDLE cohort (Memphis) presented the biggest impact on results of the leave-one-cohort-out (Table S8) and leave-one-site-out (Table S9) analyses: All the significant associations detected in the primary analysis became null. However, the exclusion of most other study sites did not cause meaningful changes in the result. Comparing the fully adjusted fixed effects models (i.e., the primary analysis) to fixed effects models with site–covariate interactions as well as mixed-effects models both with and without site–covariate interactions, results were generally consistent. We found attenuation in the association of first trimester $PM_{2.5}$ with Total Problems score and the associations of $PM_{2.5}$ in age 2–4 y with both outcomes in the mixed-effects models, but inclusion of site–covariate interactions corrected these attenuations, raising the possibility of site-specific confounding that is only apparent when one of the sites with a smaller population is upweighted in the mixed-effects model (Table S10).

Discussion

We used a large, combined sample from three sociodemographically diverse pregnancy cohorts situated in six U.S. cities to examine the associations of the two regulated air pollutants— NO_2 and $PM_{2.5}$—with child behavioral problems and cognitive performance at age 4–6 y. Children whose mothers experienced higher NO_2 exposures during pregnancy, particularly in the first and second trimester, were more likely to have behavioral problems. Associations between prenatal NO_2 and child IQ or postnatal NO_2 with either outcome were not evident. We also found a positive association of first trimester $PM_{2.5}$ with Total Problems score; nevertheless, this association needs to be interpreted with caution because it may be driven by outliers. In addition, higher exposures to postnatal $PM_{2.5}$ when children were 2–4 y were associated with poorer child behavioral functioning and cognitive performance. The associations between $PM_{2.5}$ and Total Problems score were generally more pronounced in girls, and the inverse association between second trimester $PM_{2.5}$ and IQ was detected only in boys. Conclusions remained largely unchanged with expanded covariate adjustments and in most sensitivity analyses, but DLMs failed to confirm most critical windows being identified.

The adverse associations between prenatal NO_2 exposure and child behavior, particularly our findings for exposures in early- to midpregnancy, align with similar evidence from several previous studies. A previous CANDLE cohort study reported a 6% increased risk of externalizing behavior for each 2-ppb higher prenatal NO_2.[39] A study in Japan found increased odds of attention problems and aggressive behaviors in children with higher prenatal NO_2 exposures.[34] Similarly, another study by Ren et al. (2019)

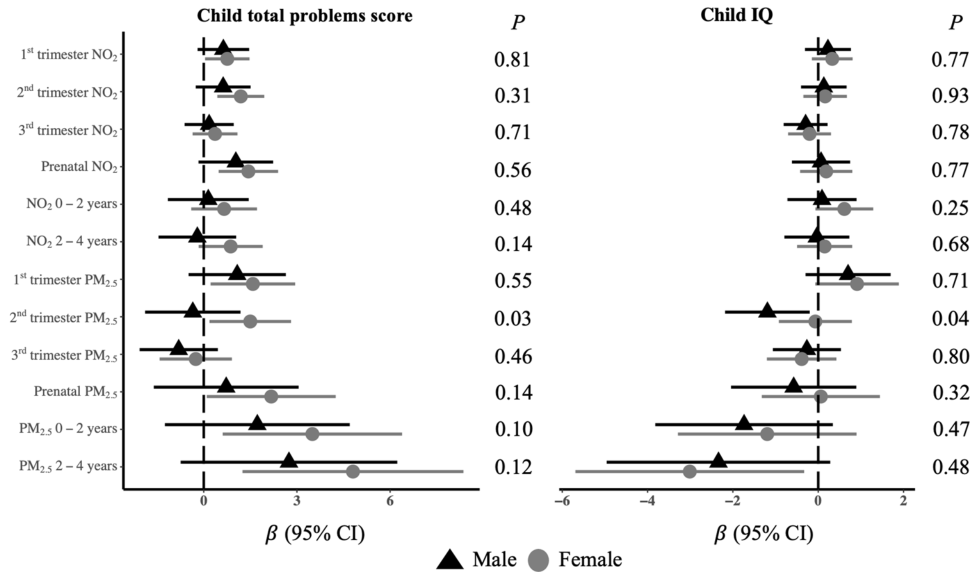

Figure 2. Shown are the estimated effects of air pollution exposures on child Total Problems score and IQ by child sex (male vs. female) in participants from the three U.S. pregnancy cohorts in the ECHO-PATHWAYS Consortium (the CANDLE, TIDES, and GAPPS study). NO_2 and $PM_{2.5}$ in each window were rescaled to 2-unit increments. In addition to the interaction term between individual air pollution exposures in each window and child sex, the linear regressions were adjusted for child sex, child age at outcome assessments, study site, child race, maternal education, log-transformed region- and inflation-adjusted household income, household members, an interaction between household members and income, marital status, maternal age at delivery, birth order, pregnancy smoking, pregnancy alcohol consumption, maternal depression, maternal IQ, child secondhand smoking exposure, and Child Opportunity Index (the domains of educational and economic opportunity) in corresponding windows with $PM_{2.5}$ and NO_2 exposures. An indicator of CBCL forms was additionally included in the analysis of Total Problems score. The *p*-value indicates the statistical significance of the interaction term. The symbols of triangles and circles indicate the effect estimate, the error bars show 95% confidence intervals, and the dotted lines show null values. Numeric data (including sample size for each association) are shown in Table S3. Note: CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CBCL, Child Behavior Checklist; ECHO, Environmental Influences on Child Health Outcomes; GAPPS, Global Alliance to Prevent Prematurity and Stillbirth; IQ, intelligence quotient; TIDES, The Infant Development and Environment Study.

reported a positive association between prenatal exposures to NO_2 and total difficulties and suggested that NO_2 in the first trimester may be more deleterious.[32] Moreover, there is increasing evidence from population studies linking prenatal air pollution exposures, including NO_2, with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders.[10,11] Prenatal air pollution may interfere with fetal neurodevelopment by inducing oxidative stress and inflammation or altering the epigenetic programming in the placenta or fetus.[12–14,81,82] However, we observed null associations between postnatal NO_2 and child behaviors, which was inconsistent with our previous finding in CANDLE,[39] as well as the two studies combining multiple cohorts in Spain.[30,83] Our results for the association between NO_2 exposures in either prenatal or postnatal windows and child IQ were also null, paralleling those from the prior CANDLE study using NO_2 estimates from a national annual model,[27] two other studies in Europe,[43,84] and one study in Taiwan.[36] However, significant adverse associations were reported in five other European studies.[31,41,85–87] The disparity in findings may be driven by variations in the air pollution prediction models, the exposure levels, the exposure duration (short-term vs. long-term), the exposure locations (school vs. home), the source of exposure (indoor vs. outdoor), outcome assessment, underlying susceptibility in study populations, or confounder selection.

The detected positive relationship of first trimester $PM_{2.5}$ with child Total Problems score was in agreement with findings from several existing studies with prenatal PM exposures in mainland China,[32] Japan,[34] Korea,[33] and Mexico City.[37] Some of our sensitivity analyses suggested a potential positive association between first trimester $PM_{2.5}$ and IQ, such as MICE and DLM, although the result was insignificant in the primary analysis. We only know of two previous studies measuring the effect of PM in specific trimester(s) on child cognitive performance. A study in Massachusetts detected no association between third trimester $PM_{2.5}$ and child IQ,[28] though the associations with first and second trimester exposures were not evaluated, and a study in Taiwan reported a null relationship of first trimester PM_{10} and child neurodevelopmental scores at 6 and 18 months.[36] Using a distributed lag modeling approach, another study showed that children in Boston with higher $PM_{2.5}$ exposure at 31–38 gestational weeks had a lower IQ at age 6,[25] the critical windows of which differed from our findings from DLM. This positive association between first trimester $PM_{2.5}$ and IQ contrasts with our hypothesis, and its interpretation may reflect the following considerations: first, this protective association may suggest potential selection bias from multiple sources. One is the enrollment criterion of women with low medical risk pregnancies in the CANDLE and TIDES cohort, and another is the fact that the outcomes are conditioned on live birth.[88,89] When the analytic sample was restricted to participants with a gestational week of 34 and above, this association became stronger, indicating that constraint on gestational age may also induce bias. Second, this result was largely attenuated when we excluded participants in Yakima, Washington, from the analysis. A potential explanation is that the spatiotemporal model may generate less accurate predictions in such a region where wildfires and agricultural burning are major sources of particulate pollution.

The associations with the greatest magnitude in our analysis were found between postnatal $PM_{2.5}$ and child behavior, particularly exposures at age 2–4 y. A similar conclusion was drawn in a German study by Fuertes et al. (2016),[29] which reported an increased risk of hyperactivity/inattention in adolescents with higher exposures of $PM_{2.5}$ mass and absorbance at 10 y and 15 y address. However, in an analysis from the Project Viva cohort, significant associations between postnatal $PM_{2.5}$ averaged in

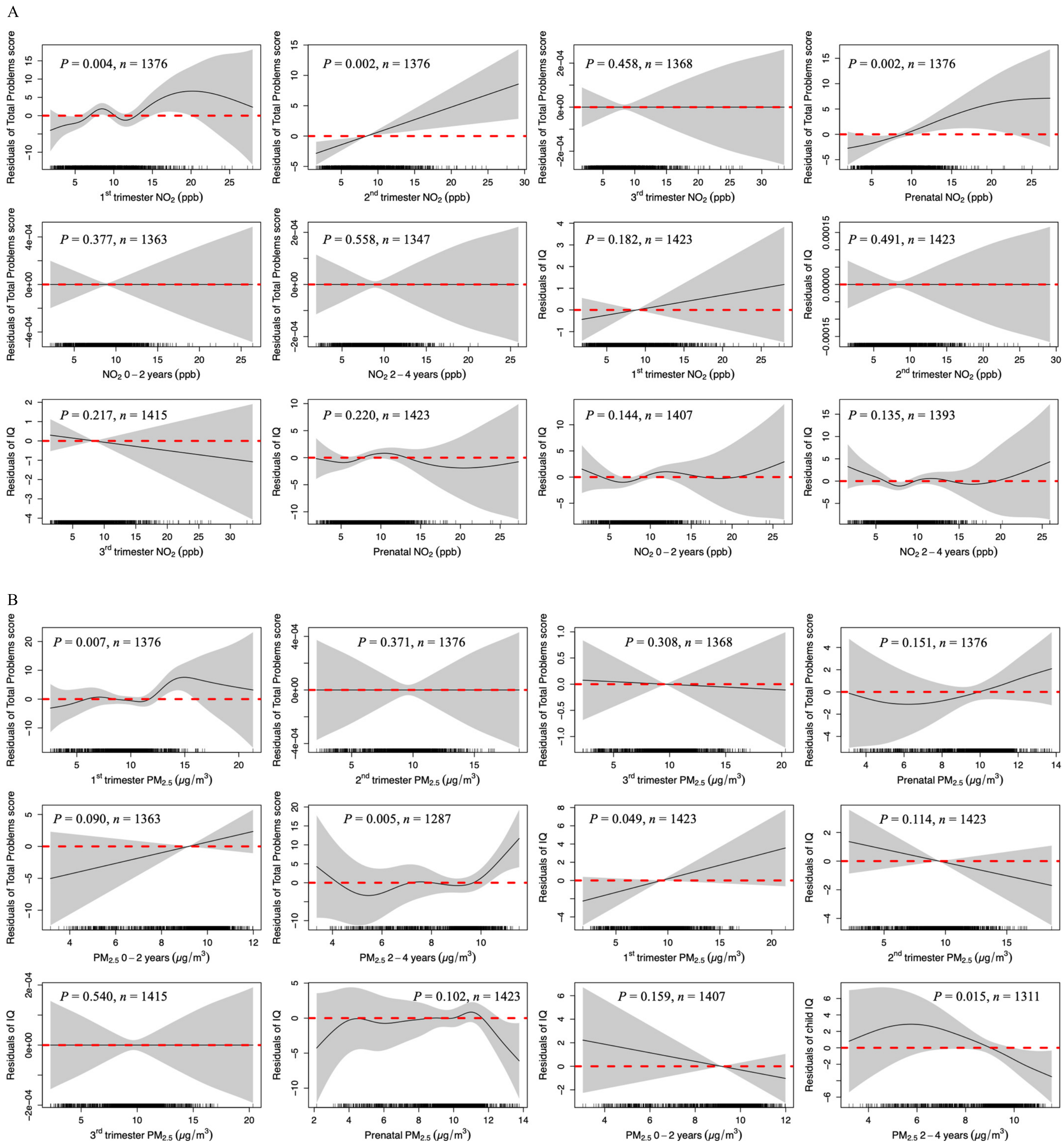

Figure 3. Shown are the graphic examination of the linearity of associations of NO_2 and $PM_{2.5}$ in each window with child Total Problems score and IQ from the fully adjusted generalized additive models in the overall analytic sample of three cohorts. The models were controlled for child sex, child age at outcome assessments, study site, child race, maternal education, log-transformed region- and inflation-adjusted household income, household members, an interaction between household members and income, marital status, maternal age at delivery, birth order, pregnancy smoking, pregnancy alcohol consumption, maternal depression, maternal IQ, child secondhand smoking exposure, and Child Opportunity Index (the domains of educational and economic opportunity) in corresponding windows with $PM_{2.5}$ and NO_2 exposures. An indicator of CBCL forms was additionally included in the analysis of Total Problems score. The *p*-value indicates the statistical significance of the association. The *n* indicates the analytic sample size. Black solid lines represent the potential nonlinear associations, gray bands are 95% CIs, and red dotted lines show null values. Note: CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CBCL, Child Behavior Checklist; CI, confidence interval; ECHO, Environmental Influences on Child Health Outcomes; GAPPS, Global Alliance to Prevent Prematurity and Stillbirth; IQ, intelligence quotient; TIDES, The Infant Development and Environment Study.

different windows and teacher-rated behavioral problems and executive functions were detected only in minimally adjusted models.[90] Our estimated effects of postnatal $PM_{2.5}$ on child IQ were also relatively strong. This result is consistent with two studies based on multiple cohorts in Spain, which reported a reduced growth in work memory among children 7–11 y of age with higher $PM_{2.5}$ exposure from commutes or at school.[30,83] Nevertheless, a study in Upstate New York with relatively low air pollution exposures showed mixed associations between $PM_{2.5}$ assessments and risk of failure on developmental screening using Ages and Stages Questionnaires at 8 to 36 months of age.[26] Another study in Massachusetts found a null association between $PM_{2.5}$ in early childhood and child IQ at age 8 y.[28] In comparison with younger children, 2- to 4-y-old children are more likely to stay outdoor for longer periods and are usually more active, which may increase their susceptibility to air pollution.[91] According to a conceptual framework proposed by Tulve et al. (2016), postnatal air pollution interplays with inherent characteristics, activities and behaviors, and other stressors from built, natural, and social environments and influences child learning, communication, response to stress, and general psychological well-being.[92] In addition, laboratory and imaging studies have shown that the number of neural connections explodes in the first and second year of life,[93] and brain size increases 4-fold, reaching 90% of adult volume by age 6 y.[1,94–97] Inhaled particles can invade deep in the lung and translocate along the olfactory nerve into the olfactory bulb.[22] A pilot study in healthy children and young dogs similarly exposed to high air pollution in Mexico City showed a significant up-regulation of inflammatory markers and histological changes in target brain areas.[98] Studies in animals also observed inflammatory responses in the prefrontal cortex and the striatum after air pollution exposure—the regions related to executive functions such as working memory.[99–103] These findings provide strong mechanistic support for the hypothesis that inhaled air pollutants may trigger oxidative stress and promote inflammatory markers across the impaired blood brain barrier, which result in microglial activation and elevated cytokine expression, and in turn cause CNS damage relevant for behavioral and cognitive function.

Our results somewhat suggested stronger associations between $PM_{2.5}$ and child behavioral functioning in girls, particularly with postnatal $PM_{2.5}$. Neither the study in Germany[29] nor the previous analysis in the CANDLE cohort[39] found sex differences in the associations between postnatal PM and child behaviors. Nevertheless, the study in Mexico City reported a stronger association between first trimester $PM_{2.5}$ and reduced adaptive skills in boys. In addition, we found an inverse association between second trimester $PM_{2.5}$ and IQ only in boys, which agrees with much existing literature showing more pronounced findings in boys,[25,30,35,41–43] but disagrees with the three U.S. studies with null findings.[26,27,104] Research has identified several sex differences in neurodevelopment, including morphological, physiological, and chemical differences.[40] Although animal studies have shown that males are more susceptible to airborne metals than females are, which is potentially explained by sex-specific altered dopamine function,[105] other evidence from laboratory science support a protective mechanism for boys via neuroprotective effects of androgens against oxidative stress.[106]

Our study has several important strengths. First, we combined three pregnancy cohorts into a large analytic sample with high sociodemographic diversity and controlled for several important confounders harmonized across cohorts, including individual and neighborhood SES indicators,[107] maternal depression, and maternal IQ. The approach of pooling data helps leverage the spatiotemporal contrast in air pollution assessments and strengthens the external generalizability of the study results by increasing the diversity of participants. Second, we used spatiotemporally resolved air pollution predictions from a well-validated modeling approach based on individually geocoded residential addresses in six U.S. cities across multiple years, allowing us to exploit small-scale spatial variability in the pollutant surfaces over several windows in both pre- and postnatal periods. Last, we provided rigorous training for examiners and implemented robust protocols to collect standardized objective assessments of child cognitive performance. The data for both outcome measures were collected using standardized and validated neuropsychological testing tools and went through strict quality control.

There are also limitations to be acknowledged. One is the parent-report method for ascertaining child behaviors. Previous research has shown that parents report child psychological problems more often and of greater severity than teachers, suggesting combined reports from multiple sources may improve reliability.[108] However, the study with participants from the Adolescent Brain Cognitive Development cohort in the United States found little psychometric evidence for maternal psychopathology biasing reports of child behavior problems.[109] Use of parent report alone is common in epidemiological studies, given the ease of data collection. Another limitation is the heterogeneity among the three studies and sites in terms of exposure levels, air pollution compositions, frequency of address data collection, outcome assessment instruments, examiners, and measurement methods for covariates, which could induce measurement errors of various magnitudes. We performed several sensitivity analyses to investigate the impacts of certain heterogeneities on the detected associations in a pooled sample. Although the results from our leave-one-cohort-out and leave-one-site-out analyses indicated that the CANDLE study contributed the most to the findings, likely due to its large sample size, the comparisons between fixed-effects models and mixed-effects models with or without site–covariate interactions suggested that the roles of site heterogeneity and potential site-specific confounding on the estimated associations were relatively minor. The third concern is the potential inaccuracy in air pollution assessments. Our prediction model, like other modeling approaches, may produce complex forms of measurement error that can distort the true associations.[110,111] The current analysis did not account for indoor exposures or exposures in the other locations, such as day care, preschool, or daily commutes. We also lacked other air pollutants that were linked with child neurodevelopment in previous research, such as black carbon, ozone, PAHs, and sulfur dioxide.[10,11] Moreover, collinearity of exposures across windows may cause inaccurate identification of critical window; we thus implemented constrained DLM to verify our results. However, the results from DLMs were largely unmatched with our primary findings. Defining exposure windows *a priori* is particularly appealing, because the results are easy to interpret and to compare, and the evidence can be used to inform interventions directly. Certain clinical problems are likely to cluster in different trimesters, such as teratogenesis[112] or miscarriage[113] in the first trimester and bleeding[114] in the third trimester. We also expect tremendous physical, behavioral, social, and emotional advancements to occur in children when they turn age 2. However, these predefined windows may not reflect many important developmental milestones[115] nor correspond to relevant vulnerable periods of neurodevelopmental impairments. On the contrary, the results from DLMs are very sensitive to model specification, and they could generate spurious significant windows or fail to capture windows when the smoothness is imposed incorrectly.[116] In such manner, neither method has generated completely valid conclusions, and the sensitive exposure periods identified by our analysis merit further study. Furthermore, we were missing 16% of the maternal IQ measurements. Based on our assessment of the ROC curve, the assumption of missing at random was likely valid, and the results from both the complete cases analysis and the multiple imputation were considered robust.[75,117] Because multiple imputation may not be readily compatible with DLMs or generalized additive models, we employed it as an alternative approach to verify the findings from the complete cases analysis. Nevertheless, we cannot rule out potential selection bias with confidence, given the discrepancy of results from the two analytic approaches. In addition, residual confounding may exist. Previous studies found adverse individual and joint neurobehavioral associations with transportation noise and traffic-related air pollution in children,[31,118] but we did not control for noise due to data unavailability. Last, our findings may need to be interpreted with caution owing to the multiple comparisons.

Despite these limitations, our study extends earlier findings that have raised concern of reduced behavioral functioning and cognitive performance in children following NO_2 and $PM_{2.5}$ exposures in early life. We used highly refined exposure assessments across several pre- and postnatal windows in U.S. settings with modest air pollution levels. Aside from filling the methodological gaps in the current literature, our study explores the most relevant exposure window, compares the findings across two neurodevelopmental measures, and highlights the extra vulnerability to different neurodevelopmental impairments in each sex when exposed to air pollution. Enhanced understanding of population vulnerabilities to common ambient air pollutants are necessary to ensure that regulatory policies provide adequate protection for all.

Acknowledgments

This research is supported by the ECHO-PATHWAYS consortium [National Institutes of Health (NIH): 1UG3OD023271, 4UH3OD023271, 1R01HL109977, and P30ES007033]. The CANDLE study is funded by both the Urban Child Institute and NIH (1R01HL109977). The TIDES study is funded by NIH (TIDES I: R01ES01686; TIDES II: 1R01ES25169). Air pollution models were developed under STAR research assistance agreements, No. RD831697 (MESA Air) and RD-83830001 (MESA Air Next Stage), RD83479601 (University of Washington Center for Clean Air Research), and R83374101 (MESA Coarse), awarded by the U.S. Environmental Protection Agency (EPA), with additional grants R56ES026528, R01ES023500, and R01ES025888 from the National Institute of Environmental Health Sciences (NIEHS) and P01AG055367 from the National Institute on Aging (NIA). Funding was also provided by Kresge Foundation Grant No. 243365. E.B. is supported by the NIH (P30 ES005022). M.H. is supported in part by the University of Washington NIEHS sponsored Biostatistics, Epidemiologic and Bioinformatic Training in Environmental Health (BEBTEH) Training Grant (NIEHS T32ES015459). This manuscript has not been formally reviewed by the U.S. EPA. The views expressed in this document are solely those of the authors, and the U.S. EPA does not endorse any products or commercial services mentioned in this publication.

The data used for this study are not publicly available, but deidentified data may be available on request, subject to approval by the internal review board and under a formal data use agreement. Contact the corresponding author for more information. The computing code in R can be obtained from the corresponding author via email request.

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