Original Research Article

ENVIRONMENTAL EPIDEMIOLOGY

OPEN

Does early life phthalate exposure mediate racial disparities in children's cognitive abilities?

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Background: Early life exposure to phthalates may be associated with reduced cognition. However, it is unknown if disproportionate exposure to phthalates contributes to racial disparities in children's intellectual abilities.

Methods: We used data from 253 mother-child pairs in Cincinnati, OH (the Health Outcomes and Measures of the Environment study, 2003–2006). We measured urinary concentrations of 11 phthalate metabolites twice during pregnancy and up to six times in childhood. We evaluated children's cognitive abilities at ages 5 and 8 years. Using mediation models, we quantified covariate-adjusted direct and indirect effects of race on children's Full-Scale Intelligence Quotient (IQ) scores for individual phthalate metabolite concentrations during gestation and childhood.

Results: Average IQ scores among Black children (n = 90) were 7.0 points lower (95% confidence interval [CI] = −12, −1.8) than among White children (n = 145) after adjustment for socioeconomic factors. Urinary monobenzyl phthalate and monoethyl phthalate (MEP) concentrations during gestation and childhood were higher among Black than White children. We did not observe evidence that phthalate concentrations mediated the race-IQ association, with the exception of MEP. Childhood MEP concentrations partially mediated the race-IQ association. For instance, each 10-fold increase in MEP concentrations at age 2 years contributed to a 1.9-point disparity in IQ scores between Black and White children (95% CI = −4.7, 0.7). Other phthalate metabolite concentrations during pregnancy or childhood did not mediate the race-IQ association.

Conclusions: Despite observing racial disparities in exposure to some phthalates and IQ, we found little evidence that phthalates contribute to IQ disparities.

Keywords: Racial disparities; Child intelligence; IQ; Phthalates; Gestational exposure; Childhood exposure

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J.M.B. served as an expert witness in litigation related to perfluorooctanonic acid contamination in drinking water in New Hampshire. Any funds he received from this arrangement were/are paid to the Brown University and cannot be used for his direct benefit (e.g., salary/fringe, travel). The other authors have no conflicts to report.

The results reported herein correspond to specific aims of grant R01 ES024381 to investigator J.M.B.; R01 ES020349 to investigators A.C., B.P.L., and K.Y.; R01 ES011261 to investigator B.P.L.; and R01 ES014575 to investigators B.P.L. and K.Y. from the National Institutes of Health.

Data and Code Acquisition: Computing code can be obtained from the corresponding author (M.A.P.) upon request. Data from the Health Outcomes and Measures of the Environment (HOME) study are available upon request. The HOME study principal investigators have actively engaged in collaborative data-sharing projects. We welcome new collaborations with other investigators. Interested investigators in the HOME study data can explore data options at the following location and use the available link to contact the investigators to discuss collaborative opportunities: https://homestudy.research.cchmc.org/. The Data Sharing Committee meets regularly to review proposed research projects and ensure that they do not overlap with extant projects and are an efficient use of scare resources (e.g., cord blood).

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Environmental Epidemiology (2022) 6:e205

Received: 5 November 2021; Accepted 1 March 2022

Published online 15 March 2022

DOI: 10.1097/EE9.0000000000000205

Introduction

Phthalates are a class of chemicals used in personal care and consumer products, including cosmetics, pharmaceuticals, vinyl flooring, medical supplies, food packaging, and plastic toys.[1–7] Human exposure can occur through dermal absorption, inhalation, or ingestion.[1,4,8] Phthalates are quickly excreted from the body (<24 hours), but exposure is chronic and ubiquitous in the US population, including among vulnerable subpopulations like pregnant women, infants, and children.[3,9] Exposure may be higher in infants and children than adults due to differences in physiology, diet, and behaviors.[9–14]

Phthalates are suspected developmental neurotoxicants.[15–23] Some epidemiologic studies[24,25] report an inverse association of gestational[17–22] or childhood phthalate exposure[16,18–20] with cognitive abilities (i.e., Intelligence Quotient [IQ]) in children. While measures of intelligence are imperfect, they are strong predictors of educational achievement and work performance.[26–30] Racial disparities in child IQ have been documented in the United States and abroad, such that individuals who identify as Black or have darker skin colors have lower measured IQ relative to their White peers.[31–33] Parental cognition and genetics alone do not explain the full heterogeneity in child IQ,[34,35] emphasizing

What this study adds

Phthalates are neurotoxicants associated with diminished cognitive abilities in children. Racial disparities in children's phthalate exposure and cognitive abilities have been documented previously, but it is unclear if disproportionate exposure to phthalates contributes to disparities in child cognition. Using mediation models, urinary concentrations of monoethyl phthalate but not other phthalates partly mediated racial disparities in child cognitive abilities. While racial disparities in exposure to some phthalates and child cognition exist, we found little evidence to suggest phthalates contribute to disparities in child cognition.

the need to consider external factors such as environmental exposures and socioeconomic features.[36] Further, race is a social construct, not a biological variable. No genetic basis exists to explain racial disparities in IQ, indicating that disparities in cognitive abilities are most likely related to environmental factors.[31,33,37]

Phthalate exposure is ubiquitous in the United States (US), but urinary concentrations of some phthalates are consistently higher in the Black population.[13,38] Thus, highly exposed populations may be more likely to experience phthalate-related health consequences than those with lower levels of exposure. Moreover, prior work suggests that racial and ethnic disparities in reproductive, neonatal, and cardiometabolic health outcomes may be related to racial and ethnic differences in phthalate exposure.[13,38–42] For example, some phthalate-containing products, particularly hair products, are more frequently marketed to and used by the Black communities.[43] This highlights how certain subpopulations may be more exposed and thus vulnerable to the adverse effects of phthalates.[43] Despite the recognition that racial and ethnic differences exist in phthalate exposure and child IQ, no study has evaluated whether phthalate exposure mediates the relation between race and child IQ.

To evaluate the potential for phthalate metabolite concentrations during gestation and childhood to mediate the race–cognitive abilities relation, we employed previously defined methods for evaluating how environmental exposures contribute to racial disparities.[44] The framework outlined by Bellavia et al utilizes multiple mediation analyses to evaluate the contribution of an environmental exposure of interest on the association between race and health outcomes in cases where there is an unequal distribution of both the exposure and outcome. The goal of this approach is to identify modifiable sources of environmental exposures to reduce (and eliminate) unequal distributions of exposures by developing interventions to reduce exposure-related health disparities.

Using data from the Health Outcomes and Measures of the Environment (HOME) study, we quantified racial disparities in gestational and childhood phthalate exposure and assessed the extent that phthalates mediate the relation between race and child IQ. We hypothesized that racial disparities in phthalate exposure would partly explain the disparity in cognitive abilities between Black and White children. While this study focused on phthalates, it also serves a proof-of-principle analysis of other environmental toxicants as potential explanatory factors of racial disparities in child IQ.

Methods

Study participants

The HOME study is a general population, prospective pregnancy and birth cohort study. Information regarding recruitment and data collection details have been previously published.[45] Briefly, we recruited 468 pregnant women from 1263 eligible women from nine prenatal clinics affiliated with three delivery hospitals in the greater Cincinnati, OH area between 2003 and 2006. Inclusion criteria specified women be at least 18 years old, 16 ± 3 weeks of gestation, HIV negative, not taking medications for seizures and/or thyroid disorders, living in homes built before 1978, and not having a diagnosis of diabetes, bipolar disorder, schizophrenia, or cancer the resulted in radiation treatment or chemotherapy. The Institutional Review Board at the Cincinnati Children's Hospital Medical Center and all participating hospitals approved this study (protocol code 01-8-5, 2008-0022 and dates of approval: 29 May 2002, 6 August 2007, and 4 August 2011). All participating mothers provided their written, informed consent for themselves and their children.

Of 468 women who enrolled, 67 dropped out before delivery. Among the 389 live-born, singleton infants, our analysis included mother-child pairs that had at least one measure of child IQ at ages 5 or 8 years, at least one urinary phthalate concentration during gestation and childhood, and no missing covariate information (n = 7). We further restricted the analytic sample to include children who identified as Black or White. We excluded those children who identified as other races due to small sample size. Our final sample included 253 mother-child pairs (eFigure 1; http://links.lww.com/EE/A183).

Urinary phthalate metabolite concentration assessment

Study staff collected maternal urine samples at approximately 16 and 26 weeks of gestation in polypropylene specimen cups. We collected child urine samples at ages 1, 2, 3, 4, 5, and 8 years. Among children who were not toilet trained, we collected urine by placing surgical inserts in clean diapers. We lined training potties with inserts to collect urine from children who were in the process of being toilet trained. Urine from inserts was collected with a syringe and expressed into a collection cup in the laboratory. For children who were toilet trained, caregivers assisted in the collection of urine using polypropylene specimen cups. We followed previously described protocols to minimize external contamination of urine samples.[46,47] All urine samples were refrigerated for less than 24 hours before processing and stored at ≤–20 °C until chemical analysis at the Centers for Disease Control and Prevention (CDC).

Using a modified method of online solid phase extraction coupled with isotope dilution high-performance liquid chromatography–tandem mass spectrometry, CDC staff measured the urinary phthalate metabolite concentrations.[13] We measured urinary concentrations of mono(3-carboxypropyl) phthalate (MCPP), mono-isobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono-n-butyl phthalate (MBP), monocarboxyoctyl phthalate (MCOP), monocarboxynonyl phthalate (MCNP), and monoethyl phthalate (MEP). We used three oxidative di(2-ethylhexyl) phthalate (DEHP) metabolites (mono-2-ethyl-5-hydroxyhexyl phthalate, mono-2-ethyl-5-oxohexyl phthalate, and mono-2-ethyl-5-carboxypentyl phthalate [MECPP]) to create a summary DEHP metabolite measure (i.e., ΣDEHP) for both gestational and childhood samples. To calculate concentrations of ΣDEHP (in ng/mL), we divided each DEHP metabolite concentration by its molar mass, summed the individual concentrations, and then multiplied the molar sum by the molar mass of MECPP.[48]

We did not measure MCOP or MCNP concentrations in maternal urine samples because the method for these biomarkers had not yet been developed. We could not measure concentrations of MBP, MiBP, or MEHP from child urine samples collected at ages 1 to 3 years, as these metabolites were detected in the diaper inserts used during collection.[9] The limits of detection (LODs) for the phthalate metabolites ranged from ~0.1 to ~1 ng/mL. Values below the LOD were given a value of the LOD/$\sqrt{2}$ (eTable 3; http://links.lww.com/EE/A183).[49] We accounted for urine dilution using urinary creatinine concentrations as described previously.[50]

Phthalate metabolite concentrations (ng/mL) were first creatinine standardized and $\log_{10}$ transformed before we conducted measurement error correction. Briefly, we accounted for phthalate exposure measurement error using a previously described regression calibration approach.[51] For gestational phthalate concentrations, we used a linear mixed model with a random intercept to estimate subject-specific geometric mean creatinine-standardized urinary phthalate concentrations across the two measurement occasions (i.e., 16 and 26 weeks).[52] Our model for phthalate concentrations collected on the ith mother at the jth measurement occasion during gestation: $Y_{ij} = \mu_i + \varepsilon_{ij}$, where $\mu_i \sim N(\mu, \sigma_B^2)$ and $\varepsilon_{ij} \sim N(0, \sigma_W^2)$. Under this model, the reliability of observed geometric mean phthalate concentration for the ith mother across gestation, $\bar{y}_i$ is given $R_i = \sigma_B^2 / (\sigma_B^2 + \frac{\sigma_W^2}{n_i})$,

where σ_B^2 and σ_W^2 are the between-subject and within-subject variance components, respectively, and n_i = 1–2 is the number of available phthalate measures during gestation.

While this calibration approach is appropriate when geometric mean phthalate concentrations show no time trends across measurement occasions, this was not the case for childhood concentrations, which varied quadratically with child age.[47] Therefore, we used a more complex linear mixed-effects model to account for measurement error in childhood phthalate measures. Thus, we included subject-specific age and age-squared terms for the age of urine sample collection from age 1 to 8 years. We included subject-specific intercepts and linear age slopes, while age squared was fixed. For each subject, we used the estimated best linear unbiased predictor to calculate phthalate metabolite concentrations at each time point and averaged across childhood. The average childhood value was calculated by dividing the area under the estimated trajectories of phthalate metabolite concentrations curve by the length of time (age, 1–8 years). This method accounts for measurement error, individual variation in the number of samples ascertained, and exposure time trends in urinary phthalate metabolite concentrations. For the remainder of the manuscript, we refer to these measurement error corrected values as urinary phthalate metabolite concentrations.

Cognitive outcomes

Three trained examiners assessed children's cognitive abilities using the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) at age 5 years (n = 202) and the Wechsler Intelligence Scale for Children-IV (WISC-IV) at age 8 years (n = 220).[53–55] Following initial training and certification on these assessments, quality control checks were unannounced and completed (by K.Y.) every 6 months to ensure IQ measures were properly administered and accurately scored. Both instruments assess children's overall intellectual abilities (Full-Scale Intelligence Quotient [FSIQ]) based on subscales for verbal comprehension, working memory, processing speed, and others. In this analysis, we focused on FSIQ as our primary outcome. The FSIQ scores from the WPPSI-III are comparable to those from the WISC-IV, and thus we averaged them if more than one measurement was available to maximize sample size and accommodate our modeling approach.[53,54] We used standardized FSIQ scores (i.e., mean = 100 and SD = 15) based on the US normative data. Higher scores indicate better cognitive performance.

Covariate assessment

We used directed acyclic graphs to identify potential confounders that may be associated with both race and IQ, considering how confounders may bias the association between race and child IQ through exposure to phthalates during gestation and childhood (eFigure 2; http://links.lww.com/EE/A183 and eFigure 3; http://links.lww.com/EE/A183). Sociodemographic and maternal factors were collected using standardized questionnaires administered by trained interviewers. Child race was determined based on maternal report and assessed separately from maternal race. Child sex was abstracted from hospital medical charts.[56] We derived maternal prepregnancy body mass index (BMI) using self-reported height and weight and imputed weight for mothers with missing data.[57] Briefly, a SuperLearner algorithm was used to predict prepregnancy weight based on covariates found to be significantly associated with weight from HOME study participants with nonmissing data.[58] These covariates included maternal education, marital status, maternal race, insurance status, parity, income, cotinine concentrations, height, and chart-abstracted weight between 13 and 19 weeks of gestation. We assessed secondhand and active tobacco smoke exposure during pregnancy by averaging cotinine concentrations from serum collected at 16 and 26 weeks of gestation and using previously established thresholds to determine active, secondhand, and nonsmoking (unexposed) status using serum cotinine were ≥0.3, <3.0 to ≥0.015, and <0.015 ng/mL, respectively.[59] Maternal cognitive abilities were assessed when children were ≥1 year using the Wechsler Abbreviated Scale of Intelligence.[60] In primary analyses, we adjusted for maternal age, prepregnancy BMI, household income, $\log_{10}$-transformed cotinine concentration, and maternal FSIQ scores.

Statistical analyses

We calculated univariate summary statistics and characterized distributions of maternal sociodemographic and reproductive factors by child race. We further explored the distribution of urinary phthalate metabolite concentrations across visits by calculating univariate statistics and creating violin plots.[61] We also calculated mean child FSIQ scores by strata of the key covariates stratified by race.

Mediation analyses

First, we quantified the racial disparities in child FSIQ scores. We used a linear mixed model to estimate unadjusted and covariate-adjusted differences in FSIQ scores between Black and White children. This represents the total effect. Second, we examined racial disparities in average gestational and childhood urinary phthalate metabolite concentrations by examining univariate statistics and percentage differences in concentrations of urinary phthalate metabolites between Black and White children. In cases where we identified racial differences in average child urinary phthalate metabolite concentrations, we investigated if differences in urinary phthalate concentrations were also present at individual time points at ages 1, 2, 3, 4, 5, and 8 years.

Third, for phthalates that differed by race, we conducted mediation analyses following previously established methods for evaluating health disparities by Bellavia et al.[44] We evaluated if associations between child race and average FSIQ score were mediated by gestational or childhood urinary phthalate metabolite concentrations using the R package, Mediation.[44,62] This package estimates the average causal indirect effects, average direct effects, and total effects based on previously established methods for linear structural equation modeling.[63]

We estimated the covariate-adjusted, average direct (association between race and child FSIQ), and average indirect effects (association between race and child FSIQ through average gestational and childhood urinary phthalate concentrations). Note that in models of average phthalate metabolite concentrations for childhood, we only included urinary phthalate concentrations from ages 1, 2, 3, 4, and 5 years, as the outcome of childhood FSIQ score included values at ages 5 and 8 years.

To assess mediation by average gestational and childhood urinary phthalate concentrations, we focused on the natural indirect effect, which is the effect of child race on FSIQ that operates only by changing the value of urinary phthalate metabolite concentrations, as this provides information on the pathways where disparities in child FSIQ originate. We also present the controlled direct effects, which are the effects of child race on child FSIQ score after fixing values of urinary phthalate concentrations (eFigure 4; http://links.lww.com/EE/A183).

Secondary and sensitivity analyses

We conducted mediation analyses to quantify the total, direct, and indirect effects of select phthalate metabolites on the association between child race and child FSIQ using phthalate concentrations at individual time points during childhood. Note that for mediation analyses at age 8 years, child FSIQ at age

8 years was used as the outcome (as opposed to average child FSIQ, which includes FSIQ scores ascertained at ages 5 and 8 years).

We conducted sensitivity analyses to assess the robustness of our results to various adjustments. In addition to previously specified covariates, we adjusted for child sex, quality, and quantity of the caregiving environment as measured using the Home Observation for Measurement of the Environment (HOME inventory),[64] time-varying blood lead concentrations, neighborhood socioeconomic position, maternal educational attainment, and parity. HOME inventory measures were assessed by study staff during home visits when children were 1 year of age. The HOME inventory is designed to measure the quality and quantity of stimulation and support available to children in their home.[64] In addition to previously identified covariates, we also adjusted for blood lead concentrations at each time point where the relation between phthalates and FSIQ were assessed. We collected whole blood samples from women at 16 and 26 weeks of gestation and children at ages 1, 2, 3, 4, 5, and 8 years using collection materials prescreened for lead contamination.[65] Blood lead concentrations were quantified at the Centers for Disease Control and Prevention laboratories using inductively coupled plasma mass spectrometry.[66] Neighborhood socioeconomic position among HOME study participants was previously assessed using data from 2000 US census records.[67,68] For each participant's 2000 US census tract at 20 weeks of gestation, neighborhood socioeconomic position scores were calculated based on log median household income, percentage of households with interest, dividend, or rental income, the log median value of housing unit, percent of residents who completed high school or college, and percentage of residents with executive, managerial, or professional occupations. For each measure, *Z* scores were calculated, summed, and categorized into terciles where lower scores represent lower socioeconomic position. We conducted statistical analyses using R Studio (version 4.0.3; R Development Core Team).[69]

Results

Univariate statistics: study participants and FSIQ scores

Among 253 mother-child pairs, 90 (38%) were Black children and 145 (62%) were White children. Compared with White children, Black children were more likely to have mothers who were younger (<25 years at the time of gestation) and had acquired less education, with lower household incomes, who were more likely to smoke during pregnancy, be multiparous, and have higher prepregnancy BMI (Table 1; eTable 1; http://links.lww.com/EE/A183). For both Black and White children, FSIQ scores were positively associated with maternal age, maternal education, and household income (Table 2).

In unadjusted analyses, FSIQ scores among Black children were 16 points lower (β = −16.0 [95% confidence interval (CI) = −19.4, −12.7]) than among White Children. After adjusting for covariates, Black children had FSIQ scores 7 points (β = −7.0 [95% CI, −12.1, −1.8]) lower than White children.

Univariate statistics: mediators (phthalate metabolites)

Urinary MCPP, MiBP, MBzP, MBP, and ΣDEHP concentrations were lower during gestation relative to childhood (Figure 1; eTable 2; http://links.lww.com/EE/A183). During gestation and childhood, MBzP (gestation percentage difference, 16 [95% CI = 13, 21]; childhood percentage difference, 13 [95% CI = 12, 15]) and MEP (gestation percentage difference, 15 [95% CI = 11, 19]; childhood percentage difference, 21 [95% CI = 19, 24]) concentrations were higher in Black compared with White children (eTable 2; http://links.lww.com/EE/A183). During pregnancy, urinary ΣDEHP concentrations were higher in White than Black mothers. All other phthalate metabolite concentrations were similar during gestation and childhood in Black and White participants (percentage differences for average gestation or average childhood, <13; Figure 2). Thus, for subsequent analyses, we focused on MBzP and MEP concentrations.

Table 1.

Characteristics of mother-child dyads with follow-up at age 5 and/or 8 years by child race, according to covariates: the HOME study (2003–2006)

Variable	Full sample n (%)	Black n (%)	White n (%)
Overall	253 (100)	90 (36)	145 (57)
Maternal age (years)			
<25	57 (23)	45 (50)	8 (5)
25 to <35	154 (61)	40 (44)	104 (72)
35+	42 (17)	5 (6)	33 (23)
Maternal education			
High school or less	62 (25)	51 (57)	7 (5)
Some college	71 (28)	31 (34)	37 (26)
Completed college	120 (47)	8 (9)	101 (70)
Maternal race			
Non-Hispanic Black	83 (33)	82 (91)	1 (0)
Non-Hispanic White	152 (60)	5 (6)	142 (98)
Other	18 (7)	3 (3)	2 (1)
Annual income			
<$30,000	82 (32)	70 (78)	9 (6)
$30,000–$75,000	77 (30)	17 (19)	55 (38)
≥$75,000	94 (37)	3 (3)	81 (56)
Maternal smoking[a]			
Unexposed	78 (31)	5 (6)	66 (56)
Secondhand smoking	116 (46)	40 (44)	71 (49)
Active smoking	59 (23)	45 (50)	8 (6)
Parity			
0	114 (45)	29 (32)	73 (50)
1	79 (31)	29 (32)	46 (32)
2+	60 (24)	32 (36)	26 (18)
Prepregnancy BMI (kg/m^2)			
Normal/underweight: <25	125 (49)	32 (36)	83 (57)
Overweight: ≥25 to <30	65 (26)	23 (26)	38 (26)
Obese: ≥30	63 (25)	35 (39)	24 (17)
Child sex			
Female	140 (55)	57 (63)	76 (52)

Percentages reflect columns (e.g., race) within each study sample characteristic.

[a]Maternal smoking during pregnancy estimated based on maternal serum cotinine concentrations during pregnancy. Unexposed smoking exposure defined as having serum cotinine concentrations <0.015 ng/mL, secondhand smoking exposure is defined by serum cotinine concentrations between 0.015 and <3.00 ng/mL, and active smoking includes those with serum cotinine concentrations ≥3.00 ng/mL.

Mediation analyses

Gestational phthalate metabolite concentrations did not independently contribute to racial disparities in child FSIQ (Table 3). Average childhood MEP concentrations showed modest evidence for mediation, but not MBzP. Each 10-fold increase in average childhood MEP concentrations contributed to −1.1 point (95% CI = −3.0, 0.8) difference in the natural indirect effect between race and FSIQ, though the confidence interval includes the null. The direct effect of race on child FSIQ scores, controlling for average childhood MEP concentration, was modestly diminished (β = −5.8 [95% CI = −12, −0.4]).

Secondary analyses

The natural indirect effects of MEP on IQ appeared to be stronger during early childhood (Figure 3). The strongest natural indirect effect of MEP on child FSIQ scores was observed at age 2 years (β = −1.9 [95% CI = −4.7, 0.7]; eTable 4; http://links.

Table 2.

Full-scale Intelligence Quotient scores averaged[a] from ages 5 and 8 years according to covariates among mother-child dyads with child race, according to covariates: the HOME study (2003–2006)

	Non-Hispanic Black		Non-Hispanic White	
Variable	**n**	**Mean ± SD**	**n**	**Mean ± SD**
Overall	90	91 ± 13	145	107 ± 12
Maternal age (years)				
<25	45	89 ± 15	8	101 ± 14
25 to <35	40	91 ± 11	104	107 ± 12
35+	5	103 ± 13	33	108 ± 13
Maternal education				
High school or less	51	88 ± 14	7	98 ± 17
Some college	31	92 ± 13	37	103 ± 13
Completed college	8	102 ± 5.9	101	109 ± 11
Annual income				
<$30,000	70	89 ± 14	9	98 ± 19
$30,000 to $75,000	17	95 ± 11	55	104 ± 12
≥$75,000	3	103 ± 6.6	81	110 ± 10
Maternal smoking[b]				
Unexposed	5	96 ± 7.2	66	106 ± 12
Secondhand smoking	40	91 ± 12	71	107 ± 13
Active smoking	45	91 ± 17	8	111 ± 17
Parity				
0	29	88 ± 14	73	109 ± 13
1	29	91 ± 13	46	107 ± 10
2+	32	93 ± 13	26	103 ± 12
Prepregnancy BMI (kg/m^2)				
Normal/underweight: <25	32	88 ± 15	83	108 ± 12
Overweight: ≥25 to <30	23	95 ± 11	38	107 ± 13
Obese: ≥30	35	90 ± 13	24	104 ± 14
Child sex				
Male	33	89 ± 13	69	105 ± 13
Female	57	92 ± 14	76	109 ± 12

[a]Average FSIQ values represent the arithmetic mean of repeated child FSIQ scores. In cases where children only had one FSIQ measure, that value was used to represent the mean. Of the full analytic sample (n = 253), n = 169 children had two measures of FSIQ ascertained at 5 and 8 yrs (67%).

[b]Maternal smoking during pregnancy estimated based on maternal serum cotinine concentrations during pregnancy. Unexposed smoking exposure defined as having serum cotinine concentrations <0.015 ng/mL, secondhand smoking exposure is defined by serum cotinine concentrations between 0.015 and <3.00 ng/mL, and active smoking includes those with serum cotinine concentrations ≥3.00 ng/mL.

lww.com/EE/A183). While the 95% CI of the indirect effect estimate included the null value, the residual disparity in FSIQ after controlling for MEP was attenuated to less than 5 points (β = –4.9 [95% CI = –11.5, 1.6]; Figure 4).

Sensitivity analyses

We conducted sensitivity analyses for MEP. Additional adjustment for child sex, caregiving environment (HOME scores), or parity did not substantially change the pattern of results (eTable 5; http://links.lww.com/EE/A183). However, the total effect of race diminished once we adjusted for additional socioeconomic and environmental factors. Specifically, adjustment for maternal neighborhood socioeconomic position during gestation reduced the racial disparity in child FSIQ scores from 7.0 points (95% CI = –12.1, –1.8) to 6.1 points (95% CI = –11.7, –0.6). Adjusting for time-varying blood lead concentrations also decreased the disparity in child FSIQ scores, with the strongest indirect effect of MEP on child FSIQ observed at age 1 year from 7.0 points to 6.4 points (95% CI = –12.4, –0.4). Adjusting for maternal educational attainment also reduced the racial disparity in child FSIQ from 7.0 points to 6.3 points (95% CI = –11.5, –1.1). In fully adjusted models, where we considered all primary covariates and those included in sensitivity analyses, the racial disparity in child FSIQ was further attenuated to 3.4 points (95% CI = –10.5, 3.7).

Discussion

By applying mediation methods to a longitudinal birth cohort, we sought to determine if racial disparities in children's cognitive abilities could be explained by early life phthalate exposure. During gestation and early childhood, urinary concentrations of MBzP and MEP were higher among Black than White children. Furthermore, child FSIQ scores were on average 7 points lower among Black children than White children after adjusting for socioeconomic factors. We did not observe compelling evidence that phthalate concentrations mediated racial disparities in child FSIQ, with the exception of MEP. We speculate this could be, in part, due to the disparities in urinary MEP concentrations observed between Black and White children, whereas urinary concentrations of other phthalates did not differ substantially.

There was some evidence that MEP weakly mediated the association between race and child FSIQ. Other investigators have documented racial disparities in child FSIQ[31–33] and differences in phthalate exposure across racial groups.[13,38,39,43,70] Moreover, some studies report associations between gestational and early life phthalate exposure with decreased child IQ.[16–22,24,25] Direct and indirect effects of all phthalate metabolites showed an inverse association with child cognitive abilities, with the exception of MCPP during childhood (β = 1.5 points [95% CI = 0.2, 3.2]). This finding was counterintuitive, as we did not expect phthalates to have a protective effect; however, these results could be spurious as most indirect coefficients were centered around the null. Further, MCPP is a nonspecific phthalate metabolite, as it represents a breakdown product of several other higher molecular weight phthalate diesters.[71] Consistent with our prior work in the HOME study, higher urinary MEP concentrations during childhood were associated with lower FSIQ.[16] The lack of stronger mediating effects might be due to the relatively modest association that MEP and other phthalates have with child cognitive abilities. Note, while prior work in the HOME study[16] did not identify strong evidence for sex-specific associations, future work may want to consider this in analyses investigating health disparities.

MEP is of particular interest for several reasons. First, urinary concentrations of MEP are substantially higher in Black populations than White ones.[5,72,73] Independent of socioeconomic position, Black women have higher body burdens of some phthalates and other environmental chemicals than White women, partly due to consumer beauty product use.[38,74–77] In addition, Black women who are pregnant reported more use and frequency of use of hair care products during pregnancy than White women.[42,78] Second, diethyl phthalate (DEP), the parent compound of MEP, is commonly used in a variety of consumer products such as makeup, nail polish, perfume, deodorant, and various hair products (spray, dyes, mousse, crème rinse, nutrients, and conditioners).[5,25–28,72,79] The primary route of exposure for DEP is dermal absorption and suggests that frequent use of DEP containing products may result in higher internal body burdens of MEP compared to phthalates with different routes of exposure.[72] In fact, frequent use of hair products during pregnancy, more commonly used among Black than White women, may be associated with decreases in gestational age,[42] which is a predictor for child neurodevelopmental deficits.[80] Some of these products are heavily marketed to Black communities, highlighting how cosmetics can be an environmental injustice[81] but also a potentially modifiable source of exposure.[42] This is an important consideration for future work, as consumers generally are often unaware of harmful chemical exposures present in their personal care products.[81–85] Differences in exposure

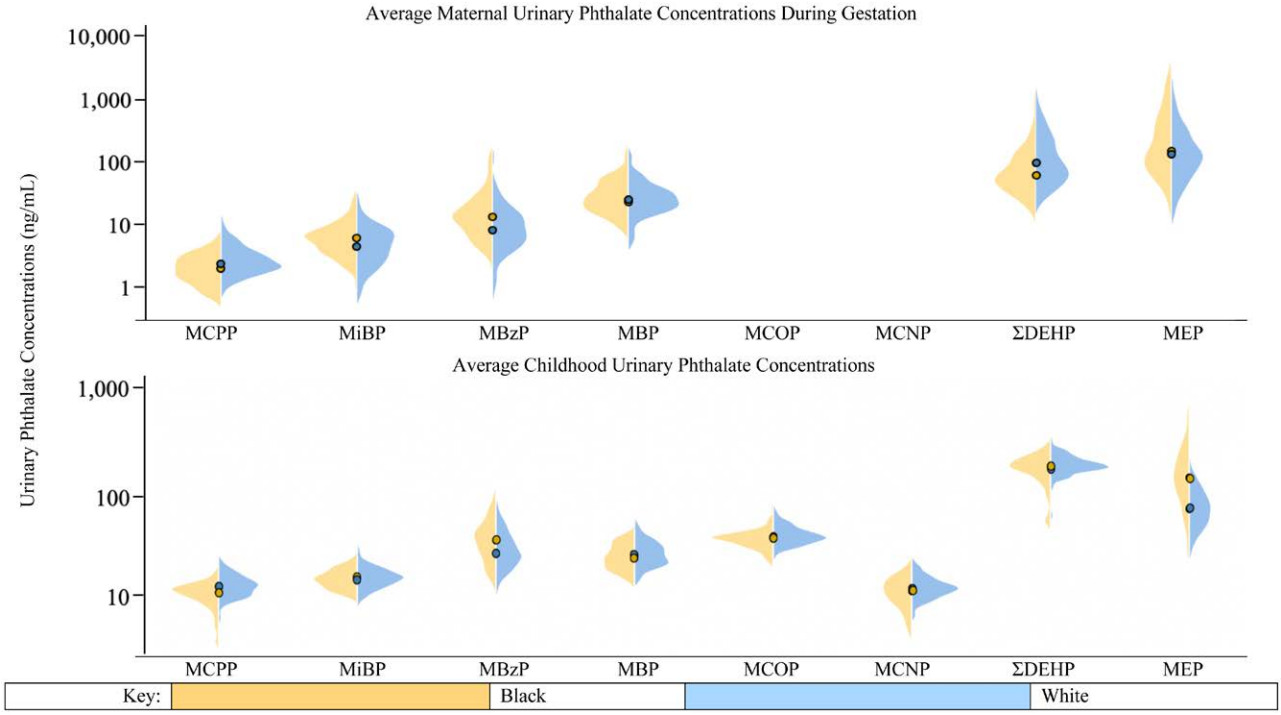

Figure 1. Violin plots of error corrected urinary phthalate metabolite concentrations averaged for gestation and childhood periods among mother-child dyads: the HOME study (2003–2006). The shaded area represents the density function of phthalate metabolite concentrations, and the dot represents the median. Repeated maternal urinary phthalate metabolites assessed at 16 and 26 weeks of gestation. Repeated child urinary phthalate metabolites assessed at ages 1, 2, 3, 4, and 5 years. Note, the average value of urinary phthalate concentrations does not include those collected at age 8 years since the primary outcome, average FSIQ consists of scores from ages 5 and 8 years. Concentrations of ΣDEHP (in ng/mL) were calculated using the following formula: ΣDEHP (ng/mL) = (MECPP [ng/mL]/308.33 g/mol + MEHHP [ng/mL]/294.347 g/mol + MEOHP [ng/mL]/292.331 g/mol) × 308.33 g/mol.

to phthalate-containing products could, in part, be due to discriminative advertising practices,[82,83] directed to maintain European, White beauty standards (i.e., hair relaxers and skin lighteners).[84,86]

Our study has some limitations. First, the sample size was modest, and it varied during follow-up. We retained fewer Black than White families, which may result in selection bias. The reductions in sample size due to loss to follow-up also

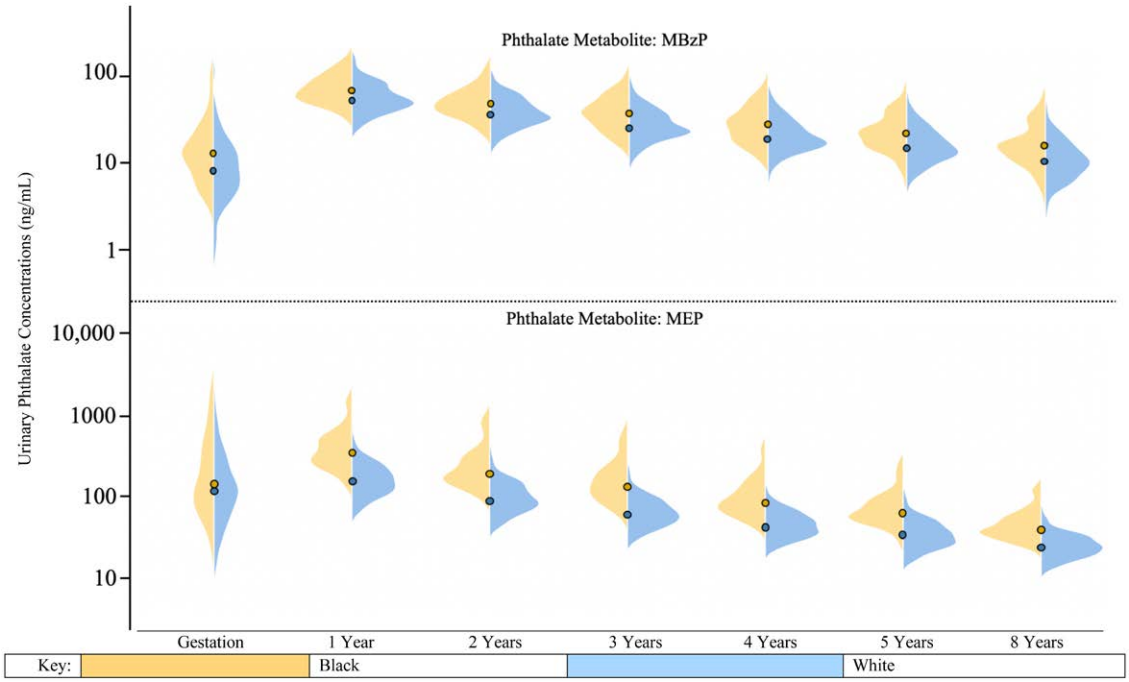

Figure 2. Violin plots of error corrected urinary phthalate metabolite concentrations during gestation and childhood among mother-child dyads: the HOME study (2003–2006). The shaded area represents the density function of phthalate metabolite concentrations, and the dot represents the median. Repeated maternal urinary phthalate metabolites assessed at 16 and 26 weeks of gestation.

Table 3.

Adjusted[a] direct and indirect associations between child race and average child FSIQ scores at ages 5 and/or 8 years[b] mediated through gestational and childhood urinary phthalate metabolite concentrations[c]: the HOME study (2003–2006)

Metabolite	Visit	Gestation[c] β (95% CI)	P	Childhood[d] β (95% CI)	P
MCPP	Direct effect	−6.7 (−11.9, −1.6)	0.01	−8.6 (−13.8, −3.3)	<0.01
	Indirect effect	−0.2 (−1.7, 1.3)	0.82	1.5 (0.2, 3.2)	0.02
MiBP	Direct effect	−7.0 (−12.3, 1.9)	<0.01	−7.1 (−12.2, −1.9)	0.01
	Indirect effect	0.1 (−0.3, 0.7)	0.72	0.0 (−0.7, 0.5)	0.86
MBzP	Direct effect	−7.2 (−12.6, −1.5)	0.02	−7.4 (−12.2, −2.3)	<0.01
	Indirect effect	0.1 (−0.4, 0.7)	0.77	0.5 (−0.3, 1.7)	0.23
MBP	Direct effect	−7.0 (−11.5, −1.9)	<0.01	−6.9 (−11.9, −1.9)	<0.01
	Indirect effect	−0.1 (−0.5, 0.3)	0.81	−0.1 (−0.9, 0.5)	0.70
MCNP[e]	Direct effect	—	—	−7.1 (−12.5, −1.7)	0.01
	Indirect effect	—	—	0.0 (−0.7, 0.7)	0.91
MCOP[e]	Direct effect	—	—	−7.1 (−12.2, −1.6)	<0.01
	Indirect effect	—	—	0.1 (−0.6, 1.0)	0.72
ΣDEHP[f]	Direct effect	−6.3 (−11.8, −1.0)	0.01	−7.0 (−12.3, −1.7)	0.01
	Indirect effect	−0.6 (−1.9, 0.4)	0.21	0.0 (−0.7, 0.7)	0.92
MEP	Direct effect	−7.0 (−12.2, −2.0)	<0.01	−5.8 (−11.6, −0.4)	0.03
	Indirect effect	0.1 (−0.4, 0.8)	0.78	−1.1 (−3.0, 0.8)	0.24

[a]Adjusted for maternal age (continuous), prepregnancy BMI (continuous), income (continuous), log-10 transformed average gestational cotinine concentration (continuous), and maternal FSIQ scores (continuous).

[b]Average FSIQ values represent the arithmetic mean of repeated child FSIQ scores. In cases where children only had one FSIQ measure, that value was used to represent the mean.

[c]Repeated maternal urinary phthalate metabolites assessed at 16 and 26 weeks of gestation.

[d]Repeated child urinary phthalate metabolites assessed at ages 1, 2, 3, 4, and 5 yrs. Note, the average value of urinary phthalate concentrations does not include those collected at age 8 yrs since the primary outcome, average FSIQ consists of scores from ages 5 and 8 yrs.

[e]We did not measure MCNP or MCOP concentrations from maternal urine samples, as the method for these biomarkers had not yet been developed at the time of assays.

[f]Concentrations of ΣDEHP (in ng/mL) were calculated using the following formula: ΣDEHP (ng/mL) = (MECPP [ng/mL]/308.33 g/mol + MEHHP [ng/mL]/294.347 g/mol + MEOHP [ng/mL]/292.331 g/mol) × 308.33 g/mol.

reduce statistical power and precision, limiting our ability to observe subtler associations. Second, measures of child cognition, including assessing IQ, are historically controversial.[26–30] Despite efforts to reduce racial, ethnic, and socioeconomic biases in tools for assessing intelligence, some biases remain.[31,33,37]

Third, we were unable to consider multiple mediators in our analysis to consider both sources of phthalate exposure (i.e., daily personal care product use or fast-food consumption) in addition to phthalate biomarkers, as recommended by Bellavia et al.[44] While assessing urinary concentrations of phthalate metabolites can provide an assessment of phthalate exposure from multiple sources, it remains difficult to directly translate these findings to personal recommendations or policy.[44] For example, it may be more practical to intervene on behavior patterns related to phthalate-containing product use as a modifiable exposure, rather than any one specific phthalate metabolite.[1] Future work could consider phthalate exposure sources, such as hair or beauty products, in addition to biomarkers of phthalates when investigating racial disparities in child FSIQ.

Fourth, while we adjusted for many relevant covariates, residual confounding remains a possibility. For example, adjusting for income as a measure of socioeconomic status may not fully capture the cumulative effects of daily experiences for minority populations, such as racism or chronic stress.[33,37] Further, given that adjustment for socioeconomic and environmental factors attenuated the racial differences in IQ by almost half of an SD in IQ scores, additional environmental factors are likely to play a major role in explaining racial disparities in IQ. This is further supported from sensitivity analyses, where additional adjustment for socioeconomic position, blood lead concentrations, and parity attenuated the effect of race on the association between phthalates and FSIQ. In fully adjusted models where we considered all covariates from primary and sensitivity analyses, we observed a large attenuation of racial

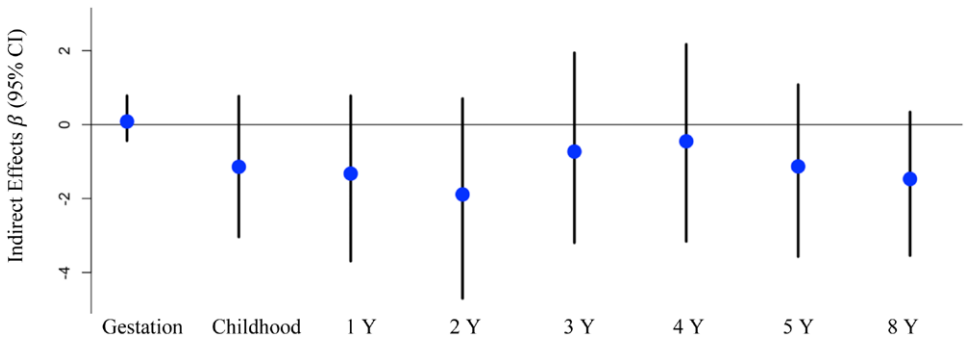

Figure 3. Adjusted indirect associations between child race and average child FSIQ at ages 5 and/or 8 years mediated through gestational and childhood urinary MEP concentrations: the HOME study (2003–2006). Adjusted for maternal age (continuous), prepregnancy BMI (continuous), income (continuous), log-10 transformed average gestational cotinine concentration (continuous), and maternal FSIQ scores (continuous). Repeated maternal urinary phthalate metabolites assessed at 16 and 26 weeks of gestation. Repeated child urinary phthalate metabolites assessed at ages 1, 2, 3, 4, and 5 years. Note, the average value of urinary phthalate concentrations does not include those collected at age 8 years since the primary outcome, average FSIQ consists of scores from ages 5 and 8 years.

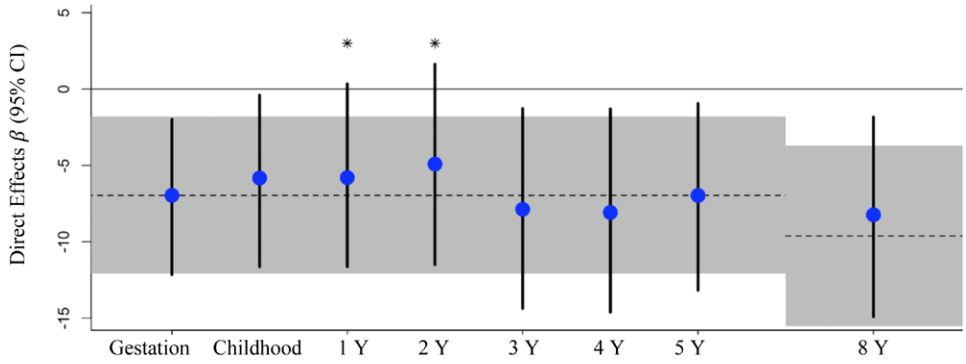

Figure 4. Adjusted direct associations between child race and average child FSIQ at ages 5 or 8 years before (dotted line and gray band) and after (point and whisker) controlling for gestational or childhood urinary MEP concentrations: the HOME study (2003–2006). Adjusted for maternal age (continuous), prepregnancy BMI (continuous), income (continuous), log-10 transformed average gestational cotinine concentration (continuous), and maternal FSIQ scores (continuous). Repeated maternal urinary phthalate metabolites assessed at 16 and 26 weeks of gestation. Repeated child urinary phthalate metabolites assessed at ages 1, 2, 3, 4, and 5 years. Note, the average value of urinary phthalate concentrations does not include those collected at age 8 years since the primary outcome, average FSIQ consists of scores from ages 5 and 8 years. The shaded area and dashed line represents the total effect of child race on average child FSIQ score. Note that the total effect for average FSIQ score only corresponds to time points assessed before age 8 years. The total effect for age 8 years is specific to the FSIQ score obtained at age 8 years. The solid horizontal line at 0 indicates no difference in racial disparities in child FSIQ scores. The asterisk indicates a nonsignificant controlled direct effect.

differences in IQ, emphasizing the potential for multiple maternal, child, and community-level factors to be responsible for disparities in child IQ scores. It is also important to reiterate that race is a social construct, rather than a biological variable. As such, including race as a variable in our models does not capture the totality of minority and marginalized people's experience that may impact child cognitive development. Further, we were underpowered to examine other race or ethnicities in this study, and given the regional nature of the study location (Cincinnati, OH), our findings may not be generalizable to other major US cities. While we considered blood lead levels as an additional coexposure, we did not consider other known chemicals (i.e., organophosphates or polychlorinated biphenyls).[17,87] Future work may consider other exposures, as well as chemical mixtures as potential mediators of the race-cognitive abilities relation.[88]

Fifth, it is possible our study findings are subject to type I error (in the case of MEP), as we did not account for multiple comparisons. We attempted to mitigate this by conducting our statistical analyses in a stepwise fashion, as to reduce the overall number of statistical tests. Further, secondary and sensitivity analyses were only conducted for MEP, as this was the only phthalate metabolite that was found to partly mediate the relation between child race and cognitive abilities.

This study had several strengths. First, we had extensive biomarkers of phthalate exposure and two measures of cognitive ability. Most published studies only had one phthalate biomarker, which is subject to substantial within-person variation due to the episodic nature of phthalate exposure and the short half-life of phthalates.[3,9,89,90] Second, we used regression calibration to repeated urinary phthalate concentrations from gestation and early childhood to account for measurement error. Third, we applied previously established epidemiological methods to evaluate phthalates as a source of racial disparities in child FSIQ.[44]

Conclusion

We observed racial disparities in child cognition and exposure to some phthalates during gestation, infancy, and childhood. Overall, we did not find that phthalates mediated racial disparities in child IQ. However, further studies are warranted to determine if efforts to reduce exposure to neurotoxicants may diminish some of the disparities in cognitive abilities observed between Black and White children.

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