Title

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Journal

Environmental Health Perspectives, 131(12)

ISSN

1542-4359

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Publication Date

2023-12-01

DOI

10.1289/ehp12831

Peer reviewed

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP12831.

Racial and Ethnic Disparities in Phthalate Exposure and Preterm Birth: A Pooled Study of Sixteen U.S. Cohorts

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Background: Phthalate exposures are ubiquitous during pregnancy and may contribute to racial and ethnic disparities in preterm birth.

Objectives: We investigated race and ethnicity in the relationship between biomarkers of phthalate exposure and preterm birth by examining: *a*) how hypothetical reductions in racial and ethnic disparities in phthalate metabolites might reduce the probability of preterm birth; and *b*) exposure–response models stratified by race and ethnicity.

Methods: We pooled individual-level data on 6,045 pregnancies from 16 U.S. cohorts. We investigated covariate-adjusted differences in nine urinary phthalate metabolite concentrations by race and ethnicity [non-Hispanic White (White, 43%), non-Hispanic Black (Black, 13%), Hispanic/Latina

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Supplemental Material is available online (https://doi.org/10.1289/EHP12831).

J.M.B. reported grants from the National Institutes of Health during the conduct of the study and served as an expert witness for plaintiffs in litigation related to perfluoroalkyl substances–contaminated drinking water for Morgan & Morgan law firm outside the submitted work. T.F.M. reported research support to their institution and equity from NxPrenatal Inc.; serving on the scientific advisory board of and equity from Mirvie Inc.; and serving on the scientific advisory board of and cash payment from Hoffmann-La Roche and Comanche Biopharma.

Received 1 February 2023; Revised 17 November 2023; Accepted 27 November 2023; Published 20 December 2023.

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(38%), and Asian/Pacific Islander (3%)]. Using g-computation, we estimated changes in the probability of preterm birth under hypothetical interventions to eliminate disparities in levels of urinary phthalate metabolites by proportionally lowering average concentrations in Black and Hispanic/Latina participants to be approximately equal to the averages in White participants. We also used race and ethnicity-stratified logistic regression to characterize associations between phthalate metabolites and preterm birth.

Results: In comparison with concentrations among White participants, adjusted mean phthalate metabolite concentrations were consistently higher among Black and Hispanic/Latina participants by 23%–148% and 4%–94%, respectively. Asian/Pacific Islander participants had metabolite levels that were similar to those of White participants. Hypothetical interventions to reduce disparities in metabolite mixtures were associated with lower probabilities of preterm birth for Black [13% relative reduction; 95% confidence interval (CI): −34%, 8.6%] and Hispanic/Latina (9% relative reduction; 95% CI: −19%, 0.8%) participants. Odds ratios for preterm birth in association with phthalate metabolites demonstrated heterogeneity by race and ethnicity for two individual metabolites (mono-*n*-butyl and monoisobutyl phthalate), with positive associations that were larger in magnitude observed among Black or Hispanic/Latina participants.

Conclusions: Phthalate metabolite concentrations differed substantially by race and ethnicity. Our results show hypothetical interventions to reduce population-level racial and ethnic disparities in biomarkers of phthalate exposure could potentially reduce the probability of preterm birth. https://doi.org/10.1289/EHP12831

Introduction

Preterm birth is a major cause of neonatal mortality and morbidity that may perpetuate impacts on intergenerational health.[1] In the United States, preterm birth rates increased over the past several decades, reaching a peak of 10.5% during the period 2021–2022.[2,3] Furthermore, racial and ethnic disparities in preterm birth are prevalent. In 2021, the highest proportions of preterm births occurred among non-Hispanic Black (14.7%), non-Hispanic Native Hawaiian or other Pacific Islander (12.6%), non-Hispanic American Indian or Alaskan Native (12.3%), and Hispanic or Latino populations (10.2%), with a lower proportion among the non-Hispanic White (9.5%) and Asian (9.2%) populations.[2] Racial and ethnic disparities in preterm birth are attributable to a number of complex and interrelated factors. Structural racism is widely considered to be the primary upstream cause of racial and ethnic disparities in preterm birth and can take many forms,[4] such as systemic barriers to economic opportunity,[5,6] residential segregation,[6,7] or increased exposure to psychosocial stressors.[8,9] For example, housing policies at the national and local levels can create residential segregation by race and ethnicity, which can have profound impacts on the place-based resources necessary to promote healthy living among residents (e.g., accessible food stores, employment opportunities, social services, and parks and recreational facilities). Collectively, these forces can shape racial and ethnic inequities in health, including preterm birth.[6]

One understudied pathway by which social and structural determinants can increase preterm birth risk is by increasing disparities in environmental exposures, including synthetic chemicals used in consumer and personal care products.[6,10] There are racial and ethnic disparities in chemical exposures from beauty products,[11] as well as from certain processed foods that are likely to have higher contaminant levels.[12] Prenatal exposure to synthetic chemicals, including phthalates, is increasingly considered an important risk factor for preterm birth and its racial and ethnic disparities.[13,14] Phthalates are used extensively in commercial goods, such as personal care products, food packaging materials, and medications.[15] Because of their widespread use, urinary phthalate metabolites are ubiquitous in the U.S. population and may be especially concerning among pregnant individuals.[16–18] Phthalate exposure is hypothesized to be associated with a range of pregnancy complications, including preterm birth,[18] by mechanisms such as dysregulation of biological processes involving inflammation, oxidative stress, endocrine activity, placental development and function, and epigenetic and transcriptomic regulations, among other interrelated and complex processes.[19–22]

Nationally representative data has shown racial and ethnic differences in urinary phthalate metabolite concentrations among nonpregnant populations, with non-Hispanic Black women exhibiting the highest exposure levels.[17,23–25] Differences in phthalate exposures may arise from racial and ethnic differences in personal care product use and composition,[11,14,23,26] as well as differences in dietary exposures.[10,12,27,28] These proximate drivers of exposure have been shown to be influenced by systems of power and oppression such as structural racism.[11] For example, racial residential segregation impacts food landscapes and dietary behavior such as fast food consumption,[28] which has been associated with greater phthalate exposure.[12,27] These associations often exist independent of socioeconomic status. For example, predominately Black residential areas in New York City have higher densities of fast food restaurants than predominately White areas, and high-income Black neighborhoods have exposures similar to those of low-income Black neighborhoods.[28]

Given the relevance of phthalate exposures to racial health equity, prior cohort studies in the United States have sought to characterize racial and ethnic differences in phthalate exposure during pregnancy but were limited by relatively small sample sizes across racial and ethnic groups.[14,16,29–31] Additional characterization of exposure disparities in the context of pregnancy is crucial because patterns of consumer product use may change during pregnancy in ways that differ by racial or ethnic background[32,33] and because gestation may be a susceptible period for exposure.

In a pooled analysis of 16 prospective pregnancy cohorts in the United States, we found that hypothetically reducing levels of a urinary phthalate metabolite mixture was associated with fewer preterm births.[18] In extending that work and using the same pooled data, our goal for the present study was to examine the role of racial and ethnic disparities in the relationship between phthalate exposure and preterm birth. First, we sought to characterize racial and ethnic disparities in urinary phthalate metabolite concentrations and examine how hypothetical interventions to remove these exposure disparities could reduce preterm births. Second, we investigated whether associations between urinary phthalate metabolite concentrations and preterm birth varied across racial and ethnic groups in a stratified analysis. This research was addressed with the understanding that co-occurring social and environmental factors, and not underlying genetic differences,[4] influence the likelihood of phthalate exposures across racial and ethnic groups and lead to differential susceptibility to exposure effects.

Methods

Study Design and Population

The Pooled Study of Phthalate Exposure and Preterm Birth comprises data from 16 studies of phthalate exposure in pregnancy conducted in the United States, with data published through May 2019.[18] The primary eligibility criteria for study inclusion in the pooled analysis were that the study used an observational study design, was conducted in the United States or a U.S. territory (e.g., Puerto Rico), included >50 participants, enrolled participants during or prior to index pregnancy, gathered information about gestational age at delivery, and measured phthalate metabolites in urine

specimens collected during pregnancy.[18] All participants had live births between 1983 and 2018.[18] Ethics approval was granted from the respective institutional review board (IRB) or human research ethics committee of participating institutions. Written or verbal informed consent was provided by participants. Analysis of the data from all of the included cohorts at the National Institute of Environmental Health Sciences (NIEHS) was deemed exempt by the NIEHS IRB.

The design characteristics of participating studies have been previously described in detail.[18] Study acronyms and citations are provided in Table S1. Gestational age at delivery was determined by date of last menstrual period, early pregnancy ultrasonography, date of conception in pregnancies using assisted reproductive technologies, or a combination thereof.[18] We used delivery prior to 37 wk' gestation to identify preterm births. Our final analytic sample included 6,045 participants.[18] We defined race and ethnicity using self-reported responses in each participating study (Table S1). Categories were harmonized across studies to maximize sample size. These included: non-Hispanic White (Caucasian, White), non-Hispanic Black (African American, Black), Hispanic/Latina (Hispanic, Latino, Latin American Indigenous heritage), Asian/Pacific Islander (Asian, Pacific Islander, Native Hawaiian, South Asian), and other races (Native American, Alaskan Native, >1 racial identity, or "Other"). Hereafter, we will use the terms Black and White to describe results for non-Hispanic Black and non-Hispanic White participants. In addition, we use the term Hispanic/Latina because this was the terminology used in questionnaires administered to most participants across studies (Table S1), which is a recommended practice for publishing research findings.[34] However, we recognize that these terms, rather than others like Latinx, may not fully capture the gender identity of all participants.

Phthalate Exposure Assessment

Phthalate metabolite concentrations were measured in participant urine samples collected during pregnancy. Methods of urine collection and metabolite analysis were previously described in detail.[18] In brief, individual studies primarily collected spot urine samples at one to several times across pregnancy, though certain studies conducted more intensive pooled urine sampling [Markers of Autism Risk in Babies-Learning Early Signs (MARBLES), The North Carolina Early Pregnancy Study (EPS)].[18] Phthalate metabolite measurements were performed separately by each cohort using the same or similar methodology. Online solid-phase extraction and high-performance liquid chromatography was used to extract phthalate metabolites following enzymatic hydrolysis of phthalate metabolite conjugates. Isotope dilution with tandem mass spectrometry was used to detect metabolites. For the purposes of this study, we included the following nine metabolites based on those measured in the most studies (≥14 studies) and detected in sufficient numbers of participants (>50% of participants): monoethyl phthalate (MEP), mono-*n*-butyl phthalate (MBP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(3-carboxypropyl) phthalate (MCPP).[18] The limit of detection (LOD) for phthalate metabolites was previously described and is shown in Table S2.[18] Phthalate metabolites included in this analysis were detectable in at least 96% of urine samples, except for MEHP and MCPP (83% and 90% detection, respectively).[18]

Statistical Analysis

As previously described,[18] we used multiple imputation by chained equations to impute: *a*) phthalate metabolite concentrations below the LOD without instrument-read values; and *b*) missing covariates. We generated 10 imputed datasets using 20 chained iterations per dataset and pooled results using Rubin's rules.[35] Imputation was done in R (version 4.2.1; R Development Core Team) using the *mice* package (version 3.11.0),[36] using tobit regression of log-transformed exposure for phthalate measurements below the LOD (*qgcomp* package; version 2.7.0).[37,38] As previously described,[18] we performed covariate-adjusted standardization to correct metabolite concentrations for urine dilution, which was done to: *a*) account for factors that potentially influenced measures of hydration and urinary phthalate metabolites[39]; and *b*) combine specific gravity- or creatinine-corrected values.[40] We accounted for relevant predictors of urinary dilution during standardization, including maternal race and ethnicity, education, age, prepregnancy body mass index (BMI), gestational age at urine sampling, year of delivery, and study center.[41–44] Model-fitted values for each participant were estimated separately for urinary creatinine and specific gravity, and the ratio measure of fitted to observed urine dilution measures were then multiplied by the observed phthalate metabolite concentration to produce dilution-corrected values.[18] After dilution standardization, we calculated the geometric mean (GM) of repeated within-participant phthalate metabolite concentrations, and concentrations were divided by the interquartile range (IQR) to standardize concentrations across studies and facilitate interpretability.[18] We used GM instead of single spot urine samples so that each participant would have only one exposure measurement and because averaging across repeated spot urine samples has been shown to provide a more stable estimate of exposure across the course of pregnancy.[45,46] Spearman correlations between phthalate metabolite concentrations were examined within racial and ethnic groups.

Disparities in urinary phthalate metabolite concentrations. We used adjusted GMs to examine racial and ethnic disparities in urinary phthalate metabolite concentrations. The GM of an individual urinary metabolite for each race and ethnicity group was estimated by multiple linear regression, in which we regressed the log-transformed phthalate metabolite on a set of covariates. Along with race and ethnicity, we adjusted models for risk factors selected *a priori* as potential risk factors of phthalate exposure, including study (categorical: 16 indicators), highest level of education (categorical: <high school, high school, some college, college graduate, graduate school), maternal age, prepregnancy body mass index (BMI, continuous: kilograms/square meter), and delivery year (categorical: 1983–2000, 2001–2010, 2011–2020) (Figure S1). Delivery year was included because the pooled studies varied according to calendar years of data collection, as well as race and ethnicity, so adjusting for this factor was done to ensure differences in GMs were not because of variation across time periods. GMs were calculated by Equation 1, where y_i is the log-transformed metabolite concentration, β_0 is the log-GM in the referent category (White, referent level of each covariate), $\beta_{1,j}$ is the coefficient for race and ethnicity category j in the referent level of each covariate, $\beta_{2,h}$ are coefficients for *a priori* selected covariates, and ε is the error term:

$$y_i = \beta_0 + \sum_j \beta_{1,j} Race_j + \sum_h \beta_{2,h} covariate_h + \varepsilon. \quad (1)$$

The GM for White participants at the referent level of other covariates (less than high school education, delivery year in the period 1983–2000, Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) cohort, and average maternal age and prepregnancy BMI) was estimated by exponentiating β_0, whereas the GM for race and ethnicity category j was estimated by exponentiating the sum of $\beta_0+\beta_{1,j}$. For categorical variables, the PROTECT cohort was selected as the referent group because it had the largest sample size and other referent levels were chosen based on order presented in

descriptive results. The percentage difference in GMs for race and ethnicity category j in comparison with the referent category (White) in strata of covariates was calculated by: $(\exp(\beta_{1,j}) - 1) \times 100\%$. White participants were selected *a priori* as the referent group for exposure contrasts, because we expected exposure levels in this group to be lowest based on prior literature.[47] We performed a sensitivity analysis to examine whether racial and ethnic differences in exposures were potentially explained by social determinants of health. We evaluated percentage differences in GMs across racial and ethnic categories that were additionally stratified by education level as an indicator of social determinants of health, with the hypothesis that similar patterns in phthalate metabolite disparities would be observed across education levels.

Hypothetical interventions to reduce phthalate exposure. To evaluate the extent to which racial and ethnic disparities in preterm birth could be explained by disparities in phthalate exposures, we used g-computation to evaluate the probability of preterm birth following hypothetical interventions to change the overall mixture of nine phthalate metabolites within race and ethnicity groups to have similar GMs with the referent (White) group. The only groups selected for comparison were Black and Hispanic/Latina participants because the number of preterm birth cases were enough to compare pre- and postintervention probabilities of preterm birth. Correspondingly, because of limited subsample sizes for preterm births, we were unable to conduct hypothetical intervention analyses within Asian/Pacific Islander ($n = 23$ preterm) and participants of other races ($n = 8$ preterm).

In our approach, g-computation works by first fitting a logistic regression model of preterm birth, given our exposures (phthalate metabolite concentrations) and confounders of interest, and then using that model to predict the probability of preterm birth under exposure levels corresponding to a hypothetical intervention.[48,49] We operationalized exposure disparities as the percent difference in the GMs of the phthalate metabolite concentrations by race and ethnicity, as calculated above. Thus, the hypothetical interventions reduced phthalate metabolite levels for Black and Hispanic/Latina participants so that final covariate-adjusted GMs for individuals in those groups were approximately equal to those observed among White participants. For each participant, the hypothetical intervention was to reduce concentrations of each phthalate metabolite based on the participant's race and ethnicity. For each phthalate metabolite, the posthypothetical intervention value of phthalate metabolite concentration (X_{post}) for participants from race and ethnicity group j was calculated by Equation 2, where X_{pre} is the observed phthalate metabolite concentration, GM_j was the adjusted GM for group j, and GM_{ref} was the adjusted GM in the referent group (White):

$$X_{post} = X_{pre} \times \frac{GM_{ref}}{GM_j}. \quad (2)$$

Within a given racial and ethnic group, this resulted in a shift in the overall distribution of urinary phthalate metabolite levels so that the final adjusted GM, although not the percentiles of the distribution, were approximately equal to that observed among White participants (Figure 1). The proportional reduction in the GM for each phthalate metabolite by racial and ethnic group j are displayed in Table S3. We did not reduce exposures below the race-specific minima to reduce model extrapolation. Finally, we obtained predicted probability of preterm birth for the two exposure scenarios (X_{post} and X_{pre} for all phthalate metabolites simultaneously) using race-stratified logistic regression models (described below) and compared the average predictions across the two scenarios using g-computation. The 95% CIs were estimated using nonparametric bootstrapping (2.5th and 97.5th percentiles across 2,000 iterations).[50] A sample R code for g-computation analyses is given in the Supplemental Material.

Heterogeneity in associations between phthalate metabolites and preterm birth by race and ethnicity. Second, we evaluated effect measure modification by race and ethnicity for the associations between phthalate metabolites and preterm birth. We fit stratified multivariable logistic regression models to estimate odds ratios (ORs) and 95% CIs, which we adjusted for covariates that were measured across all pooled studies. We selected covariates *a priori* from the literature and based on a directed acyclic graph (Figure S1), including maternal age at enrollment, education, prepregnancy BMI, delivery year, and study.[14,30,31,51] As with the hypothetical intervention analyses, we only examined associations among Black, Hispanic/Latina, and White participants because there were too few preterm births among Asian/Pacific Islander and other racial groups. We conducted statistical tests of effect measure modification using the augmented product term approach, because the covariates could have racial and ethnic-dependent associations with preterm birth.[52] We compared nested models with and without an interaction term between each phthalate metabolite and race and ethnicity groups using Wald tests. Both models included covariate by race and ethnicity product terms (i.e., augmented product terms) for all covariates except study due to instances of collinearity with race and ethnicity (e.g., PROTECT). Wald test p-values <0.10 were considered statistically significant.[52] All statistical analyses were performed in R (version 4.2.1), and sample code for g-computation analyses is provided in the Supplemental Material.

Results

Participant Demographics

Participants were 43% White, 13% Black, 38% Hispanic/Latina, and 3% Asian/Pacific Islander. Racial and ethnic composition differed between cohorts (Table 1; Figure 2), which was expected because certain cohorts were designed to recruit from specific racial and ethnic groups [e.g., PROTECT, Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), Columbia Center for Children's Environmental Health (CCCEH)]. The proportion of participants who delivered preterm also differed by race and ethnicity (Table 1). Black and Asian/Pacific Islander participants had the highest proportions of preterm births (11.5% and 11.3%, respectively), with lower proportions observed among White and Hispanic/Latina participants (9.1% and 7.7%, respectively). Racial and ethnic disparities were also observed for most sociodemographic characteristics. Nearly 70% of White and 82% of Asian/Pacific Islander participants had completed college or graduate school, in comparison with 15% of Black and 13% of Hispanic/Latina participants. White and Asian/Pacific Islander participants were also more likely to have a prepregnancy BMI $<25\ \mathrm{kg/m^2}$ and be >30 y of age than participants from other racial and ethnic groups.

Disparities in Urinary Phthalate Metabolite Concentrations

Racial and ethnic differences in pregnancy-averaged urinary phthalate metabolite concentrations were apparent when examining distributions of percentiles (Figure 3; Table S4) as well as proportional differences in crude and adjusted GMs (Figure 4; Table S3). Adjusted GMs were generally lower than crude GMs. Black participants had the highest urinary concentrations for all metabolites (23%–148% higher adjusted GM concentrations in comparison with White participants). For example, the adjusted GM of MEP among Black participants was 148% higher (95% CI: 119%, 182%) than that observed for White participants. Similarly, Hispanic/Latina participants had higher concentrations for all urinary phthalate metabolites, with adjusted GMs ranging

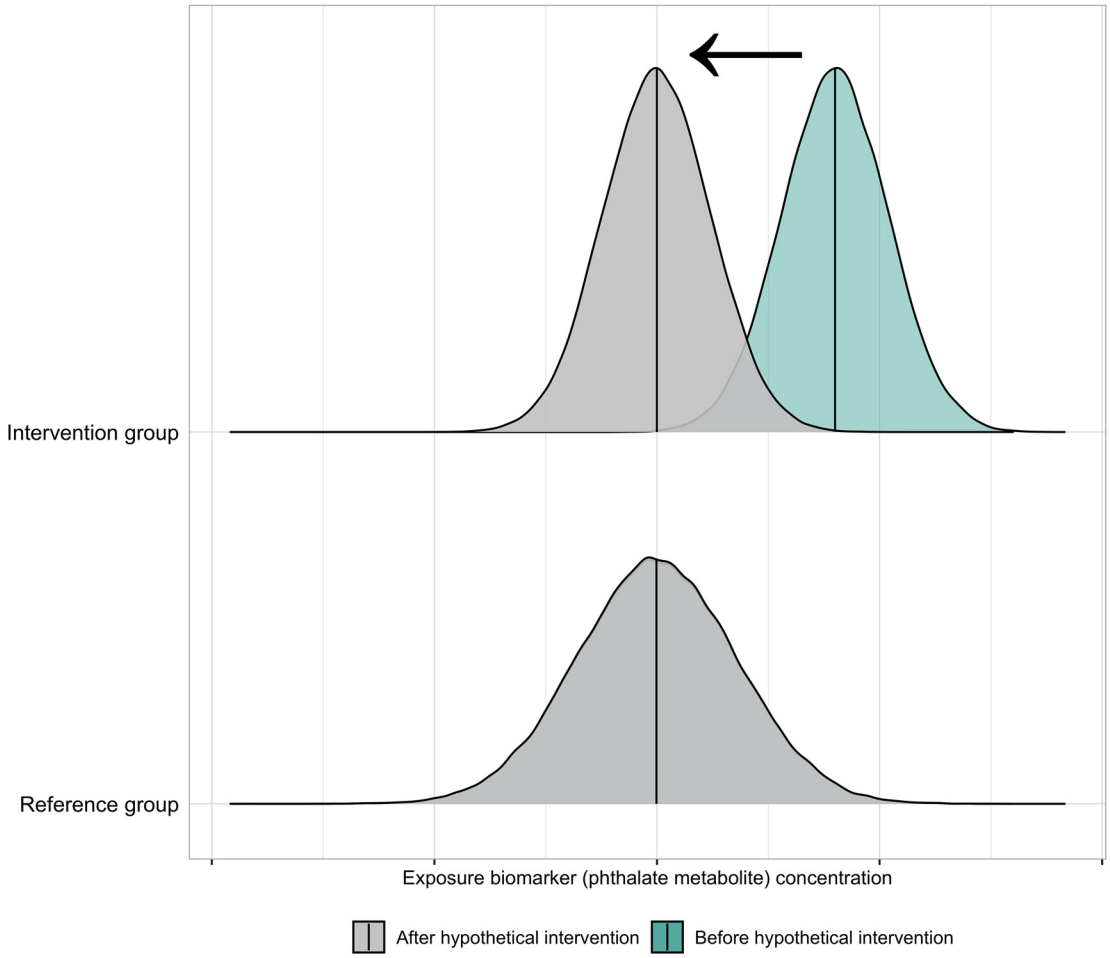

Figure 1. Visual representation of the hypothetical interventions applied to equitably reduce urinary phthalate metabolite concentrations. The figure displays simulated distributions on the natural log scale for a single phthalate metabolite among an intervention and reference group. The hypothetical intervention applies a proportional reduction to exposure among all members of the intervention group to make the adjusted geometric mean of the exposure biomarker (phthalate metabolite) concentration approximately equal to that of the reference group. Consequently, the hypothetical intervention shifts but does not change the shape of the distribution of the exposure in the intervention group, as shown by the "before" and "after" intervention distributions. Interventions were applied to all metabolites simultaneously in g-computation models.

from 5% to 94% higher in comparison with White participants. Although Asian/Pacific Islander participants had significantly higher concentrations of several metabolites (MBP, MiBP, MEHP) in comparison with White participants, concentrations of other phthalate metabolites were only slightly higher (MEHHP, MECPP, MEOHP) or lower (MEP, MBzP, MCPP) in comparison with those observed in White participants, with confidence intervals including the null (reference level). Our sensitivity analysis did not show evidence that racial and ethnic disparities in urinary phthalate metabolite concentrations were driven by differences in education (Figure S2; Table S5), our best available proxy measure of socioeconomic status, because proportional differences in adjusted GMs were similar across participant education levels. We were unable to examine residual confounding by other metrics of socioeconomic status (e.g., income) because of limited data availability. Correlation patterns of metabolite concentrations were similar by race and ethnicity (Figure S3).

Hypothetical Interventions to Reduce the Mixture of Phthalate Metabolites

Overall, hypothetical interventions predicted fewer preterm births for both Black and Hispanic/Latina participants, but confidence intervals indicated that results were also statistically consistent with a wide range of change in preterm births (Figure 5; Table S6). Reducing the mixture of phthalate metabolite concentrations among Black participants to what was observed among White participants was predicted to prevent 15 preterm births per 1,000 live births (change in preterm births $= -15$, 95% CI: -41, 10). This represented a 13% proportional difference (95% CI: -34%, 9%) in preterm deliveries among Black participants. After the intervention, the number of predicted preterm births per 1,000 live births among Black participants was 103 (95% CI: 71, 139). The hypothetical intervention among Hispanic/Latina participants was also predicted to result in fewer preterm births. Reducing the phthalate metabolite mixture was predicted to prevent seven preterm births per 1,000 live births (95% CI: -14, 1) among Hispanic/Latina participants, a 9% reduction (95% CI: -19%, 1%).

Heterogeneity in associations between phthalate metabolites and preterm birth by race and ethnicity. Overall, we did not observe consistent evidence of effect modification by race and ethnicity for odds ratios of preterm birth in association with phthalate metabolites (Figure 6; Table S7). However, of the nine differences tested, two were statistically significant before and after covariate adjustment (Wald test p-values <0.10 for MBP and MiBP). For MBP, effect estimates in stratified models were

Table 1. Distribution of participant characteristics in the pooled phthalate and preterm birth study, overall and by race and ethnicity.

	Overall[a]	White[b]	Black[b]	Hispanic/Latina[b]	Asian/Pacific Islander[b]	Other race[b]
Characteristics	6,045 (100%)	2,579 (43%)	802 (13%)	2,309 (38%)	204 (3%)	126 (2%)
Gestational age at delivery (wk)	39.1 (1.9)	39.2 (1.8)	38.8 (2.0)	39.0 (1.8)	38.9 (2.0)	39.2 (2.0)
Preterm delivery [*n* (%)]						
Term	5,486 (91.1)	2,345 (90.9)	710 (88.5)	2,132 (92.3)	181 (88.7)	118 (93.7)
Preterm	534 (8.9)	234 (9.1)	92 (11.5)	177 (7.7)	23 (11.3)	8 (6.3)
Maternal age (y)	29.1 (6.1)	32.0 (4.9)	25.7 (6.0)	26.7 (5.6)	33.4 (4.8)	29.3 (6.4)
Missing (*n*)	13	8	1	4	0	0
Maternal education [*n* (%)]						
Less than high school	1,044 (18.5)	45 (1.9)	195 (26.0)	793 (35.0)	1 (0.5)	10 (8.3)
High school	706 (12.5)	114 (4.9)	213 (28.4)	352 (15.6)	7 (3.7)	20 (16.5)
Some college	1,409 (25.0)	328 (14.1)	221 (29.5)	816 (36.1)	15 (7.9)	29 (24.0)
College graduate	1,262 (22.4)	861 (37.1)	82 (10.9)	229 (10.1)	55 (28.9)	35 (28.9)
Graduate school	1,222 (21.7)	971 (41.9)	39 (5.2)	73 (3.2)	112 (58.9)	27 (22.3)
Missing [*n* (%)]	377	260	52	46	14	5
Maternal prepregnancy BMI (kg/m^2)	25.7 (6.0)	24.8 (5.3)	28.3 (7.6)	25.8 (5.7)	23.2 (3.9)	26.6 (6.6)
Missing (*n*)	481	320	25	113	19	4
Delivery year [*n* (%)]						
1983–2000	919 (15.3)	197 (7.6)	136 (17.0)	574 (24.9)	7 (3.4)	5 (4.0)
2001–2010	2,106 (35.0)	1,172 (45.4)	355 (44.3)	448 (19.4)	95 (46.6)	36 (28.6)
2011–2020	2,995 (49.8)	1,210 (46.9)	311 (38.8)	1,287 (55.7)	102 (50.0)	85 (67.5)
Maternal smoking during pregnancy [*n* (%)]						
No	5,490 (92.3)	2,344 (91.2)	677 (86.4)	2,172 (95.8)	196 (97.5)	101 (80.8)
Yes	459 (7.7)	227 (8.8)	107 (13.6)	96 (4.2)	5 (2.5)	24 (19.2)
Missing (*n*)	71	8	18	41	3	1
Study [*n* (%)][c]						
PROTECT	1,101 (18.2)	3 (0.1)	0 (0.0)	1,087 (47.1)	0 (0.0)	2 (1.6)
TIDES	779 (12.9)	511 (19.8)	95 (11.8)	68 (2.9)	49 (24.0)	47 (37.3)
LIFECODES	480 (7.9)	283 (11.0)	76 (9.5)	71 (3.1)	36 (17.6)	14 (11.1)
Healthy Start	444 (7.3)	255 (9.9)	49 (6.1)	109 (4.7)	16 (7.8)	15 (11.9)
CHAMACOS	429 (7.1)	7 (0.3)	0 (0.0)	414 (17.9)	4 (2.0)	4 (3.2)
CCCEH	389 (6.4)	0 (0.0)	132 (16.5)	257 (11.1)	0 (0.0)	0 (0.0)
HOME	389 (6.4)	237 (9.2)	120 (15.0)	9 (0.4)	5 (2.5)	13 (10.3)
EARTH	385 (6.4)	327 (12.7)	11 (1.4)	0 (0.0)	32 (15.7)	15 (11.9)
MSSM	362 (6.0)	76 (2.9)	107 (13.3)	178 (7.7)	1 (0.5)	0 (0.0)
SFF	353 (5.8)	296 (11.5)	6 (0.7)	31 (1.3)	16 (7.8)	2 (1.6)
RDS	318 (5.3)	158 (6.1)	151 (18.8)	3 (0.1)	4 (2.0)	2 (1.6)
HEBC	189 (3.1)	133 (5.2)	23 (2.9)	26 (1.1)	6 (2.9)	1 (0.8)
MARBLES	179 (3.0)	99 (3.8)	10 (1.2)	38 (1.6)	27 (13.2)	5 (4.0)
EPS	126 (2.1)	120 (4.7)	3 (0.4)	0 (0.0)	2 (1.0)	1 (0.8)
MMIP	68 (1.1)	56 (2.2)	4 (0.5)	2 (0.1)	3 (1.5)	3 (2.4)
Rutgers	54 (0.9)	18 (0.7)	15 (1.9)	16 (0.7)	3 (1.5)	2 (1.6)

Note: BMI, body mass index; CCCEH, Columbia Center for Children's Environmental Health; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; EARTH, Environment and Reproductive Health Study; EPS, The North Carolina Early Pregnancy Study; Healthy Start, Healthy Start Study; HEBC, Harvard Epigenetic Birth Cohort; HOME, Health Outcomes and Measures of the Environment Study; MARBLES, Markers of Autism Risk in Babies-Learning Early Signs; MMIP, Michigan Mother-Infant Pairs Project; MSSM, Children's Environmental Health Study at the Mount Sinai School of Medicine; PROTECT, Puerto Rico Testsite for Exploring Contamination Threats; RDS, Reproductive Development Study; Rutgers, Rutgers University; SD, standard deviation; SFF, Study for Future Families; TIDES, The Infant Development and the Environment Study.
[a]The total sample size across categories does not always sum to the overall sample size of $n = 6{,}045$ because a total of $n = 25$ participants were missing race and ethnicity information.
[b]Each race and ethnic category represents a composite measure used to maximize sample size and consistency between pooled studies, including non-Hispanic White (Caucasian, White), non-Hispanic Black (African American, Black), Hispanic/Latina (Hispanic, Latino, Latin American indigenous heritage), Asian/Pacific Islander [Asian, Pacific Islander (PI), Native Hawaiian, South Asian], and Other races (Native American, Alaskan Native, >1 racial identity, or "Other").
[c]A total of $n = 25$ participants were missing race and ethnicity information, including 9, 9, 5, and 2 participants from PROTECT, TIDES, HOME, and SFF, respectively. Acronym and full study names are defined in Table S1.

similar among White (OR = 0.95; 95% CI: 0.77, 1.17) and Black participants (OR = 1.10; 95% CI: 0.78, 1.55) but higher among Hispanic/Latina participants (OR = 1.34; 95% CI: 1.08, 1.68). For MiBP, effect estimates for Black participants (OR = 1.83; 95% CI: 1.19, 2.81) and Hispanic/Latina participants (OR = 1.29; 95% CI: 1.02, 1.64) were both higher than what was observed for White participants (OR = 0.93; 95% CI: 0.73, 1.18).

Discussion

In a pooled analysis of more than 6,000 pregnancies, we observed large racial and ethnic disparities in urinary phthalate metabolite concentrations. Specifically, Black and Hispanic/Latina participants had up to 148% and 94% higher average concentrations, respectively, than White participants after adjustment for covariates. Furthermore, g-computation results suggested that the probability of preterm birth among these groups would be lower if they had urinary phthalate metabolite concentrations approximately equal to those among White participants. Our prior study of overall associations showed four phthalate metabolites (MBP, MiBP, MECPP, and MCPP) were individually associated with higher odds of preterm birth.[18] In the present study, we observed some evidence that these odds ratios significantly differed by participant race and ethnicity, where two of the four metabolites (MBP and MiBP) associated with preterm birth in our prior overall analysis exhibited effect estimates that were greater in magnitude for Black and/or Hispanic/Latina participants.[18] These findings suggest that, in the United States, racial and ethnic disparities in phthalate exposure are important contributors to differences in preterm birth. Overall, our findings support the hypothesis that reducing the disparities in exposure to multiple phthalates would reduce preterm births among systematically marginalized racial and ethnic groups.

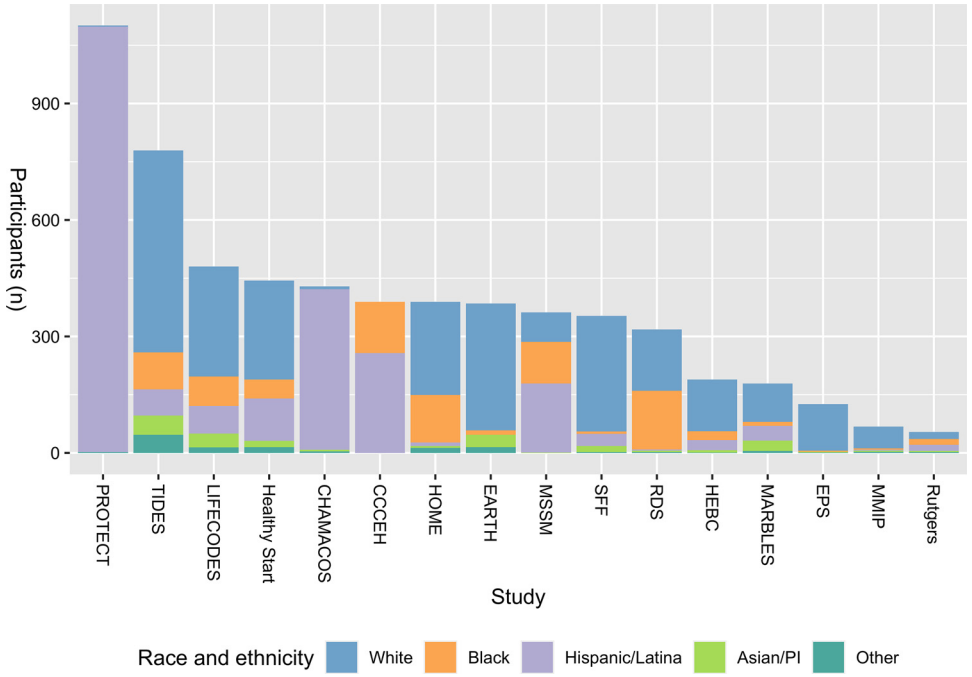

Figure 2. Distributions of participant race and ethnicity within each of the 16 studies included in the Pooled Study of Phthalate Exposure and Preterm Birth. Each racial and ethnic category represents a composite measure to maximize sample size and consistency, including non-Hispanic White (White: Caucasian, White), non-Hispanic Black (Black: African American, Black), Hispanic/Latina (Hispanic, Latino, Latin American indigenous heritage), Asian/Pacific Islander (Asian, PI, Native Hawaiian, South Asian), and Other races (Native American, Alaskan Native, >1 racial identity, or "Other"). Values for sample size and proportions are provided in Table 1. Note: CCCEH, Columbia Center for Children's Environmental Health; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; EARTH, Environment and Reproductive Health Study; EPS, The North Carolina Early Pregnancy Study; Healthy Start, Healthy Start Study; HEBC, Harvard Epigenetic Birth Cohort; HOME, Health Outcomes and Measures of the Environment Study; MARBLES, Markers of Autism Risk in Babies-Learning Early Signs; MMIP, Michigan Mother-Infant Pairs Project; MSSM, Children's Environmental Health Study at the Mount Sinai School of Medicine; PI, Pacific Islander; PROTECT, Puerto Rico Testsite for Exploring Contamination Threats; RDS, Reproductive Development Study; Rutgers, Rutgers University; SFF, Study for Future Families; TIDES, The Infant Development and the Environment Study.

Preterm birth in the United States, which increased from 9.6% of pregnancies in 2015 to 10.2% in 2019, remains a leading cause of infant death and disability in U.S. children.[53] Preterm birth is also a major racial and ethnic health inequity in the United States, where, in 2021, the probabilities of preterm birth for non-Hispanic Black (14.7%), Hispanic (10.2%), and American Indian/Alaska Native (12.3%) pregnancies were all higher than those observed in non-Hispanic White pregnancies (9.5%).[2] The most cited explanations for these disparities, specifically for the largest gap observed between non-Hispanic Black and non-Hispanic White births, are socioeconomic differences, genetic variation, and smoking, but rigorous investigation has dispelled these hypotheses because racial and ethnic disparities in preterm birth still exist after accounting for these factors.[4,54] In the present analysis, we found that the racial and ethnic disparities in phthalate exposure observed may be important contributors to the parallel disparities in preterm birth. For example, we estimated that jointly reducing exposure to nine phthalates among Black participants in our study to the levels observed among White participants would result in 13% fewer preterm births among Black participants. Correspondingly, the predicted probability of preterm birth among Black participants after the hypothetical intervention more closely resembled that observed among White participants [103 (95% CI: 71, 139) vs. 93 (95% CI: 82, 105) per 1,000 live births, respectively]. Although the preintervention preterm birth probability was lower for Hispanic/Latina participants [75 (95% CI: 65, 86) per 1,000 live births] than White participants, the hypothetical intervention was still estimated to result in an additional 9% (95% CI: −18%, 0.8%) decrease in preterm births. Confidence intervals for the effects of the hypothetical interventions included the null, reflecting statistical uncertainty in estimates. Nevertheless, these data are consistent with the hypothesis that reducing disparities in phthalate exposure would help to mitigate preterm birth rates among key demographic groups in the United States.

Our approach to examining the impact of hypothetical reductions in phthalate exposures on preterm birth exemplifies how we can move beyond simply examining effect modification to investigate environmental contributors to racial health inequities. We note that our study question is about the effects of phthalates, where we contrast the expected number of preterm births that we would observe under two different distributions of phthalates. This question is distinct from a mediation question, where we might ask how much of the causal effect of race is mediated by phthalates. Following previously proposed guidelines,[4,55] our study investigated effect size differences in combination with examination of exposure differences by race and ethnicity. We observed that the differences in preterm birth could be driven, in part, by disparities in phthalate exposure. Furthermore, our novel application of g-computation in this context simultaneously allowed us to: *a*) estimate the impact of reducing all phthalate metabolites simultaneously (i.e., the mixture effect); and *b*) visualize probabilities of preterm birth under a scenario where phthalate metabolite levels were equitable across racial and ethnic groups.

One of the assumptions of g-computation, for causal inference, as implemented in our approach, is that outcome models are correctly specified. In our approach, this means that the underlying logistic models are assumed to be correct, and our sensitivity analyses suggest this is appropriate, given limited effect measure modification. As Robins and Hernán note, there

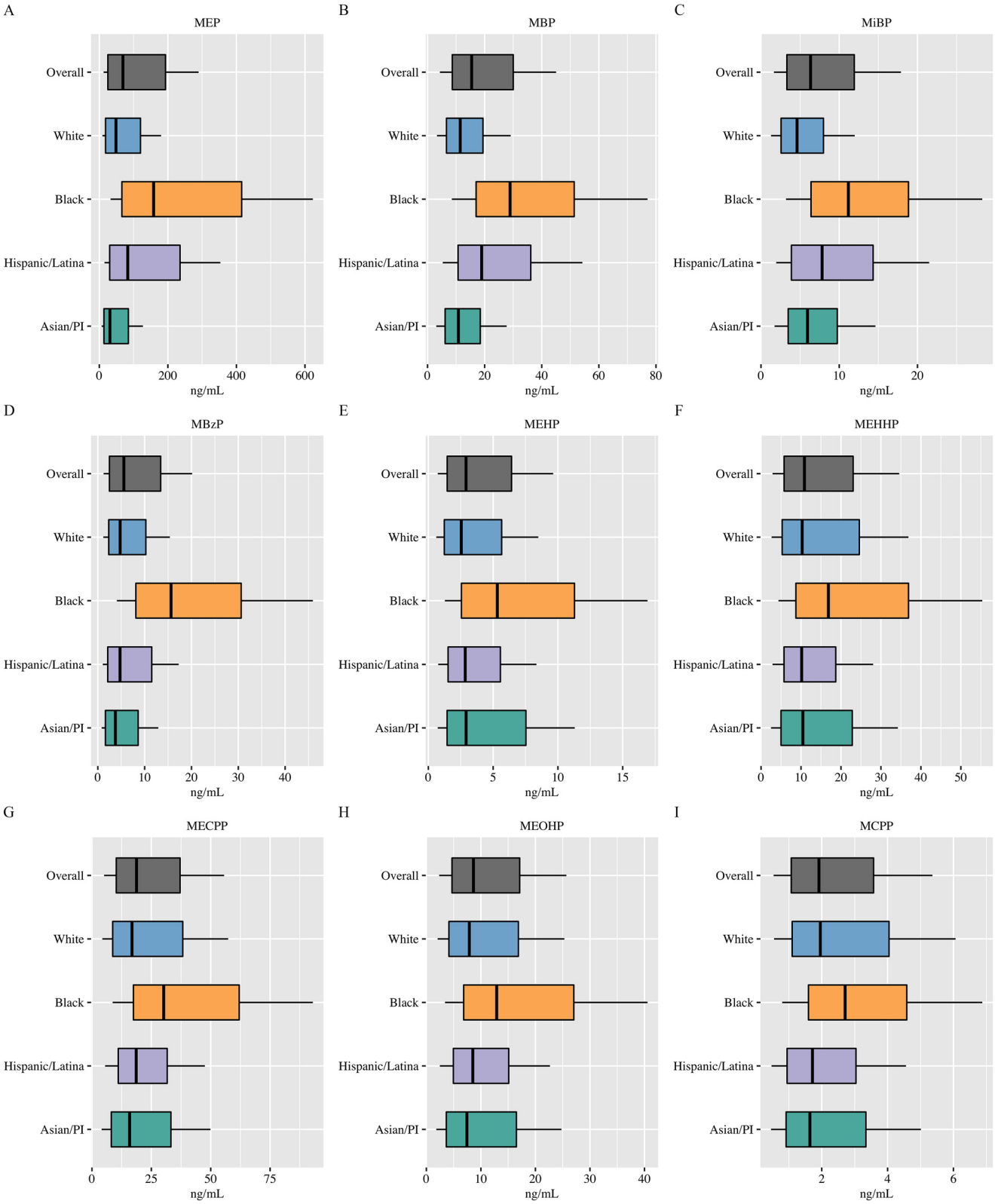

Figure 3. Boxplot distributions of pregnancy-averaged urinary phthalate metabolite concentrations in the Pooled Phthalate and Preterm Birth Study, overall and by race and ethnicity. Concentrations were standardized by urine dilution. Each box shows the 25th, 50th, and 75th percentiles. The upper whisker represents 1.5 times the 75th percentile, whereas the lower whisker represents 0.5 times the 25th percentile, stopping at the limit of detection. Values above or below whiskers not shown. Plotted values and sample sizes are displayed in Table S4. The range of LOD and proportion of samples below LOD are displayed in Table S2. If measures were under the LOD and no instrument-read values were available, values were multiply imputed. Phthalates metabolites are: MEP, MBP, MiBP, MBzP, MEHP, MEHHP, MECPP, MEOHP, and MCPP. Note: LOD, limit of detection; MBP, mono-*n*-butyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, monoisobutyl phthalate; PI, Pacific Islander.

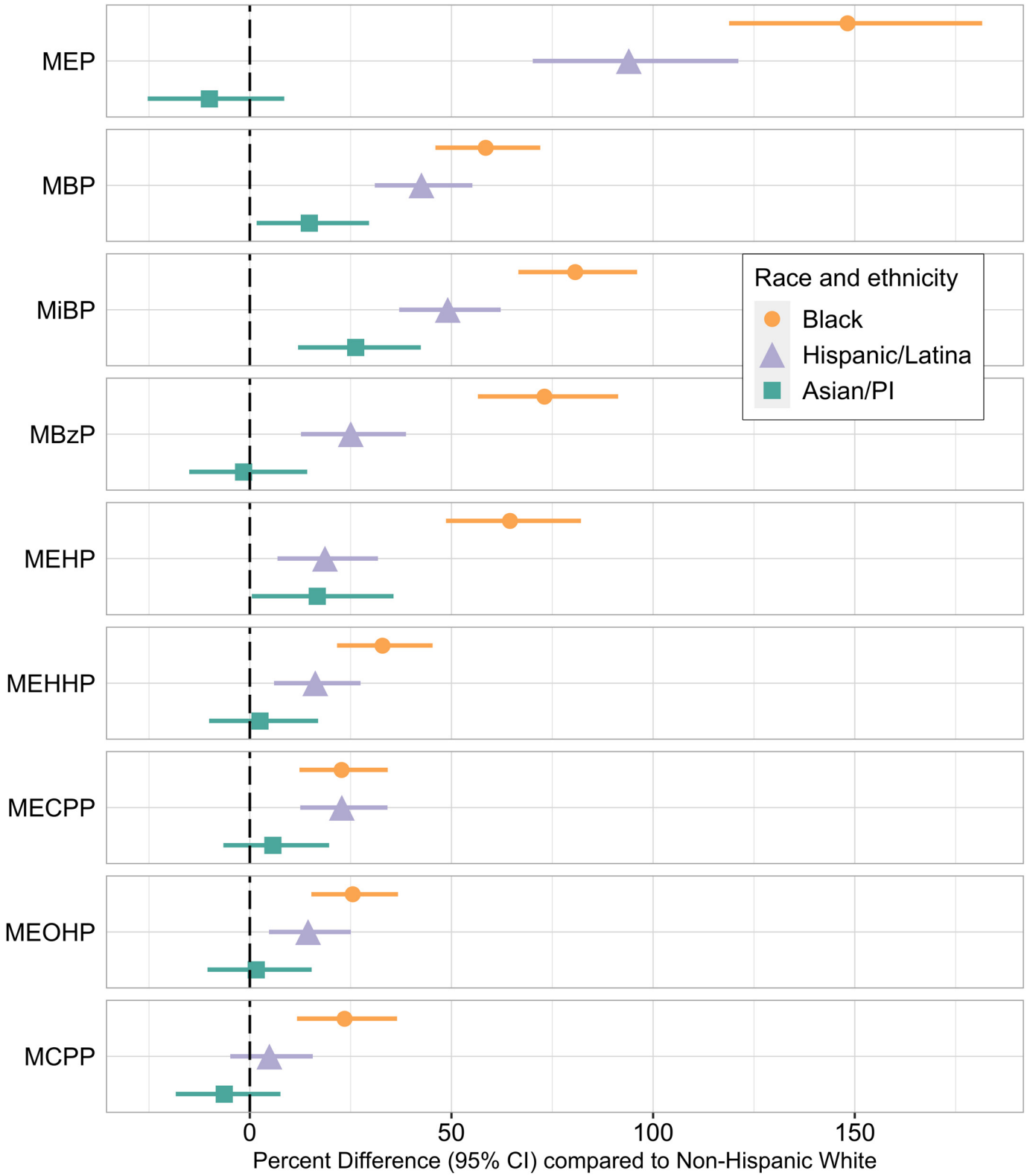

Figure 4. Adjusted percent differences in pregnancy-averaged urinary phthalate metabolite concentrations in the Pooled Phthalate and Preterm Birth Study for non-Hispanic Black (Black), Hispanic/Latina, or Asian/PI participants in comparison with non-Hispanic White participants. Estimates represent the percent difference and 95% CIs in adjusted geometric means of urinary phthalate metabolite concentrations. Values were estimated by multiple linear regression and adjusted for maternal age, education, prepregnancy BMI, delivery year, and study. Concentrations were corrected for urine dilution. Plotted values are provided in Table S3. Phthalates metabolites are: MEP, MBP, MiBP, MBzP, MEHP, MEHHP, MECPP, MEOHP, and MCPP. Note: BMI, body mass index; CI, confidence interval; MBP, mono-*n*-butyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, monoisobutyl phthalate; PI, Pacific Islander.

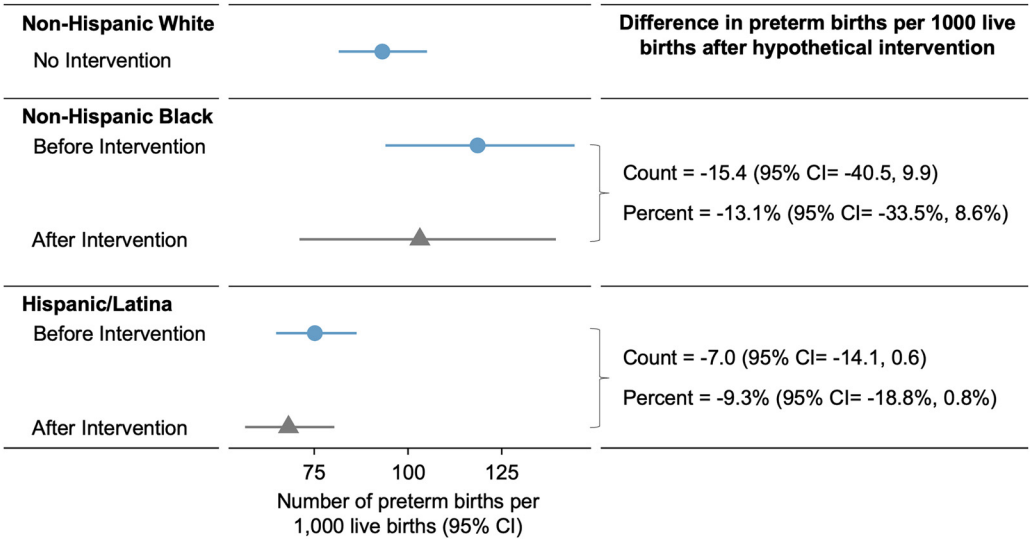

Figure 5. Preterm births per 1,000 live births before and after a hypothetical intervention to reduce concentrations of all urinary phthalate metabolites to the distributions observed among non-Hispanic White participants in the Pooled Study of Phthalate Exposure and Preterm Birth. Predicted probability of preterm birth without an intervention was applied to Non-Hispanic White participants because this population had the lowest adjusted geometric mean concentrations of each metabolite. Results were estimated from g-computation following multivariable logistic regression stratified by race and ethnicity and adjusted for maternal age, education, prepregnancy BMI, delivery year, and study. Point estimates and 95% CIs are provided in Table S6. Note: BMI, body mass index; CI, confidence interval.

are no needed assumptions about the validity of the exposure models.[56] In our approach, our choice to model exposure based on observed distributions does not affect the validity of our model given the distributional goals we set are, in principle, achievable. Here, we have modeled exposures for the express purpose of quantifying an exposure disparity. Thus, our approach estimates the impact of eliminating the disparity because it is quantified by the difference in GMs of exposures. The additional assumptions necessary are standard causal assumptions, which we previously described in the context of phthalate metabolite mixtures and preterm birth.[18] Perhaps most relevantly, we assume treatment variation irrelevance. For our analysis, this assumption is akin to a "no side-effects" assumption, whereby we assume that we could lower phthalate metabolite levels through an intervention that would not change other determinants of preterm birth.[57,58] This may not be met, because changing phthalate exposure is likely to result in changes to other exposures as well. This highlights the need to study true interventions in an approach with intersectional perspectives.[59] Overall, however, our hypothetical intervention analysis provides needed information in the path toward achieving health equity through reducing disparities in a ubiquitous class of chemicals with well-document disparities by race and ethnicity.

The racial and ethnic disparities in phthalate exposure we observed in our pooled study are consistent with prior evidence. A study using a large ($n = 38{,}080$) and representative cross-sectional sample of women living in the United States also observed racial and ethnic differences in urinary phthalate metabolites, including 78% higher MEP concentrations among non-Hispanic Black in comparison with non-Hispanic White participants.[47] Similar to our sensitivity analysis examining phthalate exposure disparities across educational strata as an indicator of socioeconomic status, that study found racial and ethnic disparities in phthalate metabolite concentrations existed across income levels.[47] Evidence from prospective pregnancy cohort studies have also provided evidence consistent with our results.[16,29,31] In a recent pilot study of data pooled data from nine U.S. cohorts, adjusted differences in urinary phthalate metabolite concentrations between Hispanic (any race) and non-Hispanic White participants were of similar magnitude to differences observed in our study.[16] For example, concentrations of MEP displayed the largest differences, with 108% higher (95% CI: 19%, 266%) levels among Hispanic in comparison with non-Hispanic White participants.[16] Unlike most previous studies, we examined racial and ethnic differences in phthalate metabolite concentrations after adjustment for covariates. We recognize that many of these factors (education, age in pregnancy, prepregnancy BMI, etc.) result, in part, from racism and potential drivers of exposure disparities. However, we sought to examine exposure disparities that persist for reasons beyond those we were able to measure. Adjustment attenuated associations, indicating that socioeconomic and other factors play a role in the exposure disparities. Of note, attenuation could also be attributable to mediation of associations by the covariates. However, even after adjustment, racial and ethnic differences in phthalate metabolite concentrations were still substantial.

The racial and ethnic disparities in phthalate metabolite levels are likely related to differences in factors such as consumer product use[60,61] and diet.[27,62] We did not have data on such factors among study participants. We expect that these differences are because of disparities in access to products and foods with lower phthalate levels, a consequence of systematic environmental differences attributable to a multitude of factors including structural racism.[11,63] Although our results cannot determine specific interventions that would equitably reduce phthalate metabolite concentrations among Black and Hispanic/Latina participants, we expect that the lower postintervention levels are feasible in society because such distributions were actually observed among White participants. In our study, the largest racial and ethnic disparities were for metabolites derived from phthalate commonly used in personal care products, including metabolites of diethyl, di-*n*-butyl, and diisobutyl phthalate. These parent chemicals are typically used as fragrance additives, and high levels have been detected in a range of hair products marketed to Black women.[60] The corresponding use of such products is also higher among non-Hispanic Black women in comparison with non-Hispanic White women,[64] which may translate to higher urinary phthalate metabolite concentrations.[65] Future intervention strategies should

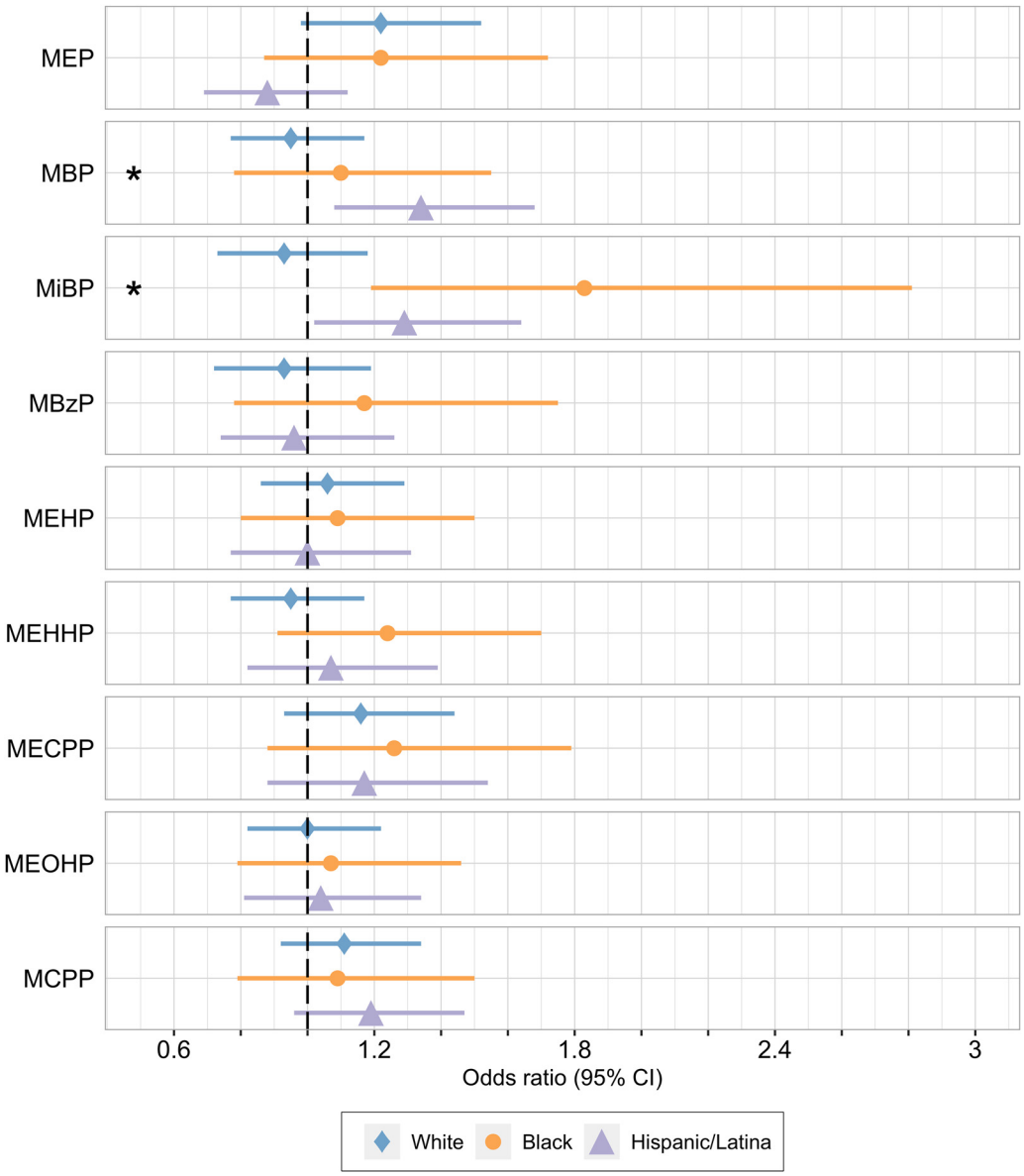

Figure 6. Associations between urinary phthalate metabolites and preterm birth in models stratified by race and ethnicity in the Pooled Phthalate and Preterm Birth Study. Odds ratios and 95% CI represent estimated odds of preterm birth in comparison with term birth per overall IQR increase in each phthalate metabolite. Associations were estimated by multiple logistic regression models stratified by race and ethnicity. All models were adjusted for study, maternal age, education, prepregnancy BMI, and delivery year. An asterisk (*) indicates $p < 0.10$ from augmented Wald tests, which compared nested models with and without an interaction term between phthalate metabolite and race and ethnicity. Point estimates, 95% CI, and Wald tests are provided in Table S7. Phthalates metabolites and IQRs in ng/mL are: MEP, 168.2; MBP, 21.4; MiBP, 8.6; MBzP, 11.0; MEHP, 5.0; MEHHP, 17.3; MECPP, 26.9; MEOHP, 12.4; and MCPP, 2.5. Note: CI, confidence interval; IQR, interquartile range; MBP, mono-*n*-butyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, monoisobutyl phthalate.

be developed using the evidence and well-established theories from the fields of environmental justice and health equity.[10,11,26] For example, racism, sexism, and classism intersect in Black hair discrimination, which penalizes Black people, especially Black women, for wearing their hair in natural styles.[11] In this scenario, Black women may be pressured to maintain their hair in certain styles to achieve and maintain economic opportunities, and the products used to transform and maintain those hairstyles can have higher levels of phthalates and subsequently increase exposures.[11,26] Explicit consideration of such variation in the cumulative social factors that contribute to exposure risk is critical to advance strategies to reduce and prevent exposures.[10,11]

Marginalized racial and ethnic populations may also be more susceptible to phthalate exposures through diet.[12,62,66] Increasing evidence shows that consumption of ultraprocessed foods, including fast food, may increase phthalate exposures.[12,27,62] Ultraprocessed foods are ready-to-eat items that are made with minimal whole foods and provide low nutritional value,[67] and consumption may be higher among people of color.[68,69] Phthalate levels may be higher in these foods because of the materials used in processing or packaging materials.[70] Reasons for the higher ultraprocessed food consumption among these groups are multifactorial but likely involve policies on housing and food subsidies, food deserts, and employment inequities.[5–7] Historical and ongoing housing policies create residential segregation along racial and ethnic lines, which adversely

impact the food landscape.[6,71] Such policies reduce access to fresh food and increase access to ultraprocessed foods,[72] thus increasing potential dietary phthalate exposures. Further, food subsidies that keep prices low for ultraprocessed rather than fresh foods can potentiate this issue by increasing access and consumption within lower-income communities.[68]

Real-world interventions to mitigate these diverse sources of exposure could take the form of behavioral interventions,[73,74] regulations, or voluntary consumer market campaigns.[75,76] At the individual level, consumers can attempt to avoid purchasing personal care or food items that may contain phthalates. However, accessibility and cost may impact the availability of "phthalate-free" products,[77] which could differentially impact marginalized groups.[10] Moreover, it is difficult for consumers to identify phthalate-free goods, even with the aid of consumer guides.[75] Few consumer guides conduct independent product testing and instead rely on potentially inaccurate or nondescriptive product labels.[78] In addition, the evidence for the effectiveness of interventions on personal care and food products to reduce phthalate exposures is mixed,[73,74,79–81] which is likely because of the multifactorial nature of environmental phthalate exposure.[75] Finally, although individual-level behavior interventions may provide some immediate reduction in phthalate exposures,[74] it is difficult to determine how to scale such interventions to benefit entire populations.

Regulations and consumer market actions are other ways to reduce disparities in phthalate metabolite concentrations at the population level.[76] Legislative options could limit the use of phthalates in personal care products, like cosmetics and other beauty products, particularly those intended for women. The U.S. Consumer Product Safety commission now limits the use of phthalates in children's toys,[82] but few such restrictions currently exist for products intended for women of reproductive age. However, regulations proposed by public interest groups (e.g., Breast Cancer Prevention Partners, Campaign for Safe Cosmetics) have recently made progress.[83] At the end of 2022, the U.S. Congress passed the Modernization of Cosmetics Regulation Act of 2022, which has provisions aimed at reducing exposure to phthalates in consumer products among the public and people working in professional salons. For example, the new law improves the ability of the U.S. Food and Drug Administration(U.S. FDA) to access cosmetic product ingredients in the event of adverse events and requires the U.S. FDA to consider international requirements regarding fragrance allergens when considering new regulations or threshold levels.[83] However, among other concerns, public interest groups point out that the new law does not require product ingredient transparency to the public.[83] In addition, although the law allows states to maintain previously existing laws banning the use of specific ingredients in cosmetic products, public interest groups have objected to the law's preemption of states establishing new cosmetic safety regulations that exceed federal regulations.[83]

The U.S. FDA can regulate phthalates in food and beverages. Recently, the U.S. FDA revoked authorization for 23 of 28 phthalates permitted in food contact and packaging applications.[84] Although this action may seem promising to reduce phthalate exposures in the United States, there are caveats to the apparent progress. First, the decision to revoke authorization for the 23 phthalates was based on an industry-backed petition, which stated that use of those 23 chemicals had already been discontinued.[84] In other words, the revoked authorization for these phthalates is unlikely to have additional meaningful impact on dietary exposure. Second, the U.S. FDA did not revoke authorization for the other five phthalates, including DEHP and DEHP replacements, despite petitioning from public interest groups.[84] The U.S. FDA stated that petitions to remove these additional five compounds were denied because they did not demonstrate that those phthalates were unsafe for the approved food additive uses.[84] Thus, there is still abundant opportunity for the U.S. FDA to reduce population-level phthalate exposures from food materials.

Our study had several strengths. Combining data from 16 U.S. studies resulted in a large racially and ethnically diverse study population, with large enough sample sizes for Black, Hispanic/Latina, and White groups to estimate exposure disparities and their influence on preterm birth probabilities. In addition, because we included nearly all U.S. studies published before May 2019 with data on prenatal urinary phthalate metabolite concentrations, our results may have greater generalizability than previous studies investigating exposure disparities. Last, our approach to evaluating joint reductions in phthalate metabolites reflects the reality that pregnant populations are exposed to multiple phthalates simultaneously. This approach addresses the longstanding recommendation by the National Academies for regulatory agencies to consider coexposure to multiple phthalates for more accurate cumulative risk assessments.[85] Further, our study has applied an environmental justice approach with a solution-oriented lens to understand the extent to which a highly prevalent class of chemicals with well-documented racial and ethnic disparities contributes to a persistent health disparity. We acknowledge that this study is an initial step on the path to addressing disparities in phthalate exposures and associated health impacts such as preterm birth, and we hope this provides a framework for future studies to leverage.

Our study also had several limitations. Despite our large sample size, no studies in our dataset focused on recruiting from Asian/Pacific Islander or Native American/Alaska Native populations. Our overall and preterm birth sample sizes for these groups were therefore limited and we were unable to estimate the impacts of hypothetical interventions. These groups deserve attention in future studies, especially because we found that Asian/Pacific Islander participants in our study had elevated exposures to several phthalate metabolites and higher proportions of preterm birth in comparison with White participants. In the United States, those who identify as Native American/Alaska Native are also more likely than those who identify as non-Hispanic White to deliver preterm, and to our knowledge, phthalate exposure levels in this group have not been explored.[53] Our sample size also restricted us to evaluating racial and ethnic categories that were broadly defined, obscuring the inherent heterogeneity that exists within each group. For example, we were unable to account for nativity status, acculturation, or immigration status, which are particularly important in the U.S. context for those identifying as Black or Hispanic.[86,87] Further, it has been established that the Asian race category in the United States is heterogenous and should be disaggregated.[88,89] Because of the limited number of harmonized covariates available across the pooled studies,[18] we used education as a primary indicator of socioeconomic status, which would have been improved by including additional information (e.g., income). However, prior studies have shown that maternal education is a strong predictor of U.S. preterm birth disparities,[90] and results of our sensitivity analysis of exposure disparities across education levels were similar to prior evidence using income strata.[47]

We also recognize there was variation in exposure assessment methods across studies,[18] potentially producing measurement error. However, we adjust for known confounders and chose to average across repeated spot urine samples to improve our exposure characterization.[45,46] In addition, if selection into our study cohorts was strongly related to both phthalate exposure as well as race and ethnicity, that relationship may have biased our findings. However, our prior work demonstrated that associations between phthalate metabolites and preterm birth

were not significantly heterogeneous across study cohorts, so this is unlikely to be a major source of bias.[18] Our study may be subject to selection bias or confounding if phthalate exposure caused pregnancy to not result in a live birth.[91] However, given that our central aim was to investigate associations among live births, it is unlikely to be a large source of bias. Last, our pooled analysis was specifically designed to assess the influence of phthalate exposure on preterm birth, which left us unable to address the potential influence of unmeasured environmental chemical and nonchemical exposures that may act independently or together with phthalates to influence racial and ethnic disparities in probabilities of preterm birth, such as other endocrine-disrupting chemicals,[92] air pollution,[93] ambient temperature,[94] greenspace,[95] psychosocial stress,[96] employment inequities,[97] and access to care.[98] Future work that incorporates a more complete exposome approach to this research question will likely improve the ability for public health interventions to successfully reduce preterm birth across racial and ethnic groups.

Conclusions

In an analysis harmonizing data from nearly all U.S. cohort studies that measured urinary phthalate metabolites during pregnancy before May 2019, Black and Hispanic/Latina participants had significantly higher urinary concentrations of most phthalate metabolites in comparison with White participants. Hypothetical interventions to reduce these racial and ethnic disparities predicted reductions in preterm births. We also observed some evidence that ORs for associations between phthalate metabolites and preterm birth differed by participant race and ethnicity, where ORs were greatest in magnitude among Black or Hispanic/Latina participants for two of the four phthalate metabolites that were associated with preterm birth in the overall study population. These findings support the need to reduce phthalate exposures among systematically marginalized people.

Acknowledgments

This research was supported in part by the Intramural Research Program of the National Institutes of Health (NIH)/National Institute of Environmental Health Sciences (NIEHS, ZIAES103321). The project was also supported by the NIEHS (grants P42ES017198 to Dr. Alshawabkeh, P30ES005022 to Dr. Barrett, R21ES031231 to Dr. Bloom, P01ES009605 and R24ES028529 to Dr. Eskenazi, R01ES021369 and U24ES028529-06 to Dr. Holland, R01ES024381 to Dr. Braun, R01ES030078 to Dr. Buckley, P42ES017198 to Dr. Cordero, R01ES022934 to Dr. Dabelea, P30ES010126 and P01ES09584 to Dr. Engel, R01ES013543, R01ES014393, and R01ES08977 to Dr. Factor-Litvak, R01ES009718 to Dr. Hauser, ES013543 to Dr. Herbstman, P30ES023513 to Dr. Hertz-Picciotto, P30ES000002 for Dr. James-Todd, Z01ES103333 to Dr. Jukic, R01ES031591 and P42ES017198 to Dr. Meeker, R01ES031657 to Dr. Messerlian, P01ES022844 and R01ES017500 to Dr. Padmanabhan, T32ES007018 to Ms. Rosen, R01ES0125169 to Dr. Sathyanarayana, R21ES025551 and R24ES028533 to Dr. Schmidt, R01ES016863 and R01ES016863-02S4 to Dr. Swan, P30ES005022 to Dr. Weinberger, P01ES011261 to Dr. Lanphear), NIH (grants UH3OD023251 to Dr. Alshawabkeh, UH3OD023365 to Dr. Hertz-Picciotto, P30ES005022 to Dr. Rich, UH3OD023342 to Dr. Schmidt), U.S. Environmental Protection Agency (grants R82670901 and R827039 to Dr. Engel, R82670901 to Dr. Eskenazi), National Institute of Diabetes and Digestive and Kidney Diseases (grant R01DK076648 to Dr. Dabelea), National Cancer Institute (grant R21CA128382 to Dr. Michels), National Center for Advancing Translational Sciences (grant UL1TR001881 to Dr. Wang), and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (grant R21HD058019 to Dr. Weinberger).

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention (U.S. CDC). Use of trade names is for identification only and does not imply endorsement by the U.S. CDC, the Public Health Service, or the U.S. Department of Health and Human Services. The analysis of deidentified specimens at the U.S. CDC was determined not to constitute engagement in human subjects research.

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