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Associations Between Prenatal Urinary Biomarkers of Phthalate Exposure and Preterm Birth
A Pooled Study of 16 US Cohorts

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IMPORTANCE Phthalate exposure is widespread among pregnant women and may be a risk factor for preterm birth.

OBJECTIVE To investigate the prospective association between urinary biomarkers of phthalates in pregnancy and preterm birth among individuals living in the US.

DESIGN, SETTING, AND PARTICIPANTS Individual-level data were pooled from 16 preconception and pregnancy studies conducted in the US. Pregnant individuals who delivered between 1983 and 2018 and provided 1 or more urine samples during pregnancy were included.

EXPOSURES Urinary phthalate metabolites were quantified as biomarkers of phthalate exposure. Concentrations of 11 phthalate metabolites were standardized for urine dilution and mean repeated measurements across pregnancy were calculated.

MAIN OUTCOMES AND MEASURES Logistic regression models were used to examine the association between each phthalate metabolite with the odds of preterm birth, defined as less than 37 weeks of gestation at delivery (n = 539). Models pooled data using fixed effects and adjusted for maternal age, race and ethnicity, education, and prepregnancy body mass index. The association between the overall mixture of phthalate metabolites and preterm birth was also examined with logistic regression. G-computation, which requires certain assumptions to be considered causal, was used to estimate the association with hypothetical interventions to reduce the mixture concentrations on preterm birth.

RESULTS The final analytic sample included 6045 participants (mean [SD] age, 29.1 [6.1] years). Overall, 802 individuals (13.3%) were Black, 2323 (38.4%) were Hispanic/Latina, 2576 (42.6%) were White, and 328 (5.4%) had other race and ethnicity (including American Indian/Alaskan Native, Native Hawaiian, >1 racial identity, or reported as other). Most phthalate metabolites were detected in more than 96% of participants. Higher odds of preterm birth, ranging from 12% to 16%, were observed in association with an interquartile range increase in urinary concentrations of mono-n-butyl phthalate (odds ratio [OR], 1.12 [95% CI, 0.98-1.27]), mono-isobutyl phthalate (OR, 1.16 [95% CI, 1.00-1.34]), mono(2-ethyl-5-carboxypentyl) phthalate (OR, 1.16 [95% CI, 1.00-1.34]), and mono(3-carboxypropyl) phthalate (OR, 1.14 [95% CI, 1.01-1.29]). Among approximately 90 preterm births per 1000 live births in this study population, hypothetical interventions to reduce the mixture of phthalate metabolite levels by 10%, 30%, and 50% were estimated to prevent 1.8 (95% CI, 0.5-3.1), 5.9 (95% CI, 1.7-9.9), and 11.1 (95% CI, 3.6-18.3) preterm births, respectively.

CONCLUSIONS AND RELEVANCE Results from this large US study population suggest that phthalate exposure during pregnancy may be a preventable risk factor for preterm delivery.

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Preterm birth is a leading cause of neonatal mortality and morbidity.[1] The societal burden of preterm birth is particularly high in the US,[2] with approximately 10% of pregnancies delivered preterm annually.[3] While the underlying risk factors for most preterm births are unknown, exposure to environmental chemicals like phthalates may play a role.

Phthalates are synthetic chemicals used in everyday consumer products such as personal care items and food processing or packaging.[4] Exposure can occur through many sources, including household dust, diet, and personal care products like cosmetics.[5] Consequently, phthalate exposure is ubiquitous among pregnant individuals.[6,7] Human and animal studies suggest that prenatal phthalate exposure is associated with adverse effects on children's neurodevelopment and male reproductive tract development.[8,9] While several studies have found positive associations between prenatal biomarkers of phthalate exposure and preterm birth,[10-16] others have shown null[17-20] or inverse[21-23] associations. This may be partly due to the limited number of preterm births included, differences in exposure assessment methods, and variation in the baseline risk of preterm birth and phthalate exposure.

The purpose of this analysis was to pool individual-level data from 16 prospective studies conducted in the US[11,12,14,17,21-32] and examine associations between prenatal urinary biomarkers of phthalate exposure and preterm birth. We also considered the potential influence of exposure to an overall phthalate mixture and evaluated how hypothetical interventions to reduce this exposure could impact preterm birth.

Key Points

Question Is phthalate exposure during pregnancy associated with preterm birth?

Findings In this pooled analysis of 16 studies in the US including 6045 pregnant individuals, phthalate metabolites were quantified in urine samples collected during pregnancy. Higher urinary metabolite concentrations for several prevalent phthalates were associated with greater odds of delivering preterm, and hypothetical interventions to reduce phthalate exposure levels were associated with fewer preterm births.

Meaning In this large observational study, urinary biomarkers of common phthalates used in consumer products were a risk factor for preterm birth.

Methods

Study Population

In May 2019, we systematically reviewed the literature to identify epidemiologic studies conducted in the US with data on urinary phthalate metabolites quantified during pregnancy and gestational age at delivery (eMethods 1 and 2 in the Supplement). We focused on US studies to facilitate generalizability of results to the US general population, which experiences relatively high levels of phthalate exposure[33] and high rates of preterm birth.[34] Of 21 unique studies, 17 had sufficient sample size (N > 50) and 16 corresponding authors agreed to collaborate (eFigure 1 in the Supplement). Participating studies received ethics approval from the institutional review board or human research ethics committees from their respective institutions. Participants provided written or verbal informed consent. Analysis of anonymized data sets sent to the National Institute of Environmental Health Sciences was deemed to not be human subjects research by the National Institute of Environmental Health Sciences institutional review board. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Study acronyms and design characteristics are provided in **Table 1**, and eligibility criteria are described in eTable 1 in the Supplement. All studies prospectively enrolled participants during prepregnancy (North Carolina Early Pregnancy Study [EPS][14] and Environment and Reproductive Health Study [EARTH][27]) or pregnancy and all participants had live births between 1983 and 2018. The only case-control study included was LIFECODES,[11] a study of preterm birth nested within a prospective cohort. Studies provided gestational age at delivery (defined by last menstrual period, early pregnancy ultrasonography, date of conception in pregnancies using assisted reproductive technologies, or some combination thereof). We defined preterm birth as delivery prior to 37 weeks' gestation. Our final analytic sample included 6045 participants after excluding 1136 of 7181 participants in the total pooled sample (eFigure 1 and eTable 2 in the Supplement).

Phthalate Exposure Assessment

Participants provided urine samples during pregnancy for quantification of phthalate monoester metabolites. Urinary phthalate metabolites are the preferred biomarker of phthalate exposure[35] and are highly stable in urine samples stored at ≤20 °C, as they were for all cohorts.[36,37] All studies collected spot urine samples, except for EPS[14] and Markers of Autism Risk in Babies-Learning Early Sign (MARBLES)[29] that pooled multiple samples prior to measurement (eTable 1 in the Supplement). Phthalate metabolite measurements were performed separately by cohort. Most studies measured at the US Centers for Disease Control and Prevention (CDC) or using CDC-developed methods, and targeted the same metabolites as the CDC biomonitoring program. Briefly, after enzymatic hydrolysis of phthalate metabolite conjugates, phthalate metabolites were extracted from urine using online solid phase extraction, separated by high-performance liquid chromatography, and detected by isotope dilution tandem mass spectrometry. The analysis of deidentified specimens at the CDC was determined not to constitute engagement in human subjects research. We included 11 metabolites based on availability in at least 50% of participants (eTable 4 in the Supplement): monoethyl phthalate, mono-n-butyl phthalate (MBP), monoisobutyl phthalate, monobenzyl phthalate, mono(2-ethylhexyl) phthalate, mono(2-ethyl-5-hydroxyhexyl) phthalate, mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-oxohexyl) phthalate, mono(3-carboxypropyl) phthalate (MCPP), monocarboxy-isooctyl phthalate, and monocarboxy-isononyl phthalate.

Table 1. Study Design Elements Among Cohorts Included in the Pooled Phthalate and Preterm Birth Study Population (N = 6045)

Study	No. of individuals	Preterm birth, No. (%)	Years of delivery[a]	Location	Primary method for determining gestational age	Mean gestational age at enrollment, wk[b]
Puerto Rico Testsite for Exploring Contamination Threats (PROTECT)[12]	1101	100 (9.1)	2011-2018	Puerto Rico	Last menstrual period and ultrasonography	11
The Infant Development and the Environment Study (TIDES)[24]	779	69 (8.9)	2011-2013	California, Minnesota, Washington, and New York	Ultrasonography or physician estimate	12
LIFECODES[11]	480	130 (27.1)	2007-2009	Massachusetts	Last menstrual period and ultrasonography	10
Healthy Start Study (Healthy Start)[17]	444	14 (3.2)	2012-2014	Colorado	Medical record	18
Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS)[25]	429	27 (6.3)	1999-2001	California	Medical record	14
Columbia Center for Children's Environmental Health (CCCEH)[26]	389	14 (3.6)	1999-2006	New York	Medical record	33
Health Outcomes and Measures of the Environment Study (HOME)[23]	389	37 (9.5)	2003-2006	Ohio, Kentucky	Last menstrual period	16
Environment and Reproductive Health Study (EARTH)[27]	385	27 (7.0)	2005-2017	Massachusetts	Medical record and guidelines for medically assisted reproduction	Prepregnancy[c]
Children's Environmental Health Study at the Mount Sinai School of Medicine (MSSM)[22]	362	28 (7.7)	1998-2002	New York	Last menstrual period	31
Study for Future Families (SFF)[21]	353	17 (4.8)	2000-2005	California, Minnesota, Missouri, and Iowa	Medical record or last menstrual period	25
Reproductive Development Study (RDS)[28]	318	28 (8.8)	2011-2014	South Carolina	Ultrasonography	20
Harvard Epigenetic Birth Cohort (HEBC)[30]	189	12 (6.3)	2007-2009	Massachusetts	Medical record	10
Markers of Autism Risk in Babies-Learning Early Signs (MARBLES)[29]	179	12 (6.7)	2007-2014	California	Medical record	20
The North Carolina Early Pregnancy Study (EPS)[14]	126	5 (4.0)	1983-1986	North Carolina	Day of implantation	Prepregnancy[c]
Michigan Mother-Infant Pairs Project (MMIP)[31]	68	2 (2.9)	2010-2013	Michigan	Medical record	11
Rutgers University[32]	54	17 (31.5)	2009-2010	New Jersey	Medical record	26

[a] Data harmonization details for year of delivery data are provided in eMethods 2 in the Supplement.

[b] Mean gestational age at enrollment is based on participants included in this study.

[c] All urine samples analyzed in this study were collected after conception and during pregnancy (at least 1 week prior to delivery).

Statistical Analyses

Using multiple imputation by chained equations, we simultaneously imputed (1) phthalate biomarker concentrations below the limit of detection without instrument-read values (eMethods 3 in the Supplement) and (2) missing covariates (eTable 5 in the Supplement). We performed all subsequent analyses on the imputed data sets and pooled results using Rubin's rules.[38] Studies measured urinary specific gravity or creatinine to account for urine dilution (eTable 1 in the Supplement). We used covariate-adjusted standardization to correct phthalate metabolite concentrations for urine dilution (eMethods 4 in the Supplement).[39,40] Most studies (9 of 16) quantified phthalate metabolites in multiple (range, 2-10) urine samples (eTable 1 in the Supplement). After dilution standardization, we calculated the within-participant geometric mean of phthalate metabolite concentrations across pregnancy. Subsequently, we natural-log–transformed concentrations and standardized concentrations by dividing by the interquartile range (IQR) to facilitate interpretability.

We used multivariable logistic regression to examine associations of mean pregnancy phthalate metabolites with odds of preterm birth. Odds ratios and 95% CIs were interpreted as the change in log-odds of preterm birth per 1-IQR increase in mean phthalate metabolite concentration. Crude models adjusted for study (via fixed effects for each study) and adjusted models included additional covariates that were measured across all 16 studies. We selected primary confounders a priori from the literature, including self-reported maternal race and ethnicity (categorical),[18,41,42] education (categorical),[12,17,18,28,41] maternal age at enrollment (years),[12,18,28,41] and prepregnancy body mass index.[17,18,28,41] Race and ethnicity was used as a confounder based on the consistent disparities in preterm birth[43] and environmental exposures[41] experienced by minoritized racial and ethnic populations in the US, which is driven by social determinants including racism and discrimination.[44] We defined race and ethnicity by combining several self-identified categories to maximize sample size and consistency across pooled studies, including non-Hispanic Black, Hispanic/Latina, non-Hispanic White, and other (including American Indian/Alaskan Native, Native Hawaiian, >1 racial identity, or reported as other).

We used 2 complementary methods, quantile g-computation and standard g-computation, to examine the association of an overall mixture of phthalate metabolites and preterm birth. The mixture included all metabolites except monocarboxy-isooctyl phthalate and monocarboxy-isononyl phthalate, which were excluded a priori because fewer participants (n = 3758) and studies (10 total) quantified these biomarkers. This provided 5471 participants (14 studies) for the mixture analyses (eTable 6 in the Supplement). We used quantile g-computation to examine the odds of preterm birth per

IQR increase in all phthalate metabolites in the mixture.[45] We used standard g-computation to estimate the probability of preterm birth following several hypothetical interventions to reduce concentrations of the phthalate metabolite mixture,[46] which provides potentially more interpretable results than model coefficients.[47,48] Hypothetical interventions reduced each metabolite in the mixture by 10% to 90% in 10% increments. The 95% CIs were estimated using nonparametric bootstrapping (2.5th and 97.5th percentiles across 2000 iterations).[46] We transformed results to be interpreted as the estimated number of preterm births prevented per 1000 live births by contrasting each hypothetical intervention with no intervention.

We conducted several sensitivity analyses. (1) To assess heterogeneity in effect estimates by study, we qualitatively compared estimates from fixed-effect models to mixed models in which we specified study indicator as a random intercept[49]; used Wald tests of goodness of fit for an interaction term between study and metabolite in the primary model[49]; and examined differences in effect estimates after we fit models that drop participants from single cohorts. This leave-1-out analysis provides a way to examine how overall results may have been influenced by individual cohorts. (2) We used Wald tests to assess potential differences in confounding across studies by fitting a series of models that additionally included interaction terms between study and each of the following covariates: maternal age, prepregnancy body mass index, race and ethnicity, and education. (3) We fit models additionally adjusted for precision variables associated with phthalate exposure or preterm delivery, including delivery year, smoking, or parity. (4) We assessed potential effect measure modification by fetal sex using model stratification and a nonstratified model with an interaction term between phthalate metabolite and sex.[24] (5) We examined nonlinearity in associations by fitting quadratic terms. (6) We examined metabolite associations with gestational age at delivery (continuous) using multivariable linear regression using the same covariates but applied inverse probability of sampling weights to account for the LIFECODES study design.[50] We chose not to conduct sensitivity analyses for other pregnancy complications (eg, preeclampsia) because evidence suggests such conditions are potentially on the causal pathway between phthalate exposure and preterm birth.[51-53] We considered Wald tests or interactions statistically significant if 2-sided *P* values were less than .05. We performed analyses using R version 4.0.3 (R Foundation).

Results

Study Characteristics

The overall study population consisted of 6045 pregnant individuals (mean [SD] age, 29.1 [6.1] years), of whom 539 (9%) delivered preterm (eFigure 1 in the Supplement). Overall participant characteristics are presented in **Table 2** and characteristics by study are shown in eTable 3 in the Supplement. A total of 802 individuals (13.3%) were Black, 2323 (38.4%) were Hispanic/Latina, 2576 (42.6%) were White, and 328 (5.4%) had other race and ethnicity (including American Indian/Alaskan Native, Native Hawaiian, >1 racial identity, or reported as other). Participant characteristics were similar between individuals who delivered term vs preterm (Table 2). Concentrations of urinary phthalate metabolites included for analysis were detectable in 96% or more of urine samples, except for mono(2-ethylhexyl) phthalate (83%) and MCPP (90%) (eTable 5 in the Supplement) and were highest for monoethyl phthalate, MBP, and MECPP (eTable 7 in the Supplement). Correlations were highest between metabolites with shared parent chemicals (eFigure 2 in the Supplement). Overall, there was substantial overlap in the distributions of phthalate metabolite concentrations across studies (eFigure 3 in the Supplement). However, concentrations for several metabolites (eg, monobenzyl phthalate, MCPP) were higher for EPS,[14] which was the only study to collect samples in the 1980s.

Associations With Preterm Birth

Regression analyses showed that higher concentrations of most phthalate metabolites were associated with slightly higher odds of preterm birth (**Figure 1**). After covariate adjustment, there was a 12% to 16% higher odds of preterm birth associated with an IQR increase in urinary concentrations of MBP (OR, 1.12 [95% CI, 0.98-1.27]), mono-isobutyl phthalate (OR, 1.16 [95% CI, 1.00-1.34]), MECPP (OR, 1.16 [95% CI, 1.00-1.34]), and MCPP (OR, 1.14 [95% CI, 1.01-1.29]). Other phthalate metabolites also displayed positive but nonsignificant associations. An IQR increase in the mixture of 9 phthalate metabolites was associated with 25% higher odds of preterm birth (OR, 1.25 [95% CI, 0.88-1.77]), although the confidence interval included the null. Based on results from g-computation, hypothetical interventions to reduce the phthalate metabolite mixture were estimated to prevent a mean of 2 to 32 preterm births per 1000 live births (**Figure 2**). For example, reducing the mixture of phthalate metabolite concentrations by 10%, 30%, or 50% was estimated to prevent 1.8 (95% CI, 0.5-3.1), 5.9 (95% CI, 1.7-9.9), and 11.1 (95% CI, 3.6-18.3) preterm births per 1000 live births, respectively.

Sensitivity Analyses

Fixed-effects and random-effects models produced nearly equivalent estimates and metabolite by study interactions were not statistically significant (eTable 8 in the Supplement), indicating minimal heterogeneity by study. Magnitudes of associations were similar after excluding participants from individual study populations (eFigure 4 in the Supplement). However, associations were attenuated for MBP, MECPP, and MCPP after exclusion of LIFECODES participants.[11] Heterogeneity in confounding was not detected (eTable 9 in the Supplement). We did not observe differences in associations when models were additionally adjusted for precision variables (delivery year, smoking, or parity) (eTable 10 in the Supplement) or evidence of effect measure modification by fetal sex (eTable 11 in the Supplement). We did not find evidence of nonlinear associations (eTable 12 in the Supplement). Importantly, direction of associations was consistent when gestational age at delivery was evaluated continuously (eTable 13 in the Supplement).

Table 2. Distributions of Participant Characteristics Overall and by Preterm Birth Outcome in the Pooled Phthalate and Preterm Birth Study

Characteristic[a]	No. (%)		
	Overall	Term birth[b]	Preterm birth[b]
Total	6045 (100)	5506 (91)	539 (9)
Gestational age at delivery, mean (SD), wk	39.1 (1.9)	39.5 (1.2)	34.8 (2.5)
Missing, No. (%)	0	0	0
Maternal age, mean (SD), y	29.1 (6.1)	29.0 (6.1)	30.0 (6.4)
Missing, No. (%)	16 (0.3)	16 (0.3)	0
Maternal race and ethnicity[c]			
Non-Hispanic Black	802 (13.3)	710 (88.5)	92 (11.5)
Hispanic/Latina	2323 (38.4)	2145 (92.3)	178 (7.7)
Non-Hispanic White	2576 (42.6)	2342 (90.9)	234 (9.1)
Other	328 (5.4)	297 (90.5)	31 (9.5)
Missing	16 (0.3)	12 (75)	4 (25)
Maternal education			
<High school	1045 (17.3)	960 (91.9)	85 (8.1)
High school	706 (11.7)	633 (89.7)	73 (10.3)
Some college	1410 (23.3)	1294 (91.8)	116 (8.2)
College graduate	1263 (20.9)	1141 (90.3)	122 (9.7)
Graduate school	1223 (20.2)	1109 (90.7)	114 (9.3)
Missing	398 (6.6)	369 (92.7)	29 (7.3)
Maternal prepregnancy body mass index[d]	25.7 (6.0)	25.6 (5.9)	26.6 (6.5)
Missing	496 (8.2)	448 (8.1)	48 (8.9)
Delivery year			
1983-2000	919 (15.2)	858 (93.4)	61 (6.6)
2001-2010	2113 (35.0)	1865 (88.3)	248 (11.7)
2011-2020	3013 (49.8)	2783 (92.4)	230 (7.6)
Maternal smoking during pregnancy			
No	5499 (91.0)	5012 (91.1)	487 (8.9)
Yes	463 (7.7)	419 (90.5)	44 (9.5)
Missing	83 (1.4)	75 (90.4)	8 (9.6)
Fetal sex			
Female	2870 (47.5)	2631 (91.7)	239 (8.3)
Male	3109 (51.4)	2814 (90.5)	295 (9.5)
Missing	66 (1.1)	61 (92.4)	5 (7.6)
Parity			
Nulliparous	3027 (50.1)	2780 (91.8)	247 (8.2)
Parous	2940 (48.6)	2662 (90.5)	278 (9.5)
Missing	78 (1.3)	64 (82.1)	14 (17.9)

[a] Characteristics represent distributions prior to imputation. Data harmonization details for all characteristics are provided in eMethods 2 in the Supplement.

[b] Preterm birth was defined as <37 weeks of completed gestational age at delivery.

[c] Each race and ethnicity category represents a composite measure to maximize sample size and consistency between pooled studies, including non-Hispanic Black (African American, Black), Hispanic/Latina (Hispanic, Latino, Latin American indigenous heritage), non-Hispanic White, and other (American Indian/Alaskan Native, Native Hawaiian, and/or >1 racial identity).

[d] Body mass index was calculated as weight in kilograms divided by height in meters squared.

Discussion

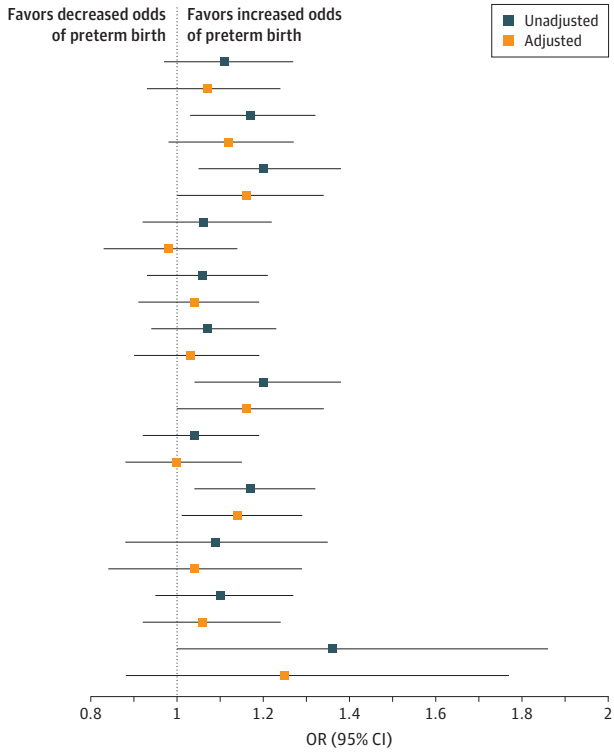
In this pooled analysis of more than 6000 pregnancies from 16 prospective studies in the US, we observed that higher maternal pregnancy concentrations of several urinary phthalate metabolites, particularly MBP, mono-isobutyl phthalate, MECPP, and MCPP, were associated with higher odds of preterm birth. While ORs were seemingly small in magnitude, g-computation estimates suggested that joint reductions in phthalate metabolites could produce significant population-level reductions in preterm births. Our findings suggest that exposure to multiple phthalates is associated with an increased risk of preterm birth.

At the population-level, modest effect sizes can be important when exposures are widespread and the outcome is prevalent.[54] The imprecision of our estimates, as reflected by our confidence intervals, may be related to inconsistencies of methods used across pooled studies. Several studies quantified phthalates using spot urine samples collected at single time points in different periods of pregnancy,[17,21,22,26,30-32] and such isolated measures are not ideal estimators of long-term exposure to be attributable to short half-life.[55] Further, we did not have the data to subdivide preterm births into those that were spontaneous vs indicated, which may be important for assessing risk.[11,12]

Our results are important to consider in the context of the literature. As in our study, urinary metabolites of di-n-butyl

Figure 1. Forest Plot of Associations Between Urinary Phthalate Metabolite Concentrations and Preterm Birth

Phthalate metabolite	Sample size	OR (95% CI)
MEP	6045	1.11 (0.97-1.27)
		1.07 (0.93-1.24)
MBP	6045	1.17 (1.03-1.32)
		1.12 (0.98-1.27)
MiBP	5991	1.20 (1.05-1.38)
		1.16 (1.00-1.34)
MBzP	5991	1.06 (0.92-1.22)
		0.98 (0.83-1.14)
MEHP	6045	1.06 (0.93-1.21)
		1.04 (0.91-1.19)
MEHHP	6045	1.07 (0.94-1.23)
		1.03 (0.90-1.19)
MECPP	5471	1.20 (1.04-1.38)
		1.16 (1.00-1.34)
MEOHP	6045	1.04 (0.92-1.19)
		1.00 (0.88-1.15)
MCPP	5673	1.17 (1.04-1.32)
		1.14 (1.01-1.29)
MCOP	3758	1.09 (0.88-1.35)
		1.04 (0.84-1.29)
MCNP	3794	1.10 (0.95-1.27)
		1.06 (0.92-1.24)
Mixture	5471	1.36 (1.00-1.86)
		1.25 (0.88-1.77)



Associations represent the odds ratios (ORs) and 95% CIs of preterm birth per interquartile range increase in mean pregnancy urinary phthalate metabolite concentration in the Pooled Phthalate and Preterm Birth Study (N = 6045). The interquartile range (ng/mL) of each metabolite is as follows: monoethyl phthalate (MEP), 168.2; mono-n-butyl phthalate (MBP), 21.4; mono-isobutyl phthalate (MiBP), 8.6; monobenzyl phthalate (MBzP), 11.0; mono(2-ethylhexyl) phthalate (MEHP), 5.0; mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), 17.3; mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), 26.8; mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), 12.4; mono(3-carboxypropyl) phthalate (MCPP), 2.5; monocarboxy-isooctyl phthalate (MCOP), 18.5; and monocarboxy-isononyl phthalate (MCNP), 2.2 (eTable 7 in the Supplement). Single metabolite results were estimated by multivariable logistic regression models and mixture results were produced by quantile g-computation models. Unadjusted models adjusted for study as a fixed effect. Adjusted models were adjusted for study, maternal age, race and ethnicity, education, and prepregnancy body mass index. Missing covariate values were multiply imputed for all models. The metabolites MCOP and MCNP were excluded from the mixtures analysis owing to limited sample size across cohorts.

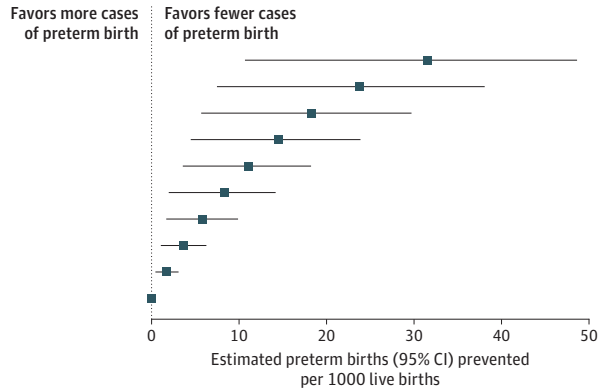
phthalate, di-isobutyl phthalate, and di(2-ethylhexyl) phthalate have been associated with reduced gestational age at delivery or increased likelihood of preterm birth in several prospective US studies included here[11-14,26,31,32] as well as studies from China[16] and Mexico.[15] Although null[17-20,56] or contradictory[14,21-23] associations have also been observed, associations between metabolites of these parent chemicals and preterm birth appear to be more consistent than other phthalate metabolites. Variation across studies with respect to magnitudes of association and statistical significance is expected owing to differences in (1) sample size and preterm birth prevalence, (2) metabolite distributions, (3) exposure assessment approaches, (4) gestational age at exposure assessment, and (5) geographic location, where some populations may have different underlying susceptibilities or patterns of exposure.[33,34] While pooling data cannot address all systematic biases, our study directly addressed several limitations by achieving larger sample size and examining associations across wide distributions of phthalate biomarkers.

The mechanistic pathway between phthalate exposure and preterm birth is unclear, but several lines of evidence provide biologic plausibility for a relationship. Associations of phthalate metabolites with preterm birth may be mediated by oxidative stress and inflammation at the maternal-fetal interface.[57,58] Additional mechanisms may include dysregulated trophoblast differentiation and endocrine disruption, as phthalate biomarkers have been associated with downregulated expression of placental genes responsible for these processes.[59]

Our findings provide additional evidence of the need to reduce phthalate exposures among pregnant individuals, which could take the form of behavioral interventions or regulations. Although phthalate exposure can occur through many sources and environments,[4,7,60,61] there has been a longstanding scientific effort to accurately determine whether a single source drives the majority of human exposure.[62] The US Consumer Product Safety Commission attempted to estimate exposure by source and found food and medications, not children's toys, were the primary sources of exposure.[63] Unfortunately, there is still substantial uncertainty in the primary source of exposure. In the US, phthalate exposure varies widely by sociodemographic factors,[64] including whether a person is pregnant,[65] at a disadvantaged socioeconomic status,[64,66] or is of a particular marginalized race or ethnicity.[66]

Figure 2. Estimated Number of Prevented Preterm Births per 1000 Live Births Under Hypothetical Interventions to Reduce the Overall Mixture of Phthalate Metabolite Concentrations in Maternal Urine

Exposure intervention	Estimated preterm births (95% CI) prevented per 1000 live births
90% Reduction	31.6 (10.6-48.6)
80% Reduction	23.8 (7.5-38.1)
70% Reduction	18.3 (5.7-29.7)
60% Reduction	14.5 (4.5-23.9)
50% Reduction	11.1 (3.6-18.3)
40% Reduction	8.3 (2.0-14.2)
30% Reduction	5.9 (1.7-9.9)
20% Reduction	3.7 (1.1-6.3)
10% Reduction	1.8 (0.5-3.1)
0% Reduction	0 [Reference]



Estimates represent the difference in mean probability of preterm birth following a series of hypothetical interventions to proportionally reduce concentrations of 9 phthalate metabolites in the pooled study population (n = 5471), including monoethyl phthalate, mono-n-butyl phthalate, mono-isobutyl phthalate, monobenzyl phthalate, mono(2-ethylhexyl) phthalate, mono(2-ethyl-5-carboxypentyl) phthalate, mono(2-ethyl-5-oxohexyl) phthalate, mono(2-ethyl-5-hydroxyhexyl) phthalate, and mono(3-carboxypropyl) phthalate. G-computation was implemented to estimate probabilities from a multivariable logistic regression model, which adjusted for study, maternal age, race and ethnicity, education, and prepregnancy body mass index. Differences were multiplied by 1000 to estimate the rate per 1000 live births. The 95% CIs were estimated using quantiles of the nonparametric bootstrap distribution across 2000 iterations. Estimations were performed on a single randomly chosen imputed data set.

Targeted interventions may help modify consumer behaviors that lead to phthalate exposures, such as altering the type of personal care products purchased.[67,68] However, behavioral approaches are difficult to implement on a population scale because of the vast number of available consumer products containing phthalates and the limited ability of US consumers to access accurate ingredient lists.[69] For example, the US Food and Drug Administration does not require phthalates to be listed as ingredients when designated as part of the fragrance. Alternatively, interventions to reduce exposures through diet have had mixed results.[68,70] Compounding these difficulties, economic disparities may make access to phthalate-free products and diet more difficult for certain populations.[28,41] Past public health efforts have successfully led to federally mandated restrictions on the use of certain phthalates in consumer products intended for children,[4,71] but few restrictions exist for products intended for people who are pregnant. The US Food and Drug Administration also has the power to regulate phthalates in food, but 28 phthalates are currently allowed as food additives or in food contact materials.[72] Given this reality, Project TENDR (Targeting Environmental Neuro-Development Risks) recommends a multipronged approach to reducing human exposure to multiple phthalates, including regulations at the federal and state levels, as well as voluntary action on the part of retailers and manufacturers.[8]

Our analysis of hypothetical interventions to reduce exposure to the phthalate mixture, regardless of whether reductions occur via behavioral or regulatory mechanisms, helps to highlight the potential magnitude of effect that population-level phthalate exposure may have on preterm birth, meanwhile addressing the fact that realistic interventions will change exposure to multiple phthalates simultaneously, rather than one at a time. Based on the rate of about 90 preterm births per 1000 live births birth in the pooled study population, hypothetical interventions of 10% to 50% would correspond with an estimated mean of 2% to 12% reduction in preterm births. Given that most individuals are exposed to multiple phthalates, regulatory approaches to mitigate population-level health effects from phthalates would be most effective when considering phthalates as a class, rather than as individual chemicals.[8] We took an approach used by previous studies[48,73,74] and evaluated a range of possible decrements in exposure. This approach allowed us to evaluate whether any reductions, large or small, in phthalate exposure would be worth pursuing based on the potential to result in fewer preterm births in community settings. Our results are consistent with the hypothesis that modest, but potentially feasible, reductions in phthalate exposure could reduce rates of preterm birth. However, our results should be interpreted cautiously in light of the assumptions required for causality (eMethods 5 in the Supplement).[48] Although g-computation is often used to facilitate causal inference,[75] it is still a statistical model and thus we opt for associational rather than causal language. Regardless, "preterm births prevented" uses causal language because there is not useful associational language for this statistic.

Strengths and Limitations

Our study represents the largest prospective investigation of phthalate exposure in pregnancy and preterm birth, to date and to our knowledge, and includes individual-level data from almost all US studies that have quantified phthalate metabolites in pregnancy. Thus, we were not restricted to studies that only published on associations with preterm birth or gestational age at birth[25,27,30] and avoided publication bias. Pooled participant characteristics (eg, exposure distributions, geographic locations, education, and race and ethnicities) were

more diverse than any single prior study, which provided better representation of the US population. Further, our mixtures approach helped reflect the reality that pregnant individuals are exposed to a variety of phthalates in their environments, which should be a central consideration for any future policies intended to reduce phthalate exposures.[8]

Several limitations in our study are important to acknowledge. First, there was variation in exposure assessment methods across studies. This may have produced measurement error of metabolites, which could have contributed to observed exposure differences and could not be disentangled from true differences in exposure levels across the study populations. However, there was large overlap in distributions across studies, and we adjusted for known confounders. Although calculating mean values across multiple spot urine samples can improve characterization of exposure,[76] single spot urine samples may provide lower accuracy.[77] Second, ORs from our statistical approach will tend to overestimate risk ratios, which are arguably more interpretable. We selected a logistic model to ensure that the model predictions remain within logical bounds without placing constraints on the phthalate distribution, and we use g-computation to allow easier interpretation of results. Third, we were also unable to examine potentially important confounders, such as diet.[78] Concentrations of certain phthalate biomarkers are higher in individuals who have diets high in ultraprocessed food, fast food, or meat and dairy.[60,61,79] Because some parameterizations of poor diet that include these foods are also associated with increased risk of preterm birth,[80] residual confounding may exist in our analysis. However, phthalate exposure can come from many dietary pathways,[70] so the role of diet in this relationship is uncertain.

Conclusions

In this pooled analysis of 16 prospective US studies, higher concentrations of several urinary phthalate metabolites in pregnancy were associated with preterm birth. These findings highlight the need for public health and policy measures to reduce phthalate exposures among pregnant individuals.

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Supplementary Online Content

Welch BM, Keil AP, Buckley JP, Calafat AM, Christenbury KE, Engel SM, O'Brien KM, Rosen EM, James-Todd T, Zota AR, Ferguson KK, and the Pooled Phthalate Exposure and Preterm Birth Study Group. Associations Between Prenatal Urinary Biomarkers of Phthalate Exposure and Preterm Birth: A Pooled Study of 16 US Cohorts.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods A-D

A. Description of study identification and inclusion in the pooled analysis

We performed a comprehensive search of PubMed for articles published through May 13th, 2019 to identify potentially eligible cohorts. The following terms were used in independent PubMed searches: "phthalates and gestation"; "phthalates and gestational"; "phthalates and preterm"; and "phthalates and pregnancy." Abstracts and methods sections of articles were reviewed to determine eligibility. Cohorts were considered potentially eligible for inclusion in the pooled analysis if the article: was published in English (original or translation); used an epidemiologic study design; was conducted in the United States of America (USA) or a USA territory (e.g., Puerto Rico); enrolled women during or prior to pregnancy; gathered information about gestational age at delivery; and measured ≥1 urinary phthalate metabolite in maternal urine collected during pregnancy.

In total, we identified 21 unique pregnancy cohorts that fit these criteria. Our final inclusion criteria were that a study had >50 participants and responded to our data transfer requests. We excluded 4 studies due to participant sample sizes of ≤50[1-4] and 1 study due to no response from the corresponding author.[5] This provided a total of 16 eligible studies that were included in this pooled analysis. The study design for selecting studies and eligible participants is described in eFigure **1**.

B. Description of data harmonization

B.1. Variables used to determine preterm birth

- *Gestational age at enrollment and delivery*. Gestational age at enrollment and delivery was provided by all studies and converted to completed weeks (to first decimal) if not already provided as such. EPS participants were recruited before pregnancy so all gestational age at enrollment was set to "0." HEBC participants did not have a gestational age for first urine collection provided, but the value was set to 10 weeks based on the reported median value.[6] As detailed in Table 1, gestational age was defined by last menstrual period, early pregnancy ultrasound, date of conception in pregnancies utilizing assisted reproductive technologies (ARTs), or some combination thereof.
- *Preterm birth*. Preterm birth was defined as having a gestational age at delivery of <37 weeks, while term birth was ≥37 weeks gestation.

B.2. Variables used to assess phthalate exposures

- *Limit of detection (LOD) flags for phthalate biomarker concentrations*. Studies provided variables with specific LOD values for each biomarker measurement. Additionally, variables were provided or generated that flagged concentrations based on the LOD value, including the following categories: At or Above LOD; Below LOD-Instrument-Read Value; Below LOD-Imputed; Below LOD-Other (Reported as N/A, unknown, or 0); and Missing. Any concentrations below the LOD, but not explicitly stated as being an instrument-read value, were subsequently imputed as described in eMethods part C. Missing biomarker concentrations were not altered.
- *Urine specific gravity (SG) and creatinine*. Continuous values for SG and creatinine were provided for all studies.
- *Gestational age at urine collection*. This variable was reported in weeks and based on gestational age as described in eMethods B.1.

B.3. Variables used as primary confounders

- *Maternal race/ethnicity*. Categories of race/ethnicity were self-reported by participants of all studies, but a wide range of categories were reported. Thus, we generated a composite measure of self-identified categories that were combined 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), Other (American Indian/Alaskan Native, Native Hawaiian, >1 racial identity).
- *Maternal education*. Maternal education was provided in different forms by studies. We summarized education to include the following categorical levels: less than high school (did not graduate); high school (graduated); some college (attended but did not graduate); college graduate (graduated undergraduate); graduate school. The "some college" category includes participants who reported attending some college or some technical school or 13-15 years of education. The "college graduate" category includes participants who reported receiving an undergraduate degree and/or attending ≥16 years of education. The "graduate school" category includes participants who reported receiving some graduate work or a graduate/advanced degree, as well as ≥17 years of education. Education information was not collected among HEBC participants,[6] but values were multiply imputed for the purposes of regression analyses.

- *Maternal age.* Maternal age was reported continuously for all studies except MSSM, which reported age as a categorical variable. The original categorical levels of maternal age among MSSM participants were: Less than 20; 20-<25; 25-<30; 30-<35; and ≥35; which we replaced with the continuous values 19, 22, 27, 32, and 37, respectively.
- *Maternal body mass index (BMI) –pre- and early pregnancy.* BMI values were reported as continuous values of kg/m^2. Prepregnancy BMI values were used whenever available, but early pregnancy values were used if prepregnancy values were unavailable (i.e., RDS). BMI measures were not available for SFF and Rutgers participants,[7, 8] but these values were multiply imputed for purposes of regression analyses.

B.4 Covariates used for descriptive statistics and/or as predictors in imputation models

- *Year of delivery.* The final variable of year measured on a continuous scale. For LIFECODES, TIDES, PROTECT, Healthy Start, RDS, MMIP, MSSM, EARTH, MARBLES, Rutgers, and SFF studies, year of delivery was available. For CHAMACOS, CCCEH, HOME, and EPS studies, year was abstracted based on year of urine collection which may differ in some pregnancies from year of delivery. For HEBC, a range of years was available from study notes from publications.[6, 9] For HEBC, the median of the year from the range was assigned to all the participants in that study. Additionally, there were 60 participants of SFF missing year of delivery, which was also imputed as 2002 based on the median from the range of years in the cohort (2000-2005).
- *Fetal sex.* Fetal sex was provided as male or female by all studies.
- *Parity*. Parity was recategorized as nulliparous or parous. A participant was categorized as parous if they reported having ≥1 prior pregnancy. Participants of MSSM were all nulliparous based on study design.[9]
- *Smoking.* A participant was categorized as "yes" for smoking in pregnancy if they reported ever smoking during pregnancy. Participants in HOME and CCCEH were categorized based on serum cotinine values, with "yes" defined by values ≥3 ng/mL.[10, 11]
- *Assisted Reproductive Technology (ART).* ART was categorized as "yes" if the participant reported using any of the following methods for the index pregnancy: IVF, ICSI, Donor Egg, or Other. ART was only used as a predictor in imputation models because it was only measured in a subset of studies (**eTable 3**).
- *Preeclampsia*. Dichotomous preeclampsia values (yes/no) were provided by all studies. Participants were reported as "no" if they reported "don't know", as was the case with CHAMACOS. Preeclampsia was only used as a predictor in imputation models.
- *Household income.* Income was only used as a predictor in imputation models because it was only measured in a subset of studies (**eTable 3**). Final income categories reflect household income and are coded into $10,000 range groupings (e.g. "Less than $10,000," "$10,000 - $19,999") until the household income exceeds $70,000. All incomes above $70,000 are grouped together (e.g., "$70,000+"). Original data from studies were in the form of income ranges. Additionally, the study dates for the different study ranged from 1983 to 2018. To account for the variability in reporting and collection times, we took the following steps. First, each participant was assigned their mean of the range of income. If income was reported as "$X or more", we retained the lowest income level within that range (e.g., if the range was "$150,000 or more," participants' income was coded as $150,000). Second, we account for inflation by calculating the inflation index for each study as of January 2020 using the Bureau of Labor Statistics Inflation Calculator. Inflation index is calculated using the original and current year. Original year was selected from the delivery year of each participant as described above. Third, we multiplied the income calculated in Step 1 with the inflation index calculated in Step 2. Fourth, using the adjusted income, household income was placed into $10,000 ranges. The lowest income level across the studies for the original "$X or more" ranges was $70,000, thus, for the current study, the highest category is "$70,000 or more."

C. Multiple imputation

The goal for performing multiple imputation by chained equations (MICE) was to simultaneously impute: 1) phthalate metabolite concentrations below the limit of detection (LOD); and 2) missing covariate observations. We imputed phthalate metabolite concentrations below the LOD exclusively in the case where no instrument-read values were available (**eTable 5**). The proportions of samples with concentrations below the LOD that required imputation were relatively small across phthalate metabolites and ranged from 0.3% to 11% (**eTable 5**). Values below the LOD were imputed using a left-censored linear regression. The model assumed a log-normal distribution for each metabolite that was constrained to be between zero and the LOD, but allowed for the LOD value to vary within and across individuals (i.e., batch- and cohort-specific values). Missing covariate values were imputed by multivariate chained equations that used either predictive mean matching, logistic regression, or multinomial logistic regression for continuous, binary, and categorical covariates, respectively.[12] Primary covariates that were imputed included fetal sex (male;

female) and the primary confounders of maternal age (years), race/ethnicity (non-Hispanic [NH] white; NH Black; Hispanic/Latina; Other), education (<high school; high school; some college; college graduate; graduate school), and prepregnancy body mass index (BMI).

Predictors used in MICE algorithms for concentrations below LOD and missing covariates included gestational age at delivery (weeks), gestational age at sample collection (weeks), study indicator (categorical, including sub-sites within study for TIDES and SFF), fetal sex (male; female), phthalate metabolite concentrations (continuous), and the previously listed set of confounders. Additionally, we included other covariates as predictors that were likely to be related to missing values, which is appropriate and improves accuracy of imputations when values may be missing not at random.[13] These predictors included preeclampsia (yes; no), parity (nulliparous; parous), smoking in pregnancy (yes; no), and use of assisted reproductive technology (yes; no).

We generated 10 imputed datasets using 20 chained iterations per dataset. Convergence of imputations was determined from trace plots of every imputed variable. Imputations were deemed to achieve adequate convergence based on minimal to no trends and strong mixing in concentrations across imputed data sets and iterations.[12] Imputation was carried out in R using MICE in the *mice* package (version 3.11.0).[13] Left-censored imputation of metabolite concentrations below LOD was done using the mice.impute.leftcenslognorm function from the *qgcomp* package (version 2.7.0).

D. Methods to standardize phthalate metabolite concentrations by urine dilution

We implemented covariate-adjusted standardization to correct phthalate metabolite concentrations for urine dilution.[14, 15] This approach estimates a dilution-corrected value for each metabolite concentration. The covariate adjustment accounts for covariates that may influence hydration status (urinary specific gravity [SG] or creatinine), urinary phthalate metabolite concentrations, and/or an outcome of interest (i.e., preterm birth).[14] The method facilitates pooling data by allowing for comparisons of SG- and creatinine-standardized biomarker concentrations on the same scale.[15]

We fit cohort-specific models to generate fitted (covariate-adjusted) SG and creatinine values. In this study, we specified the following variables as relevant covariate predictors based on evidence in prior studies: maternal race/ethnicity, education, age, prepregnancy BMI, gestational age at urine sampling, and year of delivery.[15-18] Categorical covariates were included to account for studies with multiple study centers (TIDES and SFF). For example, SFF urine dilution model included a categorical variable indicating specific study-site locations in different states, including CA, MN, MO, and IA.[7] We used SG values if participants had both SG and creatinine values available (**eTable 1**): this included participants of the CHAMACOS and CCCEH studies.[10, 19]

For creatinine, we first fit a linear model for log-transformed creatinine concentrations as a function of the covariates, which is used to generate model-fitted values of creatinine for each participant.[14] These values were subsequently exponentiated to provide covariate-adjusted, or model-fitted, creatinine concentrations. We then created creatinine-standardized phthalate metabolite concentrations using the following formula: $E_{cor} = E_{obs} \times \frac{Cr_{fit}}{Cr_{obs}}$, where E_{cor} is the creatinine-standardized phthalate metabolite concentration, E_{obs} is the observed phthalate metabolite concentration, Cr_{fit} is the model-fitted creatinine concentration, and Cr_{obs} is the observed creatinine concentration. For SG, we used a modified version of this method previously established.[15] We first generated model-fitted values of SG for each participant by fitting a linear model for log-transformed SG as a function of the same covariate set. These values were subsequently exponentiated to provide covariate-adjusted, or model-fitted, SG values for every participant. We then created SG-standardized phthalate metabolite values using the following formula: $E_{cor} = E_{obs} \times \frac{SG_{fit}-1}{SG_{obs}-1}$, where E_{cor} is the SG-standardized phthalate metabolite concentration, E_{obs} is the observed phthalate metabolite concentration, SG_{fit} is the model-fitted SG value, SG_{obs} is the observed SG value. Since both the creatinine and SG approaches are based upon using the ratio of observed to fitted concentrations, the ratio measure is unitless. Thus, the resulting standardized phthalate metabolite concentrations from either method can be directly compared and are in the original units of the phthalate metabolite concentration (ng/mL).

E. Assumptions of g-computation necessary to infer causality

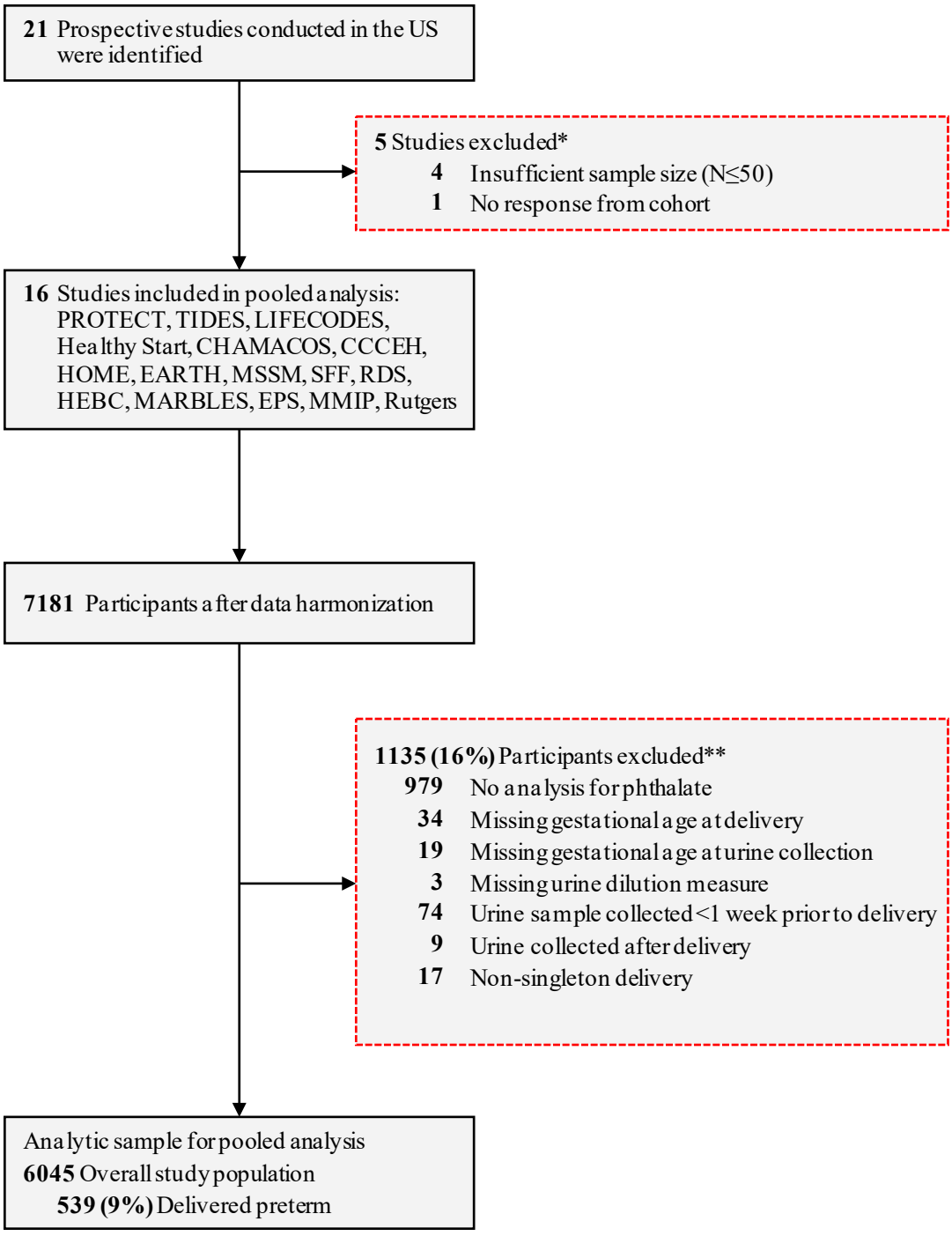
We used g-computation to determine potential changes in preterm birth following a range of hypothetical interventions that produced lower concentrations of a mixture of urinary phthalate metabolites within our pooled study population. The use of g-computation to evaluate hypothetical interventions is common for epidemiologic analyses in many subject areas, including environmental health,[20-23] as well as to improve interpretability of results or infer possible causal effects.[24] However, inferring possible causality requires a set of assumptions to be met. Within the context of exposure mixtures[20] and preterm birth, the more relevant assumptions include:

- *Correct model specification*. An assumption that our primary model correctly represents the true relationship between urinary phthalates and preterm birth. Given the results for individual metabolite models that included quadratic terms (eTable 12), our assumption of a linear scale was likely met. Although it is possible that metabolite by metabolite

interactions were possible, including any such interactions would decrease the translatability of results, which was the primary goal for this g-computation analysis.

- *Exchangeability*. An assumption that there is no outstanding source of selection bias or confounding in our results. Within the context of our study, this assumption may be violated if selection bias was produced from phthalate exposure causing pregnancy to not result in a live birth.[25] However, given our study is principally interested in investigating associations among live births, it is unlikely to be a large source of bias. Another source of residual confounding could be diet, which can be a source of phthalate exposure[26] and risk factor for preterm birth.[27] Given phthalate exposure can come from many dietary pathways,[28] so the role of diet in is uncertain.
- *Positivity*. An assumption that there is a nonzero probability that phthalate metabolite concentrations can take on all possible values under the hypothetical interventions. This assumption is formally met within our analysis because phthalates can theoretically take on any nonnegative values, and we constrained phthalate concentrations from going below observed minimums. Our approach evaluated joint effects from simultaneously reducing all phthalate metabolites, which likely provides improved translatability to real-world exposure distributions.[20]
- *No measurement error of exposure*. An assumption that urinary phthalates were measured without systematic error. Variability in phthalate metabolite concentrations and use of single spot urine samples across certain studies may have been attributed to measurement error.
- *Treatment variation irrelevance*. An assumption that the effect of reducing phthalates via unspecified interventions will not product unanticipated impacts that adversely influence preterm birth. A relevant example may be that an intervention on one phthalate results in the substitution for another phthalate that also has an adverse influence on preterm birth. We recognize this assumption may not be fully achievable until the potential preterm birth effects of any such replacements are known.

eFigure 1. Flow diagram of study participant selection and exclusion in the Pooled Phthalate and Preterm Birth Study



Detailed description of study inclusion criteria provided in eMethods A and the exclusions by study are provided in eTable 2.

eTable 1. Additional study design elements of cohorts included in the Pooled Phthalate and Preterm Birth Study population

Study	Eligibility criteria	Recruitment sites	Type of urine sampling	Lab location and method	Urine dilution measure [a]	Urine samples per pregnancy average (med [min, max])
PROTECT	• Age 18-40 years • Residence within the Northern Karst aquifer region • Did not use oral contraceptives within the three months prior to pregnancy • No use of *in vitro* fertilization to become pregnant • No major preexisting medical conditions (e.g., diabetes)	Hospitals and health clinics in northern coast region of Puerto Rico	Spot	CDC[29]	SG	2 (1, 3)
TIDES	• Age ≥18 years • <13 weeks gestation • English speaking • No major pregnancy complications • Plans to deliver at participating hospital	Obstetrical medical centers at: 1) UCSF; 2) UMN; 3) URMC; and 4) SCH/UW	Spot	University of Washington[30] and CDC[29]	SG	2 (1, 3)
LIFECODES	• Non-anomalous fetus • Live singleton birth • Plans to delivery at BWH	Tertiary care clinics of Brigham Women's Hospital in Boston, Massachusetts	Spot	NSF International[29]	SG	4 (1, 4)
Healthy Start	• Age ≥16 years • <24 weeks gestation • No prior stillbirth, diabetes, asthma, cancer, or serious psychiatric illness	Obstetric clinics at the University of Colorado Hospital in Aurora, Colorado	Spot	CDC[29]	Creatinine	1 (1, 1)
CHAMACOS	• English or Spanish speaking • ≤20 weeks pregnant • ≥18 years old • Low income (Medi-Cal California Medicaid eligible) • Intention to deliver at county hospital	Six prenatal clinics serving farmworkers in Salinas Valley, California	Spot	CDC[29]	SG & creatinine	2 (1, 2)
CCCEH	• Age 18-35 years • First prenatal visit <20 weeks gestation • African American or Dominican identity • Living in northern Manhattan or South Bronx for ≥1 year prepregnancy • No tobacco or drug use in pregnancy No chronic medical conditions (HIV, diabetes, hypertension)	Prenatal clinics at Harlem and New York (NY) Presbyterian hospitals in NY City, NY	Spot	CDC[29]	SG & creatinine	1 (1, 1)

Study	Eligibility criteria	Recruitment sites	Type of urine sampling	Lab location and method	Urine dilution measure [a]	Urine samples per pregnancy average (med [min, max])
HOME	• Age ≥18 years • 16±3 weeks gestation • Living in surrounding counties and intention to deliver at participating clinics • Living in home (no mobile/trailer home) built ≤1978 (related to original focus on lead exposure) • No chronic medical conditions (HIV, diabetes, bipolar disorder, schizophrenia, chemotherapy- or radiation-treated cancer) • No genetic abnormalities or birth defects	Prenatal practices of three hospitals in region surrounding Cincinnati, Ohio	Spot	CDC[29]	Creatinine	2 (1, 2)
EARTH	• Age 18-46 years (women) • One prepregnancy urine sample taken prior to conception of index pregnancy (only pregnancy measures evaluated here)	Massachusetts General Hospital Fertility Center in Boston, Massachusetts	Spot	CDC[29]	SG	3 (1, 3)
MSSM	• Primiparous (first pregnancy/nulliparous) • No chronic conditions (diabetes, hypertension, thyroid disease) • No serious pregnancy complications (delivery <32 weeks, or fetal genetic abnormalities or malformations) or change in residence outside NY City	Prenatal clinic and private practices at Mount Sinai Medical Center in NY City, NY	Spot	CDC[31]	Creatinine	1 (1, 1)
SFF	• Age ≥18 years • Natural conception • No severe pregnancy complications • Live within 50 miles of clinic Participated in postpartum follow-up study	Prenatal clinics of university hospitals in: 1) Los Angeles, California; 2) Minneapolis, Minnesota; 3) Columbia, Missouri; and 4) Iowa City, Iowa	Spot	CDC[32]	Creatinine	1 (1, 1)
RDS	• Age ≥18 years • First trimester ultrasound confirmed pregnancy • No fetal genetic anomalies or aneuploidy • No use of progesterone or other steroids • No chronic medical conditions (diabetes, thyroid or other endocrine disorder)	Medical University of South Carolina in metropolitan area of Charleston, South Carolina	Spot	National Institute of Standards and Technology, Charleston, South Carolina[32]	SG	1 (1, 2)

Study	Eligibility criteria	Recruitment sites	Type of urine sampling	Lab location and method	Urine dilution measure [a]	Urine samples per pregnancy average (med [min, max])
HEBC	• Women participated in prior enrollment studies and contributed first-trimester urine sample between 2007-2009 • No chronic medical conditions (diabetes, chronic hypertension)	Clinics and private practices affiliated with the Brigham and Women's Hospital in Boston, Massachusetts	Spot	CDC[29]	SG	1 (1, 1)
MARBLES	• High risk of delivering child who will develop autism spectrum disorder (ASD), primarily because previously delivered child who developed ASD • Age ≥18 years • English fluency • Lives within 2.5 hours of Davis/Sacramento region	Recruitment occurred primarily through California Department of Developmental Services, along with other sources (other studies, provider referrals), in Northern California	First morning void or 24 hour	CDC[29]	SG	3 (1, 10)*
EPS	• No diagnosed fertility problems • No chronic medical conditions	Recruitment via community advertisements in North Carolina	Pooled urine sample (3 samples collected over 3-week period)	CDC[29]	Creatinine	1 (1, 1)*
MMIP	• Age ≥18 years • Naturally conceived	Recruitment occurred during first prenatal visit at University of Michigan OG/GYN facility in Ann Arbor, Michigan	Spot	NSF International[33]	SG	1 (1, 1)
Rutgers	Age ≥18 years	Recruited from the High-Risk Obstetric Clinic at Robert Wood Johnson University Hospital, part of Rutgers University, in New Brunswick, New Jersey	Spot	Rutgers University[8]	SG	1 (1, 1)

Abbreviations: SG, specific gravity; med, median

[a] If both SG and creatinine were available, only SG was used.

* EPS and MARBLES combined (pooled) repeated urine samples together prior to measuring phthalate metabolites.

eTable 2. Description of participant exclusions and final sample size in the Pooled Phthalate and Preterm Birth Study population

	Original sample		Reason for exclusion (n)							Pooled analysis
	N	Excluded[a] (n [%])	No analysis for phthalates[b]	Missing gestational age at delivery	Missing gestational age at urine collection[c]	Missing urine dilution measure	Urine collected <1 week prior to delivery	Urine collected after delivery	Non-singleton delivery	Analytic sample (N)
Overall	7181	1136 (16)	979	34	19	3	74	9	17	6045
PROTECT	1128	27 (2)	24	0	0	0	3	0	0	1101
TIDES	969	190 (20)	187	0	0	0	1	0	2	779
LIFECODES	482	2 (0)	0	2	0	0	0	0	0	480
Healthy Start	446	2 (0)	0	2	0	0	0	0	0	444
CHAMACOS	596	167 (28)	167	0	0	0	0	0	0	429
CCCEH	456	67 (15)	0	29	4	0	29	5	0	389
HOME	389	0 (0)	0	0	0	0	0	0	0	389
EARTH	386	1 (0)	0	0	0	0	1	0	0	385
MSSM	404	42 (10)	22	0	3	1	12	4	0	362
SFF	955	602 (63)	575	1	0	0	20	0	6	353
RDS	319	1 (0)	0	0	0	0	1	0	0	318
HEBC	195	6 (3)	0	0	0	0	0	0	6	189
MARBLES	186	7 (4)	0	0	0	0	4	0	3	179
EPS	130	4 (3)	3	0	0	1	0	0	0	126
MMIP	68	0 (0)	0	0	0	0	0	0	0	68
Rutgers	72	18 (25)	1	0	12	1	4	0	0	54

[a] Study-specific percent value provided

[b] If all phthalate metabolite concentrations were missing for a participant, it was assumed that no urine samples were collected during pregnancy.

[c] Participants were excluded if gestational age at urine collection was missing because it was possible collection could have occurred <1 prior to delivery.

eTable 3. Participant characteristics (n [%] or mean [SD]) by study (a-p)

	a. PROTECT	b. TIDES	c. LIFECODES [a]	d. Healthy Start	e. CHAMACOS	f. CCCEH
Sample size (n)	1101	779	480	444	429	389
Delivery (n)						
Term	1001 (90.9)	710 (91.1)	350 (72.9)	430 (96.8)	402 (93.7)	375 (96.4)
Preterm	100 (9.1)	69 (8.9)	130 (27.1)	14 (3.2)	27 (6.3)	14 (3.6)
Gestational age at delivery (weeks)	38.9 (2.0)	39.3 (1.8)	38.0 (2.8)	39.5 (1.3)	39.0 (1.8)	39.3 (1.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal age (years)	27.1 (5.5)	31.0 (5.5)	32.1 (5.4)	28.2 (6.1)	26.8 (5.3)	25.3 (4.8)
Missing	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal race/ethnicity (n)						
Non-Hispanic White	0 (0.0)	511 (65.6)	283 (59.0)	255 (57.4)	7 (1.6)	0 (0.0)
Non-Hispanic Black	0 (0.0)	95 (12.2)	76 (15.8)	49 (11.0)	0 (0.0)	132 (33.9)
Hispanic/Latina	1101 (100.0)	68 (8.7)	71 (14.8)	109 (24.5)	414 (96.5)	257 (66.1)
Other	0 (0.0)	96 (12.3)	50 (10.4)	31 (7.0)	8 (1.9)	0 (0.0)
Missing	0 (0.0)	9 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal education (n)						
Less than high school	228 (20.7)	61 (7.8)	17 (3.5)	60 (13.5)	337 (78.6)	147 (37.8)
High school	108 (9.8)	48 (6.2)	49 (10.2)	71 (16.0)	49 (11.4)	139 (35.7)
Some college	602 (54.7)	95 (12.2)	73 (15.2)	98 (22.1)	18 (4.2)	69 (17.7)
College graduate	119 (10.8)	240 (30.8)	143 (29.8)	100 (22.5)	25 (5.8)	30 (7.7)
Graduate school	26 (2.4)	326 (41.8)	187 (39.0)	115 (25.9)	0 (0.0)	4 (1.0)
Missing	18 (1.6)	9 (1.2)	11 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal prepregnancy BMI (kg/m^2)	25.3 (5.5)	25.7 (6.4)	25.8 (6.0)	25.7 (6.4)	27.2 (5.3)	25.6 (5.9)
Missing	61 (5.5)	7 (0.9)	0 (0.0)	0 (0.0)	9 (2.1)	6 (1.5)
Delivery year (n)						
1983-2000	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	377 (87.9)	102 (26.2)
2001-2010	0 (0.0)	0 (0.0)	480 (100.0)	0 (0.0)	52 (12.1)	287 (73.8)
2011-2018	1101 (100.0)	779 (100.0)	0 (0.0)	444 (100.0)	0 (0.0)	0 (0.0)
Maternal smoking during pregnancy (n)						
No	1069 (97.1)	718 (92.2)	452 (94.2)	412 (92.8)	406 (94.6)	332 (85.3)
Yes	17 (1.5)	57 (7.3)	28 (5.8)	32 (7.2)	23 (5.4)	8 (2.1)
Missing	15 (1.4)	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	49 (12.6)
Fetal sex (n)						
Female	516 (46.9)	397 (51.0)	213 (44.4)	204 (45.9)	211 (49.2)	203 (52.2)
Male	579 (52.6)	382 (49.0)	267 (55.6)	240 (54.1)	218 (50.8)	186 (47.8)
Missing	6 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parity (n)						
Nulliparous	538 (48.9)	393 (50.4)	214 (44.6)	220 (49.5)	142 (33.1)	179 (46.0)
Parous	550 (50.0)	332 (42.6)	266 (55.4)	224 (50.5)	287 (66.9)	209 (53.7)
Missing	13 (1.2)	54 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

	g. HOME	h. EARTH	i. MSSM [b]	j. SFF	k. RDS	l. HEBC

Sample size (n)	389	385	362	353	318	189
Delivery (n)						
Term	352 (90.5)	358 (93.0)	334 (92.3)	336 (95.2)	290 (91.2)	177 (93.7)
Preterm	37 (9.5)	27 (7.0)	28 (7.7)	17 (4.8)	28 (8.8)	12 (6.3)
Gestational age at delivery (weeks)	39.0 (1.8)	39.4 (1.7)	39.3 (1.6)	39.3 (1.6)	38.8 (1.8)	38.9 (1.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal age (years)	29.3 (5.8)	34.7 (3.9)	23.9 (5.6)	30.2 (5.1)	27.7 (5.6)	32.9 (5.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	13 (3.7)	0 (0.0)	0 (0.0)
Maternal race/ethnicity (n)						
Non-Hispanic White	237 (60.9)	327 (84.9)	76 (21.0)	296 (83.9)	158 (49.7)	133 (70.4)
Non-Hispanic Black	120 (30.8)	11 (2.9)	107 (29.6)	6 (1.7)	151 (47.5)	23 (12.2)
Hispanic/Latina	9 (2.3)	0 (0.0)	178 (49.2)	31 (8.8)	3 (0.9)	26 (13.8)
Other	18 (4.6)	47 (12.2)	1 (0.3)	18 (5.1)	6 (1.9)	7 (3.7)
Missing	5 (1.3)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
Maternal education (n)						
Less than high school	41 (10.5)	0 (0.0)	104 (28.7)	7 (2.0)	30 (9.4)	0 (0.0)
High school	54 (13.9)	0 (0.0)	76 (21.0)	19 (5.4)	57 (17.9)	0 (0.0)
Some college	93 (23.9)	0 (0.0)	94 (26.0)	72 (20.4)	79 (24.8)	0 (0.0)
College graduate	115 (29.6)	127 (33.0)	0 (0.0)	134 (38.0)	85 (26.7)	0 (0.0)
Graduate school	81 (20.8)	207 (53.8)	0 (0.0)	120 (34.0)	49 (15.4)	0 (0.0)
Missing	5 (1.3)	51 (13.2)	88 (24.3)	1 (0.3)	18 (5.7)	189 (100.0)
Maternal prepregnancy BMI (kg/m^2)	26.6 (6.5)	24.2 (4.3)	23.5 (4.5)	NA	29.2 (7.1)	25.5 (6.0)
Missing	0 (0.0)	0 (0.0)	1 (0.3)	353 (100.0)	1 (0.3)	1 (0.5)
Delivery year (n)						
1983-2000	0 (0.0)	0 (0.0)	310 (85.6)	4 (1.1)	0 (0.0)	0 (0.0)
2001-2010	389 (100.0)	144 (37.4)	52 (14.4)	349 (98.9)	0 (0.0)	189 (100.0)
2011-2018	0 (0.0)	241 (62.6)	0 (0.0)	0 (0.0)	318 (100.0)	0 (0.0)
Maternal smoking during pregnancy (n)						
No	335 (86.1)	289 (75.1)	300 (82.9)	339 (96.0)	276 (86.8)	183 (96.8)
Yes	53 (13.6)	96 (24.9)	62 (17.1)	13 (3.7)	39 (12.3)	6 (3.2)
Missing	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.9)	0 (0.0)
Fetal sex (n)						
Female	208 (53.5)	185 (48.1)	163 (45.0)	146 (41.4)	133 (41.8)	99 (52.4)
Male	181 (46.5)	200 (51.9)	199 (55.0)	150 (42.5)	185 (58.2)	87 (46.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	57 (16.1)	0 (0.0)	3 (1.6)
Parity (n)						
Nulliparous	171 (44.0)	320 (83.1)	362 (100.0)	187 (53.0)	128 (40.3)	71 (37.6)
Parous	216 (55.5)	65 (16.9)	0 (0.0)	165 (46.7)	190 (59.7)	117 (61.9)
Missing	2 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.5)

	m. MARBLES	n. EPS	o. MMIP	p. Rutgers
Sample size (n)	179	126	68	54
Delivery (n)				
Term	167 (93.3)	121 (96.0)	66 (97.1)	37 (68.5)
Preterm	12 (6.7)	5 (4.0)	2 (2.9)	17 (31.5)
Gestational age at delivery (weeks)	38.9 (1.6)	40.0 (1.8)	39.6 (1.1)	37.6 (2.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal age (years)	34.0 (5.0)	29.0 (3.6)	31.7 (4.6)	33.2 (6.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal race/ethnicity (n)				
Non-Hispanic White	99 (55.3)	120 (95.2)	56 (82.4)	18 (33.3)
Non-Hispanic Black	10 (5.6)	3 (2.4)	4 (5.9)	15 (27.8)
Hispanic/Latina	38 (21.2)	0 (0.0)	2 (2.9)	16 (29.6)
Other	32 (17.9)	3 (2.4)	6 (8.8)	5 (9.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal education (n)				
Less than high school	5 (2.8)	0 (0.0)	0 (0.0)	8 (14.8)
High school	8 (4.5)	9 (7.1)	5 (7.4)	14 (25.9)
Some college	72 (40.2)	26 (20.6)	6 (8.8)	13 (24.1)
College graduate	69 (38.5)	46 (36.5)	18 (26.5)	12 (22.2)
Graduate school	25 (14.0)	45 (35.7)	31 (45.6)	7 (13.0)
Missing	0 (0.0)	0 (0.0)	8 (11.8)	0 (0.0)
Maternal prepregnancy BMI (kg/m^2)	26.8 (6.9)	21.1 (2.8)	25.4 (5.5)	NA
Missing	0 (0.0)	0 (0.0)	3 (4.4)	54 (100.0)
Delivery year (n)				
1983-2000	0 (0.0)	126 (100.0)	0 (0.0)	0 (0.0)
2001-2010	115 (64.2)	0 (0.0)	2 (2.9)	54 (100.0)
2011-2018	64 (35.8)	0 (0.0)	66 (97.1)	0 (0.0)
Maternal smoking during pregnancy (n)				
No	161 (89.9)	120 (95.2)	65 (95.6)	42 (77.8)
Yes	8 (4.5)	6 (4.8)	3 (4.4)	12 (22.2)
Missing	10 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Fetal sex (n)				
Female	75 (41.9)	59 (46.8)	32 (47.1)	26 (48.1)
Male	104 (58.1)	67 (53.2)	36 (52.9)	28 (51.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parity (n)				
Nulliparous	2 (1.1)	60 (47.6)	31 (45.6)	9 (16.7)
Parous	171 (95.5)	66 (52.4)	37 (54.4)	45 (83.3)
Missing	6 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)

SD, standard deviation; BMI, body mass index; ART, assisted reproductive technology; NA, not assessed

[a] LIFECODES was a case-control study of preterm birth; [b] Year of delivery was assigned as the median year, 2000 (see eMethods)

eTable 4. Urinary metabolites of phthalate and phthalate alternative compounds measured in the Pooled Phthalate and Preterm Birth study

						Pooled sample		
Parent chemical [a]			Metabolite			Cohort	Participants	Analysis [b]
Name	Abbrev.	MW	Name	Abbrev.	MW	(16 total)	(N=6045)	
Dimethyl-phthalate	DMP	194	Monomethyl phthalate	MMP	180	5	23%	Excluded
Diethyl phthalate	DEP	222	Monoethyl phthalate	MEP	194	16	100%	**Included**
Di-n-butyl phthalate	DBP	278	Mono-n-butyl phthalate	MBP	222	16	100%	**Included**
			Mono(3-hydroxybutyl) phthalate	MHBP	238	4	24%	Excluded
Di-isobutyl phthalate	DiBP	278	Mono-isobutyl phthalate	MiBP	222	15	99%	**Included**
			Mono-hydroxyisobutyl phthalate	MHiBP	238	4	24%	Excluded
Benzylbutyl phthalate	BzBP	312	Monobenzyl phthalate	MBzP	256	15	99%	**Included**
Dicyclohexyl phthalate	DCHP	330	Mono-cyclohexyl phthalate	MCHP	248	1	1%	Excluded
Di(2-ethylhexyl) phthalate	DEHP	391	Mono(2-ethylhexyl) phthalate	MEHP	278	16	97%	**Included**
			Mono(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP	294	16	100%	**Included**
			Mono(2-ethyl-5-carboxypentyl) phthalate	MECPP	308	14	91%	**Included**
			Mono(2-ethyl-5-oxyhexyl) phthalate	MEOHP	422	16	100%	**Included**
Di(2-ethylhexyl) terephthalate	DEHTP	391	Mono(2-ethyl-5-hydroxyhexyl) terephthalate	MEHHTP	294	2	7%	Excluded
			Mono(2-ethyl-5-carboxypentyl) terephthalate	MECPTP	308	2	7%	Excluded
Di-n-octyl phthalate (and other high MW phthalates)	DNOP	391	Mono(3-carboxypropyl) phthalate	MCPP	252	14	93%	**Included**
			Mono-n-octyl phthalate	MOP	278	1	1%	Excluded
Di-isononyl phthalate	DNP	419	Monoisononyl phthalate	MNP	292	5	24%	Excluded
			Monooxoisononyl phthalate	MONP	292	2	7%	Excluded
			Monocarboxy-isooctyl phthalate	MCOP	322	10	57%	**Included**
1,2-Cyclohexane dicarboxylic acid, diisononyl ester	DINCH	425	Monocarboxy-isooctyl ester, 1,2-cyclohexane-dicarboxylic acid	MCOCH	172	4	19%	Excluded
			Monohydroxy-isononyl ester, 1,2-cyclohexane dicarboxylic acid	MHiNCH	314	5	38%	Excluded
Di-isodecyl phthalate	DDP	447	Monocarboxy-isononyl phthalate	MCNP	322	10	58%	**Included**
			Monoisodecyl phthalate	MDP	306	1	1%	Excluded

[a] Parent compounds are ordered by molecular weight (MW; g/mol).

[b] Analysis decision identifies whether metabolite was included or excluded from primary analyses. A given metabolite was included if it was measured in ≥10 cohorts and ≥50% of all participant samples.

eTable 5. Limits of detection (LOD) for phthalate metabolites and distribution of samples with concentrations above and below LOD

Biomarker	LOD range [a] (ng/ml)	Number of observations	% >LOD	% <LOD	% <LOD with instrument-read values [b]	% <LOD without instrument-read values [c]
MEP	0.40 - 1.20	11391	99.5%	0.5%	0.2%	0.3%
MBP	0.10 - 2.00	11391	98.3%	1.6%	0.3%	1.3%
MiBP	0.10 - 1.04	11337	97.3%	2.7%	0.7%	2.0%
MBzP	0.10 - 1.00	11337	96.2%	3.9%	1.3%	2.6%
MEHP	0.05 - 1.20	11391	82.5%	17.5%	6.5%	11.0%
MEHHP	0.10 - 1.00	11391	99.2%	0.8%	0.2%	0.6%
MECPP	0.20 - 1.00	10672	99.9%	0.1%	0.0%	0.1%
MEOHP	0.10 - 1.07	11391	99.1%	0.9%	0.1%	0.8%
MCPP	0.16 - 1.00	10874	90.3%	9.7%	4.2%	5.5%
MCOP	0.20 - 0.70	7094	99.0%	1.1%	0.4%	0.7%
MCNP	0.20 - 0.60	7130	97.0%	3.0%	0.8%	2.2%

[a] LOD is presented as a range because of variation across studies.

[b] Instrument-read values were used when available for concentrations <LOD.

[c] Concentrations <LOD were multiply imputed when instrument-read values were not available.

eTable 6. Sample size for each urinary phthalate metabolite across studies

Biomarkers[a]	MEP	MBP	MiBP	MBzP	MEHP	MEHHP	MECPP	MEOHP	MCPP	MCOP	MCNP
Overall											
Cohorts	16	16	15	15	16	16	14	16	14	10	10
Sample size	6045	6045	5991	5991	6045	6045	5471	6045	5673	3758	3794
Study											
PROTECT	1101	1101	1101	1101	1101	1101	1101	1101	1101	1101	1101
TIDES	779	779	779	779	779	779	779	779	779	754	754
LIFECODES	480	480	480	480	480	480	480	480	480	NM	NM
Healthy Start	444	444	444	444	444	444	444	444	444	444	444
CHAMACOS	429	429	429	429	429	429	429	429	429	429	429
CCCEH	389	389	389	389	389	389	389	389	389	146	146
HOME	389	389	389	389	389	389	389	389	389	NM	NM
EARTH	385	385	385	385	385	385	385	385	385	372	372
MSSM	362	362	362	362	362	362	362	362	362	NM	NM
SFF	353	353	353	353	353	353	151	353	353	18	54
RDS	318	318	318	318	318	318	NM	318	NM	NM	NM
HEBC	189	189	189	189	189	189	189	189	189	189	189
MARBLES	179	179	179	179	179	179	179	179	179	179	179
EPS	126	126	126	126	126	126	126	126	126	126	126
MMIP	68	68	68	68	68	68	68	68	68	NM	NM
Rutgers	54	54	NM	NM	54	54	NM	54	NM	NM	NM

NM, not measured

[a] The only biomarkers excluded from mixtures analyses were MCOP and MCNP.

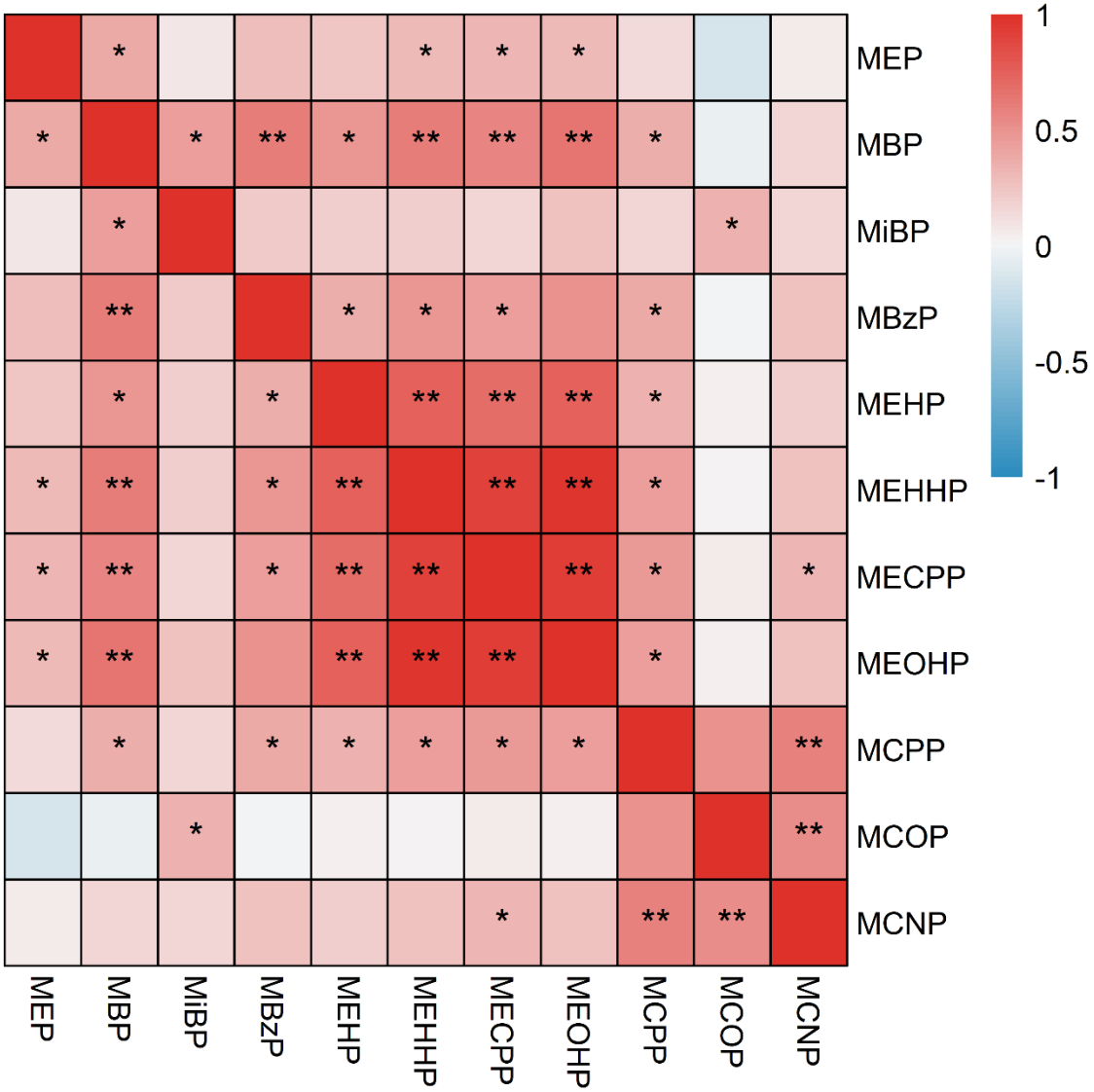
eTable 7. Distribution of pregnancy-averaged urinary phthalate metabolite concentrations (ng/mL)

Metabolite[a]	Cohorts	Sample size	GM	25th percentile	Median	75th percentile	IQR
MEP	16	6045	73.04	25.0	68.9	193.2	168.2
MBP	16	6045	16.06	8.7	15.5	30.1	21.4
MiBP	15	5991	6.16	3.3	6.3	11.9	8.6
MBzP	15	5991	5.93	2.5	5.6	13.4	11.0
MEHP	16	6045	3.12	1.5	2.9	6.4	5.0
MEHHP	16	6045	11.96	5.8	10.9	23.0	17.3
MECPP	14	5471	20.63	10.2	18.8	37.0	26.8
MEOHP	16	6045	9.29	4.7	8.6	17.1	12.4
MCPP	14	5673	2.05	1.1	1.9	3.6	2.5
MCOP	10	3758	10.06	4.1	9.2	22.7	18.5
MCNP	10	3794	2.36	1.4	2.2	3.6	2.2

GM, geometric mean; IQR, interquartile range

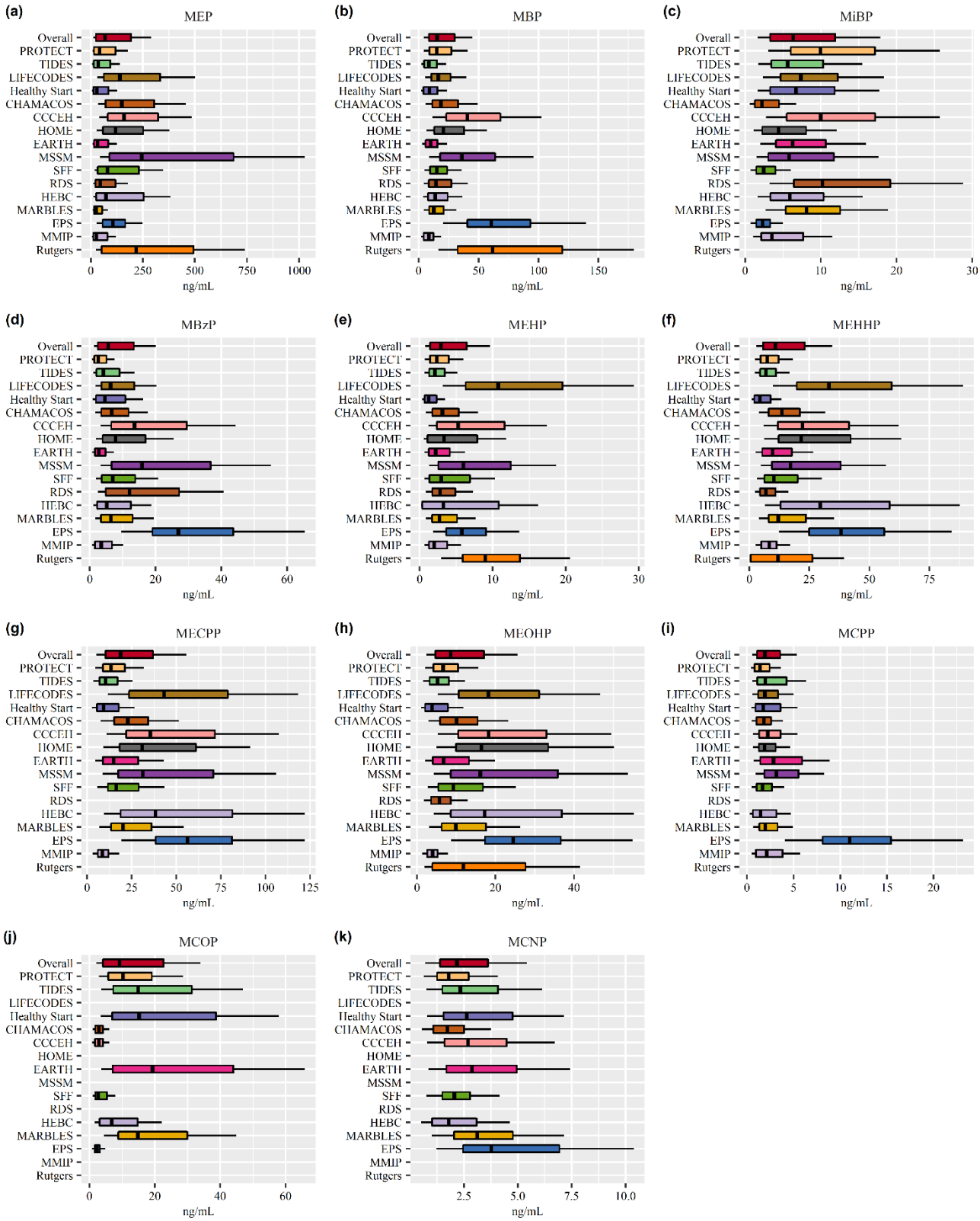
[a] Biomarker concentrations were corrected for urine dilution before pregnancy-averages were calculated; thus, all values are corrected for urine dilution.

eFigure 2. Spearman correlations between pregnancy-averaged concentrations of urinary phthalate metabolites



Asterisks indicate absolute correlation values between 0.3 and 0.5 (*), or greater than 0.50 (**).

eFigure 3. Distributions of pregnancy-averaged phthalate metabolite concentrations (a-k) in the Pooled Phthalate and Preterm Birth Study (overall) and by study



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 while the lower whisker represents 0.5 times the 25th percentile, stopping at the limit of detection. Values above or below whiskers not shown. Studies are ordered by the relative size of the study population.

eTable 8. Heterogeneity by study in main effects using fixed effect, random effect, and interaction models

		Fixed effect [a,b]		Random effect [a,c]		Heterogeneity in main effect (Wald test) [d]
Metabolite	n	OR (95% CI)	Variance	OR (95% CI)	Variance	Study*Metabolite
MEP	6045	1.07 (0.93,1.24)	0.0051	1.08 (0.94,1.24)	0.0050	0.35
MBP	6045	1.12 (0.98,1.27)	0.0045	1.13 (0.99,1.28)	0.0044	0.17
MiBP	5991	1.16 (1.00,1.34)	0.0058	1.17 (1.01,1.35)	0.0055	0.85
MBzP	5991	0.98 (0.83,1.14)	0.0065	0.97 (0.83,1.13)	0.0062	0.62
MEHP	6045	1.04 (0.91,1.19)	0.0048	1.06 (0.93,1.21)	0.0046	0.06
MEHHP	6045	1.03 (0.90,1.19)	0.0049	1.04 (0.91,1.18)	0.0047	0.28
MECPP	5471	1.16 (1.00,1.34)	0.0056	1.17 (1.01,1.35)	0.0053	0.54
MEOHP	6045	1.00 (0.88,1.15)	0.0046	1.01 (0.89,1.15)	0.0044	0.32
MCPP	5673	1.14 (1.01,1.29)	0.0039	1.13 (1.00,1.28)	0.0037	0.39
MCOP	3758	1.04 (0.84,1.29)	0.0119	1.08 (0.88,1.32)	0.0107	0.35
MCNP	3794	1.06 (0.92,1.24)	0.0059	1.05 (0.91,1.22)	0.0057	0.63

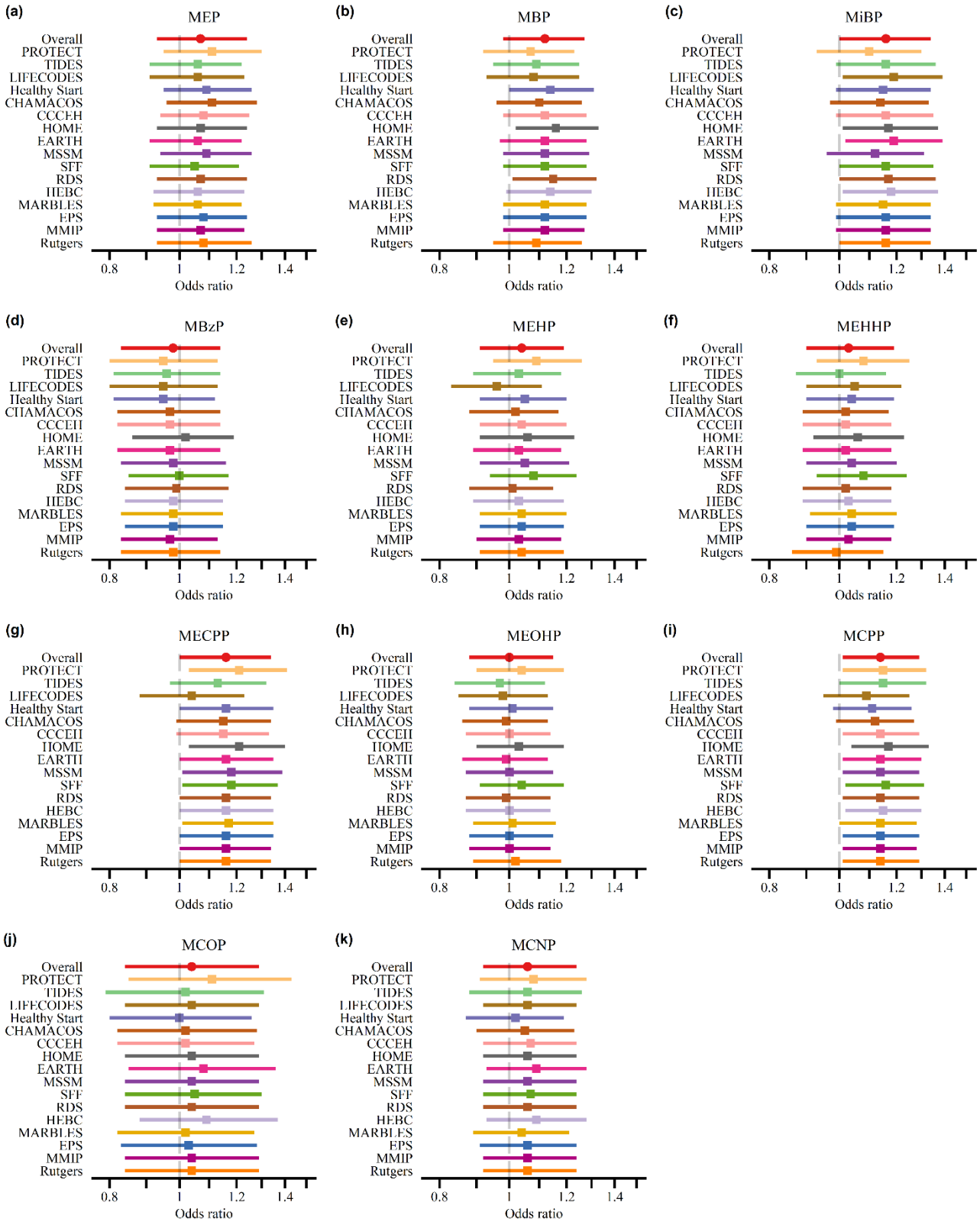
[a] OR and 95% confidence interval (CI) represent estimated odds of preterm birth compared to term birth per interquartile range increase in individual biomarker. Associations were estimated by multiple logistic regression models. All models adjusted for maternal age, race/ethnicity, education, and prepregnancy BMI. Variance estimates represent the standard error squared from non-transformed model estimates.

[b] Fixed effect adjusted models include study cohort as fixed effect covariate.

[c] Random effect models included study cohort as a random intercept.

[d] *P* values from Wald tests that compared fixed effect models with and without study by metabolite interaction term.

eFigure 4. Comparison of main effects (odds ratios) when excluding individual studies



Odds ratios and 95% confidence intervals represent estimated odds of preterm birth compared to term birth per interquartile range increase in individual phthalate metabolite. Associations were estimated by multiple logistic regression models that included all participants (Overall), or excluded participants from each study. All models adjusted for maternal age, race/ethnicity, education, and prepregnancy BMI. Studies are ordered by the relative size of the study population

eTable 9. Effect estimates and Wald tests for tests of heterogeneity in confounding by study

			Heterogeneity in confounding *P* values from Wald tests of interaction models [b]							
		Primary model	Study*Age		Study*prepregnancy BMI		Study*Race/Ethnicity[c]		Study*Education[c]	
Metabolite	n	OR (95% CI)	OR (95% CI)	Wald	OR (95% CI)	Wald	OR (95% CI)	Wald	OR (95% CI)	Wald
MEP	6045	1.07 (0.93,1.24)	1.08 (0.94,1.24)	0.42	1.07 (0.93,1.23)	0.98	1.26 (1.02,1.56)	0.92	1.07 (0.92,1.26)	0.50
MBP	6045	1.12 (0.98,1.27)	1.11 (0.97,1.27)	0.44	1.12 (0.98,1.28)	0.98	1.03 (0.84,1.27)	0.93	1.09 (0.92,1.29)	0.56
MiBP	5991	1.16 (1.00,1.34)	1.16 (1.00,1.35)	0.40	1.16 (1.00,1.35)	0.96	1.02 (0.82,1.28)	0.94	1.15 (0.96,1.38)	0.56
MBzP	5991	0.98 (0.83,1.14)	0.98 (0.83,1.15)	0.42	0.98 (0.83,1.14)	0.97	0.95 (0.75,1.19)	0.94	0.98 (0.81,1.18)	0.55
MEHP	6045	1.04 (0.91,1.19)	1.04 (0.90,1.19)	0.42	1.04 (0.91,1.20)	0.98	1.03 (0.86,1.23)	0.94	1.00 (0.85,1.18)	0.48
MEHHP	6045	1.03 (0.90,1.19)	1.04 (0.90,1.19)	0.42	1.04 (0.91,1.19)	0.98	0.94 (0.77,1.16)	0.94	0.91 (0.76,1.10)	0.39
MECPP	5471	1.16 (1.00,1.34)	1.16 (1.00,1.34)	0.36	1.17 (1.01,1.35)	0.95	1.26 (1.04,1.53)	0.93	1.19 (1.00,1.43)	0.49
MEOHP	6045	1.00 (0.88,1.15)	1.00 (0.88,1.15)	0.42	1.01 (0.88,1.15)	0.98	0.99 (0.81,1.20)	0.94	0.95 (0.81,1.12)	0.48
MCPP	5673	1.14 (1.01,1.29)	1.14 (1.01,1.28)	0.36	1.14 (1.01,1.29)	0.96	1.14 (0.97,1.34)	0.94	1.14 (0.99,1.31)	0.39
MCOP	3758	1.04 (0.84,1.29)	1.04 (0.84,1.29)	0.47	1.04 (0.84,1.29)	0.97	1.09 (0.80,1.50)	0.99	1.10 (0.86,1.42)	0.70
MCNP	3794	1.06 (0.92,1.24)	1.06 (0.91,1.23)	0.45	1.07 (0.92,1.24)	0.98	1.12 (0.91,1.36)	1.00	1.12 (0.94,1.35)	0.71

[a] OR and 95% confidence interval (CI) represent estimated odds of preterm birth compared to term birth per interquartile range increase in individual biomarker. Associations were estimated by multiple logistic regression models. All models adjusted for maternal age, race/ethnicity, education, and prepregnancy BMI.

[b] *P* values from Wald tests that compared models with and without designated interaction term.

[c] Models testing interactions between study and a categorical confounder (i.e., maternal race/ethnicity and education) required fitting a different subset of participants due to small subcategory sample sizes within individual studies. Thus, studies with limited to no confounder strata variation (e.g., race/ethnicity among PROTECT) were dropped from certain metabolite-specific models.

eTable 10. Comparison of odds ratio (OR) estimates for preterm birth with additional adjustment for year of delivery, maternal smoking, and parity

Metabolite	n	Primary model OR (95% CI)[a]	Delivery Year OR (95% CI)[a,b]	Smoking OR (95% CI)[a,b]	Parity OR (95% CI)[a,b]
MEP	6045	1.07 (0.93, 1.24)	1.07 (0.93, 1.23)	1.07 (0.93, 1.24)	1.08 (0.93, 1.24)
MBP	6045	1.12 (0.98, 1.27)	1.11 (0.97, 1.27)	1.12 (0.98, 1.27)	1.12 (0.98, 1.27)
MiBP	5991	1.16 (1.00, 1.34)	1.17 (1.00, 1.36)	1.16 (1.00, 1.34)	1.16 (1.00, 1.34)
MBzP	5991	0.98 (0.83, 1.14)	0.97 (0.83, 1.13)	0.98 (0.83, 1.14)	0.97 (0.83, 1.14)
MEHP	6045	1.04 (0.91, 1.19)	1.03 (0.89, 1.17)	1.04 (0.91, 1.19)	1.04 (0.91, 1.19)
MEHHP	6045	1.03 (0.90, 1.19)	1.02 (0.89, 1.17)	1.03 (0.90, 1.19)	1.03 (0.90, 1.19)
MECPP	5471	1.16 (1.00, 1.34)	1.14 (0.98, 1.33)	1.16 (1.00, 1.34)	1.16 (1.00, 1.34)
MEOHP	6045	1.00 (0.88, 1.15)	0.99 (0.86, 1.13)	1.00 (0.88, 1.15)	1.00 (0.88, 1.15)
MCPP	5673	1.14 (1.01, 1.29)	1.14 (1.00, 1.28)	1.14 (1.01, 1.29)	1.14 (1.01, 1.29)
MCOP	3758	1.04 (0.84, 1.29)	1.06 (0.85, 1.31)	1.04 (0.84, 1.29)	1.04 (0.84, 1.29)
MCNP	3794	1.06 (0.92, 1.24)	1.06 (0.91, 1.23)	1.06 (0.92, 1.24)	1.06 (0.92, 1.24)

[a] OR and 95% confidence interval (CI) represent estimated odds of preterm birth compared to term birth per interquartile range increase in individual biomarker. Associations were estimated by multiple logistic regression models.

[a] Primary model adjusted for maternal age, race/ethnicity, education, and prepregnancy BMI.

[b] Same adjustment as primary model[a], but additionally adjusted for the respective variable listed, including: categorical variable based on year of delivery (i.e., 1983-2000, 2001-2010, or 2011-2018); dichotomous variable based on any level of maternal smoking in pregnancy (i.e., yes or no); or dichotomous variable for parity (i.e., nulliparous or parous).

eTable 11. Odds ratio (OR) for preterm birth in the overall study population and stratified by fetal sex

Metabolite	n[a]	OR (95%CI)[b]	Wald[c]
MEP			
Overall	6045	1.07 (0.93, 1.23)	0.72
Female	2899	1.08 (0.87, 1.33)	
Male	3146	1.06 (0.88, 1.29)	
MBP			
Overall	6045	1.12 (0.98, 1.28)	0.33
Female	2899	1.22 (1.00, 1.50)	
Male	3146	1.04 (0.87, 1.24)	
MiBP			
Overall	5991	1.16 (1.00, 1.35)	0.21
Female	2873	1.13 (0.90, 1.42)	
Male	3118	1.17 (0.96, 1.44)	
MBzP			
Overall	5991	0.98 (0.83, 1.14)	0.37
Female	2873	1.06 (0.83, 1.34)	
Male	3118	0.90 (0.73, 1.12)	
MEHP			
Overall	6045	1.04 (0.90, 1.19)	0.71
Female	2899	1.01 (0.83, 1.23)	
Male	3146	1.05 (0.87, 1.26)	
MEHHP			
Overall	6045	1.04 (0.90, 1.19)	0.72
Female	2899	1.05 (0.85, 1.29)	
Male	3146	1.02 (0.85, 1.23)	
MECPP			
Overall	5471	1.16 (1.00, 1.34)	0.85
Female	2640	1.16 (0.94, 1.45)	
Male	2831	1.17 (0.96, 1.44)	
MEOHP			
Overall	6045	1.01 (0.88, 1.15)	0.97
Female	2899	0.99 (0.81, 1.20)	
Male	3146	1.02 (0.85, 1.22)	
MCPP			
Overall	5673	1.14 (1.01, 1.29)	0.24
Female	2740	1.18 (0.99, 1.42)	
Male	2933	1.11 (0.94, 1.31)	
MCOP			
Overall	3758	1.05 (0.84, 1.30)	0.44
Female	1801	0.95 (0.69, 1.32)	
Male	1957	1.15 (0.86, 1.54)	
MCNP			
Overall	3794	1.07 (0.92, 1.24)	0.96
Female	1817	1.06 (0.85, 1.32)	
Male	1977	1.10 (0.88, 1.36)	

[a] Stratum-specific sample size (n) varied between imputations.

[b] OR and 95% confidence interval (CI) represent estimated odds of preterm birth compared to term birth per interquartile range increase in individual biomarker. Associations were estimated by multiple logistic regression models. All models adjusted for maternal age, race/ethnicity, education, and prepregnancy BMI. The overall model additionally adjusted for maternal fetal sex (male/female) to allow for Wald test estimates of nested models.

[c] *P* values from Wald tests come from tests of nested models that included an interaction between phthalate biomarker and fetal sex.

eTable 12. Urinary phthalate metabolite specified using non-linear term

		Quadratic term[a,b]	
Metabolite	n	OR (95% CI)[a]	*P* value
MEP	6045	0.99 (0.88, 1.10)	0.81
MBP	6045	1.06 (0.97, 1.16)	0.22
MiBP	5991	1.02 (0.97, 1.08)	0.41
MBzP	5991	0.93 (0.82, 1.06)	0.29
MEHP	6045	1.02 (0.94, 1.12)	0.63
MEHHP	6045	1.03 (0.94, 1.13)	0.49
MECPP	5471	0.95 (0.87, 1.04)	0.26
MEOHP	6045	1.00 (0.92, 1.08)	0.91
MCPP	5673	1.02 (0.95, 1.09)	0.65
MCOP	3758	0.95 (0.78, 1.16)	0.63
MCNP	3794	1.05 (0.98, 1.13)	0.15

[a] OR and 95% confidence interval (CI) represent estimated odds of preterm birth compared to term birth per interquartile range increase in individual biomarker. Associations were estimated by multiple logistic regression models. Primary model adjusted for maternal age, race/ethnicity, education, and prepregnancy BMI.

[b] Metabolite concentrations were specified as linear and quadratic terms. The coefficient and *P* value for the quadratic term are shown.

eTable 13. Estimated change (β) in length of gestation (weeks) per IQR increase in urinary phthalate biomarkers

Metabolite	n	Change in length of gestation (weeks, 95% CI)[a]
MEP	6045	-0.03 (-0.10,0.04)
MBP	6045	-0.09 (-0.16,-0.03)
MiBP	5991	-0.08 (-0.15,-0.01)
MBzP	5991	-0.07 (-0.14,0.00)
MEHP	6045	-0.01 (-0.07,0.05)
MEHHP	6045	-0.03 (-0.10,0.03)
MECPP	5471	-0.06 (-0.13,0.01)
MEOHP	6045	-0.01 (-0.07,0.06)
MCPP	5673	-0.05 (-0.10,0.01)
MCOP	3758	-0.05 (-0.14,0.04)
MCNP	3794	-0.01 (-0.07,0.06)

[a] Multiple linear regression models specified study cohort as categorical covariate. Sampling weights were implemented to account for LIFECODES case-control study design. All models adjusted for maternal age, race/ethnicity, education, and prepregnancy BMI.

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