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Midpregnancy Phthalate and Phenol Biomarkers in Relation to Infant Body Composition: The Healthy Start Prospective Cohort

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Background: Gestational phthalate and phenol exposure disrupts adipogenesis, contributing to obesity in mice. Whether gestational phthalate or phenol exposure is associated with infant body composition has not been investigated in humans.

Objective: We examined associations between biomarkers of phthalate and phenol exposure in midpregnancy and infant size and body composition at birth and at 5 months of age.

Methods: Analyses were conducted among 438 infants from the Healthy Start prospective pregnancy cohort. Sixteen phthalate and phenol biomarkers were quantified in spot urine samples collected at 24–28 wk of gestation. Infant outcomes measured at birth and at 5 months of age included size [weight (in grams)] and body composition [fat and lean masses (in grams); percentage fat mass]. Single- (linear) and multipollutant (quantile g-computation) models were used to estimate associations of phthalate and phenol biomarkers with infant outcomes at birth and at 5 months of age. Models were adjusted for sociodemographics, sample collection timing, and lifestyle factors and used to examine for effect modification by infant sex.

Results: In single-pollutant models, mono-benzyl phthalate and di-*n*-butyl phthalate were inversely associated with percentage fat mass [β: −0.49 (95% CI: −0.91, −0.08) and −0.51 (95% CI: −1.02, 0.01), respectively] in male but not female infants at birth. Similar, but less precise, associations were observed at 5 months of age. In multipollutant models, a 1-quartile increase in the phthalate and phenol biomarker mixture was inversely associated with percentage fat mass at birth [−1.06 (95% CI: −2.21, 0.1)] and at 5 months of age [−2.14 (95% CI: −3.88, −0.39)] among males, but associations were null among females [0.48 (95% CI: −0.78, 1.75) and −0.64 (95% CI: −2.68, 1.41), respectively]. Similar associations were observed with infant weight.

Conclusion: In this U.S.-based prospective cohort, gestational phthalate and phenol biomarkers were inversely associated with infant weight and fat mass, particularly in males. https://doi.org/10.1289/EHP12500

Introduction

Regular use of phthalates and phenols in consumer products has led to frequent and chronic exposure to these chemicals,[1] including among pregnant women. Gestational exposure to phthalates and phenols has been linked to adverse fetal growth outcomes, including reductions in ultrasound measures of fetal weight[2,3] and birthweight.[4–6] However, although these observations are supported by *in vivo* animal models, much of the epidemiologic literature remains inconsistent with respect to the direction and magnitude of the effect.[7]

This heterogeneity in the epidemiologic literature may be partially explained by a focus on birthweight. Weight is a composite measure of fat mass (i.e., adipose) and lean mass (i.e., skeletal weight, muscle tissue, and other organs) and—although fat mass only accounts for ∼12%–15% of birthweight—almost half of the variance in birthweight can be explained by fat mass.[8] Several phenols have been shown to influence the fate of stem cells toward the adipocyte lineage and away from osteoblasts,[9,10] and several phthalates, including di(2-ethylhexyl) phthalate (DEHP), have been shown to promote adipogenesis and alter the expression of key adipogenic pathways, such as peroxisome proliferator activated receptor gamma.[11–13] Therefore, more specific measures of body composition may help to clarify effects of gestational exposure to phthalates and phenols on fetal growth outcomes.

To our knowledge, no human studies have explicitly examined the influence of gestational exposure to phthalates and phenols on neonatal or infant body composition. Moreover, there is limited literature on the joint effects of these chemicals on infant size and growth outcomes, despite moderate-to-high correlation between these exposures. To address this literature gap, we examined single- and multipollutant associations between biomarkers of phthalate and phenol exposure in midpregnancy with infant size and body composition at birth and at 5 months of age in the Healthy Start cohort.

Methods

Study Participants and Design

The Healthy Start study is a prospective cohort study that recruited 1,410 pregnant individuals ≥16 years of age with singleton pregnancies, enrolled before 24 wk of gestation from obstetrics clinics at the University of Colorado Hospital within the Anschutz Medical Campus of the University of Colorado-Denver between 2009 and 2014. Participants were excluded if they had a

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history of stillbirth or extremely preterm birth, had diabetes, asthma treated with steroids, cancer, or medication-dependent psychiatric illness. Of the original 1,410 individuals enrolled, 19 experienced fetal demise and an additional 9 withdrew prior to delivery.

Study procedures included four research visits: two visits during pregnancy at a median [interquartile range (IQR)] of 17 (15–20) and 27 (25–29) wk of gestation, one visit at delivery, and one visit at a median (IQR) of 5 (4–6) months postnatally. Research visits included questionnaires, sample collection, and anthropometric and body composition measures conducted by study staff. The present analysis was conducted among a convenience sample of 446 pregnant individuals who provided spot urine samples during the second study visit. We additionally restricted our sample based on having infant body composition assessed at delivery ($n = 424$) or postnatal ($n = 358$) visits. The final analytic sample comprised 438 infants. A subset of 24 participants agreed to provide three spot urine samples every 2 wk after the second study visit at a median (IQR) of 30 (26–31), 32 (29–33), and 34 (31–35) wk of gestation.[14]

Ethics approval was obtained from the Colorado Multiple Institutional Review Board and all participants provided written informed consent prior to the first study visit. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

Urinary Biomarkers of Phthalates and Phenols

Spot urine samples were collected in sterile collection cups and stored at −80°C until ready for shipment. Urinary concentrations of phthalate metabolites and phenols were measured at the CDC laboratory according to previously published guidelines.[15,16] The phthalate metabolites included in analyses were monoethyl phthalate (MEP), mono-benzyl phthalate (MBzP), mono-3-carboxypropyl phthalate (MCPP), mono carboxyisooctyl phthalate (MCOP), and mono carboxyisononyl phthalate (MCNP), mono-*n*-butyl phthalate (MnBP), mono-hydroxybutyl phthalate (MHBP), mono-isobutyl phthalate (MiBP), mono-hydroxyisobutyl phthalate (MHiBP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), and mono-2-ethyl-5-carboxypentyl phthalate (MECPP). We also calculated the molar sum of the di-*n*-butyl phthalate metabolites (ΣDBP from MnBP and MHBP), the di-isobutyl phthalate metabolites (ΣDiBP from MiBP and MHiBP), and the DEHP metabolites (ΣDEHP from MEHP, MEHHP, MEOHP, and MECPP). Molar concentrations were converted to nanograms per milliliter by multiplying DBP, DiBP, and DEHP by the molecular weights of MnBP, MiBP, and MECPP, respectively.[17] The phenols included in analyses were 2,4 dichlorophenol, 2,5 dichlorophenol, bisphenol A (BPA), bisphenol S (BPS), benzophenone-3, methyl paraben, propyl paraben, and triclosan. Two other phthalate metabolites (monomethyl phthalate and mono-isononyl phthalate) and two phenols (ethyl paraben and butyl paraben) were measured by the lab but excluded from analyses owing to the large numbers (>30%) of values below the limit of detection (LOD).[18] For concentrations below the LOD, we obtained instrument values when possible or substituted one-half the minimum reported value for that biomarker, as has been done previously in this cohort.[14]

Urine creatinine concentrations were measured at the CDC using a Roche/Hitachi Cobas 6000 Analyzer (Roche Diagnostics). The O'Brien method[19] was used to correct for urinary creatinine. For this, we identified age and prepregnancy body mass index (BMI) category of the gestational parent, and gestational week at sample collection as significant ($p < 0.05$) predictors of urinary creatinine. Models were fit to predict urinary creatinine based on these variables, and we standardized exposure biomarkers for each participant using the following formula: $E_{cr} = E_o \times \frac{Cr_p}{Cr_o}$, where E_{cr} is the creatinine-standardized exposure biomarker concentration, E_o is the observed exposure biomarker concentration, Cr_p is the predicted creatinine concentration from our model, and Cr_o is the observed creatinine concentration.

Infant Outcomes

Primary infant outcomes were infant size and body composition, including total body mass (i.e., weight in grams), fat mass (in grams; percentage), and lean mass (in grams) measured using whole body air displacement plethysmography (PEA POD; COSMED, Inc.) within 72 h of delivery and again at ∼5 months of age. The PEA POD is a validated instrument that relies on a two-compartment model for estimating body mass in infants.[20,21] PEA POD measures were conducted in duplicate and, if measures deviated by >2%, in triplicate; the average of the closest two measures was used for analyses. Fat mass percentage was calculated as fat mass/(fat mass + lean mass) × 100.

Secondary infant outcomes included sex-specific *z*-scores for weight-for-age and weight-for-length based on the World Health Organization's Growth Standards,[22] fat mass and lean mass indexes, and rapid infant growth. Length measures were conducted by study staff in duplicate or—if measures deviated by >1 cm—triplicate; the average of the closest two measures was used for analyses. Fat and lean mass indexes accounted for infant size by dividing by squared infant length [fat mass index: fat mass (in kilograms)/length $(\text{in meters})^2$; lean mass index: lean mass (in kilograms)/length $(\text{in meters})^2$].[23] Rapid infant growth was calculated for a change in weight-for-age and weight-for-length *z*-scores between delivery and 5 months of age of >0.67.[24,25]

Covariates

Model covariates were determined *a priori* from a directed acyclic graph (Figure S1).[26] A study questionnaire ascertained characteristics of the gestational parent including age, race and ethnicity (categorized as Hispanic or Latina, non-Hispanic White or Caucasian, Non-Hispanic Black or African American, all others), prepregnancy BMI (categorized as ≤24.9, 25.0–29.9, ≥30.0 kg/m^2), highest education level completed [<12th grade, high school degree or General Education Development (GED), some college or associate's degree, 4-y college degree, graduate degree], previous pregnancies (categorized as any, none), and any smoking during pregnancy (yes, no). Participants selected the race and ethnicity category they identified as from the following categories: Hispanic or Latina, White or Caucasian, Black or African American, Asian or Pacific Islander, American Indian or Alaskan Native, or other. Diet during pregnancy [usual intake Healthy Eating Index (HEI-2010) score and daily calories][27] was derived from 24-h diet recalls. Physical activity during pregnancy [metabolic equivalent for task (MET)-hours/week][28] was derived from the Pregnancy Physical Activity Questionnaire. Variables derived from medical records included infant sex assigned at birth (male, female) and total gestational weight gain.[29,30] Final models were adjusted for age, race and ethnicity, prepregnancy BMI category, highest education level completed, any previous pregnancies, smoking during pregnancy, gestational age at biological sample collection, infant sex, diet during pregnancy, physical activity during pregnancy, and gestational weight gain. In models for infant outcomes at the 5-month follow-up, we additionally adjusted for infant age.

Self-identified race and ethnicity were included in models owing to culturally driven patterns of personal care product

use,[31] diet,[32] and unmeasured social factors (e.g., stress, discrimination) impacting exposure and outcome status.[33,34] We did not adjust for gestational age at birth or pregnancy complications because they could be mediators of our association of interest.[35]

Statistical Analysis

Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc.) and R (version 4.0.4; R Development Core Team). Analyses were performed on a subset of participants with complete data for urinary biomarker concentrations and either delivery or 5-month outcomes ($n = 438$). Variable distributions and descriptive statistics for covariates and outcomes [means ± standard deviations (SDs) and n (%)] as well as exposures (quartiles) were examined. Covariate and outcome distributions were examined and compared for the enrolled, analytic, and subset samples, as well as for included (analytic sample) and excluded participants. Exposure and outcome correlations were determined using Spearman rank correlation and visualized using a heatmap. For each exposure, the intraclass correlation coefficients (ICCs) were calculated from a subset of participants who provided urine samples at three 2-wk intervals in mid-to-late pregnancy, as previously reported.[14] A linear mixed effects model was fit to each log-transformed creatinine-standardized biomarker to determine ICCs in this subset. For comparison, we calculated the mean ICC in studies from a 2022 review on variability in urine biomarkers.[36] These mean ICCs were calculated only for studies of pregnancy and were preferentially limited to creatinine- or specific-gravity standardized ICCs if multiple ICCs were provided within a single study. Exposure concentrations were log-transformed for analyses.

In our analytic sample, missing covariate data included usual intake HEI-2010 score ($n = 2$), usual intake daily calories ($n = 4$), and gestational age at biological sample collection ($n = 3$). Fifteen participants were missing outcomes at birth, and 81 were missing outcomes at the 5-month follow-up. Missing covariate and outcome data in the analytic sample was imputed using 20 multiple chained equations and included all variables from our main models in addition to gestational age at delivery, age at postnatal visit, infant length and length-for-age z-scores, HEI-2010 score and daily calories from the 24-h dietary recall closest to the second study visit, energy expenditure and rate of gestational weight gain for the first and second trimesters,[30] conditions complicating pregnancy (hypertension, hypertensive disorders of pregnancy, asthma, diabetes, thyroid disease, psychiatric disorders), mode of delivery, and any birth complications.

Prior to running analyses, we assessed the linearity of the associations by testing quadratic terms in multipollutant models. These initial data checks did not suggest strong deviations from linearity. Furthermore, based on prior literature,[7,37] we sought to explore sex-specific associations through examination of effect modification by infant sex. These models required the assumption of linearity. We therefore proceeded with single- and multipollutant analyses under the assumption of linearity as described below.

Single-Pollutant analysis. Multivariable linear regression models were used to estimate the β and 95% confidence interval (CI) for the difference in each continuous infant outcome per log-unit increase in creatinine-standardized phthalate or phenol biomarker concentration. Models for outcomes at birth and at 5 months of age were run separately. Multivariable Poisson models with robust standard errors estimated the relative risk (RR) and 95% CI of experiencing rapid infant growth in weight-for-age or weight-for-length per log-unit increase in creatinine-standardized phthalate or phenol biomarker concentration. In a secondary analysis, we examined effect modification by infant sex.

Multipollutant analysis. In multipollutant analyses, quantile g-computation were used to estimate the effect of simultaneously increasing all exposure biomarkers within the mixture by 1 quartile on each infant outcome.[38] Parametric generalized linear regression models estimated the β and 95% CI for each continuous infant outcome. Models for outcomes at birth and at 5 months of age were run separately. Parametric generalized binomial regression models estimated the marginal RR and 95% CI for rapid infant growth in weight-for-age or weight-for-length. Models were run separately for each exposure biomarker mixture: phthalates (Phthalate mixture), phenols (Phenol mixture), and phthalates and phenols (Overall mixture). The Phthalate mixture model was adjusted for phenols, and the Phenol mixture model adjusted for phthalates. In secondary analyses, we examined effect modification by infant sex using the qgcompint package.[39]

Sensitivity analyses. We imputed covariate and outcome data in our primary analysis given that multiple imputation of missing data is generally always preferred to ignoring missingness.[40] However, to ensure that our imputation approach did not bias results, we repeated our primary analyses for a complete case data set ($n = 326$).

Given that prior studies involving phthalates frequently lack adjustment for diet and other lifestyle confounders,[7] we created unadjusted and minimally adjusted models and reran the primary analyses for better comparability to the literature. Minimally adjusted models included age, race and ethnicity, prepregnancy BMI, highest education level completed, any previous pregnancies, smoking during pregnancy, gestational age at biological sample collection, and infant sex assigned at birth. Models at 5 months of age additionally adjusted for infant age.

To ensure covariates could not be along the causal pathway (i.e., to ensure temporality), we created models with alternate adjustments and reran the primary analyses. These alternate adjustments included age, race and ethnicity, prepregnancy BMI, highest education level completed, any previous pregnancies, smoking during pregnancy, gestational age at biological sample collection, HEI-2010 score and daily calories from the 24-h dietary recall closest to the second study visit, and energy expenditure and rate of gestational weight gain for the first and second trimesters. Models at 5 months additionally adjusted for infant age.

Urinary concentrations of phthalate and phenol biomarkers have short half-lives,[41] resulting in exposure misclassification and attenuation bias.[42] Posteriori disattenuation has been shown to reduce bias resulting from the use of one urine sample to assess exposure.[42,43] Thus, in a sensitivity analysis, we performed posteriori disattenuation of our single-pollutant linear regression models[43] by dividing estimates and standard errors by their ICCs from the subset.

Results

Descriptive Analysis

Of the 1,410 pregnant individuals enrolled in the Healthy Start cohort, our analytic sample comprised 438 infants with complete exposure and PEA POD assessments at either birth or the 5-month follow-up. Characteristics in the analytic sample appeared generally similar to the enrolled sample, but there were differences in sample characteristics between the enrolled, analytic, and subset samples (Table S1). Notably, more participants in the subset sample identified as non-Hispanic White or Caucasian. Some differences were also observed between included (analytic) and excluded samples (Table S2). For example, included (analytic) participants had a lower energy expenditure, higher gestational weight gain, and smaller infants. Pregnant participants in our analytic sample were generally highly educated (47.9% with at least a 4-y degree), multiparous (62.3%), and nonsmokers (92.7%), with a BMI of $\leq 24.9\,kg/m^2$ (53.7%) (Table 1). A quarter identified as Hispanic

Table 1. Participant characteristics for the analytical sample ($n = 438$), Healthy Start cohort, 2009–2014.

Characteristics	Mean ± SD or *n* (%)
Maternal age (y)	28.1 ± 6.1
Self-identified race and ethnicity	
Hispanic or Latina	106 (24.2)
Non-Hispanic White or Caucasian	251 (57.3)
Non-Hispanic Black or African American	53 (12.1)
All others[a]	28 (6.4)
Prepregnancy BMI (kg/m^2)	
≤24.9	235 (53.7)
25.0–29.9	123 (28.1)
≥30.0	80 (18.3)
Highest education level completed	
<12th grade	59 (13.5)
High school degree or GED	72 (16.4)
Some college or associate's degree	97 (22.2)
4-y college degree	96 (21.9)
Graduate degree	114 (26.0)
Any previous pregnancies	
Yes	273 (62.3)
No	165 (37.7)
Smoking during pregnancy	
Yes	32 (7.3)
No	406 (92.7)
Diet (usual intake)	
HEI-2010 score	55.7 ± 14.1
Daily calories	2,060.7 ± 393.0
Physical activity (MET-h/wk)	
Energy expenditure for entire pregnancy	175.3 ± 70.7
Gestational weight gain (kg)	13.8 ± 6.3
Gestational age at biological sample collection (wk)	27.5 ± 2.5
Infant sex assigned at birth	
Male	234 (53.4)
Female	204 (46.5)

Note: Missing data includes usual intake HEI-2010 score ($n = 2$), usual intake daily calories ($n = 4$), gestational age at biological sample collection ($n = 3$). GED, General Education Development; MET, metabolic equivalent for task; SD, standard deviation.
[a]All others included self-identified Asian or Pacific Islander, American Indian or Alaskan Native, or other.

or Latina, 12.1% identified as Non-Hispanic Black or African American, 57.3% identified as non-Hispanic White or Caucasian, with the rest (6.4%) identifying as Asian or Pacific Islander, American Indian or Alaskan Native, or other. Participants typically provided their urine sample in the morning (94.8%). Infants were delivered at a mean of 39 ± 1.3 wk of gestation, with a mean weight of 3,133.5 ± 414.1 g.

Correlations between measures of size (weight, weight-for-age, weight-for-age *z*-score) and adiposity (fat mass percentage, grams, index) ranged from 0.37 to 0.78, with stronger correlations observed between these measures at 5 months of age than at birth (Figure S2). We observed moderate (>0.60) positive correlations within, but not between, phthalates and phenols (Figure S3). Given the high (>0.90) positive correlations and shared parent compounds, ΣDBP, ΣDiBP, and ΣDEHP were used in subsequent analyses. Most phthalate metabolites and phenols were highly detected in urine (average percentage detection ∼95%) and ICCs for three repeated measures at 2-wk intervals in a subset of 24 participants ranged from 0.00 for ΣDBP to 0.86 for benzophenone-3 (Table 2). As expected owing to the short time frame between repeated samples in midpregnancy, ICC values in the Healthy Start cohort were generally higher than those observed in prior pregnancy studies, as summarized in a recent review (Tables S3–S4).[36]

Single-Pollutant Analysis

We identified several notable associations between individual phthalate and phenol biomarkers and infant outcomes (Figure 1; Tables S5–S6) based on the magnitude of the effect estimate, width of CIs, and consistency of associations across primary and secondary outcomes. MBzP was inversely associated with infant weight [β: −29 (95% CI: −60, 2.6) g], fat mass [−8.3 (95% CI: −20, 2.9) g; −0.16 (95% CI: −0.46, 0.14) %], and lean mass [−20 (95% CI: −46, 5.6) g] at birth; associations were attenuated at 5 months of age. MEP was inversely associated with infant weight [−61 (95% CI: −120, 1.2) g] and fat mass [−37 (95% CI: −74, −0.93) g; −0.29 (95% CI: −0.68, 0.1) %], but not with lean mass [−23 (95% CI: −67, 20) g] at 5 months of age. No biomarkers were individually associated with risk of rapid infant growth (Table S7).

There was evidence of effect modification of the association between phthalates biomarkers and infant size and fat mass by infant sex, with results suggesting inverse associations with infant weight and fat mass among males but not females (Figure 2). At birth, ΣDBP and ΣDiBP were inversely associated with infant weight in males and had null (ΣDBP) or positive (ΣDiBP) associations in females ($p_{interaction} \leq 0.09$ for all comparisons) (Tables S8–S9). Also at birth, MBzP and ΣDBP were inversely associated with infant fat mass for males, whereas associations for females were null (MBzP) or positive (ΣDBP) ($p_{interaction} \leq 0.02$ for all comparisons). Conversely, MCNP was inversely associated with fat mass in females, whereas associations were null in males ($p_{interaction} \leq 0.07$ for all comparisons). Sex-based disparities persisted at 5 months of age but were less precise (Tables S10–S11). Several biomarkers were generally positively associated with the RR of rapid infant growth in weight-for-age (MBzP, ΣDBP, ΣDEHP) or weight-for-length (propyl paraben) in males and inversely associated with the RR of rapid infant growth in females, although effect sizes were small ($p_{interaction} \leq 0.09$ for all comparisons) (Table S12). Results were consistent across primary and secondary study outcomes.

Multipollutant Analysis

Based on the magnitude of the effect estimate, width of CIs, and consistency of associations across primary and secondary outcomes, we determined phthalate and phenol biomarkers mixtures were associated with infant outcomes (Figure 3; Table S13). Associations were stronger at 5 months of age than at birth and were strongest for the Overall mixture of phthalate and phenol biomarkers than for the Phthalate and Phenol mixtures analyzed individually. For example, a 1-quartile increase in the Phthalate mixture was inversely associated with fat mass percentage at birth and at 5 months of age [−0.10 (95% CI: −0.69, 0.50) and −0.88 (−1.8, 0.05), respectively]. This association for the Phenol mixture was −0.31 (95% CI: −1.08, 0.46) and −0.72 (95% CI: −1.91, 0.47), respectively. For the Overall mixture, this association was −0.37 (95% CI: −1.25, 0.51) and −1.37 (95% CI: −2.74, −0.01), respectively.

Similar to single-pollutant analysis, male infants were disproportionately smaller for increased phthalate and phenol exposure biomarkers (Table S14). Of note, male infants had lower fat mass at birth [−20 (95% CI: −48, 7.1) g and −0.49 (95% CI: −1.23, 0.25) %] and at 5 months of age [−140 (95% CI: −240, −35) g and −1.26 (95% CI: −2.38, −0.15) %] for a 1-quartile increase in the Phthalate mixture; associations were null in female infants ($p_{interaction} \leq 0.38$ for all comparisons). Similar associations were observed for the Overall mixture. For example, male infants had lower fat mass percentage at birth [−1.06 (95% CI: −2.21, 0.1)] for a 1-quartile increase in the Overall mixture; female infants had no notable differences in fat mass percentage [0.48 (95% CI: −0.78, 1.75)] for the same time frame ($p_{interaction} = 0.07$). For a 1-quartile increase in the Phthalate, Phenol, and Overall mixtures, male infants had a generally heightened risk of rapid growth and female infants had a lower risk of rapid growth, although CIs

Table 2. Description of biomarkers (μg/g creatinine) in gestational urine samples.

Biomarker	Abbreviation	Healthy Start analytic sample ($n = 438$)[a] LOD (μg/L)	Percentage detected (%)	Percentile 25th	50th	75th	Healthy Start subset ($n = 24$)[b] ICC	Roggeman et al.[36,c] ICC
Phthalates								
Mono-ethyl phthalate	MEP	0.6	99.8	16.0	34.6	99.9	0.60	0.45
Mono-benzyl phthalate	MBzP	0.3	97.3	2.3	5.6	12.6	0.48	0.48
Mono-3-carboxypropyl phthalate	MCPP	0.2	96.3	1.1	2.1	4.2	0.23	0.21
Mono carboxyisooctyl phthalate	MCOP	0.2	100.0	8.5	18.6	48.0	0.25	0.26
Mono carboxyisononyl phthalate	MCNP	0.2	99.1	1.9	3.1	5.6	0.18	0.08
Mono-*n*-butyl phthalate	MnBP	0.4	96.6	5.1	11.2	18.3	0.04	0.43
Mono-hydroxybutyl phthalate	MHBP	0.4	72.1	0.6	1.2	2.0	0.52	—
ΣDi-*n*-butyl phthalate metabolites[d]	ΣDBP	—	—	5.6	12.3	20.1	0.00	—
Mono-isobutyl phthalate	MiBP	0.2	98.9	3.9	8.2	14.4	0.59	0.42
Mono-hydroxyisobutyl phthalate	MHiBP	0.4	95.4	2.2	3.8	6.3	0.57	—
ΣDi-isobutyl phthalate metabolites[e]	ΣDiBP	—	—	6.3	12.1	20.2	0.61	—
Mono-2-ethylhexyl phthalate	MEHP	0.5	72.8	0.5	1.2	2.5	0.58	0.28
Mono-2-ethyl-5-hydroxyhexyl phthalate	MEHHP	0.2	99.3	2.5	5.0	10.2	0.28	0.21
Mono-2-ethyl-5-oxohexyl phthalate	MEOHP	0.2	99.1	2.6	4.7	8.9	0.31	0.24
Mono-2-ethyl-5-carboxypentyl phthalate	MECPP	0.2	100.0	6.8	11.2	20.4	0.39	0.28
ΣDi(2-ethylhexyl) phthalate metabolites[f]	ΣDEHP	—	—	13.6	24.1	43.3	0.36	—
Phenols								
2,4 dichlorophenol	—	0.1	96.1	0.4	0.6	1.2	0.74	—
2,5 dichlorophenol	—	0.1	95.0	0.8	1.8	5.7	0.84	—
Bisphenol A	BPA	0.1	97.7	0.6	1.1	1.9	0.39	0.20
Bisphenol S	BPS	0.1	87.0	0.2	0.3	0.6	0.25	0.20
Benzophenone-3	—	0.2	99.5	36.3	110.3	438.9	0.86	—
Methyl paraben	—	1.0	100.0	47.8	142.5	343.4	0.82	0.47
Propyl paraben	—	0.1	100.0	5.2	27.6	95.0	0.79	0.49
Triclosan	—	1.0	92.7	4.6	15.3	63.4	0.83	—

Note: Biomarkers are creatinine-standardized based on the O'Brien method.[19] ICC, intraclass correlation coefficient; LOD, limit of detection.
[a]Analytic sample of the Healthy Start cohort conducted during 2009–2014 enrolled participants who provided a urine sample midpregnancy and had at least one time point with outcome assessment.
[b]Subset within Healthy Start cohort conducted during 2009–2014 enrolled participants who provided at least three urine samples in mid-to-late pregnancy.
[c]Mean value calculated from the 2022 review by Roggeman et al.[36] on variability in urine biomarkers of nonpersistent chemical exposures. Mean values calculated only for studies of pregnancy, and preferentially limited to creatinine or specific-gravity standardized ICCs when multiple ICCs were provided in one study. Missing ICCs are for biomarkers without values provided in the review. See Tables S3 and S4 for more details.
[d]Sum of di-*n*-butyl phthalate metabolites: MnBP and MHBP.
[e]Sum of di-isobutyl phthalate metabolites: MiBP and MHiBP.
[f]Sum of di(2-ethylhexyl) phthalate metabolites: MEHP, MEOHP, MEHHP, and MECPP.

were imprecise and included the null. Results were consistent across primary and secondary study outcomes.

Sensitivity Analyses

In the complete case analysis, birthweight was inversely associated with MBzP [−45 (95% CI: −79, −12)] and ΣDBP [−59 (95% CI: −100, −14)] (Table S15). Further, fat mass at birth was inversely associated with 2,4 dichlorophenol [−0.36 (95% CI: −0.71, −0.01)] and 2,5 dichlorophenol [−0.25 (95% CI: −0.47, −0.02)] (Table S16). Findings from single-pollutant models for rapid infant growth (Table S17) and multipollutant models were similar to our primary analysis (Table S18).

Associations for unadjusted (Tables S19–S22), minimally adjusted (Tables S23–S26), and alternate (Tables S27–S30) models were similar to those from our primary analysis, although the magnitude of associations was stronger in fully adjusted models from our primary analysis. For example, a 1-quartile increase in the Overall mixture was inversely associated with infant percentage fat mass at 5 months of age in unadjusted [−0.77 (95% CI: −2.08, 0.54)], minimally [−1.33 (95% CI: −2.69, 0.04)], alternate [−1.36 (95% CI: −2.75, 0.04)], and fully [−1.37 (95% CI: −2.74, −0.01)] adjusted models.

Single-pollutant linear regression estimates were generally strengthened but less precise with posteriori disattenuation (Tables S31–32). For example, MBzP was associated with a −60 (−130, 5.2)-g difference in weight at birth using corrected estimates; this difference was −29 (−60, −2.6) g in our primary analysis.

Discussion

Biomarkers of nonpersistent consumer product chemicals including phthalates and phenols were highly detected among pregnant participants in the Healthy Start study. Exposure to many contemporary phthalates and phenols (e.g., DEHP, BPA) has been decreasing as exposure to replacement chemicals (e.g., BPS) have increased.[44] However, the high detection in this study population is in line with several U.S. studies occurring during 2010–2016[45,46] Concentrations of phenol biomarkers measured midpregnancy were imprecisely inversely associated with infant size (weight) and adiposity at birth and at 5 months of age. Prior observational studies have reported inconsistent and insignificant findings between gestational exposure to phenols and fetal growth outcomes, as summarized in a 2019 review.[6] We found that concentrations of phthalate biomarkers measured midpregnancy—in particular MBzP and ΣDBP—were inversely associated with infant size and fat mass at birth and at 5 months of age. This is in line with prior observational studies that have reported more consistent but overall modest associations between gestational exposure to phthalates and fetal growth outcomes, as summarized in a 2019 review.[7] Combined exposure to phthalates and phenols midpregnancy was inversely associated with infant size and fat mass at birth and at 5 months of age. In stratified models, these associations were observed only among male rather than female infants; the latter exhibited either null or positive associations between exposures and fat mass, although CIs were imprecise. To our knowledge, this is the first study to examine infant body composition in relation to

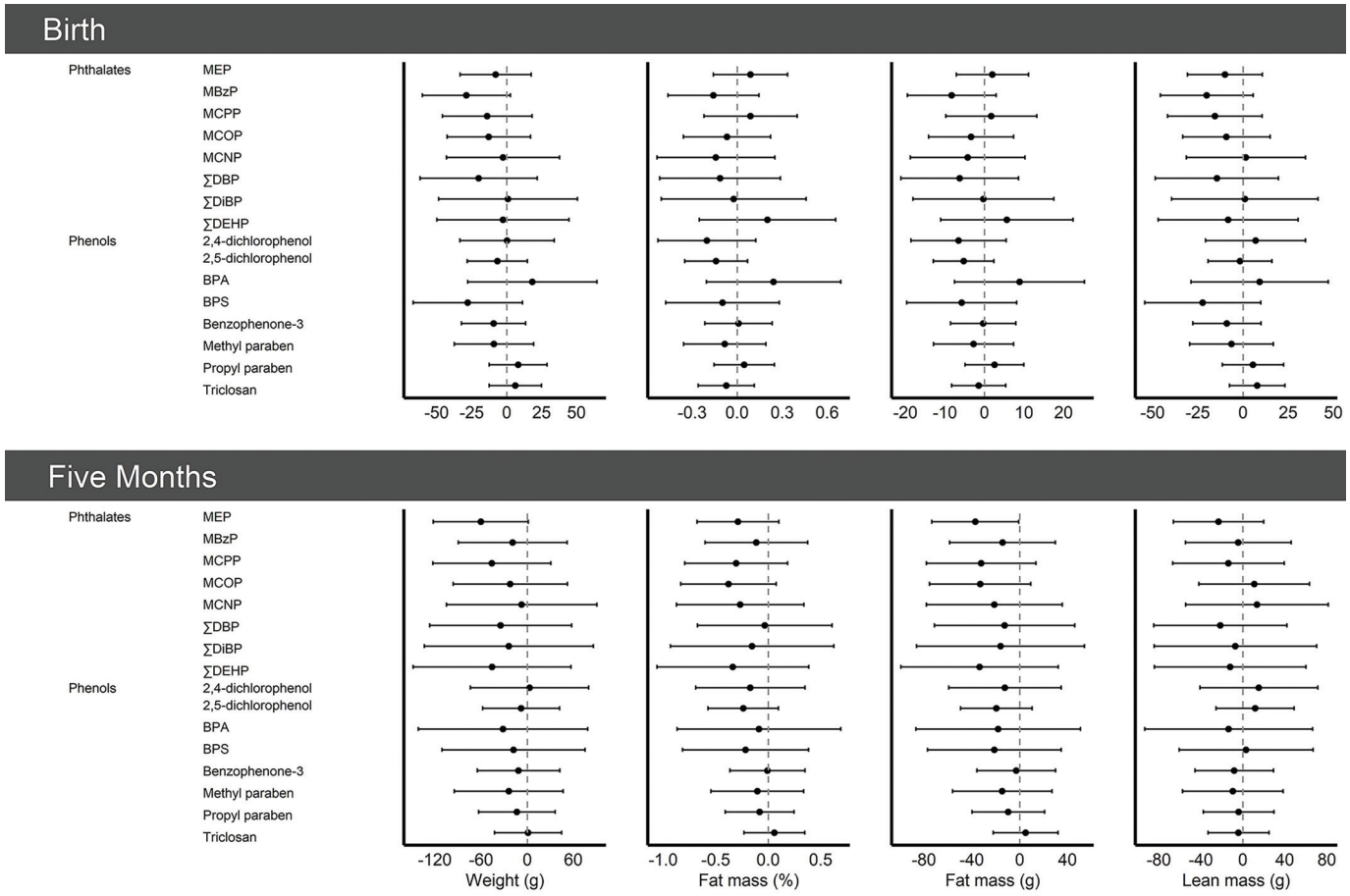

Figure 1. Single-pollutant model results [β (95% CI)] per log-unit increase in creatinine-standardized midpregnancy phthalate or phenol biomarker concentration with infant size and body composition at birth and at 5 months of age in the analytic sample ($n = 438$), Healthy Start cohort, 2009–2014. Models were adjusted for age, race and ethnicity, prepregnancy body mass index category, highest education level completed, any previous pregnancies, smoking during pregnancy, gestational age at biological sample collection, infant sex, diet during pregnancy, physical activity during pregnancy, and gestational weight gain. In models for infant outcomes at the 5-month follow-up, we additionally adjusted for infant age. See Tables S5 and S6 for more details. Note: BPA, bisphenol A; BPS, bisphenol S; CI, confidence interval; MBzP, mono-benzyl phthalate; MCNP, mono carboxyisononyl phthalate; MCOP, mono carboxyisooctyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEP, mono-ethyl phthalate; ΣDBP, sum of the of di-*n*-butyl phthalate metabolites; ΣDEHP, sum of di(2-ethylhexyl) phthalate metabolites; ΣDiBP, sum of di-isobutyl phthalate metabolites.

gestational phthalate and phenol exposures. Given evidence suggesting gestational phthalate and phenol exposure may be associated with reduced fetal growth[7] and laboratory studies linking phthalates and phenols to impaired adipogenesis,[9–12] further studies to clarify the association between these chemical exposures during pregnancy and body composition and growth outcomes are needed.

The *in utero* environment has a profound effect on fetal development. Exposure to nonpersistent chemicals including phthalates and phenols during pregnancy has been inversely associated with fetal growth in animal and epidemiologic studies.[7] However, evidence from the epidemiologic studies has been equivocal, potentially due to inconsistencies and limitations in outcome assessment. Ultrasound measures of fetal growth are error-prone[47,48] and constrained in their depiction of fetal anatomy,[49] and birthweight is a proxy measure of fetal growth composed of multiple compartments, including fat and lean mass. Reliance on these measures has provided incomplete insight into associations and potentially obscured the clinical implications of fetal exposure to phthalates and phenols. Birthweight has a U-shaped association with obesity, particularly among males,[50] and rapid infant growth is a recognized risk factor for obesity.[51] However, anthropometric measures likely reflect lean mass more than fat mass.[52] Recent studies from Healthy Start and an Ethiopian cohort have reported that neonatal fat mass exhibits a U-shaped association with later adiposity,[53] with the smallest infants experiencing rapid fat accretion and subsequently an adverse metabolic profile.[52] In the present study, we observed poor-to-moderate correlations between measures of infant size and adiposity, suggesting body weight is not a strong marker of adiposity. Precise assessments of infant fat and lean mass using noninvasive methods, such as air displacement plethysmography, could therefore provide further clarification of the effects of gestational phthalate and phenol exposures on adiposity development and metabolic health.

Adipogenesis initiates at ∼14 wk of gestation, adipocytes form at ∼20 wk, fat lobules form at ∼28 wk, and adipose tissue accrual accelerates in the third trimester with lipid accretion rates peaking close to delivery (36–40 wk of gestation).[54] The number and size of adipocytes are programmed *in utero* in response to environmental and metabolic cues, through processes under endocrine regulation and with sex-based differences.[13,55] Sex differences in adiposity emerge as early as birth, and individuals assigned female sex at birth tend to have more fat mass than those assigned male alongside greater gains in adiposity in infancy.[56] Males and females both express estrogen and androgen receptors in adipose tissue, but females tend to have higher expression of estrogen receptors than males.[57] This sexual dimorphism helps drive differential adipocyte metabolism and expansion, with estrogens

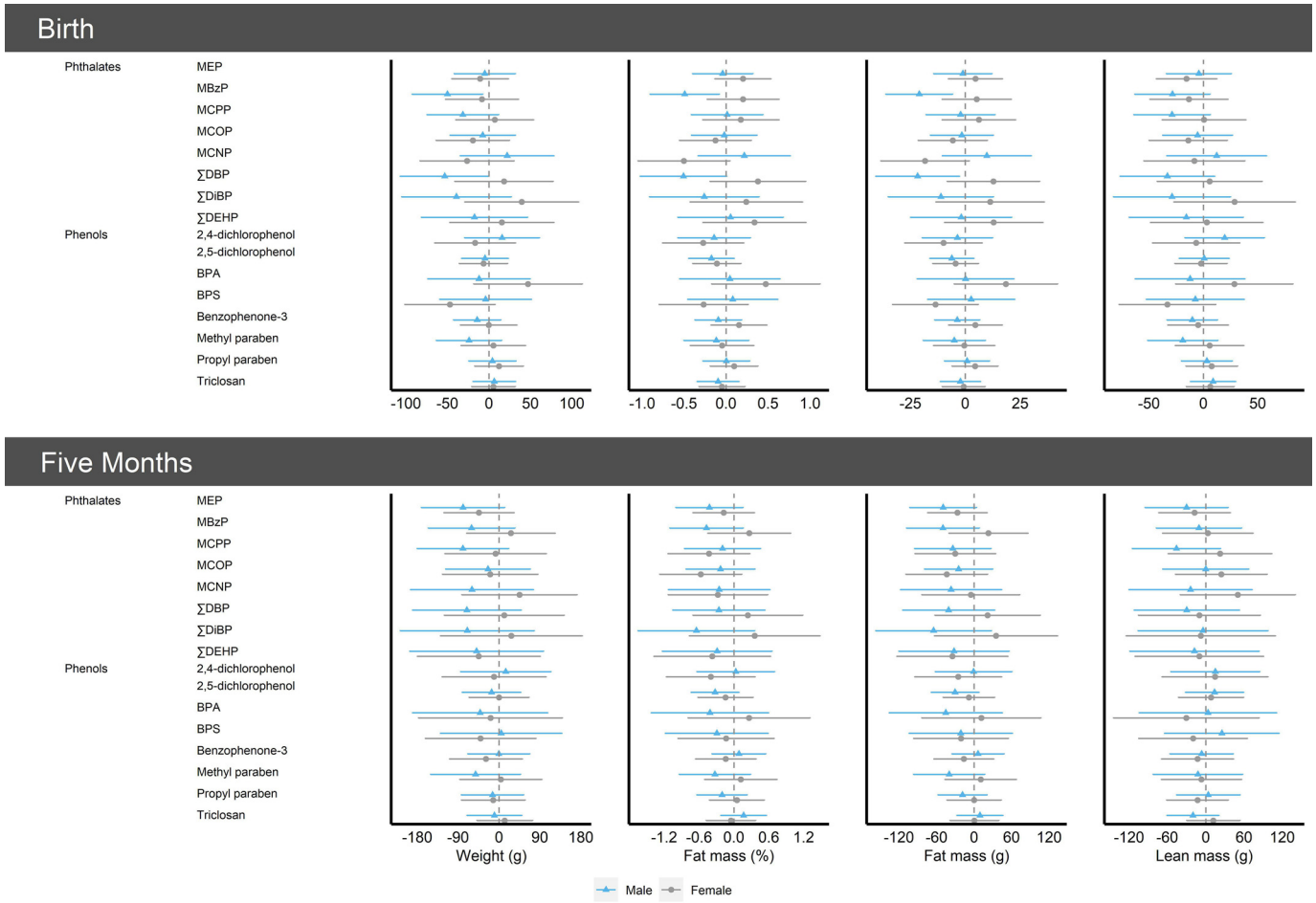

Figure 2. Single-pollutant model results [β (95% CI)] per log-unit increase in creatinine-standardized midpregnancy phthalate or phenol biomarker concentration with infant size and body composition at birth and at 5 months of age by infant sex in the analytic sample ($n = 438$), Healthy Start cohort, 2009–2014. Models were adjusted for age, race and ethnicity, prepregnancy body mass index category, highest education level completed, any previous pregnancies, smoking during pregnancy, gestational age at biological sample collection, infant sex, diet during pregnancy, physical activity during pregnancy, and gestational weight gain. In models for infant outcomes at the 5-month follow-up, we additionally adjusted for infant age. See Tables S8–S11 for more details. Note: BPA, bisphenol A; BPS, bisphenol S; CI, confidence interval; MBzP, mono-benzyl phthalate; MCNP, mono carboxyisononyl phthalate; MCOP, mono carboxyisooctyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEP, mono-ethyl phthalate; ΣDBP, sum of the of di-*n*-butyl phthalate metabolites; ΣDEHP, sum of di (2-ethylhexyl) phthalate metabolites; ΣDiBP, sum of di-isobutyl phthalate metabolites.

enhancing preadipocyte proliferation and differentiation into insulin-sensitive adipocytes and lipolysis and androgens performing opposing functions.[57] In rat models, phthalates decrease the number of adipocytes at birth but increase the size and lipid storage of adipocytes, resulting in an adaptive catch-up adipogenesis and subsequent adipose tissue dysfunction and glucose intolerance, particularly in male rats.[13] In mice models, phenols increase the number of adipocytes at birth by changing the fate of stem cells toward the adipocyte lineage and away from osteoblasts.[9,10] Several phthalates and phenols are endocrine disrupters, and they can mimic or alter sex steroid levels and thereby differentially affect adipose tissue development in males and females.[7,57,58] However, although laboratory studies and biologic plausibility support a link between gestational phthalate and phenol exposures with obesity, epidemiologic evidence of these effects is scarce.

Our study is the first to focus on associations with infant body composition, but several observational studies have investigated associations with childhood body composition.[59–68] These cohorts have reported positive,[61,62,66,67] inverse,[60,63–65] and no associations[59,68] between gestational phthalate or phenol exposures with childhood adiposity. Although associations were commonly sexually dimorphic, there is little agreement in prior literature regarding whether males or females are disproportionately affected by exposure. Ferguson et al. recently reported gestational phthalate exposures [MEP (median concentration in ng/mL = 37.3), MBzP (4.5), MCPP (2.0), MBP (9.0), MiBP (6.0), MCOP (15.7), ΣDEHP (0.09 nmol/mL)] inversely associated with adiposity *z*-scores at birth (weight-for-length) and positively associated with adiposity *z*-scores (BMI) at 3 and 4 years of age, with slightly higher magnitude of associations in males, in a prospective pregnancy cohort conducted at four U.S. sites with recruitment during 2010–2012.[69] Placing our results into the context of these prior laboratory and epidemiologic studies, midpregnancy phthalate and, to a lesser extent, phenol exposure appears to be influencing adipogenesis in a sex-dependent manner to result in initial decreases in infant fat mass among males. By 5 months of age, we continued to note lower fat mass with increased gestational phthalate and phenol exposure, although these associations were less precise. We also noted a heightened risk of rapid infant growth (i.e., catch-up growth) in exposed males. Differences in associations at birth and at 5 months of age might suggest some findings could be spurious, particularly those observed in single-pollutant models. On the other hand, it might also suggest a pattern of development whereby gestational

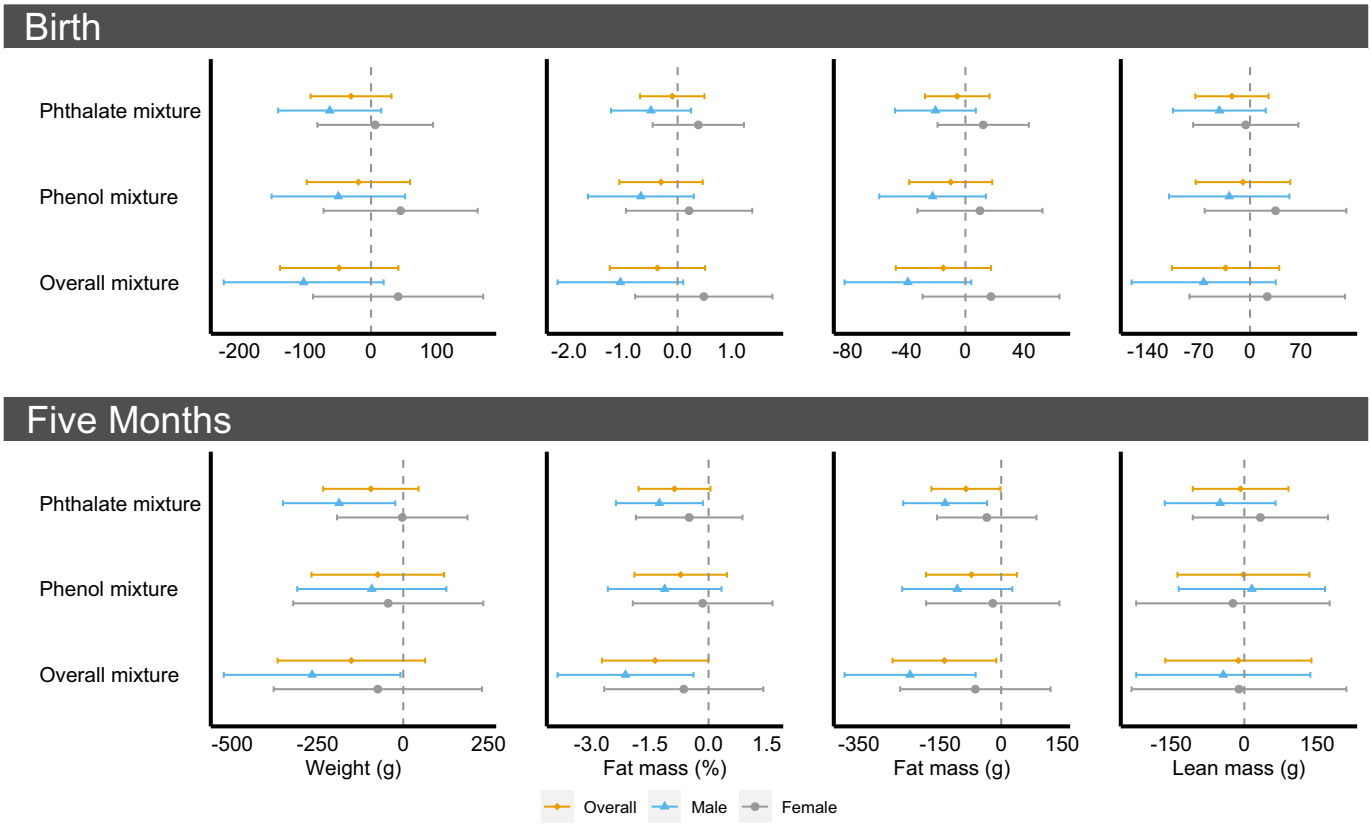

Figure 3. Multipollutant model results [β (95% CI)] per 1-quartile increase in creatinine-standardized midpregnancy phthalate or phenol biomarker concentration with infant size and body composition at birth and at 5 months of age overall and by infant sex in the analytic sample ($n = 438$), Healthy Start cohort, 2009–2014. Models were adjusted for age, race and ethnicity, prepregnancy body mass index category, highest education level completed, any previous pregnancies, smoking during pregnancy, gestational age at biological sample collection, infant sex, diet during pregnancy, physical activity during pregnancy, and gestational weight gain. In models for infant outcomes at the 5-month follow-up, we additionally adjusted for infant age. See Tables S13 and S14 for more details. Note: CI, confidence interval.

phthalate and phenol exposure results in initial decreases in adiposity followed by rapid fat accretion from birth through infancy and into childhood. At 5 months of age, we may have been capturing a window of time when the difference in size and fat mass between exposed and unexposed infants narrows as fat accretion accelerates in exposed infants. Follow-up beyond 5 months of age should enable a better understanding of the potential long-term effects of gestational phthalate and phenol exposures on body composition and growth.

Our results should be considered in light of study limitations. Although a relatively large sample ($n = 438$) was analyzed, this convenience sample represents approximately one-third of the full Healthy Start study and may not be generalizable. We note some differences in risk of rapid infant growth, whereby our analytic sample had higher infant fat mass and risk of rapid growth in weight-for-length by the postnatal visit than the excluded sample. Participants in our analytic sample had lower gestational energy expenditure and higher gestational weight gain, which may explain these differences in postnatal infant growth and fat outcomes. Encouragingly, these differences were not present at the neonatal visit, appeared generally small in magnitude (e.g., fat mass was 25% vs. 24% in the included and excluded samples, respectively), and did not occur for risk of rapid growth in weight-for-age. Further, multiple imputation of covariates and outcomes should have provided unbiased estimates for associations.[40,70] A complete case sensitivity analysis provided comparable findings to our primary analysis. Other sources of bias may be due to the use of only one time point for exposure assessment, which results in attenuation bias (i.e., bias toward the null).[43] To correct for this bias, it is recommended that posteriori disattenuation be applied using internal rather than external ICCs.[42] In single-pollutant analyses, we applied a posteriori disattenuation sensitivity analysis for continuous outcomes to correct for this bias. Unfortunately, in single-pollutant analyses for noncontinuous outcomes and all multipollutant analyses, we were unable to apply bias correction methods owing to the categorization of the outcomes and exposures. We also noted that the associations were usually greater in magnitude with adjustment for confounders, suggesting negative confounding. Thus, associations in our study, which were generally modest and imprecise, may actually have been greater than observed. Our ICCs were generally higher than those observed in prior pregnancy studies, likely owing to the 2-wk intervals for exposure assessment occurring within one window. This allowed us to characterize midpregnancy exposure, but even after correction, nonclassical error may arise in case we did not target the relevant exposure window when assessing exposure. Adipogenesis initiates after the first trimester and continues until delivery. We therefore hypothesize that midpregnancy is an exposure window with high relevance for fetal adipose development.

Our study had several strengths. Study results were robust to numerous modeling approaches, adjustments, outcome definitions, and in sensitivity analyses. A strength of our multipollutant modeling approach is that quantile g-computation allowed us to quantify the total mixture effect on our outcomes.[38] Mixture methods have been underused in the phthalate and phenol literature,[71] but are crucial for the appropriate specification and quantification of the human exposure experience. Quantile g-computation is advantageous for its interpretability, computational ease, and minimal

bias, as well as its ability to incorporate nonlinearity and nonadditivity of mixture components.[38] Other criticisms of prior epidemiologic studies include inadequate adjustment for potential confounders. Phthalates and phenols are commonly found in food packaging and may be more common among those with obesogenic dietary patterns,[7,72] making adjustment for diet of critical importance. Reassuringly for other studies of these associations, additional adjustment for diet quality, total dietary intake, physical activity, and gestational weight gain did not substantially influence model results. Finally, we examined numerous primary and secondary outcomes, finding consistent results across outcomes. Notably, study conclusions remained the same for weight and weight-for-age *z*-score outcomes, and across all means of assessing fat mass (percentage, grams, and fat mass index).

Conclusions

In this U.S.-based prospective cohort, midpregnancy phthalate and phenol exposure was modestly inversely associated with infant weight and adiposity before 5 months of age, particularly in males. Our findings suggest midpregnancy phthalate and phenol exposure may have sexually dimorphic impacts on adipogenesis, resulting in initial decreases in fat mass, which may be followed by rapid growth among male infants. Additional follow-up is needed to understand the potential clinical implications of observed associations.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the U.S. Department of Health and Human Services.

Data access may be provided upon reasonable request and a proposal submitted to the Healthy Start cohort study team.

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