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Prenatal Maternal Phthalate Exposures and Trajectories of Childhood Adiposity from Four to Twelve Years

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Declaration of interests

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Abstract

Background/Aim: Adiposity trajectories reflect dynamic process of growth and may predict later life health better than individual measures. Prenatal phthalate exposures may program later childhood adiposity, but findings from studies examining these associations are conflicting. We investigated associations between phthalate biomarker concentrations during pregnancy with child adiposity trajectories.

Methods: We followed 514 mother-child pairs from the Mexico City PROGRESS cohort from pregnancy through twelve years. We measured concentrations of nine phthalate biomarkers in 2nd and 3rd trimester maternal urine samples to create a pregnancy average using the geometric mean. We measured child BMI z-score, fat mass index (FMI), and waist-to-height ratio (WHtR) at three study visits between four and 12 years of age. We identified adiposity trajectories using multivariate latent class growth modeling, considering BMI z-score, FMI, and WHtR as joint indicators of latent adiposity. We estimated associations of phthalates biomarkers with class membership using multinomial logistic regression. We used quantile g-computation to estimate the potential effect of the total phthalate mixture and assessed effect modification by sex.

Results: We identified three trajectories of child adiposity, a “low-stable”, a “low-high”, and a “high-high” group. A doubling of the sum of di (2-ethylhexyl) phthalate metabolites (ΣDEHP), was associated with 1.53 (1.08, 2.19) greater odds of being in the “high-high” trajectory in comparison to the “low-stable” group, whereas a doubling in di-isononyl phthalate metabolites (ΣDiNP) was associated with 1.43 (1.02, 2.02) greater odds of being in the “low-high” trajectory and mono (carboxy-isononyl) phthalate (MCNP) was associated with 0.66 (0.45, 97) lower odds of being in the “low-high” trajectory. No sex-specific associations or mixture associations were observed.

Conclusions: Prenatal concentrations of urinary DEHP metabolites, DiNP metabolites, and MCNP, a di-isodecyl phthalate metabolite, were associated with trajectories of child adiposity. The total phthalate mixture was not associated with early life child adiposity.

Keywords

Phthalates; Children’s environmental health; Environmental epidemiology; Mixtures analysis

1. Introduction

Trajectories of childhood adiposity are predictors of later life cardiometabolic diseases (Barraclough et al., 2019; Norris Tom et al., 2021) and may have greater clinical implications than a single BMI measurement or overall BMI (Aris et al., 2019; Juonala et al., 2012; Owen et al., 2009). Early life exposures to environmental toxicants may lead to altered adiposity in early childhood that tracks through to adulthood via structural and functional changes in endocrine and adipocyte signaling. Longitudinal environmental health studies that do not consider adiposity trajectories may miss important trends that correlate with life stages at greater risk for later cardiometabolic risk.

Phthalates are prevalent chemicals with widespread use in consumer and industrial products (Wormuth et al., 2006). Although phthalates are rapidly metabolized and excreted, because

of recurrent and frequent exposures, urinary phthalate biomarkers are ubiquitously detected in United States and Mexican populations, including pregnant women (Katsikantami et al., 2016; López-Carrillo et al., 2010; Wu et al., 2020). Research in experimental models suggests that phthalates may act as environmental "obesogens"(Hao et al., 2012; Lin et al., 2011; Schmidt et al., 2012), though human studies examining prenatal phthalate exposures and childhood adiposity present inconsistent or conflicting findings. Age differences may help to explain these associations, as the risk for obesity changes across childhood. For instance, the sum of urinary concentrations of prenatal di (2-ethylhexyl) phthalate metabolites (ΣDEHP) was negatively associated with fat mass from four to nine years in one study(Buckley et al., 2016b), while it was positively associated with multiple adiposity indicators from five to 12 years in another(Harley et al., 2017). Mono-3-carboxypropyl phthalate (MCPP) was positively associated with overweight status from four to seven years of age (Buckley et al., 2016a), while later work in the same cohort observed that monobenzyl phthalate (MBzP) was negatively associated with adiposity at age eight (Shoaff et al., 2017). In other cohorts, prenatal MBzP urinary concentrations were inversely associated with child's BMI z-score from eight to 14 years (Yang et al., 2018).

Our objectives were to: 1) determine if prenatal urinary concentrations of individual phthalate biomarkers are associated with trajectories of child adiposity from four to 12 years and with general longitudinal childhood adiposity; 2) investigate associations of the overall phthalate mixture; and 3) characterize sex-specific effects.

2. Material and Methods

2.1 Study Participants

We used information from the Programming Research in Obesity, Growth Environment and Social Stress (PROGRESS) study, a prospective birth cohort that enrolled pregnant women in Mexico City, Mexico, from 2007 to 2011. Enrollment details are described elsewhere (Braun et al., 2014; Burris et al., 2013). Of the 948 women that delivered a live birth and agreed to follow-up, 786 had prenatal phthalate metabolites measurements. We excluded six women who reported smoking during pregnancy due to the adverse effects of prenatal tobacco smoke exposure on child development. Children were followed-up at a four-, six-, and eight-year visit with 573 children returning for the four-year follow-up visit and 514 with at least one other follow-up. All study protocols were approved by the institutional review boards of the participating institutions (Icahn School of Medicine human subject's management #12-00751, Instituto Nacional de Salud Pública project #560, and Columbia University Human Research Protection Office protocol #AAAR0689). The involvement of the Centers for Disease Control and Prevention (CDC) laboratory did not constitute engagement in human subjects' research. Women provided written informed consent and children provided assent of study protocols.

2.2 Quantification of Maternal Urinary Phthalate Metabolites

We collected maternal spot urine samples during the 2nd and 3rd trimester visits. Samples were analyzed for 15 phthalate metabolites at the CDC by isotope dilution high-performance liquid chromatography coupled with tandem mass spectrometry as previously described

(Silva et al., 2007). The limits of detection (LODs) ranged from 0.2 to 1.2 μg/L, with the detection frequency ranging from 100% to 81% (Supplemental Table S1). For concentrations reported to be below the LOD, we used the instrument reported value, as this may provide more information than a LOD based imputation (Schisterman et al., 2006), and has previously not altered associations between phthalates and other cardiometabolic risk factors in this population in comparison to an $LOD/\sqrt{2}$ imputation (Kupsco et al., 2021). To adjust for urinary dilution, we standardized biomarker concentrations by urine specific gravity (Duty et al., 2005), which was measured using a digital handheld refractometer (AR200, Reichert Technologies, Buffalo, NY). We replaced missing specific gravity values for 101 2nd trimester urine samples using the median value (1.016) (Wu et al., 2020).

2.3 Measurement of Child Adiposity

Children were followed-up at a four-year (N = 514; age range = 4.0 – 6.8; mean = 4.8), a six-year (N = 506; age range = 6.0 – 9.7; mean = 6.7), and an eight-year visit (N = 463; age range = 8.1 – 11.7; mean = 9.7) for adiposity assessments. Trained staff collected child weight and standing height twice using a professional digital scale (Health-o-meter, McCook, IL) and averaged the values. BMI z-scores were estimated using the World Health Organization guidelines (de Onis et al., 2007; de Onis and World Health Organization (WHO), 2006). We estimated fat mass using Tetrapolar bioelectrical impedance with the InBody 370 (Biospace Co, Ltd, Cerritos, CA) at the four-year visit and part of the six-year visit, then switched to the Inbody 230 in the six-year visit and the eight-year visit. As values on these two instruments differed systematically, we used a robust linear model fit on a calibration set of 36 children with concurrent measures to adjust the values ($R^2 = 0.99$) (Renzetti et al., 2017). Fat mass index (FMI) was calculated as $Fat\ Mass\ /\ Height\ (m)^2$. Waist circumference was measured above the iliac crests using a SECA measuring tape and waist to height ratio (WHtR) was calculated as the ratio between waist circumference and child height.

2.4 Covariates

We obtained prenatal covariate information from baseline questionnaires. An index of socioeconomic status (SES) was calculated based on the AMAI rule 13×6 that we collapsed into a relative three-level index of low, medium, and high (Carrasco, 2002). Covariates were selected based on directed acyclic graphs including: child sex, maternal age at enrollment, pre-pregnancy BMI (kg/m^2) estimated from 2nd trimester weight as previously described (Soria-Contreras et al., 2020), parity (primiparous or multiparous), education (< high school, high school, or > high school) and SES at enrollment. We included date at first urine collection, which was associated with the exposures and outcomes, as a representation of long-term and seasonal trends. For longitudinal mixed-effects models of adiposity, we additionally included linear and quadratic terms for child age at each measurement to control for changes in outcomes with age. Models specified with only child age and sex were not meaningfully different from fully adjusted models, so we present fully adjusted models throughout.

2.5 Statistical Analyses

2.5.1 Phthalate Exposure Biomarkers—Phthalates metabolite data were treated as previously described (Kupsco et al., 2021; Wu et al., 2020). In brief, we obtained an estimate of pregnancy-wide exposures as the geometric mean of the 2nd and 3rd trimesters for each metabolite. To reduce dimensionality and account for high correlations among metabolites from the same parent compound, we calculated the molar sums for di (2-ethylhexyl) phthalate (ΣDEHP), di-iso-butyl phthalate (ΣDiBP), di-isononyl phthalate (ΣDiNP), and di-n-butyl phthalate (ΣDBP). The final nine phthalate biomarkers included in our analyses were: ΣDEHP, ΣDiBP, ΣDiNP, ΣDBP, MBzP, mono-2-ethyl-5-carboxypentyl terephthalate (MECPTP), mono (carboxy-isononyl) phthalate (MCNP), MCPP, and monoethyl phthalate (MEP), which were log2 transformed to reduce the influence of high values.

2.5.2 Multivariate Latent Class Growth Models—To empirically identify trajectories of childhood adiposity, we implemented multivariate latent class growth modeling (LCGM) with child BMI z-score, WHtR, and FMI as joint height-adjusted measures of underlying latent adiposity. First, we constructed trajectory models using non-centered BMI z-score, WHtR and FMI, that allowed for different starting adiposity values for each child. Next, we constructed trajectory models that centered BMI z-score, WHtR, and FMI at each child's starting value. These approaches allow us to capture both trajectories of change irrespective of starting adiposity and those dependent on a starting adiposity value.

We used the R package *lcmm* to construct our trajectory models (Proust-Lima et al., 2017), including child-specific random intercepts in all analyses and age-specific random intercepts in non-centered models. We systematically evaluated varying model parameters to determine the best fitting models. We considered: 1) varying the number of classes from two to five; 2) modeling age as a linear or a quadratic term; 3) inclusion of outcome-specific random intercepts; and 5) multiple specifications of the link function for each adiposity outcome, including linear, quantile splines (2 to 3 knots), or equidistant splines (3 or 4 knots). To select the final models, we required a posterior probability > 0.7 and a class size greater than 10% of the population, then compared Bayesian information criterion to select the best fitting model. We confirmed model validity by verifying odds of correct classification > 5 and relative entropy values ~1 using *LCTMtools* (Lennon et al., 2018). We assigned each child to a trajectory class. To assess sex differences in adiposity trajectories, we fit new LCGM models considering sex and its interaction with the linear and quadratic terms of age for the fixed and mixture effects.

Final LCGM models for non-centered adiposity outcomes included: three classes, linear and quadratic fixed effects for child age at follow-up, and three quantile splines on each adiposity outcome. Final LCGM models for centered adiposity outcomes included: three classes, linear and quadratic terms for age centered at the first visit, and splines with four equidistant knots on BMI z-score and FMI, and a linear link function on WHtR. For the centered adiposity outcomes, the splines transformation entailed parameters at the boundary of the parameter space, which led to a lack of convergence. To correct this, the best positions from the original models for the quadratic I-splines with nodes at 4.2 for BMI z-score and at

10.8 for FMI were fixed at their starting values and models were refit without re-estimating those parameters. Model diagnostics are available in Supplemental Table S4.

2.5.3 Associations between Phthalate Biomarkers and Adiposity Trajectories and Longitudinal Adiposity Indicators.—To estimate associations between individual phthalate biomarkers and trajectories of adiposity, we ran covariate-adjusted, multinomial logistic regressions with class membership as the outcome using the stable low trajectory class as the reference category. Models included all log 2-transformed phthalate biomarkers in a single model. Results can be interpreted as the odds of being in a trajectory class per doubling of phthalate biomarker. To identify sex-specific associations, we used the sex-specific trajectories to determine class membership, then ran multinomial logistic regressions with the population stratified by child sex or including interactions between sex and each phthalate biomarker.

We used multivariable linear mixed-effects models with a random intercept for subject to estimate associations between the nine phthalate biomarkers and child BMI z-score, FMI, and WHtR, including all nine phthalate biomarkers in each model. We investigated child sex as an effect measure modifier by testing interaction terms of child sex and each phthalate biomarker and ran sex-stratified models to determine sex-specific effect estimates. Effect estimates are expressed as the change of the outcome per doubling in the exposure with the 95% confidence intervals (CI).

2.5.4 Mixture Analysis with Quantile G-Computation—We investigated the associations of the total biomarker mixture with trajectory class membership and longitudinal BMI z-score, FMI and WHtR in outcome-specific models, using quantile g-computation (Keil et al., 2020). Quantile g-computation calculates a weighted sum of all phthalate biomarkers based on their quantiles, then estimates the effect of increasing all exposures by one quantile simultaneously on the outcome, conditional on covariates, using a generalized linear mixed model implementation of g-computation with a random intercept for subject. We converted phthalate biomarkers into quartiles and ran 1000 bootstraps to estimate confidence bounds of the overall mixture effect. This can be interpreted as either the relative risk of membership in a trajectory class in comparison to the reference class per quartile increase in total phthalates or, for the continuous longitudinal outcomes, as the effect of increasing the total phthalates by one quartile on child BMI z-score, WHtR, or FMI.

2.5.5 Sensitivity Analyses—To determine if trimester-specific associations were driving our results, we repeated analyses with 2nd and 3rd trimester phthalate biomarkers. We also repeated multinomial logistic regression and linear mixed-effect models with each phthalate biomarker in separate models to determine the impact of co-exposure confounding on our results. We altered the number of trajectories from three to two or four to determine the robustness of our results under alternative specifications of the trajectories.

All statistical analysis were conducted using R software version 3.5.1 (R Core Team, 2018) and statistical significance was assessed at alpha = 0.05.

3. Results

3.1 Study Participant Characteristics

At enrollment, mothers were on average 27.7 years of age, of lower socioeconomic status, and with less than a high school education (Table 1). Of the 514 children included in the analysis 455 children attended all three visits and 59 children attended the four-year visit and either follow-up visit. Maternal characteristics at enrollment of children included in the analysis did not materially differ from those who were excluded (Supplemental Table S2). Average child BMI z-scores, fat mass, and FMI increased across follow-ups, while WHtR remained constant (Table 1). Adiposity outcomes were highly correlated within visits (Pearson's r = 0.82 – 0.92) (Supplemental Figure S1). Intraclass correlation coefficients for BMI z-score, FMI and WHtR were 0.73, 0.51 and 0.64, respectively.

MEP and ΣDEHP had the highest concentrations in maternal urine during pregnancy (Supplemental Table S3). Phthalate biomarkers had low to moderate correlations (Pearson's r = 0.12 – 0.75) (Supplemental Figure S2). The lowest correlations were observed between MEP and other biomarkers (r = 0.12 – 0.27) and the highest correlation was detected between MCPP and ΣDBP metabolites (r = 0.75). Women included in our analyses had lower urinary MCPP, ΣDBP, ΣDiBP and MBzP concentrations than women whose child missed the four-year follow-up (Supplemental Table S3).

3.2 Childhood adiposity trajectories from four to twelve years

We characterized three trajectories of childhood adiposity based on non-centered and centered outcomes. For non-centered outcomes, we identified a "low-stable" (N = 260), a "low-high" (N = 147), and a "high-high" (N = 107) class within our population (Figure 1A). The "low-stable" class was characterized by average starting BMI z-scores of approximately zero. BMI z-scores and FMI remained stable through 12 years, while WHtR decreased slightly over time. The "low-high" class was characterized by adiposity indicators that remained low through the six-year visit, then increased sharply from six years to eight years. Children in the "high-high" class started with the greatest values for each adiposity outcome. In the "high-high" class, BMI z-scores and WHtR increased early then stabilized, while FMI increased steadily.

Centered trajectories characterized a "stable" class (N = 221), a "slow increasing" (N = 175), and a "high increasing" (N = 118) class (Figure 1B). The "slow increasing" class remained stable until the six-year visit then increased, while the "high increasing" increased immediately after the first visit. While there was considerable overlap between the "stable" and "low-stable" trajectory classes, the increasing and higher adiposity classes were more dissimilar (Supplemental Table S5).

3.3 Phthalate-specific and overall mixture associations with childhood adiposity trajectories and overall adiposity

ΣDEHP was associated with increased odds of being in the "high-high" class (Adjusted Odds Ratio = 1.53 [1.08, 2.19]; p = 0.02), but with lower odds of being in the "low-high" class (0.73 [0.52, 1.00]; p = 0.05) in comparison to the "low-stable" group (Figure 2A). A

doubling of ΣDiNP was also associated with 1.43 (1.02, 2.02) greater odds of being in the "low-high" class (p = 0.04). A doubling in MCNP resulted in 0.66 (0.45, 97) lower odds of being in the "low-high" trajectory (p = 0.03). For centered adiposity trajectories, MCNP was borderline associated with lower odds of being in the "slow increasing" class (0.70 [0.48, 1.01]; p = 0.06) (Figure 2B). When individual adiposity outcomes were examined longitudinally throughout childhood, prenatal urinary MCNP was also negatively associated with child BMI z-score (−0.18 [−0.36, 0.002]; p = 0.05) (Figure 2C). Total prenatal phthalate biomarkers were not associated with childhood adiposity (Table 2). The greatest positive weights were observed for ΣDEHP (0.72 – 0.51), whereas the greatest negative weights were observed for MCPP (−0.68 – −0.06) (Supplemental Figure S3).

3.4 Sex-Specific Associations

Adiposity trajectories for male and female children were highly similar (Supplemental Figure S4), with no meaningful differences between the number of males and females in each class (Supplemental Table S6). We observed no sex-specific associations between urinary phthalate biomarkers and adiposity trajectories (Supplemental Figure S5A–B). MCPP concentrations were negatively associated with FMI (−0.58 [−1.04, −0.12]; p = 0.02) and WHtR (−0.015 [−0.026, −0.003]; p = 0.02) in males but not in females (0.21 [−0.30,0.32] for FMI; and 0.007 [−0.006,0.019] for WHtR). Similar to the results in the full population, no mixture associations were observed (Supplemental Table S7 and Supplemental Figure S6).

3.5 Sensitivity Analyses

Correlations between phthalate metabolite concentrations measured in the 2nd and 3rd trimesters were low to moderate depending on the metabolite (Pearson's R = 0.16 – 0.39; Supplemental Figure S7). Evaluating 2nd and 3rd trimester phthalate biomarkers separately revealed no meaningful trimester-specific differences (Supplemental Figure S8). Specifying separate models for each individual phthalate biomarker resulted in slightly attenuated effect estimates for associations with trajectory class membership, though the direction of effect was retained (Supplemental Figure S9A and S9B). The association between MNCP concentrations and longitudinal BMI z-score was attenuated (Supplemental Figure S9C). Specifying two to four adiposity trajectory classes produced similar groups as in the main analyses (Supplemental Figure S10–S13). The overall associations of phthalate biomarkers with trajectory classes remained consistent.

4. Discussion

4.1 Trajectories of Childhood Adiposity

Modeling strategies using centered and non-centered outcomes provide similar yet distinct insight into changes in child adiposity. Adiposity indicators that are not centered at the earliest visit capture children who may already have elevated adiposity at the start of follow-up, reflecting increases in adiposity prior to four years. We observe this phenomenon in the "high-high" class of children. In contrast, by examining centered adiposity outcomes, we are able to profile children who have the greatest changes in BMI independent of starting values.

Several studies have observed childhood adiposity trajectories similar to those presented here that are predictive of later life cardiometabolic health risk (Blond et al., 2020; Lycett et al., 2020; Norris Tom et al., 2021). Australian children in early and late rising BMI groups had greater atherogenic lipoprotein expression at age fourteen years in comparison to a normal BMI group, although those who were early risers had worse cardiometabolic profiles (Barraclough et al., 2019), suggesting that the trajectories identified here are relevant for later cardiometabolic risk. Others populations demonstrate that although all overweight trajectories associate with increased cardiometabolic risk in adulthood in comparison to normal classes, the trajectory classes that start normal then increase to obesity have worse cardiometabolic profiles than trajectories that started with a higher BMI (Norris Tom et al., 2021). Furthermore, membership in moderate and high BMI trajectories in childhood was associated with greater risk of hypertension, type 2 diabetes, and dyslipidemia (Yuan et al., 2020). Taken together, these studies suggest that we were able to identify trajectories that provide meaningful insight into future cardiometabolic risk.

4.2 Comparison of Prenatal Phthalates and Childhood Adiposity to Previous Literature

A growing number of studies have examined associations between prenatal phthalates exposures and childhood adiposity with inconsistent results, which may be due to differences in biomarker concentrations or developmental timing of exposures, the metabolites quantified, timing of follow-up, or other population characteristics. A recent review on the effects of early life DEHP exposures on rodent obesity found a significant positive effect on fat weight and a nonsignificant negative effect on body weight (Wassenaar and Legler, 2017). Population studies have reported positive (Harley et al., 2017), exposure timing-dependent (Shoaff et al., 2017), and nonlinear associations (Yang et al., 2018) with prenatal DEHP biomarker concentrations. Although we observed no differences by sex, studies have reported opposing associations between prenatal ΣDEHP and adiposity in boys and girls, however, results vary between studies (Buckley et al., 2016a; Vafeiadi et al., 2018). Furthermore, experimental research has found obesogenic effects of DEHP only in males (Fan et al., 2020) or only in females (Klöting et al., 2015; Neier et al., 2019b). That we did not observe any sex-specific associations may be due to our small sample size when stratifying the population by sex. Future studies on sex-specific associations of phthalates with adiposity trajectories would benefit from a larger population.

We also observed greater odds of being in the “low-high” adiposity class with increasing ΣDiNP concentrations. DiNP has been used as an industrial alternative for DEHP. Mice perinatally exposed to DiNP have greater body weights (Neier et al., 2019a), as well as greater abdominal circumference accompanied by sex-specific changes in fatty acid, lipid, and cholesterol composition (Huang et al., 2019; Yang et al., 2021). Human population studies investigating associations between prenatal concentrations of DiNP metabolites, such as MCOP, with childhood adiposity have reported either null (Berman et al., 2020; Harley et al., 2017) or weakly positive (Berger et al., 2021) associations. More research on DiNP is needed to determine its potential as an environmental obesogen.

Finally, we observed an association between prenatal MCNP, a metabolite of DiDP, and lower odds of being in the “slow-increasing” class and a negative association with BMI

z-score. One study observed positive associations between prenatal MCNP and odds of being overweight/obese at five years of age (Berger et al., 2021), suggesting the importance of further research on DiDP to evaluate its potential impacts on child health.

We observed little evidence for an association of the total prenatal phthalate biomarker mixture with childhood adiposity, which could be explained opposing directions of effect by different phthalate biomarkers as shown by biomarker weights. To date, few studies have investigated mixture associations of phthalate metabolites. One study found that the sum of five high-molecular-weight phthalate metabolites was associated with lower BMI z-scores in boys and higher BMI z-scores in girls at 4 and 7 years of age (Valvi et al., 2015). We also previously observed negative associations between the prenatal phthalate biomarker mixture and child triglycerides and non-high density lipoprotein levels in the PROGRESS cohort (Kupsco et al., 2021).

4.3 Potential Mechanisms of Action

Exposure to environmental stressors during pregnancy can program future child health via effects on developing cells (La Merrill and Birnbaum, 2011). Obesogenic impacts of phthalates may arise from their role as peroxisome-proliferator-activated receptor (PPAR) agonists (Hao et al., 2012). Mono-2-ethylhexyl phthalate (MEHP), the hydrolytic monoester metabolite of DEHP, activates human and rodent PPARα and PPARγ receptors *in vitro*, leading to expression of key PPAR target genes and metabolites (Ellero-Simatos et al., 2011; Feige et al., 2007; Hurst and Waxman, 2003). Prenatal MEHP concentrations may also activate PPARγ responses *in vivo* (Hao et al., 2012). DEHP replacements, DiNP and DiDP, induced adipocyte differentiation and expression of adipocyte specific genes *in vitro*, potentially via binding of PPARγ (Pomatto et al., 2018; Zhang et al., 2019). *In silico* analyses of phthalate binding to human PPAR subtypes found that DiDP had high affinity for PPARγ (Josh et al., 2014). The effects of DiNP on rodent liver hepatocyte proliferation, palmitoyl-CoA oxidase activity, and enzymes involved in β- and ω-oxidation of fatty acids were also found to be PPARα dependent (Valles et al., 2003). Aberrant activation of the PPAR signaling pathways during early development may result in long term disruption of adipose tissue metabolism leading to altered childhood adiposity.

4.4 Strengths and Limitations

This study has several strengths, including implementation of a sophisticated trajectory modeling approach to provide new information on the impact of prenatal phthalates exposures on childhood adiposity and use of a novel mixture method to assess the overall effects. We characterized a mean measure of phthalate biomarker concentrations from two prenatal time points, which may be more reliable than measures from a single spot urine sample. Phthalate biomarker concentrations vary throughout pregnancy, from day to day, and within a 24-hour period (Johns et al., 2015; Wu et al., 2020). In the present analysis, the phthalate biomarker concentrations measured in the 2nd to 3rd trimester were only weakly correlated, indicating that individual spot measures are likely unreliable. However, while residual measurement error is likely present, our sensitivity analyses of 2nd and 3rd trimester phthalate biomarker concentrations did not reveal substantial differences in associations between trimesters.

Although we adjusted for a number of relevant confounders in our analyses, our associations may be impacted by residual or unmeasured confounding. Consumption of packaged and processed foods is a source of phthalates exposure (Buckley et al., 2019), and an unhealthy diet during pregnancy may contribute to childhood adiposity via maternal BMI or other cardiometabolic factors. Unfortunately, prenatal dietary information was unavailable in this cohort. Furthermore, we were unable to account for certain negative confounders, which may contribute to certain null findings. For instance, over the counter supplements can be an important source of phthalates exposures (Kelley et al., 2012); however, maternal supplement use may indicate a greater health consciousness that could result in lower childhood adiposity. Similarly, electronics have been demonstrated to also contain phthalates (Yang et al., 2020); however, high electronics use may also be indicative of a higher socioeconomic status that was not captured by our SES variable. Because our adiposity measures were collected beginning at four years, we were unable to examine infant peak adiposity or adiposity nadir, which are also relevant for cardiometabolic risk (Aris et al., 2019). Finally, our study population consisted of Mexican children and may not be generalizable to other populations.

5. Conclusions

In sum, prenatal urinary concentrations of biomarkers of three high molecular weight phthalates were associated with differing trajectories of mid-childhood adiposity, which may be relevant for adult cardiometabolic risk. However, we observed no evidence for an association of the phthalate biomarker mixture, nor any robust sex-specific effects suggesting that research in larger, diverse populations is necessary to fully understand the impacts of prenatal phthalate exposures on childhood adiposity. Future research should explore the contribution of childhood lifestyle factors, such as physical activity and diet, to these associations and how they may modify the impact of prenatal phthalates exposures on child adiposity. Furthermore, analysis of the pathways that may be mediating this relationship, such as birthweight or timing of pubertal onset, would provide greater insight into the factors contributing to our findings. Finally, additional analysis with growth trajectories from birth through adolescence would provide stronger evidence for the ability of the prenatal environment to shape adult cardiometabolic risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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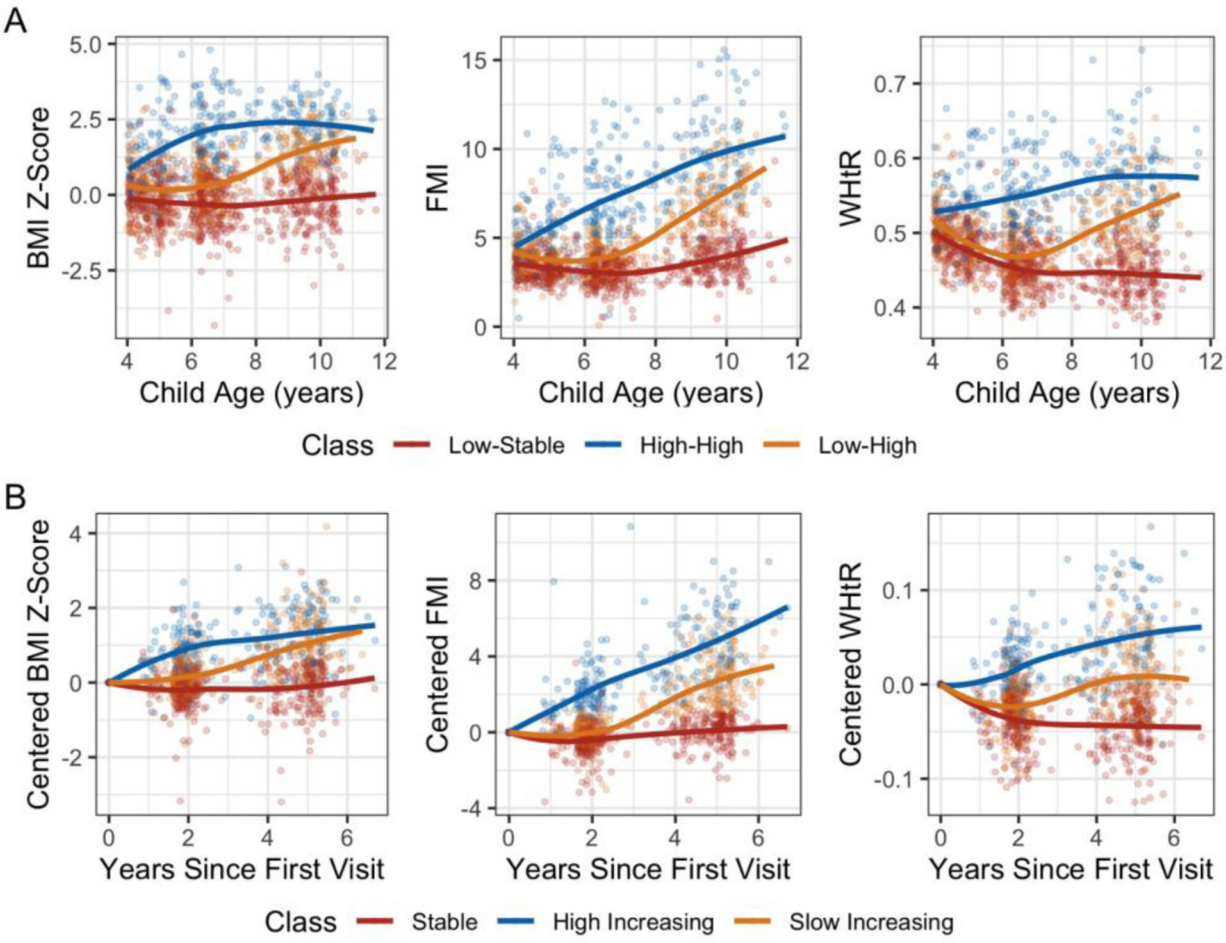

Figure 1.

Adiposity trajectory classes identified by latent class growth modeling for A) non-centered BMI z-score, FMI and WHtR, and B) first visit centered BMI-zscore, FMI, and WHtR. Colors indicate class membership (red: “low-stable”/”stable”, blue: “high-high”/”high-increasing” and orange: “low-high”/”slow increasing”) and smooth loess curves describe the trend of each trajectory. LCGM models for non-centered adiposity outcomes included linear and quadratic fixed effects for child age at follow-up, random intercepts for age and subject and link functions of 3 quantile splines on each adiposity outcome. LCGM models for centered adiposity outcomes included: linear and quadratic terms for age centered at the 4-year visit, random intercepts for subject, 4 equidistant splines on BMI z-score and FMI, and a linear link function on WHtR.

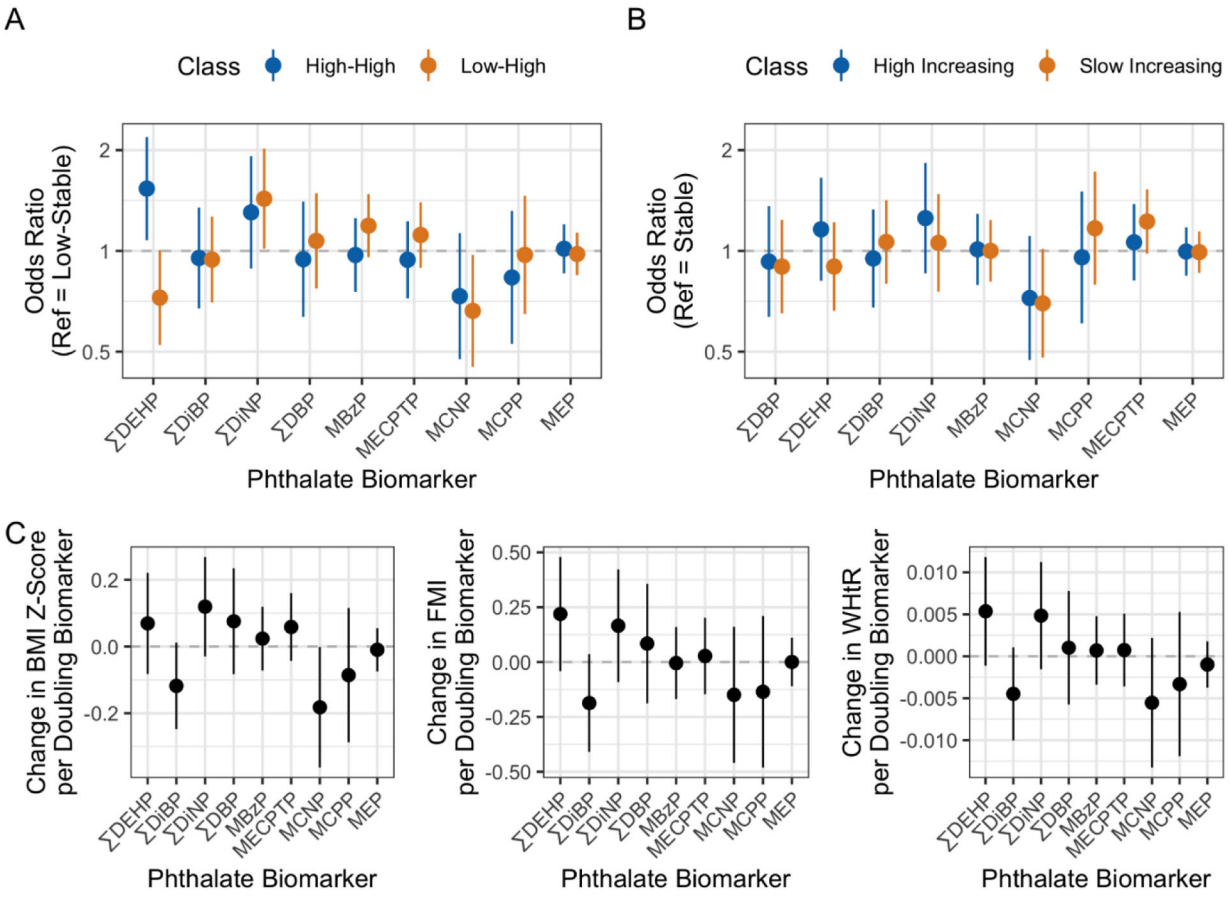

Figure 2.

Associations of 2nd and 3rd trimester geometric mean urinary phthalate metabolites with A) non-centered adiposity trajectory classes, B) centered adiposity trajectory classes, and C) overall BMI z-score, fat mass index (FMI) and WHtR (waist-to-height ratio), using multinomial logistic regression with the “low-stable” and “stable” classes as the reference groups (A and B, respectively), or linear mixed-effects models (C). Logistic regression model estimates are presented as odds ratios per doubling of metabolite concentrations with 95% confidence intervals (CI’s). Colors represent the comparison classes (blue: “high-high” or “high-stable”; yellow: “low-high” or “high increasing”. Linear mixed-effects models are presented as the change in outcome per doubling of phthalate biomarker with 95% CI’s. All models included all 9 phthalate biomarkers and were adjusted for maternal age, maternal pre-pregnancy BMI, parity, socioeconomic status, education, child sex, and date and phthalate measurement. Mixed-effects models were additionally adjusted for linear and quadratic terms for child age at visit.

Table 1.

Characteristics of PROGRESS children included at each follow-up visit.

	Four year visit		Six year visit		Eight year visit	
	N	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**
Child Age (years)	514	4.8 ± 0.57	506	6.7 ± 0.57	463	9.7 ± 0.67
Height (cm)	514	106 ± 5.4	506	118 ± 6.0	463	135 ± 7.5
Waist Circumference (cm)	514	52.6 ± 5.3	506	56.4 ± 7.7	463	67.3 ± 10.7
Waist to Height Ratio	514	0.5 ± 0.04	506	0.48 ± 0.05	463	0.5 ± 0.07
BMI Z-score	514	0.23 ± 1.1	506	0.4 ± 1.3	463	0.87 ± 1.3
Fat Mass (kg)	511	4.4 ± 1.9	505	6.0 ± 3.5	462	11.3 ± 6.0
Fat Mass Index (kg/m^2)	511	3.9 ± 1.5	505	4.2 ± 2.1	462	6.0 ± 2.8
Child Sex						
Female	258	50.2	256	50.6	234	50.5
Male	256	49.8	250	49.4	229	49.5
Maternal Characteristics at Enrollment	**Four year visit Population**		**Six year visit Population**		**Eight year visit Population**	
Age (years)	514	27.7 ± 5.7	506	27.8 ± 5.7	463	27.7 ± 5.7
Pre-Pregnancy BMI (kg/m^2)	514	26.4 ± 4.1	506	26.4 ± 4.1	463	26.5 ± 4.1
Parity						
Multi-parous	320	62.3	314	62.1	290	62.6
Primi-parous	194	37.7	192	37.9	173	37.4
Socioeconomic Status						
Low	267	51.9	261	51.6	243	52.5
Medium	195	37.9	193	38.1	176	38
High	52	10.1	52	10.3	44	9.5
Education						
Less than High School	208	40.5	203	40.1	188	40.6
High School	180	35	178	35.2	165	35.6
More than High School	126	24.5	125	24.7	110	23.8

Table 2.

Associations of a quartile increase in the total phthalates mixture with overall adiposity and adiposity trajectories as measured by quantile g-computation (N = 514).

Model Type	Outcome	Rate Ratio/ Effect Estimate (95% CI)*	P Value
Centered Trajectories	Stable (N = 221)	1.00 (Ref)	
	High Increasing (N = 118)	1.12(0.94, 1.35)	0.19
	Slow Increasing (N = 175)	0.99 (0.85, 1.14)	0.90
Non-Centered Trajectories	Low Stable (N = 260)	1.00 (Ref)	
	Low-High (N = 147)	1.01 (0.85, 1.19)	0.93
	High-High (N = 107)	1.07 (0.87, 1.31)	0.51
Overall Adiposity	BMI Z-score	0.02 (−0.10, 0.14)	0.73
	FMI	0.08 (−0.13, 0.28)	0.47
	WHtR	0 (0, 0)	0.93

*All models adjusted for maternal age, maternal pre-pregnancy BMI, parity, socioeconomic status, education, child sex, and date and phthalate measurement. Mixed-effects models were additionally adjusted for linear and quadratic terms for child age at visit.