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Fetal and Infancy Exposure to Phenols, Parabens, and Phthalates and Anthropometric Measurements up to 36 Months, in the Longitudinal SEPAGES Cohort

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BACKGROUND: Endocrine-disrupting chemicals may play a role in adiposity development during childhood. Until now literature in this scope suffers from methodologic limitations in exposure assessment using one or few urine samples and missing assessment during the infancy period.

OBJECTIVES: We investigated the associations between early-life exposure to quickly metabolized chemicals and post-natal growth, relying on repeated within-subject urine collections over pregnancy and infancy.

METHODS: We studied the associations of four phenols, four parabens, seven phthalates, and one nonphthalate plasticizer from weekly pooled urine samples collected from the mother during second and third trimesters (median 18 and 34 gestational weeks, respectively) and infant at 2 and 12 months of age, and child growth until 36 months. We relied on repeated measures of height, weight and head circumference from study visits and the child health booklet to predict growth outcomes at 3 and 36 months using the Jenns-Bayley nonlinear mixed model. We assessed associations with individual chemicals using adjusted linear regression and mixtures of chemicals using a Bayesian kernel machine regression model.

RESULTS: The unipollutant analysis revealed few associations. Bisphenol S (BPS) at second trimester was positively associated with all infant growth parameters at 3 and 36 months, with similar patterns between exposure at third trimester and all infant growth parameters at 3 months. Mono-*n*-butyl phthalate (MnBP) at 12 months was positively associated with body mass index (BMI), weight, and head circumference at 36 months. Mixture analysis revealed positive associations between exposure at 12 months and BMI and weight at 36 months, with MnBP showing the highest effect size within the mixture.

CONCLUSIONS: This study suggests that exposure in early infancy may be associated with increased weight and BMI in early childhood, which are risk factors of obesity in later life. Furthermore, this study highlighted the impact of BPS, a compound replacing bisphenol A, which has never been studied in this context. <https://doi.org/10.1289/EHP13644>

Introduction

Phenols, parabens and phthalates are endocrine-disrupting chemicals (EDCs) used in plastics, lining of food cans, toys, and personal care products, among others.¹ Given their widespread use, exposure is ubiquitous.^{2–4}

EDCs can interfere with the endocrine system through pathways involving nuclear receptors implicated in the control of adipogenesis and weight gain^{5,6} and thus may play a role in obesity development.⁷ A growing body of literature has investigated the associations between short half-life EDCs and body mass index (BMI) in childhood, with inconclusive results. As an example, two meta-analyses on the associations between phthalate exposure and BMI during childhood had divergent conclusions, with one suggesting decrease of BMI z-score with prenatal exposure but no association with postnatal exposure and the other including studies

with pre- and postnatal exposure in the same model reporting an increased BMI in childhood.^{8,9} Furthermore, some studies have suggested a gender-specific effect of EDCs on anthropometric measures and obesity (reviewed by Ribeiro et al.¹⁰).

Methodological limitations in exposure assessment from too few urine samples collected may partly explain these mixed epidemiological results. Phenols, parabens, and phthalates are quickly metabolized and excreted in urine. Their half-lives are generally estimated to be <24 h in humans.^{11–15} This and the temporal variability in exposure during and between days (diet, use of personal care products, for example) lead to high within-subject temporal variability of urinary metabolite concentrations.⁴ Most studies examining their health effects used one or few urine samples to measure their metabolite concentrations leading to measurement error and bias in dose–response functions.¹⁶ Repeated sample collection, possibly followed by pooling of multiple samples, is a way to reduce such bias for those compounds with high within-subject variability.^{17,18}

Furthermore, most studies investigating the associations between EDCs and adiposity in childhood focused on prenatal or childhood exposure (children 3 y of age or older) and were missing exposure during infancy, a critical period when EDCs may alter the programming of the metabolic system, leading to susceptibility for weight gain and risk of obesity in later life.¹⁹ In addition, for some compounds, such as DINCH (1,2-Cyclohexane dicarboxylic acid, diisononyl ester) used in replacement of high molecular weight phthalates,²⁰ which has never been studied in relation to childhood growth, exposure level during infancy has been shown to be equivalent to or even higher than those experienced in adulthood.³ Studies on other substitutes, such as bisphenol S (BPS), are also scarce. Most studies have investigated the association of single chemicals,

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whereas the joint effect of the overall mixture of EDCs on child growth has been poorly investigated.²¹ The few studies assessing mixture effects lacked exposure data during infancy.^{22–24}

Our objective was to investigate the associations between early-life exposure to EDCs and postnatal growth, using repeated within-subject urine collections during pregnancy and early infancy, including assessment of new EDCs such as BPS and DINCH metabolites. We assessed the effect of individual chemicals and mixtures of chemicals. We also examined whether infant sex was an effect modifier.

Methods

Study Population

This study was based on the SEPAGES [Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effet sur la Santé (Assessment of Air Pollution Exposure during Pregnancy and Effect on Health)] cohort in which 484 pregnant women were recruited in the area of Grenoble, France.²⁵ Women were enrolled between July 2014 and July 2017 before 18 gestational weeks and followed up until delivery. At baseline and at each trimester of their pregnancy, women either filled out questionnaires or underwent questionnaire administration to gather data on sociodemographic factors, medical history, treatments employed, tobacco usage, passive smoking exposure during pregnancy, home attributes, dietary patterns, and sleep duration.²⁵ To be included women had to be older than 18 y of age, with a singleton pregnancy, be enrolled in the French social security system, speak and write French, plan to give birth in one of the four maternity wards of the Grenoble urban areas, and to not plan to live outside the Grenoble urban area within 2 y.

Both parents gave informed consent to participate. The SEPAGES study was approved by the relevant ethical committees [CNIL, Commission Nationale de l'Informatique et des Libertés (National Commission on Informatics and Liberty); CCTIRS, Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (Advisory Committee on the Treatment of Information on Research in the Field of Health); CPP, Comité de Protection des Personnes Sud-Est (South-East Ethics Committee)].

Urine Collection and Exposure Assessment

Women were asked to collect three urine samples per day (morning, midday, evening) during 7 consecutive days twice during pregnancy, at approximately the second and third trimesters [median 18; interquartile range (IQR): 16–19; and 34 (IQR: 32–35) gestational weeks, respectively]. Then, women were asked to collect a urine sample from their child once a day during 7 consecutive days at 2 months of age [median 7 (IQR: 6.3–8.3) wk] and 12 months [median 52.9 (IQR: 51.7–54.7) wk] using a cotton pad inserted in the diaper.²⁵

Urine samples were then pooled within subject and within period using a previously described and validated protocol.^{16–18} In brief, equal volumes of all the samples collected over a given collection week were pooled to obtain one weekly pool per subject. Number of urine sample per pool are presented in Table 1.

An aliquot of each pool was sent on dry ice with a temperature sensor to the Norwegian Institute of Public Health, where 8 phenols,² 4 parabens,² 13 phthalate metabolites³ (corresponding to seven parent compounds), and two DINCH metabolites³ were measured (Excel Table S1). Phenols and parabens were measured using ultra-performance liquid chromatography coupled to mass spectrometry (UPLC-MS/MS),²⁶ and phthalates and DINCH metabolites were measured using high-performance

Table 1. Description of the study population from the SEPAGES cohort ($n = 364$,^a 2014–2017, France).

Characteristics	Median (percentile 25, 75) or n (%)
Maternal age at inclusion (y)	32.3 (30.0, 35.2)
Maternal weight before pregnancy (kg)	59.0 (53.4, 66.0)
Maternal height (cm)	164.6 (160.9, 169.2)
Maternal education (years after high school) (2 missing)	
Up to 3 y	57 (15.7%)
4 y or more	305 (84.3%)
Maternal ethnicity (3 missing)	
Caucasian	351 (97.2%)
Other	10 (2.8%)
Parity	
Nulliparous	165 (45.3%)
Parous	199 (54.7%)
Father weight (kg) (33 missing)	75.7 (69.3, 83.4)
Father height (cm) (37 missing)	178.5 (174.6, 182.2)
Child sex	
Male	194 (53.3%)
Female	170 (46.7%)
Child still breastfed at 3 months of life (9 missing)	
Yes	292 (82.3%)
No	63 (17.7%)
Child exposure to tobacco smoke from <i>in utero</i> to 2 months (28 missing)	
Yes	48 (14.3%)
No	288 (85.7%)
Child age at the 3 y clinical visit (year) (39 missing)	3.1 (3.0, 3.1)
Child BMI (kg/m ²)	
Predicted at 3 months	16.1 (15.4, 16.9)
Predicted at 36 months	15.6 (14.9, 16.4)
Measured at 3 y clinical visit (39 missing)	16.1 (15.2, 16.9)
Child weight (kg)	
Predicted at 3 months	5.8 (5.5, 6.2)
Predicted at 36 months	14.0 (13.2, 15.2)
Measured at 3 y clinical visit (39 missing)	14.3 (13.5, 15.6)
Child height (cm)	
Predicted at 3 months	60.4 (59.0, 61.7)
Predicted at 36 months	95.0 (92.9, 96.9)
Measured at 3 y clinical visit (38 missing)	95.3 (93.0, 97.3)
Child head circumference (cm)	
Predicted at 3 months	40.4 (39.8, 41.2)
Predicted at 36 months	49.7 (49.0, 50.6)
Measured at 3 y clinical visit (41 missing)	49.6 (48.7, 50.5)
Number of measurements included in the prediction models	
Child weight	14 (12, 16)
Child height	14 (12, 15)
Child head circumference	13 (11, 15)
Number of urine sample per pool	
Second trimester of pregnancy	21 (20, 21)
Third trimester of pregnancy	21 (20, 21)
2 months of age	7 (6, 7)
12 months of age	6 (5, 7)
Age at the begging of each measurement week (wk)	
Gestational age at measurement week T2	17.6 (16.4, 18.7)
Gestational age at measurement week T3	33.9 (32.0, 35.1)
2 months of age (1 missing)	7.0 (6.3, 8.3)
12 months of age (1 missing)	52.9 (51.7, 54.7)

^aMother-child pairs with biomarker concentrations measured in four pools of urine samples and predicted child growth.

liquid chromatography coupled to tandem mass spectrometer (HPLC-MS/MS).²⁷

At 2 months of age, phthalate and DINCH metabolites were assessed in only a subset of infants ($n = 152$) due to budget constraints³; thus this time point was not considered for this substance family in the current analysis.

Previous analyses relying on free and conjugated concentrations, showed that no external contamination was observed for prenatal samples, nor for neonatal and infant samples, with the exception of bisphenol A (BPA) at 2 and 12 months, and methylparaben at 12 months.² Thus, for these specific chemicals/timing, both total and conjugated concentrations were reported for the unpollutant models; however, only total concentrations were entered in the mixture model.

Postnatal Growth

Child weight, height, and head circumference were measured at birth by the medical maternity staff and during study visits at 2, 12, and 36 months by a trained SEPAGES fieldworker. In addition, all weight, height, and head circumference measurements performed by health care practitioners on children between 0 and 36 months of age were copied from the child's health booklet (a booklet that, in France, contains all the medical information necessary to monitor the health of the child up to the age of 18 y and is routinely completed by health care practitioners).

For each child, weight, height, and head circumference were predicted at 3 and 36 months by fitting the Jemss-Bayley growth model using all available measurements, with the exception of weight measurements during the postnatal weight-loss period (from birth to day 3) because the model assumes a monotonic shape.^{28–30} We used a mixed effect approach³¹ to account for the heterogeneity in the number of measurements (from the child's health booklet, because of missed study visits or loss to follow-up). Many studies have shown that this model performed well in comparison with others in different populations,^{28,32–34} and especially in different child cohort studies in France.^{28,34} It allows researchers to model growth curve trajectories for children with a number of measurements lower than the number of parameters in the model (which is not possible with an individual modeling approach) by shrinking them toward the mean trajectory. We selected the children with at least two measures to reduce the uncertainty about the individual growth trajectories. Then the curve trajectories were used to predict weight, height, and head circumference at 3 and 36 months. We chose 3- and 36-month time points because they are predictive of the risk of obesity in later life,³⁴ and 36 months was the oldest age with available growth measurements when this work was initiated. Then, BMI was calculated at 3 and 36 months from predicted weight and height as weight/height² in kg/m².

Statistical Analysis

We included all mother–child pairs with chemical urinary concentrations for all four time windows (three for phthalate and DINCH metabolites) and with growth prediction [$n = 364$ (75%); Supplementary Figure S1]. Mother–child pairs not included in the analysis lacked data regarding exposure during pregnancy (5 women did not provide urine samples during pregnancy, 2 did not provide urine samples during the second trimester, and 23 did not provide urine samples during the third trimester) and infancy (18 with no urine sample at both 2 and 12 months, 16 did not provide urine samples at 2 months, and 56 did not provide urine samples at 12 months of age).

Triclocarban and bisphenols AF, B, and F were quantified in <5% of urine samples and were therefore excluded from further analyses. Chemicals with 30% or more values below the limit of detection (LOD) (BPS and butylparaben) were categorized as below the LOD, from the LOD to limit of quantification (LOQ), and above the LOQ; other chemicals were log-transformed. For the remaining chemicals, concentrations below the LOD and between the LOD and LOQ were imputed by values randomly drawn between 0 and the LOD and between the LOD and the LOQ,

respectively, following the underlying distribution of concentrations.^{35,36} Between-sample variations in urine processing and assay conditions were addressed through a two-step standardization approach^{30,37}: first, identifying factors potentially affecting biomarker levels (sample transport time, thaw time, and analytical batches) using multiple linear regressions adjusted for potential confounders (maternal age, education, prepregnancy BMI, parity, date, season, and specific gravity), considering Wald's p -value <0.20 as significant (Excel Table S2)³⁸; second, for each biomarker we subtracted the β values associated with the conditions from the measured concentrations.

Molar sums of metabolites (unit: μ moles/L) from the same parent compounds were computed as follows:

Diisononyl phthalate [Σ DiNP] = $ohMiNP/308.2 + oxoMiNP/306.2 + cx-MiNP/322.2$, Di(2-ethylhexyl) phthalate [Σ DEHP] = $MEOHP/292 + MECPP/308 + MEHP/278 + MEHHP/294 + MMCHP/308.3$, DINCH = $ohMINCH/314.42 + oxoMINCH/312.4$ and used in all the analyses instead of individual concentrations.

Chemicals concentrations were not adjusted for marker of urine dilution (either specific gravity or creatinine) because it has been suggested that such markers classically used when relying on spot samples are not necessary or even counterproductive for pooled samples.¹⁷

The comparison between included and excluded women from the analysis was performed using Kruskal-Wallis test for continuous variables and chi-squared for categorical variables. Pearson correlations were calculated between infant growth parameters and between urinary chemicals concentrations.

First, we investigated the associations between the individual chemicals at each time point (second and third trimesters, 2 and 12 months of age) and growth prediction at 3 and 36 months, separately for BMI, weight, height, and head circumference, using linear regressions adjusted for potential confounders (listed below). Betas are given for one unit increase in ln-transformed chemicals; in other words, betas correspond to a 2.72-fold increase in chemical concentrations. We report all associations with $p < 0.05$ in the "Results" section. Associations with p -values between 0.05 and 0.10 were also reported as a trend when the chemical was associated ($p < 0.05$) with another growth parameter.

Then, we investigated the overall effect of the chemical mixtures using a Bayesian kernel machine regression (BKMR) approach with 50 000 iterations with the Markov chain Monte Carlo (MCMC) algorithm.³⁹ This model allows researchers to adequately consider the complexity of the implications of chemical mixtures on postnatal growth parameters, taking into account correlated chemicals, their potential interaction, and nonlinear associations. For each postnatal growth time point, we evaluated the overall association, simultaneously taking into account all the exposure time points using a hierarchical variable selection BKMR (hBKMR) for which chemicals were grouped by time of measurement.⁴⁰ We then also estimated the effect of the chemical mixture at each timing of exposure separately (one model for each timing of exposure). The overall mixture effect was given by a figure showing the expected change in postnatal growth parameter with concomitant increase in quantiles of all exposure biomarkers in comparison with no exposure. When this graph was suggestive of an effect, we provided the posterior inclusion probability (PIP) for each chemical representing their relative importance and plotted the estimated effect of an increase from the 25th to 75th percentile in a single chemical concentration when all other chemical concentrations were fixed at either their 25th, 50th, or 75th percentiles.

For the BKMR analysis all chemicals were entered as continuous and scaled; for BPS and butylparaben (chemicals with more

than 30% of values below the LOD), we kept machine-measured values above the LOD and replaced values below the LOD by the LOD/ $\sqrt{2}$, because BKMR does not accommodate for categorical exposure.

All analyses (linear regression for unipollutant model and BKMR for mixture analysis) were adjusted for following potential confounders: maternal age (<35 vs. ≥ 35 y at inclusion), maternal prepregnancy weight (continuous), maternal height (continuous), paternal weight (continuous), paternal height (continuous), parity (nulliparous vs. parous), breastfeeding status [binary for outcomes assessed at 3 months (still breastfeeding at 3 months, Yes vs. No), or continuous (in weeks) for outcomes assessed at 36 months], maternal education (up to 3 y vs. 4 or more years after high school), child sex (males vs. females), infant history of passive smoking [include *in-utero* passive smoking (i.e., maternal smoking during pregnancy), Yes vs. No]. The coding of adjustment factors was based on their relationship with the outcomes identified using semiparametric modeling approaches and selected by the lower Akaike Information Criterion (AIC).⁴¹ Imputation of missing values were performed for covariates using the median for continuous variables [father height ($n = 37$), father weight ($n = 33$), and breastfeeding duration ($n = 9$)] and the mode for categorical variables [breastfeeding at 3 months ($n = 9$), maternal educational level ($n = 2$), and infant history of passive smoking ($n = 28$)].

We further assessed the potential effect modification by infant sex, for linear regressions we added an interaction term between exposure and child sex. Sex-stratified analysis was performed for p -values of interaction <0.1, except for BPS and butylparaben, which presented a sample size in some categories that was too small to be stratified. For BKMR analysis, because testing interaction with the mixture was not possible, all models were sex-stratified. This analysis was motivated by the fact that sex-specific effect of EDCs on anthropometric measures and obesity has been previously suggested.¹⁰

In sensitivity analyses, linear regression analyses for individual chemicals were further *a*) performed after removing for exposure and outcome all values below first and above 99th percentiles to investigate effects of extreme values; *b*) performed on the measured weight, height, head circumference and BMI at the SEPAGES clinical study visit at 36 months of age; *c*) adjusted for specific gravity measured in each pool because such adjustment has been classically used in studies relying on spot samples.

Analyses were performed using R (version 4.1.3; R Development Core Team); most of the computations presented in this paper were performed using the GRICAD infrastructure (<https://gricad.univ-grenoble-alpes.fr>), which is supported by Grenoble research communities. The R codes are available in the Supplementary Material ("R CODES") and in the following GitLab repository: <https://gitlab.univ-grenoble-alpes.fr/iab-env-epi>.

Results

Description of the Study Population

Women were in median 32.3 y old [IQR: 30.0–35.2], highly educated (84.4% had studied 4 or more years after high school), and 45.5% were nulliparous (Table 1). At 2 months of age, 13.2% of the children have been exposed to tobacco smoke (including maternal smoking during pregnancy; Table 1). Mother–child pairs included in the study only differed from the remaining ones not included by maternal ethnicity (96.4% vs. 78.3% were Caucasian, respectively), father weight (75.7 kg vs. 79.1 kg, respectively), and timing of breastfeeding, with 80.2% were still breastfeeding at 3 months vs. 50.5% for the remaining (Excel Table S3). Correlation

between predicted infant growth at 3 and 36 months ranged from 0.54 for BMI to 0.93 for head circumference (Supplementary Figure S2). At 36 months, predicted and measured growth parameters were highly correlated (all $\rho > 0.90$, Supplementary Figure S3). Distribution of measured chemicals are presented in Excel Table S4. Overall, chemical detection rates were high for the metabolites included in the analysis, and all concentrations were above the LOD for phthalates (Excel Table S4). Among phenols, BPS and butylparaben were the least detected, from 16.5% values above the LOD at 2 months to 70.9% at 12 months and from 8.5% at 2 months to 36.8% at 12 months, for BPS and butylparaben, respectively (Excel Table S4). Overall, the matrix of correlation between urinary chemical concentrations highlighted small correlations between time windows of assessment, whereas within the same time windows of assessment, we observed overall moderate to high correlation between parabens (ρ ranged from 0.16 to 0.83) and between most phthalate metabolites (0.09–0.80). Lower correlation coefficients were observed between phenols (0.02–0.24) (Supplementary Figure S4).

Unipollutant Model

Regarding parabens, butylparaben was the only paraben for which associations were detected (Figure 1; Excel Table S5). Associations differed by timing of exposure, specifically, women with exposure between the LOD and the LOQ at the second trimester ($n = 45$) on average, had children with a lower BMI [$\beta = -0.42$ kg/m²; 95% confidence interval (CI): $-0.77, -0.07$ kg/m²] and weight ($\beta = -582$ g; 95% CI: $-1,012, -152$ g) at 36 months, whereas exposure at the third trimester ($n = 40$) was only associated with a decreased height at 36 months ($\beta = -1.07$ cm; 95% CI: $-1.96, -0.17$ cm). Children having a butylparaben concentration above the LOQ at 12 months ($n = 92$) tended to have a smaller weight, height, and head circumference at 36 months (p -values ranged from 0.04 to 0.08).

Three of the four phenols showed associations with growth parameters (Figure 1; Excel Table S5). Women having a BPS concentration above the LOQ at the second trimester ($n = 84$) tended to have children with a higher BMI ($\beta = 0.41$ kg/m²; 95% CI: 0.11, 0.70 kg/m² at 3 months and $\beta = 0.29$ kg/m²; 95% CI: 0.01, 0.56 kg/m² at 36 months), weight and height at both 3 and 36 months (p -values ranged from 0.001 to 0.05; Excel Table S5). A similar pattern of association was observed with quantified exposure at the third trimester ($n = 81$) and predicted BMI, weight, and head circumference at 3 months (p -values ranged from 0.02 to 0.08; Excel Table S5). Conversely, the only associations observed with postnatal BPS exposure, were a decreased height at 36 months ($n = 22$, $\beta = -1.51$ cm, 95% CI: $-2.73, -0.29$ cm), and a decreased head circumference at 3 months of age ($\beta = -0.40$ cm; 95% CI: -0.83 to 0.03 cm) among those with quantified BPS at 2 months. Regarding BPA, exposure at 2 months of age was negatively associated with BMI ($\beta = -0.18$ kg/m²; 95% CI: $-0.32, -0.04$ kg/m²) and weight ($\beta = -89$ g; 95% CI: $-160, -18$ g) at 3 months. However, the associations disappeared when studying the conjugated BPA concentrations instead of the total one. Last, triclosan at the third, but not the second, trimester, was associated with a decreased BMI ($\beta = -0.06$ kg/m²; 95% CI: $-0.12, -0.01$ kg/m²) and an increased height ($\beta = 0.13$ cm; 95% CI: $-0.01, 0.28$ cm) at 36 months. No significant association was observed for benzophenone-3.

A few phthalate metabolites were associated with postnatal BMI, weight, or head circumference but not associated with height (Figure 1; Excel Table S5).

Mono-*n*-butyl phthalate (MnBP) urinary concentrations at 12 months, but not at the other time points, was associated with a

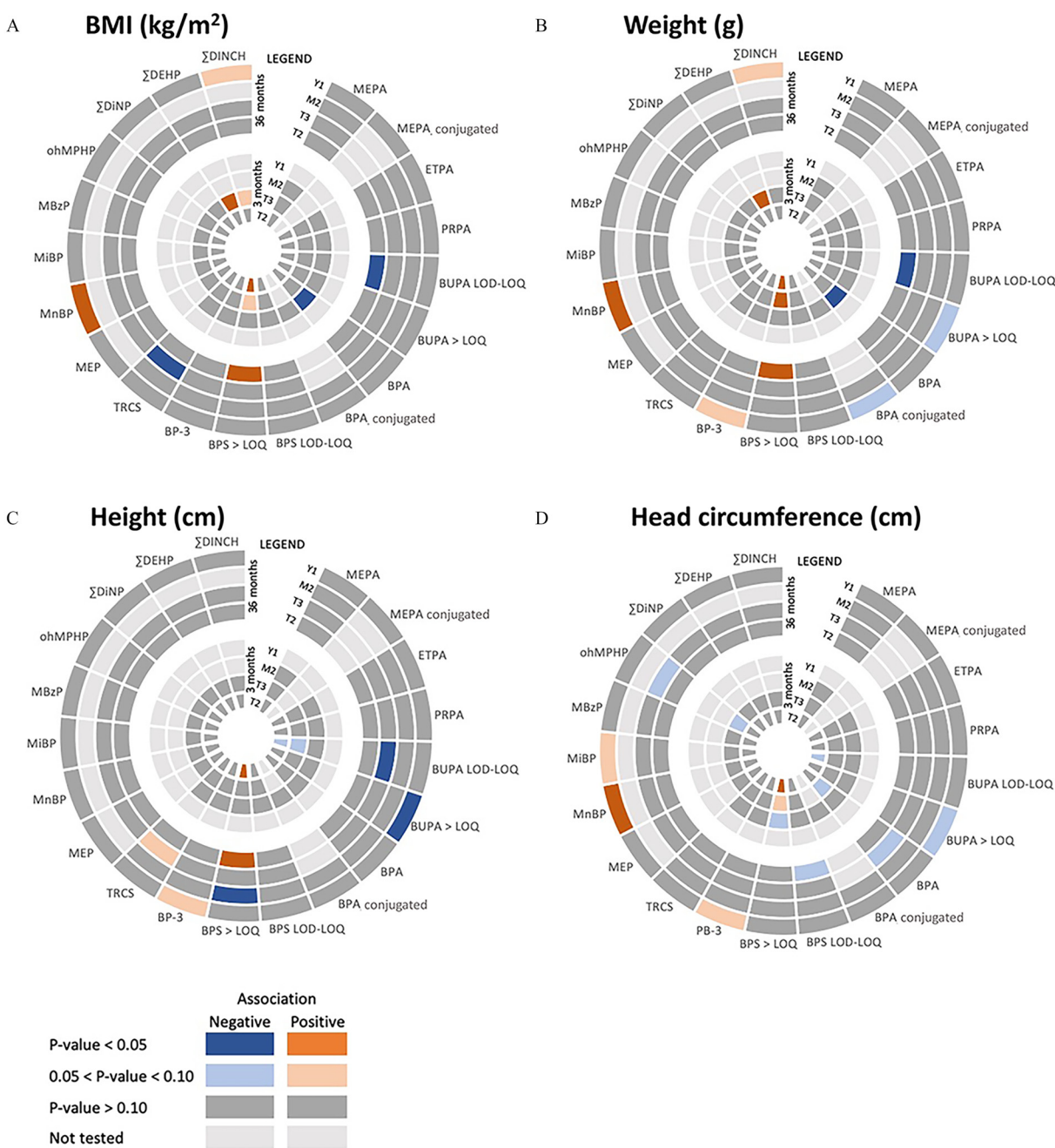


Figure 1. Adjusted associations between individual biomarker concentrations measured in pools of urine samples collected during trimesters 2 and 3 (maternal urine) and 2 months and 12 months of age (infant urine) and child predicted (A) BMI (in kg/m²), (B) weight (in g), (C) height (in cm) and (D) head circumference (in cm) at 3 and 36 months ($n = 364$ from the SEPAGES cohort, 2014–2017, France) (corresponding to Excel Table S5). Adjusted for: maternal age (<35 vs. ≥ 35), maternal prepregnancy weight (continuous), maternal height (continuous), paternal weight (continuous), paternal height (continuous), parity (nulliparous vs. parous), breastfeeding status (binary at 3 months or continuous until 48 wk for later outcomes), maternal education (up to 3 y vs. 4 or more years), child sex (males vs. females), infant history of passive smoking (including *in utero* passive smoking, Yes vs. No). Note: Due to budgetary restriction, phthalates and DINCH metabolites concentrations in children’s urine at 2 months of age were not measured. Conjugated phenols were only studied when potential contamination had been previously highlighted. BMI, body mass index; BP-3, benzophenone-3; BPA, bisphenol A; BPA conjugated, bisphenol A conjugated form; BPS, bisphenol S; BUPA, butylparaben; DEHP, di(2-ethylhexyl) phthalate; DINCH, 1,2-Cyclohexane dicarboxylic acid, diisononyl ester; DiNP, diisononyl phthalate; ETPA, ethylparaben; LOD, limit of detection; LOQ, limit of quantification; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; MEPA, methylparaben; MEPA conjugated, methylparaben conjugated form; MiBP, mono-*i*-butyl phthalate; MnBP, mono-*n*-butyl phthalate; ohMPPHP, 6-hydroxy monopropylheptyl phthalate; PRPA, propylparaben; TRCS, triclosan.

higher BMI ($\beta = 0.17$ kg/m²; 95% CI: 0.02, 0.32 kg/m²), weight and head circumference at 36 months (p -values ranged from 0.01 to 0.02). Σ DEHP at the third trimester was associated with both a higher BMI of 0.26 kg/m² (95% CI: 0.03, 0.48 kg/m²) and a weight of 122 g (95% CI: 10, 234 g) at 3 months of age but not at 36 months.

Unipollutant Sex-Specific Model

p -Value testing the interaction with child sex revealed effect modifications for eight of the studied chemicals [methylparaben, propylparaben, BPA, benzophenone-3, monobenzyl phthalate (MBzP), 6-hydroxy monopropylheptyl phthalate

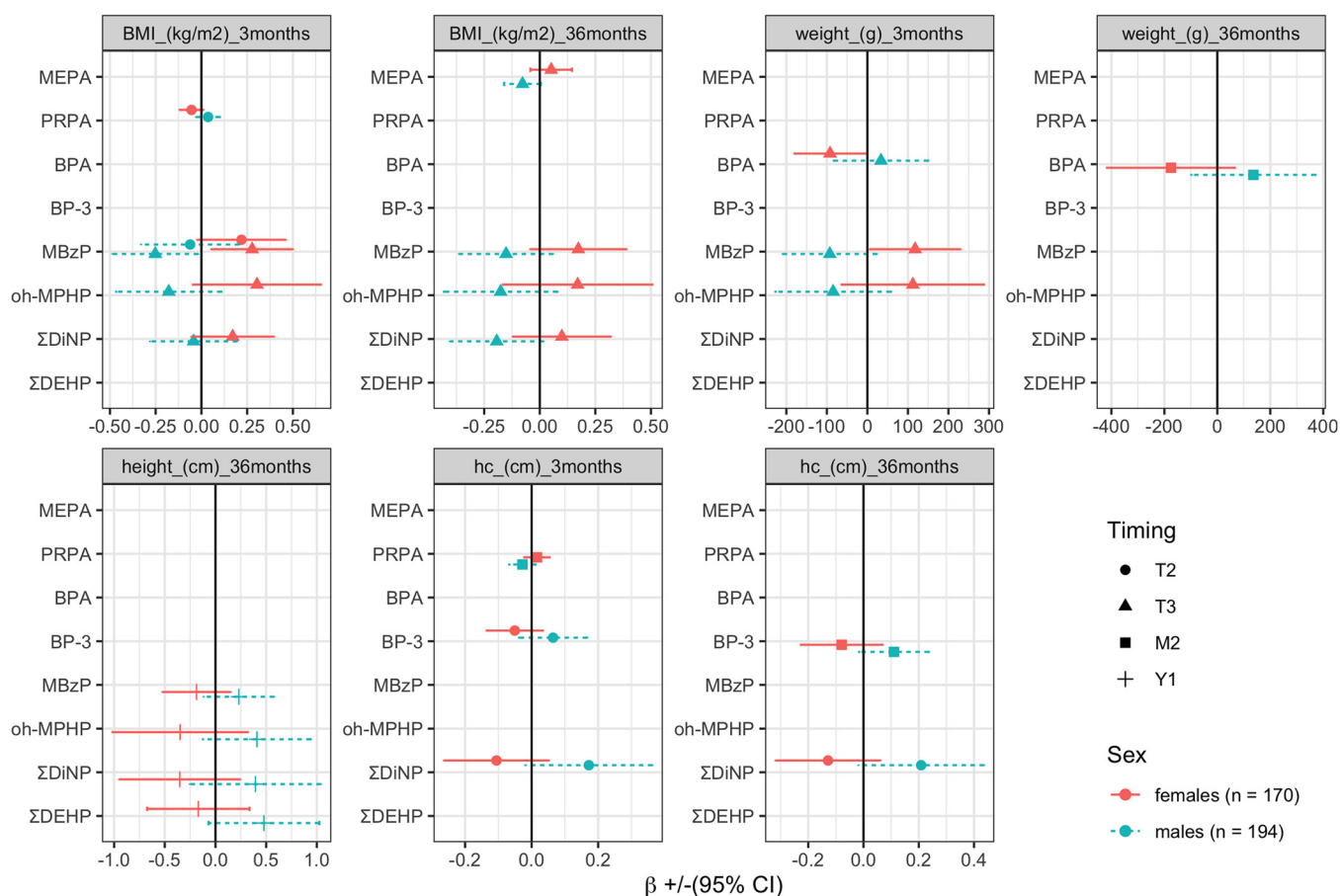


Figure 2. Sex-stratified adjusted associations between individual biomarker concentrations measured in pools of urine samples collected during trimesters 2 and 3 (maternal urine) and 2 months and 12 months of age (infant urine) and child predicted anthropometric measurements at 3 and 36 months ($n = 364$ from the SEPAGES cohort, 2014–1017, France). Geometrical forms indicate the estimates; horizontal lines, the 95% CIs; vertical lines, the null (corresponding to Excel Table S6). Adjusted for maternal age (<35 vs. ≥ 35), maternal prepregnancy weight (continuous), maternal height (continuous), paternal weight (continuous), paternal height (continuous), parity (nulliparous vs. parous), breastfeeding status (binary at 3 months or continuous until 48 wk for later outcomes), maternal education (up to 3 y vs. 4 or more years), infant history of passive smoking (include *in utero* passive smoking, Yes vs. No). Sex-stratified analysis were performed only when linear regressions p -values of interaction was below 0.1. Beta are given for one unit increase in ln-transformed chemicals; in other words betas correspond to 2.7-fold increase in chemicals concentration. Analyses on BUPA and BPS were not tested because of small sample size. Due to budgetary restriction, phthalates and DINCH metabolites concentrations in children’s urine at 2 months of age were not measured. Adjusted for maternal age, maternal prepregnancy weight, maternal height, paternal weight, paternal height, parity, breastfeeding status, maternal education, infant history of passive smoking. Note: BMI, body mass index; BP-3, benzophenone-3; BPA, bisphenol A; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; DiNP, diisononyl phthalate; M2, 2 months of age; MBzP, monobenzyl phthalate; MEPA, methylparaben; oh-MPHP, 6-hydroxy monopropylheptyl phthalate; PRPA, propylparaben; T2, second trimester; T3, third trimester; Y1, 12 months of age.

(oh-MPHP), Σ DiNP, Σ DEHP; p -value of interaction <0.10; Excel Table S6].

After stratification, isolated sex-specific associations were observed. Methylparaben at the third trimester tended to be negatively associated with BMI at 36 months among males, whereas propylparaben at the second trimester tended to be negatively associated with BMI at 3 months among females. BPA at the third trimester and 2 months tended to be associated with a decreased weight among females at 3 and 36 months, respectively (Figure 2; Excel Table S6). Among phthalates, MBzP, oh-MPHP, and Σ DiNP at the third trimester tended to be negatively associated with BMI at 3 and 36 months among males and positively among females. A positive association among males and negative among females was observed for Σ DiNP at the second trimester and head circumference at both time points.

BKMR

Hierarchical BKMR (hBKMR) analysis combining all exposure windows in the same model did not show association with

postnatal growth (Supplementary Figure S5; Excel Table S7; Excel Table S8). In the BKMR analysis evaluating each window separately, prenatal mixtures were not associated with postnatal growth, whereas mixtures of chemicals at 2 (only included phenols and parabens) and 12 months tended to be associated with increased BMI at 36 months (Figure 3; Excel Table S9). The highest PIP for mixtures at 2 months was BPA, whereas ethylparaben showed the highest effect (Figure 4A; Excel Table S10), two compounds that were not associated with BMI at 36 months in the unipollutant model (p -values of 0.26 and 0.13, respectively). The highest PIP for mixtures measured at 12 months was observed with Σ DiNP, which was not associated with BMI in the unipollutant model, whereas MnBP showed the highest effect, which was consistent with the unipollutant results (Figure 4B; Excel Table S10).

The mixture measured at 12 months was also associated with an increased weight at 36 months (Supplementary Figure S6; Excel Table S9), where MnBP had the highest PIP and showed a significant positive effect (Figure 5; Excel Table S10), consistent with the unipollutant results.

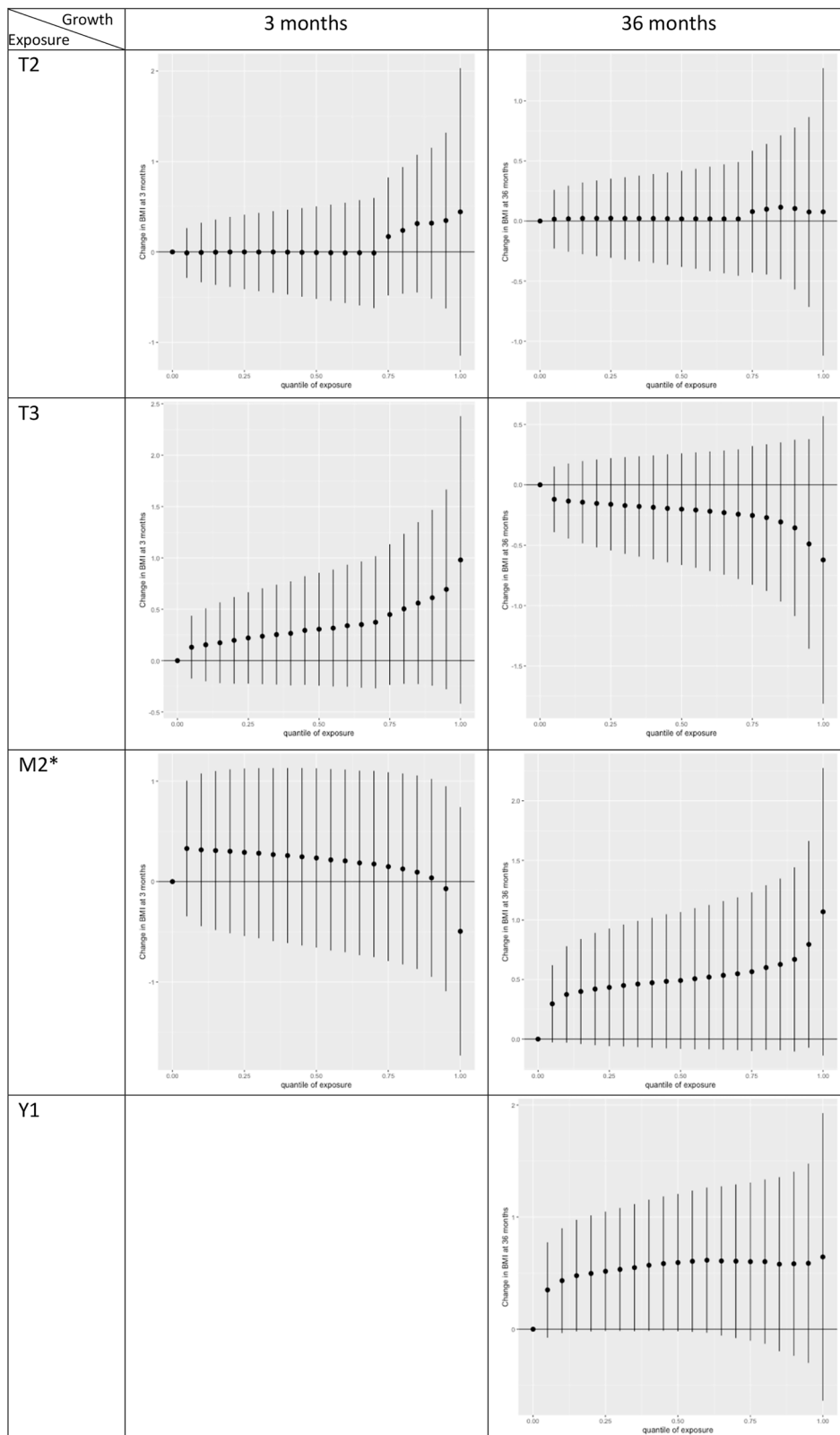


Figure 3. Change in body mass index (BMI, in kg/m^2)—Independent BKMR—Change in BMI for each 5% increase in exposure to chemicals mixture ($n = 364$ from the SEPAGES cohort, 2014–2017, France). Dots indicate the estimates; vertical lines, the 95% CIs; horizontal lines, the null (corresponding to Excel Table S9). Adjusted for: maternal age (<35 vs. ≥ 35), maternal prepregnancy weight (continuous), maternal height (continuous), paternal weight (continuous), paternal height (continuous), parity (nulliparous vs. parous), breastfeeding status (binary at 3 months or continuous until 48 wk for later outcomes), maternal education (up to 3 y vs. 4 or more years), child sex (males vs. females), infant history of passive smoking (include in-utero passive smoking, Yes vs. No). Note: *Due to budgetary restriction, phthalates and DINCH metabolites concentrations in children’s urine at 2 months of age were not measured. BKMR, Bayesian kernel machine regression; BMI, body mass index; CI, confidence interval.

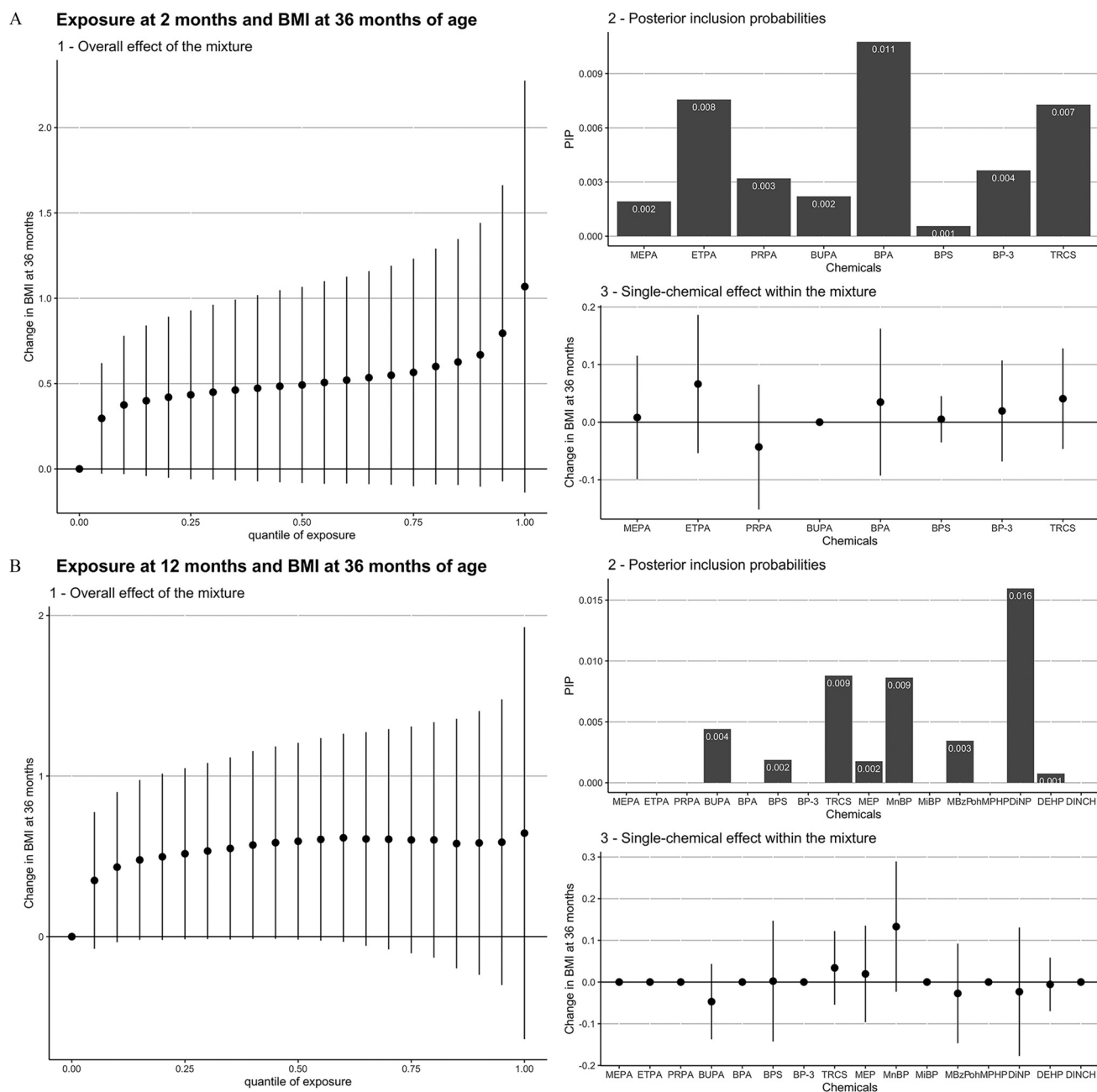


Figure 4. Change in body mass index (BMI, in kg/m^2) at 36 months associated with chemicals exposure at (A) 2 months and (B) 12 months of age ($n = 364$ from the SEPAGES cohort, 2014–2017, France). Panel 1: change for each 5% increase in exposure to the mixture; Panel 2: PIPs; and Panel 3: estimated effect and 95% CI of an increase from the 25th to 75th percentile in a single chemical concentration when all other exposure biomarkers are fixed at the 50th percentile. Dots indicate the estimates; vertical lines, the 95% CIs; horizontal lines, the null (corresponding to Excel Table S9 and Table S10). Adjusted for: maternal age (<35 vs. ≥ 35), maternal prepregnancy weight (continuous), maternal height (continuous), paternal weight (continuous), paternal height (continuous), parity (nulliparous vs. parous), breastfeeding status (continuous until 48 wk), maternal education (up to 3 y vs. 4 or more years), child sex (males vs. females), infant history of passive smoking (include *in utero* passive smoking, Yes vs. No). Note: Due to budgetary restriction, phthalates and DINCH metabolites concentrations in children's urine at 2 months of age were not measured. BMI, body mass index; BP-3, benzophenone-3; BPA, bisphenol A; BPS, bisphenol S; BUPA, butylparaben; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; DINCH, 1,2-Cyclohexane dicarboxylic acid, diisononyl ester; DiNP, diisononyl phthalate; ETPA, ethylparaben; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; MEPA, methylparaben; MiBP, mono-iso-butyl phthalate; MnBP, mono-*n*-butyl phthalate; ohMPHP, 6-hydroxy monopropylheptyl phthalate; PIP, posterior inclusion probability; PRPA, propylparaben; TRCS, triclosan.

No association was detected with postnatal height and head circumference in the mixture models (Supplementary Figures S7 and S8; Excel Table S9).

BKMR Sex-Specific Model

In the sex-specific analysis, hBKMR analysis combining all exposure windows in the same model showed significant

associations with BMI at 36 months among males. Males exposed to the 75th percentile of mixture concentrations had a higher BMI at 36 months of $1.3 \text{ kg}/\text{m}^2$ (95% CI: $-0.1, 2.7 \text{ kg}/\text{m}^2$), in comparison with no exposure (Supplementary Figure S9; Excel Table S11). Exposure at 2 months had the highest group PIP, with triclosan having the highest relative importance (Excel Table S12).

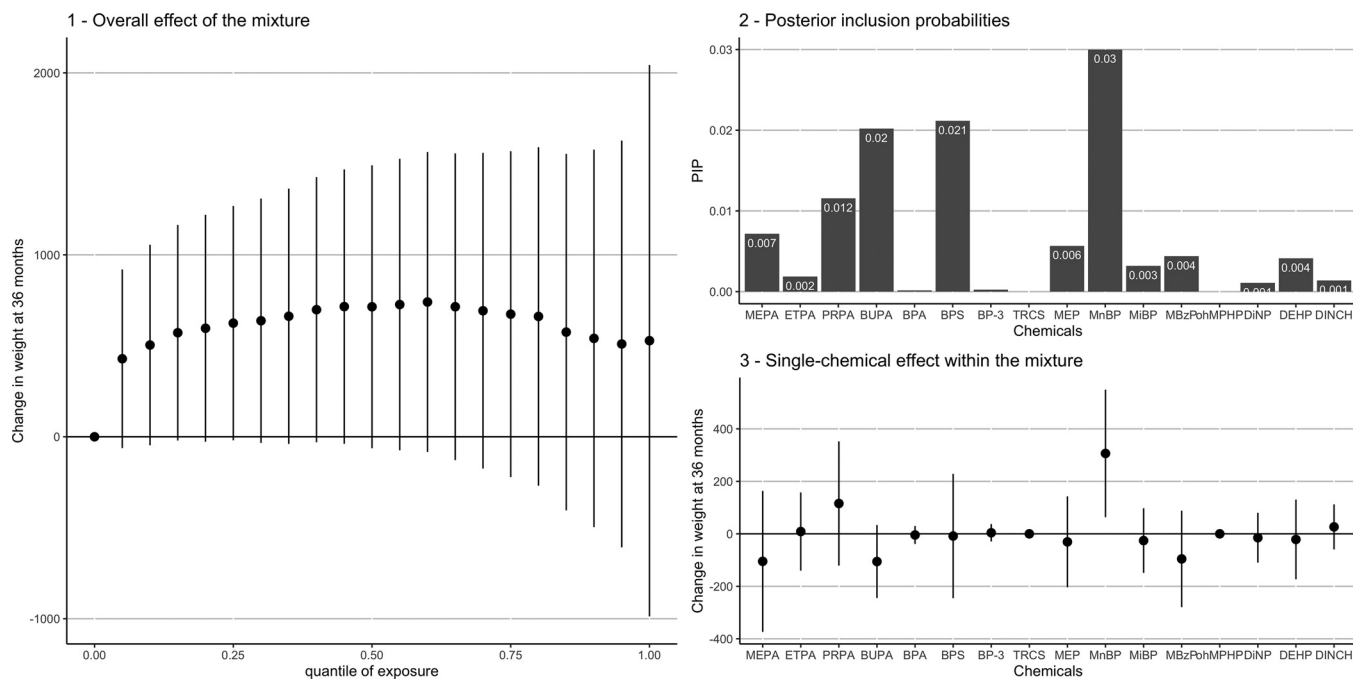


Figure 5. Change in weight (in g) at 36 months associated with chemicals exposure at 12 months of age ($n = 364$ from the SEPAGES cohort, 2014–2017, France). Panel 1: change for each 5% increase in exposure to the mixture; Panel 2: PIPs; and Panel 3: estimated effect and 95% CI of an increase from the 25th to 75th percentile in a single chemical concentration when all other exposure biomarkers are fixed at the 50th percentile. Dots indicate the estimates; vertical lines, the 95% CIs; horizontal lines, the null (corresponding to Excel Table S9 and Excel Table S10). Adjusted for: maternal age (<35 vs. ≥ 35), maternal pre-pregnancy weight (continuous), maternal height (continuous), paternal weight (continuous), paternal height (continuous), parity (nulliparous vs. parous), breast-feeding status (continuous until 48 wk), maternal education (up to 3 y vs. 4 or more years), child sex (males vs. females), infant history of passive smoking (include *in utero* passive smoking, Yes vs. No). Note: Due to budgetary restriction, phthalates and DINCH metabolites concentrations in children’s urine at 2 months of age were not measured. BP-3, benzophenone-3; BPA, bisphenol A; BPS, bisphenol S; BUPA, butylparaben; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; DINCH, 1,2-Cyclohexane dicarboxylic acid, diisononyl ester; DiNP, diisononyl phthalate; ETPA, ethylparaben; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; MEPA, methylparaben; MiBP, mono-*iso*-butyl phthalate; MnBP, mono-*n*-butyl phthalate; ohMPHP, 6-hydroxy monopropylheptyl phthalate; PIP, posterior inclusion probability; PRPA, propylparaben; TRCS, triclosan.

Similarly, in sex-stratified mixture analysis by windows of exposure, males exposed to the 75th percentile of the mixture concentrations had a higher BMI at 36 months of 1.2 kg/m² (95% CI: 0.3, 2.1 kg/m²) for mixture concentrations at 2 months and 1.0 kg/m² (95% CI: 0.1, 1.9 kg/m²) for mixture concentrations at 12 months, in comparison with no exposure (Figure 6; Excel Table S13). Similar to hBKM analysis, the highest PIP among males was seen for triclosan (Supplementary Figure S10A; Excel Table S14), a compound that was not associated with BMI in the unipollutant model. In the 12 months mixture, MnBP showed the highest effect, consistent with the unipollutant results (Supplementary Figure S10B; Excel Table S14).

Similar patterns of association were observed with weight at 36 months (positive association among males with the 12 months mixture; Supplementary Figure S11; Excel Table S13), with MnBP showing the highest PIP (Supplementary Figure S12; Excel Table S14).

No associations were detected in girls, neither with postnatal height, nor head circumference (Supplementary Figure S13 and S14; Excel Table S13).

Sensitivity Analysis

Analysis further adjusted for specific gravity gave similar results, whereas associations generally became stronger (Excel Table S15). For example, this analysis revealed associations between exposure to benzophenone-3 at 12 months and weight and height at 36 months (p -values of 0.04 and 0.02, respectively) that were not significant in our main analysis (p -values of 0.06 and 0.09).

Analysis performed after removing first and last percentile of exposure and outcome gave similar results and strengthened some associations (Excel Table S16). Among parabens, the association between ethylparaben at 2 months and BMI and weight at 36 months became significant (p -values of 0.02 and 0.03, respectively, in comparison with 0.13 and 0.25, respectively) and consistent with our BKMR results on BMI (Figure 2A); as the negative association between propylparaben at the second trimester and weight and height at 3 months of age (p -values 0.05 and 0.03, respectively, in comparison with 0.48 and 0.21, respectively). Among phthalates, MiBP at the second trimester was negatively associated with weight, with head circumference at 3 and 36 months, and with height at 36 months; Σ DEHP at second trimester was negatively associated with head circumference at 3 and 36 months (p -values of 0.01 and 0.04, respectively, in comparison with 0.07 and 0.12, respectively) (Excel Table S16).

Relying on measurements at 36 months instead of predicted values showed similar patterns, with one additional isolated association that became significant between MEP at 12 months and increased BMI ($\beta = 0.15$ kg/m²; 95% CI: 0.01, 0.29 kg/m²) at 36 months (Excel Table S17) in comparison with the main analysis ($\beta = 0.10$ kg/m²; 95% CI: -0.04, 0.23 kg/m²).

Discussion

Based on repeated within-subject urine collections over pregnancy and infancy, we found an association between postnatal exposure to a mixture of EDCs and increased BMI and weight at 36 months of age, which appeared to be stronger among boys. In the unipollutant models, only few compounds were consistently

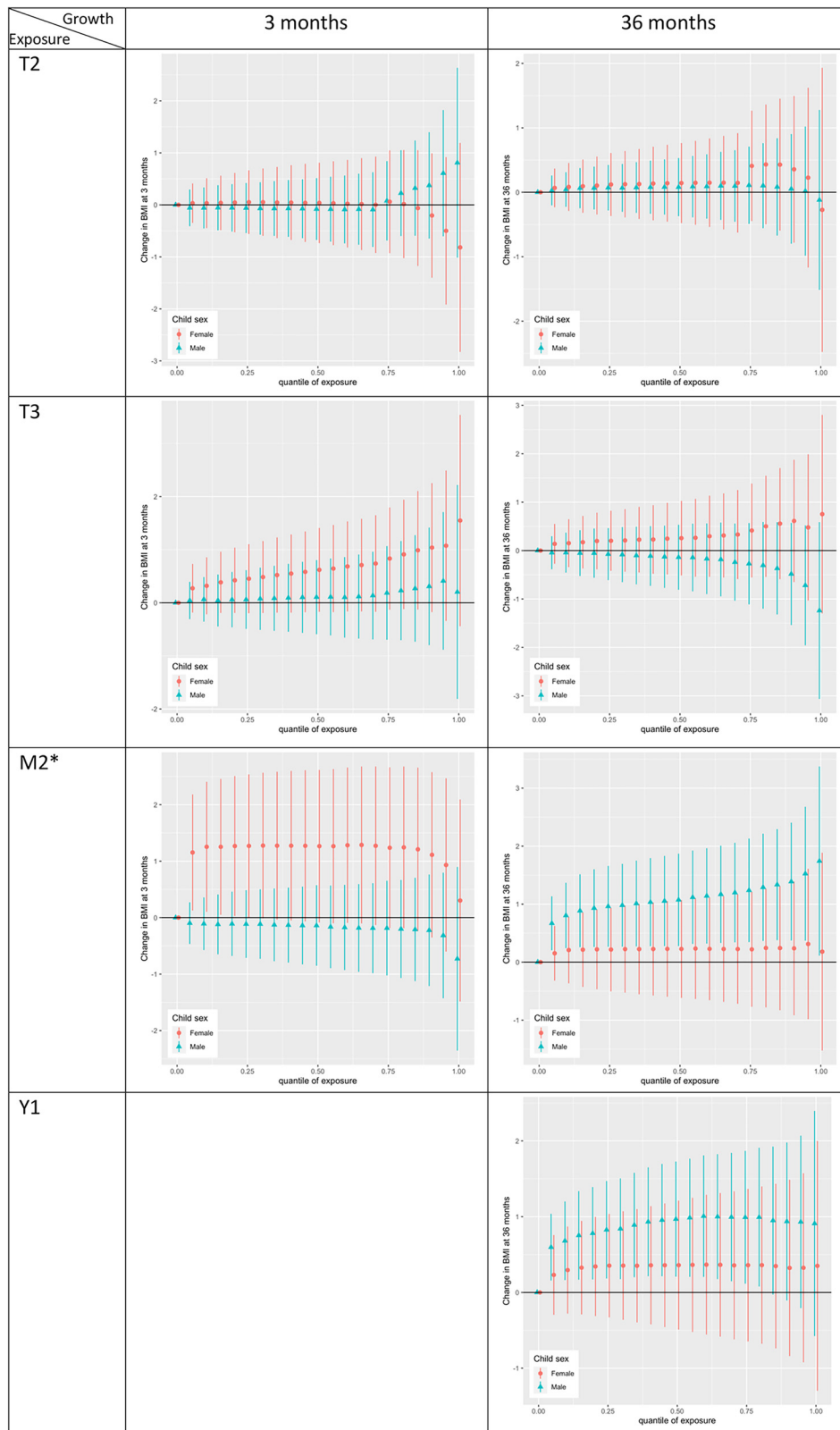


Figure 6. Sex-stratified BKMR (males, $n = 194$; females, $n = 170$) —change in BMI (in kg/m^2) for each 5% increase in exposure to chemicals mixture separately for females and males ($n = 364$ from the SEPAGES cohort, 2014–2017, France). Dots indicate the estimates; vertical lines, the 95% CIs; horizontal lines, the null (corresponding to Excel Table S13). Adjusted for: maternal age (<35 vs. ≥ 35), maternal prepregnancy weight (continuous), maternal height (continuous), paternal weight (continuous), paternal height (continuous), parity (nulliparous vs. parous), breastfeeding status (binary at 3 months or continuous until 48 wk for later outcomes), maternal education (up to 3 y vs. 4 or more years), infant history of passive smoking (include *in utero* passive smoking, Yes vs. No). Note: *Due to budgetary restriction, phthalates and DINCH metabolites concentrations in children’s urine at 2 months of age were not measured. BKMR, Bayesian kernel machine regression; BMI, body mass index; CI confidence interval.

associated with growth outcomes. These included BPS at the second trimester positively associated with all infant growth parameters and MnBP at 12 months associated with increased BMI, weight, and head circumference at 36 months. No modification by child sex was suggested for this association.

Regarding the unipollutant results, among phenols, prenatal exposure to BPS at the second trimester was associated with an increase in all infant growth parameters. To our knowledge this is the first study investigating the associations between BPS exposure during pregnancy and early infancy and postnatal growth. Three cross-sectional studies among children of 6 y of age or older have been conducted in the United States. Among them, two did not find associations,^{42,43} whereas one study on 1,831 children and adolescents (6 to 19 y of age) reported positive associations between BPS exposure and obesity risk.⁴⁴ We also observed an isolated association between total BPA at 2 months and decreased BMI and weight at 3 months, which disappeared when the concentration of the conjugated form alone was used, suggesting that this association may result from external contamination. Our findings on BPA were not consistent with most previous published studies that reported positive⁴⁵ or no association,^{46,47} with the exception of one US study conducted on 297 children from Cincinnati, Ohio, that reported an inverse association between early childhood (1–2 y of age) urinary concentration of BPA and BMI at 2–5 y of age, mostly among girls.⁴⁸ We also reported an isolated negative association between triclosan at the third trimester and BMI at 36 months, which is not consistent with previously published papers.^{24,49,50}

Among parabens, only butylparaben showed associations with child growth. These associations were all negative, whereas among the low number of studies investigating the associations between parabens and child growth, one reported a positive association between *n*-butylparaben and child fat percentage among boys.⁵¹

Among phthalates, we found positive associations between Σ DEHP at third trimester and BMI and weight at 3 but not at 36 months, which is inconsistent with the conclusion from a recent meta-analysis that reported negative associations between prenatal Σ DEHP and childhood BMI.⁹ However, two individual studies that focused on early childhood (<2 y of age) also reported positive associations,^{52,53} including one among 990 Chinese girls that reported a positive association between prenatal Σ DEHP and BMI *z*-score at 3 months but not later during infancy, supporting our results.⁵² Regarding MnBP, a metabolite of dibutyl-phthalate (DBP), most previous studies focused on prenatal exposure and reported positive associations with adiposity^{54,55} and BMI,^{52,56,57} whereas we did not find association with prenatal exposure. Few studies, mainly cross-sectional, looked at postnatal exposure and all assessed exposure in children after 4 y of age. One found no association between MnBP measured in urine at 4, 5, and 8 y and adiposity at 8 y,⁵⁸ whereas other studies reported positive associations,^{55,59,60} supporting our finding on the positive association between MnBP and children growth, despite the difference in the age ranges (from 4 to 15 y of age). Among the three studies reporting positive associations, one conducted among 500 children between ages 4 and 6 y, found stronger associations among girls.⁵⁵

Our mixture analysis results showed associations between infant exposure to the mixture and higher BMI and weight at 3 y that were stronger in males. Although effect modification by child sex may result from interaction of EDCs with nuclear hormone receptors, including estrogen and androgen receptors,⁶¹ our results should be interpreted cautiously because our sample size was limited (194 males and 170 females), and most studies relying on child urinary chemical concentrations have reported stronger associations among girls for individual chemicals.^{48,62}

Comparison of our mixture analysis with previous publications is not straightforward because most studies performing mixture analysis only investigated the impact of prenatal exposure, a time point that was not associated with postnatal growth in our study, in line with previous reports.^{52,63,64} Only one cross-sectional study conducted on 2,372 children 6–19 y of age used BKMR to assess the mixture of phenols and phthalates on obesity risk and BMI and found positive trends,⁶⁵ supporting our findings.

Obesogenic effects of EDCs may result from their interferences with hormone receptors of the nuclear receptor family,⁶¹ such as the estrogen receptors, with either agonist or antagonist effects depending on the EDCs.⁶⁶ EDCs can also impact the thyroid hormone pathway.⁶⁷ Phthalates may have proinflammatory effects through up-regulation of the peroxisome proliferator-activated receptors (PPARs) and/or the induction of cyclooxygenase-2 expression. Finally, EDCs can also affect the aryl hydrocarbon receptor (AhR) known to be involved in the regulation of lipogenesis and glucose homeostasis.^{68,69}

The sample size of our study was modest and may not allow the detection of small effects. However, the unique urine collection of our study (up to 42 urine samples during pregnancy and 14 during first year of life) should better represent early-life exposure, decrease bias in the effect estimates,¹⁶ and thus increase the potential to detect effects that previous studies of similar sample size but using one urine sample may not have revealed. Residual confounding may have occurred; BPA and BPS concentrations may be a surrogate for factors predictive of child overweight, such as maternal and child eating behaviors, that we were not able to account for. Although BKMR model allows to address multicollinearity in exposure, nonlinearity, and coexposure bias,^{39,70} an overall risk association may not be observed when both positive and negative associations with the outcome exist for the chemicals considered in the mixture.

This study is the first to consider exposure during prenatal and early postnatal life, two crucial periods for child development. Thanks to the longitudinal design we had a large number of growth measurements for most individuals. The Jenks-Bayley prediction model, describing the child growth trajectory,²⁸ allowed us to predict growth parameters at exactly the same age for all children, taking into account repeated measurements and potential missing data. When this work was initiated, data were only available for children until the age of 3 y; however, effects of chemicals may potentially become apparent during later stages of childhood, underscoring the need of longer follow-up. Moreover, decrease in growth in early life (prior to 3 y of age) may lead to catch-up growth or obesity later in childhood.

In conclusion, this study suggested that exposure to a mixture of short half-life EDCs in early infancy may be associated with increased weight and BMI in childhood, a risk factor for obesity in later life. Both unipollutant and mixture models highlighted an effect of MnBP exposure at 12 months on the adiposity growth. The unipollutant model also showed associations between prenatal BPS exposure and an increase in all growth parameters. Further investigations are needed for this compound because it has never been studied in a similar context. This study added to the scarce literature on the impact of exposure to short half-life EDCs in early infancy. Further epidemiological studies should assess exposure during this critical period for child development.

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