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Early-life exposures to phenols, parabens and phthalates and fat mass at 3 years of age in the SEPAGES cohort

Maude Colombini [a], Barbara Heude [b], Sarah Lyon-Caen [a], Cathrine Thomsen [c], Amrit K. Sakhi [c], Séverine Valmary-Degano [d], Sam Bayat [e,f], Rémy Slama [a], Claire Philippat [a], Marion Ouidir [a,*]

[a] University Grenoble Alpes, Inserm U 1209, CNRS UMR 5309, Team of Environmental Epidemiology Applied to Development and Respiratory Health, Institute for Advanced Biosciences, 38000, Grenoble, France
[b] Université Paris Cité and Université Sorbonne Paris Nord, Inserm, INRAE, Center for Research in Epidemiology and StatisticS (CRESS), F-75004, Paris, France
[c] Norwegian Institute of Public Health, Department of Food Safety, Oslo, Norway
[d] BB-0033-00069 (Biobank of Grenoble), Univ. Grenoble-Alpes, Inserm U1209, CNRS UMR5309, Institute for Advanced Biosciences, CHU Grenoble-Alpes, F-38000, Grenoble, France
[e] Department of Pulmonology and Physiology, Grenoble University Hospital, La Tronche, France
[f] Synchrotron Radiation for Biomedicine Laboratory (STROBE), Inserm UA07, Grenoble Alpes University, Grenoble, France

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ABSTRACT

Background: Early-life exposure to short half-life chemicals may influence adiposity growth, a precursor to obesity. Previous studies often relied on limited urine samples that inadequately represent exposure during pregnancy or infancy. Additionally, childhood adiposity is commonly estimated using body mass index, which does not accurately reflect body composition. We aimed to investigate associations between early-life exposures to phenols, parabens, phthalates and fat mass percent at 3 years of age among 341 mother-child couple from the SEPAGES cohort. We further assessed potential effect modification by sex.

Methods: We measured 8 phenols, 4 parabens, 13 phthalates and 2 non-phthalate plasticizer metabolites from weekly pooled urine sample collected from mothers during pregnancy (three urine samples a day, median 18 and 34 gestational weeks), and from their infant (one urine sample a day, at 2 and 12 months). Clinical examinations at 3 years included standardized skinfold thickness measurements and bioelectrical impedance analysis to calculate fat mass percentage.

Results: Positive associations were identified between prenatal exposures to bisphenol S, mono-benzyl phthalate (MBzP), monoethyl phthalate (MEP), and mono-n-butyl phthalate and fat mass percentage at 3 years, while triclosan showed a negative association. MBzP and MEP showed effect modification by sex, with stronger associations among females. No significant associations were detected for postnatal exposures.

Conclusion: This study suggests associations between prenatal exposures to short half-life chemicals and percent fat mass in preschool children. Furthermore, this study is the first investigating the impact of prenatal bisphenol S exposure, highlighting the need for investigation of this overlooked compound.

1. Introduction

Childhood obesity has increased in the last decades and has become a public health issue (de Onis et al., 2010; Ebbeling et al., 2002), with increased risks for cardiometabolic disease (such as diabetes and high cholesterol), asthma, and psycho-social problems (Ebbeling et al., 2002; Jebeile et al., 2022; Sahoo et al., 2015). Because childhood obesity often persists into adulthood, it is a risk factor of adult obesity and cardiometabolic diseases in later life (Odegaard et al., 2013; Singh et al., 2008; Weihrauch-Blüher et al., 2019). Usually, obesity is assessed using body mass index (BMI), which is easy to measure but does not accurately reflect the body composition such as fat and fat-free mass. The standard method to assess body composition is dual-energy X-ray absorptiometry (DXA) (Lifshitz et al., 2016; Shepherd et al., 2017), which uses low-dose X-ray beams to measure bone mineral density, fat mass, and lean mass. However, this method is expensive and difficult in routine clinical

* Corresponding author.
E-mail address: marion.ouidir@univ-grenoble-alpes.fr (M. Ouidir).

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practice, especially for children. Bioelectrical impedance analysis (BIA) is a performant promising tools to assess body composition (Clasey et al., 2011; Goran et al., 1996; Jensen et al., 2015), being fast, non-invasive and with no X-ray, which makes it of interest for children.

Obesity is caused by different factors: unhealthy diet, lack of physical activity, and genetic, social, environmental, and behavioral determinants (Nicolaidis, 2019; Swift et al., 2014). Among environmental determinants of obesity, some endocrine disrupting chemicals (EDCs) are known to be obesogenic (Casals-Casas and Desvergne, 2011; Nicolaidis, 2019). EDCs are chemical compounds that interfere with the normal functioning of the endocrine system and can cause effects on human health (Gore et al., 2015; Kahn et al., 2020) and more specifically EDCs can interact with nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs)-gamma, involved in regulating adipogenesis and weight gain (Casals-Casas and Desvergne, 2011; Grün and Blumberg, 2006) and may contribute to the development of obesity (Elobeid and Allison, 2008). EDCs can also interfere with the estrogen receptors, leading to different effects based on sex (Swedenborg et al., 2009). EDCs are found in various product categories, including pesticides, plasticizers like phthalates and bisphenols, and preservatives such as triclosan and parabens. Phenols and phthalates are present in our daily environment, such as plastic food storage containers, toys, and personal care products (Liao and Kannan, 2014; Yan et al., 2009), leading to ubiquitous exposure.

Studies have shown that phenols, parabens and phthalates can cross the placental barrier and be measured in cord blood and amniotic fluid (Philippat et al., 2013; Song et al., 2020). The prenatal period is a critical period, particularly sensitive to metabolic disruptions and programmed effects, as highlighted by research on the programming of adipogenesis and osteogenesis (Grün and Blumberg, 2006). Several studies have suggested that prenatal exposure to phenols and phthalates is associated with an increased risk of childhood obesity (Yang et al., 2018). However, results are inconsistent and depend on the studied exposures. For example, prenatal bisphenol A has been found to have a positive association with childhood obesity (i.e. obesogenic effects) in some studies (Braun et al., 2019; Hoepner et al., 2016; Valvi et al., 2013), but none (Berger et al., 2021; Braun et al., 2014; Ouidir et al., 2024; Philippat et al., 2014) in others. Results for prenatal paraben exposure are more consistent, with mostly a positive association with adiposity in childhood (Berger et al., 2021; Højsager et al., 2021; Leppert et al., 2020; Philippat et al., 2014).

Association between early postnatal exposures and child adiposity have been less frequently described in the literature. Among the few previously published studies, most found neither associations with bisphenol A (Braun et al., 2014; Harley et al., 2013; Hoepner et al., 2016; Ouidir et al., 2024), nor triclosan (Buser et al., 2014; Kalloo et al., 2018; Ouidir et al., 2024). Only two studies investigated the impact of postnatal exposure to phthalates, one reported a positive association for females and a negative association for males for MBzP and BMI z-score at 4–6 years (Vafeiadi et al., 2018), the other reported positive a association for BMI and MnBP (Ouidir et al., 2024).

The heterogenicity of results could in part be explained by the fact that phenols and phthalates are quickly metabolized and excreted, giving short half-lives (inferior to 24 h) leading to a high within-subject variability in urinary concentrations, depending on behavior (meals, cosmetics used) during the hours prior to sampling (Kim et al., 2018; Ye et al., 2011). Until now, most studies have used only one sample to assess exposures (Buckley et al., 2016a; Valvi et al., 2013; Wu et al., 2018), leading to a bias in the dose-response function (Perrier et al., 2016). To be more representative, several samples a day for several days, ideally at different time points of the pregnancy/infancy must be collected, possibly followed by pooling of multiple samples to reduce analysis cost (Philippat and Calafat, 2021; Vernet et al., 2019).

In response to concerns about their potential health threat regulations and legislations have been implemented for some compounds and thus the introduction of new compounds such as bisphenol S and bisphenol F as replacement of bisphenol A (Rochester and Bolden, 2015), and 1,2-Cyclohexane dicarboxylic acid, diisononyl ester (DINCH) as replacement of high molecular weight phthalates (Schütze et al., 2014). Those relatively new compounds have been studied once in relation to childhood BMI (Ouidir et al., 2024), where bisphenol S and DINCH tended to be associated with increased growth parameters.

Our objective was to investigate the association between early-life exposure to phenols, parabens, and phthalates and adiposity at 3 years of age. We further assessed potential effect modification by child sex, as suggested in prior research.

2. Methods

2.1. Study population

This study is based on the SEPAGES (*Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effet sur la Santé*) cohort, a French mother-child cohort, which included pregnant women, fathers and the future child (Lyon-Caen et al., 2019). All women were included between July 2014 and July 2017 in the Grenoble area, France. The eligibility criteria were being pregnant by less than 19 gestational weeks (GW) at inclusion, older than 18 years, having a singleton pregnancy, and planning to give birth in one of the four maternity wards from Grenoble area, France. Finally, out of the 2321 women approached meeting the eligible criteria, 484 (20.9%) women were included in the cohort and followed-up during pregnancy, then their children were followed (Lyon-Caen et al., 2019).

All pregnant women gave informed consent to participate, and both parents gave informed consent for their children. This study was approved by the French ethical committees (*Commission Nationale de l'Informatique et des Libertés* [CNIL] and *Comité de Protection des Personnes Sud-Est* [CPP])

2.2. Urine samples collection

Mothers collected three urine samples a day (morning, midday, and evening) during seven consecutive days at two different periods: during the early second trimester, median 18 GW (percentiles 25–75: 16–19 GW) and third trimesters of pregnancy, median 34 GW (percentiles 25–75: 32–35 GW). Then, parents collected children's urine using a cotton gaze insert in the diaper (without stool), one spot a day for 7 day at two months, median 7 weeks (percentiles 25–75: 6–8 weeks) and one year, median 53 weeks (percentiles 25–75: 52–55 weeks). Participants stored urine samples in their freezer (−20 °C). Urine collection tubes and cryotubes were in high-density polyethylene and polypropylene certified without BPA. At the end of the measurement week, SEPAGES field workers picked-up the urine samples and transported them to the certified biobank of the Grenoble University Hospital (bb-0033-00069). The biobank thawed the samples at 4 °C overnight and made within-subject weekly pools by pooling equal volumes of all the spot urine samples collected over the collection week. The procedure has been previously described by Rolland (Rolland et al., 2020) and Philippat (Philippat et al., 2021). Pooling biospecimen within-subjects in periods allows a better power without increased costs related to assessing all samples individually and has shown to be a good proxy compared to pooling the whole volume of samples collected (Perrier et al., 2016; Vernet et al., 2019).

2.3. Exposures assessment

Exposures in the weekly urine pools were measured by the Norwegian Institute of Public Health (NIPH), Oslo (Norway). Urine samples were sent to NIPH on dry ice with a temperature sensor. Total concentration of 8 phenols, 4 parabens, 13 phthalates metabolites and 2 non-phthalate plasticizer metabolites were measured (Supplementary Table S1) (Philippat et al., 2021; Rolland et al., 2020). Phenols

(including 5 bisphenols (A, S, F, B, AF), benzophenone-3 (BP-3), triclosan and triclocarban) and parabens (methylparaben, ethylparaben, propylparaben, butylparaben) were measured using ultra performance liquid chromatography coupled to mass spectrometry (UPLC-MS/MS) (Sakhi et al., 2018). The accuracy estimated through a validation experiment of the method ranged from 75% to 120% (Sakhi et al., 2018). The 13 phthalate metabolites (corresponding to 7 parent compounds: monoethyl phthalate [MEP], mono-n-butyl phthalate [MnBP], mono-isobutyl phthalate [MiBP], mono-benzyl phthalate [MBzP], 6-hydroxymono-propyl-heptyl phthalate [oh-MPHP], di(2-ethylhexyl) phthalate [DEHP] and diisononyl phthalate [DiNP]) and the 2 non-phthalate plasticizer metabolites (corresponding to the parent compound DINCH) were measured using high performance liquid chromatography coupled to tandem mass spectrometer (HPLC-MS/MS), with the accuracy of the method ranging from 70% to 125% (Sabaredzovic et al., 2015).

Due to limited funds, for the urine samples collected at 2 months of age we were able to assessed phthalate metabolites for only 152 infants (Philippat et al., 2021), thus this time point was not considered for this substance family in the current analysis.

2.4. Child growth measurements at 3 years

In total 379 children participated to the 3-year visit. The visit performed by a trained SEPAGES fieldworker included weight (kg) and height (cm) measurements using a standardized procedure where children wore light indoor clothing and had to take off socks, shoes, belts, hats, and all objects. Then, subscapular and triceps skinfold thickness (mm) were measured. Additionally, a BIA was performed using the BodyStat 1500 MDD (Bodystat, Isle of Man, UK) for which children had to follow some recommendations: no drink for at least 60 min before being measured, empty bladder, remove all metallic objects (e.g. earrings, belt), remove right shoe and sock. The children laid on the back on a non-conductive surface, spreading the legs (20–25 cm until a thigh gap), and the arms (10 cm on the side). For measurement, 4 disposable adhesive electrodes were placed on the dorsal sites, 2 on the left hand (one on the up of the third metacarpal, one on the wrist), 2 others on the left foot (one on the ankle between both malleolus, one between the up of the second and the third metatarsal), with at least 5 cm gap between both electrodes. To ensure representativeness, all measurements above-mentioned were measured at least twice by trained professionals and were averaged. If measurements were too distant (more than 5%), a third measurement was performed.

All these measurements allowed to compute fat free mass (FFM, kg) using an equation developed in children between 4 and 9 years (Goran et al., 1996), and already used in several epidemiological studies (Saldanha-Gomes et al., 2017).

$$Fat\ free\ mass = (0.16 \times subscapular\ skinfold) + (0.33 \times weight) + (0.11 \times triceps\ skinfold) - \left(0.16 \times \frac{Height^2}{Resistance}\right) - (0.43 \times sex) - 2.4.$$

Skinfolds are in millimeters, weight in kilograms, height in centimeters, resistance in ohm and sex is coded as 0 for females and 1 for males. We selected Goran equation according to different criteria: ethnicity, age: before puberty, children without disease, data available in SEPAGES cohort, and sex-specific.

Subsequently, the percentage of fat mass (%FM, in %) was computed using the following equation: ((infant weight - infant fat free mass)* 100)/infant weight). Of the 379 children who attended the 3 years visit, fat mass could be calculated for 341 children.

2.5. Statistical analysis

2.5.1. Standardization and transformation of metabolite concentrations

In 94% of the urine pools, triclocarban, bisphenols F, B, and AF were below the limit of detection (LOD) and were not included in statistical analysis (Supplementary Table S2). Chemicals detected in less than 70% of samples or quantified in less than 50% of the samples were categorized as below the LOD, between the LOD to the limit of quantification (LOQ) and above the LOQ; specifically, bisphenol S and butylparaben all periods and propylparaben and ethylparaben concentrations at 2 months postnatal. To evaluate potential contamination from the diapers in children urine samples, total and free forms of phenol concentrations were measured and then we regressed the free against conjugated forms using the Akritas-Thiel-Sen non-parametric linear regression (Helsel et al., 2012), as described elsewhere (Rolland et al., 2020). Bisphenol A (at 2 month and 1-year) and methylparaben (at 1 year) showed a potential contamination, thus both total and conjugated concentrations (total concentration less free concentration) were used in the analysis for these substances at these time point. For the remaining compounds and periods data total concentrations were used as continuous variables and singly imputed by values randomly selected between 0 and the LOD and between the LOD and the LOQ, respectively, based on the estimated underlying distribution (Lubin et al., 2004). Then, to reduce bias of between-sample variations related to differences in urine processing and assay, we standardized concentrations for continuous exposures, using a 2-steps approach (Mortamais et al., 2012). Sampling conditions were considered: sample transport time from volunteer's home to the biobank, time during which the individual samples were thawed at 4 °C during the pooling procedure (defreeze time) and analytical batches.

Multiple linear regressions were performed between each metabolite and their sampling conditions, regressions were adjusted for potential confounders: mother's age at conception, mother's pre-pregnancy BMI, mother parity, specific gravity, season, and date of measurements. We identify the condition with a non-negligible effect on each biomarker concentration (Wald's p-value <0.20), and subtracted the β values associated with the conditions from the measured concentration to obtain standardized concentrations (Supplementary Table S3).

Molar sums of metabolites (unit: μmoles/l) from the same parent compounds were computed as follow: ΣDiNP = *ohMiNP*/308.2 + *oxoMiNP*/306.2 + *cxMiNP*/322.2, ΣDEHP = *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.

Finally, concentrations were ln-transformed to approach normality and then used in the linear regression leading to betas given for one unit increase in ln-transformed chemicals, corresponding to 2.72-fold increase in chemical concentrations.

2.5.2. Associations between individual compound and fat mass

Multiple adjusted linear regressions were performed between percentage of fat mass and each compound (individual metabolites or molar sum) at each time point. We further investigate the potential effect modification by infant sex, by adding an interaction term between biomarker concentration and infant sex in the linear regression, when p-value of interaction was <0.20, sex-stratified analysis was performed.

Linear regressions were adjusted for: maternal age (<35 vs. ≥ 35 years at inclusion), maternal pre-pregnancy weight (continuous), maternal height (continuous), paternal weight (continuous), paternal height (continuous), parity (nulliparous vs. parous), breastfeeding duration (continuous, in week), maternal education (up to 4 years vs. more years after high school), child sex (males vs. females), and infant history of passive smoking (yes/no). Analyses were not adjusted for a marker of urine dilution since a previous study showed that it is not always suitable for pooled samples (Philippat and Calafat, 2021).

Imputation of missing values was performed for covariates using the median for continuous variables (mother height [n = 1], father height

[n = 34]. father weight [n = 30]and breastfeeding duration [n = 7]) and the mode for categorical variables (maternal educational level [n = 2], and infant history of passive smoking [n = 2]).

2.5.3. Sensitivity analyses

Then sensitivity analyses were performed by 1) further adjusting for specific gravity measured in each pool, 2) removing the extreme values (below 1st and above 99th percentiles) of exposures and fat mass.

All data analyses were performed with R version 3.6.3.

3. Results

3.1. Description

Most women were highly educated with a high degree of education (Master's degree or higher, N = 198, 58 %) lived with a partner (N = 338, 99%) and were mostly parous (N = 191, 56%; Table 1). The majority of SEPAGES mothers had a pre-pregnancy BMI in normal range (BMI between 18.5 and 25 kg/m^2, N = 258, 76%), according to the WHO classification.

At the 3-years clinical visit, children weighted on average 14.6 kg (percentiles 25–75: 13.6–15.7 kg) with 13.4 % (percentiles 25–75: 11.1–16.4 %) of fat mass (Table 2). While males tended to have higher weight than females (median 14.7 kg for males and 14.2 kg for females, p = 0.03), BMI were similar and conversely males had lower percentage of fat mass than females (median 11.6 % for males and 16.1 % for females, p < 0.01). Fat mass showed moderate correlations with weight (Pearson correlation r = 0.33) and BMI (r = 0.52; Supplementary Fig. S1).

Of the 341 children with fat mass measurements, chemical data were available for all of their mothers (n = 340 at s trimester and n = 336 at the third trimester) and 335 children (n = 323 at 2 months and n = 308 at 12 months (Supplementary Table S2 and Supplementary Fig. S2). We observed overall low to moderate correlations between the different measurement weeks (Supplementary Fig. S3). However, we observed low to high correlation between concentrations within the same time point, specifically between parabens (Spearman correlation estimates rho ranged from 0.27 to 0.78), between phenols (rho ranged from 0. 07 to 0.30), between phthalates (rho ranged from 0.11 to 0.76).

Table 1
Population characteristics (N = 341 from the SEPAGES cohort).

Population characteristics	N (%) or Median [P25-P75]
Maternal Age at inclusion (years)	
<35	243 (71)
≥35	98 (29)
Parity	
Nulliparous	150 (44)
Parous	191 (56)
Maternal pre-pregnancy weight (kg)	58.5 [53.5–65]
Maternal height (cm, 1 missing[a])	164.8 [160.7–169.3]
BMI (kg/m^2, 1 missing[a])	21.4 [19.7–23.7]
<18.5	25 (7)
18.5< BMI <25	258 (76)
25< BMI <30	45 (13)
>30	12 (4)
Maternal education (after high school)	
Up to 4 years	141 (41)
4 or more years	198 (58)
Missing[a]	2 (<1)
Maternal relationship status	
Living with a partner	338 (99)
Living alone	3 (<1)
Paternal weight (kg, 30 missing[a])	75.0 [69.3–83.2]
Paternal height (cm, 34 missing[a])	178.5 [174.2–182.2]
Child sex	
Male	185 (54)
Female	156 (46)
Birth weight (g)	3300 [3060–3580]
Birth height (cm, 1 missing[a])	50 [49–52]
Birth head circumference (cm, 7 missing[a])	35.0 [34.0–35.5]
Breastfeeding (weeks, 7 missing[a])	26.3 [17.1–43.3]
Child history of passive smoking	
Yes	80 (23)
No	259 (76)
Missing[a]	2 (<1)

[a] For analysis missing values were imputed.

Table 2
Anthropometric measurements of the children at the 3-years clinical visit (N = 341 from the SEPAGES cohort).

Measurements	All Median [P25-P75]	Males (N = 185) Median [P25-P75]	Females (N = 156) Median [P25-P75]	p*
Age at the visit (year, 1 missing)	3.1 [3.0–3.1]	3.1 [3.0–3.1]	3.1 [3.0–3.1]	**0.02**
Weight (kg)	14.6 [13.6–15.7]	14.7 [13.8–15.8]	14.2 [13.4–15.6]	**0.03**
Height (cm)	95.2 [93.0–97.8]	95.5 [93.8–98.0]	95.0 [92.2–97.0]	**<0.01**
BMI (kg/m^2)	16.1 [15.2–16.9]	16.1 [15.3–16.7]	16.1 [15.1–16.9]	0.88
Subscapular fold (mm)	5.2 [4.7–6.1]	5.1 [4.6–5.8]	5.6 [4.9–6.5]	**<0.01**
Triceps fold (mm)	8.3 [7.3–9.8]	7.9 [7.1–9.3]	8.8 [7.7–10.5]	**<0.01**
Fat free mass (kg)	12.5 [11.7–13.4]	12.9 [12.2–13.8]	12.0 [11.3–12.8]	**<0.01**
Fat mass (%)	13.4 [11.1–16.4]	11.6 [10.0–13.4]	16.1 [13.8–18.8]	**<0.01**

Note: * p-values from Student test comparing males vs. females; bold highlights p-values <0.05.
Abbreviations: BMI: body mass index, P25: percentile 25, P75: percentile 75.

3.2. Associations between individual compound and fat mass

Most association were seen with second trimester's exposure and were positive. Regarding exposure assessed during the second trimester, exposure to bisphenol S levels above LOQ at the second trimester was significantly associated with a 1.49% increased fat mass (beta coefficient (β) = 1.49, 95% confidence interval (CI) = 0.65 to 2.32, Table 3), compared to exposure levels below LOD. Urinary concentrations of several phthalate metabolites, MEP, MnBP and MBzP, were associated with increased fat mass (β = 0.36, 95% CI = 0 to 0.72; β = 0.77, 95% CI = 0.16 to 1.38 and β = 0.74, 95% CI = 0.27 to 1.22, respectively).

Regarding exposure assessed during the third trimester, triclosan was negatively associated with fat mass (β = −0.19, 95% CI = −0.37 to −0.01) and ∑DiNP tended to be negatively associated with fat mass (β = −0.39, CI = −0.84 to 0.06).

Regarding postnatal exposures, there were no significant associations between infant urinary concentration and fat mass percent. Exposure to butylparaben levels above LOQ at two months tended to be associated with increased fat mass at 3 years of age (β = 1.08, 95% CI = −0.14 to 2.29, Table 3), compared to exposure levels below LOD. Also, MnBP concentration at one year tended to be positively associated with fat mass (β = 0.97, 95% CI = −0.13 to 2.07).

3.3. Effect modification by sex

Interaction analysis with child sex revealed effect modifications for some phthalate metabolites (i.e. MEP, MBzP, ∑DiNP) and ∑DINCH at either second or third trimester of pregnancy with mostly stronger positive association among females (p-value of interaction <0.20, Table 3). Specifically, after sex stratification, MEP at second trimester was positively associated with fat mass among females (β = 0.67, 95% CI = 0.01 to 1.35) but not among males (β = 0.10, 95% CI = −0.31 to 0.51; Fig. 1 and Supplementary Table S4). MBzP was positively

Table 3
Adjusted regressions for associations of postnatal exposures with fat mass percent at 3 years of age.

Exposures	2nd trimester (N = 341)				3rd trimester (N = 341)				2 Months (N = 335)				1 Year (N = 335)			
	β	[95% IC]	p	p-int	β	[95% IC]	p	p-int	β	[95% IC]	p	p-int	β	[95% IC]	p	P-int
MEPA	0.02	[-0.22 to 0.26]	0.89	0.35	0.02	[-0.15 to 0.20]	0.80	0.29	0.08	[-0.22 to 0.37]	0.61	0.85	0.00	[-0.38 to 0.37]	0.99	
MEPAconjugated[a]													0.07	[-0.10 to 0.24]	0.42	**0.16**
ETPA	−0.03	[-0.27 to 0.21]	0.81	0.62	−0.05	[-0.29 to 0.19]	0.67	0.74					0.05	[-0.31 to 0.42]	0.77	0.52
ETPA LOD-LOQ									−0.91	[-2.93 to 1.11]	0.38					
ETPA > LOQ									−0.43	[-2.41 to 1.54]	0.67					
PRPA	−0.08	[-0.20 to 0.05]	0.22	0.36	0.02	[-0.09 to 0.13]	0.74	0.83					0.18	[-0.12 to 0.47]	0.24	0.73
PRPA LOD-LOQ									0.21	[-1.46 to 1.88]	0.80					
PRPA > LOQ									−0.17	[-0.93 to 0.58]	0.65					
BUPA LOD-LOQ	0.32	[-0.75 to 1.39]	0.55		0.90	[-0.16 to 1.96]	0.10		−0.50	[-1.53 to 0.52]	0.33		−0.16	[-1.34 to 1.03]	0.80	
BUPA > LOQ	0.45	[-0.79 to 1.69]	0.48		0.15	[-1.02 to 1.33]	0.80		1.08	[-0.14 to 2.29]	0.08		−0.39	[-1.24 to 0.46]	0.37	
BPA	0.14	[-0.29 to 0.56]	0.53	0.76	−0.14	[-0.51 to 0.23]	0.47	0.54	0.03	[-0.92 to 0.98]	0.95		−0.70	[-1.73 to 0.33]	0.18	
BPAconjugated[a]									–0.03	[-0.37 to 0.30]	0.85	0.96	–0.16	[-0.54 to 0.23]	0.42	0.26
BPS LOD-LOQ	−1.08	[-2.65 to 0.50]	0.18		0.36	[-1.2 to 1.93]	0.65		0.58	[-0.16 to 1.33]	0.13		−0.03	[-1.05 to 0.98]	0.95	
BPS > LOQ	1.49	[0.65 to 2.32]	**<0.01**		0.12	[-0.74 to 0.99]	0.78		0.15	[-1.37 to 1.68]	0.84		0.06	[-0.80 to 0.93]	0.89	
BP-3	0.09	[-0.14 to 0.32]	0.46	0.65	−0.05	[-0.29 to 0.20]	0.70	0.61	−0.09	[-0.75 to 0.58]	0.80	0.28	0.57	[-0.35 to 1.48]	0.22	0.71
Triclosan	−0.06	[-0.24 to 0.11]	0.47	0.63	−0.19	[-0.37 to −0.01]	**0.03**	0.54	−0.20	[-0.91 to 0.51]	0.58	0.55	−0.28	[-1.04 to 0.48]	0.48	0.57
MEP	0.36	[0.00 to 0.72]	**0.05**	**0.10**	0.12	[-0.22 to 0.47]	0.48	**0.13**					0.62	[-0.35 to 1.60]	0.21	0.79
MnBP	0.77	[0.16 to 1.38]	**0.01**	0.79	−0.20	[-0.76 to 0.35]	0.47	0.48					0.97	[-0.13 to 2.07]	0.09	0.68
MiBP	0.32	[-0.26 to 0.89]	0.28	0.37	−0.06	[-0.58 to 0.46]	0.81	**0.09**					0.52	[-0.44 to 1.47]	0.29	0.52
MBzP	0.74	[0.27 to 1.22]	**<0.01**	**0.05**	−0.03	[-0.47 to 0.41]	0.88	**<0.01**					0.19	[-0.53 to 0.91]	0.60	0.67
ohMPHP	0.23	[-0.38 to 0.84]	0.47	0.29	−0.40	[-1.01 to 0.20]	0.19	0.37					0.37	[-0.94 to 1.69]	0.58	0.75
∑DiNP	0.26	[-0.20 to 0.72]	0.27	**0.11**	−0.39	[-0.84 to 0.06]	0.09	0.85					0.24	[-0.33 to 0.81]	0.40	0.91
∑DEHP	0.49	[-0.11 to 1.09]	0.11	0.49	0.13	[-0.51 to 0.78]	0.68	0.57					0.23	[-0.26 to 0.72]	0.36	0.93
∑DINCH	−0.06	[-0.44 to 0.32]	0.76	0.72	0.02	[-0.34 to 0.38]	0.90	**0.16**					0.17	[-0.22 to 0.56]	0.39	0.60

Note: Adjusted for: mother pre-pregnancy weight, mother height, mother age at conception, mother education, mother parity, father weight, father height, duration breastfeeding, child history of passive smoking and child sex.
P-int: Interaction p-value between sex.
Chemicals categorized were not tested for sex-specific interaction because of small sample size.
Bold highlights p-values <0.05 and p-values interaction <0.2.
Because of budgetary restriction, phthalates and DINCH metabolites concentrations in children urine at 2 months of age were not measured.
Abbreviations: T2: second trimester, T3: third trimester, LOD: limit of detection, LOQ: limit of quantification, MEPA: methylparaben, MEPA conjugated: methylparaben conjugated form, ETPA: ethylparaben, PRPA: propylparaben, BUPA: butylparaben, BPA: bisphenol A, BPA conjugated: bisphenol A conjugated form, BPS: bisphenol S, BP-3: benzophenone-3, MEP: monoethyl phthalate, MnBP: mono-n-butyl phthalate, MiBP: mono-iso-butyl phthalate, MBzP: monobenzyl phthalate, ohMPHP: 6-hydroxy monopropylheptyl phthalate, DiNP: Diisononyl phthalate, DEHP: Di(2-ethylhexyl) phthalate, DINCH: 1,2-Cyclohexane dicarboxylic acid, diisononyl ester.
[a] Because of a potential contamination MEPA and BPA were also used as conjugated form.

associated with fat mass among females (β = 1.22, 95% CI = 0.49 to 1.96 at s trimester and β = 0.66, 95% CI = -0.02 to 1.34 at third trimester) and negatively associated with fat mass among males (β = −0.66, 95% CI = -1.23 to −0.10 at third trimester). ∑DiNP at second trimester tended to be positively associated with fat mass among females (β = 0.68, 95% CI = −0.07 to 1.42) but not among males (β = −0.18, 95% CI = −0.77 to 0.40).

While no modification in effects based on sex was found at 2 months, methylparaben at 1-year tended to be positively associated with fat mass among females (β = 0.26, 95% CI = −0.04 to 0.56), but not among males (β = −0.02, 95% CI = −0.22 to 0.19).

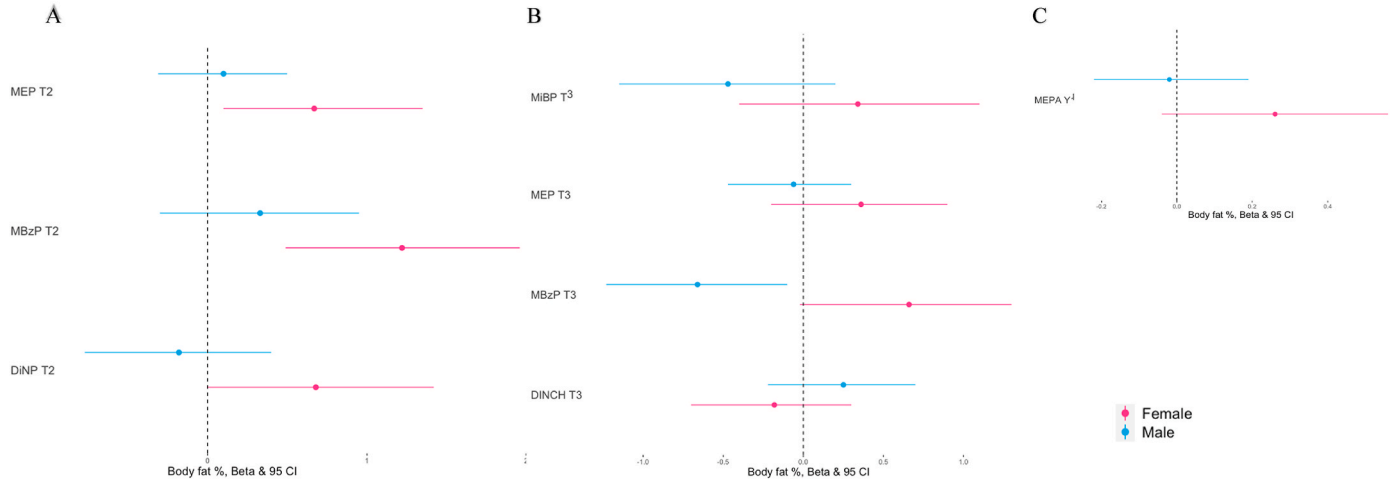

Fig. 1. Sex-stratified change in body fat mass (%) at 3 years with chemicals exposure A) during the second trimester, B) during the third trimester, C) at 1-year.
Note: Dots indicate the estimates; horizontal lines, the 95% CIs; vertical dashed lines, the null.
Adjusted for: mother pre-pregnancy weight, mother height, mother age at conception, mother education, mother parity, father weight, father height, duration breastfeeding, child history of passive smoking.
T2: 2nd trimester: N = 340, Males N = 184, Females N = 156.
T3: 3rd trimester: N = 336, Males N = 185, Females N = 151.
M2: 2-month: N = 323, Males N = ,175 Females N = 148.
Y1: 1-year: N = 308, Males N = 163, Females N = 145.
Abbreviations: MEPA: methylparaben, MEP: monoethyl phthalate, MiBP: mono-iso-butyl phthalate, MBzP: monobenzyl phthalate, DiNP: Diisononyl phthalate, DINCH: 1,2-Cyclohexane dicarboxylic acid, diisononyl ester.

3.4. Sensitivity analysis

Results of the sensitivity analysis further adjusted for specific gravity (Supplementary Table S5) and Analyses after removing values below 1st and above 99th percentiles (Supplementary Table S6) gave overall similar results to those of our main analysis.

4. Discussion

Relying on a large number of repeated within-subject urine samples during pregnancy, our study highlighted mainly positive associations between prenatal exposure to phenols and phthalates and child fat mass at 3 years of age. Specifically, prenatal exposures to bisphenol S, MEP, MnBP and MBzP were associated with an increase of fat mass, while triclosan was associated with a decreased fat mass. Furthermore, prenatal exposure to MEP and MBzP showed effect modification by sex with a strongest positive association among females. Postnatal exposure was not associated with fat mass at 3 years of age, possibly due to higher inter-day variability and error risk from using one urine sample per day instead of three, as done during pregnancy.

Regarding phenols, while we observed a positive association between bisphenol S exposure in the second trimester and fat mass at 3 years of age, the comparison with previous studies is not straightforward since our study is only the second to investigate the association of prenatal and early-postnatal exposures to bisphenol S and child adiposity. The only one other study from Ouidir et al. using the same cohort, found also a positive association at second trimester with BMI (Ouidir et al., 2024). However, three studies investigated children bisphenol S exposure in later ages (between 6 and 12 years, assessed with only one urine sample) and childhood-adolescent obesity, two studies did not find any associations (Gajjar et al., 2022; Liu et al., 2019) whereas others reported a positive association (Chen Zee et al., 2013; Jacobson et al., 2019).

For bisphenol A, most studies reported positive association between prenatal bisphenol A and adiposity in childhood (Braun et al., 2019; Buckley et al., 2016b; Hoepner et al., 2016; Valvi et al., 2013) whereas our study did not find any significant association either with prenatal and early postnatal exposure, which is consistent with some previous studies for prenatal (Berger et al., 2021; Braun et al., 2014; Ouidir et al., 2024; Philippat et al., 2014) and all postnatal studies (Braun et al., 2014; Harley et al., 2013; Hoepner et al., 2016; Ouidir et al., 2024). Our finding of negative association between exposure to triclosan during 2nd trimester and the percentage of fat mass, is in line with the previous paper on BMI from this cohort(Ouidir et al., 2024) but differ from previous studies. Most previous studies did not report any significant association between triclosan and infant adiposity (Berger et al., 2021; Buckley et al., 2016b; Kalloo et al., 2018; Philippat et al., 2014), while a study found a positive association with weight z-score among females at two years (using three urine samples during pregnancy to assess triclosan, N = 850) (Wu et al., 2018). Finally, postnatal exposure to triclosan was not associated with fat mass, in line with previous studies (Buser et al., 2014; Kalloo et al., 2018; Ouidir et al., 2024).

Regarding parabens, we did not find any association either with prenatal exposure or postnatal exposure. However, previous studies have reported a positive association between child adiposity and prenatal butylparaben (Højsager et al., 2021), propylparaben (Berger et al., 2021) and methylparaben (Philippat et al., 2014).

For 13 of the 16 phthalate metabolites studied, we did not find any associations, aligning with some previous prenatal studies (Buckley et al., 2016a; Nidens et al., 2021; Ouidir et al., 2024). However, we reported a positive association between child fat mass at 3 years of age and prenatal exposure to MEP, MBzP and MnBP, in line with previously published studies (Berger et al., 2021; Botton et al., 2016; Harley et al., 2017).One study reported positive associations between prenatal MEP, MnBP, MBzP and obesity, BMI, waist circumference at 5 years of age (using two urine samples during pregnancy, N = 341)(Harley et al., 2017), and another showed a positive association between MEP and BMI at 5 years of age (using two urine samples during pregnancy, N = 309) (Berger et al., 2021). Regarding postnatal exposure, one study reported positive association between MnBP and BMI (Ouidir et al., 2024), and another study (age between 4 and 6 years) reported association for MBzP, with positive association for females and negative for males (Vafeiadi et al., 2018).

In our study we reported effect modification by sex with prenatal

exposure to MEP and MBzP, with stronger positive associations among females and a negative association between MBzP at third trimester among males. Our results regarding MBzP are in lines with previous studies, one reporting a positive association for BMI with MBzP for females and negative for males (Ouidir et al., 2024) and the other showing a negative association between BMI and non-DEHP for males (Maresca et al., 2016).

Finally, this study is one of the first to investigate the association with adiposity in children for DINCH a compound used to replace DEHP. The only one other study did not find any associations (Ouidir et al., 2024), in line with our results. However, our study revealed potential effect modifications by child sex, where the association seemed to be negative for females and positive for males. Further research is necessary to explore the impact of prenatal exposure to DINCH on adiposity in later-life.

Different hypotheses could explain disparities between studies, such as variations in timing and number of urine sample collected, the children's age at the adiposity assessment and differences in the methods used to evaluate fat mass. Specifically, regarding children's age, all studies selected had pre-pubertal children, but all of them assessed postnatal exposures among children older than those in our study. Then, regarding the dosage of biomarkers, previous studies used between one and three urine samples during pregnancy or infancy (Braun et al., 2014; Kalloo et al., 2018; Maresca et al., 2016; Wu et al., 2019), compared to up to 42 urine samples during pregnancy and 14 during infancy in this study.

The obesogenic impacts of phenols and phthalates may arise from their interactions with hormone receptors within the nuclear receptor family (Swedenborg et al., 2009). These include sex steroid hormone receptors, xenobiotic sensors, and metabolic regulators such as glucocorticoid and thyroid receptors (Nakiwala et al., 2022). Phenols and phthalates can also act as either agonists or antagonists on estrogen receptors, depending on the specific compound (Le Magueresse-Battistoni et al., 2018). Phthalates are known to impact the aryl hydrocarbon receptor (AhR), which plays a key role in regulating lipogenesis and glucose homeostasis (Sato et al., 2008; Thackaberry et al., 2003). Finally, phenols and phthalates have also pro-inflammatory effects through upregulation of the peroxisome proliferator-activated receptors (PPARs) and induction of cyclooxygenase-2 expression. Our observed positive association between prenatal exposure and childhood adiposity, contrasted with the lack of association for early-life exposure, underscores the heightened sensitivity of the in utero period to metabolic disruptions, aligning with the hypothesis of the developmental origins of health and disease (Barker, 1998; Grün and Blumberg, 2006).

This study has some strengths and limitations. First, we acknowledge that the sample size is modest limiting our ability to detect small effect. However, the collection of repeated urine samples in our study (up to 42 urine samples per pregnant women and up to 14 per children), combined with the within-subject pooling, should be more representative of their exposure and decreases bias in the effect estimates (Perrier et al., 2016; Vernet et al., 2019), and thus increase the potential to detect effects. This method allows for greater power than previous studies of a similar sample size, but using only one urine sample may not have revealed the full extent of variability. Second, thanks to the longitudinal design we were able to consider exposure during prenatal and early post-natal life, two crucial periods for child development. Third, we acknowledge that there were no available data regarding children's diet and physical activity, it could be interesting to incorporate these variables as adjustments in our regression models. Finally, using BIA and the Goran equation is a strength due to its performance compared to the gold standard measurement, explaining 91% of the variation in total fat mass as measured by the standard method, DXA (Goran et al., 1996). Furthermore, we used the Goran's equation that have been performed among healthy children and suitable for the SEPAGES children (in term of ethnicity, age), whereas other equations were not suitable in term of age (Clasey et al., 2011; Houtkooper et al., 1989; Slaughter et al., 1988) or did not account for skinfolds and children's sex (Clasey et al., 2011; Jensen et al., 2015).

In conclusion, this study adds on the scarce literature on the impact of early-life exposure to phenols, parabens and phthalates. We found significant association between prenatal exposures and fat mass in preschool children: specifically, bisphenol S, MEP, MBzP, MnBP were associated with an increase of fat mass, while triclosan was associated with a decreased fat mass. MEP, MiBP, MBzP, ∑DiNP, showed a stronger positive effect among females.

Furthermore, this is the first study investigating the effect of early-life exposure to bisphenol S and child body fat mass, and as we reported potential obesogenic effect of the chemicals, this highlights the need of further research on this new compound.

CRediT authorship contribution statement

Maude Colombini: Writing – original draft, Formal analysis, Data curation. **Barbara Heude:** Writing – review & editing, Resources. **Sarah Lyon-Caen:** Writing – review & editing, Project administration. **Cathrine Thomsen:** Writing – review & editing, Resources. **Amrit K. Sakhi:** Writing – review & editing, Resources. **Séverine Valmary-Degano:** Writing – review & editing, Resources. **Sam Bayat:** Writing – review & editing, Investigation. **Rémy Slama:** Writing – review & editing, Funding acquisition. **Claire Philippat:** Writing – review & editing, Funding acquisition. **Marion Ouidir:** Writing – review & editing, Supervision.

Conflicts of interest

The authors declare they have nothing to disclose.

Data availability

Data used in this study are confidential and can be provided upon a reasonable request and after approval of the SEPAGES steering committee.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.120555.

Data availability

Data will be made available on request.

References

Barker, D.J., 1998. In utero programming of chronic disease. Clin. Sci. Lond. Engl. 95, 115–128, 1979.

Berger, K., Hyland, C., Ames, J.L., Mora, A.M., Huen, K., Eskenazi, B., Holland, N., Harley, K.G., 2021. Prenatal exposure to Mixtures of phthalates, parabens, and other phenols and obesity in five-year-Olds in the CHAMACOS cohort. Int. J. Environ. Res. Public. Health 18, 1796. https://doi.org/10.3390/ijerph18041796.

Botton, J., Philippat, C., Calafat, A.M., Carles, S., Charles, M.-A., Slama, R., 2016. Phthalate pregnancy exposure and male offspring growth from the intra-uterine period to five years of age. Environ. Res. 151, 601–609. https://doi.org/10.1016/j.envres.2016.08.033.

Braun, J.M., Lanphear, B.P., Calafat, A.M., Deria, S., Khoury, J., Howe, C.J., Venners, S. A., 2014. Early-life bisphenol a exposure and child body mass index: a prospective cohort study. Environ. Health Perspect. 122, 1239–1245. https://doi.org/10.1289/ehp.1408258.

Braun, J.M., Li, N., Arbuckle, T.E., Dodds, L., Massarelli, I., Fraser, W.D., Lanphear, B.P., Muckle, G., 2019. Association between gestational urinary bisphenol a concentrations and adiposity in young children: the MIREC study. Environ. Res. 172, 454–461. https://doi.org/10.1016/j.envres.2019.02.038.

Buckley, J.P., Engel, S.M., Mendez, M.A., Richardson, D.B., Daniels, J.L., Calafat, A.M., Wolff, M.S., Herring, A.H., 2016a. Prenatal phthalate exposures and childhood fat mass in a New York city cohort. Environ. Health Perspect. 124, 507–513. https://doi.org/10.1289/ehp.1509788.

Buckley, J.P., Herring, A.H., Wolff, M.S., Calafat, A.M., Engel, S.M., 2016b. Prenatal exposure to environmental phenols and childhood fat mass in the Mount Sinai Children's Environmental Health Study. Environ. Int. 91, 350–356. https://doi.org/10.1016/j.envint.2016.03.019.

Buser, M.C., Murray, H.E., Scinicariello, F., 2014. Association of urinary phenols with increased body weight measures and obesity in children and adolescents. J. Pediatr. 165, 744–749. https://doi.org/10.1016/j.jpeds.2014.06.039.

Casals-Casas, C., Desvergne, B., 2011. Endocrine Disruptors: from endocrine to metabolic disruption. Annu. Rev. Physiol. 73, 135–162. https://doi.org/10.1146/annurev-physiol-012110-142200.

Chen Zee, E., Cornet, P., Lazimi, G., Rondet, C., Lochard, M., Magnier, A.M., Ibanez, G., 2013. Effets des perturbateurs endocriniens sur les marqueurs de la périnatalité. Gynécologie Obstétrique Fertil 41, 601–610. https://doi.org/10.1016/j.gyobfe.2013.08.012.

Clasey, J.L., Bradley, K.D., Bradley, J.W., Long, D.E., Griffith, J.R., 2011. A new BIA equation estimating the body composition of young children. Obesity 19, 1813–1817. https://doi.org/10.1038/oby.2011.158.

de Onis, M., Blössner, M., Borghi, E., 2010. Global prevalence and trends of overweight and obesity among preschool children. Am. J. Clin. Nutr. 92, 1257–1264. https://doi.org/10.3945/ajcn.2010.29786.

Ebbeling, C.B., Pawlak, D.B., Ludwig, D.S., 2002. Childhood obesity: public-health crisis, common sense cure. Lancet 360, 473–482. https://doi.org/10.1016/S0140-6736(02)09678-2.

Elobeid, M.A., Allison, D.B., 2008. Putative environmental-endocrine Disruptors and obesity: a review. Curr. Opin. Endocrinol. Diabetes Obes. 15, 403–408. https://doi.org/10.1097/MED.0b013e32830ce95c.

Gajjar, P., Liu, Y., Li, N., Buckley, J.P., Chen, A., Lanphear, B.P., Kalkwarf, H.J., Cecil, K. M., Yolton, K., Braun, J.M., 2022. Associations of mid-childhood bisphenol A and bisphenol S exposure with mid-childhood and adolescent obesity. Environ. Epidemiol. Phila. Pa 6, e187. https://doi.org/10.1097/EE9.0000000000000187.

Goran, M., Driscoll, P., Johnson, R., Nagy, T., Hunter, G., 1996. Cross-calibration of body-composition techniques against dual-energy X-ray absorptiometry in young children. Am. J. Clin. Nutr. 63, 299–305. https://doi.org/10.1093/ajcn/63.3.299.

Gore, A.C., Chappell, V.A., Fenton, S.E., Flaws, J.A., Nadal, A., Prins, G.S., Toppari, J., Zoeller, R.T., 2015. EDC-2: the endocrine Society's second Scientific statement on endocrine-disrupting chemicals. Endocr. Rev. 36, E1–E150. https://doi.org/10.1210/er.2015-1010.

Grün, F., Blumberg, B., 2006. Environmental Obesogens: Organotins and endocrine disruption via nuclear receptor Signaling. Endocrinology 147, s50–s55. https://doi.org/10.1210/en.2005-1129.

Harley, K.G., Aguilar Schall, R., Chevrier, J., Tyler, K., Aguirre, H., Bradman, A., Holland, N.T., Lustig, R.H., Calafat, A.M., Eskenazi, B., 2013. Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort. Environ. Health Perspect. 121, 514–520. https://doi.org/10.1289/ehp.1205548.

Harley, K.G., Berger, K., Rauch, S., Kogut, K., Claus Henn, B., Calafat, A.M., Huen, K., Eskenazi, B., Holland, N., 2017. Association of prenatal urinary phthalate metabolite concentrations and childhood BMI and obesity. Pediatr. Res. 82, 405–415. https://doi.org/10.1038/pr.2017.112.

Helsel, D.R., Helsel, D.R., Helsel, D.R., 2012. Statistics for Censored Environmental Data Using Minitab and R, second ed. Wiley, Hoboken, N.J. https://doi.org/10.1002/9781118162729.

Hoepner, L.A., Whyatt, R.M., Widen, E.M., Hassoun, A., Oberfield, S.E., Mueller, N.T., Diaz, D., Calafat, A.M., Perera, F.P., Rundle, A.G., 2016. Bisphenol A and adiposity in an Inner-City birth cohort. Environ. Health Perspect. 124, 1644–1650. https://doi.org/10.1289/EHP205.

Højsager, F.D., Kyhl, H.B., Frederiksen, H., Juul, A., Andersson, A.-M., Andersen, M.S., Grøntved, A., Jensen, T.K., 2021. Prenatal exposure to butyl paraben is associated with fat percentage in 7-year-Old boys. J. Clin. Endocrinol. Metab. 106, e2633–e2638. https://doi.org/10.1210/clinem/dgab167.

Houtkooper, L.B., Lohman, T.G., Going, S.B., Hall, M.C., 1989. Validity of bioelectric impedance for body composition assessment in children. J. Appl. Physiol. 66, 814–821. https://doi.org/10.1152/jappl.1989.66.2.814.

Jacobson, M.H., Woodward, M., Bao, W., Liu, B., Trasande, L., 2019. Urinary bisphenols and obesity prevalence among U.S. Children and adolescents. J. Endocr. Soc. 3, 1715–1726. https://doi.org/10.1210/js.2019-00201.

Jebeile, H., Kelly, A.S., O'Malley, G., Baur, L.A., 2022. Obesity in children and adolescents: epidemiology, causes, assessment, and management. Lancet Diabetes Endocrinol. 10, 351–365. https://doi.org/10.1016/S2213-8587(22)00047-X.

Jensen, S.M., Ritz, C., Ejlerskov, K.T., Mølgaard, C., Michaelsen, K.F., 2015. Infant BMI peak, breastfeeding, and body composition at age 3 y. Am. J. Clin. Nutr. 101, 319–325. https://doi.org/10.3945/ajcn.114.092957.

Kahn, L.G., Philippat, C., Nakayama, S.F., Slama, R., Trasande, L., 2020. Endocrine-disrupting chemicals: implications for human health. Lancet Diabetes Endocrinol. 8, 703–718. https://doi.org/10.1016/S2213-8587(20)30129-7.

Kalloo, G., Calafat, A.M., Chen, A., Yolton, K., Lanphear, B.P., Braun, J.M., 2018. Early life Triclosan exposure and child adiposity at 8 Years of age: a prospective cohort study. Environ. Health Glob. Access Sci. Source 17, 24. https://doi.org/10.1186/s12940-018-0366-1.

Kim, Sujin, Lee, S., Shin, C., Lee, J., Kim, Sunmi, Lee, A., Park, J., Kho, Y., Moos, R.K., Koch, H.M., Kim, Sungkyoon, Choi, K., 2018. Urinary parabens and triclosan concentrations and associated exposure characteristics in a Korean population—a

comparison between night-time and first-morning urine. Int. J. Hyg Environ. Health 221, 632–641. https://doi.org/10.1016/j.ijheh.2018.03.009.
Le Magueresse-Battistoni, B., Vidal, H., Naville, D., 2018. Sex-specific metabolic alterations induced by environmental pollutants. Curr. Opin. Toxicol., Mechanistic Toxicology: Metabolic Disruption in Environmental Diseases 8, 1–7. https://doi.org/10.1016/j.cotox.2017.11.007.
Leppert, B., Strunz, S., Seiwert, B., Schlittenbauer, L., Schlichting, R., Pfeiffer, C., Röder, S., Bauer, M., Borte, M., Stangl, G.I., Schöneberg, T., Schulz, A., Karkossa, I., Rolle-Kampczyk, U.E., Thürmann, L., von Bergen, M., Escher, B.I., Junge, K.M., Reemtsma, T., Lehmann, I., Polte, T., 2020. Maternal paraben exposure triggers childhood overweight development. Nat. Commun. 11, 561. https://doi.org/10.1038/s41467-019-14202-1.
Liao, C., Kannan, K., 2014. A Survey of Alkylphenols, bisphenols, and triclosan in personal care products from China and the United States. Arch. Environ. Contam. Toxicol. 67, 50–59. https://doi.org/10.1007/s00244-014-0016-8.
Lifshitz, F., Hecht, J.P., Bermúdez, E.F., Gamba, C.A., Reinoso, J.M., Casavalle, P.L., Friedman, S.M., Rodriguez, P.N., 2016. Body composition analysis by dual-energy X-ray absorptiometry in young preschool children. Eur. J. Clin. Nutr. 70, 1203–1209. https://doi.org/10.1038/ejcn.2016.38.
Liu, B., Lehmler, H.J., Sun, Y., Xu, G., Sun, Q., Snetselaar, L.G., Wallace, R.B., Bao, W., 2019. Association of bisphenol A and its Substitutes, bisphenol F and bisphenol S, with obesity in United States children and adolescents. Diabetes Metab. J 43, 59–75. https://doi.org/10.4093/dmj.2018.0045.
Lubin, J.H., Colt, J.S., Camann, D., Davis, S., Cerhan, J.R., Severson, R.K., Bernstein, L., Hartge, P., 2004. Epidemiologic evaluation of measurement data in the presence of detection limits. Environ. Health Perspect. 112, 1691–1696. https://doi.org/10.1289/ehp.7199.
Lyon-Caen, S., Siroux, V., Lepeule, J., Lorimier, P., Hainaut, P., Mossuz, P., Quentin, J., Supernant, K., Meary, D., Chaperot, L., Bayat, S., Cassee, F., Valentino, S., Couturier-Tarrade, A., Rousseau-Ralliard, D., Chavatte-Palmer, P., Philippat, C., Pin, I., Slama, R., 2019. Deciphering the impact of early-life exposures to highly variable environmental factors on Foetal and child health: design of SEPAGES couple-child cohort. Int. J. Environ. Res. Public. Health 16, 3888. https://doi.org/10.3390/ijerph16203888.
Maresca, M.M., Hoepner, L.A., Hassoun, A., Oberfield, S.E., Mooney, S.J., Calafat, A.M., Ramirez, J., Freyer, G., Perera, F.P., Whyatt, R.M., Rundle, A.G., 2016. Prenatal exposure to phthalates and childhood body size in an urban cohort. Environ. Health Perspect. 124, 514–520. https://doi.org/10.1289/ehp.1408750.
Mortamais, M., Chevrier, C., Philippat, C., Petit, C., Calafat, A.M., Ye, X., Silva, M.J., Brambilla, C., Eijkemans, M.J., Charles, M.-A., Cordier, S., Slama, R., 2012. Correcting for the influence of sampling conditions on biomarkers of exposure to phenols and phthalates: a 2-step standardization method based on regression residuals. Environ. Health 11, 1–14. https://doi.org/10.1186/1476-069X-11-29.
Nakiwala, D., Noyes, P.D., Faure, P., Chovelon, B., Corne, C., Gauchez, A.S., Guergour, D., Lyon-Caen, S., Sakhi, A.K., Sabaredzovic, A., Thomsen, C., Pin, I., Slama, R., Philippat, C., 2022. Phenol and phthalate effects on thyroid hormone levels during pregnancy: relying on in Vitro assays and Adverse Outcome Pathways to Inform an epidemiological analysis. Environ. Health Perspect. 130, 117004. https://doi.org/10.1289/EHP10239.
Nicolaidis, S., 2019. Environment and obesity. Metabolism, Role of Environment in Initiation and Progression of Illnesses 100, 153942. https://doi.org/10.1016/j.metabol.2019.07.006.
Nidens, N., Krönke, A., Jurkutat, A., Schlingmann, M., Poulain, T., Nüchter, M., Kiviranta, H., Körner, A., Vogel, M., Lindh, C., Bornehag, C.-G., Kiess, W., 2021. Associations of prenatal exposure to phthalates and one phthalate substitute with anthropometric measures in early life: results from the German LIFE Child cohort study. Best Pract. Res. Clin. Endocrinol. Metab. 35, 101532. https://doi.org/10.1016/j.beem.2021.101532.
Odegaard, A.O., Choh, A.C., Nahhas, R.W., Towne, B., Czerwinski, S.A., Demerath, E.W., 2013. Systematic examination of infant size and growth Metrics as risk factors for overweight in young adulthood. PLoS One 8, e66994. https://doi.org/10.1371/journal.pone.0066994.
Ouidir, M., Cissé, A.H., Botton, J., Lyon-Caen, S., Thomsen, C., Sakhi, A.K., Sabaredzovic, A., Bayat, S., Slama, R., Heude, B., Philippat, C., 2024. Fetal and infancy exposure to phenols, parabens, and phthalates and anthropometric measurements up to 36 Months, in the longitudinal SEPAGES cohort. Environ. Health Perspect. 132, 057002. https://doi.org/10.1289/EHP13644.
Perrier, F., Giorgis-Allemand, L., Slama, R., Philippat, C., 2016. Within-subject pooling of Biological samples to reduce exposure Misclassification in biomarker-based studies. Epidemiology 27, 378. https://doi.org/10.1097/EDE.0000000000000460.
Philippat, C., Botton, J., Calafat, A.M., Ye, X., Charles, M.-A., Slama, R., EDEN Study Group, 2014. Prenatal exposure to phenols and growth in boys. Epidemiol. Camb. Mass 25, 625–635. https://doi.org/10.1097/EDE.0000000000000132.
Philippat, C., Calafat, A.M., 2021. Comparison of strategies to efficiently combine repeated urine samples in biomarker-based studies. Environ. Res. 192, 110275. https://doi.org/10.1016/j.envres.2020.110275.
Philippat, C., Rolland, M., Lyon-Caen, S., Pin, I., Sakhi, A.K., Sabaredzovic, A., Thomsen, C., Slama, R., 2021. Pre- and early post-natal exposure to phthalates and DINCH in a new type of mother-child cohort relying on within-subject pools of repeated urine samples. Environ. Pollut. 287, 117650. https://doi.org/10.1016/j.envpol.2021.117650.
Philippat, C., Wolff, M.S., Calafat, A.M., Ye, X., Bausell, R., Meadows, M., Stone, J., Slama, R., Engel, S.M., 2013. Prenatal exposure to environmental phenols: concentrations in amniotic fluid and variability in urinary concentrations during pregnancy. Environ. Health Perspect. 121, 1225–1231. https://doi.org/10.1289/ehp.1206335.
Rochester, J.R., Bolden, A.L., 2015. Bisphenol S and F: a systematic review and comparison of the hormonal activity of bisphenol A Substitutes. Environ. Health Perspect. 123, 643–650. https://doi.org/10.1289/ehp.1408989.
Rolland, M., Lyon-Caen, S., Sakhi, A.K., Pin, I., Sabaredzovic, A., Thomsen, C., Slama, R., Philippat, C., SEPAGES study group, 2020. Exposure to phenols during pregnancy and the first year of life in a new type of couple-child cohort relying on repeated urine biospecimens. Environ. Int. 139, 105678. https://doi.org/10.1016/j.envint.2020.105678.
Sabaredzovic, A., Sakhi, A.K., Brantsæter, A.L., Thomsen, C., 2015. Determination of 12 urinary phthalate metabolites in Norwegian pregnant women by core-shell high performance liquid chromatography with on-line solid-phase extraction, column switching and tandem mass spectrometry. J. Chromatogr. B Analyt. Technol. Biomed. Life. Sci. 1002, 343–352. https://doi.org/10.1016/j.jchromb.2015.08.040.
Sahoo, K., Sahoo, B., Choudhury, A.K., Sofi, N.Y., Kumar, R., Bhadoria, A.S., 2015. Childhood obesity: causes and consequences. J. Fam. Med. Prim. Care 4, 187–192. https://doi.org/10.4103/2249-4863.154628.
Sakhi, A.K., Sabaredzovic, A., Papadopoulou, E., Cequier, E., Thomsen, C., 2018. Levels, variability and determinants of environmental phenols in pairs of Norwegian mothers and children. Environ. Int. 114, 242–251. https://doi.org/10.1016/j.envint.2018.02.037.
Saldanha-Gomes, C., Heude, B., Charles, M.-A., de Lauzon-Guillain, B., Botton, J., Carles, S., Forhan, A., Dargent-Molina, P., Lioret, S., 2017. Prospective associations between energy balance-related behaviors at 2 years of age and subsequent adiposity: the EDEN mother–child cohort. Int. J. Obes. 41, 38–45. https://doi.org/10.1038/ijo.2016.138.
Sato, S., Shirakawa, H., Tomita, S., Ohsaki, Y., Haketa, K., Tooi, O., Santo, N., Tohkin, M., Furukawa, Y., Gonzalez, F.J., Komai, M., 2008. Low-dose dioxins alter gene expression related to cholesterol biosynthesis, lipogenesis, and glucose metabolism through the aryl hydrocarbon receptor-mediated pathway in mouse liver. Toxicol. Appl. Pharmacol. 229, 10–19. https://doi.org/10.1016/j.taap.2007.12.029.
Schütze, A., Kolossa-Gehring, M., Apel, P., Brüning, T., Koch, H.M., 2014. Entering markets and bodies: Increasing levels of the novel plasticizer Hexamoll® DINCH® in 24 h urine samples from the German Environmental Specimen Bank. Int. J. Hyg Environ. Health 217, 421–426. https://doi.org/10.1016/j.ijheh.2013.08.004.
Shepherd, J., Ng, B., Sommer, M., Heymsfield, S.B., 2017. Body composition by DXA. Bone 104, 101–105. https://doi.org/10.1016/j.bone.2017.06.010.
Singh, A.S., Mulder, C., Twisk, J.W.R., Van Mechelen, W., Chinapaw, M.J.M., 2008. Tracking of childhood overweight into adulthood: a systematic review of the literature. Obes. Rev. 9, 474–488. https://doi.org/10.1111/j.1467-789X.2008.00475.x.
Slaughter, M.H., Lohman, T.G., Boileau, R.A., Horswill, C.A., Stillman, R.J., Van Loan, M. D., Bemben, D.A., 1988. Skinfold equations for estimation of body fatness in children and youth. Hum. Biol. 60, 709–723.
Song, S., He, Y., Zhang, T., Zhu, H., Huang, X., Bai, X., Zhang, B., Kannan, K., 2020. Profiles of parabens and their metabolites in paired maternal-fetal serum, urine and amniotic fluid and their implications for placental transfer. Ecotoxicol. Environ. Saf. 191, 110235. https://doi.org/10.1016/j.ecoenv.2020.110235.
Swedenborg, E., Power, K.A., Cai, W., Pongratz, I., Rüegg, J., 2009. Regulation of estrogen receptor beta activity and implications in health and disease. Cell. Mol. Life Sci. CMLS 66, 3873–3894. https://doi.org/10.1007/s00018-009-0118-z.
Swift, D.L., Johannsen, N.M., Lavie, C.J., Earnest, C.P., Church, T.S., 2014. The role of Exercise and physical activity in weight Loss and Maintenance. Prog. Cardiovasc. Dis. 56, 441–447. https://doi.org/10.1016/j.pcad.2013.09.012.
Thackaberry, E.A., Bedrick, E.J., Goens, M.B., Danielson, L., Lund, A.K., Gabaldon, D., Smith, S.M., Walker, M.K., 2003. Insulin regulation in AhR-null mice: embryonic cardiac enlargement, neonatal macrosomia, and altered insulin regulation and response in pregnant and aging AhR-null females. Toxicol. Sci. Off. J. Soc. Toxicol. 76, 407–417. https://doi.org/10.1093/toxsci/kfg229.
Vafeiadi, M., Myridakis, A., Roumeliotaki, T., Margetaki, K., Chalkiadaki, G., Dermitzaki, E., Venihaki, M., Sarri, K., Vassilaki, M., Leventakou, V., Stephanou, E. G., Kogevinas, M., Chatzi, L., 2018. Association of early life exposure to phthalates with obesity and cardiometabolic Traits in childhood: sex specific associations. Front. Public Health 6, 327. https://doi.org/10.3389/fpubh.2018.00327.
Valvi, D., Casas, M., Mendez, M.A., Ballesteros-Gómez, A., Luque, N., Rubio, S., Sunyer, J., Vrijheid, M., 2013. Prenatal bisphenol a urine concentrations and early rapid growth and overweight risk in the offspring. Epidemiol. Camb. Mass 24, 791–799. https://doi.org/10.1097/EDE.0b013e3182a67822.
Vernet, C., Philippat, C., Agier, L., Calafat, A.M., Ye, X., Lyon-Caen, S., Hainaut, P., Siroux, V., Schisterman, E.F., Slama, R., 2019. An Empirical validation of the within-subject biospecimens pooling approach to Minimize exposure Misclassification in biomarker-based studies. Epidemiol. Camb. Mass 30, 756–767. https://doi.org/10.1097/EDE.0000000000001056.
Weihrauch-Blüher, S., Schwarz, P., Klusmann, J.-H., 2019. Childhood obesity: increased risk for cardiometabolic disease and cancer in adulthood. Metabolism, Obesity: the 21st century epidemic 92, 147–152. https://doi.org/10.1016/j.metabol.2018.12.001.
Wu, C., Li, J., Xia, W., Li, Y., Zhang, B., Zhou, A., Hu, J., Li, C., Zhao, H., Jiang, M., Hu, C., Liao, J., Huo, W., Chen, X., Xu, B., Lu, S., Cai, Z., Xu, S., 2018. The association of repeated measurements of prenatal exposure to triclosan with fetal and early-childhood growth. Environ. Int. 120, 54–62. https://doi.org/10.1016/j.envint.2018.07.022.
Wu, C., Xia, W., Li, Y., Li, J., Zhang, B., Zheng, T., Zhou, A., Zhao, H., Huo, W., Hu, J., Jiang, M., Hu, C., Liao, J., Chen, X., Xu, B., Lu, S., Cai, Z., Xu, S., 2019. Repeated measurements of paraben exposure during pregnancy in relation to fetal and early childhood growth. Environ. Sci. Technol. 53, 422–433. https://doi.org/10.1021/acs.est.8b01857.

Yan, X., Calafat, A., Lashley, S., Smulian, J., Ananth, C., Barr, D., Silva, M., Ledoux, T., Hore, P., Robson, M.G., 2009. Phthalates biomarker Identification and exposure estimates in a population of pregnant women. Hum. Ecol. Risk Assess. HERA 15, 565–578. https://doi.org/10.1080/10807030902892554.

Yang, C., Lee, H.K., Kong, A.P.S., Lim, L.L., Cai, Z., Chung, A.C.K., 2018. Early-life exposure to endocrine disrupting chemicals associates with childhood obesity. Ann. Pediatr. Endocrinol. Metab. 23, 182–195. https://doi.org/10.6065/apem.2018.23.4.182.

Ye, X., Wong, L.-Y., Bishop, A.M., Calafat, A.M., 2011. Variability of urinary concentrations of bisphenol A in spot samples, first morning Voids, and 24-Hour collections. Environ. Health Perspect. 119, 983–988. https://doi.org/10.1289/ehp.1002701.