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Prenatal exposure to mixtures of phthalates and phenols and body mass index and blood pressure in Spanish preadolescents

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ABSTRACT

Background: Pregnant women are simultaneously exposed to several non-persistent endocrine-disrupting chemicals, which may influence the risk of childhood obesity and cardiovascular diseases later in life. Previous prospective studies have mostly examined single-chemical effects, with inconsistent findings. We assessed the association between prenatal exposure to phthalates and phenols, individually and as a mixture, and body mass index (BMI) and blood pressure (BP) in preadolescents.

Methods: We used data from the Spanish INMA birth cohort study (n = 1,015), where the 1st and 3rd- trimester maternal urinary concentrations of eight phthalate metabolites and six phenols were quantified. At 11 years of age, we calculated BMI z-scores and measured systolic and diastolic BP. We estimated individual chemical effects with linear mixed models and joint effects of the chemical mixture with hierarchical Bayesian kernel machine regression (BKMR). Analyses were stratified by sex and by puberty status.

Results: In single-exposure models, benzophenone-3 (BP3) was nonmonotonically associated with higher BMI z-score (e.g. Quartile (Q) 3: β = 0.23 [95% CI = 0.03, 0.44] vs Q1) and higher diastolic BP (Q2: β = 1.27 [0.00, 2.53] mmHg vs Q1). Methyl paraben (MEPA) was associated with lower systolic BP (Q4: β = −1.67 [−3.31, −0.04] mmHg vs Q1). No consistent associations were observed for the other compounds. Results from the BKMR confirmed the single-exposure results and showed similar patterns of associations, with BP3 having the

Abbreviations: BKMR, Bayesian kernel machine regression; BMI, body mass index; BP, blood pressure; BPA, bisphenol A; BP3, benzophenone-3; BUPA, butyl paraben; condPIP, conditional posterior inclusion probability; CVDs, cardiovascular diseases; DEHP, sum of di(2-ethylhexyl) phthalate metabolites; ETPA, ethyl paraben; GAMM, generalised additive mixed model; groupPIP, group posterior inclusion probability; ICC, intraclass correlation coefficient; INMA, Infancia y Medio Ambiente; IQR, interquartile range; LOD, limit of detection; MBzP, mono-benzyl phthalate; MEP, mono-ethyl phthalate; MEPA, methyl paraben; MECPP, mono-(2-ethyl-5-carboxy-pentyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MiBP, mono-iso-butyl phthalate; MnBP, mono-n-butyl phthalate; NIPH, Norwegian Institute of Public Health; PPARγ, peroxisome proliferator-activated receptor gamma; PRPA, propyl paraben; RAAS, rennin-angiotensin-aldosterone system; SD, standard deviation; UHPLC-MS/MS, ultra-high performance liquid chromatography coupled to tandem mass spectrometry.

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highest importance in the mixture models, especially among preadolescents who reached puberty status. No overall mixture effect was found, except for a tendency of higher BMI z-score and lower systolic BP in girls.
Conclusions: Prenatal exposure to UV-filter BP3 may be associated with higher BMI and diastolic BP during preadolescence, but there is little evidence for an overall phthalate and phenol mixture effect.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide (Roth et al., 2020). Obesity and high blood pressure (BP) are well-known risk factors that predispose individuals to the occurrence of CVDs. Children and adolescents with obesity and/or high BP levels are more likely to become obese and hypertensive as adults, manifesting the importance of health prevention and management early in life (Chen and Wang, 2008; Simmonds et al., 2016).

Pregnant women are exposed to phthalates and phenols, two groups of non-persistent endocrine disrupting chemicals. These compounds are widely found in a multitude of consumer products, such as flexible (high-molecular phthalates) and hard plastics (bisphenol A (BPA)), and personal care products (low-molecular phthalates and parabens), including sunscreen agents (benzophenone-3 (BP3)) (Gore et al., 2015). Therefore, although they are quickly metabolized in the human body and excreted in the urine, their exposure is ubiquitous, multi-source, multi-route, and often chronic (Gore et al., 2015; Lu et al., 2018). These chemicals can cross the blood-placenta barrier (Gil-Solsona et al., 2021; Schönfelder et al., 2002; Silva et al., 2004), and have been hypothesized to promote metabolic changes that may compromise early fetal developmental processes and influence the risk of offspring obesity and CVDs later in life (Egusquiza and Blumberg, 2020; Haverinen et al., 2021). The disruption of steroid and thyroid hormones, the activation of peroxisome proliferator-activated receptor γ (PPARγ), and the generation of reactive oxygen species are among the mechanisms by which exposure to phthalates and phenols may alter the fetal programming of cardiovascular function and adipogenesis, as supported by experimental studies (Aboul Ezz et al., 2015; Hao et al., 2013; Hu et al., 2013; Ishihara et al., 2003; Saura et al., 2014; Shen et al., 2009; Shin et al., 2020a).

Although many prospective birth cohort studies have assessed the association between prenatal phthalates and BPA with offspring BMI, and BP levels to a lesser extent, the level of evidence remains inconsistent due to mixed results, as shown in Appendix 1. Evidence is even less conclusive for other phenols of widespread use and emerging concern, such as the parabens and BP3, due to the limited research in prospective birth cohorts (see Appendix 1). For instance, only four and two studies assessed the association between prenatal exposure to parabens with BMI (Berger et al., 2021; Leppert et al., 2020; Reimann et al., 2021; Vrijheid et al., 2020) and BP levels (Montazeri et al., 2022; Warembourg et al., 2019), respectively. All of them obtained null associations except for prenatal PRPA levels linked with increased BMI (Berger et al., 2021), and prenatal ETPA exposure with a higher risk of overweight only in girls (Leppert et al., 2020). Similarly, of four studies that included BP3 among the exposures (Buckley et al., 2016; Montazeri et al., 2022; Vrijheid et al., 2020; Warembourg et al., 2019), only one reported reduced levels of body fat % in girls (Buckley et al., 2016).

Most of the above-mentioned studies have only considered exposure to a single chemical at a time. The reality, however, is that phthalates and phenols are found in many consumer products, and therefore, individuals can be regularly exposed to mixtures of these chemicals. Additionally, there is experimental evidence of a joint and interactive effect of those compounds on adipogenic differentiation, involving multiple mechanisms of action, further supporting the need for mixture models (Biemann et al., 2014; Völker et al., 2022). Only six prospective birth cohort studies have considered these two groups of endocrine-disrupting chemicals at the same time. In the HELIX study, including 6 European cohorts, prenatal exposure to phthalates and phenols was assessed together with a wide range of other environmental exposures in relation to obesity and BP (Vrijheid et al., 2020; Warembourg et al., 2019). Only prenatal BPA was found to be associated with increased BP levels in childhood (Warembourg et al., 2019). In these studies, exposome-wide association study and deletion-substitution-addition variable selection algorithm were used, which did not allow for assessing the effect of the chemical mixture. In the Spanish Infancia y Medio Ambiente (INMA) Sabadell cohort, (Agay-Shay et al., 2015) used principal component analysis to assess the effect of the mixture of many endocrine-disrupting chemicals and found that a component mainly characterized by several phthalates was associated with lower risk of being overweight/obese at 7 years. In this same cohort, Montazeri et al., (2021) used a Bayesian weighted quantile sum regression and found no evidence for an association between a phthalate/phenol mixture and BP at 11 years. In the US CHAMACOS cohort, using Bayesian kernel machine regression (BKMR), some associations were observed between a mixture of several phthalate metabolites and BMI at 5 and 12 years of age (Berger et al., 2021; Harley et al., 2017). Conversely, in a Mexican cohort, although some associations were found between individual phthalate metabolites and BMI trajectories, using the quantile G-computation modelling approach, no mixture associations were observed (Kupsco et al., 2022).

These studies have been limited by their modest sample size (between 300 and 400 participants), which gives limited statistical power, especially for the estimation of sex-specific effects. Also, the whole chemical mixture of phthalates and phenols was only assessed in one study in relation to BMI at 5 years (Berger et al., 2021) and one study in relation to BP at 11 years (Montazeri et al., 2022). Moreover, as described by Perng et al., 2021), the joint effect of phthalates and phenols on metabolic disruption has rarely been assessed during preadolescence, a sensitive period characterized by the hormonal onset of puberty with endocrine changes and increases in lean and fat mass. Thus, the present study aims to fill these critical knowledge gaps by examining whether prenatal exposure to phthalates and phenols (individually and in combination) are associated with BMI and BP in a sample of around 1,000 Spanish preadolescents.

2. Methods

2.1. Study population

We used data from the INMA birth cohort study including three Spanish regions: Gipuzkoa, Sabadell, and Valencia. Women presenting for prenatal care were recruited in the 1st trimester of pregnancy (weeks 10–13 of gestation) between 2003 and 2008 (n = 2,122). Mothers were included if they (i) were resident in the study area, (ii) were at least 16 years old, (iii) had a singleton pregnancy, (iv) did not follow any assisted reproduction program, (v) wished to deliver in the reference hospital, and (vi) had no communication barriers (Guxens et al., 2012). The population for this analysis comprised 1,015 mother–child pairs with available information on at least one phthalate metabolite and/or phenol measured during pregnancy and BMI (n = 954) or BP (n = 982) measured at 11 years (except in the INMA-Valencia cohort, where BP was measured at 9 years) (Fig. S1). All participating women signed written informed consent. This study was approved by the regional ethical committees of each cohort.

2.2. Phthalates and phenols exposure assessment

Phthalates and phenols levels were measured twice in urine samples

collected during gestation. Specifically, maternal urine samples in the 1st (mean = 13.2; standard deviation (SD) = 1.5 weeks) and 3rd trimesters of pregnancy (mean = 33.1; SD = 1.9 weeks) were collected in 100-mL polypropylene containers and then aliquoted in 10 mL polyethylene tubes and stored at −20 °C prior to analysis. A small number of mothers (n = 98, <10% of the total) provided only one urine sample. We measured total urine concentrations of eight phthalate metabolites: MEP (mono-ethyl phthalate), MiBP (mono-*iso*-butyl phthalate), MnBP (mono-n-butyl phthalate), MBzP (mono-benzyl phthalate), and the following four DEHP (di(2-ethylhexyl) phthalate) metabolites: MEHP (mono-(2-ethylhexyl) phthalate), MEHHP (mono-(2-ethyl-5-hydroxyhexyl) phthalate), MEOHP (mono-(2-ethyl-5-oxohexyl) phthalate), and MECPP (mono-(2-ethyl-5-carboxy-pentyl) phthalate). Phthalate metabolites of the Gipuzkoa and Valencia cohorts were measured at the Department of Environmental Exposure and Epidemiology at the Norwegian Institute of Public Health (NIPH) (Oslo, Norway), using pooled samples (1st and 3rd trimesters) with ultra-high performance liquid chromatography coupled to tandem mass spectrometry detection (UHPLC-MS/MS) (Sabaredzovic et al., 2015). The limits of detection (LOD) ranged between 0.07 and 0.7 ng/ml. Phthalate metabolites of the Sabadell cohort were measured at the Bioanalysis Research Group at the Hospital del Mar Medical Research Institute (Barcelona, Spain) using samples separately from the 1st and 3rd trimesters also with UHPLC-MS/MS, as described in (Valvi et al., 2015a). LODs ranged from 0.5 to 1 ng/ml. We calculated the molar sums of individual metabolites (in μmol/l) of DEHP because they occur from the same parent phthalate and thus, they were highly correlated (r > 0.90).

Phenols of this analysis included four parabens (MEPA (methyl paraben), ETPA (ethyl paraben), PRPA (propyl paraben), and BUPA (butyl paraben)), BP3, and BPA. Phenols in samples from the Gipuzkoa cohort were measured at Instituto de Investigación Biosanitaria ibs. GRANADA (Granada, Spain) using pooled samples (1st and 3rd trimesters) with dispersive liquid–liquid microextraction and UHPLC-MS/MS (Vela-Soria et al., 2014); LODs ranged from 0.04 to 0.12 ng/ml. Samples from the 1st and 3rd trimesters from Sabadell and Valencia were analyzed separately at NIPH with online solid-phase extraction prior to UHPLC-MS/MS (Sakhi et al., 2018); LODs ranged from 0.03 to 0.07 ng/ml. BPA for the Sabadell cohort was measured at the Department of Analytical Chemistry laboratory at the University of Cordoba (Spain) using LC-MS/MS (Casas et al., 2013). LOD was 0.10 ng/ml.

In all cohorts, creatinine urine concentrations at each trimester (1st and 3rd) were determined using the Jaffé method (kinetic with target measurement, compensated method). Chemical concentrations were corrected for urine creatinine concentrations to adjust for urine dilution and were expressed in μg/g of creatinine. For pooled samples, we applied the mean of the two individual creatinine measurements; we verified in 20 urine samples from Valencia that measuring creatinine levels in the pool was highly correlated with the creatinine levels estimated by averaging the creatinine levels quantified in the two independent urine samples (r = 0.97). Due to the short biological half-life of the non-persistent chemicals, we used the average of the non-pooled creatinine-adjusted concentrations measured in the 1st and 3rd trimesters to provide a better estimation of exposure throughout pregnancy. Because the phthalates and phenols creatinine-adjusted concentrations were right-skewed, they were $\log_2$-transformed to obtain normal distributions.

2.3. BMI and BP outcomes

Child weight and height were measured at 11 years of age using standard protocols, without shoes and in light clothing. We calculated BMI (weight in kg/height in m^2) and age- and sex-specific BMI z-scores using the World Health Organization reference and defined overweight as a BMI z-score ≥ 85th percentile (De Onis et al., 2007). INMA nurses used a digital automatic monitor (OMRON 705IT) to measure systolic and diastolic BP at 11 years in Gipuzkoa and Sabadell, and 9 years in Valencia. After 5 min of rest, 3 consecutive measurements were taken with one-minute time intervals between them. We derived average BP at each age as the mean of the systolic and diastolic BP values.

2.4. Statistical analysis

Concentrations of phthalates and phenols above 4 times their SD (<1%) were removed since BKMR is highly sensitive to outlying values. Concentrations below the LOD were imputed using distribution-based multiple imputations by assuming a log-normal distribution of the chemicals and conditioning the imputation to the range from 0 to the LOD (Table S1). Then, they were adjusted by creatinine and $\log_2$-transformed. We performed multiple imputations by chained equations of missing values in exposure (<11%) and covariate data (<2%) to avoid the loss of participants in the study (Table S2). We generated ten complete data sets by using the ice package for Stata (Royston, 2005). A detailed description of this procedure is provided in Table S3. Distributions of covariates and chemical concentrations in imputed datasets were similar to the original dataset (Table S2). Pearson correlation coefficients were calculated to estimate the bivariate correlations between chemicals ($\log_2$-transformed).

First, we assessed potential non-linear relationships between exposures and outcomes of interest (BMI z-score, systolic and diastolic BP) using generalized additive mixed models (GAMMs; R package 'mgcv'). If the effective degrees of freedom were equal to 1, the relationship was closer to linear. GAMM models showed evidence of linearity (Fig. S2-S4) with few exceptions indicating non-linearity: BUPA and BP3 with BMI z-score (Fig. S2), BP3 with systolic BP (Fig. S3), and PRPA and BP3 with diastolic BP (Fig. S4). Therefore, we modelled chemical concentrations as both continuous and categorical variables using quartile cut-offs. Second, we assess single exposure effects with linear mixed models using the imputed data, and the results were combined using Rubin's combination rules (Little and Rubin, 2014). All models (GAMMs and linear mixed models) were adjusted for the region of residence (Gipuzkoa, Sabadell, Valencia) as a random intercept to account for within-cohort and between-cohort effects.

Third, we conducted BKMR to assess the joint effect of the exposures on BMI z-score and BP. BKMR is a non-parametric method in which the health outcome is regressed on a flexible kernel function of the mixture components (Bobb et al., 2014). It accommodates non-linearity, non-additive effects, and interactions (Bobb et al., 2014). We used a hierarchical variable selection method to identify important chemicals in the mixture managing the high correlation between exposures within chemical groups (Bobb et al., 2014). Based on Pearson correlation coefficients and also considering their common exposure sources, we classified the chemicals into two groups: (1) Phthalate metabolites (MEP, MiBP, MnBP, MBzP, and ∑DEHP), and 2) Phenols (MEPA, ETPA, PRPA, BUPA, and BP3) (Fig. 2). Initially, because of the mild or null correlations of BPA with other chemicals (0.02–0.19) (Fig. 2) (Bobb et al., 2014), BPA was included alone in a third group showing a small contribution to the overall model. Thus, in a refinement step, we ran the models without BPA. Chemicals were scaled to their SD. We calculated the group posterior inclusion probability (groupPIP) and conditional posterior inclusion probability (condPIP), which represent the probability (from 0 to 1) that a chemical within the group is included in the model (Bobb et al., 2014). We also assessed (i) the shape and direction of the exposure–response association of each chemical in relation to the health outcome when holding the other chemicals in the mixture at their median concentrations, (ii) the overall mixture effects at different percentiles, and (iii) two-way chemical interactions while holding the other exposures at their median values. Model convergence was assessed visually using trace plots. BKMR was fitted with the R package "bkmr" using the Markov chain Monte Carlo algorithm with 10,000 iterations. We only used the first imputed dataset as it is not currently possible to use multiple imputed datasets with the BKMR function. BKMR models also included region of residence as a random intercept.

Potential covariates for model adjustment were selected based on a priori knowledge (Casas et al., 2013; Valvi et al., 2015b) and a directed acyclic graph approach (Fig. S5). These were obtained through interviewer-administered questionnaires answered by mothers at recruitment and included: maternal age at pregnancy (in years), pre-pregnancy BMI (kg/ m^2), educational level (low, middle, high), and smoking in pregnancy ("yes" if they smoke at the moment of recruitment/no). We additionally examined if the Mediterranean diet adherence score confounded the associations since it is an indicator of maternal quality diet that considers nutrients that may affect the health outcomes and can interact with prenatal phthalates and phenols concentrations (Fernández-Barrés et al., 2016). Passive smoking during pregnancy (yes/no) was also assessed since previous studies have shown that it can influence levels of non-persistent chemicals in pregnant women (Casas et al., 2013; Darvishmotevalli et al., 2019; Wang et al., 2020) and childhood obesity (Vrijheid et al., 2020). As coefficient estimates did not change, these variables were not retained (data not shown). Gestational age (in weeks) and birth weight (in grams), collected by clinical records, may be mediating factors in the association of prenatal phthalates and phenols exposures and BMI/BP at preadolescence (Fig. S5). Therefore, we did not adjust associations for these variables as we were interested in the total effect of prenatal phthalates and phenols exposures on BMI and BP outcomes (VanderWeele, 2009). Models with systolic and diastolic BP outcomes were additionally adjusted for the child's age (years), sex (male/female), and height (cm). Since phthalates and phenols can interfere with sex hormones (Braun, 2017), their potential health effects may be sex-dependent. Therefore, we stratified all models (linear mixed models and BKMR) by sex. In the linear mixed models, we tested sex-interaction by inserting cross-product terms (exposure*sex using a p-value threshold of 0.10). In the BKMR, separate models were run for girls and boys.

In sensitivity analyses, we repeated all the models with BP z-scores standardized by age, sex and height in the overall study population and stratified by sex. We also repeated all models by using the complete-case dataset (n = 773). Multipollutant models adjusted for the 10 exposure variables were also performed to compare the results with the BKMR ones. Because most of the preadolescents reached puberty onset at 11 years, we stratified our analyses by puberty status (prepuberty/puberty), which was rated by their parents using the Pubertal Development Scale (Carskadon and Acebo, 1993). Furthermore, we stratified by sex after excluding participants in the prepuberty stage (approximately one-third) to assess if sex-specific associations remained the same in preadolescents who reached puberty.

Data cleaning, multiple imputations, and mixed models were performed using Stata version 16 (Stata Corporation, College Station, TX, USA). Pearson correlations, GAMMs, and BKMR were conducted in R version 4.1.0 (R Foundation, Vienna, Austria).

3. Results

3.1. Study population characteristics

Complete details of the characteristics of the study population (N = 1,015) are shown in Table 1. At 11 years, 42% of children were either overweight or obese. Mothers included in the analyses were slightly older, had a higher educational level, and were less likely to smoke during pregnancy (Table S4). The log_2-transformed creatinine-adjusted prenatal non-persistent chemical concentrations are presented in Fig. 1. MEP and MEPA were the chemicals with the highest levels (median = 225.90; interquartile range (IQR) = 363.20 and median = 204.34; IQR = 366.10 μg/g creatinine, respectively), and BUPA and BPA were those with the lowest levels (median = 2.77; IQR = 8.94 and median = 2.82; IQR = 2.91 μg/g creatinine, respectively) (Table S1). Pearson's correlations heat map revealed low to moderate correlations within the phthalate metabolites (r = 0.12–0.45), and low to high (r = 0.16–0.83) within-group correlations for parabens and BP3 (Fig. 2). BPA showed low or null correlation coefficients with the other chemicals (r = 0.02–0.19) (Fig. 2).

Table 1
Maternal and offspring characteristics of the study population.

Maternal characteristics	N = 1,015
Region of residence – n (%)	
Gipuzkoa	262 (25.81%)
Sabadell	424 (41.77%)
Valencia	329 (32.41%)
Education completed – n (%)	
Primary	224 (21.99%)
Secondary	411 (40.46%)
University	380 (37.55%)
Smoking during pregnancy – n (%)	
None	722 (70.99%)
Yes*	293 (29.01%)
Age at pregnancy (years) – mean (SD)	30.93 (3.83)
Pre-pregnancy BMI (kg/m^2) – mean (SD)	23.52 (4.21)
Offspring characteristics	
Sex – n (%)	
Girls	500 (49.26%)
Boys	515 (50.74%)
Puberty – n (%)	
Prepuberty	295 (29.06%)
In puberty	720 (70.94%)
Gestational age (weeks) – mean (SD)	39.74 (1.37)
Birth weight (g) – mean (SD)	3271.10 (435.27)
Age at BMI z-score assessment (years) – mean (SD)	11.02 (0.44)
BMI (kg/m^2) – mean (SD)	19.46 (3.56)
BMI z-score – mean (SD)	0.71 (1.21)
Overweight – n (%)	
Yes	398 (41.72%)
No	556 (58.28%)
Age at BP assessment (years) – mean (SD)	10.41 (0.98)
Systolic BP (mmHg) - mean (SD)	103.54 (9.46)
Diastolic BP (mmHg) - mean (SD)	59.60 (7.47)

Abbreviations: SD (standard deviation), BMI (body mass index), BP (blood pressure),
* Includes women who quit smoking during current pregnancy.

3.2. Prenatal non-persistent chemicals in association with BMI in preadolescents

Table 2 shows results from the linear mixed models for BMI z-score. All the associations were null except for BP3 that in the second and third quartile was associated with a higher BMI z-score (Quartile (Q) 2: β = 0.22 [95% CI = 0.01, 0.42]; Q3: β = 0.23 [95% CI = 0.03, 0.44]) (Table 2). Fig. 3 shows results from the BKMR model for the BMI z-score. Holding all other chemicals at their medians, BP3 was associated with a higher BMI z-score, confirming the direction of the coefficient estimates found in the single-exposure models (Fig. 3A). We did not observe any association between the whole chemical mixture and BMI z-score (Fig. 3C) nor any bivariate interactions among the chemicals.

After stratifying by sex, the nonmonotonic association reported in the mixed models between BP3 and BMI z-score was only clearly observed among girls in the BKMR univariate plots (Fig. S6 A1, B1). BP3 was also the most contributing compound in the phenols group in girls (Fig. S6 B1). The joint effect of the chemical mixture showed a slightly increasing trend for girls and decreasing for boys, when all the chemicals were at their 60th percentile or above, compared to their 50th percentile; however, credible intervals contained the null (Fig. 6A). No interactions between chemicals were observed in girls or boys.

3.3. Prenatal non-persistent chemicals in association with BP in preadolescents

The single-exposure models revealed null associations between the non-persistent chemicals and systolic BP, except for a negative

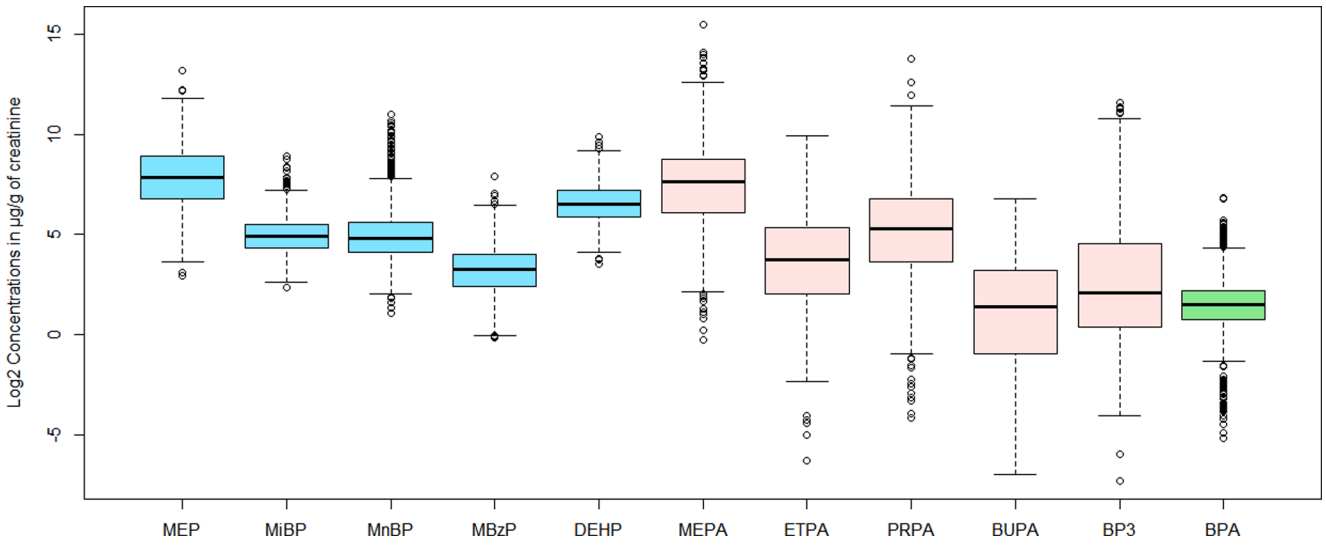


Fig. 1. Logarithm transformed (log_2) creatinine-adjusted prenatal non-persistent chemical concentrations. Abbreviations: MEP (mono-ethyl phthalate), MiBP (mono-*iso*-butyl phthalate), MnBP (mono-n-butyl phthalate), MBzP (mono-benzyl phthalate), DEHP (sum of di(2-ethylhexyl) phthalate metabolites), MEPA (methyl paraben), ETPA (ethyl paraben), PRPA (propyl paraben), BUPA (butyl paraben), BP3 (benzophenone-3), BPA (bisphenol A).

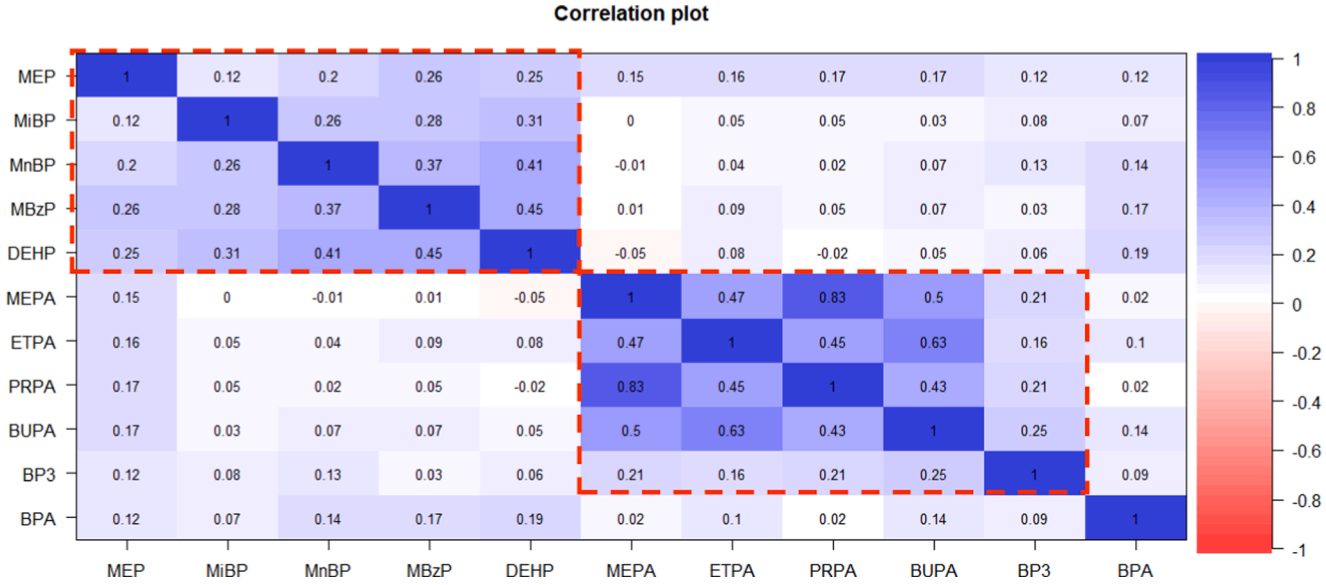


Fig. 2. Correlation heatmap using Pearson's correlation coefficients. Groups of chemicals included in the mixture model are squared in red. Abbreviations: MEP (mono-ethyl phthalate), MiBP (mono-*iso*-butyl phthalate), MnBP (mono-n-butyl phthalate), MBzP (mono-benzyl phthalate), DEHP (sum of di(2-ethylhexyl) phthalate metabolites), MEPA (methyl paraben), ETPA (ethyl paraben), PRPA (propyl paraben), BUPA (butyl paraben), BP3 (benzophenone-3), BPA (bisphenol A). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

association with MEPA in the highest quartile (Q4: β = -1.67 [95% CI = -3.31, −0.04] mmHg vs Q1) (Table 2). Consistently, the BKMR showed an inverse association between MEPA and systolic BP when the other chemicals were fixed at their median (Fig. 4A). We did not observe any effect of the overall chemical mixture with systolic BP (Fig. 4C); also, no interactions between chemicals were observed.

The negative association observed in the overall population between MEPA and systolic BP was only observed in boys and in the BKMR model (Fig. S7 A2), but this phenol presented a low condPIP (0.17) (Fig. S7 B2). In boys, ∑DEHP was also associated with a decrease in systolic BP (p-interaction = 0.10) (Table S5), which was confirmed in the BKMR univariate plots (Fig. S7 A2) and by being the exposure with the highest influence in the mixture (condPIP = 0.63) (Fig. S7 B2). For boys, no effect of the overall mixture was observed (Fig. 6B). In girls, the single-exposure models revealed a decrease in systolic BP linked to BUPA (p-interaction = 0.05) (Table S5). This was supported by the BKMR model with BUPA showing a sharp linear decrease in systolic BP when holding all other chemicals at their medians (Fig. S7 A1), its high condPIP (0.91) (Fig. S7 B2), and the negative joint effect of the mixture, although not statistically significant (Fig. 6B). No interactions between chemicals were observed in boys and girls.

With respect to diastolic BP and in the single-exposure models, BP3 was the only compound associated with this outcome showing an increase in diastolic BP but only in the second quartile of exposure (Q2: β = 1.27 [95% CI = 0.00, 2.53] mmHg) (Table 2). This nonlinear positive association was also observed in the BKMR model when all the other chemicals remained at their median (Fig. 5A); being the chemical with the highest contribution within the mixture (condPIP = 0.74) (Fig. 5B). No overall mixture effect was found (Fig. 5C) and no interactions were suggested graphically.

Table 2
Adjusted associations[a] between prenatal non-persistent chemical concentrations and BMI and BP at preadolescence in single-exposure models.

		BMI z-score (n = 954)		Systolic BP (n = 982)		Diastolic BP (n = 981)	
		β	(95 %CI)	β	95 %CI	β	95 %CI
Phthalate metabolites							
MEP	Per log_2 increase	0.01	(-0.02, 0.05)	0.05	(-0.24, 0.35)	0.04	(-0.20, 0.23)
	Q2 (110.67–225.90 μg/g)	0.05	(-0.16, 0.26)	−0.24	(-1.96, 1.48)	0.91	(-0.41, 2.23)
	Q3 (225.91–473.86 μg/g)	0.17	(-0.04, 0.38)	1.00	(-0.70, 2.69)	0.30	(-1.09, 1.69)
	Q4 (473.87–9379.85 μg/g)	0.05	(-0.17, 0.27)	0.19	(-1.64, 2.01)	0.40	(-1.06, 1.87)
MiBP	Per log_2 increase	−0.03	(-0.08, 0.03)	−0.11	(-0.54, 0.33)	0.10	(-0.25, 0.46)
	Q2 (20.37–30.22 μg/g)	−0.03	(-0.24, 0.18)	−0.25	(-1.84, 1.34)	0.66	(-0.67, 2.00)
	Q3 (30.23–45.27 μg/g)	−0.06	(-0.27, 0.15)	−0.61	(-2.29, 1.08)	0.13	(-1.23, 1.49)
	Q4 (45.28–486.99 μg/g)	−0.11	(-0.33, 0.12)	−0.96	(-2.63, 0.71)	0.37	(-1.02, 1.76)
MnBP	Per log_2 increase	0.01	(-0.03, 0.04)	−0.17	(-0.51, 0.17)	−0.21	(-0.49, 0.07)
	Q2 (17.15–27.14 μg/g)	0.13	(-0.07, 0.33)	0.18	(-1.48, 1.84)	0.76	(-0.60, 2.11)
	Q3 (27.15–46.66 μg/g)	0.02	(-0.18, 0.22)	0.05	(-1.74, 1.84)	−0.42	(-1.93, 1.08)
	Q4 (46.67–2101.18 μg/g)	0.04	(-0.17, 0.25)	−0.29	(-2.19, 1.60)	−0.34	(-2.02, 1.34)
MBzP	Per log_2 increase	0.00	(-0.04, 0.04)	0.01	(-0.36, 0.38)	0.06	(-0.23, 0.35)
	Q2 (5.22–9.37 μg/g)	0.03	(-0.18, 0.24)	−0.57	(-2.27, 1.12)	−0.27	(-1.66, 1.11)
	Q3 (9.38–16.38 μg/g)	0.01	(-0.20, 0.23)	−1.13	(-2.89, 0.63)	−0.48	(-1.86, 0.89)
	Q4 (16.39–238.35 μg/g)	0.01	(-0.20, 0.21)	−0.17	(-1.96, 1.62)	0.20	(-1.21, 1.61)
∑DEHP	Per log_2 increase	0.00	(-0.05, 0.06)	−0.13	(-0.58, 0.33)	0.02	(-0.35, 0.40)
	Q2 (55.77–88.34 μg/g)	−0.02	(-0.22, 0.18)	−0.44	(-2.10, 1.22)	−0.19	(-1.52, 1.13)
	Q3 (88.35–139.74 μg/g)	−0.01	(-0.21, 0.19)	−0.97	(-2.78, 0.84)	−0.02	(-1.44, 1.39)
	Q4 (139.75–941.59 μg/g)	−0.01	(-0.23, 0.20)	−0.37	(-2.13, 1.39)	0.11	(-1.34, 1.56)
Phenols							
MEPA	Per log_2 increase	−0.01	(-0.03, 0.02)	−0.12	(-0.30, 0.06)	−0.08	(-0.23, 0.06)
	Q2 (69.54–204.34 μg/g)	−0.11	(-0.32, 0.10)	−0.54	(-2.14, 1.05)	−0.09	(-1.39, 1.21)
	Q3 (204.35–435.62 μg/g)	−0.05	(-0.26, 0.16)	−0.58	(-2.19, 1.03)	−0.31	(-1.62, 1.00)
	Q4 (435.63–45927.09 μg/g)	−0.19	(-0.40, 0.02)	**−1.67**	**(-3.31, −0.04)**	−0.56	(-1.89, 0.78)
ETPA	Per log_2 increase	−0.01	(-0.03, 0.01)	0.00	(-0.17, 0.16)	−0.01	(-0.13, 0.12)
	Q2 (4.35–13.75 μg/g)	0.09	(-0.11, 0.30)	−0.47	(-2.09, 1.16)	0.60	(-0.70, 1.90)
	Q3 (13.76–42.11 μg/g)	−0.01	(-0.21, 0.20)	−0.37	(-2.00, 1.26)	0.54	(-0.76, 1.83)
	Q4 (42.12–980.02 μg/g)	−0.10	(-0.31, 0.10)	−0.37	(-2.01, 1.26)	−0.08	(-1.37, 1.21)
PRPA	Per log_2 increase	0.00	(-0.02, 0.02)	−0.08	(-0.24, 0.08)	−0.01	(-0.14, 0.11)
	Q2 (13.07–41.41 μg/g)	−0.14	(-0.35, 0.07)	−1.20	(-2.80, 0.39)	−0.14	(-1.43, 1.16)
	Q3 (41.42–114.51 μg/g)	−0.15	(-0.36, 0.06)	−0.32	(-1.92, 1.29)	−0.59	(-1.89, 1.48)
	Q4 (114.52–14132.26 μg/g)	−0.03	(-0.24, 0.17)	−0.89	(-2.48, 0.71)	0.19	(-1.11, 1.48)
BUPA	Per log_2 increase	0.00	(-0.02, 0.02)	−0.07	(-0.21, 0.08)	0.01	(-0.10, 0.13)
	Q2 (0.54–2.77 μg/g)	0.09	(-0.12, 0.29)	−0.30	(-1.89, 1.29)	−0.01	(-1.30, 1.27)
	Q3 (2.78–9.47 μg/g)	0.05	(-0.16, 0.25)	−0.82	(-2.43, 0.78)	0.27	(-1.01, 1.54)
	Q4 (9.48–110.00 μg/g)	−0.12	(-0.33, 0.09)	−0.67	(-2.28, 0.94)	0.24	(-1.06, 1.55)
BP3	Per log_2 increase	0.01	(-0.01, 0.02)	0.03	(-0.10, 0.16)	0.04	(-0.07, 0.15)
	Q2 (1.30–4.17 μg/g)	**0.22**	**(0.01, 0.42)**	1.01	(-0.55, 2.56)	**1.27**	**(0.00, 2.53)**
	Q3 (4.18–23.68 μg/g)	**0.23**	**(0.03, 0.44)**	0.14	(-1.45, 1.73)	0.53	(-0.75, 1.82)
	Q4 (23.69–3115.95 μg/g)	0.13	(-0.07, 0.34)	0.77	(-0.81, 2.36)	0.94	(-0.35, 2.22)
BPA	Per log_2 increase	−0.01	(-0.03, 0.03)	−0.05	(-0.31, 0.21)	−0.05	(-0.26, 0.16)
	Q2 (1.69–2.82 μg/g)	0.15	(-0.05, 0.35)	0.21	(-1.40, 1.81)	0.00	(-1.37, 1.38)
	Q3 (2.83–4.59 μg/g)	0.00	(-0.21, 0.20)	0.17	(-1.43 1.77)	−0.14	(-1.52, 1.24)
	Q4 (4.60–116.06 μg/g)	0.06	(-0.14, 0.26)	−0.84	(-2.48, 0.79)	−0.75	(-2.07, 0.58)

Abbreviations: BMI (body mass index), MEP (mono-ethyl phthalate), MiBP (mono-*iso*-butyl phthalate), MnBP (mono-n-butyl phthalate), MBzP (mono-benzyl phthalate), ∑DEHP (sum of di(2-ethylhexyl) phthalate metabolites), MEPA (methyl paraben), ETPA (ethyl paraben), PRPA (propyl paraben), BUPA (butyl paraben), BP3 (benzophenone-3), BPA (bisphenol A).

[a] Linear mixed models adjusted for maternal age, education, smoking in pregnancy and pre-pregnancy BMI. Blood pressure models were additionally adjusted by child's age, sex and height. Region of residence was included as random intercept. Second (Q2), third (Q3) or fourth quartile (Q4) compared with first. Statistically significant coefficient intervals at $p < 0.05$ are highlighted in bold.

No sex interaction was observed in the single-exposure models ($p > 0.10$; Table S5). In these models, BP3 was the only chemical associated with an increase in diastolic BP, but only in boys (Q2: β = 1.86 [95% CI = 0.01, 3.72] mmHg) (Table S5). This association was confirmed in BKMR models (Fig. S8 A2, B2). In girls, BP3 was the chemical with the highest importance in the mixture model (condPIP = 0.76) (Fig. S8 B1) and showed a nonlinear positive association after holding the other chemicals at their medians (Fig. S8, A1). As for the overall population, no overall mixture effect was found (Fig. 6C) and no interactions between chemicals were detected.

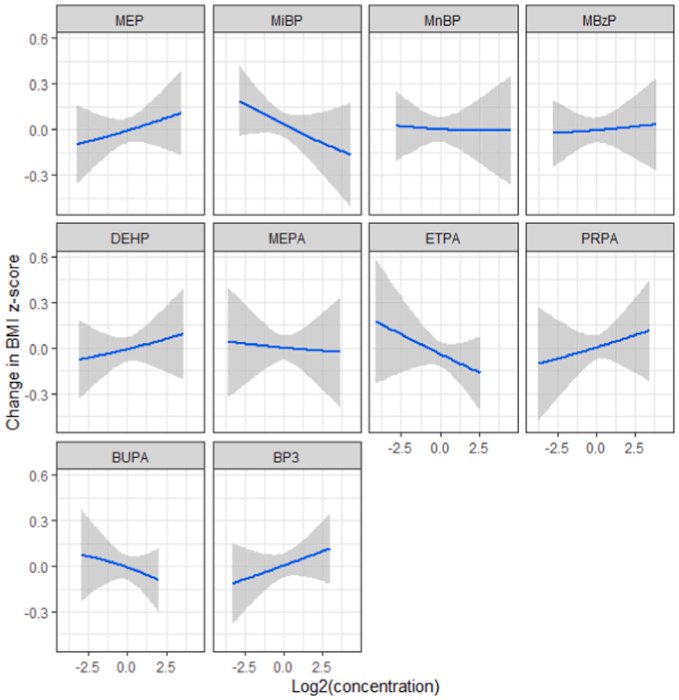
3.4. Sensitivity analyses

Similar findings were observed using the z-score of BP instead of the raw BP variables (Table S6, Figure S9, S10) and restricting all the analyses to complete cases. Multipollutant model showed similar estimates for BP3 and BMI z-score and stronger estimates for MEPA and systolic BP (Table S7). Conversely, estimates of BP3 and diastolic BP were no longer statistically significant (Table S7). Among preadolescents who reached puberty status, the associations of BP3 with a higher BMI z-score and diastolic BP were strengthened (e.g. BMI z-score Q3: β = 0.30 [95% CI = 0.07, 0.54]) and diastolic BP (Q2: β = 1.91 [95% CI = 0.40, 3.43] mmHg) (Table S8). Moreover, effect estimates of BP3 with all the outcomes were stronger in sex-stratified analyses after excluding children in prepuberty status (Table S9 and Figures S11-S13).

4. Discussion

In this Spanish population of pregnant women with common exposure to phthalates and phenols, prenatal urinary concentrations of BP3

A)



B)

Chemicals	GroupPIP	CondPIP
MEP	0.23	0.28
MiBP	0.23	0.24
MnBP	0.23	0.18
MBzP	0.23	0.12
∑DEHP	0.23	0.17
MEPA	0.31	0.10
ETPA	0.31	0.24
PRPA	0.31	0.10
BUPA	0.31	0.37
BP3	0.31	0.20

C)

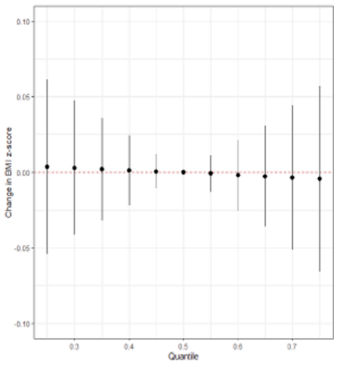
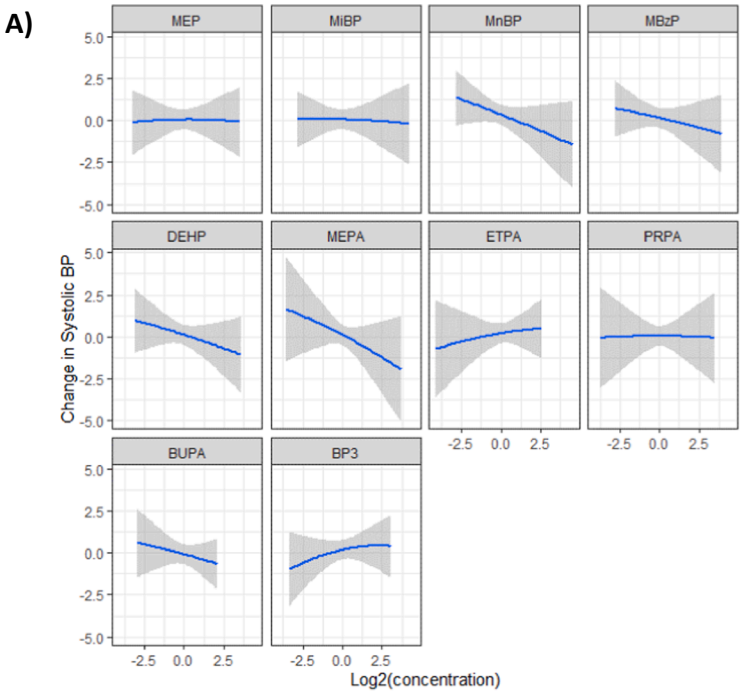


Fig. 3. Summary estimates from BKMR on the association between mixtures of log_2 scaled non-persistent chemicals and BMI z-score in preadolescence adjusted by maternal age, education, smoking in pregnancy and pre-pregnancy BMI; region of residence was included as random intercept. **(A)** Exposure-response associations for each chemical when the others are fixed at their median. **(B)** Group and conditional posterior inclusion probabilities (GroupPIP and CondPIP) of each chemical in the mixture-response function for BMI z-score. **(C)** Joint effect of prenatal non-persistent chemicals mixture on BMI z-score at preadolescence (Credible intervals overlapping the null depicted with the broken line indicate no significant effects). Abbreviations: BMI (body mass index), BKMR (Bayesian kernel machine regression), MEP (mono-ethyl phthalate), MiBP (mono-*iso*-butyl phthalate), MnBP (mono-n-butyl phthalate), MBzP (mono-benzyl phthalate), DEHP (sum di(2-ethylhexyl) phthalate metabolites), MEPA (methyl paraben), ETPA (ethyl paraben), PRPA (propyl paraben), BUPA (butyl paraben), BP3 (benzophenone-3).

were consistently linked with increased BMI z-score and diastolic BP at 11 years across single and mixture modelling approaches. These effects were further evidenced among preadolescents who reached puberty status. We also observed that MEPA was associated with a decreased systolic BP, while BUPA and ∑DEHP were associated with decreased systolic BP in girls and boys, respectively; however, all these associations were not consistent across single and mixture models. Although no overall mixture effect nor chemical interactions were detected, in girls, we observed a tendency of higher BMI z-score and decreased systolic BP of the chemical mixture, yet non-statistically significant. Results from this study highlight the benefit of combining two complementary models, considering their advantages and disadvantages. For instance, single-pollutant models may show straightforward results with interpretable effect estimates, providing an important step in assessing complex exposure patterns. However, advanced approaches able to overcome the constraints of complex exposure data structures (e.g. correlation, high-dimensionality) may be required to address more complex questions about the effect mixtures, including their joint effects or identification of interactions (Braun et al., 2016).

Only two previous studies from the CHAMACOS cohort in the US have also assessed the association between prenatal mixtures of phthalates and phenols with obesity-related outcomes in childhood (Berger et al., 2021; Harley et al., 2017). Both studies combined single-exposure models with BKMR, as we did in the present study. Harley et al., (2017) visually explored the exposure–response associations obtained from BKMR between phthalates and BMI at 12 years of age; neither PIPs nor joint mixture effects were analyzed. They observed trends of phthalates that were similar to ours, and a significant association between MEP and higher BMI that in our study was only observed in the single-exposure models and in girls (Table S5). In Berger et al., (2021), PRPA was associated with higher BMI and overweight/obesity risk at 5 years in single pollutant models and it was the most relevant chemical in the mixture. In our study, PRPA showed inconsistent results among single-exposure and BKMR models and it had a low contribution to the mixture (condPIP = 0.10). In Berger et al., (2021) BP3 was also considered in the mixture but it tended to be associated with reduced BMI at 5 years in both single and mixture models and it had a low contribution (PIP = 0.02). Berger et al., (2021) also reported a slightly increasing trend of BMI linked to the overall mixture, which in our study was only observed in girls. The null overall mixture effect observed in all the study populations (i.e. CHAMACOS and INMA) could be partly explained by the different sense of directions of the chemicals, which may have neutralized the joint effect. This has been observed in *in vitro* studies where the estrogenic activity of BPA can suppress the adipogenic effects of PPARγ activators DEHP and tributyltin during adipogenesis, for example (Biemann et al., 2014; Jeong and Yoon, 2011). We may hypothesize that inconsistencies between the CHAMACOS and the INMA studies may be due to: (i) the dissimilarity of sociodemographic and genetic background between mothers from both cohorts (i.e. most of CHAMACOS' mothers were of Latin ethnicity who lived in the US<5 years, younger, had a low educational level and household income, and more than half were overweight), which may have contributed to differences in the use of chemical-associated personal care products in pregnancy (Perng et al., 2021; Preston et al., 2021); (ii) in relation to the previous point, the different concentrations of chemicals, which were higher in CHAMACOS for both PRPA and BP3; (iii) the sample size (~300 in CHAMACOS vs ~ 1000 in INMA); (iv) the different chemicals considered into the mixture which can modify the joint effect and the contribution of each chemical (i.e. in Berger et al., (2021) more phthalates and triclosan were included whereas BUPA and MEPA were not included); v) the distinct age at outcome examination (5 years in CHAMACOS vs 11 years in INMA); and (vi) the different statistical approaches used since Berger et al., 2021 did not consider hierarchical clustering of chemicals in the BKMR as we did, which allowed us to



B)

Chemicals	GroupPIP	CondPIP
MEP	0.09	0.32
MiBP	0.09	0.17
MnBP	0.09	0.16
MBzP	0.09	0.16
∑DEHP	0.09	0.19
MEPA	0.16	0.21
ETPA	0.16	0.15
PRPA	0.16	0.10
BUPA	0.16	0.15
BP3	0.16	0.39

C)

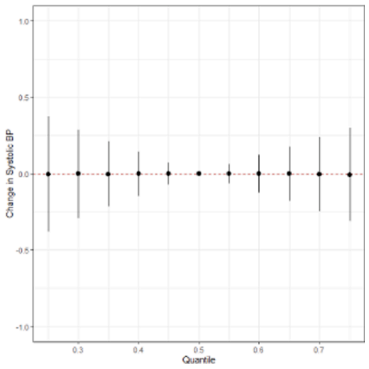


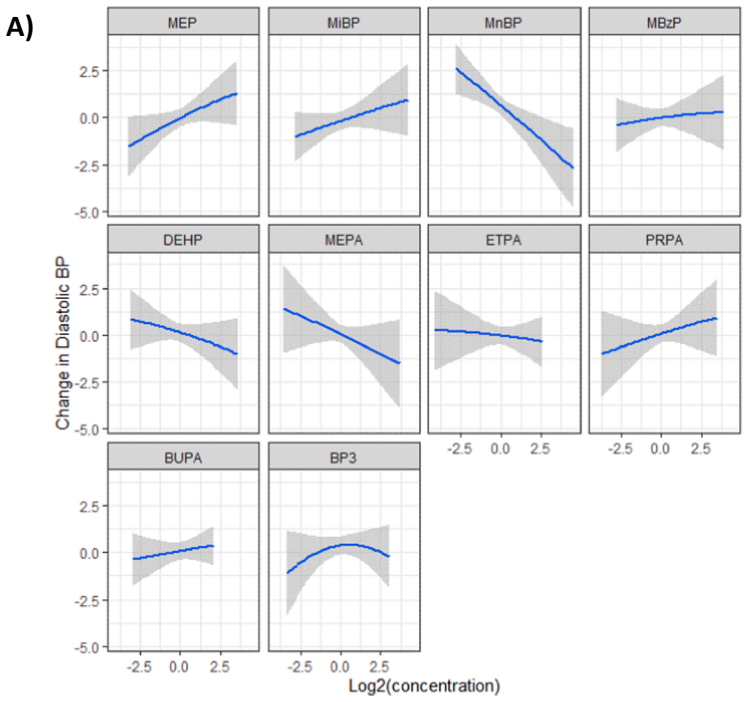
Fig. 4. Summary estimates from BKMR on the association between mixtures of log_2 scaled non-persistent chemicals and systolic BP in preadolescence adjusted by maternal age, education, smoking in pregnancy, pre-pregnancy BMI, sex, height and age at outcome assessment; region of residence was included as random intercept. (A) Exposure-response associations for each chemical when the others are fixed at their median. (B) Group and conditional posterior inclusion probabilities (GroupPIP and CondPIP) of each chemical in the mixture-response function for systolic BP. (C) Joint effect of prenatal non-persistent chemicals mixture on systolic BP at preadolescence (Credible intervals overlapping the null depicted with the broken line indicate no significant effects). Abbreviations: BP (blood pressure), BMI (body mass index), BKMR (Bayesian kernel machine regression), MEP (mono-ethyl phthalate), MiBP (mono-*iso*-butyl phthalate), MnBP (mono-n-butyl phthalate), MBzP (mono-benzyl phthalate), DEHP (sum of di(2-ethylhexyl) phthalate metabolites), MEPA (methyl paraben), ETPA (ethyl paraben), PRPA (propyl paraben), BUPA (butyl paraben), BP3 (benzophenone-3).

group the chemicals accounting for their correlations and it can modify models' performance and output.

To our knowledge, the relationship between prenatal mixtures of phthalates and phenols with postnatal systolic and diastolic BP has only been assessed recently in the INMA-Sabadell cohort (Montazeri et al., 2022) with a sample of 416 participants, in which no evidence for single or mixture associations with BP at 11 years was found. Conversely, in this study with a larger sample size, we found that BP3, MEPA, BUPA, and ∑DEHP were associated with changes in diastolic BP, with some sex-specific associations. The improvement of statistical power may have contributed to the identification of sex-specific effects in the present study. Aside from Montazeri et al., (2021) and Warembourg et al., (2019), no previous study has assessed the individual associations of phenols other than BPA with BP (see Appendix 1). As for BMI, no overall mixture effect was found with systolic and diastolic BP. However, we did observe a sharp downward trend between the mixture and systolic BP, driven by BUPA, in girls. Because parabens have potential estrogenic activity (Nowak et al., 2018), we speculate that the decrease in systolic BP only seen in girls could be mediated by a downregulation of the rennin-angiotensin-aldosterone system (RAAS), a major regulator of systemic BP, via estrogenic pathways (Medina et al., 2020). Finally, results for prenatal ∑DEHP and lower systolic BP in boys are partly consistent with the negative association between prenatal ∑DEHP metabolites and lower systolic and diastolic BP in boys and girls at 4–6 years observed in the Greek Rhea cohort (Bowman et al., 2019; Vafeiadi et al., 2018; Valvi et al., 2015a).

In our study, prenatal exposure to BP3 was associated with higher BMI and diastolic BP levels at preadolescence in both sexes, and in single and mixture modelling approaches. Only in BKMR, BP3 was also associated with higher systolic BP. These associations were further consistent and stronger in preadolescents who reached puberty onset. Puberty is considered one of the developmental windows, besides fetal and neonatal life, in which endocrine-disrupting chemicals are more likely to act at any level in the "hypothalamic-pituitary–gonadal-peripheral tissues' axis" (Gore et al., 2015). Epidemiological studies assessing the prenatal effects of BP3 on obesity and BP are scarce. Apart from the CHAMACOS study (Berger et al., 2021), another study in the US assessed prenatal BP3 and obesity in 170 4–9 years-old children and reported a decreased body fat mass % in girls (Buckley et al., 2016). Likewise, in the HELIX subcohort, prenatal BP3 was associated neither with child BMI nor BP (Vrijheid et al., 2020; Warembourg et al., 2019). The present study is the first to assess and identify associations of prenatal BP3 alone and in a mixture of non-persistent chemicals in relation to BMI and BP at preadolescence in a big sample size (n ~ 1,000). Our results shed light on BP3 potential metabolic disrupting effects in puberty due to fetal development exposure. Benzophenones are UV light filters used in sunscreens to absorb and dissipate the UV radiation and in cosmetics to prevent damage to colour and scent, being probably the reason why higher BP3 exposure has been observed in females in biomonitoring studies (Calafat et al., 2008).

Developmental effects of BP3 exposure on adipogenesis may be mediated through its estrogen-like and anti-androgenic activity (Blüthgen et al., 2012; Kerdivel et al., 2013; Kim and Choi, 2014; Majhi et al., 2020; Schlumpf et al., 2001; Schreurs et al., 2005; Wang et al., 2016; Watanabe et al., 2015), the decrease in thyroid hormone balance (Lee et al., 2018), and the upregulation of PPARγ, a direct transcriptional regulator of human adipogenesis that contributes to adipocyte differentiation and insulin sensitization (Shin et al., 2020b; Wnuk et al., 2019). The mechanisms underlying BP3 effects on blood pressure could be indirectly via BP3 obesogen-like effects, or directly through the disruption of steroid and thyroid hormone molecular pathways, which may alter RAAS (Barreto-Chaves et al., 2010). Furthermore, recent



B)

Chemicals	GroupPIP	CondPIP
MEP	0.08	0.28
MiBP	0.08	0.10
MnBP	0.08	0.11
MBzP	0.08	0.25
∑DEHP	0.08	0.25
MEPA	0.16	0.11
ETPA	0.16	0.08
PRPA	0.16	0.05
BUPA	0.16	0.03
BP3	0.16	0.74

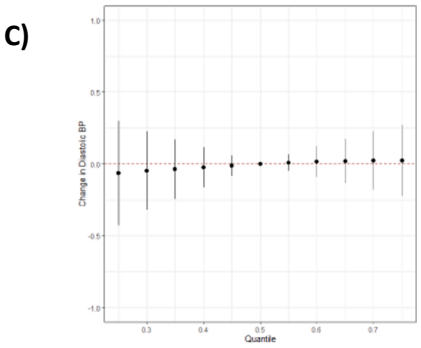


Fig. 5. Summary estimates from BKMR on the association between mixtures of $\log_2$ scaled non-persistent chemicals and diastolic BP in preadolescence adjusted for maternal age, education, smoking in pregnancy, pre-pregnancy BMI, sex, height and age at outcome assessment; region of residence was included as random intercept. (A) Exposure-response associations for each chemical when the others are fixed at their median. (B) Group and conditional posterior inclusion probabilities (GroupPIP and CondPIP) of each chemical in the mixture-response function for diastolic BP. (C) Joint effect of prenatal non-persistent chemicals mixture on diastolic BP at preadolescence (Credible intervals overlapping the null depicted with the broken line indicate no significant effects). Abbreviations: BP (blood pressure), BMI (body mass index), BKMR (Bayesian kernel machine regression), MEP (mono-ethyl phthalate), MiBP (mono-*iso*-butyl phthalate), MnBP (mono-n-butyl phthalate), MBzP (mono-benzyl phthalate), DEHP (sum of di(2-ethylhexyl) phthalate metabolites), MEPA (methyl paraben), ETPA (ethyl paraben), PRPA (propyl paraben), BUPA (butyl paraben), BP3 (benzophenone-3).

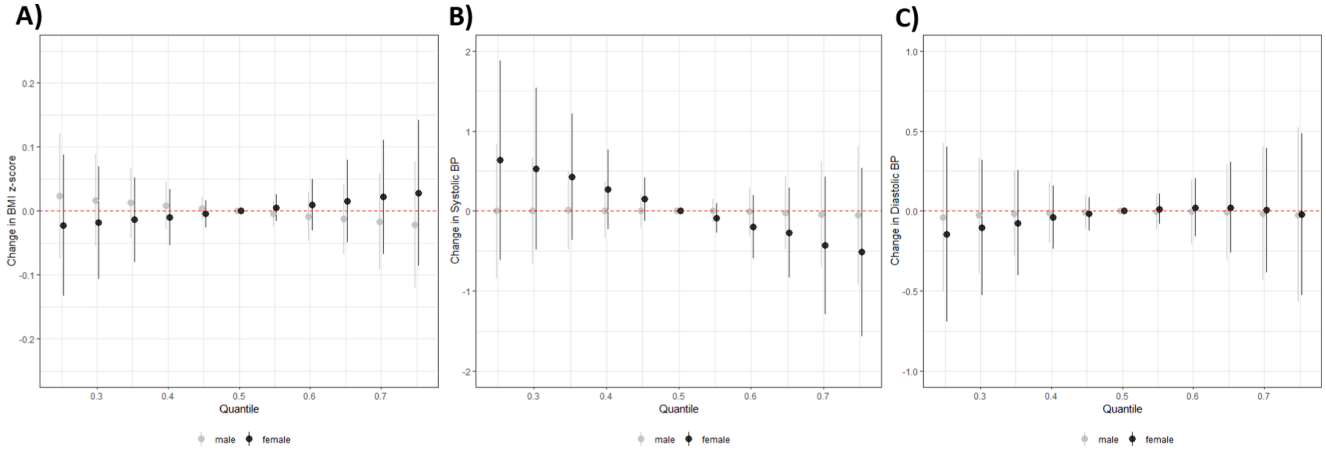


Fig. 6. Sex-stratified analysis. Joint effect of $\log_2$ scaled prenatal non-persistent chemicals mixture on BMI z-score (A), systolic BP (B), and diastolic BP (C) stratified in girls and boys shown in black and grey lines, respectively. Credible intervals overlapping the null depicted with the broken line indicate no significant effects. Summary estimates from BKMR were adjusted for maternal age, education, smoking in pregnancy, pre-pregnancy BMI; region of residence was included as random intercept. Height, and age at outcome assessment were additionally adjusted in the BP models. Abbreviations: BP (blood pressure), BMI (body mass index), BKMR (Bayesian kernel machine regression).

studies with animal models have reported BP3 exposure to induce free radical production and the downregulation of antioxidant enzymes (Liu et al., 2015; Rodríguez-Fuentes et al., 2015), which may eventually influence the early development of the cardiovascular system (Ávila et al., 2015). The non-monotonic exposure–response relationships found in this study suggest that the health effects of BP3 can occur even at low doses of exposure (Vandenberg et al., 2012). Of interest, the magnitude of the association between BP3 and BMI z-score (e.g. Q2: $\beta = 0.22$ [95% CI = 0.01, 0.42]) was very similar to associations found in adolescence of the INMA Menorca cohort in relation to prenatal exposure to hexachlorobenzene and BMI z-score (tertile 2: $\beta = 0.24$ [95% CI: 0.01, 0.47]) (Güil-Oumrait et al., 2021). Although BP3 has a short biological half-life (<24 h) (Kim and Choi, 2014), it is one of the phenols with the lowest intraindividual variability (Vernet et al., 2018). However, the intraclass correlation coefficient of a spot urine sample collected during pregnancy is still low (between 0.39 (Mínguez-Alarcón et al., 2019) and 0.62

(Meeker et al., 2013), meaning that in studies collecting between 1 and 3 urine samples per women, a large percentage of the study population may still be misclassified. Epidemiological studies collecting repeated urine samples during pregnancy are urgently needed to yield consistent and interpretable results (LaKind et al., 2019).

Our study has several strengths. To our knowledge, this is the first study conducted on the associations between prenatal phthalate and phenols mixture exposure and BMI and BP in preadolescence. With the benefits of a sample size of around 1,000 mother and child pairs, which enabled us to assess sex-specific effects, and the use of a flexible BKMR approach, we addressed the issues of multicollinearity, non-linearity and co-exposure bias (Lazarevic et al., 2019). The inclusion of chemicals widely found in personal care products, such as parabens and BP3, that have been considered safe toxicologically and therefore rarely assessed, along with the examination at the preadolescence stage are also strengths of this study.

However, our findings should be interpreted with caution due to the following limitations. First, measurement error may exist in the exposure assessment of phthalates and phenols with high temporal variability since we only used mostly 2 spot urine samples. In studies assessing mixtures of non-persistent chemicals relying on spot urine samples, the chances of a given chemical being selected might be lower for compounds with a low ICC (Agier et al., 2020). This can explain the null associations observed in our study for highly variable non-persistent chemicals like some phthalates and BPA, for which attenuation bias may be as high as 80% (Perrier et al., 2016). Therefore, and as mentioned before, serial urine measurements obtained over the pregnancy would contribute to minimizing biases and elucidate if other chemicals rather than BP3 are associated with BMI and BP (Agier et al., 2020). This will also allow to assess the effects in each trimester separately. Second, although we adjusted by pre-pregnancy BMI, an important determinant of BP both in pregnancy (Savitri et al., 2016) and in the offspring (Ludwig-Walz et al., 2018), residual confounding may have occurred due to unmeasured maternal BP levels for example. Similarly, due to lack of information, we have not tested the potential effect modifier of maternal BMI at the time of outcome assessment. Fourth, we only considered phthalates and phenols although the foetus is simultaneously exposed to other endocrine disruptors that can potentially affect cardiovascular health in childhood and later stages (Güil-Oumrait et al., 2021; Lee et al., 2020). However, and consistent with our study, exposome studies have reported that correlations between exposures belonging to different groups of chemicals (e.g. between phthalates and phenols) are much lower than among exposures in the same group (e.g. within phthalates) (Tamayo-Uria et al., 2019). Therefore, we do not expect our estimates to be largely affected by other chemical groups not considered in the present study. Another limitation is that we performed quite a large number of comparisons, which may have led to spurious findings. For this reason, we have focused on the BP3 results because they are the most consistent ones across outcomes and modelling approaches. Lastly, we have not included other measurements that represent a more reliable measure of adiposity and obesity such as body fat % or waist-to-height ratio (Brambilla et al., 2013; Güil-Oumrait et al., 2021), and we assessed health effects at a single time point (11 years). Future research with improved exposure assessment and better characterization of the cardiometabolic risk is needed to elucidate the potential impact of prenatal exposure to endocrine-disrupting chemicals on metabolic disorders in children and adolescents.

5. Conclusion

This study suggests that prenatal exposure to UV-filter BP3 may be associated with higher BMI and diastolic BP in puberty, two well-established risk factors for CVD later in life. Findings from this study highlight the necessity of providing stricter regulations for limiting production and use of this compound, and the importance of public health awareness for pregnant women for using cosmetics that are BP3 free. These results need to be confirmed in future studies using a thoughtful sampling design based on many urines collected during pregnancy and mixture modelling approaches.

CRediT authorship contribution statement

Nuria Güil-Oumrait: Conceptualization, Methodology, Software, Validation, Formal analysis, Writing – original draft, Visualization. **German Cano-Sancho:** Methodology, Software, Writing – review & editing. **Parisa Montazeri:** Methodology, Writing – review & editing. **Nikos Stratakis:** Methodology, Software, Writing – review & editing. **Charline Warembourg:** Methodology, Software, Writing – review & editing. **Maria-Jose Lopez-Espinosa:** Resources, Data curation, Writing – review & editing. **Jesús Vioque:** Resources, Data curation, Writing – review & editing. **Loreto Santa-Marina:** Resources, Data curation, Writing – review & editing. **Alba Jimeno-Romero:** Resources, Data curation, Writing – review & editing. **Rosa Ventura:** . **Nuria Monfort:** . **Martine Vrijheid:** Conceptualization, Methodology, Resources, Data curation, Writing – review & editing, Project administration, Funding acquisition. **Maribel Casas:** Conceptualization, Methodology, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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 1. . Studies on prenatal exposure to non-persistent chemicals and cardiovascular outcomes (ordered by year and author)

Ref.	Recruitment time	Cohort (Country)	Size	Exposure assessment (in pregnancy)	Outcome assessment	Covariates	Statistical analyses	Main results
Phthalate metabolites								
Ferguson et al., 2022	2010–2012	TIDES (US)	425	Average of 1st and 3rd trimester urines	Weight and BMI z-score at 1 y (only boys), 3 y, 4 y and 6 y (using CDC ref.)	Maternal age, race/ethnicity, education level, pre-pregnancy BMI, study site and smoking in pregnancy	Linear mixed models Group-based trajectory models	MEP, MBzP, MCPP, MCOP ↑ z-BMI at 4 y MnBP, MCPP ↑ z-BMI at 3 y
Kupsco et al., 2022	2007–2011	PROGRESS (Mexico)	514	Average of 2 urines	Adiposity trajectories from 4 to 12 y (BMI z-score using WHO ref., FMI, WHtR)	Maternal age, pre-pregnancy BMI, parity, socioeconomic status, education, child sex	Multivariate latent class growth Multinomial logistic regression Multivariable linear mixed models Quantile G-computation	ΣDEHP ↑ high-high trajectory ΣDiNP ↑ low–high trajectory MCNP ↓ low–high trajectory No mixture associations
Montazeri et al., 2022	2004–2006	INMA-Sabadell (Spain)	416	Average of 1st and 3rd trimester urines (including MEPA, ETPA, PRPA, BUPA, BPA, BP3, triclosan)	SBP, DBP, PWV, CRAE, CRVE at 11 y	Maternal age, pre-pregnancy BMI, gestational weight gain, smoking in pregnancy, social class, parental cardiovascular history, child sex and age, gestational age at birth	Linear regressions BWQS	BPA ↓ PWV, MIBP ↑ CRAE, MEPA and BUPA ↓ CRVE No mixture associations
Berger et al., 2021	1999–2000	CHAMACOS (US)	309	Average of 1st and 3rd trimester urines (including MEPA, PRPA, BPA, triclosan, 2,4-dichlorophenol, 2,5-diclorophenol, BP3)	BMI z-score at 5 y (using CDC ref.) Overweight/obesity status	Maternal age, education, years lived in the US, poverty status, childhood frequency of fast-food intake at 5 y	Linear/logistic regression BHM BKMR	MEP, MCNP, PRPA ↑ BMI z-score/ overweight status in linear mixed models, BKMR, BMHOverall mixture ↑ BMI z-score (not significant)
Berman et al., 2021a	1989–1991	Raine Study – Gen 2 (Australia)	462 girls	Pool of 1st and 3rd trimester maternal serum	Change in height and weight z-scores (birth to 2 y), height (birth to 20 y), z-BMI (using CDC ref.) from 2 to 20 y and %BF at 20 y	Birthweight, gestational age, midparental height z-score, BMI at 8 y, pre-pregnancy BMI, smoking during pregnancy and age at menarche	Cox and linear regressions	Non-significant associations
Berman et al., 2021b	1989–1991	Raine Study – Gen 2 (Australia)	300 boys	Pool of 1st and 3rd trimester maternal serum	BMI z-score (using CDC ref.) from 2 to 20 y, and %BF at 20 y	Gestational age, birthweight, mid-parental height z-score and maternal BMI	Linear mixed models	MiBP ↑ BMI z-score (2–11 y and 11–20 y), MCPP ↓ % fat MiDP ↑ % BFLMWP ↑ (2–11 y)
Sol et al., 2020b	2002–2006	Generation R Study (the Netherlands)	1128	Average of 1st, 2nd, and 3rd trimester urines (including weighted molar sums of LMWP, HMWP, DEHP, DNOP, phthalic acid, total bisphenol (BPA + BPS + BPF))	BMI z-score (using the Dutch reference growth charts), total body fat mass, pericardial fat, total visceral fat at 10 y	Maternal age, education, parity, ethnicity, pre-pregnancy BMI, maternal diet quality score, alcohol consumption and smoking in pregnancy, child's age and sex	Linear regressions	Phthalic acid ↑ BMI z-score, pericardial fat index LMWP ↑ pericardial fat index
Vrijheid et al., 2020	1999–2010	HELIX sub-cohort (six European cohorts)	1301	1 spot urine (including MEPA, ETPA, PRPA, BUPA, BPA, BP3, triclosan)	z-BMI (using WHO ref.), waist circumference, skinfold thickness, at 6–12 y	Sex, cohort, maternal education, maternal age, pre-pregnancy BMI, parity and parental country of birth	Linear regressions ExWAS DSA	Non-significant associations
	2008–2011		481					

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Ref.	Recruitment time	Cohort (Country)	Size	Exposure assessment (in pregnancy)	Outcome assessment	Covariates	Statistical analyses	Main results
Lee et al., 2020		EDC (South Korea)		2nd trimester urine spot	BMI z-score (using WHO ref.), % BF, % skeletal muscle and SMI at 6 y	Maternal age, education, household income	Linear regressions	ΣDEHP and MnBP ↓ SMI; MEHHP and MnBP ↓ BMI z-score (girls)
Sol et al., 2020a	2002–2006	Generation R Study (the Netherlands)	1064	Average of 1st, 2nd, and 3rd trimester urines in pregnancy (weighted molar sums of LMWP, HMWP, DEHP, DNOP, phthalic acid, total bisphenol (BPA + BPS + BPF))	SD scores of SBP and DBP at 10 years	Child's age and sex, maternal age, education, parity, ethnicity, pre-pregnancy BMI, alcohol consumption and smoking in pregnancy	Linear regressions	3rd trimester HMWP, DEHP, DNOP ↓ SBP and DBP (girls)2nd trimester total bisphenol and BPA ↑SBP (boys)
Bowman et al., 2019	2001–2003	Mexico (ELEMENT)	223	1st, 2nd and 3rd trimester urine spots	WC, triceps and subscapular skinfold thickness, BMI z-score (using the WHO ref.) at 8–14 y and at 9–17 y	Specific gravity, age, maternal education	GEE	1st trimester MBP, MiBP, and MBzP ↑ skinfold thickness, z-BMI and WC (girls) 2nd trimester MBzP ↓ skinfold thickness, BMI z-score and WC (boys)
Heggeseth et al., 2019	1999–2000	CHAMACOS (US)	335	1st and 3rd trimester urines	BMI z-score trajectories 11 visits between 2 and 14 y (using CDC ref.)	Pre-pregnancy BMI, smoking during pregnancy, gestational weight gain, diet quality index during pregnancy, years living in the US, age, marital status, and education	Growth mixture model	MEP ↑ BMI z-score as children get older (not linear)
Warembourg et al., 2019	1999–2010	HELIX sub-cohort (six European cohorts)	1301	1 spot urine in pregnancy (including MEPA, ETPA, PRPA, BUPA, BPA, BP3, triclosan)	SBP and DBP at 6–11 y	Cohort, maternal age, educational level, pre-pregnancy BMI, parity, parental country of birth, child's age, sex and height	ExWAS DSA	MBzP ↓ SBP BPA ↑ DBP
Vafeiadi et al., 2018	2007–2009	Rhea (Greece)	500	1 spot urine	BMI z-score (internal standardization), WC, skinfold thicknesses, BP SD scores, and lipids (4 and 6 y). Leptin, adiponectin, CRP at 4 y	Child's sex and age, maternal age, education, pre-pregnancy BMI and smoking in pregnancy	GEEs	ΣDEHP ↓ WC (boys) and ↑WC (girls) MEP ↓ SBP z-score at 4 y MnBP and MBzP ↓ DBP z-score MiBP ↑ total cholesterol
Yang et al., 2018	1997–2005	ELEMENT (Mexico)	249	1 spot urine (including BPA)	BMI trajectories from birth to 14 y	Maternal education and BMI at 1-month postpartum	Mixed models	Girls: MECPP ↑ highest BMI trajectories Boys: MiBP, MBzP, MEHP, and MEHHP ↑ highest BMI trajectories
Yang et al., 2017	1997–2005	ELEMENT (Mexico)	249	1 spot urine (including BPA)	WC, triceps and subscapular skinfold thicknesses,z-BMI (using WHO ref.) at 8–14 y	Maternal age, years of education, BMI at 1-month postpartum	Linear regression models	MBzP ↓ BMI z-score
Harley et al., 2017	1999–2000	CHAMACOS (US)	345	Average of 1st and 3rd trimester urines	BMI and WC z-scores (using CDC ref.) at 5, 7, 9, 10.5, 12 y. % BF at 9, 10.5 and 12 y	Maternal age, education, years living in the US, smoking in pregnancy, poverty status, child's food insecurity, child's fast food consumption, prenatal BPA	GEEsBKMR (only assessment of univariate associations)	MEP, MnBP, MEHP ↑ BMI, WC z-scores and % BF at multiple ages. MEP, MnBP, MEHP ↑ overwt/obese at 12 y MnBP and MCPP only ↑ in boys
	2003–2006	HOME (US)	219	Average of 1st and 3rd trimester urines		Maternal age, race, marital status,	Linear regressions	

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Ref.	Recruitment time	Cohort (Country)	Size	Exposure assessment (in pregnancy)	Outcome assessment	Covariates	Statistical analyses	Main results
Shoaff et al., 2017					BMI z-score (using the CDC ref), WC, %BF at 8 y	insurance, income, education, parity, cotinine, depressive symptoms, mid-pregnancy BMI, food security, fruit/ vegetable and fish consumption during pregnancy, prenatal vitamin use, child's sex and age		MBzP ↓ adiposity
Botton et al., 2016	2003–2006	EDEN (France)	520 boys	2nd trimester urine spot	Repeated BMI -> postnatal growth trajectories (0–5 y)	Maternal age, height and BMI, active and passive smoking during pregnancy, education, recruitment center, gestational age, weight gain during pregnancy and parity	Linear regressions Mixed models GEE	MEP ↑ weight growth velocity (from 2 to 5 y), ↑ BMI at 5 y
Buckley et al., 2016b	1998–2002	MSSM (US)	180	3rd trimester urine spot	% BF at 4–9 y	Pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, and breastfeeding	Linear mixed models	Non-significant associations
Buckley et al., 2016a	1998–2006	Pool from MSSM, CCCEH, HOME cohorts (US)	707	1 spot urine	BMI z-scores at 4–7 y (using CDC ref.) Overweight/obesity status	Cohort, maternal race, maternal age, education, work status during pregnancy, pre-pregnancy BMI, maternal height, gestational weight gain, smoking during pregnancy, natural log creatinine, calendar date of urine collection, parity, breastfeeding, child's sex and age	Linear mixed models	MCPP ↑ overweight/ obesityMEP, ∑DEHP ↓ BMI z-score (only in girls)
Maresca et al., 2016	1998–2006	CCCEH (US)	330	3rd trimester urine spot	BMI z-score (using CDC ref.) at 5 and 7 y, %BF and WC at 7 y	Child's age, maternal pre-pregnancy obesity, birth weight, maternal race, maternal receipt of public assistance during pregnancy, and urinary specific gravity	PCA GEE	Boys: non-DEHP component ↓ BMI z-score, ↓ WC, ↓ %BF
Valvi et al., 2015	2004–2006	INMA-Sabadell (Spain)	391	Average of 1st and 3rd trimester urines	Difference in z-weight between 0 and 6 mo. BMI z-score (using WHO ref.) at 1, 4, 7 yWHtR, SBP and DBP z-scores (internal standardisation) at 4 and 7 y	Child's sex and age, and maternal country of origin, age at delivery, parity, education, social class, pre-pregnancy BMI, and smoking in pregnancy	GEE	Boys: ΣHMWPm ↓ z-weight difference and BMI z-score. Girls: ΣHMWPm ↑ z-weight difference and zBMI ΣHMWPm and ΣLMWPm ↓ SBP z-score
Agay-Shay et al., 2015	2004–2006	INMA-Sabadell (Spain)	470	Average of 1st and 3rd trimester urines (including BPA and metals and persistent chemicals in maternal blood 1st trimester)	BMI z-score (using WHO ref.) at 7 yOverweight (BMI > 85th p)	Child's sex and age, gestational age, birth weight, maternal country of origin, age, pre-pregnancy BMI, weight gain during pregnancy, social class and smoking in pregnancy	Linear/logistic regressions PCA	T2 of phthalate factor ↓ overweight
Phenols BPA, BP3 and parabens								

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Ref.	Recruitment time	Cohort (Country)	Size	Exposure assessment (in pregnancy)	Outcome assessment	Covariates	Statistical analyses	Main results
Montazeri et al., 2022. See page 1 Berger et al., 2021. See page 1								
Leppert et al., 2020	2006–2008	LINA (Germany)	392	3rd trimester urine (MEPA, ETPA, PRPA, BUPA)	BMI at 1–8 yOverweight (IOTF cutoff)	Child's sex, smoking during pregnancy, parental education, gestational age at birth, siblings, breastfeeding duration and maternal age	GEE	BUPA ↑ overweight (girls)
Ouyang et al., 2020	2012–2013	China	218	Spot urine (BPA)	BMI z-scores (using the WHO ref.), SBP, DBP, plasma glucose, serum lipids (HDL, LDL, cholesterol, triglycerides), insulin	Maternal urinary creatinine, passive smoking, hypertensive disorders in pregnancy, infant low gestational age status, child's age, passive smoking, breastfeeding	Linear regressions	BPA ↑ SBP and DBP (girls)
Braun et al., 2019	2008–2011	MIREC (Canada)	719	1st trimester urine (BPA)	BMI z-score (using WHO ref.), subscapular skinfold, triceps skinfold, WC, hip circumference at 3 y	Maternal race, education, age, marital status, smoking during pregnancy, pre-pregnancy BMI, household income, and study centre	Linear regressions	BPA ↑ waist-to-hip ratioBPA ↑ WC and subscapular skinfold thickness (girls)
Junge et al., 2018	2006–2008	LINA (Germany)	552	3rd trimester urine (BPA)	BMI z-score (using WHO ref.) at 1 and 6 y	Child's sex, smoking during pregnancy, parental education, solid food introduction, gestational age at delivery, n° of household members, early delivery	GEE Mediation analysis	BPA ↑ BMI z-score
Yang et al., 2018. See page 3 Yang et al., 2017. See page 3								
Bae et al., 2017	2008–2011	EDC (South Korea)	645	2nd trimester urine (BPA)	SBP and DBP at 4 y	Child's age, sex, height, weight, birth weight, gestational age at birth, maternal age, parental history of hypertension, father's education, environmental tobacco smoke, duration of vigorous physical activity/ week, and current infection.	Piecewise regression	BPA ↑ DBP
Buckley et al., 2016c	1998–2002	MSSM (US)	173	3rd trimester urine (BPA, BP3, 2,5-dichlorophenol, triclosan)	BMI z-score (using CDC ref.), %BF at 4–9 y	Maternal race, age, education, work status, smoking during pregnancy, height, pre-pregnancy BMI, gestational weight gain; prenatal ∑DEHP metabolites concentrations; breastfeeding; child's age and physical activity at follow-up	Linear mixed models	BP3 ↓ %BF (girls)
Hoepner et al., 2016	1999–2006	CCCEH (US)	375	Spot urine (BPA)	BMI z-score (using CDC ref.) at 5 and 7,	Pre-pregnancy obesity, maternal	Linear regressions	BPA ↑ FMI, %BF, and WC at 7 y

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Ref.	Recruitment time	Cohort (Country)	Size	Exposure assessment (in pregnancy)	Outcome assessment	Covariates	Statistical analyses	Main results
					FMI, %BF and WC at 7 y	race, prenatal ∑DEHP, prenatal urinary specific gravity, birth weight, gestational age		
Vafeiadi et al., 2016	2007–2009	Rhea (Greece)	500	1st trimester urine (BPA)	BMI z-score (internal standardization) (6 months to 4 y), WC, skinfold thickness, SBP, DBP, serum lipids, CRP, adipokines at 4 y, BMI growth trajectories	Maternal education, age, pre-pregnancy BMI, working status during pregnancy, child sex, z-score of birth weight for gestational age and breastfeeding status	Linear mixed models	BPA ↑ BMI, WC, skinfold thickness (boys), and ↓ BMI (girls)
Agay-Shay et al., 2015. See page 4								
Braun et al., 2014	2003–2006	HOME (US)	297	Average of 2nd and 3rd trimester urines (BPA)	BMI z-scores (using the US National Center for Health Statistics) at 2–5 y (3 times), WC at 4 and 5 y	Maternal race, marital status, parity, age at delivery, household income, education, employment, insurance, BMI at 16 weeks, depressive symptoms at baseline, and prenatal serum cotinine	Linear mixed models	Non-significant associations
Harley et al., 2013	1999–2000	CHAMACOS (US)	311	Average of 1st and 2nd urines (BPA)	BMI z-score (using CDC ref.) and WC at 2, 3, 5, 7 and 9 y, %BF at 9 y	Maternal pre-pregnancy BMI, household income, education, years living in the US, smoking during pregnancy, soda consumption during pregnancy, and child's fast food and sweet consumption at 9 y	Linear/logistic regressions GEE	BPA ↓ BMI, ↓ % BF, ↓ obesity (girls)
Valvi et al., 2013	2004–2006	INMA-Sab (Spain)	402	Average of 1st and 3rd trimester urines (BPA)	Rapid child growth (z-weight gain > 0.67 in the first 6 months), BMI z-score (using WHO ref.) and WC z-score (internal standardization) at 14 months and 4 y	Child's sex and age maternal country of origin, age at delivery, education, parity, pre-pregnancy BMI, and smoking during pregnancy	Linear regressions	BPA ↑ WC and BMI z-score at 4 y
Reimann et al., 2021	2014–2017	Belgium (ENVIRONAGE)	218	Placenta (MEPA, ETPA, PRPA, BUPA)	BMI z-score (using WHO ref.) trajectories (1 to 8 y)	Sex, ethnicity, gestational age and birth weight, maternal age, maternal smoking, education, pre-pregnancy BMI, gestational diabetes, alcohol consumption during pregnancy, parity	Mixed models	ETPA ↓ BMI z-score

BF, body fat; BHM, Bayesian hierarchical modelling; BKMR, Bayesian kernel machine regression; BMI, body mass index; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; BP3, benzophenone-3; BUPA, butyl paraben; CDC, Centers for Disease Control and Prevention; CRAE, central retinal artery equivalent; CRP, C-reactive protein; CRVE, central retinal vein equivalent; DBP, diastolic blood pressure; DEHP, di(2-ethylhexyl) phthalate metabolites; DiNP, Diisononyl phthalate; DNOP, Di-n-octyl phthalate; DSA, deletion-substitution-addition variable selection algorithm; ETPA, ethyl paraben; ExWAS, Exposome-wide association study; FMI, fat mass index; GEE, generalized estimating equations; HDL, high-density lipoprotein; HMWP, high-molecular-weight phthalates; IOTF; International Obesity Task Force; LDL, low-density lipoprotein; LMWP, low-molecular-weight phthalates; MBzP, mono-benzyl phthalate; MEP, mono-ethyl phthalate; MEPA, methyl paraben; MCOP, Monocarboxyoctyl phthalate; MCNP, Monocarboxy-isononly phthalate; MCPP, mono-(2-ethyl-5-carboxy-pentyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MiBP, mono-*iso*-butyl phthalate; MiDP, monoisodecyl phthalate, MnBP, mono-n-butyl phthalate; PCA, principal component analysis; PRPA, propyl paraben; PWV, pulse wave velocity; SBP, systolic blood pressure; SD, standard deviation; SMI, skeletal muscle index; y, years; WHO, World Health Organization; WC, waist circumference; WHtR; Waist-to-Height Ratio.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107527.

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