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Paraben exposures and satiety hormones in preschool children: an ENVIRONAGE study

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ABSTRACT

Background: Exposure to environmental pollutants has been associated with obesogenic effects, yet evidence in young children remains sparse. Parabens, widely used as antimicrobial preservatives in personal care products, may disrupt satiety hormones during early life, potentially influencing long-term metabolism and weight regulation.

Methods: This cross-sectional study analyzed urinary methyl, ethyl, propyl, and butylparaben (MeP, EtP, PrP, BuP) levels in 4–6-year-old children from the ENVIRONAGE birth cohort using ultra-performance liquid chromatography/tandem mass spectrometry. Plasma satiety hormones (leptin, pancreatic polypeptide, glucagon-like peptide 1, and peptide YY) were measured via (radio-)immunoassays. Associations were assessed in 188 samples using covariate-adjusted linear regression, sex-stratified analysis, and mixture modeling (quantile g-computation and Bayesian kernel machine regression). Additionally, the role of BMI was investigated by partial correlation analysis.

Results: As more than 96 % of the BuP measurements were below the LOQ, only the values of MeP, EtP and PrP were used for further statistical analysis. A doubling in PrP was associated with an 5.34 % [95 % Confidence Interval: 1.58 %, 9.23 %] increase in leptin, and BKMR indicated a positive linear association between parabens and leptin. Additional sensitivity analyses were indicative of sex-specific differences in the relationship between parabens, BMI and leptin levels.

Conclusions: PrP may increase leptin levels, contributing to obesogenic effects in young children. Given rising childhood metabolic disorders, further longitudinal studies are needed to assess PrP exposure risks in personal care products.

1. Introduction

Globally, the prevalence of childhood obesity has surged dramatically over the past four decades, mirroring the rise in adult obesity (Simmonds et al., 2016) and predisposing children to long-term health issues in adulthood, including cardiovascular and metabolic diseases (Lindberg et al., 2020; Reilly and Kelly, 2011). Recently, the environmental obesogen hypothesis was introduced, suggesting that exposure to endocrine-disrupting synthetic chemicals in personal care products during prenatal or early life stages may predispose individuals to

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increased fat storage and obesity (Darbre, 2017; Grun and Blumberg, 2009). Parabens have been used as low-cost antimicrobial agents in pharmaceuticals and personal care products for over a century (Ana and Paula, 2016; Elder, 1984). Consequently, dermal absorption forms the primary exposure route for parabens (Soni et al., 2005) and internal exposure to different paraben esters in European children is estimated to be between 0.20 and 1.01 mg/kg bw/day (Gosens et al., 2014). Concerns about parabens and their endocrine-disrupting properties, reported since the early 2000s (Giulivo et al., 2016; Nowak et al., 2018; Oishi, 2001, 2002), suggest that widespread paraben exposure could contribute to the rising metabolic epidemic (Heindel and Blumberg, 2019; Heindel et al., 2015). Although parabens are rapidly metabolized in the liver and excreted in urine within hours after dermal exposure (Janjua et al., 2008; Kiwada et al., 1979; Soni et al., 2005), daily dermal contact leads to chronic exposure with biologically active forms still being detectable in human blood and tissue samples (Shin et al., 2023). One mechanism how parabens exert obesogenic effects could be by altering levels of different appetite/satiety hormones, which in turn regulate food intake. Satiety hormones released as a direct response to food intake and involved in short-time appetite regulation include glucagon-like peptide 1 (GLP1), peptide YY (PYY) and pancreatic polypeptide (PP). PP is a gut hormone that reduces appetite in humans after release from the pancreas in response to ingestion of food (Batterham et al., 2003). Likewise, GLP1 and PYY produced in intestinal L-cells promote satiety (Flint et al., 1998; Karra et al., 2009). While leptin crosses the blood-brain barrier (BBB) via saturable transport mechanisms to reach the arcuate nucleus (ARC) of the hypothalamus (Rhea et al., 2017), GLP-1, PYY, and PP signal satiety by either directly crossing the BBB or activating vagal afferents (Batterham et al., 2002; Rhea et al., 2017; Schwartz, 1983). Although leptin decreases appetite, increased leptin levels can be indicative of adverse metabolic profiles and leptin resistance (Obradovic et al., 2021) and have been suggested as a biomarker for obesity (Venner et al., 2006) and metabolic syndrome (Madeira et al., 2017).

Associations between parabens and satiety hormones have, to our knowledge, only been investigated for leptin, where race-specific differences have been found in middle-aged women in the U.S., showing an inverse association between methyl paraben and leptin in White women but a positive association in Black women (Lee et al., 2022). In another study of prenatal paraben exposure, maternal urinary benzyl paraben was positively associated with cord leptin in a Chinese mother-newborn cohort (Zhang et al., 2022).

Knowledge regarding the effects of parabens in personal care products and their influence on appetite regulation during childhood is absent, while obesity prevention is most effective when initiated early in life (Heindel and Vandenberg, 2015; Yan and Mi, 2021). Early-life environmental factors, especially during prenatal and early postnatal periods, significantly impact the likelihood of developing metabolic diseases later in life (Hsu and Tain, 2021; Tamashiro and Moran, 2010), emphasizing the crucial role of childhood health deviations in shaping long-term health. Furthermore, sex-specific differences have been reported previously for the relationship between parabens and weight measures (Guo et al., 2017a; Quirós-Alcalá et al., 2018), potentially through the estrogen-like activity of parabens, demonstrated repeatedly in *in vitro* (Kim et al., 2024; Watanabe et al., 2013; Wei et al., 2022) and *in vivo* experiments (Liang et al., 2023; Oishi, 2001, 2002; Sun et al., 2016). With this study, we hypothesized that paraben exposure in early childhood is associated with changes in satiety hormones and investigated potential relationships with BMI.

2. Material and methods

2.1. Study population

As part of the ongoing Environmental Influence on Early Aging (ENVIRONAGE) birth cohort study (Janssen et al., 2017), mothers who had not undergone planned caesareans and were able to complete Dutch-language questionnaires were enrolled upon arrival at the delivery ward of East-Limburg Hospital in Genk, Belgium. Recruitment, which began in February 2010 and is still ongoing, took place after obtaining written informed consent following procedures approved by the ethical committees of Hasselt University and East-Limburg Hospital (EudraCT B37120107805) in compliance with the principles of the Helsinki Declaration.

When the child was between four and six years old, parents were invited to complete an online questionnaire and participate in a follow-up examination. The follow-up examinations included in this study were conducted between August 2015 and April 2018. Urinary paraben levels of methyl paraben (MeP), ethyl paraben (EtP), propyl paraben (PrP) and butyl paraben (BuP) were measured in 300 randomly selected urine samples from 494 children who provided sufficient urine volume during the examination. For a subset of these children also plasma samples were available with different numbers of hormone measurements (leptin and PP N = 200, GLP1 N = 131 and PYY N = 119). Because of missing measurement values, the final sample sizes in the main analysis for the association with leptin and PP were N = 188, for GLP1 N = 123 and for PYY N = 111.

2.2. Data collection

At birth, medical records were used to collect information on the newborn's sex, delivery date, and maternal parity. Parity was categorized into three groups: mothers having their first, second, or third or more child. Additional details were gathered through a questionnaire completed by the mothers during their stay at the delivery ward and online 4 years later (Supplementary Text 1). The child's exact age at follow-up was calculated by subtracting the delivery date from the follow-up participation date, expressed in years with decimal precision. Trained examiners measured the child's height using a fixed stadiometer with 0.5 cm accuracy and weight using a digital scale to the nearest 0.1 kg. From the height and weight measurements, BMI z-scores (zBMI) were calculated according to the World Health Organization's (WHO) Child Growth Standards (World Health Organization, 2006), with the CRAN package zscorer (M Myatt and E Guevarra, 2019) taking into account the age and sex of the child.

2.3. Urinary paraben concentrations

During the follow-up examination, spot-urine samples were collected in metal-free polypropylene containers (Yvsolab, Turnhout, Belgium) and kept on ice until the end of the examination. The samples were then transferred into metal-free 50 mL Falcon tubes (VWR, Haasrode, Belgium) and stored at −20 °C for further processing.

For mass spectrometric analysis, the samples were thawed, aliquoted into 15 mL tubes, and shipped on dry ice to the Laboratory of Clinical, Forensic, and Environmental Toxicology at the University of Liège, Belgium. There, they were analyzed following a previously established protocol (Dewalque et al., 2014b) (Supplementary Text 2) using a Quattro Premier XE mass spectrometer coupled with an Acquity UPLC system (Waters, Milford, MA, USA). The limits of quantitation (LOQ) were 0.79 μg/L for MeP, 0.30 μg/L for EtP, 0.36 μg/L for PrP, and 1.00 μg/L for BuP.

2.4. Measurement of satiety hormones

Leptin and Pancreatic Polypeptide (PP) levels were measured in EDTA plasma using EMD Millipore MILLIPLEX Human Metabolic Hormone Magnetic Bead Panel, according to the manufacturer's instructions (HMH3-34K, Millipore, Merck, Darmstadt, Germany). Measurements were performed using the Bio-Plex MAGPIX multiplex reader, and data were analyzed using the Bio-Plex Manager 6.1 software (Bio-Rad). Glucagon-like peptide 1 (GLP-1) and Peptide YY (PYY) were

measured using previously validated high-sensitivity radioimmunoassay (Kreymann et al., 1988) combined with in-house methods described in Supplementary Text 3.

2.5. Statistics

2.5.1. Preprocessing of raw paraben and hormone measurements

For further use in regression analysis, MeP, EtP, and PrP exposure values below the LOQ were imputed using a truncated lognormal distribution via the R package "lnormimp" (Herbers et al., 2021). Specifically, a truncated lognormal distribution was fitted to the values above the LOQ, yielding the mean and standard deviation of the distribution. Random values between 0 and the LOQ were then imputed based on these estimates. Because the distribution of paraben values, as well as hormone levels, was right-skewed, a natural log transformation was applied to improve normality. Additionally, the paraben concentrations were adjusted for urine osmolality, measured by freezing point determination with a Knauer Semi-Micro Osmometer (K-7400S), by calculating the residuals from the regression of paraben values on osmolality values.

For the satiety hormones no imputation of missing values was performed. Because the assessment of leptin and PP concentration by immunoassay was performed on different plates, correction for batch effects was performed by standardizing the values against the plate means. The equality of variances between boys and girls regarding paraben and satiety hormone measurements was assessed by Levene's test (Levene, 1963).

2.5.2. Single pollutant analysis

To investigate the associations between paraben values and the different satiety hormones, we first selected covariates *a priori* from the literature and examined their relationship with each other. Therefore, we constructed a directed acyclic graph (DAG) (Supplementary Fig. S1), built with the online tool DAGitty 3.0 (Textor et al., 2016) for visualization. Based on the DAG, two models with different sets of covariates were constructed. Model 1 included a basic set of covariates derived from the DAG, including the minimal sufficient adjustment set of confounders derived from DAGitty (BMI z-score and ethnicity of the child and maternal education) and additional variables potentially biasing the association between parabens and satiety hormones, namely child's sex, age, and birthweight, hour of the examination (as a proxy of time since last meal), parity and household smoking. To assess the robustness of the association, Model 2 was constructed with a more extended set of covariates containing additional pregnancy-related variables. In detail, Model 2 additionally contained maternal age, maternal early pregnancy BMI and smoking status, gestational age of the child at birth and breastfeeding status of the child as covariates. All children did not eat at least 1 h before the blood collection. Because the role of BMI as either mediator or confounder was not clear from the literature, we also performed a sensitivity analysis without adjusting for BMI z-scores, assuming a mediating instead of a confounding role of body weight, to test the robustness of our results. To further elucidate the relationship between parabens and BMI and satiety hormones, we performed partial correlation analyses including sex, ethnicity, age, and birthweight of the child, parity, early-pregnancy BMI, maternal education and household smoking for the correlation between parabens and BMI z-scores and for the correlation between BMI z-scores and satiety hormones. Furthermore, we tested if sex had a moderating effect on the association between parabens and satiety hormones by calculating the p-value of the interaction term between parabens and sex and performed the multiple regression analyses and mediation analyses additionally stratified for sex. We additionally showed the results of the linear regression models as percent changes in the satiety hormone level for a doubling (100 % increase) in paraben exposure by applying the formula suggested by Benoit (2011) for log-log models.

2.5.3. Mixture analysis

We applied both quantile g-computation (Keil et al., 2020) and Bayesian Kernel Machine Regression (BKMR) (Bobb et al. 2015, 2018) to analyze the mixture effects of parabens on the different satiety hormones. These methods were selected due to their complementary strengths: while quantile g-computation estimates the average effects of changing all exposures simultaneously within a joint marginal structural model (Keil et al., 2020), BKMR enables the modeling of complex exposure-response relationships and interactions between exposures (Bobb et al., 2015).

In brief, we employed quantile g-computation using the qgcomp package (Keil et al., 2020) to assess the combined effects of log-transformed MeP, EtP, and PrP levels on log-transformed hormone values and performed 500 bootstrap iterations to estimate the 95 % confidence intervals (CI). This method estimates the impact of a one-quantile increase in all mixture components simultaneously, accounting for variability in the direction of individual exposure outcome by assigning positive or negative weights to each exposure providing relatively unbiased estimates even in smaller samples (Keil et al., 2020).

Furthermore, we applied BKMR for the mixture assessment specifying 50,000 iterations. Specifically, we estimated the posterior mean and associated 95 % CI of the estimated change in hormone levels (overall effect of paraben mixture) by estimating the differences in the outcomes when all three paraben levels simultaneously change from the 10th to 90th percentile (in 10-percentile point increments) in comparison with when they were held at their 50th percentile. We further estimated the posterior inclusion probabilities (PIPs) by multivariable-adjusted BKMR models with component-wise variable selection to assess the relative importance of individual parabens in the overall mixture effects. We then examined the significance of the paraben mixture in influencing hormone levels by estimating the change associated with an interquartile range (IQR) increase in a single pollutant while keeping the other pollutants constant at the 25th, 50th, or 75th percentile levels. To explore the potential nonlinear dose-response relationship and possible interactions within the mixture, we visualized univariate dose-response functions.

Statistical significance was defined as $p < 0.05$ in all analyses except for the interaction term between parabens and sex, where a threshold of <0.1 was handled. Data analysis was performed in RStudio (RStudio Team, 2020) using R 4.4.1.

3. Results

3.1. Demographics

The children in this study were predominantly of European origin (92 %), with a mean (SD) gestational age of 39.1 (1.7) weeks and a birth weight of 3336 (472.7) grams. At the time of examination, the average age was 4.6 (0.4) years, including 42.1 % girls in the subset of this study (Table 1). Most of the mothers were primiparous (54 %), had achieved a higher educational level (60.9 %) and never smoked (67.8 %), while in a third of the children's households, one of the parents had been smoking between birth and follow-up examination. The average values of the satiety hormones measured in the children's plasma are shown in Table 1. The variance did not differ significantly between boys and girls (Supplementary Table S1). The population characteristics in our subset were comparable to those of all children in our cohort who attended the follow-up examination during the same period, except for household smoking exposure, which was slightly higher (30.6 % vs 27.1 %). Additionally, the characteristics were consistent between the different subsets (Supplementary Table S2).

3.2. Urinary paraben measurements

As more than 96 % of the BuP measurements were below the LOQ, only the values of MeP (99.5 % > LOQ), EtP (66.8 % > LOQ) and PrP

Table 1
Population characteristics of n = 202 participants with paraben quantification and at least one hormone measurement.

Characteristics	Mean (SD) or n (%)	N
Child		
Girls, n	85 (42.1 %)	202
Ethnicity, European	184 (92 %)	200
Gestational age, weeks	39.1 (±1.7)	202
Birthweight, g	3336 (±472.7)	202
Breastfeeding at any point, yes	135 (72.6 %)	186
Age, years	4.6 (±0.4)	202
BMI, kg/m^2	16.1 (±1.4)	202
Overweight/obese, IOTF[a]	27 (14.7 %)	184
Household smoking exposure ever, n	59 (30.6 %)	193
Urinary osmolality, mOsm/kg	718.8 (±261.4)	201
Pancreatic Polypeptide (PP), pg/mL[b]	114.9 [71.1–176.7]	200
Leptin, ng/mL[b]	0.4 [0.3–0.6]	200
Glucagon-like peptide 1 (GLP-1), pmol/L[b]	35.10 [28.1–48.4]	131
Peptide Y.Y. (PYY), pmol/L[b]	22.8 [13.7–32.8]	119
Mother		
Age at delivery, years	30.1 (±4.4)	202
BMI early pregnancy, kg/m^2	24.3 (±4.4)	202
Education level, n		202
Low	20 (9.9 %)	
Middle	59 (29.2 %)	
High	123 (60.9 %)	
Smoking during index pregnancy, n		202
Never	137 (67.8 %)	
Stopped before index pregnancy	42 (20.8 %)	
Smoked during pregnancy	23 (11.4 %)	
Parity, n		202
1	109 (54.0 %)	
2	72 (35.6 %)	
≥3	21 (10.4 %)	

[a] The International Obesity Task Force (IOTF) z-score cut-offs correspond to sex-specific scores of BMI at ages 2–18, 25 kg/m^2 for overweight and 30 kg/m^2 for obesity.
[b] Median and [IQR].

(90.5 % > LOQ) were used for further statistical analysis. The 10 % trimmed means of urinary paraben levels were 63.3 μg/L, 1.5, and 7.2 μg/L, [median values: 25.4 (μg/L), 1 (μg/L), 5.1 (μg/L)] respectively, for MeP, EtP, and PrP. The medians, geometric means, interquartile ranges (IQRs), and percentages above LOQ are shown in Supplementary Table S3. The imputed, natural log-transformed, and residualized paraben values were moderately correlated with each other (PrP and MeP: r = 0.46, p = 9.7e-12; MeP and EtP: r = 0.34, p = 6.2e-07; and PrP and EtP r = 0.30, p = 1.3e-05 respectively).

3.3. Associations between urinary parabens and plasma satiety hormones in single exposure models

We found that PrP levels in urine were associated with higher leptin values (Table 2, Fig. 1) in a linear regression model adjusted for a basic set of covariates, including the BMI z-score (β = 0.075, p = 0.0053), translating to an increase of 5.34 % [95 % Confidence Interval (CI): 1.58 %, 9.23 %] in leptin levels for a doubling of PrP. In a model with a more extended set of covariates including additional pregnancy-related variables (Model 2, Supplementary Table S4) and in the sensitivity analysis without adjustment for BMI z-scores (Supplementary Table S5), this association remained statistically significant (β = 0.080, p = 0.0069 and β = 0.078 and p = 0.018 respectively).

None of the other associations between different parabens and satiety hormones had a p-value below 0.05 (Table 2). Only for the association between PrP and PP was the interaction term for sex statistically significant (p = 0.036) (Table 2). In the stratified analysis, the association showed a positive trend for boys with an increase of 3.56 % [−2.17 %, 10.62 %] in PP for a doubling of PrP compared to an inverse trend for girls with a decrease of −3.14 % [−11.08 %, 5.03 %] in leptin for a doubling in PrP (Supplementary Tables S6 and S7). Also, some associations between other paraben esters and satiety hormones showed divergent trends for boys and girls (Supplementary Tables S6 and S7).

3.4. Relationship between zBMI, urinary parabens and hormone levels, including sex-specific effects

In the partial correlation analysis adjusting for sex, ethnicity, age and birthweight of the child, parity, household smoking, early-pregnancy BMI and highest educational attainment of the mother, we did not find statistically significant correlations between the paraben esters and zBMI when analyzing all participants (Supplementary Table S8). When performing the sex-stratified analyses, we observed in boys a positive correlation between EtP and zBMI (r = 0.24, p = 0.014) and trends for an inverse correlation between PrP and zBMI (r = −0.18, p = 0.065) compared to a positive trend in girls (r = 0.23, p = 0.051) (Supplementary Table S8). In the partial correlation analysis between zBMI and satiety hormones, adjusting for sex, ethnicity, age and birthweight of the child, parity, household smoking, hour of the examination, early-pregnancy BMI and highest educational attainment of the mother, only zBMI and leptin levels were significantly correlated in the total

Table 2
Associations between urinary parabens and plasma satiety hormones in 4-year-olds analyzed with multiple linear regression analysis. The percent change in satiety hormone level is shown for a doubling in paraben exposure.

Satiety hormones[a]	Parabens log (μg/L)[a]	β [95 %CI]	%Δ [95 %CI]	P	P interaction term sex
Leptin log(pg/mL)[b]	**MeP**	3.0e-2 [-2.3e-2, 0.13]	2.10 % [-1.36 %, 5.68 %]	0.24	0.66
	EtP	1.5e-2 [-3.8e-2, 6.8e-2]	1.05 % [-2.57 %, 4.81 %]	0.57	0.22
	PrP	7.5e-2 [2.3e-2, 0.13]	5.34 % [1.58 %, 9.23 %]	5.3e-3 **	0.88
PP log(pg/mL)[b]	**MeP**	−2.0e-3 [-5.9e-2, 5.5e-2]	−0.14 % [-4.01 %, 3.90 %]	0.95	0.12
	EtP	−2.0e-2 [-8.0e-2, 4.0e-2]	−1.39 % [-5.42 %, 2.81 %]	0.51	0.25
	PrP	−8.0e-3 [-6.9e-2, 5.3e-2]	−0.55 % [-4.57 %, 3.72 %]	0.80	0.036*
GLP1 log(pmol/L)[c]	**MeP**	5.6e-3 [-4.3e-2, 5.4e-2]	0.39 % [-4.13 %, 3.77 %]	0.82	0.41
	EtP	−2.0e-2 [-8.0e-2, 4.0e-2]	−0.90 % [-5.66 %, 2.54 %]	0.51	0.54
	PrP	9.2e-3 [-4.4e-2, 6.2e-2]	0.64 % [-4.33 %, 4.49 %]	0.73	0.49
PYY log(pmol/L)[d]	**MeP**	9.7e-2 [-2.4e-2, 0.22]	7.16 % [-1.64 %, 16.36 %]	0.11	0.96
	EtP	1.1e-2 [-0.14, 0.12]	−0.79 % [-9.47 %, 8.24 %]	0.86	0.15
	PrP	−1.5e-2 [-0.15, 0.12]	−1.06 % [-10.15 %, 8.54 %]	0.82	0.25

The models were adjusted for sex, ethnicity, age, birthweight and BMI z-score of the child, hour of the examination, parity and highest educational attainment of the mother and household smoking.
[a] Paraben and hormone values were natural log transformed and residuals were retrieved from regressing the paraben values against urinary osmolality measurements.
[b, c, d] Sample sizes per analysis: b = 188; c = 123; d = 111.
Significance levels *< 0.05, **< 0.01 and *< 0.1 for the interaction term.

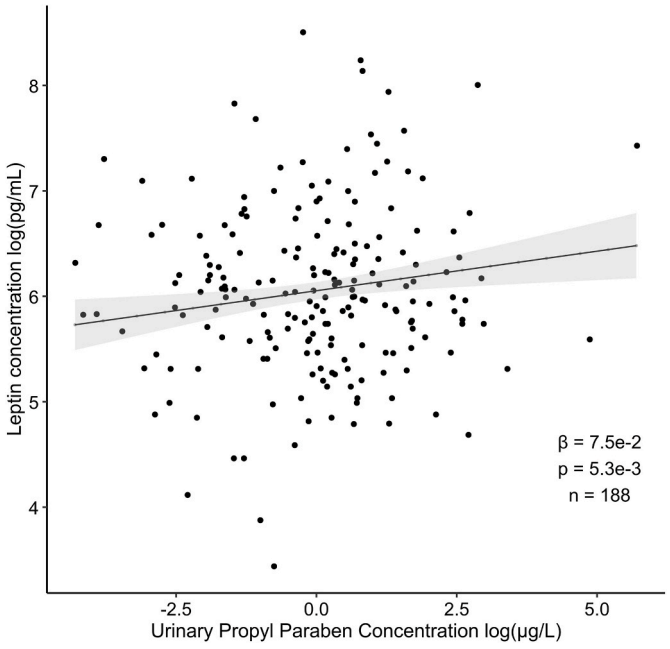

Fig. 1. Association between the residuals of natural log-transformed urinary propylparaben (PrP) concentrations regressed against urinary osmolality measurements and natural log-transformed plasma leptin levels in an adjusted linear regression model with 95 % confidence intervals (grey band). The model was adjusted for sex, ethnicity, age of the child, birthweight and BMI z-score of the child, hour of the examination, parity, highest educational attainment of the mother and household smoking. The grey band indicates the 95 % confidence interval.

population (r = 0.57, p = 7.9e-16) and the sex-stratified analysis (boys: r = 0.56, p = 3.7e-9; girls: r = 0.65, p = 2.4e-8) (Supplementary Table S9).

3.5. Mixture effects of parabens on satiety hormones

3.5.1. Quantile g-computation

Using quantile g-computation we did not find evidence for a mixture effect between the joint exposure to MeP, EtP and PrP with one of the measured satiety hormones (Supplementary Table S10). We observed different directions of weights for the different parabens in the mixture (Supplementary Fig. S2). A one-quantile increase in the natural log-transformed paraben values regressed against urinary osmolality was associated with a 0.099-point increase in natural log-transformed leptin levels (p = 0.14). Also, for Model 2 and in the sensitivity analysis without BMI z-score, the 95 % confidence intervals included zero, indicating no statistically meaningful effect (Supplementary Tables S11 and S12, respectively).

3.5.2. Bayesian Kernel Machine Regression (BKMR)

The overall effects of the three parabens (MeP, EtP and PrP) on the levels of plasma satiety hormones estimated using BKMR indicated a statistically significant effect of the mixture for the lowest exposure percentiles. As shown in Fig. 2 and Supplementary Table S13, we found that the estimated change in log-transformed leptin levels increased with a simultaneous increase of the three parabens, from the 10th to 90th percentiles, as compared to when all pollutants are at their median, indicating a positive combined mixture effect.

These confidence intervals did not include zero when all three parabens were between their 10th and 30th percentile, resulting in a decreased estimate, and when they were at the 60th percentile, resulting in an increased estimate (Supplementary Table S13).

Assuming that the change in leptin was 0 (95 % CI) at the 50th percentile of the three parabens, the change of log leptin with the decrease in the percentile of the three parabens was as follows: 0.15 (95 % CI: −0.28 to −0.027) for the 10th percentile; −0.10 (95 % CI: −0.19 to −0.017) for the 20th percentile; −0.057 (95 % CI: 0.11 to −0.005) for the 30th percentile; and for the increase in percentile of the paraben mixture 0.021 (95 % CI: 0.001 to 0.41) for the 60th percentile (Fig. 2,

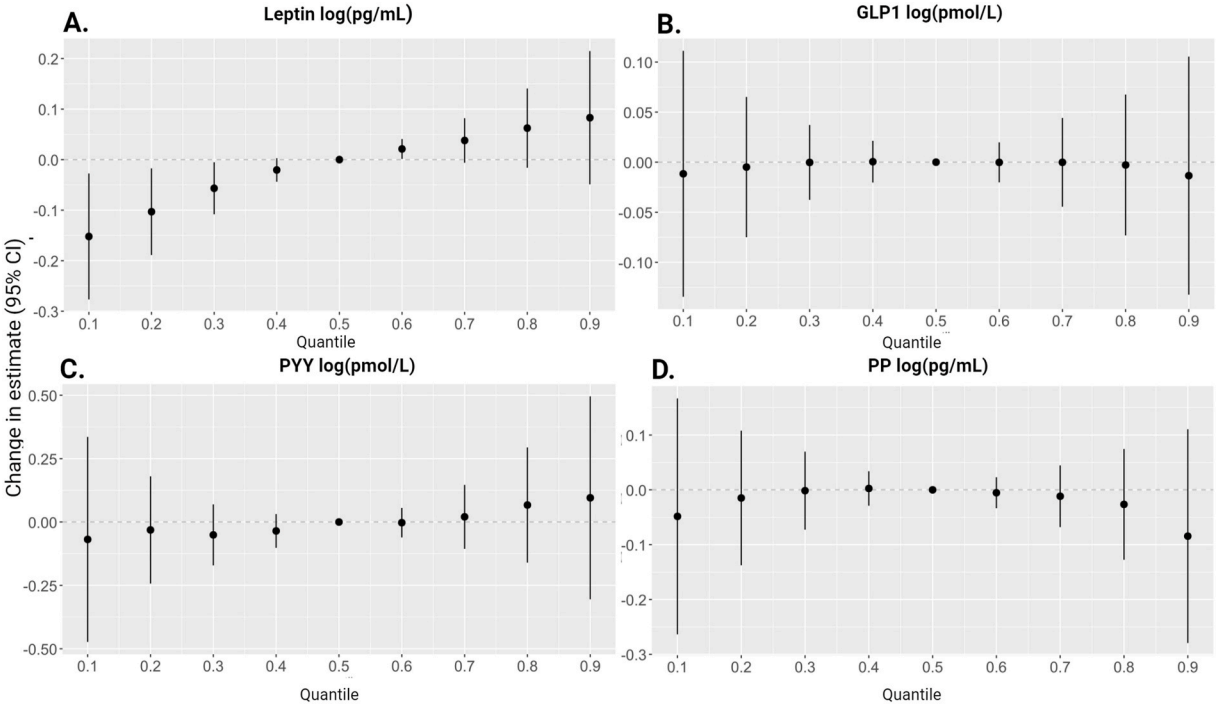

Fig. 2. Combined effects of methyl, ethyl and propyl paraben with 95 % confidence intervals. The figure shows the change in estimate when the three parabens were set at particular percentiles (ranging from 10th to 90th) compared to when all pollutants are at their 50th percentile, in models adjusted for: sex, ethnicity, age, birthweight and BMI z-score of the child, hour of the examination, parity and highest educational attainment of the mother and household smoking. The estimated effects and 95 % confidence intervals are presented as black dots and bars, respectively.

Supplementary Table S13).

We observed that PrP had the relatively highest PIP (0.043) in association with leptin levels compared with the other parabens (Supplementary Table S14). In association with PYY, the PIPs of the three parabens were about one order of magnitude higher, indicating the highest contribution to come from MeP with a PIP of 0.52. For the associations with GLP1 and PP, the PIPs were low and evenly distributed, suggesting no major contribution of either of the parabens to changes in these hormones.

Regarding the change in estimate for an IQR increase in a single paraben while the others were fixed at the 25th, 50th or 75th percentiles, we found for the association with leptin, that PrP was the only pollutant displaying a positive and significant effect, which remained constant regardless of the percentile level of the other parabens (for an IQR change in PrP: $\beta = 0.13$ for all quantiles, 95 % CI between: 0.0079, 0.26 and 0.010, 0.26) (Supplementary Fig. S3A). Furthermore, MeP showed an association with PYY, which appeared stronger when the other parabens were held at a lower percentile (for an IQR change in MeP: $\beta = 0.59$, 95 % CI: 0.10, 1.07, and $\beta = 0.60$, 95 % CI: 0.098, 1.10, when the other parabens were set at the 25th and 50th percentiles, respectively (Supplementary Fig. S3C).

Furthermore, we found the association between PrP and leptin levels to be nearly linear, only flattening with increasing uncertainties for the highest PrP values (due to a limited number of observations) (Supplementary Fig. S4A). In the univariate dose-response functions, MeP and EtP showed no effect on leptin levels. For the association with PYY, MeP showed a positive dose-response relationship, which was also linear except for the highest exposure levels (Supplementary Fig. S4C), but here the overall uncertainty was higher.

4. Discussion

Childhood obesity has sharply increased over the past four decades, raising the risk of long-term health issues in adulthood. The environmental obesogen hypothesis (Heindel and Blumberg, 2019) links this trend to prenatal or early-life exposure to endocrine disruptors in personal care products, which may promote fat accumulation and obesity.

The main finding of this study is that PrP is associated with higher leptin levels in preschool children, which may indicate a potential mechanism for the metabolic effects of this antimicrobial agent. Additionally, mixture analysis revealed varying dose-response relationships among different paraben esters, while stratified analysis indicated sex-specific differences in the association between parabens and BMI.

4.1. Paraben exposure and satiety hormone levels in preschool children

Three of the four parabens commonly used in personal care products (Food and Drug Administration, 2022; van der Schyff et al., 2022) were detected in a large proportion of urinary samples from Flemish preschool children. Among these, MeP, which has the shortest chain length and the highest water solubility, was found in nearly all samples and at the highest concentrations, which is in line with other studies (overview in Supplementary Table S15). In this study, consistent with another study of urinary paraben levels in Flemish preschool children (Dewalque et al., 2014a), the measured values were higher than in other European countries and most countries outside Europe (Supplementary Table S15). PrP showed higher values in this study (median 5.1 μg/L) than in other countries [median < LOQ in Germany (Murawski et al., 2021) and 0.4 and 2.4 μg/L in China (Guo et al. 2017b; Lu et al., 2019)] but was again comparable with levels measured in South-Korea for this age group (geometric mean 5.2 μg/L (Hong et al., 2021) vs 5.1 μg/L measured in his study). The higher values reported for Flemish preschool children compared with those in other countries may be due to variations in the demographic and geographic characteristics of the study populations, or in experimental parameters and measurement sensitivity which could also account for differences in the observed concentrations. For example, we only reported values above the LOQ to ensure the reliability of the obtained values, which resulted in a relatively higher median compared to studies using all samples above the LOD.

With 0.4 ng/mL (girls: 0.5 ng/mL, boys: 0.3 ng/mL, Supplementary Table S1), the median leptin values in this study were lower than the reference values reported for 4-year-olds in Europe (Erhardt et al., 2014). The values reported for 4-year-olds in the IDEFIX cohort were with 2.34 ng/mL (girls) and 1.09 ng/mL (boys) an order of magnitude higher (Erhardt et al., 2014). The reason for this this discrepancy could be the use of a different analytical method for leptin quantification, as results obtained with different laboratory methods may not be comparable (Erhardt et al., 2014; Loo et al., 2011). For healthy non-obese children there is not much information about reference values for PP. In a study of children between 0 and 15 years, comparable values with those in our study have been reports (233±147 pg/mL) (Hanukoglu et al., 1990). In a systematic review of PYY values in children (Wojcicki, 2012), fasting PYY levels in children aged 2–5 years were reported to range between 60 and 120 pg/mL which is higher than the 22.8 pg/mL we observed in our study. Regarding the concentration of 35 pg/mL measured in our study for GLP, a lower value of 2.8 pmol/L [IQR:2.1–3.8 pmol/L] converted to 9.23 pg/mL [IQR: 6.92–12.53 pg/mL] was reported for a population based group of 11 year old children (Stinson et al., 2021). Also here, the analytical method differed from ours which might explain the difference in obtained values.

4.2. Association between urinary parabens and satiety hormones

This study is the first to investigate associations between parabens commonly used in personal care products and satiety hormones in preschool children. We found a statistically significant association between PrP and leptin levels in preschool children. To our knowledge, this association has only been investigated in a few studies and for different age groups. Two studies investigated this association in adult women (Kolatorova et al., 2018; Lee et al., 2022). Both studies found statistically significant inverse associations for the relationship between leptin and MeP, but not for PrP, and a positive trend for the association with PrP ($\beta = 0.02$, $p = 0.66$). These inconsistent findings may reflect biological differences in the metabolic effects of endocrine disruptors or differences in hormone levels and functions for different age groups. Also, in this study, the urinary paraben values were higher than in the two studies mentioned above. Statistically, significant changes in leptin levels could only be present above a certain threshold. In the BKMR analysis, we calculated the overall effect (posterior mean) and found statistically significant associations between lower leptin levels and the lowest exposure percentiles but not for increased leptin levels associated with the highest exposure percentiles. This may not only reflect the presence of wider confidence intervals for higher paraben values due to a smaller number of observations, but could also demonstrate that the 50th reference percentile already exerts an effect with a plateau for the highest exposure levels, as suggestively indicated in Fig. 2A for the overall effect and Supplementary Fig. S4A for the individual effect of PrP. The importance of PrP for the mixture effect was also reflected by the highest PIP in comparison between the paraben esters for the association with leptin. Even though the value of 0.043 does not reach the threshold of 0.5 often used for inclusion in variable selection, PIPs should be considered in relation to each other rather than against an absolute threshold (Bobb et al., 2015; Hasan et al., 2024).

Applying quantile g-computation, we observed no statistically significant combined effects with any of the satiety hormones. Quantile g-computation allows for different directions of the individual exposure effects, which like here can partially cancel each other out (Supplementary Fig. S2). It is not unusual for different paraben esters to show different directions of effect, maybe due to their different chain length and structure resulting in different lipophilicity (El Hussein et al., 2007; Wang et al., 2015) and receptor binding-affinities (Terasaki et al.,

2009). A recent study found that MeP but not BuP exposure by daily oral gavage (100 mg/kg/day) was associated with increasing serum leptin levels in female mice (Hu et al., 2016).

We did not find associations between the different paraben esters and any of the other satiety hormones (GLP1, PP, PYY). Another study investigating the association between parabens and GLP1 in 27 women also reported null findings (Kolatorova et al., 2018). To our knowledge, no other studies have investigated the associations with these short-acting satiety hormones yet. Because these hormones peak after gastrointestinal passage before falling back to baseline levels (Wren and Bloom, 2007), detection of exposure-related changes might be hampered by the short and inconsistent assessment windows in epidemiological studies.

4.3. Clinical significance and mode of action

The clinical significance of increased leptin levels lies in the nature of leptin as a long-term regulator of energy balance. Produced mainly in adipose tissue, body fat mass and leptin levels are strongly correlated (Shimizu et al., 1997) and are already in children associated with obesity and metabolic syndrome (Madeira et al., 2017). While higher levels of other, short-acting, satiety hormones like GLP1, PYY and PP may be regarded favorable as they reduce appetite, high leptin levels can be regarded as a marker of leptin resistance at the level of hypothalamic receptors, comparable with high insulin values, indicative of insulin resistance at pancreatic β-cell level. Indeed, leptin resistance has also been associated with insulin resistance and is an additional component of metabolic syndrome (Schulze et al., 2003; Soliman et al., 2012). As we performed our study in a cohort setting with less than 15 % of the children being overweight or obese, the clinical implication regarding leptin resistance at this point may still be limited. Nevertheless, small shifts in the leptin levels at 4 years could be indicative of an increased risk of leptin resistance later in life. In 149 children aged 6–12 years at high risk for adult obesity, high baseline serum leptin concentration, were found to predicted greater BMI and fat mass at follow-up (average 4.4 years later) independent of baseline BMI/fat mass (Fleisch et al., 2007). Furthermore, a longitudinal study of leptin levels and childhood weight demonstrated that higher leptin levels at 3 years were associated with greater weight gain and adiposity at 7 years (Boeke et al., 2013).

In accordance with a study in European normal-weight prepubertal children (Erhardt et al., 2014), we found that already in preschool children, leptin levels were significantly higher in girls than in boys (6.4 pg/mL vs 5.8 pg/mL, Student t-test $p = 9.0e\text{-}09$). Interestingly, even though the interaction term for sex was not statistically significant, we found the effect of PrP in boys to be slightly higher than in girls ($\beta = 0.087$, $p = 0.024$ vs. $\beta = 0.064$, $p = 0.15$), which may point in the direction of a higher effect of PrP on leptin in the presence of less endogenous estrogen. In young children, this effect may still occur despite lower circulating estrogen levels compared to adolescents and adults (Frederiksen et al., 2020), as significant differences in serum estrogen levels and estrogen/testosterone ratios between boys and girls prior to adrenarche have previously been reported (Igarashi et al., 2021; Ikegami et al., 2001; Klein et al., 1994). In fact, it has been suggested that the estrogenic burden of parabens, especially PrP in blood, may even exceed the action of endogenous estradiol in childhood (Boberg et al., 2010).

Additionally, several studies have suggested that a mutual signaling cross-talk between estrogens and PPARγ/α influences PPARγ expression and function in obesity (Jeong and Yoon, 2011; Sato et al., 2013; Yoon, 2010). The observed differences in the association between PrP, leptin levels and BMI may suggest sex-specific variations in the underlying molecular pathways and endocrine responses to PrP.

The role of zBMI in the interplay with parabens and leptin levels could not be determined with certainty in this cross-sectional study. Research consistently shows a significant positive correlation between BMI and blood leptin levels, with higher BMI linked to elevated leptin concentrations (Lieb et al., 2008; Shimizu et al., 1997; Sitar-Tăut et al., 2021). This effect is due to the leptin production by adipose tissue, which is proportional to body fat mass. On the other hand, it is not clear from literature if parabens affect BMI (suggesting a mediating role of BMI) as reported in literature (Kim and Chevrier, 2020; Quirós-Alcalá et al., 2018) or if BMI affects the measured urinary paraben values due to "fat trapping" of the moderately lipophilic parabens (El Hussein et al., 2007; Wang et al., 2015), as suggested previously (Reimann et al., 2023), confounding the association with leptin. Generally, including a mediator as a covariate in a regression model yields lower estimates and higher p-values (Etminan et al., 2021; Schisterman et al., 2009). We observed comparable estimates and a lower p-value when including zBMI in the analysis, which is indicative of a confounding role instead of a mediating role. We also cannot exclude the possibility that BMI acts as a collider in the association between PrP and leptin levels. This would be the case if PrP would influence the BMI via leptin as a mediator, while leptin would also independently affect BMI. Conditioning on a collider, influenced by multiple exposures may introduce spurious associations between these exposures (collider bias) (Schisterman et al., 2009). This phenomenon is particularly relevant in mediation analysis, where distinguishing between direct and indirect effects is crucial. By conditioning on the outcome, bias that conflates these effects may be introduced (Elwert and Winship, 2014). For the assessment of urinary parabens, the relationship with BMI might therefore be bi-directional.

4.4. Strengths and limitations

We acknowledge the specific strengths and limitations of this study. To our knowledge, this is the first study examining the association between plasma satiety hormones and urinary paraben levels in preschool children. Employing data from an established prospective birth cohort (ENVIRONAGE) also enhances the generalizability of our findings. Furthermore, we utilized a truncated lognormal distribution for the imputation of paraben values below LOQ rather than imputing with LOQ/2. This approach resulted in more robust and unbiased estimates in the linear regression models (Herbers et al., 2021). Urine osmolality was chosen for hydration adjustment due to its direct reflection of the water-to-solute ratio, providing a physiologically relevant basis for adjustment. Unlike creatinine, which varies with factors like muscle mass and diet (Boeniger et al., 1993), and specific gravity, which can be influenced by high-molecular-weight compounds (Yeh et al., 2015), osmolality provides a robust control for urine dilution in environmental epidemiology settings and cohort studies (Middleton et al., 2016). Furthermore, we used the residuals of urinary biomarkers regressed on osmolality as our exposure metric, which aligns with the first stage of Schisterman et al.'s two-stage method (Schisterman et al., 2005) and effectively isolates hydration-related variability. Although O'Brien et al. (2016) (O'Brien et al., 2016) have shown that including osmolality directly as a covariate can yield similar or improved performance, the residual approach remains a valid and practical strategy. Despite the strengths, certain limitations should be considered. Due to the cross-sectional design of this study, we could not definitively determine the temporal sequence between paraben exposure, BMI z-scores and hormone levels. Therefore, we could not infer causality from the observed associations. The relatively small sample size may also have limited the statistical power, potentially leading to associations not reaching significance. This limitation especially affects the sex-stratified analyses in this study where the sample size is even smaller. The results of these analyses may therefore be interpreted with caution and need further validation in larger populations. Another limitation is the fact that we did not have questionnaire information about certain lifestyle characteristics like the use of personal care products, nutrition and exercise, which may influence paraben, hormone and BMI levels. Even though the children did not eat 1 h in advance of the blood sampling and we did correct for the hour of examination, residual bias in the assessment of the short-acting hormones (GLP1, PP, PYY) may have remained

due to missing information about the prandial status. Urinary paraben levels were measured using spot urine samples, which may introduce exposure misclassification due to temporal variability in the urinary concentrations of nonpersistent chemicals like parabens, potentially leading to attenuation bias in exposure-response relationships (Casas et al., 2018). However, the impact of measurement error may be mitigated, as relatively high and reproducible intraclass correlation coefficients have been reported for urinary parabens (median = 0.52), likely reflecting the steady dermal absorption of personal care products (Roggeman et al., 2022).

5. Conclusions

We found evidence suggesting that PrP may elevate leptin levels in preschool children. While leptin is primarily involved in regulation of body fat stores, its chronic elevation is associated with adverse metabolic outcomes, and our findings may point to leptin as a biological mechanism linking parabens with the growing obesity epidemic in children. Given these results, a reassessment of the safety of parabens in personal care products, particularly for young children, warrants consideration.

CRediT authorship contribution statement

Brigitte Reimann: Writing – original draft, Visualization, Methodology, Formal analysis. **Thaïs De Ruyter:** Writing – review & editing, Resources, Investigation. **Hanne Sleurs:** Writing – review & editing, Investigation. **Leen Rasking:** Writing – review & editing, Investigation. **Lore Verheyen:** Writing – review & editing, Investigation. **Nick Giesberts:** Writing – review & editing, Investigation. **Catherine Pirard:** Writing – review & editing, Resources, Investigation. **Corinne Charlier:** Writing – review & editing, Investigation. **Gary Frost:** Writing – review & editing, Resources, Investigation. **Paolo Vineis:** Writing – review & editing, Resources, Investigation. **Stefaan De Henauw:** Writing – review & editing, Resources. **Nathalie Michels:** Writing – review & editing, Resources. **Tim S. Nawrot:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Michelle Plusquin:** Writing – review & editing, Supervision, Resources, Conceptualization.

Data sharing

The data used in this study are not publicly available because they contain information that could compromise research participant privacy but are available within General Data Protection Regulation restrictions from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT in order to improve the language and readability of the manuscript. After using this tool, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the publication.

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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.2025.122300.

Data availability

Data will be made available on request.

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