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# Pregnancy Exposure to Phenols and Anthropometric Measures in Gestation and at Birth

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**Background:** Some synthetic phenols alter pathways involved in fetal development. Despite their high within-subject temporal variability, earlier studies relied on spot urine samples to assess pregnancy exposure. In this study, we examined associations between prenatal phenol exposure and fetal growth.

**Methods:** We measured concentrations of two bisphenols, four parabens, benzophenone-3, and triclosan in 478 pregnant women in two weekly pools of 21 samples each, collected at 18 and 34 gestational weeks. We used adjusted linear regressions to study associations between phenol concentrations and growth outcomes assessed twice during pregnancy and at birth.

**Results:** Benzophenone-3 was positively associated with all ultrasound growth parameters in at least one time point, in males but not females. In females, butylparaben was negatively associated with third-trimester abdominal circumference and weight at birth. We observed isolated associations for triclosan (negative) and for methylparaben and bisphenol S (positive) and late pregnancy fetal growth.

**Conclusions:** Our results suggest associations between prenatal exposure to phenols and fetal growth. Benzophenone-3 was the exposure most consistently (positively) associated across all growth parameters.

**Keywords:** Cohort; Phenol exposure; Bisphenol; Triclosan; Paraben; Pooled biospecimens; Fetal growth; Birth outcomes

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\*The members of The SEPAGES study group are listed in Acknowledgments. Data used in this study are confidential and can be provided upon a reasonable request and after approval of the SEPAGES steering committee. The source code is available in the public repository of the Team of Environmental Epidemiology applied to Development and Respiratory Health (<https://gricad-gitlab.univ-grenoble-alpes.fr/iab-env-epi>).

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Synthetic phenols are used in the manufacture of a variety of household items and personal care products. Some are endocrine disruptors and may alter endocrine pathways (e.g., thyroid, estrogen, and glucocorticoid signaling), involved in fetal growth.<sup>1</sup> Numerous epidemiologic studies have reported associations between prenatal exposure to synthetic phenols and offspring size before,<sup>2–6</sup> and at birth,<sup>7–9</sup> with possible sex-specific effects.<sup>1,8–10</sup> For most substances, the consistency across human studies is limited and the question has hardly been considered in toxicology, with the vast majority of studies focusing on growth outcomes measured at birth and not in utero.<sup>11–22</sup>

Repeated sample collection, possibly followed by pooling of multiple biospecimens, is a way to reduce bias in dose-response functions for compounds with strong within-subject variability.<sup>23,24</sup> Here, we aimed to investigate the associations between prenatal phenol exposure and fetal growth, assessing exposures from pooled maternal biospecimens collected repeatedly during pregnancy. This approach allowed us to account for the short half-life and time-varying sources of exposure to the studied phenols.

## METHODS

### Study Design and Population

We relied on mother-child pairs participating in the SEPAGES cohort (Grenoble area, France),<sup>25</sup> who collected

repeated urine samples at least once during pregnancy and had fetal or birth growth measurements available (N ranged from 433 to 475 according to the growth parameter considered; see eAppendix; <http://links.lww.com/EDE/B943> for details on inclusion criteria and flowchart). Both parents signed an informed consent before inclusion. The study was approved by the relevant ethical committees.

## Urine Sample Collection and Assessment of Prenatal Exposure

We asked the women to collect three urine samples per day (morning, midday, evening) for 7 consecutive days, generally during the second and third pregnancy trimesters (median, 18 and 34 gestational weeks, respectively). For each subject, we pooled equal volumes of all samples collected during each collection week.<sup>23,24</sup>

We measured total (free plus conjugated) urinary concentrations of 12 compounds (bisphenols A, AF, B, F, S, benzophenone-3, triclosan, triclocarban, butyl-, ethyl-, methyl-, and propylparaben) in the weekly pools using ultraperformance liquid chromatography coupled to mass spectrometry,<sup>26</sup> as detailed in the eAppendix; <http://links.lww.com/EDE/B943>.

## Assessment of Prenatal Growth and Birth Outcomes

Abdominal circumference, biparietal diameter, femoral length, and head circumference were assessed from the ultrasound examinations done as part of the routine follow-up of pregnancy in France. Here, we focused on the two measurements done after the second trimester urine collection week, corresponding to the second and third ultrasound examinations (median, 22 and 32 gestational weeks, respectively). We also measured children's weight, length, and head circumference at birth. We standardized growth outcomes by dividing them by the period-specific standard deviation. Distributions of the untransformed growth outcomes are presented in eTable 1; <http://links.lww.com/EDE/B943>.

## Statistical Analyses

We disregarded phenols that were detectable in less than 2% of urine samples (bisphenols AF, B, F, triclocarban). For bisphenol S and butylparaben, over 30% of the samples were below the limit of quantification (LOQ) and concentrations were handled as categorical variables [below limit of detection (LOD), from LOD to LOQ, above LOQ]. We handled concentrations of other phenols as continuous variables and ln-transformed them to approach normality. To account for between-sample variations related to differences in urine processing and assay, we standardized continuous exposures on sampling conditions,<sup>4,27,28</sup> with the exception of triclosan, which was not affected by urine processing and assay (for details see eAppendix; <http://links.lww.com/EDE/B943>).

We selected adjustment factors *a priori*: maternal height and prepregnancy weight, maternal age, maternal

active smoking during second trimester, maternal education level, gestational duration, child sex, and parity. We collected data on covariates by self-administered questionnaires or through face-to-face interviews and imputed missing data. For details on variable coding and imputation of missing covariates, see the eAppendix; <http://links.lww.com/EDE/B943>.

We used independent adjusted linear regression models to study the associations between each phenol concentration and each growth parameter. For size measurements assessed at the second ultrasound examination, we used phenol concentration from the weekly urine pools from the second trimester, although later size measurements were related to average phenol concentrations from trimesters 2 and 3 (eFigure 1; <http://links.lww.com/EDE/B943>). For categorized exposures measured at third trimester, we created a new summarizing category (below LOD for trimesters 2 and 3; above LOD for trimester 2 or 3; above LOD for trimesters 2 and 3). We explored sex-specific effects by adding an interaction term between each exposure biomarker and child sex. For interaction tests with *P* value below 0.2, additional sex-stratified analyses were performed.

## Sensitivity Analyses

To additionally account for exposure measurement error, we applied a mixed (random-intercept) model,<sup>29</sup> as implemented in the R *meor* package.<sup>30</sup> This model relied on one or two repeated urine pools per subject (collected at trimesters 2 and 3) to estimate the dose-response function and provide association estimates corrected for exposure measurement error (for details see eAppendix; <http://links.lww.com/EDE/B943>). To assess the effect of the concentration standardization procedure,<sup>4,27,28</sup> we ran additional analyses using non-standardized biomarker concentrations. We also performed analyses removing participants for whom the urine samples were collected after the ultrasound measurement (trimester 2: N = 4; trimester 3: N = 264).

## Research Data and Code

Data used in this study are confidential and can be provided upon a reasonable request. All analyses were conducted using R v. 4.0.5,<sup>31</sup> and RStudio v. 1.4.1106.<sup>32</sup> The source code is available in the public repository of the Team of Environmental Epidemiology applied to Development and Respiratory Health (<https://gricad-gitlab.univ-grenoble-alpes.fr/iab-env-epi>).

## RESULTS

On average, women were 32.1 years old and delivered at 40.0 gestational weeks (Table 1). Detection rates were above 81% for all retained compounds except bisphenol S (25%) and butylparaben (24%; Table 2).

Five phenols were associated with at least one growth outcome measured at third-trimester ultrasound or at birth (Figure 1, eTable 2; <http://links.lww.com/EDE/B943>). *P*

**TABLE 1.** Characteristics of the mother-child pairs included in SEPAGES couple-child cohort study (France, 2014–2017, N = 478)

Characteristic	Distribution	
	N (%)	Median [25th, 75th centiles]
<b>Maternal weight before pregnancy (kg)</b>		59.0 [54.0; 66.0]
Missing	0 (0)	
<b>Maternal height (cm)</b>		165 [161; 169]
Missing	4 (1)	
<b>Maternal age at conception (yrs)</b>		32.1 [29.9; 35.2]
Missing	0 (0)	
<b>Maternal education after high school (yrs)</b>		
<3	82 (17)	
3–4	125 (26)	
>4	268 (56)	
Missing	3 (1)	
<b>Maternal active smoking during trimester 2</b>		
≤1 cigarette/day	427 (89)	
>1 cigarette/day	11 (2)	
Missing	40 (8)	
<b>Parity before the index pregnancy</b>		
Nulliparous	219 (46)	
1 child	211 (44)	
≥2 children	48 (10)	
Missing	0 (0)	
<b>Duration of gestation (wks)<sup>a</sup></b>		40.0 [39.0; 40.7]
Missing	2 (0) <sup>b</sup>	
<b>Child sex</b>		
Female	220 (46)	
Male	256 (54)	
Missing	2 (0) <sup>b</sup>	

<sup>a</sup>Based on the date of the LMP or gestational duration assessed by the obstetrician if it differed from the LMP-based estimate by >2 wks.

<sup>b</sup>Two recruited women had ultrasound data but dropped out of the study before delivery.

LMP indicates last menstrual period.

values testing the interaction with sex were below 0.2 for several growth measurements (Figure 2, eTable 3; <http://links.lww.com/EDE/B943>).

In males, benzophenone-3 was positively associated with all ultrasound growth measurements in at least one time point (regression estimates ranging from  $\beta = 0.05$ ; 95% confidence interval:  $-0.02, 0.12$  for head circumference at trimester 2 to  $\beta = 0.1$ ;  $0.02, 0.17$  for biparietal diameter at trimester 2). When both sexes were studied together, a positive association with third-trimester head circumference was identified.

Among parabens, butylparaben concentrations were associated with decreased abdominal circumference at third trimester and decreased weight at birth. The associations tended to be stronger in female than male newborns. Methylparaben was positively associated with abdominal circumference assessed during the third trimester. We observed no association for the other parabens.

Concentrations of triclosan were associated with decreased third-trimester abdominal circumference, while bisphenol S was associated with increased third-trimester femur length.

Results of the sensitivity analyses are presented in the eAppendix; <http://links.lww.com/EDE/B943> and were overall similar to those of our main analyses.

## DISCUSSION

Epidemiologic evidence for the effect of phenols on fetal growth has been inconclusive. Indeed, recent meta-analyses on bisphenol A,<sup>8–10</sup> triclosan,<sup>7,8</sup> and parabens,<sup>8</sup> did not show clear associations between these compounds and birth outcomes, but most studies relied on a single spot urine sample to assess exposure. Since the urinary concentrations of phenols have moderate to high intraindividual variability during pregnancy,<sup>33,34</sup> exposure misclassification, attenuation bias, and power reduction are expected, making it difficult to consider lack of consistent associations as strong evidence of lack of effect.<sup>35</sup> Our study is one of the few relying on within-subject pooling of many biospecimens to assess exposure. This approach is expected to decrease attenuation bias and increase power, compared with studies of the same number of subjects relying on spot biospecimens. We observed a few associations between pregnancy phenols exposure and fetal growth outcomes. Maternal benzophenone-3 was positively associated with all ultrasound measurements, mainly in male newborns. In females, butylparaben was negatively associated with third-trimester abdominal circumference and weight at birth. We additionally observed isolated negative associations for urinary triclosan, and positive associations for methylparaben and bisphenol S and late pregnancy fetal growth. Our results, taken together with the epidemiologic evidence aggregated by the aforementioned meta-analyses, do not allow us to draw a straightforward conclusion regarding the effect of all phenols on fetal growth. Nevertheless, they may suggest a positive association between benzophenone-3 concentrations and fetal growth in utero.

## Benzophenone-3

Positive associations that we observed for benzophenone-3 and ultrasound growth measurements were more pronounced in males than females; a previous study found a nonsignificant increase in abdominal circumference and femur length in boys, and a decrease or no association in girls, respectively (N = 312).<sup>2</sup> Another study on boys did not report any associations (N = 520).<sup>4</sup> In rodents, benzophenone-3 pregnancy exposure reduced fetal,<sup>18</sup> and postnatal weight.<sup>18,19,21</sup> *In vitro*, benzophenone-3 showed antiestrogenic and antiandrogenic effects.<sup>36</sup> Human studies reported association of pregnancy benzophenone-3 with decreased maternal total triiodothyronine.<sup>37</sup> However, although triiodothyronine is implied in fetal growth regulation,<sup>38</sup> it is not clear if these potential mechanisms of action could explain the increase in anthropometric measures observed in our study.



**TABLE 2.** Average maternal urinary phenol concentrations assessed in weekly pools collected in the second and third trimesters of pregnancy, without or with standardization on sampling and assay conditions (N = 478 pregnant women).

Phenol <sup>a</sup>	LOD (μg/L)	Raw Concentrations						Standardized <sup>b</sup> Concentrations					
		Trimester 2 Urine Pool			Trimester 3 Urine Pool			Trimester 2 Urine Pool			Trimester 3 Urine Pool		
		Percentiles (μg/L)			Percentiles (μg/L)			Percentiles (μg/L)			Percentiles (μg/L)		
		>LOD (%)	5th	50th	>LOD (%)	5th	50th	>LOD (%)	5th	50th	>LOD (%)	5th	95th
Bisphenol A	0.04	99	0.7	2.0	8.6	98	0.5	1.8	9.3	0.6	1.6	7.2	98
Bisphenol S	0.1	25	<LOD	<LOD	3.0	28	<LOD	<LOD	2.9	/	/	/	/
Benzophenone-3	0.04	100	0.3	1.2	35.3	100	0.2	1.0	27.5	0.2	0.8	20.5	100
Triclosan	0.04	98	0.2	0.9	165.2	98	0.2	0.9	176.1	/	/	/	/
Butylparaben	0.07	25	<LOD	<LOD	0.7	24	<LOD	<LOD	0.8	/	/	/	/
Ethylparaben	0.04	100	0.2	0.7	32.5	99	0.2	0.7	25.0	0.3	1.0	43.9	100
Methylparaben	0.04	100	2.7	12.4	279.7	100	2.9	12.5	2415.3	2.7	13.4	276.7	100
Propylparaben	0.04	82	<LOD	0.4	63.6	81	<LOD	0.6	137.2	<LOD	0.5	67.4	83

<sup>a</sup>Bisphenols AF, B, F, and triclocarban were detected in 2% of the pooled samples and were not displayed in this table.  
<sup>b</sup>Raw concentrations were standardized on sampling and assay conditions.<sup>42,728</sup> Categorized exposure (bisphenol S, butylparaben) concentrations were not standardized. Triclosan concentrations were not standardized either as none of the considered conditions was associated with this phenol.  
LOD indicates limit of detection.

## Parabens

As for parabens, methylparaben was associated with increased third-trimester abdominal circumference. Previous studies reported a negative association in girls but not boys,<sup>2</sup> or no association when only boys were considered.<sup>4</sup> Butylparaben was associated with decreased abdominal circumference at third trimester in females, an effect not observed previously,<sup>2</sup> and decreased female weight at birth. For the latter outcome, a positive effect was estimated regardless of sex,<sup>39,40</sup> in boys,<sup>39–42</sup> and girls.<sup>39,43</sup> Other studies reported no association when both sexes were studied together,<sup>41,44,45</sup> or when only boys were considered.<sup>4,46</sup> It should be noted that detection rate of butylparaben in our study was relatively low, which could partially explain discrepancies in the results. Apart from showing estrogenic activity,<sup>47,48</sup> parabens promote adipocyte differentiation by an activation of the glucocorticoid receptor or the peroxisome proliferator-activated receptor gamma *in vitro*.<sup>49,50</sup> Human studies found that pregnancy parabens are associated with adipocyte differentiation and lipogenesis,<sup>51</sup> potentially altering fetal metabolism. Moreover, maternal butylparaben was associated with decreased total triiodothyronine,<sup>37</sup> and C-reactive protein, as well as increased isoprostane,<sup>52</sup> a marker of oxidative stress, which may itself cause fetal growth restriction.<sup>44</sup>

## Triclosan

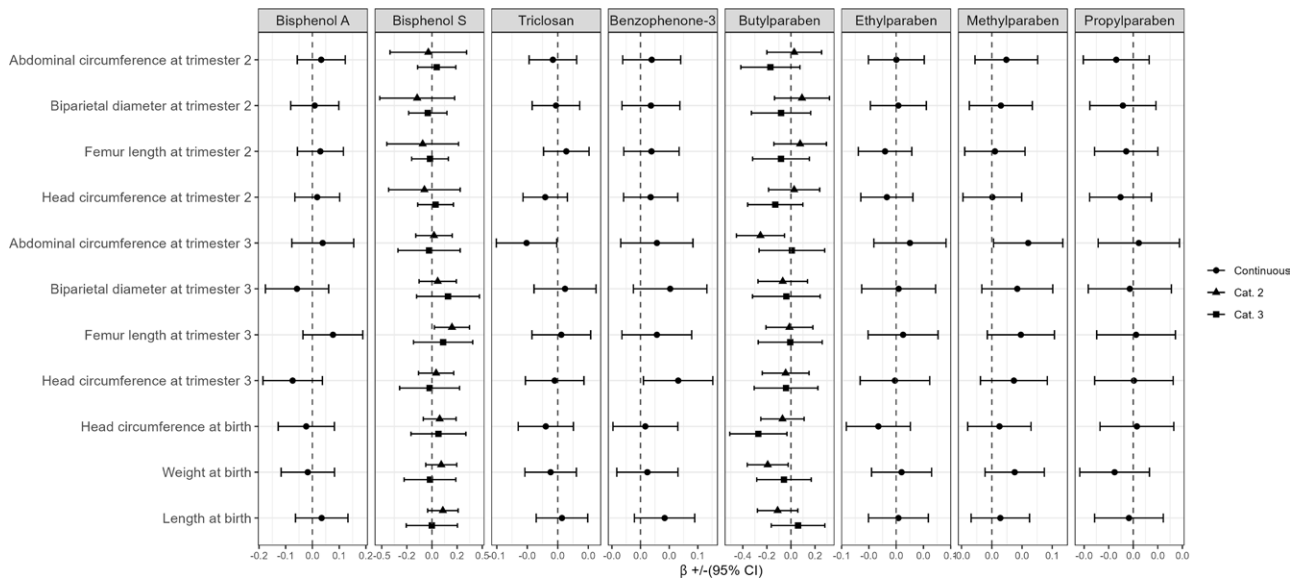
We observed negative associations between triclosan and third-trimester abdominal circumference, which is in line with effects previously reported in a study considering only boys,<sup>4</sup> but not with other studies.<sup>2,53</sup> In rodents, triclosan disturbed maternal and fetal homeostasis of thyroid hormones, which are needed for growth and development,<sup>54,55</sup> and was linked to reduced weight of fetuses<sup>17</sup> and neonate pups.<sup>16</sup> In humans, pregnancy triclosan was associated with decreased total triiodothyronine,<sup>37</sup> and increased proinflammatory cytokine IL-6 of the mother.<sup>52</sup>

## Bisphenols

We observed an increase of third-trimester femur length associated with bisphenol S concentration. A previous study in 312 children reported a positive association between this phenol and femur length in girls but not boys,<sup>2</sup> whereas others did not observe associations.<sup>5,6</sup> Bisphenol S showed testosterone-inhibiting properties in mice,<sup>56</sup> but studies on its effects on human thyroid function,<sup>57</sup> or steroid changes,<sup>58</sup> reported no associations.

## Strengths and Limitations

Our study relating phenol pregnancy exposure to fetal growth is one of the first relying on repeated collection and pooling of many (median, 42 urine samples per woman) maternal biospecimens. This approach allowed us to improve characterization of the exposure by accounting for the short half-life of the studied phenols (generally a few hours to days) and temporal variability in maternal behaviors linked to



**FIGURE 1.** Adjusted associations between pregnancy phenol concentrations and growth outcomes in utero (trimesters 2 and 3) and at birth. Trimester 2 outcomes were related to trimester 2 exposures, whereas trimester 3 and birth outcomes were related to trimesters 2 and 3 averaged exposures. Regression models were adjusted for maternal height, maternal prepregnancy weight, maternal age, maternal active smoking during trimester 2, maternal education level, gestational duration, child sex, and parity. For continuous phenol biomarker concentrations (BP-3, BPA, ETPA, MEPA, PRPA, triclosan),  $\beta$  regression estimates correspond to the change in standard deviation of the considered growth outcome associated with a 1-unit increase in standardized ln-transformed urinary phenol concentration. For categorically coded exposures (BPS, BUPA) measured at trimester 2,  $\beta$  estimates correspond to the change, expressed in standard deviations, of the growth outcome associated with phenol biomarker concentrations between LOD and LOQ (Cat. 2) or >LOQ (Cat. 3) compared with <LOD concentrations (reference). For BPS and BUPA measured at trimester 3,  $\beta$  estimates correspond to the change in standard deviation of growth outcome associated with phenol biomarker concentrations >LOD at trimester 2 or 3 (Cat. 2) or at trimester 2 and 3 (Cat. 3) compared with <LOD concentrations at trimester 2 and 3 (reference). For the original units of growth measurements refer to the eTable 1; <http://links.lww.com/EDE/B943>. BP-3 indicates benzophenone-3; BPA, bisphenol A; BPS, bisphenol S; BUPA, butylparaben; Cat., category; ETPA, ethylparaben; LOD, limit of detection; LOQ, limit of quantification; MEPA, methylparaben; PRPA, propylparaben.

exposure (e.g., food intake, use of personal care products) that are expected to bias estimates by about 40% to 80% depending on the compound, and to strongly reduce power.<sup>24,33,34</sup> Exposure misclassification and, consequently, the added value of collected repeated biospecimens per subject, depends on the temporal variability of urinary concentrations which, as shown in eTable 4; <http://links.lww.com/EDE/B943>, varies across phenols. The highest attenuation bias is expected for chemicals with the highest temporal variability [i.e., with the lowest intraclass correlation coefficient (ICC)] which, for our study, include bisphenols and methylparaben (eTable 4; <http://links.lww.com/EDE/B943>). The biospecimen pooling approach is more efficient in terms of bias and power than approaches relying on spot biospecimens, but less so than measurement error models; these require assessment of several biospecimens per subject and therefore entail higher analytical costs than biospecimens pooling.<sup>35</sup> We pooled over 40 biospecimens per subject on average, which should provide effect estimates almost as precise as those obtained using measurement error correction models for chemicals with ICC of 0.6.<sup>35</sup> For compounds with ICC of 0.2, pooling was shown to

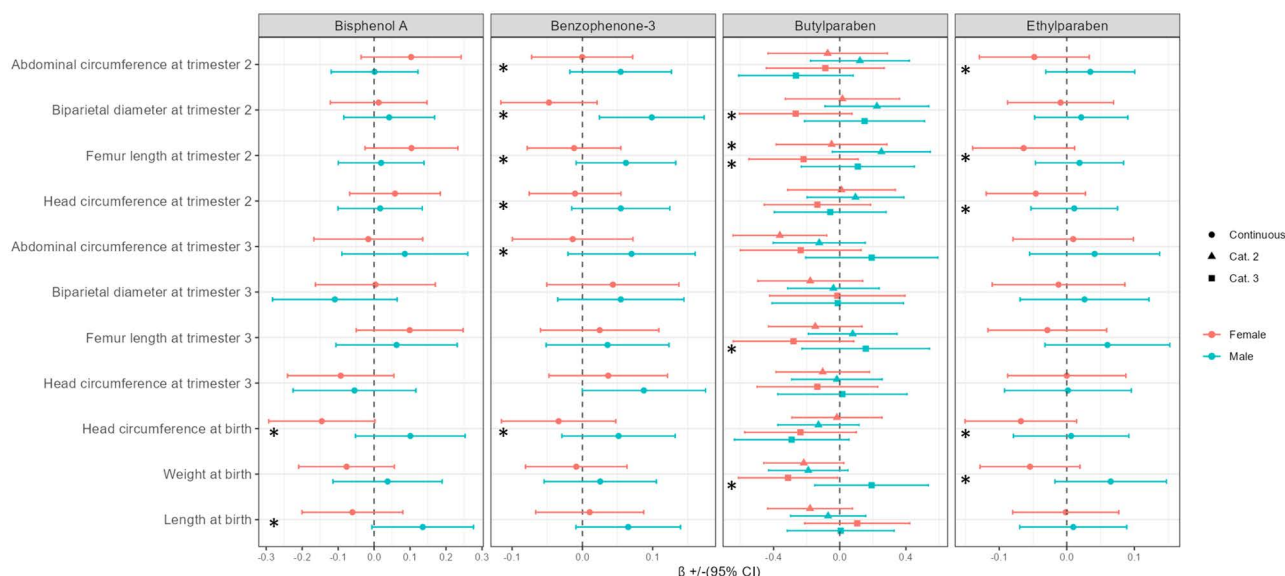
perform only slightly worse than measurement error correction models,<sup>35</sup> where greatly reducing analytical cost.

Given the high number of performed tests, cautious interpretation of the results is required as chance findings cannot be excluded. Although we did not formally rely on statistical testing nor did we correct for multiple comparisons,<sup>59</sup> it should be noted that, for a number of considered compounds, there was some (sometimes limited) a priori evidence for their effects on fetal growth or related pathways in animal models or humans.

For the third trimester and birth outcomes, we averaged phenol concentrations in trimesters 2 and 3,<sup>60</sup> an approach that may not be relevant for exposures with very short gestational windows of susceptibility. Finally, although the SEPAGES cohort provides information on a broad range of potential confounders, residual confounding by factors not considered in our analysis (e.g., maternal diet) cannot be ruled out.

## CONCLUSIONS

Our results suggest associations between pregnancy exposure to phenols and fetal growth, with benzophenone-3



**FIGURE 2.** Adjusted associations between pregnancy phenol concentrations and growth outcomes in utero (at trimester 2 and 3) and at birth in a sex-stratified analysis. Only exposures showing at least one association with a  $P < 0.2$  for an interaction term between sex and phenol concentration in the main analysis are displayed. \*Associations with  $P < 0.2$  for an interaction term between sex and phenol concentration in the main analysis. Trimester 2 outcomes were related to trimester 2 exposures while trimester 3 and birth outcomes were related to trimesters 2 and 3 averaged exposures. Regression models were adjusted for maternal height, maternal prepregnancy weight, maternal age, maternal active smoking during trimester 2, maternal education level, gestational duration, and parity. For BPS, MEPA, PRPA, and triclosan, we detected no interactions with child sex. For continuous phenol biomarker concentrations (BP-3, BPA, ETPA),  $\beta$  regression estimates correspond to the change in standard deviation of the considered growth outcome associated with a 1-unit increase in standardized ln-transformed urinary phenol concentration. For categorically coded exposure (BUPA) measured at trimester 2,  $\beta$  estimates correspond to the change, expressed in standard deviations, of the growth outcome associated with phenol biomarker concentrations between LOD and LOQ (Cat. 2) or >LOQ (Cat. 3) compared with <LOD concentrations (reference). For BUPA measured at trimester 3,  $\beta$  estimates correspond to the change in standard deviation of growth outcome associated with phenol biomarker concentrations >LOD at trimester 2 or 3 (Cat. 2) or at trimester 2 and 3 (Cat. 3) compared with <LOD concentrations at trimester 2 and 3 (reference). BP-3 indicates benzophenone-3; BPA, bisphenol A; BPS, bisphenol S; BUPA, butylparaben; Cat., category; ETPA, ethylparaben; MEPA, methylparaben; PRPA, propylparaben.

showing the most consistent associations across outcomes. Since the existing epidemiologic evidence on most compounds is limited, replication studies on pooled biospecimens are needed to better characterize the associations between maternal concentrations of synthetic phenols and fetal growth.

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CRedit authorship contribution: P.J. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.L., S.L.-C., C.P., I.P., V.S., R.S. did cohort study concept and design. S.L.-C. and J.Q. did cohort data collection. P.J., C.P., M.R., and R.S. did acquisition, analysis, or interpretation of data. P.J., C.P., and R.S. did drafting of the article. P.J. and M.R. did statistical analysis. C.P. and R.S. obtained funding. C.T., A.S., and A.K.S. did technical or material support. C.P. and R.S. did study supervision. All authors have read, commented on and approved the article.

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