Sex-specific associations of prenatal exposure to bisphenol A and its alternatives with fetal growth parameters and gestational age

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ABSTRACT

Background: Bisphenol A (BPA) can cause detrimental effects on fetal growth. However, the effects of BPA alternatives, such as bisphenol F (BPF) and bisphenol S (BPS), on fetal growth are less known.
Objective: To investigate the relationships of prenatal BPA, BPF, and BPS exposures with fetal growth parameters and gestational age.
Methods: Urinary BPA, BPF, and BPS were measured in 1,197 pregnant women before delivery in a Chinese cohort. The associations of prenatal exposure to BPA, BPF, and BPS with fetal growth parameters and gestational age were examined, and associations stratified by fetal sex were also conducted. We used a restricted cubic splines (RCS) model to examine the dose–response associations between exposures and outcomes.
Results: Maternal urinary BPA and BPF were negatively related to birth length (-0.30 cm, 95% CI: −0.44, −0.15 and −0.21 cm, 95% CI: −0.36, −0.07 comparing the extreme exposure groups, respectively, both p for trends < 0.01). These associations were more pronounced in girls with inverted U-shaped dose–response relationships. Maternal urinary BPA and BPF were positively related to ponderal index (0.05 g/cm^3 × 100, 95% CI: 0.01, 0.09 and 0.04 g/cm^3 × 100, 95% CI: 0.01, 0.08 comparing the extreme exposure groups, respectively, both p for trends = 0.02), and maternal urinary BPS was associated with shorter gestational age (-0.20 weeks, 95% CI: −0.37, −0.03 comparing the extreme exposure groups, p for trend = 0.02). These associations were only observed in girls and exhibited a linear dose–response relationship.
Conclusions: Prenatal BPA, BPF, and BPS exposures were associated with detrimental effects on fetal growth parameters, and stronger effects were noted in female infants.

1. Introduction

Bisphenol A (BPA), a high production chemical in the global world, is mainly used to manufacture polycarbonate plastics and epoxy resins, which subsequently produce numerous consumer products, including plastic food containers, medical equipment, toys, and thermal papers (Joskow et al., 2006; Liao and Kannan, 2011; Lu et al., 2013; Vandenberg et al., 2007). Given its widespread use and easy leaching from consumer products, BPA is a ubiquitous pollutant in various environmental media (Liao et al., 2012a,b; Peretz et al., 2014). Humans are constantly exposed to BPA across ingestion, dermal contact, and inhalation of contaminated environment media in their daily life (Liu et al., 2018; Vandenberg et al., 2007). BPA can be rapidly metabolized and excreted into urine from the human body (Volkel et al., 2002; Zhang et al., 2011a,b). Considerable studies have found that urinary BPA is detectable in > 90% of the general population (Artacho-Cordón et al., 2018; LaKind and Naiman, 2015; Ye et al., 2015).

BPA has been demonstrated to possess endocrine-disrupting effects and readily cross the placenta, which may cause detrimental effects on fetal growth (Balakrishnan et al., 2010; Liu et al., 2017). Evidence from toxicology studies has demonstrated that perinatal BPA exposure causes detrimental effects on fetal development and behavior at low doses (Benachour and Aris, 2009; Boudalia et al., 2014; Yang et al., 2013). Some human studies have reported the detrimental effects of prenatal BPA exposure on birth outcomes, such as the increased risk of preterm birth and decreased birth weight (Cantonwine et al., 2015; Huo et al., 2015), whereas other studies observed null or positive associations (Hu et al., 2019; Lee et al., 2014). Due to concern over the detrimental health effects of BPA, alternatives, such as bisphenol F (BPF) and bisphenol S (BPS), have been increasingly used in consumer and commercial products labeled "BPA-free" (Liao and Kannan, 2013; Rochester and Bolden, 2015a; Wu et al., 2018).

Given that BPF and BPS are structurally analogous to BPA, it is expected that BPF and BPS exhibit similar toxicological and endocrine disruptive effects on biological systems (Rochester and Bolden, 2015b). Some studies have assessed the estrogenic activities of BPF and BPS within *in vitro* reporter systems, indicating similar toxicity and estrogenic potency as BPA (Hashimoto and Nakamura, 2000; Moreman et al., 2017; Zhang et al., 2011a,b). Several studies have demonstrated that BPF exposure adversely affects uterine growth in rats (Stroheker et al., 2003; Yamasaki, 2004). Increasing evidence has also demonstrated that BPS can induce alterations of the endocrine, nervous, and embryonic systems (Ji et al., 2013; Kinch et al., 2015; Qiu et al., 2016). Furthermore, several studies using zebrafish as an experimental model have indicated a sharp decrease in the production of male and female gametes after exposure to BPS (Ji et al., 2013; Naderi et al., 2014).

With increasingly detectable concentrations and frequencies of BPF and BPS in human urine (Liao et al., 2012a,b; Rocha et al., 2018; Zhou et al., 2014), the potential health risk of exposure to these alternatives across populations, particularly infants and pregnant women, is an emerging concern. However, limited studies to date have assessed the effects of prenatal BPF and BPS exposures during pregnancy on fetal growth (Frederiksen et al., 2013; Hu et al., 2019; Huang et al., 2019; Wan et al., 2018). In this study, we sought to examine the associations between prenatal exposure to BPA and its alternatives (BPF and BPS) and fetal growth parameters, and gestational age. The effects of exposure may vary by sex based on prior studies (Buckley et al., 2017; Heggeseth et al., 2019; Vyas et al., 2019), and we further estimated the potential sex difference.

2. Materials and methods

2.1. Study participants

Our study participants were from a population-based birth cohort designed to identify the effects of environmental chemical exposures on fetal growth as previously described (Cao et al., 2016). In brief, pregnant women who resided in Wuhan and Xiaogan and waited for delivery in a local hospital from July 2011 to July 2013 were invited to participate in the cohort study. A total of 1,747 pregnant women before delivery (range: 35–47 weeks) were enrolled in this study. Of them, 1495 (86%) pregnant women provided first-morning urine samples. We further restricted the current analysis to those subjects who met the following criteria: a) aged > 18 years old; b) had singleton pregnancy; c) had available urine volume for bisphenol measurements; d) resided in the study city for>1 year. Finally, 1,197 pregnant women were included in this study. Prior to enrollment, each participant provided written informed consent, and the population-based birth cohort was approved by the Ethics Committee of Tongji Medical College.

2.2. Data collection

Upon enrollment, each mother waiting for delivery filled out a structured questionnaire conducted by well-trained investigators. Information was collected on demographic characteristics (e.g., maternal weight and height prior to conception, maternal age, parity, and marital status), lifestyles (e.g., passive smoking and alcohol consumption), socioeconomic factors (e.g., education background and household income), and case history. Maternal pre-pregnancy body mass index (BMI) was calculated by weight and height before pregnancy. Based on the Chinese standard, BMI was classified as underweight (<18.5 kg/m^2), normal (18.5–23.9 kg/m^2), and overweight or obese (≥24.0 kg/m^2). We categorized gestational weight gain as inadequate, adequate, and excessive according to the Institute of Medicine (IOM) recommendation (Rasmussen and Yaktine, 2009).

The fetal growth measurement data were retrieved from medical records, including infant sex, birth weight, birth length, and gestational age. Gestational age was estimated by the interval between the delivery date and the last menstrual period. The ponderal index was defined as follows: [(birth weight; grams)/(birth length; centimeters)^3] $\times$ 100 (Yang et al., 2019). Low birth weight was defined as newborn infants with a weight of<2500 g. Preterm birth was defined as delivery at <37 weeks completed gestation.

2.3. Urine bisphenol analysis

Maternal urine samples were collected with polypropylene cups before delivery and then stored at $-20\ °C$ until the bisphenol measurements. Concentrations of BPA, BPF, and BPS in urine samples were analyzed using a mass spectrometry method described previously (Wang et al., 2019). Briefly, a urine sample (500 μL) was spiked with 10 μL of β-glucuronidase and incubated in a water bath at $37\ °C$ for 12 h. Then, a mixed internal standard was added to the urine sample. Afterward, the mixture was centrifuged and extracted using ethyl acetate thrice. The organic layer was combined into a 15-mL polypropylene tube and evaporated to dryness under a gentle nitrogen stream. Finally, 250 μL of methanol/Milli-Q water (50%/50%, % v/v) was used to dissolve the residue. The targets were separated by ultrahigh-pressure liquid chromatography and determined by a Q Exactive mass spectrometer equipped with a heated electrospray ionization (HESI) source using multiple reaction monitoring in negative ion mode. Contamination during the sample preparation procedure was assessed by the analysis of procedural blanks. The recoveries of BPA, BPF, and BPS were in ranges of 94.5–113.5%, 81.0–93.8%, and 88.2–93.4%, respectively. The limits of detection (LODs) for BPA, BPF, and BPS were 0.04, 0.03, and 0.03 ng/mL, respectively. Urinary BPA, BPF, and BPS concentrations below the LODs were set to the values of LODs divided by $\sqrt{2}$. Urine creatinine was determined using creatinine kits (Jiancheng Bioengineering Ltd., Nanjing, China) based on the Jaffé method (Yang et al., 2017).

2.4. Data analysis

Statistical analyses were performed using Stata software (version 15.0; Stata Corp, College Station, TX), SAS (version 9.4; SAS Institute, Inc.), or R (version 3.3.2; R Development Core Team). A *p*-value < 0.05 indicated statistical significance, and a *p*-value < 0.10 was suggestive of statistical significance. Descriptive statistics for maternal and neonatal characteristics and urinary bisphenol (BPA, BPF, and BPS) concentrations were conducted.

We applied multivariable regression models to examine the associations of maternal urinary bisphenol levels with fetal growth parameters (birth weight, birth length, and ponderal index) and gestational age. The associations of maternal urinary bisphenol levels with low birth weight and preterm birth were estimated by Poisson regression models. Maternal urinary BPA and BPF levels were divided into tertiles according to the measured concentrations among the entire population, and the first tertiles were assigned as the lowest exposure group. Given the low detectable rate of BPS, we defined a three-level ordinal variable as follows: participants with urinary BPS concentrations $\leq$ LOD were defined as the lowest exposure group (reference); then participants with urinary BPS concentrations > LOD were equally divided into two sized groups (the median and high groups) according to their median concentrations of urinary BPS. Tests for linear trends were conducted by modeling integer values as ordinal categorized variables (1–3). The sex-specific associations of maternal urinary BPA, BPF, and BPS concentrations with fetal growth parameters and gestational age were assessed using a stratification analysis by infant sex. A sensitivity analysis was conducted after precluding pregnant women (n = 26) who had gestational age < 37 weeks or > 42 weeks.

For statistically significant or suggestive associations in the regression models, we further used a restricted cubic spline (RCS) model to estimate their shapes of dose–response associations, in which maternal urinary BPA, BPF, and BPS concentrations were molded as natural logarithm (Ln) transformed variables. For BPA and BPF, the median was defined as the referent value by default in the SAS macro (Desquilbet and Mariotti, 2010). Given the low detection rate for BPS, the 75th percentile value was defined as the reference. We performed a Bayesian kernel machine regression (BKMR) to evaluate the joint effects of three bisphenols (BPA, BPF, and BPS) on fetal growth parameters and gestational age. The three bisphenols as continuous variables were ln-transformed in the BKMR models.

Potential confounders were included based on biological consideration and if they altered the effect estimates > 10%. We adjusted for pre-pregnancy BMI, study city, infant sex, weight gain during pregnancy, parity, education, household income, and maternal age. Gestational age was additionally included in models of birth weight, birth length, and ponderal index. To adjust for urine dilution, all the models included urinary creatinine as a continuous variable (Barr et al., 2005).

3. Results

3.1. Characteristics of the study population

Table 1 presents the maternal and neonatal infant characteristics. The mean (±standard deviation, SD) age of 1,197 participants was 28.5 (±4.7) years old at the time of delivery. Greater than half of the participants (64.5%) lived in Wuhan and reported no history of having a previous baby (74.4%). There were few pregnant women with education levels less than primary school (4.26%) and with household income>5000 RMB CNY/month (19.20%). The mean (±SD) neonatal ponderal index, birth weight, gestational age, and birth length were 2.65 (±0.29) g/cm³ × 100, 3,331.11 (±396.63) g, 39.04 (±1.04) weeks, and 50.08 (±1.03) cm, respectively. Among the neonatal infants, 643 (53.0%) were males, 13 (1.09%) were low birth weight, and 16 (1.34%) were preterm birth. We found no significant sex differences in maternal characteristics (*p* > 0.05). However, male infants had higher birth

Table 1
Characteristics [Mean ± SD or n (%)] of maternal and neonatal infant in our study population[a].

Characteristics	Overall (n = 1197)	Boys (n = 634)	Girls (n = 563)	Sex-difference p-value
Maternal characteristics				
Maternal age (years)	28.49 ± 4.70	28.28 ± 4.87	28.72 ± 4.47	0.11
Pre-pregnancy BMI (kg/m²)				
<18.5	287 (23.98)	144 (22.78)	143 (25.44)	
18.5–23.9	779 (65.08)	424 (67.09)	355 (63.17)	
>24	128 (10.69)	64 (10.13)	64 (11.39)	0.37
GWG categories according to IOM				
Inadequate total GWG	171 (14.29)	94 (15.06)	77 (13.95)	
Adequate total GWG	400 (33.42)	224 (35.90)	176 (31.88)	
Excessive total GWG	605 (50.54)	306 (49.04)	299 (54.17)	0.21
Study city				
Xiaogan	425 (35.51)	225 (35.50)	200 (0.36)	
Wuhan	772 (64.49)	409 (64.50)	363 (0.64)	0.99
Education				
≤ Primary school	51 (4.26)	27 (4.30)	24 (4.30)	
Secondary school	601 (50.21)	324 (51.10)	277 (49.20)	
≥ College	545 (45.53)	283 (44.60)	262 (46.50)	0.80
Household income, (yuan/month)				
< 3000	580 (48.50)	301 (47.50)	279 (49.60)	
3000–5000	387 (32.30)	220 (34.70)	167 (29.70)	
≥ 5000	230 (19.20)	113 (17.80)	117 (20.80)	0.14
Parity				
Nulliparous	891 (74.40)	468 (73.80)	423 (75.13)	
Multiparous	306 (25.60)	166 (26.20)	140 (24.87)	0.60
Passive smoking				
No	545 (45.50)	297 (46.85)	248 (44.05)	
Yes	652 (54.50)	337 (53.15)	315 (55.95)	0.33
Neonatal characteristics				
Birth weight (g)	3331.11 ± 396.63	3375.03 ± 397.63	3281.65 ± 389.97	< 0.001
Birth length (cm)	50.08 ± 1.03	50.18 ± 0.96	49.98 ± 1.10	0.001
Gestational age (week)	39.04 ± 1.04	38.98 ± 1.22	39.11 ± 1.25	0.06
Pondral index (g/ cm³ × 100)	2.65 ± 0.29	2.67 ± 0.27	2.63 ± 0.31	0.02
Low birth weight	13 (1.09)	5 (0.79)	8 (1.42)	0.40
Preterm birth	16 (1.34)	8 (1.26)	8 (1.42)	0.81

Abbreviation: BMI, body mass index; GWG, gestational weight gain, IOM: International Organization of Medicine.

[a] 3 missing prenatal BMI and 21 missing GWG.

weight, birth length, and ponderal index compared with female infants ($p < 0.05$).

3.2. The distribution of maternal bisphenol exposures

A summary of maternal bisphenol exposures (BPA, BPF, and BPS) is presented in Table 2. The detection rates for maternal urinary BPA, BPF, and BPS were 94.4%, 77.1%, and 47.9%, respectively. The mean concentrations of maternal urinary BPA, BPF, and BPS were 2.10 µg/L, 0.57 µg/L, and 0.40 µg/L in all participants, respectively. The median maternal urinary concentrations of BPA, BPF, and BPS were not significantly different between boys and girls.

3.3. Associations of maternal bisphenol exposures and fetal growth parameters and gestational age

Fig. 1 presents regression coefficients (95% CI) for fetal growth parameters and gestational age associated with maternal urinary bisphenol levels by the overall population and infant sex subgroups. Among the overall population, our results showed no statistically significant associations of elevated maternal urinary BPA, BPF, and BPS concentrations with birth weight. However, we found that maternal urinary BPA and BPF levels in the highest group exhibited 0.30 cm (95% CI: −0.44, −0.15) and 0.21 cm (95% CI: −0.36, −0.07) (both p for trends < 0.01) reductions in birth length relative to the lowest tertiles, respectively. In stratified analysis by infant sex, stronger associations were observed in girls than in boys. The estimated mean decrease in birth length for the highest vs. lowest tertile of maternal urinary BPA in girls was 0.39 cm (95% CI: −0.62, −0.16) and in boys was 0.24 cm (95% CI: −0.43, −0.06) (both p for trends < 0.05), and the highest vs. lowest tertile of maternal urinary BPF was 0.26 cm in girls (95% CI: 95% CI: −0.49, −0.03) and 0.19 cm in boys (95% CI: −0.38, −0.01) (both p for trends < 0.05). RCS models further indicated inverted U-shaped dose–response relationships (p for nonlinear associations < 0.05) (Figs. 2 and 3).

Among the overall population, we observed maternal urinary BPA and BPF in relation to increased ponderal index with estimated mean increases of 0.05 g/cm^3 × 100 (95% CI: 0.01, 0.09) and 0.04 g/cm^3 × 100 (95% CI: 0.01, 0.08) for the highest vs. lowest exposure groups, respectively (both p for trends = 0.02). These associations stratified by infant sex were exclusively observed in girls. Regarding the highest vs. lowest group of maternal urinary BPA and BPF in girls, the estimated mean increase in ponderal index was 0.12 g/cm^3 × 100 (95% CI: 0.06, 0.18) (P for trend < 0.01) and 0.07 g/cm^3 × 100 (0.003, 0.13) (p for trend = 0.04), respectively. Moreover, we observed a negative association of maternal urinary BPS with gestational age (-0.20 weeks, 95% CI: −0.37, −0.03 for the highest vs. lowest exposure group, p for trend = 0.02). Similarly, the association was exclusively observed in girls; the estimated mean decrease in gestational age for the highest vs. lowest exposure group of maternal urinary BPS in girls was 0.44 weeks (95% CI: −0.69, −0.20) (p for trend < 0.01). In the RCS models, the above associations were further confirmed (p for overall association < 0.05) with linear dose–response relationships (p for nonlinear association > 0.05) (Figs. 2 and 3).

After precluding pregnant women who had gestational age < 37 weeks (preterm birth) or > 42 weeks (postmature delivery), the above-observed associations of maternal urinary bisphenol concentrations

with fetal growth parameters and gestational age remained robust (Table S1-S3). Furthermore, we observed joint effects of BPA, BPF, and BPS on birth length and ponderal index (Figure S1). The joint effect on decreasing birth length was statistically significant when the three bisphenols were greater than their 75th percentile compared to their median values; the joint effect on increasing ponderal index was statistically significant when the three bisphenols were at or greater than their 50th percentile compared to their median values. We did not observe evidence of statistically significant associations of elevated maternal urinary bisphenol concentrations with low birth weight and preterm birth (Table S4).

4. Discussion

Among this study of 1,197 pregnant women, we estimated the associations between exposure to maternal BPA and its substitutes (BPF and BPS) before delivery and fetal growth parameters and gestational age. We observed that prenatal BPA and BPF exposures were associated with the decreased birth length and increased ponderal index. We also found a negative association of prenatal BPS exposure with gestational age. In the sex-specific analyses, these associations tended to be stronger or exclusively occurred in girls. The magnitude and precision of these effect estimates were similar in the RCS analyses, demonstrating the robustness of our results. Our findings provide evidence on sex-specific associations of mother BPA, BPF, and BPS exposures with fetal growth parameters and gestational age.

The ubiquitous BPA and BPF exposures were observed in our population based on urinary measurements, but BPF exposure levels were relatively lower. The median urinary BPA concentration (0.73 µg/L) in our study was lower than those from pregnant women in China, Spain, and the United States (ranging from 1.0 to 2.6 µg/L) (Braun et al., 2011; Hoepner et al., 2013; Hu et al., 2019; Huo et al., 2015; Mortensen et al., 2014; Vernet et al., 2017; Wolff et al., 2008) but higher than that from pregnant women in Shandong, China (0.48 µg/L) (Ding et al., 2017). Furthermore, several studies have reported the medians of mother urinary BPF and BPS concentrations ranging from 0.34 to 2.16 µg/L (Asimakopoulos et al., 2016; Hu et al., 2019; Li et al., 2019b; Machtinger et al., 2018; Philips et al., 2018; Ye et al., 2015), which were higher than those in our study. Varying exposure levels of bisphenols across different studies are attributed to the differences in the timing of urine collection, demographic characteristics, and analytical methods.

Experimental studies have found that BPA exposure even at low doses can result in adverse effects on fetal growth (Kim et al., 2001; Rubin, 2011; Savabieasfahani et al., 2006), but epidemiological evidence remains inconclusive. In this study, we did not observe a significant association of maternal BPA exposure during late pregnancy with birth weight. Consistent with our results, some previous studies also reported null associations based on single or repeated urinary BPA measurements (Casas et al., 2016; Ferguson et al., 2016; Hu et al., 2019; Tang et al., 2013; Wolff et al., 2008). Other studies however found negative associations (Huo et al., 2015; Mustieles et al., 2018; Veiga-Lopez et al., 2015) or positive associations (Lee et al., 2014; Wolff et al., 2008). These discrepant results may be explained by exposure assessments, population characteristics, and sample sizes. However, we observed that prenatal BPA exposure was associated with the decreased birth length and increased ponderal index. The increased ponderal index

Table 2
Distribution of maternal urinary TCAA concentrations (µg/L).

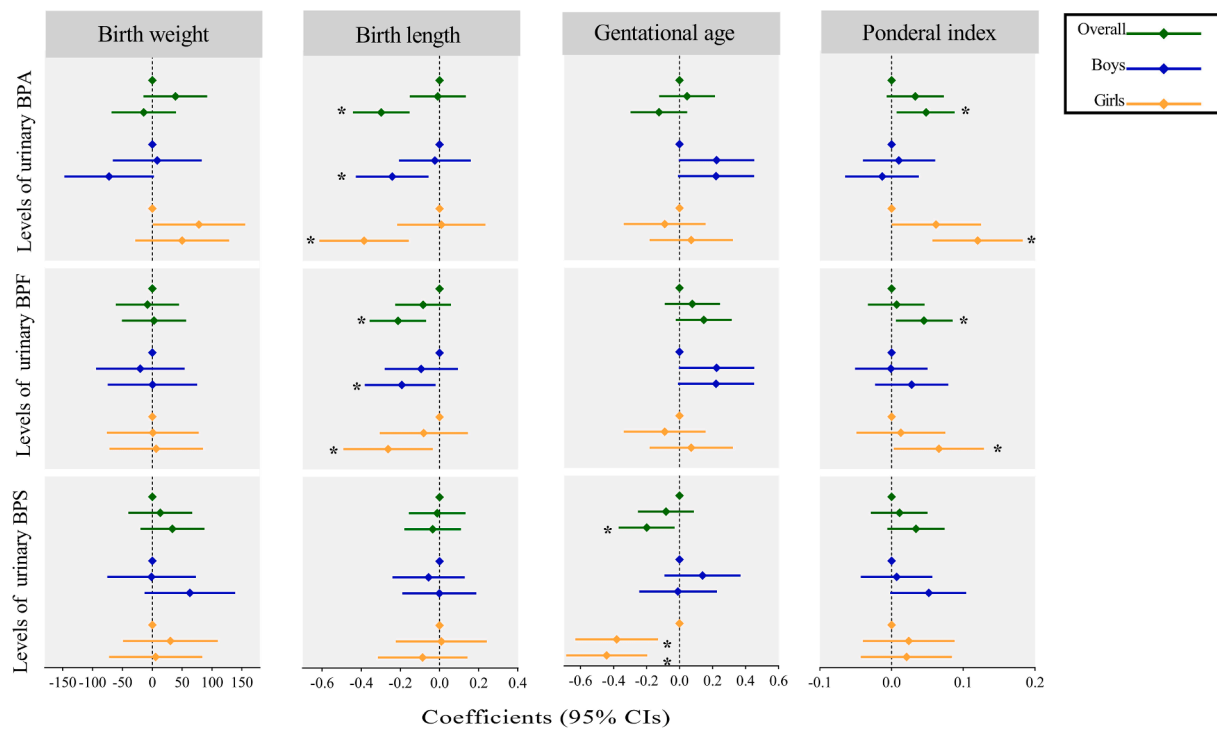| Bisphenols	Overall			Boys		Girls	
	Detection rate (%)	Mean	Median	Mean	Median	Mean	Median
BPA	94.4%	2.10	0.73	2.02	0.72	2.20	0.75
BPF	77.1%	0.57	0.07	0.60	0.07	0.54	0.08
BPS	47.9%	0.40	<LOD	0.42	<LOD	0.38	<LOD

Abbreviation: LOD, limit of detection.

Fig. 1. Associations between maternal urinary bisphenol concentrations and fetal growth parameters and gestational age in the overall population and in infant sex subgroups. All models were adjusted for urinary creatinine, maternal age, pre-pregnancy BMI, GWG, parity, household income, study city, education, and infant sex; but without infant sex for analysis of male or female. Models for birth weight, birth length, and ponderal index were additionally adjusted for gestational age. *, p < 0.05.

was possibly driven by the association with decreased birth length. In support of our results, an association of prenatal BPA exposure with an increase in the ponderal index was found in pregnant women in Korea (Lee et al., 2014). Hu et al. also found a positive association between urinary BPA concentrations during pregnancy and ponderal index among women older than 27 years of age and multiparous women (Hu et al., 2019). An increased ponderal index has been associated with adverse later-life health effects, such as diabetes mellitus, obesity, and cardiovascular diseases (Loaiza et al., 2011; Zaniqueli et al., 2019). The findings indicated that *in utero* BPA exposure may be associated with diseases later in life.

Few epidemiological studies have explored the associations of prenatal BPF and BPS exposures with fetal growth. Similar to BPA, we also reported a negative association between prenatal urinary BPF levels and birth length and a positive association with ponderal index. Inconsistent with our results, Hu et al. found no association of maternal urinary BPF with birth length in the entire trimester but observed a significant association of maternal urinary BPF in the third trimester with decreased ponderal index (Hu et al., 2019). The discrepancy between the two studies might be attributed to differences in the critical exposure windows (whole pregnancy vs. late pregnancy and/or single vs. repeated exposure assessment). Our results also revealed a significant association between prenatal BPS exposure and decreased gestational age but no association with BPF exposure. To our knowledge, only one study showed that maternal urinary BPF levels based on three repeated measurements were associated with an increased risk of preterm birth (Aker et al., 2019). Consistent with our results, two studies reported no association between maternal exposure to BPS during the entire pregnancy and preterm birth (Aker et al., 2019; Huang et al., 2019). In contrast, one study showed a negative association of maternal BPS exposure in the third trimester with preterm birth (Aung et al., 2019), and another study reported a positive association of maternal exposure to BPS in the third trimester with gestational age (Wan et al., 2018). More epidemiological studies are needed to examine the effects of prenatal BPF and BPS

exposure on fetal growth.

Because bisphenols can influence hormonal activity, the alteration of sexual differentiation may exist (Palanza et al., 2016). An experimental study in ewes revealed sex-specific effects of prenatal exposure to BPA on birth weight and birth length (Savabieasfahani et al., 2006). Earlier epidemiological studies have also reported sex differences in the associations of BPA exposure during pregnancy with fetal growth parameters (Cantonwine et al., 2015; Ferguson et al., 2018; Huo et al., 2015; Veiga-Lopez et al., 2015). In this study, we found that the associations of maternal BPA, BPF, and BPS exposures with altered fetal growth parameters were more pronounced among girls compared with boys, suggesting that female infants may be more vulnerable to *in utero* exposure to these bisphenols than males. In support of our findings, previous studies found that maternal urinary BPA was associated with an increased risk of preterm birth in female but not male infants (Cantonwine et al., 2015; Huo et al., 2015). In contrast, Ding et al. showed that prenatal BPA levels were associated with increased birth length in male infants but not in female infants (Ding et al., 2017). A Chinese cohort revealed more pronounced effect estimates between urinary BPF and BPS and decreased birth weight in boys; however, the differences were not statistically significant (Hu et al., 2019). Mothers with male fetuses may be more susceptible to estradiol in the first trimester, whereas mothers with female fetuses may be more sensitive to estriol in the second trimester (Li et al., 2020). Thus, the biotransformation and endocrine toxicity of these bisphenols by gender may explain the differences between studies.

Bisphenol exposure may affect fetal intrauterine growth by triggering endocrine disruption (Kinch et al., 2015; Rochester and Bolden, 2015a). BPA can disrupt estrogen's function by binding to estrogen receptors, and estrogen plays a pivotal role in embryo growth and development through the regulation of cell proliferation (Alonso-Magdalena et al., 2005; Watson et al., 2005). One study in Suffolk ewes found that prenatal BPA exposure adversely affects fetal growth by interfering with estrogen receptors (Savabieasfahani et al., 2006). Some studies have
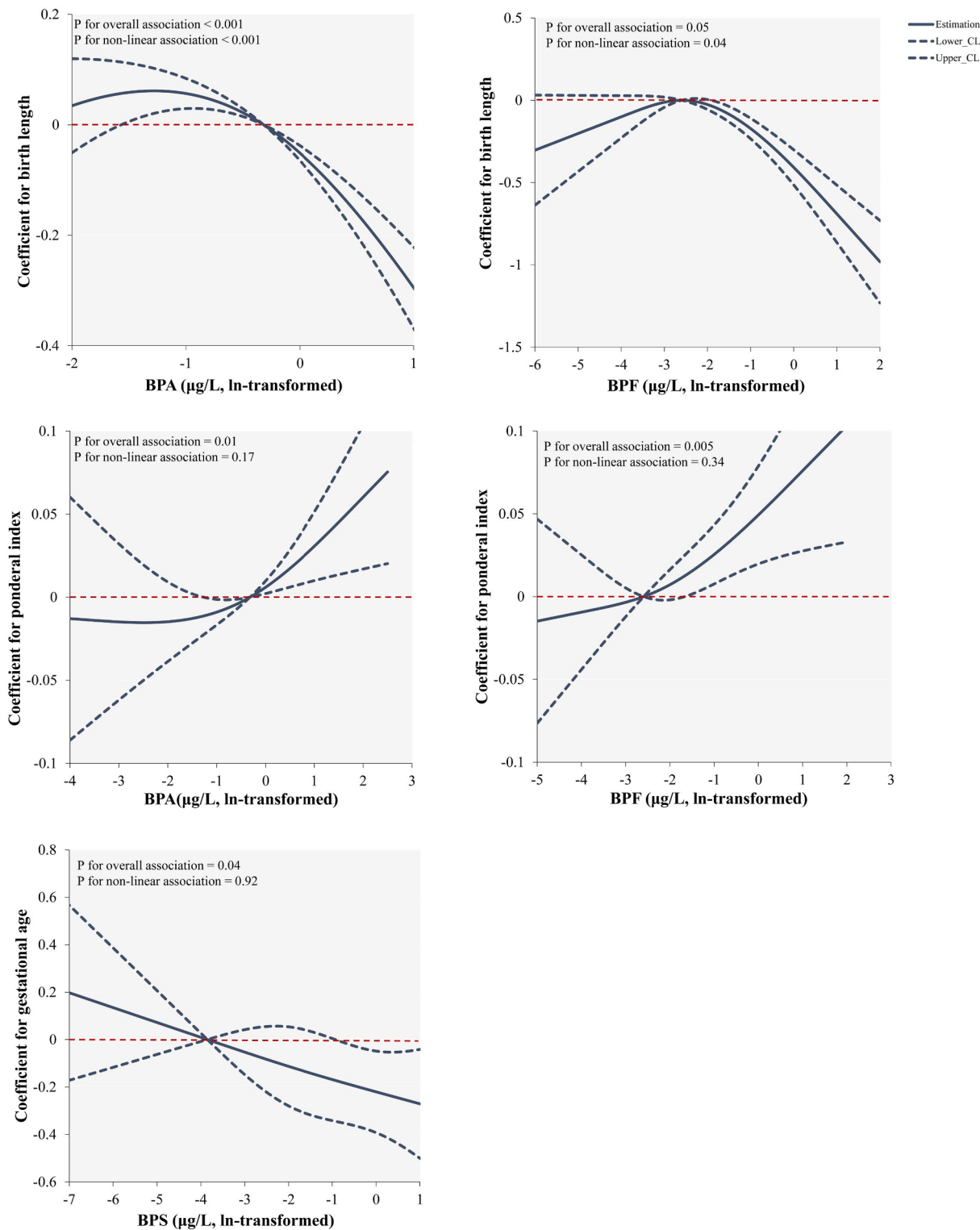
Fig. 2. Restricted cubic spline models representing the associations between ln-transformed maternal urinary bisphenol concentrations and fetal growth parameters and gestational age. All models were adjusted for urinary creatinine, maternal age, pre-pregnancy BMI, GWG, parity, household income, study city, education, and infant sex. Models for birth weight, birth length, and ponderal index were additionally adjusted for gestational age. Blue dashed lines represent 95% CIs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

shown that BPF and BPS possess endocrine-disrupting effects (Ji et al., 2013; Siracusa et al., 2018) and hormonal activities (Rochester and Bolden, 2015a; Stroheker et al., 2003), indicating mechanisms potentially similar to BPA. Moreover, the sex-dependent response to endocrine-disrupting chemicals may be due to variations in the levels of

endogenous hormones (Howdeshell et al., 1999). Davis et al. found increased expression of estrogen receptors in the brain and gonad tissues of female tilapia compared with male tilapia (Davis et al., 2008). Prenatal BPA exposure in mice could interfere with early oocyte maturation and induce reproductive effects with a decline in pregnancy rates (Ziv-
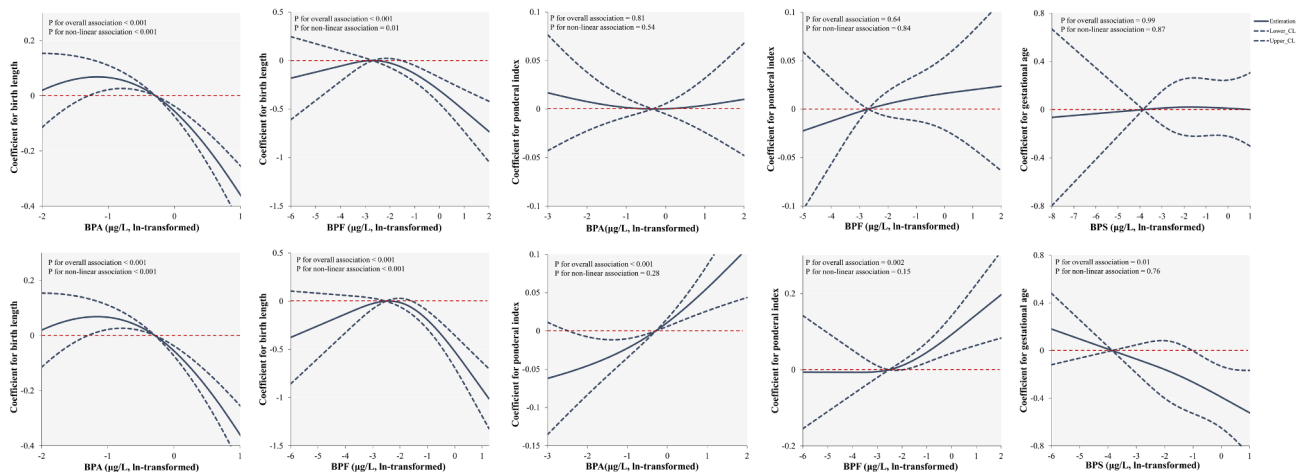
Fig. 3. Restricted cubic spline models representing the associations between ln-transformed maternal urinary bisphenol concentrations and fetal growth parameters and gestational age by infant sex. All models were adjusted for urinary creatinine, maternal age, pre-pregnancy BMI, GWG, parity, household income, study city, and education. Models for birth weight, birth length, and ponderal index were additionally adjusted for gestational age. Blue dashed lines represent 95%CIs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Gal et al., 2015). BPA may also induce decreases in testosterone 6β-hydroxylase and 2α-hydroxylase activity in male rats, which would alter testosterone levels to cause adverse growth and development (Hanioka et al., 1998). Interestingly, we found inverted U-shaped relationships between prenatal BPA and BPF exposures and birth length. This finding suggests that exposure to lower and higher doses of BPA and BPF can cause detrimental effects on fetal length growth. It has been proposed that low doses of BPA act as an estrogen to stimulate cellular responses, whereas high dose of BPA promote binding to the estrogen receptor (Rubin, 2011).

The major strength of this paper is the large-scale population-based approach with a prospective design and adjustment for a large number of potential confounders. Nevertheless, some limitations still need to be considered when weighing the findings. First, due to the high within-subject variability of urinary bisphenols (Lassen et al., 2013; Li et al., 2019a,b; Vernet et al., 2018), one single spot urine sample might produce an exposure misclassification, accordingly biasing exposure assessment of maternal bisphenol levels. However, one single spot-sampling approach in the sufficiently large population investigation has been recommended to adequately reflect the average levels of population exposure to bisphenols (Ye et al., 2011). Second, we assessed only the effects of the third trimester BPA and its alternative exposures and thus were not able to identify the susceptibility window. Hu et al. suggested that different periods of gestation had different susceptibility windows of exposure to BPF and BPS for fetal growth (Hu et al., 2019). Third, diet and personal care products are the major sources of bisphenol exposure during pregnancy (Li et al., 2019a,b; Rudel et al., 2011). Moreover, human beings can be simultaneously exposed to multiple environmental pollutants, such as persistent organic pollutants, heavy metals, and air pollutants, which have been associated with fetal growth. We did not consider these factors that might have biased the associations of exposure-outcomes.

5. Conclusion

In this cohort study, we observed significant associations of prenatal exposure to BPA and BPF with decreased birth length and increased ponderal index as well as prenatal exposure to BPS with reduced gestational age. These associations were more pronounced among girls than among boys, suggesting that exposure to bisphenols during pregnancy had sexually dimorphic effects on fetal growth. Additional studies are still needed to confirm or refute our findings of a positive association between prenatal exposure to BPA and its alternatives (BPF and BPS)

and adverse birth outcomes.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106305.

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