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Maternal urinary concentrations of bisphenol A during pregnancy and birth size in children from the Odense Child Cohort

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Abstract

Background Bisphenol A (BPA) is widely used in the manufacturing of plastics. BPA can pass the placental barrier and influence fetal development. Due to its estrogenic and anti-androgenic properties, BPA may contribute sex-specific differences in developmental effects. We examined associations between maternal urinary concentrations of BPA and birth size.

Methods In this cohort study of 832 mother-child pairs from the Odense Child Cohort, pregnant women provided spot urine samples at gestational week 28, which were analyzed for BPA by isotope diluted LC-MS/MS. Osmolality adjusted urinary BPA concentrations were categorized into quartiles. Mother-child characteristics were obtained from hospital records and questionnaires. Linear regression analyses examining the association between BPA concentrations and offspring birth size (weight, length, head, and abdominal circumference) were performed for the full cohort and stratified by offspring sex.

Results BPA was detected above the limit of detection in 85% of the urine samples with a median concentration of 1.33 ng/ml. In the full cohort, birth weight decreased significantly across increasing quartiles of maternal urinary BPA concentration, with the exception of the third quartile, which showed no significant association. In sex-stratified analyses, statistically significant decreases in birth weight were observed among male offspring in the highest quartile of maternal urinary BPA concentrations (β: -115 g, 95% CI: −225, -4, $p=0.04$) compared to male offspring of the lowest quartile and a possible dose-response association was suggested (p-trend = 0.06). No statistically significant associations were observed for birth weight amongst female offspring.

Conclusions Our findings suggest a negative association between maternal urinary BPA exposure and birth weight, driven by a lower birth weight in male offspring. Further research is required to explore the underlying mechanisms of BPA's possible sex-specific associations.

Keywords BPA, Odense child cohort, Birth characteristics, Exposure, EDCs, Urine

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Background

Bisphenol A (BPA) is a chemical compound that is used in the manufacturing of various forms of plastics. The chemical is copiously produced with a 5.3% annual growth rate in global demand and is widely applied in everyday products, such as packaging, electronics, medical equipment, and children's toys [1, 2]. As BPA is widely present in domestic products, exposure through various sources and routes occur on a daily basis, with evidence reporting that BPA was found in the urine of more than 90% of individuals tested across various countries [3].

BPA can bind to both membrane and nuclear estrogen receptors and is a recognized xenoestrogen [4]. However, other actions of BPA also include anti-androgenic properties [5, 6]. Other than being estrogenic or anti-androgenic, BPA has multiple modes of action in various biological contexts [7] and during critical development windows of the embryo [8, 9] and fetus [10, 11]. A transfer between mother and fetus has been reported in humans, where traces of BPA have been measured in placenta [12], amniotic fluid [13] and fetal cord blood [14]. This suggested transfer of BPA during pregnancy is concerning, as hormone disturbances during fetal organ development may introduce irreversible structural, physiological, and metabolic changes to the fetus [15–18].

Epidemiological literature examining the relationship between maternal BPA exposure and birth size in offspring remains inconclusive [19, 20]. Studies investigating the potential impact of sex on these associations are moreover limited and report inconsistent findings [21–24]. Birth size is considered a crucial marker of future health and extreme high or low birth size has been associated with increased cardiovascular and metabolomic disease in later life [25–28]. Given these long-term implications, elucidating the association between the prenatal exposure to BPA and birth size, along with any potential sex-effect, could enhance our understanding of the impact of BPA on birth size during sensitive fetal developmental windows.

Using data from a cohort of healthy pregnant women, this study aimed to examine the associations between maternal urinary concentrations of BPA and offspring birth size outcomes, and whether these associations were modified by offspring sex.

Methods

Study population

The study follows a prospective cohort design and is based on 832 mother-child pairs from the Odense Child Cohort, which has been described prior [29]. Pregnant women were enrolled in the cohort at Odense University Hospital between 2010 and 2012 during the early stages of their gestation (gestational weeks 8–16). Women completed a questionnaire regarding their general health and lifestyle factors and donated a fasting spot urine sample during their second trimester in gestational weeks 27 and 28 (median 28.7 weeks, range 26.4–30.4 weeks). The samples were subsequently stored at -80 °C within the Open Patient data Explorative Network (OPEN) prior to their chemical analysis. Data on maternal age at delivery, pre-pregnancy BMI, parity, maternal smoking during pregnancy, educational status and birth size outcomes were obtained from hospital obstetric and pediatric records. Ponderal index was calculated as the ratio of birth weight divided by birth length cubed (cm^3). Gestational age (GA) was calculated using the date of the last menstrual period and date of birth. Parity and ponderal index (g/cm^3) were included for descriptive purposes only.

Analysis of urinary BPA

Urinary concentrations of BPA were quantified using isotope-diluted Liquid Chromatography with tandem Mass Spectrometry (LC-MS/MS) with prior enzymatic deconjugation, as previously described [30]. The limit of detection (LOD) was 0.12 ng/ml. The urinary osmolality of each sample was measured by the freezing point depression method with an automatic cryoscopic osmometer (Osmomat °030 from Gonotec, Berlin, Germany) and used to adjust all measured BPA concentrations for the osmolality of the sample [30]. Osmolality adjustment was calculated for all samples by dividing sample concentrations with sample osmolality and multiply with median osmolality (0.63 osm/kg). Chemical analyses were performed in Copenhagen, Denmark at the Department of Growth and Reproduction at Copenhagen University Hospital – Rigshospitalet and have partly been published before [30–32].

Confounders and outcomes

Confounders were identified based on prior knowledge and included maternal age at delivery (< 20, 20–25, and > 25 years), and gestational age at birth (number of weeks) obtained from hospital records, and self-reported maternal BMI (normal weight [< 25 kg/m^2], overweight [25–34 kg/m^2], and obese [> 34 kg/m^2]), maternal smoking during gestation (no or yes), maternal education level (low: high school or less, middle: high school + 1–4 years, high: high school + > 4 years), and parity (nulliparous or multiparous). All participating women ($N = 832$) had available confounder information.

Primary outcomes were birth size outcomes obtained from hospital records, including birth weight (g) and length (cm), and head and abdominal circumference (cm). Data on birth weight was available for all offspring ($N_{males/females}$: 444/388), 827 had information on birth length ($N_{males/females}$: 440/387), 825 had information on head circumference ($N_{males/females}$: 439/386), and 821 had

information on abdominal circumference ($N_{males/females}$: 436/385).

Statistical analyses

Descriptive statistics were conducted to summarize differences in urinary BPA concentrations, presented as medians and interquartile ranges (25–75th percentiles), according to maternal characteristics stratified by all offspring and child sex assigned at birth. Differences in distributions of urinary BPA concentrations were assessed through Kruskal Wallis tests. Due to BPA concentrations not being normally distributed, these were divided into quartiles for male and female offspring separately and according to proportional group sizes and categorized as follows: reference (quartile 1, Q1), low (Q2), medium (Q3) and high (Q4). Birth size outcomes were applied in the analyses as continuous variables.

Linear regression was applied to estimate the association between quartiles of maternal second trimester BPA concentrations and birth size outcomes. Models were adjusted for confounders including maternal age, BMI, smoking and education, gestational age at birth, and parity. Linear dose-response trends across BPA quartiles were assessed by means of ordinal BPA quartiles using integer values from one to four (*p*-value for trend). Analyses were performed for all, and separately for male and female offspring.

In addition to the sex-stratified regression analyses, we included a cross product term (maternal BPA concentrations ∗ offspring sex) to explore potential interactions between offspring sex and maternal BPA concentrations. However, the interaction term was not statistically significant (*p*-value = 0.22) indicating that concentrations of BPA did not differ between sex. However, by examining potential differences within each sex separately, we account for how BPA exposures manifest differently between males and females. It has been observed that sex-specific biological differences in metabolism and hormone regulation influence how BPA is processed within the body [33].

Statistical analyses were performed in SAS Studio (2018, SAS Institute Inc., Cary, NC, USA) and R 3·6·0 (R Foundation for Statistical Computing, Vienna, Austria). Specifically, PROC GLM in SAS and the *plotrix* package in R were used for analyses and figures.

Results

Descriptive statistics of the 832 mother-child pairs included in the study are presented in Table 1 and the maternal urinary BPA concentrations are depicted in Table S1 in supplementary material. BPA urinary concentrations were detected above LOD in 85% of the urine samples ($n = 832$) with an osmolality adjusted median of 1.33 ng/ml. The majority of women were between 25 and 34 years of age, had a normal BMI, and did not smoke. Statistically significant differences in BPA concentrations were only observed between nulliparous (median 1.45 ng/ml) and multiparous women (median 1.23 ng/ml). When stratified by offspring sex, similar statistically significant differences in median concentrations of BPA were observed between nulliparous (median 1.44 ng/ml, range 0.53; 2.87) and multiparous (median 1.13 ng/ml, range 0.54; 1.97) women of female offspring.

The results of the regression analyses including all offspring are presented in Fig. 1; Table 2. When considering the full cohort, no statistically significant trends were observed across maternal urinary BPA concentration quartiles and birth outcomes. Specifically, offspring in the second quartile had a birth weight reduction of 89 g (95% CI: -167, -11, *p*-value = 0.03), and offspring in the fourth quartile had a reduction of 92 g (95% CI: -170, -14, *p*-value = 0.02). However, no statistically significant association was observed for the third quartile (β=-51 g, 95% CI; -129; 26, *p*-value = 0.19). No other patterns of associations were observed for the remaining birth outcomes for the full cohort.

The results from the sex-stratified regression models are shown in Fig. 1; Table 3. Maternal BPA exposure in the highest quartile was associated with a statistically significant lower birth weight in males, but not in female offspring. Males in the highest BPA concentration quartile had on average a 115 g lower birth weight (95% CI: – 225, -4, *p*-value = 0.04), as opposed to males in the first quartile of BPA, including a borderline statistically significant p-trend ($p = 0.06$). We observed no statistically significant trends across the other endpoints in male offspring. No statistically significant trends in birth outcomes were observed in female offspring.

Discussion

Utilizing data from 832 mother-child pairs from the Odense Child Cohort, the present study observed a decreasing birth weight in the full cohort with increasing quartiles of maternal urinary concentrations of BPA during pregnancy. However, this association was driven by male offspring, as the sex-stratified analyses revealed statistically significant associations solely for male birth weight, including a potential dose-response pattern, with no similar findings observed amongst female offspring.

Concentrations of BPA were detected above LOD in the vast majority of collected urine samples (84.6%). Similar detection rates of BPA have been reported in pregnant populations from China [34], Spain [35], and the United States [36], confirming that pregnant women are ubiquitously exposed to BPA. Moreover, the median concentration of maternal BPA in our cohort was 1.2 ng/ml ($BPA_{[osm]}$: 1.3 ng/ml), which is comparable to other birth

Table 1 Median (25–75th percentile) of maternal osmolality adjusted urinary BPA according to maternal and child characteristics in 832 mother-child pairs

Maternal and child characteristics	Bisphenol A (ng/ml(osm[a]))					
	All offspring, *N* = 832		Male offspring, *n* = 444		Female offspring, *n* = 388	
	N (%)	[ng/ml(osm[a])]	*N* (%)	[ng/ml(osm[a])]	*N* (%)	[ng/ml(osm[a])]
Maternal age (years)						
< 25	73 (8.8)	1.46 (0.59; 2.41)	42 (9.5)	1.46 (0.64; 2.52)	31 (8.0)	1.50 (0.42; 2.33)
25–34	562 (67.6)	1.30 (0.55; 2.44)	294 (66.2)	1.38 (0.53; 2.37)	268 (69.1)	1.24 (0.56; 2.45)
> 34	197 (23.7)	1.41 (0.50; 2.39)	108 (24.3)	1.41 (0.55; 2.36)	89 (22.9)	1.39 (0.45; 2.43)
Maternal pre-pregnancy BMI[b](kg/m^2)						
<20	87 (10.5)	1.33 (0.35; 1.95)	47 (10.6)	1.10 (0.35; 1.96)	40 (10.3)	1.49 (0.44; 1.98)
20–25	432 (51.9)	1.28 (0.52; 2.38)	226 (50.9)	1.31 (0.50; 2.32)	206 (53.1)	1.19 (0.52; 2.51)
> 25	313 (37.6)	1.45 (0.64; 2.51)	171 (38.5)	1.53 (0.68; 2.60)	142 (36.6)	1.34 (0.61; 2.38)
Maternal smoking during pregnancy						
No	804 (96.6)	1.32 (0.53; 2.38)	427 (96.2)	1.40 (0.53; 2.38)	377 (97.2)	1.26 (0.53; 2.38)
Yes	28 (3.4)	1.42 (0.76; 2.82)	17 (3.8)	1.21 (0.81; 2.73)	11 (2.8)	2.28 (0.22; 2.91)
Educational status						
High school or less	236 (28.4)	1.48 (0.57; 2.51)	136 (30.6)	1.55 (0.57; 2.53)	100 (25.8)	1.41 (0.57; 2.51)
High school + 1–4 years	431 (51.8)	1.26 (0.56; 2.38)	229 (51.6)	1.28 (0.50; 2.40)	202 (52.1)	1.19 (0.61; 2.38)
High School + > 4 years	165 (19.8)	1.30 (0.42; 2.24)	79 (17.8)	1.40 (0.62; 2.01)	86 (22.2)	1.29 (0.26; 2.38)
Parity						
Nulliparous	472 (56.7)	1.45 (0.55; 2.64)*	256 (48.4)	1.46 (0.56; 2.52)	216 (55.7)	1.44 (0.53; 2.87)*
Multiparous	360 (43.3)	1.23 (0.53; 2.12)*	188 (42.3)	1.29 (0.53; 2.22)	172 (44.3)	1.13 (0.54; 1.97)*
Gestational days at birth						
Preterm (< 259)	33 (3.9)	1.13 (0.62; 2.00)	17 (2.10)	1.31 (0.89; 1.87)	16 (1.90)	1.00 (0.55; 2.20)
Term (≥ 259)	799 (94.9)	1.33 (0.53; 2.43)	427 (50.7)	1.40 (0.53; 2.41)	372 (44.2)	1.28 (0.52; 2.44)
Sex						
Male	444 (53.4)	1.39 (0.55; 2.39)	444 (100.0)	1.39 (0.55; 2.39)	na	na
Female	388 (46.6)	1.28 (0.53; 2.43)	na	na	388 (100.0)	1.28 (0.53; 2.43)
Birth weight (g)						
< 3000	124 (53.4)	1.29 (0.64; 2.13)	52 (11.7)	1.55 (0.86; 2.25)	72 (18.6)	1.14 (0.57; 2.03)
3000–4000	555 (66.7)	1.40 (0.54; 2.66)	293 (66.0)	1.43 (0.47; 2.66)	262 (67.5)	1.31 (0.58; 2.64)
> 4000	153 (18.4)	1.18 (0.39; 2.12)	99 (22.3)	1.20 (0.53; 2.11)	54 (13.9)	1.08 (0.08; 2.21)
Ponderal Index (g/cm^3)						
< 2.2	83 (10.0)	1.02 (0.61; 2.00)	46 (10.4)	1.08 (0.68; 1.95)	37 (9.5)	0.92 (0.42; 2.00)
2.2-3.0	731 (87.9)	1.39 (0.55; 2.47)	388 (87.4)	1.42 (0.54; 2.46)	343 (88.4)	1.31 (0.55; 2.51)
> 3.0	18 (2.2)	1.21 (0.08; 1.43)	10 (2.3)	1.21 (0.18; 1.43)	18 (2.2)	0.74 (0.08; 2.13)

[a]Osm: osmolality

[b]BMI: body-mass index

*$p < 0.05$, Kruskal Wallis test

cohorts from Europe [22, 37], USA [38], Mexico [39], and Puerto Rico [40].

Our overall findings are consistent with those of three previous epidemiological studies [41–43]. Yet, other studies have conveyed positive associations between concentrations of BPA measured during pregnancy and birth size [23, 44]. In line with our findings from the stratified analyses, a Danish study of 88 pregnant women similarly observed that urinary concentrations of BPA were significantly associated with reduced birth weight in males, but not in females [22]. However, sex-stratified results across studies remain inconsistent. Although the interaction analysis in the present study did not reveal significant results, we performed sex-stratified analyses to further explore potential differences. In contrast, a Chinese case-control study of 452 pregnant women exhibiting higher median BPA concentrations (cases, 4.7 ng/ml, controls, 2.2 ng/ml) observed a higher risk of lower birth weight in female offspring and not male offspring [42]. It is unclear why studies observe effects that differ across outcomes for male and female offspring. However, this discrepancy may be attributed to random variation.

BPA is known to mimic endogenous estrogen by binding to estrogen receptors due to sharing a structural similarity to natural estrogens. This interference can disrupt the normal functioning of endogenous estrogens which play a key part in the development and growth of the embryo through cell proliferation [7]. Since the

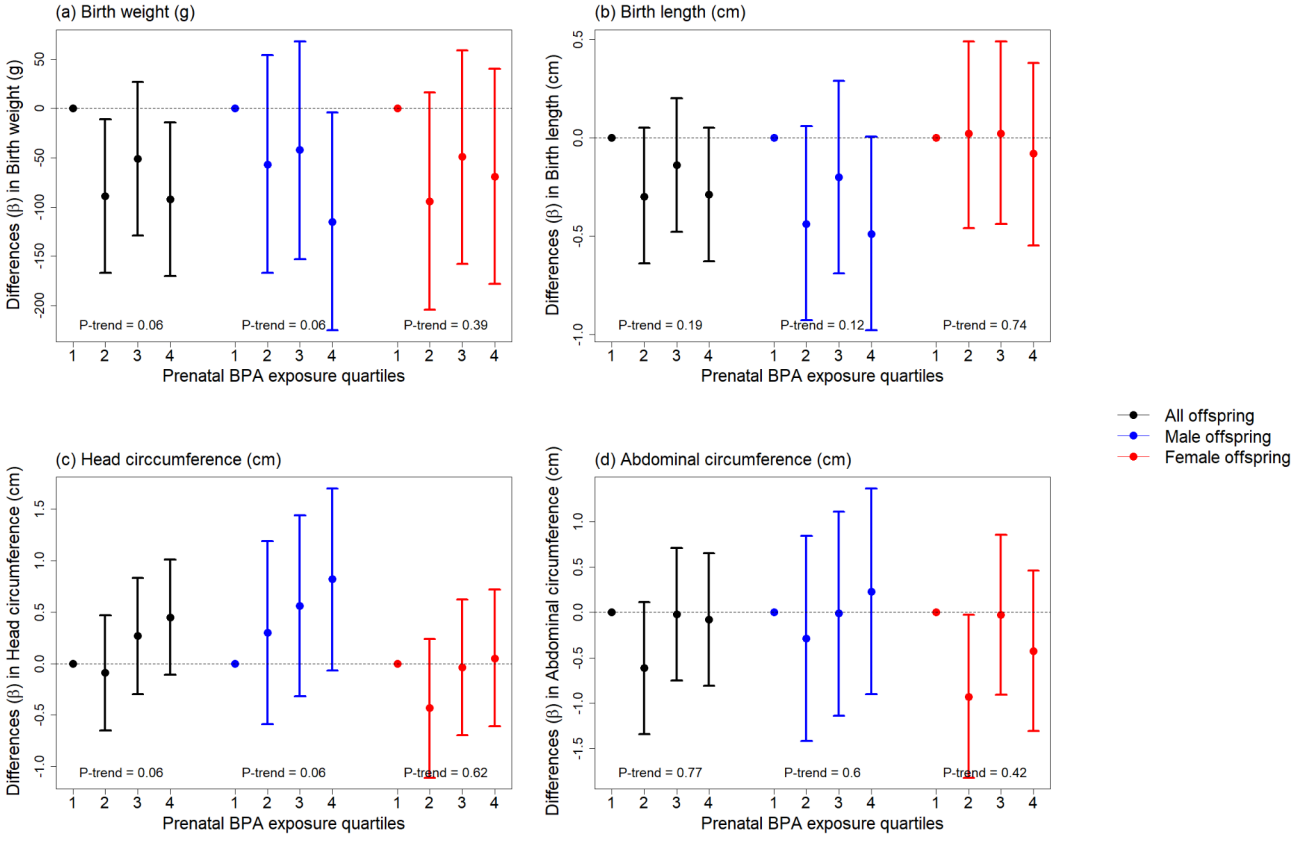

Fig. 1 Linear regression models estimating the overall and sex-stratified association between quartiles of maternal BPA concentrations and birth size outcomes

expression of estrogen receptors is different between the two sexes, it can be postulated that this variation in receptor expression may explain why some studies report differing effects. Timing of BPA exposure may also be a factor, as a study examining the relationship between BPA and estrogens across trimesters found mothers carrying male fetuses were more sensitive to estradiol in early pregnancy, while mothers carrying female fetuses were more responsive to estriol in mid-pregnancy [45]. Lastly, the differences detected in Asian versus Caucasian populations may be due to genetic or dietary differences, although this remains speculative given the lack of genetic and dietary information. The overall ambiguity in findings across studies is moreover supported by two systematic reviews, which suggest that the of lack of homogenous data, limited number of studies, and the biological complexity of BPA contribute to their mixed results [19, 20].

Notably, the association observed for birth weight for the full cohort appeared to be driven by male offspring, as these findings were only consistent for males in the sex-stratified analyses, whereas no associations were observed for female offspring. In our study, the observed impact on birth weight in males may be due to BPA's anti-androgenic ability, which involves inhibiting androgen receptor signaling [5, 6]. The difference in birth weight between male offspring in the lowest quartile and highest quartile of maternal BPA concentrations observed in our study corresponds to the average difference in birth weight between female and male offspring (110–150 g). This weight difference is often attributed to androgen activity, as individuals with a 46 XY karyotype and a complete androgen insensitivity tend to have birth weight comparable to that of females [46]. Given this, it is plausible that BPA may exert anti-androgenic effects by disrupting androgen activity leading to a lower birth weight in male offspring. A study assessing the effect of various doses of BPA in human placentas observed that 1 μM of BPA significantly increased the expression of the estrogen-related receptor gamma in female placentas, while decreasing its expression in male placentas, indicating that BPA can influence gene expression in human placentas differently across the sexes and be anti-estrogenic for male fetuses, potentially affecting important developmental processes [47]. BPA's anti-androgenic and anti-estrogenic properties may also explain the observed decrease in birth length for male offspring in the highest quartile of maternal BPA concentrations, however, this remains unclear and requires further research to fully elucidate the specific mechanisms involved. A strength

Table 2 Differences in birth outcomes in all liveborn offspring, and 95% confidence intervals in adjusted linear regression according to quartiles of osmolality adjusted bisphenol A (BPA) concentrations in urine from 832 pregnant women

BPA (ng/ml(osm))	Birth weight(g)			Birth length (cm)			Head circumference (cm)			Abdominal circumference (cm)		
	n	β, 95% CI	*p*-value	*n*	β, 95% CI	*p*-value	*n*	β, 95% CI	*p*-value	*n*	β, 95% CI	*p*-value
All children												
BPA quartile												
Q1: LOD to < 0.54	208	Reference		207	Reference		206	Reference		206	Reference	
Q2: 0.54 to < 1.33	208	-89 (-167; -11)	0.03	206	-0.30 (-0.64; 0.05)	0.08	205	-0.09 (-0.65; 0.47)	0.76	204	-0.61 (-1.34; 0.11)	0.10
Q3: 1.33 to < 2.41	208	-51 (-129; 27)	0.19	207	-0.14 (-0.48; 0.20)	0.42	207	0.27 (-0.30; 0.83)	0.35	206	-0.02 (-0.75; 0.71)	0.95
Q4: ≥ 2.41	208	-92 (-170; -14)	0.02	207	-0.29 (-0.63; 0.05)	0.09	207	0.45 (-0.11; 1.01)	0.12	205	-0.08 (-0.81; 0.65)	0.83
P-trend[a]			0.06			0.19			0.06			0.77

Abbreviations: CI, confidence interval; LOD, limit of detection; BPA, bisphenol A

All estimates adjusted for maternal age, maternal pre-pregnancy BMI, maternal smoking during pregnancy, maternal educational status, gestational age at birth, offspring sex and parity

[a]p- trend across quartiles of BPA concentrations

of the current study is the inclusion of a large study population from a Danish cohort with exhaustive information on mother-child characteristics. Urine samples enabled the quantification of BPA in urine, which is the favored matrix for measuring short half-life compounds such as BPA due to their rapid metabolism and excretion (approximately 6 h) [48]. Of note, a previous study reported that maternal urinary concentrations of BPA are strongly correlated with concentrations found in placentas and neonatal urine [49], thus supporting maternal urine concentrations as a proxy of the fetal exposure.

Participation bias may be a potential issue as only 43% of the eligible pregnant women participated in the cohort. We moreover acknowledge that the included pregnant women may not fully represent the background population of women giving birth and residing in the recruitment area of the Odense Child Cohort at that time [29]. However, as participants were unbeknownst of their bisphenol exposure and the aim of the study was to compare exposure across BPA concentrations, the mothers' representativeness of the background population is less critical. A limitation is that we only utilized single spot urine samples collected during gestational week 28, which can only provide a snapshot in time of maternal BPA exposure, and due to the intra-individual variation in BPA urine excretion [50] the current study inhabits a potential risk of exposure misclassification. It is important to note that exposure misclassification can obscure the true dose-response relationship, potentially explaining the non-linear patterns observed in females. Further, pregnant women are exposed to a multitude of different chemicals and other compounds, which can result in additive and synergistic effects. Our findings are limited to the individual effect of BPA only, and therefore studies incorporating the cocktail effects of BPA and other chemicals are required.

Furthermore, although we accounted for several appropriate covariates in our adjusted analyses, we cannot eliminate the possibility of residual confounding due to the absence of data on additional relevant factors. Given that gestational age is a well-established determinant of birth weight, we also investigated it as an outcome and whether it might mediate the observed association. However, both analyses yielded non-significant results (data not shown). These findings are consistent with a meta-analysis that found no significant associations between BPA and gestational age [51]. However, other studies have reported significant associations [34, 40].

Conclusions

Our findings suggest decreases in birth weight with increasing maternal urinary BPA concentration, including a potential dose-response pattern, solely in male offspring but not female offspring, suggesting that male

Table 3 Differences in birth outcomes stratified on offspring sex and 95% confidence intervals in adjusted linear regression models according to quartiles of osmolality adjusted bisphenol A (BPA) concentrations in urine from 832 pregnant women

BPA (ng/ml(osm))	Birth weight (g)			Birth length (cm)			Head circumference (cm)			Abdominal circumference (cm)		
	n	β, 95% CI	*p*-value	*n*	β, 95% CI	*p*-value	*n*	β, 95% CI	*p*-value	*n*	β, 95% CI	*p*-value
Male offspring												
BPA quartile												
Q1: LOD to < 0.56	111	Reference		110	Reference		111	Reference		111	Reference	
Q2: 0.56 to < 1.39	111	-57 (-167; 54)	0.31	109	-0.44 (-0.93; 0.06)	0.08	110	0.30 (-0.59; 1.19)	0.46	110	-0.29 (-1.42; 0.84)	0.61
Q3: 1.39 to < 2.40	111	-42 (-153; 68)	0.45	111	-0.20 (-0.69; 0.29)	0.43	111	0.56 (-0.32; 1.44)	0.21	111	-0.01 (-1.14; 1.11)	0.98
Q4: ≥ 2.40	111	-115 (-225; -4)	0.04	110	-0.49 (-0.98; 0.004)	0.05	110	0.82 (-0.07; 1.70)	0.07	110	0.23 (-0.90; 1.36)	0.69
P-trend[a]			0.06			0.12			0.06			0.60
Female offspring												
BPA quartile												
Q1: LOD to < 0.53	97	Reference		97	Reference		97	Reference		97	Reference	
Q2: 0.53 to < 1.28	97	-94 (-204; 16)	0.09	96	0.02 (-0.46; 0.49)	0.95	96	-0.43 (-1.11; 0.24)	0.21	96	-0.93 (-1.82; -0.03)	0.04
Q3: 1.28 to < 2.44	97	-49 (-158; 59)	0.37	97	0.02 (-0.44; 0.49)	0.93	97	-0.04 (-0.70; 0.62)	0.90	97	-0.03 (-0.91; 0.85)	0.95
Q4: ≥ 2.44	97	-69 (-178; 40)	0.22	97	-0.08 (-0.55; 0.38)	0.72	97	0.05 (-0.61; 0.72)	0.88	97	-0.43 (-1.31; 0.46)	0.34
P-trend[a]			0.35			0.74			0.62			0.74
Maternal BPA *x* Offspring sex												
P-trend[a]	832		0.18	827		0.33	829		0.65	829		0.42

Abbreviations: CI, confidence interval; LOD, limit of detection; BPA, bisphenol A

All estimates adjusted for maternal age, maternal pre-pregnancy BMI, maternal smoking during pregnancy, maternal educational status, gestational age at birth and parity

[a] *p*-trend across quartiles of BPA concentration

[b] *p*-values for the interaction term, testing the null hypothesis that the estimates for males and females are equal

offspring may be the primary drivers behind the association. The modes of action of BPA include estrogenic, anti-estrogenic and anti-androgenic mechanisms, which may explain the potential sex-specific effect of BPA on birth outcomes. However, the endocrine-related activities of BPA are multivarious and complex, thus the mechanism behind the observed associations in the present study remain to be elucidated.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01169-4.

Supplementary Material 1

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Author contributions
ALB administered the study, analysed, and interpreted data, and was a contributor in writing the manuscript. EVB acquired funding, analysed, and interpreted data and was also a contributor in writing the manuscript. CSU administered the study, interpreted data and was a contributor in writing the manuscript. YHL provided statistical expertise and analysed data. HB acquired funding and data for the Odense Child Cohort, and interpreted data. HF provided chemical expertise, quantified BPA in urine samples and interpreted data. AMA provided biological expertise and interpreted data. TKJ administered and supervised the study, acquired funding and data for the Odense Child Cohort, and was a contributor in writing the manuscript. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity. However, data may be available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was performed in accordance with the ethical standards of the local institutional committee (Region Scientific Ethical Review Committee for Southern Denmark, Project Identification Number S-20090130), the national data protection agency (the Danish Data Protection Agency, Journal Number 18/33119), and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participations before enrolment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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