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Prenatal Bisphenol A exposure and early childhood neurodevelopment in Shandong, China

Rui Pan[a,1], Caifeng Wang[a,b,1], Rong Shi[a], Yan Zhang[a], Yiwen Wang[c], Chen Cai[d], Guodong Ding[e], Tao Yuan[f], Ying Tian[a,c,**], Yu Gao[a,*]

[a] Department of Environmental Health, School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] School of Nursing, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[c] MOE-Shanghai Key Laboratory of Children's Environmental Health, Xin Hua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[d] Department of Pediatrics, Shanghai East Hospital, Tongji University School of Medicine, China
[e] Department of Respiratory Medicine, Shanghai Children's Hospital Shanghai Jiao Tong University, Shanghai, China
[f] School of Environmental Science and Engineering, Shanghai Jiao Tong University, Shanghai, China

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ABSTRACT

Background: Several epidemiological studies suggest that prenatal exposure to BPA may interfere with the neurodevelopment of pre-school and school-age children. However, a limited number of studies are available for effects during children at a younger age, especially in China.

Methods: Based on Laizhou Wan Birth Cohort (LWBC), BPA concentrations were measured in urine among 506 pregnant women during their hospital admission for delivery and neurodevelopment of their children was assessed using the Gesell Development Schedules at 12 months (n = 368) and 24 months (n = 296). Linear regression and generalized linear models were used to analyze the association between prenatal BPA exposure and the children's developmental quotient scores (DQs).

Results: The median of maternal BPA concentration was 0.48 μg/L or 1.05 μg/g creatinine. Maternal BPA concentrations were adversely associated with children DQs at 12 months of age, with a 10-fold increase in prenatal BPA concentrations correlated to 1.43-point decrease in DQs in the adaptive domain (β = −1.43; 95% CI: −2.30 to −0.56, p = 0.001). When stratified by gender, prenatal BPA concentrations were adversely associated with the adaptive domain DQs among boys (p-trend = 0.012) and girls (p-trend = 0.028) and the social domain DQs (p-trend = 0.019) only among girls. At 24 months of age, the significant adverse association was only found in the language domain among girls (β = −1.69; 95% CI: −3.23 to −0.15, p = 0.032).

Conclusion: Based on a Chinese population, we found potential impacts of prenatal BPA exposure on childhood neurodevelopment at 12 and 24 months of age, especially among girls.

1. Introduction

Bisphenol A (BPA) is mainly used in the manufacture of plastics and resins that can be found in a variety of consumer products, such as epoxy resins, polycarbonate, paperboards, dental materials and medical devices (Vandenberg et al., 2007; von Goetz et al., 2010). The human body is exposed to BPA mainly through food and drinks with direct contact with packaging material or through direct contact with several other sources (plastic material, thermal paper), making BPA frequently detected in humans, especially in children and pregnant women (Geens et al., 2012; Mielke and Gundert-Remy, 2009; Mikolajewska et al., 2015). BPA is a kind of EDCs (Endocrine Disrupting Chemicals), and its effects on children's neurodevelopment have caused worldwide concern (Mustieles et al., 2015).

Evidence from animal studies showed that exposure of pregnant rodents to BPA was associated with neurodevelopmental disorders, including hyperactivity (Anderson et al., 2013), depression (Xu et al., 2012), anxiety (Luo et al., 2014), disturbance of socio-sexual behaviors (Xu et al., 2012), and spatial learning and memory functions (Hass et al., 2016; Kuwahara et al., 2013; Wang et al., 2014). These effects

* Corresponding author. Department of Environmental Health, School of Public Health, Shanghai Jiao Tong University School of Medicine, 280 South Chongqing Road, 200025 Shanghai, China.
** Corresponding author. Department of Environmental Health, School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China.
E-mail addresses: tianmiejp@sjtu.edu.cn (Y. Tian), gaoyu_ciel@sjtu.edu.cn (Y. Gao).
[1] Rui Pan and Caifeng Wang contributed equally to this work.

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might be sex-specific (Rebuli and Patisaul, 2016).

Epidemiological studies conducted in the United States have demonstrated that BPA may increase children's neurobehavioral problems, such as anxiety (Perera et al., 2016), depression (Braun et al., 2011) and hyperactivity (Perera et al., 2012) and that the associations seemed to be different between boys and girls (Evans et al., 2014; Roen et al., 2015; Stacy et al., 2017). The current evidence raises concern over the potential health effects of prenatal BPA exposure on childhood neurodevelopment.

Previous studies have mainly reported the neurodevelopmental impacts of prenatal BPA exposure on pre-school and school-age children (4–12 years) (Braun et al. 2014, 2017; Evans et al., 2014; Harley et al., 2013; Miodovnik et al., 2011; Perera et al. 2012, 2016; Roen et al., 2015; Stacy et al., 2017). But recently, the effects on children at a younger age (0–3 years) have aroused more attention (Braun et al. 2009, 2011, 2017; Casas et al., 2015; Kim et al., 2017; Yolton et al., 2011). Early childhood is a crucial period for children's neurodevelopment (Rice and Barone, 2000). So it is necessary to study the effects of prenatal BPA on childhood neurodevelopment at the early age. While widespread use of BPA in China has been reported (Huang et al., 2012), little is known about its effects on childhood neurodevelopment in the Chinese population. With the aim to estimate the potential effects of BPA exposure on early childhood neurodevelopment in China, the present study examined the levels of BPA in pregnant women and explored their association with children's neurodevelopment assessed at 12 and 24 months of age based on a birth cohort in Shandong, China.

2. Methods

2.1. Participants

The present study was based on an ongoing prospective birth cohort in Laizhou Wan (Bay) of Bohai Sea in Shandong province, northern China, namely Laizhou Wan Birth Cohort (LWBC). From September 2010 to December 2013, we enrolled pregnant women and their newborns at a local hospital during their admission for delivery. Eligibility criteria for the study have been published elsewhere (Ding et al., 2015), including residence in the area for ≥3 years; ≥18 years of age; a singleton pregnancy; and no report of assisted reproduction, illicit drug use, AIDS or HIV infection, gestational or preexisting diabetes, or pregnancy-associated or chronic hypertension.

In total, 773 mother-infant pairs participated in the study. After excluding 228 cases without sufficient urine sample for urinary BPA and creatinine detection and 39 cases with creatinine concentrations < 0.1 g/L, 506 women were included in this study (Baseline study). In the follow-up, 368 (First follow-up) and 296 (Second follow-up) children completed the neurodevelopmental assessment at 12 months of age (± 1 week) and 24 months of age (± 1 week) respectively (Fig. 1). The study was approved by the Medical Ethics Committee of Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine.

2.2. BPA exposure assessment

Spot urine was collected from pregnant women during their hospital admission for delivery and was aliquoted and stored at −80 °C until further analysis. Urinary BPA concentrations were detected with high performance liquid chromatography–electrospray ionization tandem mass spectrometry (HPLC-MS/MS) (Agilent 1290–6490, Agilent Technologies, Little Falls, DE, USA). Detailed method has been published elsewhere (Chen et al., 2011). Briefly, 4 mL urine was thawed at 4 °C and 10 μL BPA-Dl6 (Dr. Ehrenstorfer GmbH, Augsburg, Germany) was added as internal standards. After incubation at 37 °C overnight with beta-glucuronidase/sulfatase, the samples were extracted and preconcentrated with solid phase extraction (SPE). After being dried, the residue was redissolved in methanol and further analyzed by HPLC-MS/MS. The limit of detection (LOD) of BPA was 0.1 μg/L. The recovery of BPA was 97.6% and the relative standards of intra- and inter-batch precisions were less than 15%. Urinary creatinine concentrations were measured with an automated chemistry analyzer (7100 Hitachi Medical Systems, Tokyo, Japan). Urinary BPA levels were adjusted by creatinine to correct for variable urine dilutions. Urinary creatinine concentrations < 0.1 g/L (n = 39) were too dilute for accurate analysis and were excluded for further analyze (Eskenazi et al., 2004).

2.3. Neurodevelopmental assessment

The Gesell Development Schedules (GDS) was designed to provide a neurologic and intellectual evaluation of the child at the time of testing. Children at 12 months of age and 24 months of age were administered the version of GDS for 0- to 3-year-old children revised by the Beijing Mental Development Cooperative Group (Beijing Mental Development Cooperative Group, 1985). It was adopted by the Chinese Pediatric Association and widely used in China for both research purpose (Liu et al., 2016a; Tang et al., 2014; Wang et al., 2017) and clinical assessment (Huo et al., 2011; Liu et al. 2012, 2016b). The GDS items are grouped into four domains (motor, adaptive, language and social). A developmental quotient (DQ) in each of the four specific domains was assigned to each child. The standardized mean (± SD) of the DQ was 100 ± 15. The cut-off point for differentiating normal development from developmental delay was a score of 84. Scores of 70–84 indicated moderate delay, and scores of < 70 indicated severe delay.

In the present study, testing was completed by a trained pediatrician to maximize both the reliability of the assessment and the validity of the interpretation. The tester completed formal training at Xinhua Hospital Affiliated to Shanghai Jiao Tong University School.

2.4. Statistical analysis

We analyzed the characteristics of the maternal BPA concentrations, children DQ scores (DQs) at 12 months of age and 24 months of age with initial descriptive statistics. Multiple linear regression was used to analyze the associations between BPA concentrations and DQ scores adjusted for potential confounders. LOD divided by the square root of two was used to replace levels below the LOD of BPA. Then BPA concentrations were log10 transformed because of the right-skewed distribution. To further analyze the associations, we also tested for linear trends across BPA quartiles in generalized linear models (GLM) by means of ordinal BPA quartiles using integer value from 1 to 4. As the effect of BPA may differ by gender (Evans et al., 2014; Roen et al., 2015; Stacy et al., 2017), the association between BPA exposure and neurodevelopment stratified by child gender was evaluated.

Confounders were selected if they were related to neurodevelopment in literature, including maternal age, education level, household monthly salary, pre-pregnancy BMI, passive smoking during pregnancy, parity, gestational age and child gender. The variables associated with DQs on 2 or more domains ($p < 0.15$) were further included in the final regression modes, including child gender, maternal age, maternal education level, household monthly salary, and passive smoking during pregnancy. All of the analyses were conducted on creatinine-adjusted values to correct for dilution of the urine (Braun et al., 2009).

In the sensitivity analyses, we analyzed the relationships between BPA exposure and neurodevelopment by excluding children considered to have developmental delays, so as to investigate whether developmentally delayed children affected the reliability of the results. Collinearity was tested between BPA and other pollutants with potential neurodevelopment impacts [including lead (in plasma), mercury (in plasma), pyrethroid pesticides (in urine), and perfluoroalkyl and polyfluoroalkyl substances (in plasma)] and the variance inflation factor (VIF) was calculated. All VIFs were < 5, indicating an acceptable range. Statistical analyses were carried out using SPSS 19.0 base on two-tailed tests, and $p < 0.05$ indicated statistical significance.

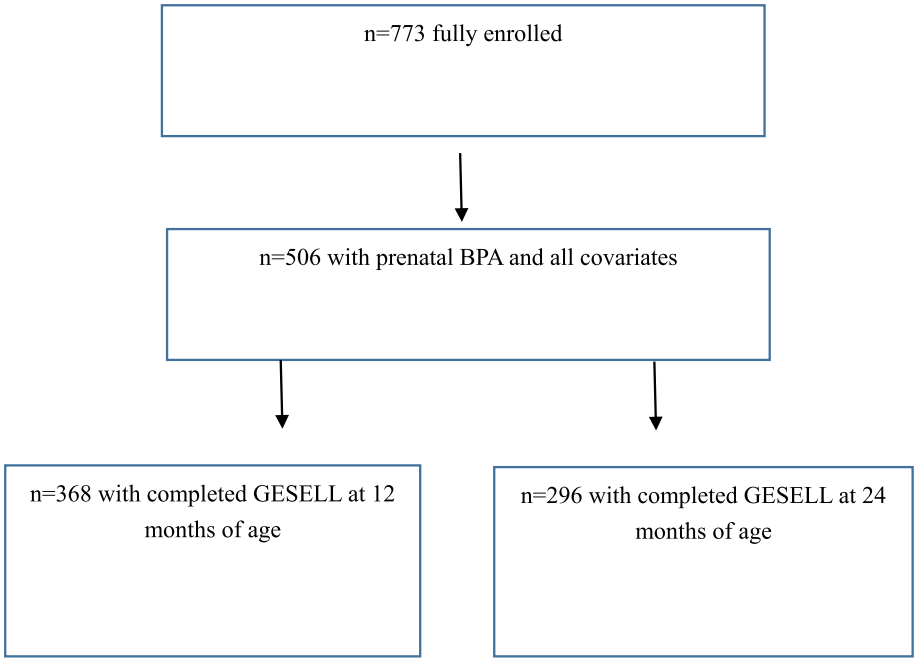

Fig. 1. Selection criteria for children included in the analysis.

3. Results

The mean maternal age of the 506 pregnant women was 28.10 ± 4.50 years old and the mean pre-pregnancy BMI was 21.86 ± 3.30 kg/m^2. The mean gestational age was 39.47 ± 1.34 weeks and 69.2% were primiparous. More than half of women (53.6%) graduated from high school or above. Less than half (40.0%) lived in households with a monthly salary over CNY (¥) 3000 yuan ($483.60). [The median household monthly salary in Shandong Province is 4000 yuan ($644.80)]. About one-third of the participants (34.6%) were exposed to passive smoking during pregnancy. Among the newborns, 52.8% were male. No substantial differences were detected in socio-demographic characteristics among the Baseline study (n = 506), First follow-up (n = 368) and Second follow-up (n = 296) (Table 1).

Table 2
Urinary BPA concentration among pregnant women in group 1 (n = 506).

	n ≥ LOD	Range	25th	50th	75th	95th
Not adjusted for creatinine (μg/L)						
BPA	438 (86.56%)	< LOD-216.56	0.19	0.48	1.41	22.45
Creatinine adjusted (μg/g)						
BPA		< LOD-609.21	0.41	1.05	3.87	45.01

BPA was detected in 86.56% of maternal urine in the study population with the median concentration of 0.48 μg/L (Table 2). The mean (± SD) DQs in the motor, adaptive, language and social domains were 106.20 ± 7.97, 100.65 ± 6.57, 96.04 ± 6.77 and 99.42 ± 6.75

Table 1
Sociodemographic characteristics of mother-infant pairs.

General information	Baseline study (N = 506)	First follow-up (N = 368)	Second follow-up (N = 296)	*P*
Continuous variables (Mean ± SD)				
Maternal age (years)	28.10 ± 4.50	27.90 ± 4.21	28.15 ± 4.23	0.721[a]
Pre-pregnancy BMI (kg/m2)	21.86 ± 3.30	21.88 ± 3.24	21.90 ± 3.35	0.988[a]
Gestational age (weeks)	39.47 ± 1.34	39.50 ± 1.30	39.54 ± 1.27	0.776[a]
Categorical variables (n%)				
Maternal education level (years)				
≤9 (Middle school)	235 (46.4)	164 (44.6)	130 (43.9)	0.899[b]
10–12 (High school)	140 (27.7)	103 (28.0)	80 (27.0)	
>12 (Greater than high school or college)	131 (25.9)	101 (27.4)	86 (29.1)	
Household monthly salary (RMB)				
≤3000	304 (60.0)	220 (59.8)	167 (56.4)	0.844[b]
3000–5000	156 (30.8)	117 (31.8)	99 (33.4)	
>5000	46 (9.1)	31 (8.4)	30 (10.1)	
Passive smoking during pregnancy				
Yes	175 (34.6)	133 (36.1)	112 (37.8)	0.646[b]
No	331 (65.4)	235 (63.9)	184 (62.2)	
Parity				
1	350 (69.2)	262 (71.2)	214 (72.3)	0.615[b]
≥2	156 (30.8)	106 (28.8)	82 (27.7)	
Infant gender				
Boy	267 (52.8)	188 (51.1)	152 (51.4)	0.867[b]
Girl	239 (47.2)	180 (48.9)	144 (48.6)	

[a] Means were compared by One-Way ANOVA.
[b] Proportions were compared by Pearson chi-square test.

Table 3
Distribution of the GDS DQ scores in children at 12 and 24 months of age.

Developmental quotient	12 months of age (n = 368)	24 months of age (n = 296)
Motor domain		
Mean ± SD	106.20 ± 7.97	104.95 ± 7.22
Normal range [n (%)]	368 (100.00%)	295 (99.67%)
Developmental delay [n (%)]	0 (0.00%)	1 (0.33%)
Adaptive domain		
Mean ± SD	100.65 ± 6.57	104.75 ± 8.19
Normal range [n (%)]	368(100.00%)	295 (99.67%)
Developmental delay [n (%)]	0 (0.00%)	1 (0.33%)
Language domain		
Mean ± SD	96.04 ± 6.77	98.32 ± 7.90
Normal range [n (%)]	350 (95.11%)	292 (98.65%)
Developmental delay [n (%)]	18 (4.89%)	4 (1.35%)
Social domain		
Mean ± SD	99.42 ± 6.75	106.94 ± 8.59
Normal range [n (%)]	366 (99.46%)	296 (100.00%)
Developmental delay [n (%)]	2 (0.54%)	0 (0.00%)

Normal range > 84 points; developmental delay ≤ 84 points for each domain.

respectively for the 12-month children; and 104.95 ± 7.22, 104.75 ± 8.19, 98.32 ± 7.90 and 106.94 ± 8.59 respectively for the 24-month children. The number (percentage) of developmental delays in the motor, adaptive, language and social domains were 0 (0.00%), 0 (0.00%), 18(4.89%), and 2 (0.54%) respectively for 12-month children; and 1 (0.33%), 1(0.33%), 4 (1.35%), and 0 (0.00%) for 24-month children (Table 3).

For children at 12 months of age, we found an inverse association between prenatal BPA concentrations and children's DQs in the adaptive domain by the trend across BPA quartiles (p-trend = 0.001). For every 10-fold increase in BPA concentrations, DQs decreased by 1.43 points (β = −1.43; 95% CI: −2.30 to −0.56, p = 0.001) (Table 4). After stratifying by child gender, we found an inverse correlation of prenatal BPA concentrations with DQs in the adaptive domain among boys (p-trend = 0.012) and girls (p-trend = 0.028). Besides, we observed significant associations between prenatal BPA concentrations and DQs in the social domain (p-trend = 0.019) only among girls. We observed no significant associations between prenatal BPA exposure and DQs in the motor domain and language domain (Table 5).

For children at 24 months of age, prenatal BPA concentrations were not associated with DQs in four domains among all children. After stratified by child gender, DQ scores in the language domain were adversely associated with prenatal BPA concentrations in girls (β = −1.69; 95% CI: −3.23 to −0.15, p = 0.032), but not in boys (Table 6).

After removing children considered to have development delays, the adverse relationship of prenatal BPA exposure and DQs on the adaptive, language and social domains still existed (Data not shown).

4. Discussion

We found that prenatal exposure to BPA was adversely associated with children's DQs in adaptive domain among all children (both in boys and girls) at 12 months of age and in social and language domains only among girls at 12 and 24 months of age respectively. The study indicated potential effects of prenatal BPA exposure on early childhood neurodevelopment, which might differ by gender.

Up to now, epidemiological studies have mainly focused on preschool and school age children (4–12 years). Adverse association was found between prenatal BPA exposure and childhood neurodevelopment in the most of these studies (Braun et al. 2014, 2017; Evans et al., 2014; Harley et al., 2013; Miodovnik et al., 2011; Perera et al. 2012, 2016; Roen et al., 2015; Stacy et al., 2017). Recently, several birth cohorts [such as the Spanish INMA-INfanciay Medio Ambiente (Childhood and Environment) birth cohort, the Health Outcomes and Measures of the Environment (HOME) study and the Children's Health and Environmental Chemicals in Korea (CHECK) cohort] also focused the effects on children at a younger age (0–3 years) (Braun et al. 2009, 2011, 2017; Casas et al., 2015; Kim et al., 2017; Yolton et al., 2011). Consistent with our results, the above studies suggested that prenatal BPA exposure was adversely associated with childhood neurodevelopment. For example, Casas et al. (2015) found that the highest tertile of urine BPA exposure was adversely associated with children's psychomotor scores at 1 year of age [n = 351, using the Bayley Scales of Infant Development (BSID)]. Braun et al. (2009, 2011) reported that maternal

Table 4
Adjusted association between BPA and neurodevelopmental scores at 12 and 24 months of age.

	n	Motor domain		Adaptive domain		Language domain		Social Domain	
		β (95% CI)	p-Value	β (95% CI)	p-Value	β (95% CI)	p-Value	β (95% CI)	p-Value
12 months									
BPA quartiles[a]									
1	94	Reference		Reference		Reference		Reference	
2	94	−0.24 (−2.56, 2.08)	0.840	−0.64 (−2.52, 1.25)	0.508	−0.10 (−2.06, 1.86)	0.922	0.73 (−1.24, 2.70)	0.466
3	94	−1.77 (−4.08, 0.55)	0.134	−2.26 (−4.14, −0.38)	0.019	−0.74 (−2.70, 1.21)	0.456	−0.92 (−2.89, 1.04)	0.357
4	94	−1.24 (−3.53, 1.06)	0.292	−2.86 (−4.73, −0.99)	0.003	−0.98 (−2.91, 0.96)	0.324	−1.07 (−3.02, 0.87)	0.279
p-trend[b]		−0.54 (−1.27, 0.19)	0.148	−1.04 (−1.63, −0.44)	0.001	−0.37 (−0.99, 0.24)	0.234	−0.51 (−1.12, 0.11)	0.108
continuous[c]	368	−0.59 (−1.65, 0.48)	0.278	−1.43 (−2.30, −0.56)	0.001	−0.31 (−1.21, 0.60)	0.506	−0.63 (−1.53, 0.27)	0.171
24 months									
BPA quartiles[a]									
1	74	Reference		Reference		Reference		Reference	
2	74	0.81 (−1.51, 3.12)	0.494	1.07 (−1.56, 3.70)	0.423	−0.90 (−3.42, 1.61)	0.481	−0.44 (−3.16, 2.29)	0.753
3	74	−1.05 (−3.37, 1.27)	0.374	2.10 (−0.54, 4.74)	0.119	−1.20 (−3.73, 1.32)	0.351	−0.51 (−3.25, 2.23)	0.715
4	74	0.82 (−1.47, 3.12)	0.480	1.21 (−1.40, 3.81)	0.363	−2.03 (−4.53, 0.46)	0.109	−0.44 (−3.16, 2.29)	0.753
p-trend[b]		0.09 (−0.65, 0.82)	0.816	0.50 (−0.33, 1.34)	0.237	−0.59 (−1.39, 0.20)	0.144	−0.34 (−1.20, 0.52)	0.441
continuous[c]	296	0.24 (−0.82, 1.31)	0.650	0.25 (−0.95, 1.45)	0.681	−1.07 (−2.21, 0.07)	0.066	−0.36 (−1.60, 0.88)	0.564

All estimates are adjusted for child gender, maternal age, maternal education level, household monthly salary, and passive smoking during pregnancy.

[a] Median (range) for Creatinine-adjusted BPA quartiles [μg/g] at 12 months of age: 1st = 0.23 (< LOD to < 0.43), 2nd = 0.73 (0.43 to < 1.14), 3rd = 1.90 (1.14 to < 4.26), 4th = 16.26 (4.26–609.19); at 24 months of age: 1st = 0.27 (< LOD to < 0.47), 2nd = 0.77 (0.47 to < 1.24), 3rd = 2.08 (1.24 to < 4.55), 4th = 18.61 (4.55–609.19).

[b] p-Value for trend across BPA quartiles.

[c] Log10-transformed BPA concentration.

Table 5
Adjusted association between BPA and neurodevelopmental scores at 12 months of age among boys and girls.

	n	Motor domain		Adaptive domain		Language domain		Social Domain	
		β (95% CI)	*p*-Value	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
Boys									
BPA quartiles[a]									
1	36	Reference		Reference		Reference		Reference	
2	52	−0.95 (−4.23, 2.33)	0.571	−1.65 (−4.26, 0.97)	0.217	−1.04 (−3.82, 1.73)	0.462	0.98 (−1.75, 3.72)	0.481
3	51	−1.91 (−5.19, 1.37)	0.253	−3.16 (−5.78, −0.55)	0.018	−1.17 (−3.95, 1.60)	0.406	−0.42 (−3.15, 2.32)	0.766
4	49	−0.95 (−4.23, 2.33)	0.571	−3.03 (−5.68, −0.39)	0.024	−0.29 (−3.09, 2.51)	0.839	0.96 (−1.80, 3.72)	0.495
p-trend[b]		−0.30 (−1.35, 0.75)	0.576	−1.07 (−1.90, −0.24)	0.012	0.01 (−0.90, 0.88)	0.986	0.11 (−0.77, 0.98)	0.811
continuous[c]	188	−0.16 (−1.64, 1.33)	0.835	−1.66 (−2.83, −0.49)	0.006	−0.18 (−1.44, 1.08)	0.778	−0.01 (−1.25, 1.23)	0.987
Girls									
BPA quartiles[a]									
1	56	Reference		Reference		Reference		Reference	
2	40	0.54 (−2.77, 3.85)	0.748	0.17 (−2.60, 2.93)	0.906	0.83 (−1.87, 3.54)	0.546	0.74 (−2.09, 3.56)	0.609
3	41	−2.12 (−5.41, 1.16)	0.205	−1.62 (−4.36, 1.13)	0.249	−0.87 (−3.56, 1.82)	0.525	−1.31 (−4.11, 1.50)	0.361
4	43	−1.83 (−5.02, 1.37)	0.262	−2.92 (−5.59, −0.25)	0.032	−1.91 (−4.52, 0.70)	0.152	−3.03 (−5.75, −0.30)	0.030
p-trend[b]		−0.74 (−1.77, 0.30)	0.161	−0.97 (−1.83, −0.10)	0.028	−0.69 (−1.54,0.15)	0.109	−1.06 (−1.94, −0.18)	0.019
continuous[c]	180	−1.00 (−2.55, 0.56)	0.207	−1.12 (−2.42, 0.19)	0.094	−0.40 (−1.69, 0.88)	0.539	−1.26 (−2.60, 0.07)	0.063

All estimates are adjusted for maternal age, maternal education level, household monthly salary, and passive smoking during pregnancy.
[a] Median (range) for Creatinine-adjusted BPA quartiles [μg/g] at 12 months of age: 1st = 0.23 (< LOD to < 0.43), 2nd = 0.73 (0.43 to < 1.14), 3rd = 1.90 (1.14 to < 4.26), 4th = 16.26 (4.26–609.19).
[b] *p*-Value for trend across BPA quartiles.
[c] log10-transformed BPA concentration.

Table 6
Adjusted association between BPA and neurodevelopmental scores at 24 months of age among boys and girls.

	n	Motor domain		Adaptive domain		Language domain		Social Domain	
		β (95% CI)	*p*-Value	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
Boys									
BPA quartiles[a]									
1	35	Reference		Reference		Reference		Reference	
2	43	1.25 (−1.94, 4.44)	0.443	2.37 (−1.29, 6.03)	0.205	0.33 (−3.17, 3.83)	0.853	1.16 (−2.64, 4.96)	0.549
3	40	−0.93 (−4.16, 2.30)	0.572	2.84 (−0.86, 6.55)	0.133	0.10 (−3.44, 3.64)	0.956	−0.06 (−3.93, 3.80)	0.974
4	34	1.48 (−1.87, 4.83)	0.386	3.00 (−0.85, 6.84)	0.126	−0.18 (−3.86, 3.49)	0.922	0.47 (−3.53, 4.46)	0.819
p-trend[b]		0.17 (−0.94,1.27)	0.769	0.91 (−0.31, 2.13)	0.142	−0.11 (−1.29, 1.06)	0.848	−0.01 (−1.29, 1.27)	0.985
continuous[c]	152	0.05 (−1.57, 1.68)	0.949	1.19 (−0.61, 2.99)	0.192	−0.28 (−2.01, 1.45)	0.749	−0.11 (−2.00, 1.77)	0.905
Girls									
BPA quartiles[a]									
1	39	Reference		Reference		Reference		Reference	
2	31	−0.20 (−3.56, 3.16)	0.906	0.13 (−3.72, 3.98)	0.946	−1.97 (−5.61, 1.67)	0.289	−2.65 (−6.58, 1.28)	0.187
3	34	−1.56 (−4.86, 1.73)	0.352	1.78 (−1.99, 5.56)	0.354	−2.41 (−5.98, 1.16)	0.186	−1.24 (−5.09, 2.61)	0.528
4	40	0.68 (−2.41, 3.77)	0.667	−0.29 (−3.84, 3.25)	0.872	−3.22 (−6.57, 0.13)	0.060	−2.52 (−6.14, 1.09)	0.171
p-trend[b]		−0.03 (−1.04, 0.97)	0.946	0.08 (−1.08,1.25)	0.889	−0.98 (−2.08, 0.11)	0.079	−0.61 (−1.79,0.57)	0.306
continuous[c]	144	0.35 (−1.07, 1.77)	0.625	−0.57 (−2.22, 1.07)	0.493	−1.69 (−3.23, −0.15)	0.032	−0.55 (−2.22, 1.11)	0.512

All estimates are adjusted for maternal age, maternal education level, household monthly salary, and passive smoking during pregnancy.
[a] Median (range) for Creatinine-adjusted BPA quartiles [μg/g] at 24 months of age: 1st = 0.27 (< LOD to < 0.47), 2nd = 0.77 (0.47 to < 1.24), 3rd = 2.08 (1.24 to < 4.55), 4th = 18.61 (4.55–609.19).
[b] *p*-Value for trend across BPA quartiles.
[c] Log10-transformed BPA concentration.

urinary BPA concentrations were positively associated with children externalizing behavior at 2 years of age [n = 249, using the Behavioral Assessment System for Children (BASC-2)], and with more anxious and depressed behavior at 3 years of age. Yolton et al. (2011) did not find significant associations between maternal BPA concentrations and children neurobehavior at 5 weeks of age, but a trend was observed towards greater hypotonia with higher BPA concentrations at 16 weeks of gestation [n = 350, using the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS)]. Kim et al. (2017) reported an adverse association between urinary BPA concentrations and children neurodevelopmental performances at 1–2 years of age [n = 73, using the BSID]. Braun et al. (2017) observed the adverse effects of prenatal urinary BPA concentrations on children social behaviors at 3 years of age [n = 537, using the Social Responsiveness Scale–2 (SRS-2)].

It is worth mentioning that, in the present study, the adverse effects of BPA on child neurodevelopment were not consistent between 12-month-old infants and 24-month-old children. In specific, effects on the adaptive domain and social domain at 12 months were no longer present at 24 months. At 24 months effects were only seen on the language domain among girls. Similar to the present study, Casas et al. (2015) also found prenatal BPA exposure was adversely associated with psychomotor development at 1 year while the association disappeared and even tend to take the opposite direction at 4 years. It is probably due to the relatively small effects of BPA on neurodevelopment as indicated by the effect size (β = −1.43) for the adaptive domain at 12 months. Besides, according to the catch-up growth theory, the growing child could make up for early delays of the development (Tanner et al., 1981). As limited evidence is available, the potential mechanism on the transient effects observed in the present study is unclear and further studies are needed to explore the longitudinal effects of BPA on early

children neurodevelopment.

Potential mechanisms have been put forward regarding the effects of prenatal BPA exposure on childhood neurodevelopment. First, gonadal hormones play an important role in neurodevelopment (Fowden et al., 2009). Due to structural similarity with estrogen and similar binding properties to the nuclear estrogen receptors (ERs), BPA has been reported to affect sex hormonal balances by binding to ERs although the binding capacity being much lower than natural estrogen (Milligan et al., 1998). Besides, the compound has also been found to inhibit key enzymes involved in steroidogenesis (Zhang et al., 2011). Thus, we speculate that the effects of BPA on children's neurodevelopment could be induced by its endocrine disrupting effects. Patisaul et al. (2008)'s study also observed that neonatal exposure to ERβ agonist (including BPA) increased anxiety and aggression in rats. Second, BPA can affect thyroid functions by binding to thyroid receptors (TRs) and subsequently disrupting the thyroid hormones (Somogyi et al., 2016), which play an important role in children's brain development. Some epidemiological studies have shown the association between prenatal BPA concentrations and children thyroid hormones (Romano et al., 2015; Chevrier et al., 2012). Furthermore, it was reported that BPA was capable of inhibiting the synaptogenic response to estradiol, which may be one of the mechanisms of BPA's effect on neurodevelopment (Leranth et al., 2008; Maclusky et al., 2005).

Besides, we observed that prenatal BPA exposure was adversely associated with DQs in the adaptive domain both in boys and girls at 12 months of age. We also found that the association between prenatal BPA exposure and DQs in the social domain at 12 months of age and the language domain at 24 months of age only existed in girls, which indicated that the effect of prenatal BPA exposure on children's neurodevelopment may differ by gender, with girls being more vulnerable than boys. Several studies have also reported gender-specific impacts of prenatal BPA exposure on children's neurodevelopment at early age (0–3 years) (Braun et al. 2009, 2011, 2017; Kim et al., 2017). Kim et al. (2017) observed an adverse association between urinary BPA exposure and child mental developmental index (MDI) scores only among girls at 1–2 years of age. The studies of Braun et al. (2009, 2011) reported an adverse relationship between maternal BPA and children neurodevelopment at 24 and 36 months of age only in girls. However, Braun et al. (2017) found that adverse associations between prenatal BPA concentrations and child behavior were stronger among boys than girls who were 3 years old. Some studies also showed that boys might be more vulnerable at an older age (4–10 years) (Harley et al., 2013; Perera et al. 2012, 2016; Roen et al., 2015). It is worth mentioning that children in the present study were much younger than in studies reporting sex-specific findings only among boys, which implies that the results of these studies might be incomparable with the present study.

The way by which BPA affects children neurodevelopment in a sex-specific manner is still unclear. However, it is well known that the human brain is a sexually dimorphic organ and is regulated by hormones (Bao and Swaab, 2011; Berenbaum and Beltz, 2011), which implies that BPA could affect neurodevelopment between boys and girls differently by impairing the hormonal balances (Cohen-Bendahan et al., 2005). Romano et al. (2015) have shown that prenatal BPA exposure may reduce thyroid stimulating hormone (TSH) among newborn girls but not in boys. As limited evidence is available in regard to the different vulnerability among boys and girls, further explorations are needed. In particular, it is worth exploring whether the sex-specific impacts of prenatal BPA exposure depend on children's age.

There are some strengths in this study. Firstly, this is the first birth cohort study to assess prenatal BPA exposure in relation to early childhood neurodevelopment in Mainland China. Besides, GDS has been widely applied in research and clinical (Liu et al. 2012, 2016a; Tang et al., 2014). Compared with other studies which used behavior measurement with assessment done by parents or teachers, the GDS was completed by a trained pediatrician and therefore this study may have fewer reporting biases. Moreover, in order to comprehensively evaluate the effects of prenatal BPA exposure on early childhood neurodevelopment, we assessed children's neurodevelopment at both 12 and 24 months of age. We observed the effects of BPA on children's neurodevelopment and the effects were different between boys and girls. Despite the small sample size, this research enriched the research evidence regarding the effects of BPA on childhood neurodevelopment.

The study has several limitations. First, it is difficult to accurately measure BPA concentrations throughout pregnancy with a single spot urine sample in late pregnancy due to a short half-life of BPA (Völkel et al., 2017). However, it has been reported that a single measurement of BPA concentrations can be predictive of long-term exposure in the same women (Mahalingaiah et al., 2008), which implies that prenatal BPA exposure remains relatively constant due to the habitual lifestyle and use of similar daily life products during pregnancy. Second, similar to other cohorts, the response rate descended along with the follow ups, which resulted in decreased and varied sample sizes in successive analyses. As no substantial differences were found in sociodemographic characteristics among the cohort study (n = 773), Baseline study (n = 506), First follow-up (n = 368) and Second follow-up (n = 296), the results in the present study were representative of the whole cohort. However, further exploration is needed in larger population. Third, although we controlled many factors (including child gender, maternal age, maternal education level, household monthly salary, and passive smoking during pregnancy) with potential effects on children's neurodevelopment as variables, some other factors that may also be associated to the outcome, such as co-exposure to other EDCs, can affect children neurodevelopment. We tested collinearity between BPA and several kinds of pollutants (including lead, mercury, pyrethroid pesticides, and perfluoroalkyl and polyfluoroalkyl substances) and the collinearity test revealed that potential confounding effects from other pollutants than BPA could be excluded.

5. Conclusions

This is the first study to explore the effect of prenatal BPA exposure on early childhood neurodevelopment in Mainland China. In this study, we found prenatal exposure to BPA with potential adverse impacts on neurodevelopment among children at 12 months of age and among girls at 24 months of age. Moreover, the effects may be gender-dependent. The present study adds to the growing evidence that BPA may effect on neurodevelopment in early childhood.

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