Associations of Bisphenol Exposure With The Risk of Gestational Diabetes Mellitus: A Nested Case-Control Study In Guangxi, China

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Research Article

Abstract

A growing number of epidemiologic studies have estimated the associations between endocrine-disrupting chemicals and gestational diabetes mellitus (GDM). However, reports on the association between bisphenol A (BPA) substitutes and GDM are limited. This investigation aimed to explore the associations of maternal serum BPA, bisphenol B (BPB), bisphenol F (BPF), bisphenol S (BPS), and tetrabromobisphenol A (TBBPA) with the risk of GDM. A nested case-control study was performed among 500 pregnant women. Associations between the serum bisphenol levels and the risk of GDM were assessed by conditional logistic regression analysis and two-mixture modeling approaches (Bayesian kernel machine regression [BKMR] and quantile g-computation). BPA and TBBPA were negatively associated with the risk of GDM in the adjusted models, respectively. Intermediate BPS levels were associated with increased odds (OR: 1.84; 95% CI: 1.04, 3.27) of GDM compared with the low concentration groups only based on the single-bisphenol models. Associations between BPA, BPS, and TBBPA with the risk of GDM were also found in the BKMR analysis. The quantile g-computation (OR: 0.55; 95% CI: 0.43, 0.69) and BKMR models revealed a statistically significant and negative joint effect of the five bisphenols on the risk of GDM. This study demonstrates the association between exposure to BPS with the increased risk of GDM. In addition, exposure to BPA and TBBPA were associated with the reduced risk of GDM. Moreover, exposure to the mixture of the five bisphenols was negatively associated with the risk of GDM.

Introduction

Gestational diabetes mellitus (GDM), which is a common complication during pregnancy, is any degree of glucose intolerance with onset or first recognition during pregnancy (American-Diabetes-Association 2013). GDM can lead to short-term and long-term health effects on mothers and their offspring, especially with a higher risk of obesity and diabetes later in life (Burlina et al. 2019). Thus, finding the potential risk factors for GDM is important. In addition to the traditional risk factors, such as maternal age, obesity, ethnicity, family history of diabetes, and high-carbohydrate diets (Ehrlich et al. 2016, Farahvar et al. 2019), some recent studies have shown that endocrine-disrupting chemicals (EDCs) may play an important role in the incidence and development of GDM (Ehrlich et al. 2016, Filardi et al. 2020, Liu et al. 2018b, Xu et al. 2020).

Bisphenol A (BPA) is an EDC that is widely used in the production of plastic products (Michałowicz 2014) and has been found in various types of human biological samples (Rochester 2013). The effects of BPA on human health have been extensively studied, with its estrogenic activity as one of its best-known outcomes. BPA can interact with estrogen receptors because of its phenolic structure, possibly resulting in estrogenic actions (Konieczna et al. 2015). Some animal studies have suggested that BPA exposure may disrupt glucose homeostasis (Batista et al. 2012, Ding et al. 2014). Previous epidemiological studies have determined a strong association between BPA and type 2 diabetes mellitus (T2DM) (Rancière et al. 2019, Sun et al. 2014). However, results on the relationship between BPA and GDM were inconsistent (Fisher et al. 2018, Hou et al. 2021, Robledo et al. 2013, Shapiro et al. 2015, Wang et al. 2017, Yang et al. 2021, Zhang et al. 2019).

Given the growing concern on the ecological and long-term health implications of bisphenols, new BPA-related chemicals have been considered to be safer alternatives for industrial applications (Owczarek et al.

2018). Considering their structural similarity to BPA, BPA analogues that are used more widely and frequently in daily life may present endocrine-disrupting effects similar to those of BPA (Rochester &Bolden 2015). However, the potential effects of these BPA substitutes on glucose homeostasis are still unclear. Therefore, we conducted a nest case-control study to explore the potential disrupting effects of exposure to bisphenol on glucose metabolism.

We quantified the serum concentrations of five bisphenols, namely, BPA, bisphenol B (BPB), bisphenol F (BPF), bisphenol S (BPS), and tetrabromobisphenol A (TBBPA). To our knowledge, few studies have assessed the associations of bisphenol mixtures with the risk of GDM. In addition to estimating the contributions of individual elements in bisphenol mixtures, exploring the effect of the overall mixture is necessary to understand the impact of bisphenols on the risk of GDM. We used two new statistical approaches known as Bayesian kernel machine regression (BKMR) (Bobb et al. 2018, Bobb et al. 2015) and quantile-based g-computation (Keil et al. 2020) to investigate the effect of the overall mixture.

Methods

Study population

The Guangxi Zhuang Birth Cohort (GZBC) is a prospective and ongoing birth cohort conducted in county-level hospitals of six major counties in Guangxi Province of China from June 2015. The baseline design, inclusion, and exclusion criteria of this cohort had been reported (Liang et al. 2020). The present study is a subset of the GZBC. In this study, women with a history of diabetes mellitus and insufficient serum sample size were excluded. A total of 100 pregnant women diagnosed with GDM were selected. For each subject with GDM, four healthy women without GDM were selected as pair-matched controls (maternal age and fetal sex). All subjects had detailed questionnaire data and medical records. All women gave their informed consent, and the study was approved by the Ethical Committee of Guangxi Medical University (No.20140305-001). After the informed consent form was signed, a standardized structured questionnaire was administered to each participant through an in-person interview to collect information.

GDM diagnosis

Oral glucose tolerance test (OGTT; 75 g) was used to screen for GDM at 24–28 weeks of gestation. GDM was diagnosed according to the Diagnostic Criteria for Gestational Diabetes Mellitus (WS311-2011) released by the Ministry of Health of China, which coincided with the recommendations by the International Association of Diabetes and Pregnancy Study Groups. Pregnant women who met one or more of the following criteria were diagnosed with GDM: (1) fasting blood glucose (FBG) was more than 5.1 mmol/L; (2) 1-hour blood glucose > 10.0 mmol/L; or (3) 2-hour blood glucose > 8.5 mmol/L. The subjects were tested in the morning after an overnight fast of at least 8 h. The first blood sample was taken to measure the FBG before 9 a.m.

Exposure assessment

Spot serum samples collected during the study visits were stored in polypropylene containers at −80 °C until further analysis. Serum bisphenol concentrations were quantified using an ultra-high liquid performance

chromatography-tandem mass spectrometer (UPLC-MS, Waters, USA) with isotope-labeled internal standards as previously described (Liang et al. 2020). Briefly, 500 μL of the serum were spiked with three isotope-labeled internal standards (i.e., BPA-D$_{16}$, BPS-^{13}C$_{12}$, and TBBPA-^{13}C$_{12}$), sodium dihydrogen phosphate dihydrate buffer (pH 5.4), and β-glucuronidase/sulfatase. The mixtures were hydrolyzed and incubated overnight in the dark at 37 °C. After the enzymatic hydrolysis, the solution was extracted twice with 2 mL of the solvent [n-hexane: acetone (7:3, v/v)] and 2 mL of methyl-tert-butyl ether. The supernatants were combined, evaporated until dry at 40 °C, redissolved in 100 μL of methanol: 0.1% ammonia solution (50:50, v/v), and filtered for instrumental analysis. The chromatographic separation was achieved by using an Acquity UPLC BEH C18 (1.7 mm, 2.1 × 100 mm, Waters, USA) analytical column with a mobile phase gradient of ammonia solution and acetonitrile. The bisphenols were detected by using negative-ion electrospray ionization mass spectrometry and multiple reaction monitoring mode. Procedure blank, solvent blank, and calibration standard samples were measured in each batch sample. As previously reported, the limits of detection (LODs) of BPA, BPB, BPF, BPS, and TBBPA were 0.193, 0.232, 0.507, 0.046, and 0.454 ng/mL, respectively (Liang et al. 2020). The determined concentration below the LOD was calculated as the LOD divided by the square root of 2. The resulting quotients were then used in the subsequent data analyses.

Covariates

For each participant, a face-to-face interview was conducted at the hospital by professionally trained interviewers using a standardized and structured questionnaire to collect information, including demography (e.g., age, ethnicity, employment status, and self-reported pre-pregnancy weight) and lifestyles (e.g., drinking and smoking before pregnancy and passive smoking during pregnancy). Moreover, maternal information (e.g., height, parity, gravidity, and pregnancy complications) and birth characteristics (e.g., sex, gestational age, and anthropometric measures) were obtained from the medical data.

Statistical analysis

Summary statistics were calculated and reported as the means ± standard deviation for continuous variables and n (%) for categorical variables in both the GDM and non-GDM groups. Continuous variables were compared using Mann-Whitney U tests, while categorical variables were compared using χ^2 tests. A natural log transformation [ln (X)] was applied to the bisphenols to normalize their distributions. This step stabilized the variances for parametric model assumptions and reduced the influence of extreme values. The distributions of bisphenol concentrations are presented as percentiles and geometric mean. Spearman's rank correlation analysis was used to explore correlations among the serum bisphenol concentrations in the study population.

We categorized participants into tertiles based on the distribution of serum BPA, BPB, BPS, and TBBPA concentrations among the whole population. Given that a high proportion of the samples was below the LOD, BPF with concentrations < LOD were classified into the low-exposure group (Referent), while those with detected concentrations were divided into the middle- (LOD-median) and high-exposure groups (≥ median) based on the median of the detected concentration levels. Conditional logistic regression analysis was employed to evaluate the risk of GDM by a serum bisphenol level, and individual serum bisphenol concentrations were modeled as continuous and categorical variables. Covariates were selected based on

either their biologic plausibility (regardless of statistical significance) or the association with GDM in the bivariate analysis ($P < 0.10$). The crude model was a basic unadjusted model. In the single-bisphenol models, covariates included maternal age, pre-pregnancy body mass index (BMI), area of residence, passive smoking during pregnancy, gravidity, parity, regular exercise, and infant sex. The multi-bisphenol model was aimed to explore the co-exposure effects of bisphenols by considering other bisphenols in one model. The linear P-values were derived by modeling the median value of each category of bisphenol as a continuous variable in the statistical model.

Given the potential effect of pre-pregnancy BMI and difference in fetal sex for the risk of GDM, stratified analyses were performed using pre-pregnancy BMI ($18.5-22.9$, ≥ 23.0 kg/m^2) and infant sex to evaluate the potential effect modification on the association between bisphenols and the risk of GDM. The BMI cut-off point of 23.0 kg/m^2 was selected for overweight subjects, according to a reported optimal cut-off value of BMI for urban Chinese female adults (Zeng et al. 2014).

Considering the possible nonlinearity and nonadditive effects among mixed bisphenols, BKMR (Bobb et al. 2018, Bobb et al. 2015) was used to assess the joint effect of all bisphenols on the risk of GDM, the impact of an individual bisphenol as part of a bisphenol mixture, the nonlinear dose–response effect of these bisphenols and the risk of GDM, and the possible interaction among different bisphenols. Predictors with a posterior inclusion probability (PIP) greater than or equal to 0.5 were considered meaningful (Lebeaux et al. 2020). Quantile-based g-computation (Keil et al. 2020) was used to corroborate the overall effect to compare with results from the BKMR models. Such computation is an adaptation of a mixture modeling method used in environmental epidemiology known as weighted quantile sum regression (Carrico et al. 2015) (WQSR). Compared with the traditional WQSR, quantile g-computation does not require the directional homogeneity of effect estimates. The covariates adjusted in the BKMR and quantile g-computation were the same as those in the single-bisphenol conditional logistic regression analysis. Serum bisphenol levels were ln-transformed in the BKMR and quantile g-computation.

All data were analyzed using R (version3.6.1; R Foundation for Statistical Computing), and a two-sided $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics of the participants are summarized in Table 1. Compared with non-GDM women, pregnant women with GDM have higher rate (33.0% vs. 22.2%) of obesity (BMI ≥ 23 kg/m^2). In addition, pregnant women with GDM were more likely to be primigravida (49.0% vs. 38.3%). No statistically significant differences between groups were observed in terms of maternal age, area of residence, passive smoking during pregnancy, gravidity, regular exercise, and infant sex.

Table 1
Characteristics of the study population according to GDM status.

Characteristic	Cases (n = 100)	Controls (n = 400)	P-value
Age(years)	30.62 ± 6.46	30.6 ± 6.41	0.99
Pre-pregnancy BMI (kg/m^2)			0.03
< 18.5	11 (11.0%)	79 (19.8%)	
18.5-22.99	56 (56.0%)	232 (58.0%)	
≥ 23	33 (33.0%)	89 (22.2%)	
Area of residence			0.76
Urban	9 (9.0%)	40 (10.0%)	
Rural	91 (91.0%)	360 (90.0%)	
Gravidity			0.29
Nulliparous	24 (24.0%)	77 (19.3%)	
Multiparous	76 (76%)	323 (80.7%)	
Parity			0.05
Primigravida	49 (49.0%)	153 (38.3%)	
Multigravida	51 (51.0%)	247 (61.7%)	
Exercise regularly			0.23
Yes	32 (32.0%)	154 (38.5%)	
No	68 (68.0%)	246 (61.5%)	
Passive smoking during pregnancy			0.11
Yes	52 (52.0%)	172 (43.0%)	
No	48 (48.0%)	228 (57.0%)	
Fetal sex			0.82
Male	55 (55.0%)	225 (56.2%)	
Female	45 (45.0%)	175 (43.8%)	

BMI, body mass index; GDM, gestational diabetes mellitus.

P-values estimates were based on Mann-Whitney U tests for continuous variables expressed as Mean ± SD, and Pearson chi-squared test for categorical variables expressed as n (%).

Maternal serum bisphenol levels are shown in Table 2. BPA had the highest detection rate (> LOD) (99.6%), followed by BPB (88.8%), BPS (82.2%), TBBPA (71.4%), and BPF (67.2%). The geometric mean BPA and

TBBPA levels in the participants with GDM were significantly lower than those in the controls ($P < 0.001$ and $P = 0.003$, respectively). BPA also showed the highest geometric mean concentration (4.726 ng/mL), followed by TBBPA (0.783 ng/mL), BPF (0.461 ng/mL), BPB (0.243 ng/mL), and BPS (0.094 ng/mL). Most of the bisphenols were significantly correlated with each other (Spearman correlation coefficients = − 0.27 to 0.32, Fig. S1)

Table 2
Distributions of serum bisphenols concentrations.

Bisphenols	Detection rate	GM	Cases	Controls	P-value	Percentiles (ng/ml)			
	(%)	(ng/ml)	(GM, ng/ml)	(GM, ng/ml)		P25	P50	P75	P95
BPA	99.6	4.726	2.016	5.848	< 0.001	2.463	5.552	10.883	24.201
BPB	88.8	0.243	0.241	0.243	0.298	0.233	0.236	0.269	0.360
BPF	67.2	0.461	0.465	0.46	0.373	<LOD	0.605	0.609	0.625
BPS	82.2	0.094	0.103	0.092	0.075	0.050	0.097	0.107	0.832
TBBPA	71.4	0.783	0.525	0.866	0.003	<LOD	0.511	1.643	7.890

LOD: limit of detection.

Bisphenol concentrations were expressed as percentiles and geometric mean (GM). P-value were derived from Mann-Whitney U tests, to distinguish differences between the two groups.

The associations of bisphenols with GDM are shown in Table 3. In the crude models, the ORs of GDM for a unit increase in the ln-transformed BPA and TBBPA were 0.40 (95% CI: 0.31, 0.51) and 0.67 (95% CI: 0.53, 0.83), respectively. After adjusting for covariates, the associations of bisphenols with GDM remained significant, and the adjusted ORs were 0.42 (95% CI: 0.33, 0.52) and 0.66 (95% CI: 0.52, 0.83) for BPA and TBBPA, respectively. In the multi-bisphenol models, each unit increase in the ln-transformed serum BPA and TBBPA resulted in 63% (95% CI: 0.28, 0.49) and 31% (95% CI: 0.53, 0.90) decrease in the risk of GDM, respectively. The concentrations of bisphenols were classified into categorical variables. Compared with the low-concentration groups, the ORs of GDM were significantly decreased in the medium- (OR = 0.28; 95% CI: 0.16, 0.49 for BPA) and high- (OR = 0.04; 95% CI: 0.02, 0.11 for BPA; OR = 0.42; 95% CI: 0.22, 0.78 for TBBPA) concentration groups in the crude models. In the single-bisphenol and multi-bisphenol models, the associations of BPA and TBBPA with GDM remained significant and negative. In addition, the OR for BPS was significantly increased in the medium-concentration groups (OR = 1.84; 95% CI: 1.04, 3.27) compared with the low-concentration groups in the single-bisphenol models.

Table 3
The association between concentrations of bisphenols and the risk of GDM.

Bisphenols	Cases/Controls	Crude models [a]	Single-bisphenol models [b]	Multiple-bisphenol models [c]
BPA				
Log [BPA]	100/400	0.40 (0.31, 0.51)	0.42 (0.33, 0.52)	0.37 (0.28, 0.49)
Low	64/101	Reference	Reference	Reference
Medium	30/135	0.28 (0.16, 0.49)	0.29 (0.16, 0.53)	0.26 (0.14, 0.49)
High	6/164	0.04 (0.02, 0.11)	0.04 (0.01, 0.10)	0.03 (0.01, 0.09)
P for trend		< 0.01	< 0.01	< 0.01
BPB				
Log [BPB]		0.93 (0.49, 1.79)	0.86 (0.44, 1.70)	0.91 (0.40, 2.06)
Low	33/132	Reference	Reference	Reference
Medium	41/132	1.23 (0.73, 2.08)	1.17 (0.68, 2.03)	1.05 (0.52, 2.14)
High	26/136	0.78 (0.45, 1.38)	0.67 (0.37, 1.22)	1.07 (0.52, 2.22)
P for trend		0.160	0.069	0.892
BPS				
Log [BPS]	100/400	1.09 (0.91, 1.30)	1.07 (0.88, 1.29)	0.95 (0.75, 1.20)
Low	15/132	Reference	Reference	Reference
Medium	45/132	1.71 (0.99, 2.96)	1.84 (1.04, 3.27)	1.63 (0.80, 3.30)
High	40/136	1.68 (0.96, 2.94)	1.69 (0.95, 3.00)	1.25 (0.60, 2.58)
P for trend		0.047	0.045	0.371
BPF				
Log [BPF]	100/400	1.04 (0.67, 1.62)	1.09 (0.67, 1.74)	0.98 (0.58, 1.66)
Low	31/133	Reference	Reference	Reference
Medium	31/127	1.05 (0.61, 1.79)	1.09 (0.62, 1.91)	1.08 (0.56, 2.11)

Bisphenols	Cases/Controls	Crude models [a]	Single-bisphenol models [b]	Multiple-bisphenol models [c]
High	38/140	1.16 (0.69, 1.97)	1.21 (0.70, 2.10)	0.76 (0.38, 1.54)
P for trend		0.671	0.570	0.804
TBBPA				
Log [TBBPA]	100/400	0.67 (0.53, 0.83)	0.66 (0.52, 0.83)	0.69 (0.53, 0.90)
Low	36/129	Reference	Reference	Reference
Medium	45/120	1.41 (0.85, 2.33)	1.31 (0.78, 2.21)	0.70 (0.35, 1.38)
High	19/151	0.42 (0.22, 0.78)	0.42 (0.22, 0.80)	0.39 (0.18, 0.84)
P for trend		< 0.01	< 0.01	< 0.01

[a] Crude model had no adjustment.

[b] Single-bisphenol model was adjusted for maternal age, pre-pregnancy BMI, area of residence, passive smoking during pregnancy, gravidity, parity, exercise regularly, and infant sex.

[c] Multiple-bisphenol model was additionally adjusted for serum levels of the other four metals except for covariates in Single-bisphenol models.

We also explored whether the associations between bisphenols and risk of GDM might be modified by fetal sex (Table S1). Significant results were only observed among women with female fetuses, and the OR for BPS was significantly increased in the high-concentration groups (OR = 2.74; 95% CI: 1.07, 7.47) compared with the low-concentration groups. We also determined whether the bisphenol-GDM associations were modified by pre-pregnancy BMI (Table S2). The OR for BPS was only significantly increased in the high-concentration groups (OR = 2.74; 95% CI: 1.07, 7.47) compared with the low-concentration groups among women with BMI $\geq$ 23.0 kg/m^2, while the per unit increase in the ln-transformed TBBPA was only associated with the risk of GDM among women with normal weight.

We visualized the BKMR model. The overall association between the bisphenol mixture and the risk of GDM is shown in the Fig. 1A. The risk of GDM decreased with the increase in exposure. The change in the ln-transformed BPS concentration from the 25th to the 75th percentile was associated with a significant increase in the risk of GDM, when other bisphenols were fixed at the 25th, 50th, and 75th percentiles. Significant and negative association was observed between the risk of GDM and BPA when all the other bisphenols were fixed at 25th, 50th, and 75th percentiles. TBBPA displayed a significant and negative effect when all the other bisphenols were fixed at the 50th and 75th percentiles (Fig. 1B). The potential nonlinear exposure−response relationships were examined using the BKMR when the levels of the other metals were held at the corresponding median concentration. Suggestion of nonlinear relationships were observed between the risk of GDM and BPA and BPS (Fig. 1C). Furthermore, the BMKR models suggested evidence of

interactions between BPA and TBBPA on the risk of GDM (Fig. 1D). The PIPs using BKMR models are summarized in Table S3.

In general, the quantile g-computation and BKMR models were in agreement that the overall effect estimates of the ln-transformed bisphenols mixtures were associations in the same direction (Figs. 1 and 2). Both mixture models suggested that ln-transformed bisphenols had a negative association with the risk of GDM (quantile g-computation: OR = 0.55; 95% CI: 0.43, 0.69).

Discussion

In the present study, we assessed independent and joint associations between the co-exposure to five bisphenols (BPA, BPB, BPF, BPS, and TBBPA) and the risk of GDM. BPA and TBBPA were associated with a decreased risk of GDM, while BPS increased the risk of GDM. To the best of our knowledge, this study is the first report on the exploration of the associations of BPB and TBBPA with the risk of GDM. We also determined a significant negative joint effect of the mixture of the five bisphenols on the risk of GDM, but BPA and TBBPA appeared to be more important than the other three bisphenols in the mixture. This result was consistent across BKMR, quantile g-computation, and multivariable conditional logistic regression models.

The maternal BPA level in the present study was higher than those previously reported (Fisher et al. 2018, Minatoya et al. 2018, Shekhar et al. 2017, Zhang et al. 2013) but lower than another study in China (Yang et al. 2021). BPS levels in this study were lower than those in some areas in China (Jin et al. 2018, Li et al. 2020). In addition, the determined concentrations of BPF were higher than those reported for Czech (median: 0.28 ng/mL) (Kolatorova Sosvorova et al. 2017) and Poland (median: 0.115 ng/mL) (Owczarek et al. 2018). BPB was previously detected at a low frequency (Cobellis et al. 2009, Jin et al. 2018, Li et al. 2020), contrary to our study, which showed a high detection frequency (88.8%) and the concentrations were higher. The reported TBBPA concentrations in the human serum from Belgium (0.08 ng/mL), Norway (0.005 ng/mL), and China (< LOD) were lower than the observed TBBPA median concentration in this study. The differences might be related to area-specific usage and production of bisphenols, dietary habits, bisphenol contaminations in food or in the aquatic environment, and different national regulations on bisphenols.

Previous epidemiological studies have also examined the associations between individual maternal bisphenol levels and the risk of GDM but mainly focused on BPA. Inconsistent results were obtained. Data from these earlier studies are presented in Table S4 (Fisher et al. 2018, Hou et al. 2021, Robledo et al. 2013, Shapiro et al. 2015, Wang et al. 2017, Yang et al. 2021, Zhang et al. 2019). These reports did not find a positive association between BPA and the risk of GDM. In a Chinese prospective cohort study, maternal urine BPA exposure was associated with a decreased risk of GDM (Wang et al. 2017). Another prospective study from China reported that BPAF and BPS might be potential risk factors of GDM. To the best of our knowledge, the present study is the first to show a significant and positive association between BPS level and the risk of GDM but a negative association between TBBPA level and the risk of GDM. We also determined that serum BPA was associated with a decreased risk of GDM.

The results showed that serum BPA was associated with the decreased risk of GDM. A study from China also reported that exposure to BPA was associated with decreased risk of GDM (Wang et al. 2017). Similar findings were obtained from Mexico, where BPA levels were lower in women with GDM (Martínez-Ibarra et al. 2019). A previous small-sample study has reported that pregnant women with high BPA levels have low ratios of GDM (Robledo et al. 2013). Some studies have shown that 17β-estradiol (E2) and xenoestrogens modulated estrogen receptors (ER) in pancreatic β-cells to prevent T2DM (Liu et al. 2009, Tiano &Mauvais-Jarvis 2012, Tiano et al. 2011). Glucose tolerance could be improved by E2 at low concentrations (10^{-8} M) via the ERα/ERβ and the G-protein coupled ER in rodent models of T2DM (Tiano et al. 2011). Given that BPA has a similar molecular structure to E2, BPA may bind to ERs and act with similar biological effects. Low doses of 1 nM and 10 nM BPA were found to significantly increase insulin content, and 1 nM BPA was equally effective as E2 when intact islets were cultivated in the presence of BPA at concentrations from 0 nM to 1000 nM (Alonso-Magdalena et al. 2005, Soriano et al. 2012). Some vivo experiments have also shown that low-dose BPA in mice led to a rapid increase in the plasma insulin and a significant decrease of glycemia (Batista et al. 2012, Nadal et al. 2009, Nadal et al. 2004). In the current study, TBBPA was also associated with the decreased risk of GDM. Given its structural resemblance to BPA, TBBPA may have an endocrine effect similar to that of BPA (Covaci et al. 2009). A study has reported that exposure to TBBPA significantly increased the expression levels of insulin (Jiang et al. 2019). However, other studies (Bellavia et al. 2018, Chiu et al. 2017) presented contrasting results in which BPA levels were positively associated with blood glucose levels among pregnant women.

We also identified a positive association between BPS and the risk of GDM. A study from China has also reported that BPS was associated with increased fasting plasma glucose (FPG) levels among pregnant women (Zhang et al. 2019). Another study on the French population showed a positive association between exposure to BPS and the incidence of T2DM (Rancière et al. 2019). The disrupting effects of BPS on glucose metabolism was also reported in animal studies (Meng et al. 2018). An experimental study showed that exposure to 1 μg/L and 10 μg/L of BPS reduced the plasma insulin levels in male Zebrafish. Such phenomenon altered the fasting glycemia, impacted the glucose homeostasis, and downregulated the expression of preproinsulin and glucagon genes on the visceral tissue after exposure to BPS (Zhao et al. 2018).

To identify the joint effects and the possible interactions among bisphenols, we used the BKMR method. The results showed a negative joint effect of the mixture of BPA, BPB, BPF, BPS, and TBBPA, and this phenomenon was consistent with that from the quantile g-computation models. This approach could be used to analyze not only the overall effect of a mixture but also the effects of each component and dose–response relationships when other metabolites were fixed a particular percentile (Valeri et al. 2017). The BMKR and quantile g-computation models suggested the negative association of BPA and TBBPA with the risk of GDM and the positive association between BPS and this risk. The results were consistent with the traditional model. We also identified the potential interaction between BPA and TBBPA perhaps because of their similar endocrine effects (Covaci et al. 2009). We also determined that BPA played the most critical role in the decreased risk of GDM under the context of various bisphenols. The other bisphenols showed a low contribution to the joint effect of the five bisphenols on the risk of GDM. We believe that the consistency across multiple modeling types strengthened our results.

In the stratified analysis, we only observed the effect of BPS on the risk of GDM among women with a female fetus. The result was consistent with a previous research (Zhang et al. 2019). The effect of the fetal sex may be related to the different levels of sex hormone in maternal circulations. A previous study has also reported the gender-specific effects of BPS (Wan et al. 2018). In addition, we only observed the effects of BPS among overweight/obese women and those of TBBPA among women with normal weight in the stratified analysis by pre-pregnancy BMI. These phenomena may be due to the high risk to GDM of overweight/obese women (Chu et al. 2007). Synergistic effect may exist between BPS and overweightness/obesity on the risk of GDM in pregnant women, while antagonistic effect may exist between TBBPA and overweightness/obesity.

This study has several strengths. Our prospective study design with a large sample size and mixture modeling approaches enabled us to evaluate individual and joint effects of exposures on the development of GDM. We used two different mixture modeling approaches, namely, BKMR and quantile g-computation, which were appropriate for identifying which bisphenol was the most predictive of the risk of GDM and calculating the overall effect of the mixture. Both approaches largely corroborated each other and generally resembled the results of the more traditional multivariable modeling. These characteristics enhanced our internal validity. Moreover, we explore the association between bisphenol A substitutes and the risk of GDM, thus providing a reference for evaluating the health effects of bisphenols.

Nevertheless, the study also has several limitations. First, the time interval between the baseline measurement of bisphenols and the period of GDM diagnosis was close due to the short duration of the entire pregnancy. Second, diet is an important source of bisphenols (Liu et al. 2018a), and this information was not available in the cohort we investigated. Future studies should further investigate the important source of bisphenols and whether those factors operate as confounders or effect modifiers of the observed associations. In addition, some other known or unknown risk factors for GDM were not considered completely, and this limitation may influence the results of the study.

Conclusion

We assessed the individual, overall, and joint exposure effects of maternal bisphenols on the maternal risk of GDM by using multiple robust statistical techniques. The results showed an inverse association between BPA and TBBPA levels and the risk of GDM. We provided the first evidence that BPS levels were positively associated with the risk of GDM. Exposure to the mixture of five bisphenols was negatively associated with the risk of GDM, and BPA displayed the most significant effect on the risk of GDM. Our findings may have important public health implications and provide a reference for evaluating the health effects of bisphenols. Further epidemiologic and experimental studies are needed to confirm these observations and to investigate the underlying molecular mechanisms.

Declarations

Authorship contribution statement

Peng Tang: Methodology, Formal analysis, Writing- original draft, Visualization. Jun Liang: Methodology, Investigation, Data curation, Validation. Qian Liao: Methodology, Validation, Investigation. Huishen Huang:

Validation, Investigation. Xiaojing Guo: Validation, Investigation. Mengrui Lin: Investigation. Bihu Liu: Investigation. Bincai Wei: Investigation. Xiaoyun Zeng: Writing - review & editing, Supervision. Shun Liu: Writing - review & editing, Supervision. Dongping Huang: Methodology, Writing - review & editing, Supervision, Funding acquisition. Xiaoqiang Qiu: Project administration, Resources, Data curation, Writing - review & editing, Supervision, Funding acquisition.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships.

Ethical approval

All participants were informed at recruitment and they signed an informed consent. Ethics approval was provided by Guangxi Medical University, China (No.20140305-001).

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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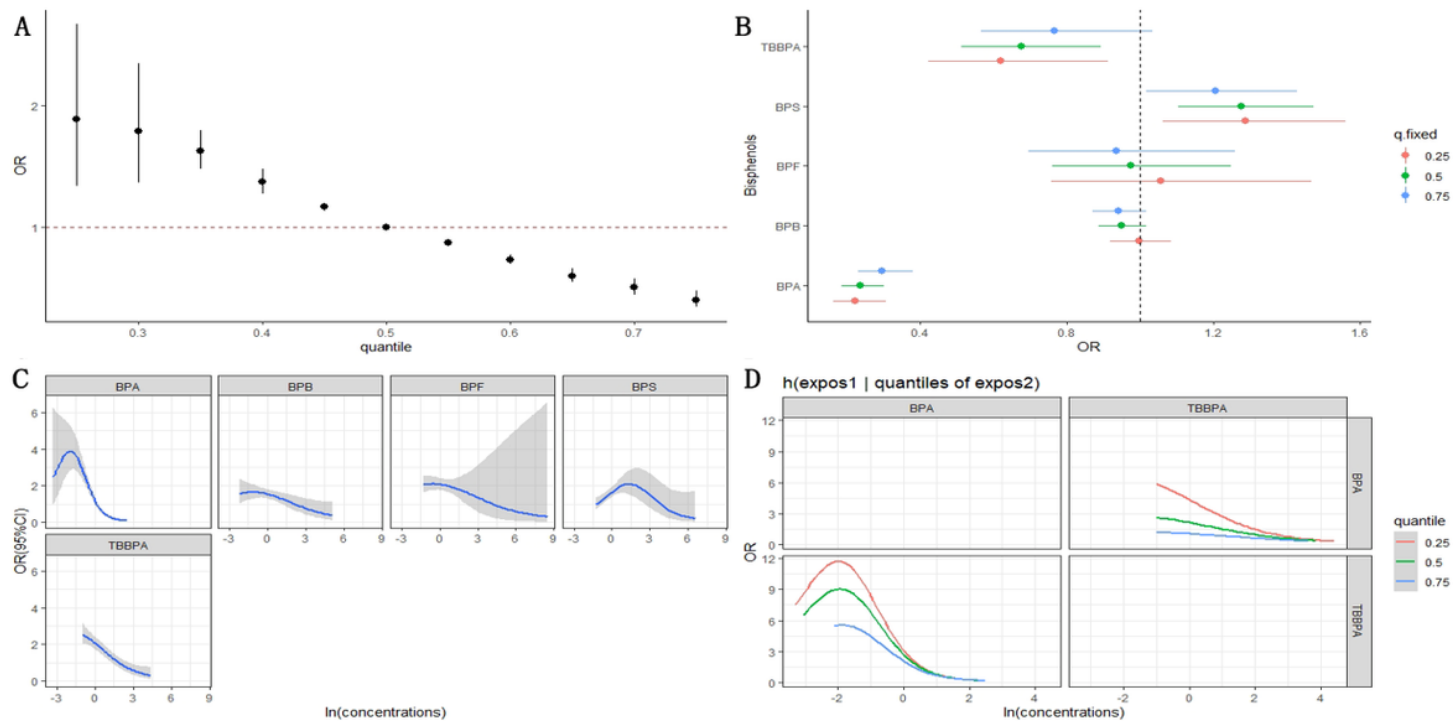
Figures

Figure 1

Associations between serum bisphenol and GDM risk among the study population by BKMR model. (A) The cumulative effect of the serum bisphenols (estimates and 95% credible intervals). Bisphenols are at a particular percentile (X-axis) compared to when exposures are all at 50th percentile. (B) The single-exposure effect (estimates and 95% credible intervals). (C) Univariate exposure response functions and 95% confidence intervals for each bisphenol with the other bisphenols fixed at the median. (D) Bivariate exposure response functions for: BPA when TBBPA fixed at either the 25th, 50th, or 75th percentile and the test of bisphenols is fixed at the median; TBBPA when BPA fixed at either the 25th, 50th, or 75th percentile and the test of bisphenols is fixed at the median.
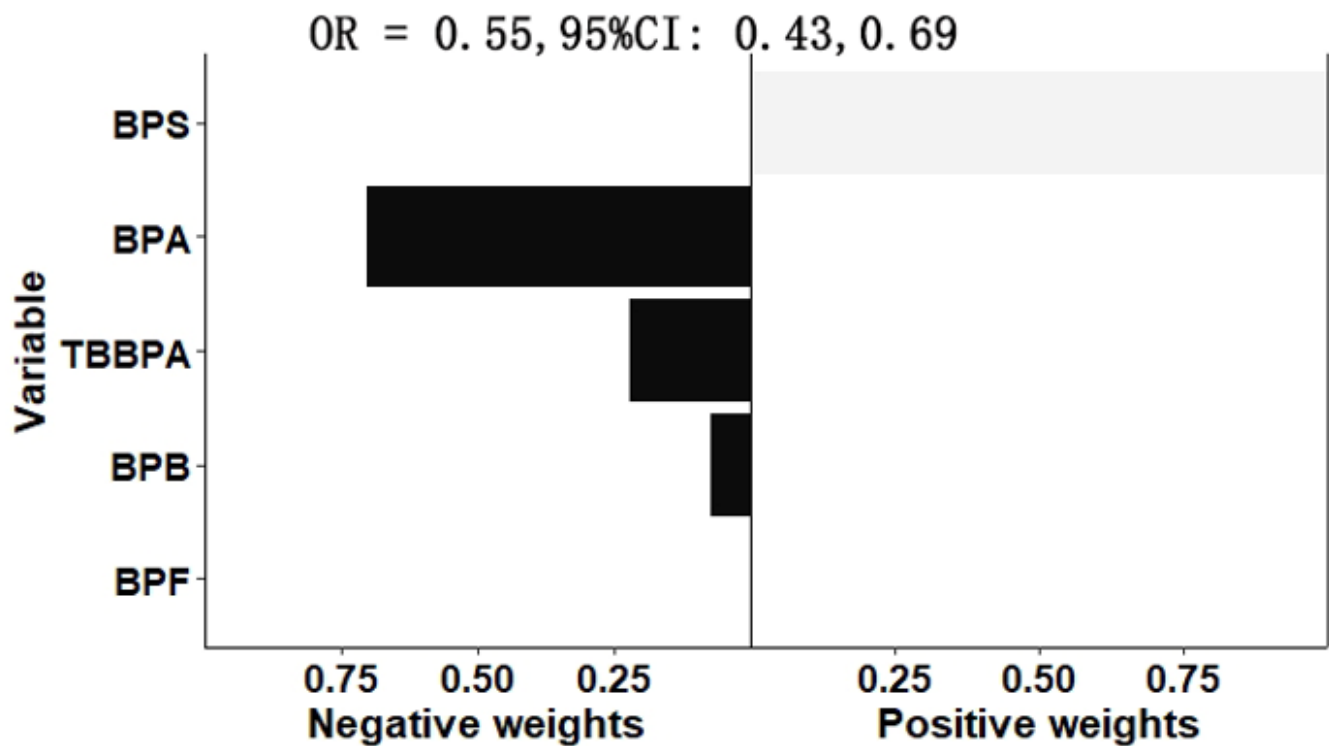
OR = 0.55, 95%CI: 0.43, 0.69

Figure 2

Association between bisphenol composite levels and the risk of GDM using Quantile-based g-computation model. The model runs in a negative direction with respect to GDM risk. Adjusted logistic regression models reveal that the quantile g-computation index predominantly consisted of contributions from BPA and TBBPA associated with decreased odds of GDM. (OR = 0.55, 95% CI: 0.43, 0.69).

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