



# Pregnancy urinary bisphenol-A concentrations and glucose levels across BMI categories

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## ABSTRACT

**Background:** Pregnancy exposure to bisphenol-A (BPA) may be associated with gestational diabetes (GDM), but evidence from human studies is limited. Moreover, adiposity is associated with both higher BPA concentrations and GDM risk, and may act as a confounder or an effect modifier of the association.

**Methods:** We included 350 term births from the Lifecodes pregnancy cohort (Boston, MA), who had 1st and 2nd trimester measures of urinary BPA concentrations available. BPA measures were SG-adjusted and categorized into quartiles (Q). Multivariable-adjusted linear regressions were used to determine the association between BPA, at both 1st and 2nd trimester, and glucose, in the overall population and by categories of 1st trimester BMI. **Results:** No clear associations were seen between BPA and glucose levels in the overall population. From stratified analyses there was suggestive evidence of effect modification by maternal 1st trimester BMI, with significant associations observed among obese/overweight participants (1st trimester BPA concentrations for Q3 vs Q1: adj.  $\beta$  = 14.1 mg/dL; 95% CI: 1.5, 26.6) (2nd trimester BPA concentrations for Q2 vs Q1: adj.  $\beta$  = 16.9 mg/dL; 95% CI: 2.6, 31.2).

**Conclusion:** No associations were found between BPA and glucose levels in the overall population. However, moderately high BPA concentrations were associated with increased glucose levels among overweight/obese women—a subgroup at high-risk of elevated glucose levels in pregnancy.

## 1. Introduction

Gestational diabetes mellitus (GDM) is an increasingly common pregnancy complication affecting ~7% of all pregnancies in the US (Dabelea et al., 2005). Developing GDM during pregnancy is associated with an increased risk of several pregnancy and perinatal complications, and may affect the long-term health of both the mother and the offspring (Fan et al., 2006; Gilmore et al., 2015). Elevated glucose levels in pregnancy, typically assessed through a glucose load test during late second trimester of pregnancy, indicate an insufficient production of insulin and are the first step in GDM diagnosis, when using a two-step screening method for this pregnancy complication (Kjos and Buchanan,

1999). While overt GDM is associated with adverse health outcomes, (Kim et al., 2002; Langer et al., 2005; Yogeve and Visser, 2009) studies also suggest elevated pregnancy glucose levels that do not cross the clinical threshold for GDM diagnosis may also confer an increased risk of adverse pregnancy and delivery outcomes, including high birth weight, (HAPO Study Cooperative Research Group, 2008) pre-eclampsia, (Bryson et al., 2003) and perinatal depression (Huang et al., 2015).

Together with lifestyle factors, environmental chemicals such as endocrine disruptors may be associated with increased glucose levels due to their proposed properties as metabolic disruptors (Heindel et al., 2015; Ehrlich et al., 2016). Bisphenol-A (BPA), in particular, is a widely

**Abbreviations:** BPA, Bisphenol-A; GDM, gestational diabetes mellitus; SG, specific gravity; IGT, impaired glucose tolerance; Q, quartiles

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used chemical for polycarbonate plastics and epoxy resin manufacturing (Vandenberg et al., 2007). Epidemiological evidence suggests that BPA is associated with an increased risk of obesity and diabetes (Sowlat et al., 2016; Stojanoska et al., 2017). Experimental studies have shown that BPA can alter normal pancreatic beta cell function, leading to insulin resistance (Weldingh et al., 2017). Furthermore, BPA has been shown to be associated with inflammation and oxidative stress, (Ferguson et al., 2016) factors that are both associated with insulin resistance and diabetes (Rashid et al., 2010; Stehouwer et al., 2002). With pregnancy being an increasingly insulin resistant state, (Sonagra et al., 2014) identifying potentially modifiable factors that could alter insulin resistance and glucose regulation in pregnancy could offer important information about higher glucose levels and GDM risk in pregnancy (Alonso-Magdalena et al., 2015).

Two epidemiological studies have investigated the association between BPA and clinically-diagnosed GDM risk (Alonso-Magdalena et al., 2015; Robledo et al., 2013) and one study investigated the association between BPA and glucose levels in pregnant populations (Chiu et al., 2017). Shapiro et al. investigated a moderately large population based in Canada, with exposure levels substantially lower than the US population, and found no association between BPA and GDM (Shapiro et al., 2015); Robledo et al. also found no associations, but this study was limited by a small sample size (Robledo et al., 2013); Chiu et al. observed an association between higher BPA concentrations and higher 2nd trimester glucose levels, but evaluated a high-risk population of women with infertility (Chiu et al., 2017). Moreover, there is limited information regarding the impact of BMI on the association between BPA and glucose levels in pregnancy. BMI is positively associated with both higher glucose levels and greater BPA exposures, (Chiu et al., 2017; Chu et al., 2007) and it may operate as a confounder as well as an effect modifier of the association. We hypothesize that BPA concentrations at the beginning of pregnancy may vary across levels of baseline BMI, resulting in different responses in terms of glucose dysregulation.

Therefore, in this study, we investigated women in the LIFECODES pregnancy cohort—a population of women delivering at a single tertiary hospital in Boston—to evaluate the prospective association between urinary BPA concentrations in the first and second trimesters of pregnancy and glucose levels. Furthermore, we investigated the potential role of BMI as a confounder and effect modifier of this association.

## 2. Methods

### 2.1. Study population

Started in 2006, the LIFECODES pregnancy cohort is an ongoing prospective study of pregnant women based at Brigham and Women's Hospital (Boston, MA). Women who are < 15 weeks gestation (median: 9.9 gestation weeks) and pregnant with not > 3 fetuses were recruited within the first trimester of pregnancy. Utilizing a self-administrated questionnaire, study participants reported information on socio-demographic and lifestyle factors. Urine and blood samples, together with anthropometric measures, were also collected at four time points coinciding with standard prenatal care visits during pregnancy (median: 9.9, 17.3, 26.1, and 35.3 weeks gestation).

Our study was based on a subsample of LIFECODES participants who were included in a nested case-control study conducted between 2006 and 2008, (Ferguson et al., 2014) with a further exclusion of participants who delivered preterm births (< 37 weeks gestation) and did not have available information on urinary BPA concentrations on both first and second study visits. In total, 350 women were included in this study. All women gave their informed consent and the study was approved by the Partners Human Subject Committee at Brigham and Women's Hospital and the University of Michigan's Health Sciences Institutional Review Board.

### 2.2. Outcome

The main outcome of this study was glucose levels from a standard, non-fasting 50-g glucose load test (GLT) administered in the second trimester of pregnancy as a part of the screening test for GDM. This was selected as the primary outcome, since all women sit for this screening test, given that Brigham and Women's Hospital uses the two-step Carpenter-Coustan criteria for diagnosis of GDM (American Diabetes Association, 2014). All women without preexisting diabetes are given a 50-g glucose load at 24–28 weeks gestation (median: 26 weeks gestation). For those women who have glucose levels  $\geq 140$  mg/dL 1-h after the glucose load, additional screening is done to diagnose GDM. We investigated glucose as a continuous outcome, and conducted sensitivity analyses with the binary outcome dichotomized at  $\geq 140$  mg/dL vs < 140 mg/dL, as an indicator of impaired glucose tolerance versus normal levels. We did not evaluate glucose levels for the second step of the GDM screening test, which includes a fasting, 100-g, 3-h oral glucose tolerance test (OGTT), as the number of women previously diagnosed with impaired glucose tolerance was quite small ( $n = 49$ ), and glucose levels from the OGTT was only available for 18 women.

The secondary outcome of this study was 1st trimester BMI, investigated as an independent outcome, as well as a possible effect modifier and confounder of the association between BPA and glucose. All BMI measurements were collected from the medical records of the study participants at the first prenatal clinical visit (median: 9.9 weeks gestation), and calculated, for each study participant, as weight (kg) divided by squared height (meters<sup>2</sup>). Early pregnancy BMI is often used as a proxy for pre-pregnancy BMI, as weight minimally changes during the time period between conception and a first trimester prenatal visit (median: 9.9 weeks gestation in the present study) (Krukowski et al., 2016).

### 2.3. Exposure assessment

From urine samples collected at the above-mentioned 4 time points, the sum of free and conjugated urinary BPA concentrations were measured using a standard protocol from the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, n.d.). In brief, spot urine samples collected during the study visits were stored at  $-80^{\circ}\text{C}$  and analyzed by NSF International (Ann Arbor, MI) using isotope dilution on-line solid phase extraction coupled with high-performance liquid chromatography–tandem mass spectrometry (SPE-HPLC-MS/MS). When detection limits were < LOD (0.4 ng/mL; 16.6% of the total samples), values were assigned by dividing the limit of detection by the square root of two (Hornung and Reed, 1990). Additional details on BPA measurements and analysis in the LIFECODES pregnancy cohort can be found in Cantonwine et al. (2016).

To account for urine dilution, we adjusted all BPA measurements for specific gravity (SG), using the formula  $P_c = P[(1.015-1)/SG-1]$ , where  $P_c$  is the SG-adjusted concentration,  $P$  is the measured urinary concentration, and 1.015 is the median SG over all samples (for both first and second trimester samples). SG-adjustment is used in the LIFECODES pregnancy cohort, as creatinine has been shown to be an unstable marker, being sensitive to the rapid physiologic changes associated with pregnancy (Barr et al., 2005). Inter and intra-variability coefficients for both uncorrected and SG-adjusted samples were similar to those observed in the entire LIFECODES population and previously reported (Cantonwine et al., 2015). After adjustment, three additional women were excluded from the analyses as they reported SG values outside the normal range ( $SG > 1.04$ ) (Boeniger et al., 1993). Given that previous studies have shown possible trimester-specific associations (Chiu et al., 2017), we evaluated the two BPA concentrations that preceded the glucose outcome measurement—one from 1st trimester (median 9.9 weeks gestation) and the other from early 2nd trimester (17.3 weeks gestation). The median differences in time between 1st and

2nd trimester BPA measurements, and later 2nd trimester glucose levels (median: 26 weeks) were 16.1 and 8.7 weeks, respectively.

## 2.4. Covariates

We considered GDM risk factors possibly associated with BPA as potential confounders of the association between BPA and GDM risk factors: maternal age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, other), baseline alcohol consumption during pregnancy (yes/no), baseline smoking status (ever/never), and educational level (college or more vs < college) (Kjos and Buchanan, 1999; DeSisto et al., 2014; Bouthoorn et al., 2015; England et al., 2004; Tobias et al., 2012). In sensitivity analyses we additionally included information on other endocrine disruptors. Specifically, we further adjusted for two urinary phthalate metabolites (mono-ethyl phthalate – MEP; mono-isobutyl phthalate – MiBP) that have been associated with GDM indicators in a previous study from this same population and could therefore confound the association between BPA and glucose (James-Todd et al., 2016).

## 2.5. Statistical analysis

For both time points of exposure assessment, we calculated geometric mean and interquartile ranges for BPA in the overall sample, as well as stratified by 1st trimester BMI and by a proxy of impaired glucose tolerance (i.e. glucose levels from the 50-g glucose load test  $\geq 140$  mg/dL). BPA concentrations in the overall sample were calculated both with and without adjustment for SG. BMI was categorized based on the National Heart Lung and Blood Institute's criteria (BMI < 21.5, 21.5–25,  $> 25$  kg/m<sup>2</sup>). Baseline characteristics are presented for the overall population, as well as stratified by 1st trimester BPA concentration (below and above the geometric mean).

We first investigated the association between urinary BPA concentrations and glucose levels in the overall population. For this, we used multivariable-adjusted linear regression models. To relax the assumption of a linear association between BPA and glucose levels we categorized time-specific urinary BPA concentrations into quartiles and estimated the mean difference in glucose levels for each quartile relative to the lowest quartile of BPA. As a sensitivity analysis, we also used restricted cubic splines to flexibly model the dose–response associations. BPA concentrations from the 1st and 2nd trimesters were independently used in two different linear regression models. These main models were replicated with and without adjustment for 1st trimester BMI to assess the impact of BMI as a confounder of the association. We next included the two measurements of 1st and 2nd trimester-specific BPA into the same statistical model, also including an interaction term, to evaluate potential antagonistic or synergistic behaviors in their combined association. We conducted several sensitivity analyses by replicating the main model further adjusting for the urinary

concentrations of specific phthalate metabolites that are associated with both BPA and glucose (i.e. MEP, MiBP) (James-Todd et al., 2016). We also adjusted for multiple births (1 versus 2–3 fetuses); parity; gestational weight gain (GWG) between the first and second medical visits; as well as included an interaction term between BMI and SG. In addition, we assessed glucose levels as a binary outcome (glucose  $\geq 140$  mg/dL vs < 140 mg/dL). For the latter, we used multivariable-adjusted logistic regression models to estimate the association between BPA concentrations at the two time points and the odds of impaired glucose tolerance (glucose  $\geq 140$  mg/dL).

Next, we investigated the role of 1st trimester BMI as a possible effect modifier of the association between BPA and continuous glucose levels. Effect modification was evaluated by estimating the associations between BPA and glucose levels stratified by categories of 1st trimester BMI. To provide the test for statistical significance of the effect modification, we also included an interaction term for BMI and BPA. As both covariates were categorical, a summary p-value for interaction was calculated by simultaneously testing the dummy variables for all combinations of exposure categories (e.g. underweight BMI vs first quartile BPA; normal BMI vs first quartile BPA).

Finally, as a secondary analysis, we investigated 1st trimester BMI as an independent outcome by assessing its cross-sectional association with 1st trimester BPA. We used linear regression models and flexibly evaluated the continuous exposure by using restricted cubic splines. For this analysis, SG-adjusted BPA concentrations were *log*-transformed due to a pronounced right-skewedness. All analyses were performed in Stata, version 14 (StataCorp, College Station, Texas). Statistical tests were two-tailed and all p-values < 0.05 were regarded to as statistically significant.

## 3. Results

Higher concentrations of 1st trimester BPA were observed among women with lower education, as well as non-Hispanic black and Hispanic women, and women with higher BMI (Table 1). In total, 76 women were underweight and 156 were overweight or obese. Overall, the average glucose level in 2nd trimester was 112 mg/dL (*sd* = 26), with 49 women (17%) with impaired glucose tolerance. Urinary concentrations of BPA in the overall sample were, on average, higher in the first trimester (geometric mean: 1.23  $\mu$ g/L) compared to the second (1.01  $\mu$ g/L). However, this difference was largely attenuated after adjusting for SG. First and second trimester BPA concentrations were higher among obese/overweight women. Second trimester BPA concentrations were lower among women with impaired glucose tolerance (Table 2).

### 3.1. BPA and pregnancy glucose: overall study population

The dose–response associations between BPA concentrations and

**Table 1**  
Baseline characteristics of the study population, overall and by 1st trimester bisphenol-A (BPA) urinary concentration.

Characteristics	Total	BPA < 1.3 $\mu$ g/L <sup>a</sup>	BPA $\geq 1.3$ $\mu$ g/L
N	347	182	165
Maternal age, mean (sd)	32 (6)	33 (5)	31 (6)
Body Mass Index, mean (sd)	25.9 (5.6)	25.3 (5.5)	26.5 (5.7)
Secondary or higher education, n (%)	141 (42)	85 (48)	56 (35)
Race/ethnicity, n (%)			
Non-Hispanic white	205 (59)	120 (66)	85 (52)
Non-Hispanic black	54 (16)	22 (12)	32 (19)
Asians	19 (5)	15 (8)	4 (2)
Hispanic	50 (14)	15 (8)	35 (21)
Other	19 (5)	10 (5)	9 (5)
Alcohol, n(%)	19 (5)	11 (6)	8 (5)
Smoking, n (%)	8 (2)	5 (3)	3 (2)

<sup>a</sup> Geometric mean of BPA in the overall sample.

Table 2

Geometric means, with interquartile range, of bisphenol-A urinary concentration over levels of 1st trimester BMI and 2nd trimester glucose levels<sup>a,b</sup>.

	1st trimester			2nd trimester		
	N	Mean	IQ range	N	Mean	IQ range
Overall sample						
Non SG-adjusted	347	1.23	(0.53, 2.48)	300	1.01	(0.28, 1.99)
SG-adjusted	347	1.3	(0.74, 2.00)	300	1.28	(0.76, 2.09)
1st trimester BMI, kg/m <sup>2</sup>						
< 21.5	76	1.14	(0.70, 1.75)	71	1.04	(0.68, 1.40)
21.5–25	111	1.18	(0.70, 2.09)	101	1.28	(0.84, 2.10)
> 25	156	1.49	(0.94, 2.09)	128	1.44	(0.84, 2.33)
2nd trimester glucose levels, mg/dL						
< 140	246	1.32	(0.77, 2.09)	220	1.27	(0.77, 2.12)
≥ 140	49	1.35	(0.78, 1.67)	41	1.09	(0.84, 1.41)

<sup>a</sup> Numbers in the stratified analyses may not sum up to the total due to missing values in 1st trimester BMI (n = 4) and 2nd trimester glucose level (n = 152).<sup>b</sup> Measurements of SG-adjusted BPA below the limit of detection (LOD) (16.6% of the total sample) were replaced with the LOD divided by the square root of 2.

glucose levels in the overall sample (Table 3, column 1) were described by a U-shape, with higher glucose levels in women with BPA concentrations in the second and third quartiles. Larger differences were seen for early 2nd trimester BPA concentrations (median: 17.3 weeks gestation) and later 2nd trimester glucose levels (median: 26 weeks gestation) (adj.  $\beta$  = 5.9 mg/dL; 95% CI: −2.7, 14.4 – Q1 vs Q2). Additional inclusion of BMI in the model (Table 3, column 2) showed limited evidence of a contribution of this covariate as a confounder of the association, as coefficients were slightly different but in the same direction and of similar size as compared to those previously observed (adj.  $\beta$  = 6.7 mg/dL CI: −1.2, 15.0 – 2nd trimester BPA Q1 vs Q2). When including both 1st and 2nd trimester measurements of BPA in the same model ( $r$  = 0.21), along with their interaction, associations were stronger but also presented wider confidence intervals (Table 3, column 3). We did not find evidence of a significant synergistic or antagonistic effect (p-value for interaction = 0.17). Results were consistent when further adjusting for MEP and MiBP. (Correlations for 1st trimester BPA with 1st trimester MEP and MiBP were  $r$  = 0.18 and  $r$  = 0.16 respectively, and the 2nd trimester BPA with 2nd trimester MEP and MiBP were  $r$  = 0.17 and  $r$  = 0.12, respectively). Consistent results were also observed when adjusting for pregnancies with twins or triplets, parity, and GWG, when taking into account a potential interaction between BMI and SG (p-value for interaction ~0.7), as well as when modeling exposures with restricted cubic splines (data not shown). Findings were also similar when modeling glucose as a binary outcome (Table 4), with no significant associations observed in the adjusted analyses.

### 3.2. BPA and pregnancy glucose: stratified by 1st trimester maternal BMI

Stratified analyses suggested different associations between BPA and glucose levels based on 1st trimester maternal BMI (Table 3, columns 4–6). When restricting the analyses to overweight/obese participants, higher glucose levels were observed among participants with higher BPA concentrations in 1st trimester (adj.  $\beta$  for Q2 vs Q1 = 11.6 mg/dL; 95% CI: −1.2, 24.4 and adj.  $\beta$  for Q3 vs Q1 = 14.1 mg/dL; 95% CI: 1.5, 26.6). Women with moderately higher concentrations of BPA in 2nd trimester also had higher glucose levels (adj.  $\beta$  for Q2 vs Q1 = 16.9 mg/dL; 95% CI: 2.6, 31.2 and adj.  $\beta$  for Q3 vs Q1 = 8.9 mg/dL; 95% CI: −4.5, 22.3, respectively). On the other hand, underweight and normal-weight women had somewhat lower glucose levels at higher BPA concentrations; however, these associations did not reach statistical significance in either of these subgroups. Furthermore, the overall test for interaction between BMI and BPA was not statistically significant (p-value = 0.21, for 1st trimester BPA; 0.11 for 2nd trimester).

### 3.3. BPA and 1st trimester BMI: secondary analysis

As a secondary analysis, we evaluated the association between BPA and 1st trimester BMI, as the latter is a risk factor of pregnancy glucose levels. Higher concentrations of 1st trimester BPA were associated with increased 1st trimester BMI. The association was non-linear, with only BPA concentrations below the median being associated with increased BMI. Compared to women with median BPA, progressively lower concentrations were associated with lower BMI, up to a difference of 3 kg/m<sup>2</sup> ( $\beta$  = −3.1 kg/m<sup>2</sup>; 95% CI: −6.3, 0; comparing lowest and median values) (Fig. 1).

## 4. Discussion

In the present study, moderate/high urinary BPA concentrations during the 1st and 2nd trimesters of pregnancy were associated, in the overall population, with moderate yet non-significant increases in glucose levels. We found suggestive evidence for 1st trimester BMI to be an effect modifier of the associations, with a significant and positive associations between BPA and glucose levels observed only among overweight/obese women. Interestingly, despite the high observed variability, a significant non-linear association was also observed in the cross-sectional comparison between 1st trimester BPA and 1st trimester BMI.

Few studies have investigated pregnancy exposure to BPA and its association with gestational diabetes (GDM) or its risk factors in pregnancy (Robledo et al., 2013; Shapiro et al., 2015; Chiu et al., 2017). Shapiro et al. evaluated clinically-diagnosed GDM in a relatively large pregnancy cohort of > 1000 Canadian women, with BPA concentrations substantially lower than those observed in US populations (Shapiro et al., 2015). The absence of significant association between BPA and GDM in their study may be due to several factors, such as the lower BPA concentrations compared to those observed in the U.S. population, evaluation of the association between 1st trimester (and not 2nd trimester) BPA concentrations with GDM, and potential differences in the BMI distribution. The study from Robledo et al., also assessing clinically-diagnosed GDM, was limited by a very small sample size that may have impacted the power to identify significant results (Robledo et al., 2013). Finally, the recent study by Chiu et al., evaluated BPA and continuous glucose levels at a similar time period to that in the current study (Shapiro et al., 2015). While the study presented a positive association between second trimester BPA and glucose levels, the findings may not be directly comparable to our study, given that the selected population was comprised of women with subfertility who were recruited from a fertility clinic; as such, their baseline risk of GDM and glucose dysregulation were significantly higher (Shapiro et al., 2015; Tobias et al., 2013). Like the Chiu et al. study, we found that the women of highest risk of GDM—those that were overweight/obese—had higher



**Table 3**  
Adjusted<sup>a</sup> differences in late second trimester<sup>b</sup> glucose levels, with 95% confidence intervals, as a function of trimester-specific<sup>c</sup> bisphenol-A urinary concentrations (quartiles of the distribution).

Overall				BMI < 21.5 <sup>d</sup>	21.5 ≤ BMI < 25	BMI ≥ 25
Multivariable adjusted <sup>a</sup>		Multivariable adjusted + BMI	Both in same model with interaction <sup>c</sup>			
Differences in glucose levels relative to Q1, mg/dL (95% CI)						
1st trimester						
Q1 (< 0.78)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
Q2 (0.79–1.31)	1.1 (–6.9, 9.1)	–0.1 (–7.0, 7.8)	9.6 (–5.0, 24.1)	–11.3 (–25.9, 3.3)	4.9 (–9.7, 19.4)	11.6 (–1.2, 24.4)
Q3 (1.32–2.10)	2.4 (–5.7, 10.6)	1.1 (–6.9, 4.0)	8.4 (–7.7, 24.5)	–9.9 (–23.7, 3.8)	–0.6 (–17.7, 16.4)	14.1 (1.5, 26.6)
Q4 (> 2.10)	–2.1 (–10.7, 6.5)	–3.7 (–12.1, 4.8)	7.4 (–15.8, 30.6)	2.0 (–15.6, 19.6)	12.2 (–5.7, 30.2)	4.0 (–8.8, 16.8)
2nd trimester						
Q1 (< 0.76)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
Q2 (0.77–1.28)	5.9 (–2.7, 14.4)	6.7 (–1.2, 15.0)	11.8 (–2.8, 26.5)	–4.8 (–18.3, 8.6)	–0.1 (–15.1, 14.9)	16.9 (2.6, 31.2)
Q3 (1.29–2.13)	2.6 (–6.2, 11.4)	0.7 (–8.0, 9.3)	14.6 (–1.5, 30.6)	–9.2 (–24.6, 6.2)	–9.3 (–25.2, 6.5)	8.9 (–4.5, 22.3)
Q4 (> 2.13)	–1.0 (–10.1, 8.0)	–2.2 (–11.1, 6.8)	7.5 (–11.9, 27.0)	–14.1 (–29.3, 1.0)	–19.1 (–35.1, –3.1)	2.1 (–11.7, 15.8)

<sup>a</sup> Adjusted for maternal age, education, race/ethnicity, alcohol consumption, smoking status.  
<sup>b</sup> (Median for glucose assessment: 26 gestation weeks).  
<sup>c</sup> (Median for 1st and 2nd trimester BPA assessment: 9.9 and 17 gestation weeks, respectively).  
<sup>d</sup> Overall test for interaction between BMI and BPA: p-value = 0.21, for 1st trimester BPA; 0.11 for 2nd trimester.  
<sup>e</sup> Test for interaction between 1st and 2nd trimester BPA: p-value = 0.17.

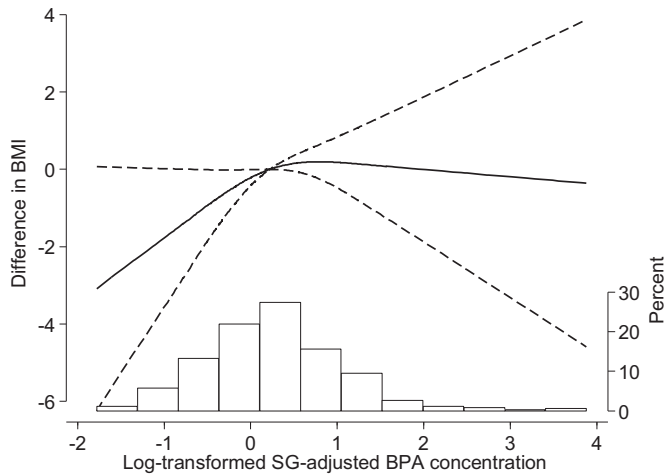
**Table 4**  
Odds ratios of impaired glucose intolerance (glucose ≥ 140 at the 26th week), and 95% CI, as a function of pregnancy bisphenol-A urinary concentration (quartiles of the distribution).

	1st trimester BPA		2nd trimester BPA	
	Unadjusted	Adjusted <sup>a</sup>	Unadjusted	Adjusted <sup>a</sup>
Q1	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Q2	1.01 (0.44, 2.32)	1.13 (0.45, 2.83)	2.71 (1.06, 6.97)	2.60 (0.93, 7.28)
Q3	1.21 (0.54, 2.73)	1.03 (0.40, 2.62)	1.40 (0.50, 3.95)	1.09 (0.35, 3.43)
Q4	0.52 (0.19, 1.46)	0.58 (0.18, 1.83)	0.73 (0.22, 2.43)	0.53 (0.14, 1.99)

<sup>a</sup> Adjusted for maternal age, education, race/ethnicity, alcohol consumption, smoking status.

glucose levels if they had moderate/high BPA concentrations. That said, like the two other published studies, we did not see an association between BPA and glucose levels or impaired glucose tolerance in the overall study population.

On the other hand, none of these previous studies have investigated the contribution of BMI as a possible effect modifier of the association between pregnancy BPA exposure and 2nd trimester glucose levels. BMI was generally evaluated as a confounder of the association (Robledo et al., 2013; Shapiro et al., 2015), and only one study presented the interaction between BMI and BPA as a secondary analysis, but without including a stratified analysis (Chiu et al., 2017). An important contribution of BMI in explaining the association between BPA and glucose is supported by the literature in non-pregnant human populations and animal studies. BPA has been shown to be associated with obesity in both human (Stojanoska et al., 2017; Oppeneer and Robien, 2015; Mirmira and Evans-Molina, 2014; LaKind et al., 2014), and animal studies (García-Arévalo et al., 2016; Yang et al., 2016). Interestingly, a cross-sectional association between first trimester BPA and BMI was confirmed in the present study, with higher BPA concentrations being associated, in a non-linear fashion, with early pregnancy BMI. In addition, being overweight/obese may be both a confounder and an effect modifier of the association. Our study is an attempt to investigate the interplay between pregnancy exposure to BPA and BMI in predicting glucose levels. We found evidence to suggest an association between BPA and glucose that might be dependent on early pregnancy BMI, documenting a positive and significant association only among overweight/obese women. This is possibly due to the fact that higher



**Fig. 1.** Multivariable adjusted differences in 1st trimester BMI as a function of 1st trimester bisphenol-A concentration. The median BPA concentration is taken as reference, and dashed lines represent 95% CI. Adjusted for maternal age, education, race/ethnicity, alcohol consumption, smoking status. The histogram represents the distribution of 1st trimester BPA in the study population.

adiposity levels imply higher levels of circulating estrogen. BPA exposure is known to have an estrogenic effect (Fitzgerald et al., 2015; Sekar et al., 2016; Cao et al., 2017), so that the dysfunction of beta cells associated with BPA (Welding et al., 2017; García-Arévalo et al., 2016; Alonso-Magdalena et al., 2006) could be further exacerbated in overweight/obese women. Such combination would lead to a greater degradation and increasing insulin resistance among overweight and obese women.

This study has several limitations. First, both exposure and outcome measures might be subject to measurement error. In addition, we only used single spot urine samples, given that we opted to evaluate both 1st and 2nd trimester measures of urinary BPA concentrations, as opposed to average concentrations at these two time points. Single spot urine samples may not be able to accurately classify long-term exposure as BPA biologic half-lives are known to be relatively short (Townsend et al., 2013). Second, information on diet is not available in the cohort investigated in this study. As food is a primary source of BPA (LaKind et al., 2014; Geens et al., 2012), future studies should further investigate the role of diet and whether dietary factors operate as confounders or effect modifiers of the observed associations. However, in the study conducted by Chiu et al., additional adjustment for dietary patterns scores (westerns and prudent patterns) did not significantly alter the associations, suggesting that these findings may be robust to additional dietary adjustments (Chiu et al., 2017). Third, it is likely that the study was underpowered to detect significant interaction and clear evidence of effect modification. Fourth, the sample design of the investigated cohort only allowed inclusion of term births. Despite term and preterm births having similar values of BPA exposure (Mirmira and Evans-Molina, 2014), this may limit the generalizability of our findings. Additional characteristics of our cohort such as the high level of education and low prevalence of smoking may also limit the generalizability of our findings. However, our cohort has a median and range of BMI that is similar to other pregnancy cohorts (Oken et al., 2014). Fifth, contrary to the previously published study investigating BPA and glucose levels in pregnancy (Chiu et al., 2017), we had no available information on subfertility status, which may partly explain the different associations observed among overweight/obese women. Sixth, this study was limited by the small number of women with diagnosed GDM, which prevented the evaluation of clinically diagnosed GDM as an independent outcome. Furthermore, we were unable to assess glucose levels from the 3-h fasting OGTT due to the small number of women with this data. However, we were able to utilize data from the standard 50-g GLT that all women take as a part of the GDM screening tests, evaluating both continuous and categorical glucose levels. Finally, while we further adjusted for phthalate metabolites that have been associated with glucose in pregnant population, it is important that future studies investigate mixtures of endocrine disrupting chemicals and their relationship with GDM and its risk factors (i.e. glucose, 1st trimester BMI, etc.) (Taylor et al., 2016). In addition, future studies will need to evaluate potential confounders of the associations unavailable in our data, such as urinary flow rate and time of last void (Hays et al., 2015).

The study also has several strengths. First, the prospective nature of the study with two exposure measurements assessed prior to the glucose levels measured as a part of the GDM screening test strengthens the interpretation of our results and reduces the risk of reverse causation. Also, evaluating BPA at two different time points during pregnancy allows for potential differences in the associations based on timing of exposure, particularly because insulin resistance increases across pregnancy. In fact, previous studies of non-persistent chemicals have found trimester-specific associations with glucose (Chiu et al., 2017; García-Arévalo et al., 2016). The two measures were also investigated in the same model with inclusion of a product term to allow for their potential interaction. Future studies with larger sample sizes should ideally integrate multiple exposure measurements to assess the trajectory of pregnancy BPA exposure as it relates to glucose levels and to the

risk of GDM. Third, we evaluated maternal BMI as a potential effect modifier, which appeared to show differences, with overweight/obese women having increased risk of higher glucose levels in pregnancy, if they had moderate concentrations of BPA.

## 5. Conclusion

In a prospective cohort study of pregnant women, we found urinary concentration of BPA to be associated with higher glucose levels among overweight/obese women, a group known to have a 2-fold increased risk of GDM. We also found BPA to be cross-sectionally associated with higher 1st trimester BMI. Given that GDM is associated with a variety of short- and long-term maternal and child health complications, these findings have potential implications for identification of a modifiable risk factor for a high-risk and increasing subgroup of the population. Future studies will need to confirm these findings and explore whether similar associations exist for the risk of GDM and related outcomes.

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## Conflict of interest

The authors declare no conflict of interest.

## Contribution

AB performed statistical analyses, interpreted the results and wrote the manuscript. RH assisted with interpretation for urinary phthalate metabolite concentrations and manuscript preparation. DC assisted with data collection and cleaning, interpretation of study results, and manuscript preparation. JM obtained funding for urinary phthalate metabolite concentrations for the study, assisted with phthalate metabolite concentration analysis and interpretation and assisted with manuscript preparation. TM provided study population and infrastructure for the Lifecodes pregnancy cohort, assisted with interpretation of results and writing and revisions of the manuscript. EWS assisted with interpretation of results and writing of the manuscript. TJT conceived of the study, assisted with data interpretation, as well as writing and interpretation of the manuscript. All authors read and approved the final manuscript.

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