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# Cadmium Body Burden and Gestational Diabetes Mellitus: A Prospective Study

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**Background:** Several studies have reported that cadmium (Cd) is associated with type 2 diabetes. However, little is known about Cd exposure and the risk of gestational diabetes mellitus (GDM).

**Objective:** We examined the association between Cd body burden in early pregnancy and the risk of GDM.

**Methods:** We conducted a prospective study of 2,026 pregnant women from a single tertiary medical center between 2013 and 2016 in Wuhan, China. Cd body burden was reflected by Cd concentrations in urine samples collected between gestational weeks 8 and 14. GDM was diagnosed according to International Association of Diabetes and Pregnancy Study Groups Consensus Panel (IADPSG) recommendations.

**Results:** The geometric mean of Cd concentrations in maternal urine of all pregnant women was 0.59 μg/L. A total of 198 (9.8%) women were diagnosed with GDM. After adjustment for potential confounders, the risk ratios (RRs) of GDM were 1.04 (95% CI: 0.74, 1.44) for the middle tertile of Cd levels and 1.36 (95%: CI: 0.98, 1.90) for the top tertile compared with the bottom tertile. In addition, we found a significant interaction between fetal sex and maternal Cd levels on the risk of GDM ($p$ for interaction = 0.03). Among women carrying male fetuses, the RR of GDM was 1.86 (95% CI: 1.14, 2.93) for the top tertile of Cd levels compared with the bottom tertile.

**Conclusions:** To our knowledge, this is the first report of an association between urinary Cd levels in early pregnancy and GDM. Our findings suggest that Cd body burden increases the risk of GDM and that the association may be modified by fetal sex. https://doi.org/10.1289/EHP2716

## Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that is first recognized during pregnancy (American Diabetes Association 2011). The prevalence of GDM has been steadily increasing in many countries, including China (Albrecht et al. 2010; Leng et al. 2015). GDM may lead to serious adverse maternal outcomes such as high cesarean section rate and preeclampsia and to detrimental infant outcomes such as macrosomia, infant respiratory distress syndrome, and neonatal hypoglycemia (Poel et al. 2012). GDM also increases the long-term risks of type 2 diabetes mellitus (Bellamy et al. 2009), obesity, and metabolic syndrome for both mothers and infants (Metzger 2007). It is noteworthy that pregnancy women are at high risk of glucose intolerance because of the insulin-desensitizing effects of hormonal products of the placenta (Buchanan and Xiang 2005). Some characteristics such as maternal age and high prepregnancy body mass index (BMI) (Leng et al. 2015) have been well-established as important risk factors. However, there is increasing evidence indicating that GDM might be caused by environmental chemical exposures, which has earned less attention than the traditional risk factors (Ehrlich et al. 2016; Shapiro et al. 2015).

Metals such as cadmium (Cd) and arsenic (As) have been reported to be involved in the etiology of type 2 diabetes or GDM in previous studies (Beck et al. 2017; Edwards and Ackerman 2016; Farzan et al. 2016). Cd is a toxic heavy metal that is widely used in batteries, pigments, coatings and plating, and stabilizers for plastics, among other applications (ATSDR 2012). Cd, which has a high soil-to-plant transfer rate, is easily emitted to the environment by nonferrous metal mining and refining, manufacturing and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal (ATSDR 2012). Cd enters the human body mainly through smoking and food ingestion, and the diet is the main source of environmental Cd exposure in nonsmokers in most parts of the world (Järup and Akesson 2009; Satarug et al. 2010). Absorbed Cd accumulates mainly in the liver and the kidney (Orłowski and Piotrowski 2003) and is primarily eliminated from the body in urine (ATSDR 2012). As is a naturally occurring element that is widely distributed in the earth's crust, and people are exposed to As worldwide (ATSDR 2007). Simultaneous exposure to Cd and As is common in real-world exposure scenarios (Tchounwou et al. 2012). In animal studies, Cd and As have been demonstrated to have diabetogenic effects, such as damage to pancreatic β cells and impairment of insulin secretion (Edwards and Ackerman 2016; Hectors et al. 2011). A growing number of population-based studies have investigated the association between Cd body burden and type 2 diabetes in the general population. Some (Afridi et al. 2008, 2013; Haswell-Elkins et al. 2007; Kolachi et al. 2011; Li et al. 2017; Schwartz et al. 2003; Son et al. 2015; Wallia et al. 2014), but not all (Barregard et al. 2013; Liu et al. 2016; Moon 2013; Nie et al. 2016; Swaddiwudhipong et al. 2010, 2012, 2015), studies have suggested that an increased risk of diabetes is associated with higher Cd exposure. However, evidence regarding the association of Cd body burden with GDM is limited. Only two previous studies have investigated the association between Cd and GDM: A nested case–control study in China suggested that Cd residues in meconium, which were measured after delivery, were associated with GDM risk (Peng et al. 2015), but a study from Canada using Cd levels in maternal blood collected in the first trimester did not find such an association (Shapiro et al. 2015). However, the Cd concentration in blood is believed to reflect recent exposure, whereas urinary Cd more approximately reflects total body burden; the half-life of Cd is 6–38 y (ATSDR 2012). Evidence from epidemiologic studies has

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also suggested the association of GDM with As exposure (Ettinger et al. 2009; Farzan et al. 2016; Peng et al. 2015), even at relatively low exposure levels (Shapiro et al. 2015).

In the present study, we collected early-pregnancy urine samples from 2,026 pregnant women and examined whether an increased risk of GDM was associated with higher urinary Cd levels, which provide a better estimation of Cd body burden. We also investigated whether the association between Cd exposure and GDM was modified by fetal sex because women carrying male fetuses have been reported to have a higher risk of GDM than those carrying female fetuses (Jaskolka et al. 2015). We also examined the potential interaction between Cd and As exposure on GDM.

## Methods

### *Study Population*

The present study was conducted between October 2013 and April 2016 at Wuhan Women and Children's Medical Care Center, a major tertiary medical center in Wuhan, China. A total of 2,592 pregnant women who met the following criteria were recruited: *a*) <16 wk of pregnancy with a singleton gestation at the time of enrollment; *b*) resident of Wuhan City; *c*) willing to have prenatal care and give birth at the study hospital. In this study, five women were excluded because of their family histories of type 2 diabetes, four were excluded because they had type 2 diabetes before pregnancy, 338 were excluded because they did not donate urine samples, and 219 were excluded because they did not take oral glucose tolerance tests (OGTTs). We only included the first delivery records for women who had two separate deliveries. All participants provided written informed consent at enrollment. The research protocol was approved by the ethics committees of Tongji Medical College, Huazhong University of Science and Technology [No. (2012)07], and Wuhan Women and Children's Medical Care Center (No. 2012003).

### *Urine Sample Collection and Cd Measurements*

Spot urine samples were collected at 13 wk of gestation, on average [range 8–14 wk, standard deviation (SD) = 0.68], and stored in polypropylene tubes at −20°C for further analysis. Urinary Cd levels were determined by inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7700, Agilent Technologies). Urinary total As levels were also measured. Urine samples were brought to room temperature (20–25°C) before analysis. After being thoroughly vortex mixed, urine samples were acidified with 1.2% (v/v) nitric acid ($HNO_3$). The resulting samples were digested at 40°C for 1 h, and then Cd and As were analyzed. The operating parameters for ICP-MS were as follows: radio frequency (RF) power, 1,550 W; auxiliary gas flow, 0.8 L/min; carrier gas flow, 0.8 L/min; plasma gas flow, 15.00 L/min; resolution (peak high 10%), 0.65–0.80 amu; sample uptake rate, 0.4 mL/min; unimodal residence time, 0.99 s; repetitions, 3 times.

We implemented stringent laboratory quality controls to ensure the accuracy of the analyses. An external quality-control sample (SRM2670a Toxic Elements in Urine, a standard reference material from the National Institute of Standards and Technology, Gaithersburg, MD, USA) was analyzed with every batch to improve the accuracy of the measurements, and the concentrations measured were within the certified range (5%). The limit of detection (LOD) values for Cd and As were 0.001 and 0.018 μg/L, respectively. Two samples were below the LOD for Cd, and one sample was below the LOD for As. These three samples were assigned a value of one-half LOD for the analyses. For Cd and As, the between-assay coefficients of variation (CVs) were 0.36% and 0.28%, respectively, and the within-assay CVs were 0.89% and 0.68%, respectively.

Concentrations of Cd and As were adjusted for variation in dilution by urinary specific gravity (SG) according to the following formula: $P_c = P_i[(SG_m - 1)/(SG_i - 1)]$, where $P_c$ = specific gravity (SG) − adjusted metabolite concentration (μg/L), $P_i$ = observed metabolite concentration, $SG_i$ = SG of the urine sample, and $SG_m$ = median SG of the cohort ($SG_m = 1.014$) (Just et al. 2010). SG was measured using a pocket refractometer while preparing urinary samples for Cd and As analysis (Atago PAL-10S; Atago).

### *Data Collection*

Standard face-to-face interviews were conducted by trained nurses within three days before or after delivery to collect information on sociodemographic characteristics (e.g., maternal age, occupation, and education) and lifestyle habits during pregnancy (e.g., smoking, passive smoking, and alcohol consumption). Passive smoking was defined as exposure of nonsmoking women to tobacco smoke during pregnancy (from her family or other people in the household or workplace) (Vardavas et al. 2016). Information on history of pregnancy complications and fetal sex was obtained from medical records. Gestational age was calculated based on the last menstrual period. Prepregnancy BMI was calculated from prepregnancy body weight and height, where self-reported prepregnancy body weight was extracted from records of the first prenatal visit to the hospital, and maternal height was measured using a stadiometer in the hospital.

### *GDM Diagnosis*

One-step GDM screening, using a 75-g OGTT, was routinely administered between gestational weeks 24 and 28 in the study hospital. Women were diagnosed with GDM according to International Association of Diabetes and Pregnancy Study Group (IADPSG) recommendations (American Diabetes Association 2011): fasting plasma glucose (FPG) ≥5.1 mmol/L (≥92 mg/dL), 1-h plasma glucose (1-h PG) ≥10.0 mmol/L (≥180 mg/dL), or 2-h plasma glucose (2-h PG) ≥8.5 mmol/L (≥153 mg/dL).

### *Statistical Analysis*

The distribution of Cd concentrations was examined, and the Wilcoxon rank test was used to compare Cd concentrations between women with and without GDM owing to the left-skewed distribution of Cd concentrations. We compared the frequency distributions of sociodemographic and lifestyle characteristics between women with and without GDM. The associations between risk of GDM and SG-corrected urinary Cd concentrations were evaluated by calculating risk ratios (RRs) and 95% confidence intervals (CIs) using Poisson regression with a robust error variance with generalized estimating equations (GEE) estimation (Zou 2004). Models were fit using SG-corrected urinary Cd concentrations as categorical variables based on tertile distribution of urinary Cd in all women, and the bottom tertile was assigned as the reference. We conducted trend tests using the median value within each tertile of urinary Cd as the score variable and evaluated the statistical significance of this predictor using the Wald test. We further examined the associations between urinary Cd levels [$\log_{10}$-transformed SG-corrected urinary Cd concentrations ($\text{Log}_{10}$-Cd)] and continuous plasma glucose (PG) concentrations (mmol/L) using multiple linear regression. A composite OGTT measure, which was the sum of PG $z$-scores for FPG, 1-h PG, and 2-h PG, was also used as an outcome variable. The $z$-score was calculated by subtracting the mean from each woman's glucose measurements in our study and dividing by the corresponding standard deviation (Lowe et al. 2012). Bivariate

**Table 1.** Selected characteristics of study population [*n* (%)].

| Characteristic | Total ($n = 2,026$) | Non-GDM ($n = 1,828$) | GDM ($n = 198$) | *p*-Value[a] |
|---|---|---|---|---|
| Age (y) | | | | <0.01 |
| <25 | 152 (7.50) | 143 (7.82) | 9 (4.55) | |
| 25–29 | 1,226 (60.52) | 1,125 (61.56) | 101 (51.01) | |
| 30–34 | 526 (25.96) | 464 (25.37) | 62 (31.31) | |
| ≥35 | 122 (6.02) | 96 (5.25) | 26 (13.13) | |
| Prepregnancy BMI ($kg/m^2$) | | | | <0.01 |
| <18.5 | 366 (18.07) | 350 (19.15) | 16 (8.08) | |
| 18.5–23.9 | 1,380 (68.31) | 1,262 (69.04) | 122 (61.62) | |
| ≥24 | 276 (13.62) | 216 (11.81) | 60 (30.30) | |
| Parity | | | | 0.01 |
| Primiparous | 1,763 (87.02) | 1,602 (87.64) | 161 (81.31) | |
| Multiparous | 263 (12.98) | 226 (12.36) | 37 (18.69) | |
| Education | | | | 0.49 |
| More than high school | 1,645 (81.19) | 1,490 (81.51) | 155 (78.28) | |
| High school | 282 (13.92) | 249 (13.62) | 33 (16.67) | |
| Less than high school | 99 (4.89) | 89 (4.87) | 10 (5.05) | |
| Occupation | | | | 0.53 |
| Employed | 1,356 (66.93) | 1,228 (67.18) | 128 (64.65) | |
| Unemployed | 664 (32.77) | 594 (32.49) | 70 (35.35) | |
| Missing | 6 (0.30) | 6 (0.33) | 0 (0.00) | |
| Passive smoking during pregnancy | | | | 0.76 |
| No | 1,450 (71.57) | 1,310 (71.68) | 140 (70.71) | |
| Yes | 574 (28.33) | 516 (28.21) | 58 (29.29) | |
| Missing | 2 (0.1) | 2 (0.11) | 0 (0.0) | |
| Hypertensive disorder in pregnancy | | | | 0.12 |
| No | 1,953 (96.40) | 1,766 (96.61) | 187 (94.44) | |
| Yes | 73 (3.60) | 62 (3.39) | 11 (5.56) | |
| Fetal sex | | | | 0.90 |
| Male | 1,066 (52.62) | 961 (52.57) | 105 (53.03) | |
| Female | 960 (47.38) | 867 (47.43) | 93 (46.97) | |

Note: BMI, body mass index; GDM, gestational diabetes mellitus.
[a]*p*-Values for difference according to chi-squared test.

summary analyses were conducted for all variables. Inclusion of covariates in final multivariable models was based on *a*) covariates associated with GDM in bivariate analyses ($p \leq 0.1$) and *b*) *a priori* knowledge of the associations with Cd levels and GDM.

Maternal age (<25 y, 25–29 y, 30–34 y, ≥35 y), maternal education (more than high school, high school, less than high school), parity (primiparous, multiparous), prepregnancy BMI ($<18.5\,kg/m^2$, $18.5–23.9\,kg/m^2$, $\geq 24.0\,kg/m^2$), hypertensive disorder in pregnancy, fetal sex (Peng et al. 2015), and passive smoking (Shaham et al. 1996) during pregnancy were included in models. Some studies have suggested that As exposure is associated with risk of GDM (Farzan et al. 2016; Shapiro et al. 2015); therefore, we included SG-corrected As levels (<17.12 μg/L SG, 17.12–28.62 μg/L SG, ≥28.62 μg/L SG) in the final models. Because pregnant women with GDM were more likely to be multiparous than non-GDM women in our study ($p = 0.01$, shown in Table 1), we further conducted stratified analyses by parity.

To evaluate the potential effect modification by fetal sex, we used two approaches: *a*) We stratified the models by fetal sex, and *b*) we included an interaction term between Cd and fetal sex in the models, where Cd was modeled in both as tertiles. In addition, because prepregnancy BMI is known to be related to the risk of GDM (Leng et al. 2015), we conducted similar interaction analyses to explore the effect modification of prepregnancy BMI on Cd-GDM association. We assessed the interaction between Cd and As on GDM by including a cross-product term of Cd and As in the model, where Cd and As were categorized into high and low levels based on the median values of their concentrations. Owing to the potential contribution of tobacco smoke to Cd exposure (ATSDR 2012), we also performed a sensitivity analysis excluding women who were exposed to passive smoke during pregnancy. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc.). Two-sided $p < 0.05$ was considered statistically significant. All presented CIs were calculated at the 95% level.

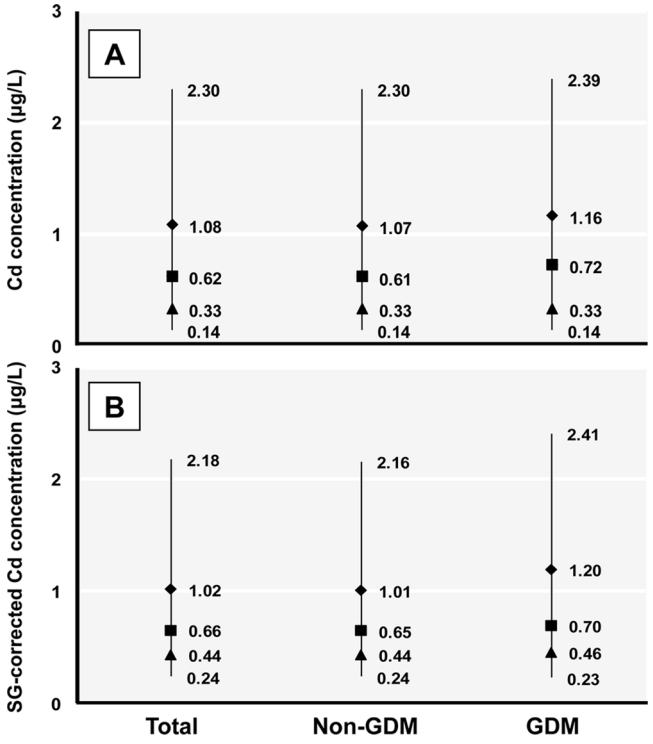


**Figure 1.** Distributions of urinary cadmium (Cd) and specific gravity (SG)-corrected Cd concentrations among total women and women with or without gestational diabetes mellitus (GDM). (*A*) Urinary Cd concentrations; (*B*) SG-corrected Cd concentrations. Squares represent median values. Triangles and diamonds represent the 25th and 75th percentiles. Solid vertical lines span the fifth to 95th percentiles. The geometric means (confidence interval) of Cd and SG-corrected Cd are 0.59 (0.48–0.70) and 0.67(0.58–0.76) μg/L, respectively.

## Results

Among the 2,026 participants, 198 (9.8%) women were diagnosed with GDM. Pregnant women with GDM were older (29.9 vs. 28.5 y), had greater prepregnancy BMI (22.4 vs. $20.8\,kg/m^2$), and were more likely to be multiparous (18.7% vs.12.4%), than the non-GDM women. There were no significant differences between women with and without GDM in educational attainment, occupational status, passive smoking, hypertensive disorder in pregnancy, and fetal sex (Table 1). Six women were missing occupation data, and two women were missing passive smoking data. No women reported smoking or alcohol consumption during pregnancy in this study.

The geometric means (GMs) of Cd and SG-corrected Cd concentrations in maternal urine of all pregnant women were 0.59 μg/L and 0.67 μg/L, respectively (Figure 1). The median value (interquartile range) of urinary Cd concentrations among all women was 0.62 (0.33–1.08) μg/L. There was no significant difference in SG-corrected Cd concentrations between women with (GM = 0.66 μg/L) and without GDM (GM = 0.73 μg/L).

There was a significant increase in the risk of GDM across increasing tertiles of SG-corrected Cd in crude GEE models [crude

**Table 2.** Associations between maternal urinary Cd levels and GDM.

| Cd concentrations (μg/L SG) | GDM/Total | RR (95% CI)[a] | RR (95% CI)[b] |
|---|---|---|---|
| All ($n = 2{,}026$) | | | |
| Low (<0.51) | 56/676 | 1.00 | 1.00 |
| Medium (0.51–0.86) | 62/675 | 1.11 (0.77, 1.59) | 1.04 (0.74, 1.44) |
| High (≥0.86) | 80/675 | 1.43 (1.02, 2.01) | 1.36 (0.98, 1.90) |
| $p$ for trend[c] | | 0.02 | 0.05 |
| Male ($n = 1{,}066$) | | | |
| Low (<0.51) | 25/350 | 1.00 | 1.00 |
| Medium (0.51–0.86) | 31/363 | 1.20 (0.72, 1.98) | 1.14 (0.70, 1.87) |
| High (≥0.86) | 49/353 | 1.94 (1.23, 3.07) | 1.86 (1.14, 2.93) |
| $p$ for trend[c] | | <0.01 | 0.01 |
| Female ($n = 960$) | | | |
| Low (<0.51) | 31/326 | 1.00 | 1.00 |
| Medium (0.51–0.86) | 31/312 | 1.04 (0.65, 1.68) | 0.97 (0.61, 1.55) |
| High (≥0.86) | 31/322 | 1.01 (0.63, 1.63) | 0.98 (0.60, 1.60) |
| $p$ for trend[c] | | 0.99 | 0.94 |
| $p$ for interaction[d] | | 0.05 | 0.03 |

Note: Cd, cadmium; CI, confidence interval; GDM, gestational diabetes mellitus; RR, risk ratio; SG, specific gravity.
[a]Unadjusted risk ratio.
[b]Adjusted for maternal age, education, maternal prepregnancy body mass index (BMI), parity, passive smoking, total arsenic level, and hypertensive disorder in pregnancy. Estimates for all women were also adjusted for fetal sex.
[c]$p$-Values for trend were derived using a continuous variable with the median value of each tertile.
[d]$p$-Values for the interaction term between maternal urinary Cd and fetal sex.

RR: low = 1; medium = 1.11 (95% CI: 0.77, 1.59); high = 1.43 (95% CI: 1.02, 2.01); $p$ for trend = 0.02]. After adjustment for a range of potential confounders (maternal age, maternal education, parity, prepregnancy BMI, hypertensive disorder in pregnancy, passive smoking, and fetal sex), the association between maternal Cd and GDM was slightly attenuated, but it remained borderline significant for the top tertile of Cd [adjusted RR: low = 1; medium = 1.04 (95% CI: 0.74, 1.44); high = 1.36 (95% CI: 0.98, 1.90); $p$ for trend = 0.05] (Table 2).

Given the evidence that fetal sex is associated with risk of GDM, we explored the effect modification by fetal sex on the association between urinary Cd and GDM. Among women carrying male fetuses, the risk of GDM increased with increasing tertiles of Cd [adjusted RR for the top vs. bottom tertile = 1.86 (95% CI: 1.14, 2.93); $p$-trend = 0.01], whereas there was no association between Cd and GDM among women carrying female fetuses [adjusted RR for the top vs. bottom tertile = 0.98 (95% CI: 0.61, 1.60); $p$-trend = 0.94] (Table 2). The interaction between urinary Cd and fetal sex on the risk of GDM was significant ($p$ for interaction = 0.03) (Table 2).

Among women with normal prepregnancy BMI (18.5–23.9 kg/m$^2$, $n = 1{,}384$), adjusted RRs increased with increasing Cd tertile, with a significant association for the top vs. bottom tertile [adjusted RR = 1.62 (95% CI: 1.04, 2.53); $p$-trend = 0.03] (Table 3). Estimates were imprecise for the high-BMI group ($n = 276$) and without a consistent trend [top vs. bottom tertile adjusted RR = 1.14 (95% CI: 0.64, 2.04); $p$-trend = 0.40). The interaction between BMI and Cd was not significant ($p = 0.42$).

We also investigated the association between continuous urinary Cd levels ($Log_{10}$-Cd) and PG concentrations. Among the overall study population, we found significant associations between $Log_{10}$-Cd and 2-h PG [β = 0.18 (95% CI: 0.04, 0.33)], as well as the PG $z$-score sum [β = 0.37 (95% CI: 0.09, 0.64)]. No significant associations were observed between $Log_{10}$-Cd and FPG or 1-h PG. Estimated associations with $Log_{10}$-Cd and 2-h PG or PG $z$-score sum were similar for women carrying male fetuses and women carrying female fetuses, although the estimates were statistically significant only for the larger subgroup of women carrying male fetuses (see Figure S1). When

**Table 3.** Associations between maternal urinary Cd levels and GDM stratified by prepregnancy BMI (kg/m$^2$).

| Cd concentrations (μg/L SG) | GDM/Total | RR (95% CI)[a] | RR (95% CI)[b] |
|---|---|---|---|
| 18.5 < BMI ≤23.9 ($n = 1{,}384$) | | | |
| Low (<0.51) | 31/455 | 1.00 | 1.00 |
| Medium (0.51–0.86) | 39/465 | 1.25 (0.77, 2.04) | 1.21 (0.77, 1.91) |
| High (≥0.86) | 52/464 | 1.73 (1.08, 2.75) | 1.62 (1.04, 2.53) |
| $p$ for trend[c] | | 0.02 | 0.03 |
| BMI ≥24.0 ($n = 276$) | | | |
| Low (<0.51) | 19/88 | 1.00 | 1.00 |
| Medium (0.51–0.86) | 16/90 | 0.82 (0.45, 1.50) | 0.70 (0.39, 1.25) |
| High (≥0.86) | 25/98 | 1.18 (0.70, 1.99) | 1.14 (0.64, 2.04) |
| $p$ for trend[c] | | 0.34 | 0.40 |
| $p$ for interaction[d] | | 0.36 | 0.42 |

Note: BMI, body mass index; Cd, cadmium; CI, confidence interval; GDM, gestational diabetes mellitus; RR, risk ratio; SG, specific gravity.
[a]Unadjusted risk ratio.
[b]Adjusted for maternal age, education, parity, passive smoking, fetal sex, total arsenic level, and hypertensive disorder in pregnancy.
[c]$p$-Values for trend were derived using a continuous variable with the median value of each tertile.
[d]$p$-Values for the interaction term between maternal urinary Cd and prepregnancy BMI.

stratified by prepregnancy BMI, associations between $Log_{10}$-Cd and normal-weight women's 2-h PG and PG $z$-score sum were similar for women with normal and high BMI but were statistically significant only for the larger group of normal-BMI women (see Figure S2).

We also explored whether the Cd-GDM associations were different between nulliparous and multiparous women by stratified analyses. No significant associations of Cd with GDM were found in either stratum. However, the RRs for GDM appeared larger in multiparous women than in nulliparous women (see Table S1). Estimates from a model including a cross-product term for Cd and As were consistent with a synergistic effect (i.e., a stronger association than expected was observed for the combined exposures based on the observed associations with Cd only and As only), although the interaction was not significant ($p = 0.09$) (see Table S2). In the sensitivity analysis that excluded women with passive smoking during pregnancy, the risk of GDM still increased across increasing tertiles of SG-corrected Cd levels, although the associations did not reach statistical significance (see Table S3).

## Discussion

In this study, we observed marginal associations between Cd body burden and the risk of GDM in the overall study population. Among women with male fetuses, the relative risk for those in the top versus bottom tertile of urinary Cd was 1.86 (95% CI: 1.14, 2.93). The association between higher urinary Cd and risk of GDM appeared to be limited to women with normal prepregnancy BMI, although differences between women with high versus normal BMI were not significant.

We are aware of only two published studies addressing the association of Cd exposure with GDM (Peng et al. 2015; Shapiro et al. 2015). Our study is most similar to the study from Canada in its prospective study design (Shapiro et al. 2015). Compared with their population, urinary Cd levels in our population were higher: GM in normal-glucose women = 0.2 μg/L and GM in GDM women = 0.3 μg/L (Shapiro et al. 2015) versus GM in normal-glucose women = 0.66 μg/L and GM in GDM women = 0.73 μg/L (the present study). Although Shapiro et al. (2015) did not suggest an association between blood Cd level in the first trimester and increased risk of GDM, the relationship remained borderline significant after adjustment for confounders

[crude odds ratio (OR) = 2.9 (95% CI: 1.2, 7.0); adjusted OR = 2.5 (95% CI: 1.0, 6.4) for highest vs. lowest quartile]. In the present study, we also found a marginally significant association of Cd level with the risk of GDM after adjustment for confounders. A nested case–control study suggested that Cd residues in meconium were associated with a high risk of GDM [adjusted OR = 16.87 (95% CI: 4.19, 67.86) for the third quartile; adjusted OR = 11.95 (95% CI: 2.97, 48.04) for the highest quartile] (Peng et al. 2015). However, those authors assessed maternal Cd exposure by Cd in meconium, which was measured after the outcome measurement. Moreover, Cd is reported to largely accumulate in the placenta; thus, Cd levels in meconium may not be an accurate reflection of total body burden (Vilahur et al. 2015). In our study, we further examined associations of Cd levels with continuous PG concentrations. Among the three glucose measures (FPG, 1-h PG, and 2-h PG), only 2-h PG had a significant association with Cd level. However, the PG *z*-score sum was also significantly correlated with Cd level. We speculate that might be the case because PG *z*-score sum is a composite measure of PG, to some extent similar to the IADPSG criteria.

More studies have addressed associations of Cd exposure with type 2 diabetes than with GDM. Although study findings are inconsistent, most suggest that Cd exposure would increase the risk of type 2 diabetes. In an analysis of NHANES III (Third National Health and Nutrition Examination Survey, 1988–1994) data, urinary Cd levels were associated with impaired fasting glucose and diabetes in a dose-dependent manner [OR = 1.24 (95% CI: 1.06, 1.45) for the middle versus bottom tertile; OR = 1.45 (95% CI: 1.07, 1.97) for the top versus bottom tertile; $p$ for trend <0.0001] (Schwartz et al. 2003). Another study (Wallia et al. 2014) of NHANES (2005–2010) reached the same conclusion [OR = 1.67 (95% CI: 1.12, 2.47) for the highest quintile of Cd levels]. A recent meta-analysis also supported the positive association between Cd exposure and risk of type 2 diabetes (Li et al. 2017).

Potential mechanisms for associations between Cd and GDM are not clear. Cd is reported to induce pancreatic β-cell death via increased reactive oxygen species (Chang et al. 2013). Notably, β cells normally increase their insulin secretion to compensate for insulin resistance during pregnancy (Buchanan and Xiang 2005). β cells undergo hyperplasia, resulting in increases in both insulin secretion and insulin sensitivity in early pregnancy, followed by progressive insulin resistance. In addition, we found evidence of effect modification on the association between Cd and GDM by fetal sex, and the association was more evident and stronger among women carrying male fetuses. To the best of our knowledge, no other study has explored effect modification on the Cd-GDM association by fetal sex. Women carrying male fetuses have been reported to have lower β-cell function and higher risk of GDM than women carrying female fetuses (Jaskolka et al. 2015; Retnakaran et al. 2015), and it has been proposed that this phenomenon might be explained by differences in the influence of male versus female fetuses on placental secretion of hormones or proteins involved in β-cell compensation (Retnakaran et al. 2015). Given the potential damage to β cells by Cd, we cautiously speculate that pancreatic β cells of women carrying male fetuses might be more vulnerable to Cd exposure. Future studies are needed to clarify the influence of fetal sex on the Cd-GDM relationship, as well as the underlying mechanisms.

Evidence of effect modification by prepregnancy BMI was inconclusive, in part because of the relatively small number of women with high prepregnancy BMI. However, associations between urinary Cd and GDM appeared to be limited to normal-weight women, perhaps as a consequence of the higher baseline risk of GDM in obese women compared with normal weight women, which might negate or obscure a smaller effect of Cd exposure (Li et al. 2014). However, potential differences in the association of Cd with GDM between normal- and high-BMI women need to be confirmed in a larger study population. We also performed sensitivity analyses that excluded women who were exposed to passive smoke during pregnancy. The risk of GDM still increased across increasing Cd tertiles, although the observed associations were weakened and became nonsignificant, which might be due to the reduced sample size; another reason for the weakening of the association might be that the women without passive smoking who remained in the analysis had relatively low Cd exposure. Finally, we found preliminary evidence of a synergistic effect of Cd and As on the risk of GDM. *In vitro*, Cd (Chang et al. 2013; El Muayed et al. 2012) and As (Lu et al. 2011; Yang et al. 2012) have both been shown to cause oxidative stress, impaired glucose-stimulated insulin release, and pancreatic β-cell death, which could lead to diabetes (Edwards and Ackerman 2016). However, although a synergistic effect of As and Cd is plausible, future studies are needed to confirm our findings.

Our study has several strengths. First, this prospective cohort study enabled us to assess Cd exposure during early pregnancy, before the onset of GDM, which helped us to avoid the potential bias caused by misclassification of Cd exposure. Second, urinary Cd provides a better reflection of the Cd body burden than blood Cd. We excluded women with type 2 diabetes, which may lead to diabetes-related changes in renal function, thereby increasing urinary excretion of Cd. Third, the interviews, medical record abstraction, and urinary total As concentration provided extensive data on potential confounders. Nevertheless, our study has some limitations. First, we did not account for the impact of micronutrient (i.e., iron, zinc and calcium) intake because participants' nutritional levels were not registered. Second, the interviews were conducted at delivery, which was after the diagnosis of GDM, which may have led to measurement error in the confounders. Third, although we excluded pregnant women with a family history of diabetes from the study population, the information on family history of diabetes was self-reported and may not have been completely accurate. Finally, some unmeasured or unknown coexposure may contribute to the risk of GDM, although we did control urinary total As.

## Conclusion

Our findings suggest that Cd body burden may be a potential risk factor for GDM and that the association may be modified by fetal sex. However, additional studies are needed to confirm these findings in other study populations.

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