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Sex Hormone-binding Globulin, Cardiometabolic Biomarkers, and Gestational Diabetes: A Longitudinal Study and Meta-analysis

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Abstract

Objective: This study investigated the prospective associations of circulating levels of sex hormone-binding globulin (SHBG) levels with cardiometabolic biomarkers and risk of gestational diabetes (GDM) during pregnancy. It also examines the longitudinal trajectory of SHBG in women with and without GDM.

Methods: We conducted a nested case-control study of 107 incident GDM cases and 214 matched controls within the Eunice Kennedy Shriver National Institute of Child Health and Human Development Fetal Growth Studies-Singleton Cohort. The cohort enrolled non-obese and obese women aged 18–40 years with a singleton pregnancy between 8 and 13 weeks of gestation from 2009 to 2013. GDM was ascertained via medical records review. Blood samples were drawn four times at gestational weeks 10–14, 15–26, 23–31, and 33–39. The prospective associations between SHBG levels and cardiometabolic biomarkers were examined using the Spearman partial correlation among the controls. The longitudinal trajectories of SHBG levels were examined among the cases and the controls. Meta-analysis of prospective studies were performed to examine the association between SHBG levels and GDM risk.

Results: SHBG levels at gestational weeks 10–14 were significantly inversely associated with fasting insulin ($r=-0.17$, $P=0.01$) and insulin resistance as measured by HOMA-IR ($r=-0.17$, $P=0.01$) at gestational week 15–26. SHBG at gestational weeks 10–14 and 15–26 was lower in cases than controls (mean ± standard deviation: (204.0 ± 97.6) *vs*. (220.9 ± 102.5) nmol/L, $P=0.16$ and (305.6 ± 124.3) *vs*. (322.7 ± 105.1) nmol/L, $P=0.14$, respectively), yet the differences were not significant. In the meta-analysis, SHBG was 41.5 nmol/L (95% confidence interval: 23.9, 59.1, $P<0.01$) significantly lower among women with GDM than without, and each 50 nmol/L increase in SHBG was significantly associated with an odds ratio of 0.85 (95% confidence interval: 0.76–0.95, $P=0.01$) for GDM.

Conclusion: Lower SHBG levels in early pregnancy were prospectively associated with higher high insulin levels and insulin resistance in mid-pregnancy and subsequent risk of GDM, independent of adiposity. SHBG may serve as a marker for the identification of high-risk pregnancies during early pregnancy.

Keywords: Diabetes, gestational; Sex binding hormones; Cardiometabolic risk markers; Cohort analysis; Longitudinal measurement; Meta-analysis

Introduction

Sex hormone-binding globulin (SHBG) is classically known as a glycoprotein that binds circulating testosterone and estradiol with high affinity and regulates their bioavailability.[1] Increasing evidence now strongly implicates SHBG in glucose metabolism and the development of type 2 diabetes. In non-pregnant populations, low circulating SHBG levels were consistently associated with hyperinsulinemia,[2] insulin resistance,[3] increased adiposity,[4] and metabolic syndrome,[5] and were predictive of type 2 diabetes.[6,7]

Pregnancy is characterized by a progressive decline in insulin sensitivity that begins near mid-pregnancy, accompanied by a compensatory increase in insulin secretion.[8]

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Exaggerated insulin resistance in pregnancy contributes to gestational diabetes mellitus (GDM),[9] and it may also contribute to gestational hypertension,[10] pre-eclampsia,[10] and adverse perinatal outcomes.[11] During pregnancy, SHBG levels rise dramatically in conjunction with major reproductive hormones.[12] Whether SHBG is involved in the regulation of glucose metabolism during pregnancy remains unclear. Cross-sectional studies conducted in late pregnancy have reported an inverse association of SHBG with fasting insulin,[13–15] and inconsistent associations with insulin resistance[14–16] and fasting glucose[13–16]; prospective studies are still lacking. In addition, although prospective studies have linked lower SHBG levels with higher GDM risk,[17–25] most of these studies did not account for adiposity,[17–21] which is strongly inversely associated with SHBG levels,[4] thus may explain the SHBG-GDM link. Further, because both SHBG levels and glucose metabolism vary over pregnancy, the association between SHBG and GDM may change over time. Only one study including 35 women with GDM has examined SHBG at multiple times during pregnancy.[18] However, its interpretation was limited by a small sample size, and a lack of adjustment for important confounders including body mass index (BMI).

In the current study, we first examined the prospective associations of maternal plasma SHBG levels with a comprehensive panel of cardiometabolic biomarkers (glucose, insulin, C-peptide, homeostasis model of assessment of insulin resistance (HOMA-IR), hemoglobin A1c (HbA1c), C-reactive protein (CRP), cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides). Then, we estimated the longitudinal association of SHBG with GDM risk across the course of pregnancy. Lastly, we performed meta-analysis of the association between SHBG levels and GDM risk using our data and existing prospective studies, with and without adjustment for adiposity.

Material and methods

Study design and population

This study was based on a nested case-control study within the Eunice Kennedy Shriver National Institute of Child Health and Human Development Fetal Growth Studies-Singleton Cohort – a multicenter, multiracial prospective pregnancy cohort. The cohort enrolled 2 334 non-obese and 468 obese women aged 18–40 years with a singleton pregnancy between 8 and 13 weeks of gestation from 2009 to 2013.[26] At enrollment, all women had a gestational age estimated from last menstrual period which was confirmed by ultrasound. Women were excluded if they had pre-existing diabetes, hypertension, or other major chronic conditions. Furthermore, non-obese women were excluded if they had lifestyle risk-factors (used illicit drugs in the past year, smoked in the past 6 months, or consumed at least one alcoholic drink per day in pregnancy), had a history of obstetric complications, or conceived using assisted reproductive technology.[26] Research approval was obtained from the institutional review boards of all participating institutions (Supplemental Digital Content, Table 1, http://links.lww.com/MFM/A4), the methods were carried out in accordance with the relevant guidelines and regulation, and the participants provided written informed consent.

In this study, 107 incident GDM cases were identified via medical record review using the Carpenter and Coustan diagnostic criteria.[27] For each case, two controls without GDM were randomly selected to match with the case on age (±2 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or Asian/Pacific Islander), and gestational week of blood collection (±2 weeks). Thus, a total of 321 women (107 cases and 214 controls) from the original cohort were included in this study. Following a standardized protocol, blood specimens were collected at four study visits at gestational weeks 10–14, 15–26, 23–31, and 33–39, respectively. The blood specimen at 15–26 weeks was collected after an overnight fast. For each study visit, participants were randomized into weekly windows to cover the entire course of pregnancy. All biospecimens were immediately processed and stored at −80°C until thawed for laboratory analysis.

Laboratory tests

For the two study visits before GDM screening (at gestational weeks 10–14 and 15–26), biomarkers were measured in all cases and the two matched controls. For the two visits after GDM screening (at gestational weeks 23–31 and 33–39), they were measured in all cases and one of the two matched controls. SHBG was measured in plasma using a sandwich immunoassay method (Roche Diagnostics, Indianapolis, IN). Fasting glucose, insulin, CRP, and lipids were measured in plasma using hexokinase, immunosorbent, immunoturbidimetric assays and enzymatic assays (Roche Diagnostics), respectively. All assays had inter- and intra-assay coefficients of variation <9% and were performed without knowledge of GDM status in a single certified laboratory.

Covariates

At the enrollment visit (gestational weeks 10–14), women reported their age, race/ethnicity, level of education, marital status, parity, and family history of diabetes in a structured questionnaire. Women in the obese cohort also reported smoking during the 6 months before pregnancy and current alcohol use. Pre-pregnancy BMI (kg/m^2) was calculated from self-reported pre-pregnancy weight and height measured at enrollment. Gestational week at each visit was calculated from the last menstrual period.

Data availability

The data sets generated during and/or analyzed during the current study are available from Eunice Kennedy Shriver National Institute of Child Health and Human Development, but restrictions apply to the availability of these data, and hence they are not publicly available yet.

Statistical analysis

Distributions of participants' characteristics and cardiometabolic markers were compared between cases and

controls using linear mixed-effects regression models for continuous variables and logistic regression with generalized estimating equations for categorical variables, taking account of the matched case-control design.

Correlations between SHBG levels at gestational weeks 10–14 and levels of cardiometabolic markers (fasting glucose, fasting insulin, C-peptide, HOMA-IR, HbA1c, CRP, total cholesterol, HDL, LDL, and triglycerides) at the subsequent visit (weeks 15–26) were estimated using partial Spearman correlation coefficient among controls adjusted for major risk factors of GDM (maternal age (years), gestational week of blood collection (weeks), pre-pregnancy BMI (kg/m^2) and family history of diabetes (yes/no)).

To examine the longitudinal trajectory of SHBG levels during pregnancy, mean values of SHBG at each study visit were plotted for cases and controls separately. They were compared between cases and controls using linear mixed-effects models accounting for the matched case-control design. To examine the prospective association between SHBG levels and GDM risk, odds ratio (*OR*) of GDM associated with SHBG levels at gestational weeks 10–14 and 15–26 were estimated using conditional logistic regression taking account of the matched case-control design, adjusting for major risk factors for GDM. Throughout the analysis to ensure the integrity of the prospective study design, we excluded one GDM case at weeks 10–14 and five GDM cases at weeks 15–26 who had blood samples collected after the diagnosis of GDM. Complete case analysis was used. The analysis were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Meta-analysis of the prospective association between SHBG levels and GDM risk

We conducted a systematic review of the literature to identify all prospective cohort or case-control studies that reported SHBG levels during pregnancy before GDM diagnosis in relation to incident GDM among pregnant women. The search was conducted in PubMed and EMBASE on literature published from January 1966 through August 2017, using keywords and subject headings combining GDM and sex hormone-binding globulin, and restricted to English-language articles and studies of human participants. The search retrieved 211 articles, of which 48 were retained after the title and abstract screening. After full-text review, ten studies were eventually included. Study characteristics and outcome measures (mean SHBG levels in pregnant women with and without GDM, and adjusted *OR* of GDM by SHBG levels) were abstracted using a standard form.

The meta-analysis of our data and existing studies estimated the difference in SHBG levels between women who subsequently developed GDM and those who did not, as well as the adjusted *OR* of GDM associated with SHBG levels across studies. To account for the heterogeneity in study populations and lab measures across studies, the pooled estimates were obtained from random-effects models.[28] In the study by Smirnakis *et al.*[18] and in our study, where two prospective SHBG measures during pregnancy were included, we used the first measure, which was closer in gestational weeks to the rest of the studies (range 5–18 weeks of gestation); this ensured that all data points included in the meta-analysis were independent of each other. Sensitivity analysis using the second measure in these two studies yielded similar results. The meta-analysis were conducted using STATA 14 (StataCorp, College Station, TX, USA).[29]

Results

As shown in Table 1, cases were more likely to have a family history of diabetes and a higher pre-pregnancy BMI compared to controls. At gestational weeks 15–26, they also had higher levels of fasting glucose, insulin, C-peptide, HOMA-IR, HbA1c, CRP, and triglycerides, and lower levels of HDL.

The correlations between SHBG levels at gestational weeks 10–14 and cardiometabolic biomarkers at weeks 15–26 among the controls are shown in Table 2. Higher SHBG levels were significantly associated with lower fasting insulin ($r=-0.17$, $P=0.01$), C-peptide ($r=-0.14$, $P=0.05$), and HOMA-IR ($r=-0.17$, $P=0.01$). Additionally, higher SHBG levels were significantly associated with higher total cholesterol (controls: $r=0.15$, $P=0.03$); they were also associated with higher triglyceride ($r=0.09$, $P=0.20$), HDL ($r=0.11$, $P=0.11$), and LDL ($r=0.11$, $P=0.13$), but the associations were not significant.

The longitudinal trajectory of SHBG levels during pregnancy are shown in Figure 1. SHBG levels increased progressively in both cases and controls over the study visits. SHBG levels were lower among cases compared to controls at weeks 10–14 ((204.0 ± 97.6) *vs.* (220.9 ± 102.5) nmol/L, $P=0.16$) and at weeks 15–26 ((305.6 ± 124.3) *vs.* (322.7 ± 105.1) nmol/L, $P=0.14$), before the screening and diagnosis of GDM, but the differences were not statistically significant. The difference diminished at weeks 23–31 and largely disappeared at weeks 33–39.

The meta-analysis of SHBG levels in pregnant women with and without GDM included 11 prospective studies with a total of 1 063 pregnant women with GDM and 3 098 without GDM. SHBG levels were measured between 5 and 18 weeks of gestation. The characteristics of the studies were shown in Supplemental Digital Content, Table 2 (http://links.lww.com/MFM/A4). The overall pooled estimate showed that mean SHBG levels were 41.5 nmol/L (95% confidence interval: 23.9–59.1) lower in women with GDM than those without (Fig. 2A). Substantial heterogeneity existed among the studies ($Q=162.95$, degree of freedom = 10, $P<0.01$; $I^2=93.9\%$, $P<0.01$). The meta-analysis of the adjusted *OR* of GDM associated with SHBG levels included five studies with a total of 757 pregnant women with GDM and 2 234 without GDM. SHBG levels were measured between 6 and 18 weeks of gestation. All studies adjusted for pre-pregnancy/early pregnancy BMI or another measure of adiposity (Supplemental Digital Content, Table 2, http://links.lww.com/MFM/A4). The pooled estimate showed that each 50 nmol/L increase in SHBG levels was associated with 15% lower GDM risk (*OR*: 0.85, 95% confidence interval: 0.76–0.95) (Fig. 2B). Substantial heterogeneity also existed among these studies ($Q=12.98$, degree of freedom = 4, $P=0.01$; $I^2=69.2\%$, $P=0.01$).

Table 1

Baseline characteristics and cardiometabolic biomarkers among women with GDM and their age- and race-matched controls in the NICHD fetal growth studies, singleton cohort.

Items	GDM cases ($n=107$)	Non-GDM controls ($n=214$)	P^*
Baseline characteristics			
Age (years)	30.5 ± 5.7	30.4 ± 5.4	–
Race/ethnicity, *n* (%)			–
Non-Hispanic white	25 (23.4)	50 (23.4)	
Non-Hispanic black	15 (14.0)	30 (14.0)	
Hispanic	41 (38.3)	82 (38.3)	
Asian/Pacific Islander	26 (24.3)	52 (24.3)	
Education, *n* (%)			0.18
Less than high-school	17 (15.9)	26 (12.1)	
High-school graduate or equivalent	15 (14.0)	23 (10.7)	
More than high-school	75 (70.1)	165 (77.1)	
Married/living with a partner, *n* (%)	92 (86.0)	167 (78.0)	0.12
Nulliparous, *n* (%)	48 (44.9)	96 (44.9)	1.00
Infant sex, *n* (%)			0.71
Male	54 (50.5)	112 (52.3)	
Female	53 (49.5)	100 (46.7)	
Unknown/missing	0 (0.0)	2 (0.9)	
Family history of diabetes, *n* (%)	40 (37.4)	48 (22.4)	<0.01
Pre-pregnancy BMI, *n* (%)			<0.01
<25.0 kg/m^2	37 (34.6)	123 (57.5)	
25.0–29.9 kg/m^2	35 (32.7)	56 (26.2)	
≥ 30.0 kg/m^2	35 (32.7)	33 (15.4)	
Unknown/missing	0 (0.0)	2 (0.9)	
Cardiometabolic biomarkers[†]			
Glucose (mg/dL)	96.8 ± 42.1	86.1 ± 11.4	<0.01
Insulin (pmol/L)	205.8 ± 248.2	117.8 ± 140.7	<0.01
C-peptide (nmol/L)	1.3 ± 0.8	0.9 ± 0.6	<0.01
HOMA-IR	8.5 ± 10.9	4.5 ± 6.3	<0.01
HbA1c (mmol/mol)	32.0 ± 3.0	35.0 ± 5.0	<0.01
HbA1c (%)	5.3 ± 0.5	5.1 ± 0.3	<0.01
CRP (mg/L)	9.2 ± 7.7	6.7 ± 7.0	<0.01
Cholesterol (mg/dL)	182.0 ± 28.9	181.0 ± 31.0	0.78
HDL (mg/dL)	58.9 ± 15.3	64.9 ± 15.5	<0.01
LDL (mg/dL)	90.7 ± 28.2	90.2 ± 26.9	0.88
Triglycerides (mg/dL)	162.4 ± 69.0	129.7 ± 48.1	<0.01

GDM: Gestational diabetes mellitus; NICHD: National Institute of Child Health and Human Development; BMI: Body mass index; HOMA-IR: Homeostasis model of assessment of insulin resistance; HbA1C: Hemoglobin A1c; CRP: C-reactive protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

[*] *P* for differences between cases and controls were obtained by linear mixed-effects models for continuous variables and binomial/multinomial logistic regression with generalized estimating equations for binary/multilevel categorical variables, accounting for matched case-control pairs. Differences in matching variables (age and race/ethnicity) between cases and controls cannot be tested.

[†] Data were available on 104–107 cases and 210–214 controls at gestational weeks 15–26.

–: Not applicable.

Table 2

Spearman partial correlations (*r*) between SHBG levels at gestational weeks 10–14 and cardiometabolic biomarkers at weeks 15–26 among non-GDM controls in the NICHD fetal growth studies-singleton cohort.

Items	r^*	*P*
Fasting glucose	−0.10	0.17
Fasting insulin	−0.17	0.01
C-peptide	−0.14	0.05
HOMA-IR	−0.17	0.01
HbA1c (%)	−0.11	0.11
CRP	−0.02	0.77
Total cholesterol	0.15	0.03
Triglyceride	0.09	0.20
HDL	0.11	0.11
LDL	0.11	0.13

SHBG: Sex hormone-binding globulin; GDM: Gestational diabetes mellitus; NICHD: National Institute of Child Health and Human Development; HOMA-IR: Homeostasis model of assessment of insulin resistance; HbA1C: Hemoglobin A1c; CRP: C-reactive protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

[*] Adjusted for maternal age (years), gestational age (weeks), pre-pregnancy BMI (kg/m^2), and family history of diabetes (yes/no).

Discussion

Our study found SHBG in early pregnancy to be prospectively inversely associated with insulin levels and insulin resistance in mid-pregnancy. In the meta-analysis of the prospective studies including our data, we found significant lower SHBG levels in early and mid-pregnancy among women who subsequently developed GDM compared to those who did not, and we estimated each 50 nmol/L increase in SHBG levels to be significantly associated with 15% reduction of GDM risk independent of adiposity and other major risk factors of GDM.

To our knowledge, the current study is the first on SHBG and cardiometabolic biomarkers with a prospective design and has the largest sample size among existing studies. Existing studies on SHBG and cardiometabolic biomarkers among pregnant women were all cross-sectional in design, where both SHBG and cardiometabolic biomarkers were measured at the time of GDM screening and diagnosis;[13–16,30,31] many of them also did not account for important confounders such as BMI.[13,15,16,30] Our

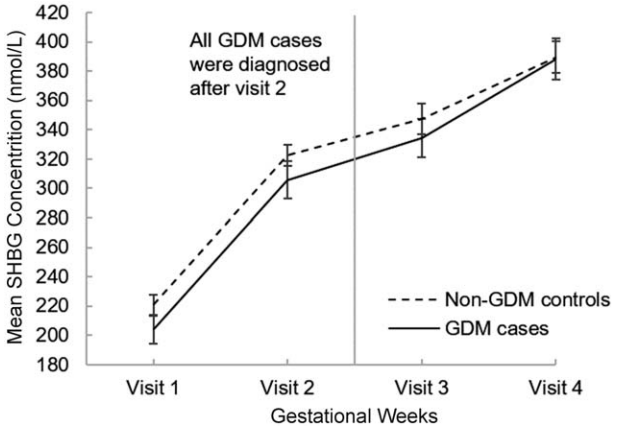

Figure 1. Mean and standard errors of SHBG concentrations at each study visit among GDM cases and non-GDM controls. Visit 1 (weeks 10–14): 104 cases and 214 controls; visit 2 (weeks 15–26): 94 cases and 212 controls; visit 3 (weeks 23–31): 102 cases and 107 controls; visit 4 (weeks 33–39): 88 cases and 103 controls. GDM: Gestational diabetes mellitus; SHBG: Sex hormone-binding globulin.

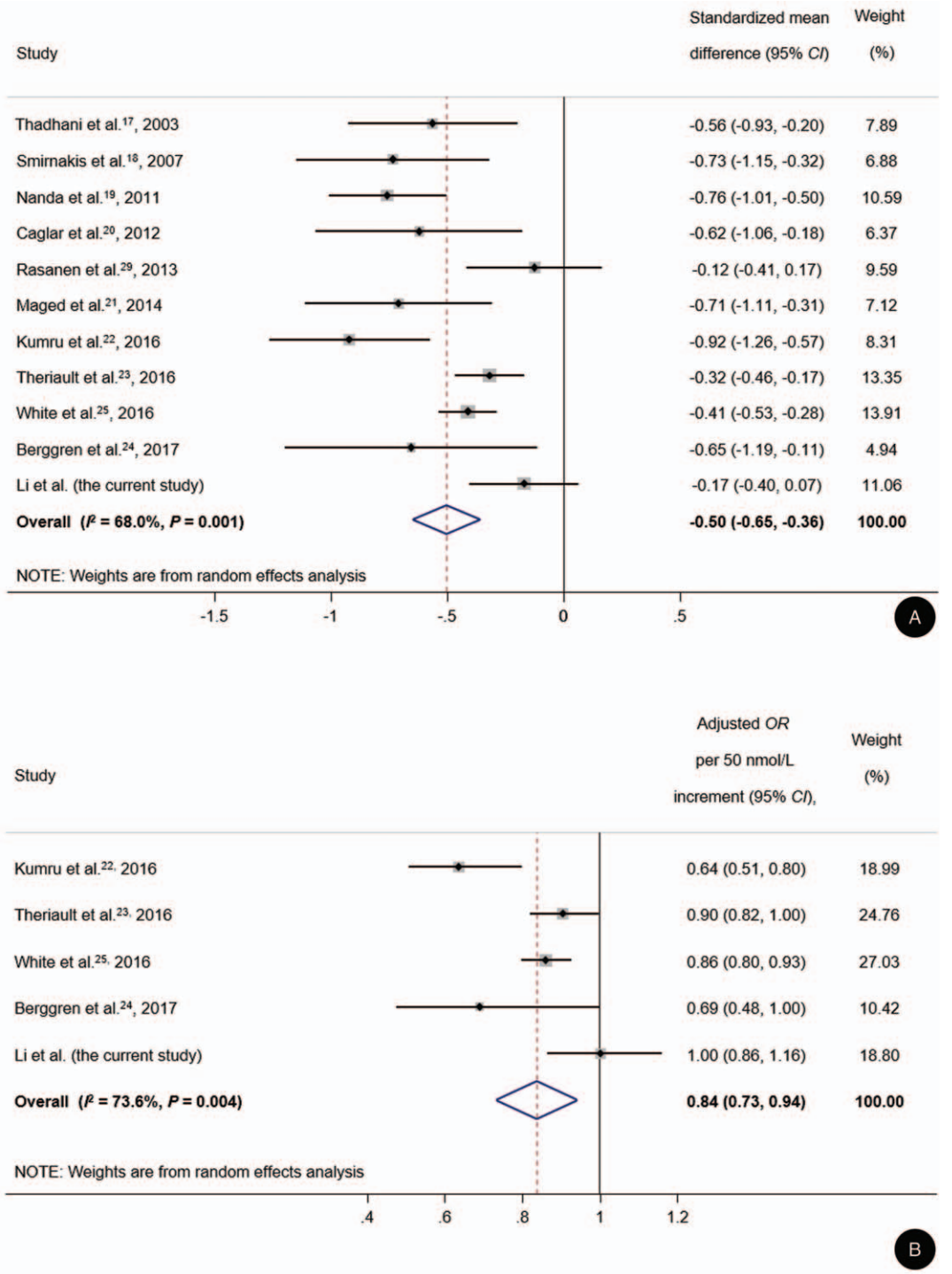

Figure 2. Meta-analysis of the association between SHBG levels and GDM risk. A Forest plot of mean differences in SHBG levels between pregnant women with and without GDM. B Forest plot of a*OR* of GDM associated with per 50 nmol/L increment in SHBG levels. The overall pooled estimate was calculated in a random-effects model. The size of the marker represents the weight each study contributed to the pooled estimate. In A, negative values indicate that SHBG levels were lower in women with GDM, and positive values indicate that SHBG levels were higher in women without GDM. In B, values below 1 indicate that SHBG levels were inversely associated with GDM risk (higher SHBG lower GDM risk), and values above 1 indicate that SHBG levels were positively associated with GDM risk. *CI*: Confidence interval; *OR*: Odds ratio; a*OR*: Adjusted odds ratio; SHBG: Sex hormone-binding globulin; GDM: Gestational diabetes mellitus.

findings of significant inverse associations of SHBG with fasting insulin[13–15] and insulin resistance[14,15] were consistent with most of the existing cross-sectional studies; another study with nonsignificant findings reported associations of the same direction.[16] Our study also found a positive association between SHBG and total cholesterol similar to reported in previous cross-sectional studies,[14,32] but it is not clear if it is driven by LDL or HDL. Pregnancy-related insulin resistance usually arise in the second half of pregnancy.[8] Thus SHBG in early pregnancy may indicate a

background of insulin resistance existing before pregnancy, which can be additive to the insulin resistance arising during pregnancy.[9]

We found suggestive evidence that SHBG levels were lower among cases compared to controls at gestational weeks 10–14 and 15–26. Such difference diminished and disappeared at weeks 23–31 and 33–39, likely because women may have changed their lifestyle or received medications after GDM diagnosis in the late second or early third trimester which improved their SHBG levels.[33] Only one other study has examined SHBG levels multiple times across pregnancy in relation to GDM.[18] Similar to our study, it found SHBG levels at both 11 and 17 weeks of gestation to be significantly lower among women with GDM than those without. Our findings did not reach statistical significance likely because the participants with GDM in our study were relatively healthy – none of them had major chronic conditions or a history of obstetric complications, and the majority were non-obese and did not have unfavorable lifestyle risk factors – thus they may have SHBG levels closer to those without GDM (see the mean SHBG levels by participants' characteristics in Supplemental Digital Content, Table 3, http://links.lww.com/MFM/A4). Indeed, when analyzing the GDM cases separately by severity (treated by insulin/medications *vs.* not treated by insulin/medications), women with severe GDM ($n=28$) had significantly lower SHBG levels at both weeks 10–14 and 15–26 compared to those without GDM, whereas women with non-severe GDM ($n=76$) had SHBG levels similar to those without GDM at both visits (data not shown). Overall, findings from our study and the previous study[18] suggest SHBG during the first and second trimester of pregnancy were consistently associated with subsequent risk of GDM.

In the meta-analysis, we found significantly lower SHBG levels among women subsequently diagnosed with GDM compared to those not diagnosed with GDM. The inverse association between SHBG levels and GDM risk held independent of adiposity and other risk factors of GDM. Previously, one meta-analysis has reported lower SHBG levels in pregnant women with GDM compared to those without.[34] Our study contributed to the evidence of an inverse association between SHBG levels and GDM risk independent of adiposity. This was made possible by including four recent studies, two of which were the largest by far (with several hundred GDM cases), published since the publication of the previous meta-analysis, as well as our own data. Substantial heterogeneity exists across the studies included in the meta-analysis, which may reflect variation in population characteristics, gestational week of blood collection, the laboratory measure of SHBG, or the method of GDM ascertainment.

Several potential mechanisms may explain the inverse associations of SHBG levels with insulin resistance and GDM risk. First, hepatic production of SHBG was downregulated by monosaccharide-induced lipogenesis,[35] linking lower SHBG levels with liver fat content[33] and liver steatosis[36]; ectopic fat deposition in the liver contributes to dyslipidemia[37] and insulin resistance,[38] and subsequently higher GDM risk. Second, SHBG is downregulated by proinflammatory cytokines and upregulated by adiponectin,[39] which is also linked to GDM risk.[40] Although Mendelian randomization studies supported a causal effect of SHBG levels in the development type 2 diabetes,[6,41] mechanisms consistent with a direct involvement of SHBG in the etiology of type 2 diabetes is yet to be discovered.

Our study has several strengths. First, it is the first study to examine the prospective associations between SHBG levels and a comprehensive panel of cardiometabolic biomarkers. Second, it had longitudinal data collection which enabled us to investigate the levels of SHBG across pregnancy in relation to GDM risk. Third, we have controlled for potential confounding from major risk factors of GDM when examining the association of SHBG levels with cardiometabolic biomarkers and GDM risk. Lastly, the study synthesized existing prospective evidence in a meta-analysis of SHBG levels and GDM risk. One limitation of our study was the low-risk profile of our cohort, which may result in limited generalizable to other populations. However, the meta-analysis combined our data with other existing studies that did not have inclusion criteria that select low-risk women, thus may better reflect the association between SHBG and GDM risk in the general population of pregnant women.

In conclusion, this study found higher SHBG levels in early pregnancy to be prospectively inversely associated with insulin levels and insulin resistance in mid-pregnancy. In the meta-analysis of prospective studies, we also found an inverse association between SHBG levels and GDM risk independent of adiposity. As insulin resistance in pregnancy may play a role gestational hypertension and pre-eclampsia,[10] and both GDM[42] and pre-eclampsia[43] are associated with adverse perinatal outcomes, SHBG levels may serve as a marker for identification of high-risk pregnancies in early pregnancy.

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Author Contributions

Meng-Ying Li analyzed data and wrote the first draft of the manuscript. Shristi Rawal contributed to the conceptualization of the study and revised the manuscript Stefanie N. Hinkle contributed to data interpretation and revised the manuscript. Ye-Yi Zhu, Fasil Tekola-Ayele, Michael Y. Tsai, and Si-Min Liu reviewed and revised the manuscript. Cui-Lin Zhang obtained funding, designed and oversaw the study, and revised the manuscript. All authors interpreted the results, revised the manuscript for impor-

tant intellectual content, and approved the final version of the manuscript. Meng-Ying Li and Cui-Lin Zhang are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of Interest

None.

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