Central Obesity Increases the Risk of Gestational Diabetes Partially Through Increasing Insulin Resistance

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Objective: This study examined the associations of central obesity measures, waist to hip ratio (WHR) and waist circumference (WC), in early pregnancy with subsequent risk of gestational diabetes mellitus (GDM) and evaluated the potential mediating role of insulin resistance markers.

Methods: Within the prospective Pregnancy Environment and Lifestyle Study cohort of 1,750 women, WC and hip circumference were measured at gestational weeks 10 to 13. In a nested case-control study within the cohort, 115 GDM cases and 230 controls had fasting serum insulin, homeostatic model assessment of insulin resistance (HOMA-IR), and adiponectin measurements at gestational weeks 16 to 19. Poisson and conditional logistic regression models were used, adjusting for established risk factors for GDM, including prepregnancy overweight or obesity.

Results: For women with WHR < 0.85, one or more established risk factors increased GDM risk 1.99-fold (95% CI: 0.99-4.02). For women with WHR ≥ 0.85 but no established risk factors, GDM risk increased 2.41-fold (95% CI: 1.14-5.06), and in those with established risk factors it increased 6.22-fold (95% CI: 3.49-11.10). Similar but attenuated results were observed for WC ≥ 88 cm. Insulin, HOMA-IR, and adiponectin levels mediated the WHR–GDM association by 9% to 11%; corresponding mediation proportions for the WC–GDM association were 35% to 41% (all $P < 0.04$).

Conclusions: Central obesity in early pregnancy represented a high-risk phenotype for GDM independent of other risk factors, including overweight or obesity, and may inform early screening and prevention strategies.

Introduction

Gestational diabetes mellitus (GDM) has emerged as the most common pregnancy complication, affecting 7% to 17% of pregnancies worldwide (1,2) and representing a growing, urgent public health concern (3). The increasing prevalence of GDM may be fueling the epidemic of adverse sequelaes, including type 2 diabetes and obesity among women and their offspring (4), forming a vicious, intergenerational cycle (5). Moreover, GDM is conventionally screened for and diagnosed at the beginning of the third trimester, leaving little time for effective interventions or treatment, which has further galvanized the need for early identification of women at high risk for GDM. Obesity is a major risk factor for GDM (6). Notably, data are mostly on overall obesity defined based on BMI; however, GDM is also frequently observed in women with a normal BMI (7). Better understanding of the heterogeneous obesity phenotypes, particularly central obesity, in relation to GDM risk may help elucidate the underlying pathophysiology and inform upstream management and preventive strategies to mitigate GDM risk.

Prospective studies have demonstrated that central obesity may increase the risk of cardiovascular diseases, diabetes, and mortality, independent of overall obesity (8-10). However, evidence has been largely confined to nonpregnant individuals. Data on the association between central obesity in early pregnancy and risk of GDM beyond established risk factors, including overall obesity as measured by BMI, are limited, mostly in small-scale studies including 10 to 80 women with GDM (11-14). In particular, waist to hip ratio (WHR) and waist circumference (WC) have been established as simple and less expensive surrogate measures of central obesity.
measures of central obesity with high correlations with intra-abdominal or visceral fat mass (15,16), whereas data on WHR or WC in early pregnancy in relation to GDM risk are scant.

Therefore, in a prospective cohort study of 1,750 multiracial/multiethnic pregnant women, we examined whether central obesity measures WHR and WC in early pregnancy were associated with risk of GDM, independent of overweight/obesity and other established risk factors recommended by existing clinical care guidelines (17,18). Furthermore, in a case-control study nested within the cohort, we assessed the incremental predictive ability of central obesity measures in addition to established risk factors and markers of insulin resistance and explored the mediating role of these markers in the central obesity–GDM risk association to gain pathophysiologic insights.

Methods

Study population and design

The study population was from the Pregnancy Environment and Lifestyle Study (PETALS), a longitudinal cohort of multiracial/multiethnic pregnant women, within which a nested case-control study of GDM etiology is under way. The study design and scope have been described in detail elsewhere (19). The source population was identified from Kaiser Permanente Northern California, an integrated health care delivery system serving 4 million members, representing approximately 30% of the northern California population, racially/ethnically and socioeconomically diverse, and representative of the population in the served geographic area (20,21). Questionnaire data and fasting blood specimens were collected at gestational weeks 10 to 13 (clinic visit 1) and 16 to 19 (clinic visit 2). The study was approved by the human subjects committee of the Kaiser Foundation Research Institute. Informed consent was obtained from all participants.

After weekly searches of the electronic health records (EHRs), pregnant women of all races and ethnicities, aged 18 to 45 and with a gestational age less than 11 weeks, were approached by telephone calls to determine eligibility. Women with multiple gestations or recognized preexisting diabetes, cancer, hepatitis C, or liver cirrhosis were excluded. Women were also excluded if termination of pregnancy, diagnosis of overt diabetes or GDM, or use of diabetes medication occurred before the baseline clinic examination (all assessed via review of the EHR). Among 1,839 singleton pregnancies enrolled in PETALS and delivered as of August 2016, 1,759 (96%) were screened for GDM. Women with missing data on WC or hip circumference were excluded (n=9), rendering a pool of 1,750 women of all races and ethnicities, aged 18 to 45 and with a gestational age less than 11 weeks, were approached by telephone calls to determine eligibility. Women with multiple gestations or recognized preexisting diabetes, cancer, hepatitis C, or liver cirrhosis were excluded. Women were also excluded if termination of pregnancy, diagnosis of overt diabetes or GDM, or use of diabetes medication occurred before the baseline clinic examination (all assessed via review of the EHR). Among 1,839 singleton pregnancies enrolled in PETALS and delivered as of August 2016, 1,759 (96%) were screened for GDM. Women with missing data on WC or hip circumference were excluded (n=9), rendering a pool of 1,750 singleton pregnancies as our analytical cohort sample. In the final analytical sample, all measurements of central obesity measures preceded the diagnosis of GDM to ensure the prospective temporal sequence.

In a nested case-control study within the cohort, we further examined the potential for insulin resistance markers to mediate the association between central obesity and GDM risk. For each identified GDM case, two women without GDM diagnosis were selected and matched on race/ethnicity, age (± 5 years), calendar time of enrollment (± 3 months), and gestational weeks at clinic visit 1 (± 3 weeks). Measurements of fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR), and adiponectin were available for 115 GDM cases and 230 matched controls. This subset of 115 cases was representative of the 186 women with GDM in the entire cohort with regard to WHR and WC measures and established GDM risk factors.

Outcome ascertainment

In this clinical setting, pregnant women were universally screened for GDM by a 50-g, 1-hour glucose challenge test around 24 to 28 weeks of gestation. Among pregnancies with glucose challenge test values above 7.8 mmol/L, a diagnostic 100-g, 3-hour oral glucose tolerance test was performed after a 12-hour overnight fast. GDM was ascertained according to the Carpenter and Coustan criteria with two or more values meeting or exceeding the following thresholds: fasting glucose 5.3 mmol/L, 1-hour 10.0 mmol/L, 2-hour 8.6 mmol/L, and 3-hour 7.8 mmol/L (22).

Exposure measures

At clinic visit 1 (10-13 gestational weeks), WC and hip circumference were measured according to standard anthropometric protocols by trained study personnel who undergo yearly recertification to ensure adherence to the standard protocol and quality control (23). Specifically, WC was measured by positioning a tape 1 inch above the umbilicus at the end of the participant’s normal expiration; hip circumference was obtained at the maximum extension of the buttocks while the participant was standing erect with her abdomen relaxed. Each measurement was taken in duplicate by the same measurer. The mean value of WC or hip circumference was calculated if the two initial measurements agreed within 1 cm. Otherwise, an additional measurement was taken, and the third recording was used. According to the World Health Organization (WHO) and American Heart Association/National Heart, Lung, and Blood Institute recommendations on cutoff points for women, central obesity was defined as WHR ≥ 0.85 or WC ≥ 88 cm (24). We also applied the ethnicity-specific cutoff points for WC (≥ 80 cm for non-Caucasians) according to the International Diabetes Federation and Adult Treatment Panel III recommendations in sensitivity analyses (25,26).

Potential covariates

Covariates were selected based on both biological and statistical considerations. A comprehensive list of a priori-selected covariates was considered, namely, risk factors recommended by existing clinical guidelines (17,18) for early GDM risk assessment, including age, race/ethnicity, previous GDM, preexisting hypertension, and family history of diabetes (all assessed by the study questionnaire and supplemented with the EHR), as well as prepregnancy BMI calculated using prepregnancy weight (in kilograms; measured closest to the last menstrual period [LMP] within 12 weeks prior from the EHR) divided by height (in meters squared; measured at clinic visit 1). Notably, overweight or obesity was defined as BMI ≥ 25.0 kg/m^2 for non-Asians or ≥ 23.0 kg/m^2 for Asians according to the WHO recommendations on race/ethnicity-specific BMI cutoffs (27). We also assessed the following variables as potential covariates: education, parity, and smoking before or during pregnancy obtained by the baseline questionnaire at clinic visit 1; gestational weight gain up to clinic visit 1 calculated by subtracting the aforementioned prepregnancy weight from weight measured at visit 1; and physical inactivity defined as < 150 min/wk of moderate-intensity physical activity (28), assessed by a validated Pregnancy Physical Activity Questionnaire (29). However, these potential covariates were not retained in the final models failing the inclusion criteria of ≥10% change in the main effect estimates. In addition, gestational age was based on the estimated date of delivery recorded in the EHR, which was determined by the woman’s self-reported LMP or by the first-trimester ultrasound if different from the LMP-based calculation by more than 1 week. Notably, given that pregnant women gain, on
average, 0.5 to 2 kg in the first trimester according to the Institute of Medicine guidelines. Gestational weight gain (30), changes in central obesity measures are expected to be small, if not minimal, up to weeks 10 to 13 of gestation. Furthermore, the effect sizes of Pearson correlation between central obesity measures and the gestational age of measurements were small (r=0.07 for WHR and WC in correlation with gestational age, respectively; both P<0.01). Nonetheless, risk estimates for WHR and WC were adjusted for gestational age of measurements to account for possible variability within the interval of gestational weeks 10 to 13.

Markers of insulin resistance
Fasting blood samples were collected after an 8- to 12-hour overnight fast at clinic visit 1 (gestational weeks 10-13) and visit 2 (gestational weeks 16-19) in a serum separator tube (SST). The SST was centrifuged within 30 minutes of blood collection at the medical center’s clinical laboratory and was transferred by couriers in the standard climate-controlled containers along with the biospecimen samples collected for routine clinical care to the Kaiser Permanente Research Bank. Once at the Kaiser Permanente Research Bank Biorepository, serum from the SST tube was aliquoted into four cryovials and stored at −80°C until being thawed immediately before assay. Given the temporal sequence of central obesity measures at visit 1 and GDM diagnosis at 24 to 28 gestational weeks, we examined markers of insulin resistance at gestational weeks 16 to 19 as potential mediators in the pathway from central obesity in early pregnancy to subsequent GDM risk. Serum concentrations of glucose were measured with an oxidation reaction using a glucose analyzer (YSI 2300 STAT PLUS, Yellow Springs, Ohio). Insulin was measured using the Millipore radioimmunoassay (St. Charles, Missouri). HOMA-IR was calculated by the following formula: fasting glucose (nmol/L) × fasting insulin (µU/mL) ÷ 22.5 (31). Adiponectin was measured by a commercially available radioimmunoassay (Millipore). Measurements were performed in duplicate, and results were reported as the mean. All assays were performed without knowledge of GDM status. All the inter- and intra-assay coefficients of variation were <6.2%.

Statistical analysis
For the cohort analyses, distributions of participant characteristics were assessed by t test for continuous variables and Pearson χ² test for categorical variables by GDM status. Univariable and multivariable Poisson regression with robust standard errors calculated crude and adjusted relative risks (RRs) of GDM associated with WHR, WC, and established risk factors for GDM. Tests of linear trend were conducted by using the median value of each ordered category or quartile and fitting it as a continuous variable in the Poisson regression models.

To assess the relative incremental predictive ability of central obesity beyond established risk factors for GDM (i.e., age ≥35 years, minority race/ethnicity, prepregnancy overweight/obesity [BMI ≥23.0 for Asians or ≥25.0 for non-Asians], family history of diabetes, previous GDM, and preexisting hypertension), multivariable Poisson regression estimated the adjusted RRs for joint categories of central obesity (i.e., WHR ≥0.85 or WC ≥88 cm) and high-risk group, defined as the presence of any of the aforementioned risk factors for GDM. We also assessed the associations of overall versus central obesity in relation to GDM risk by contrasting combined categories of central obesity and overweight/obesity, after adjusting for other established risk factors. In sensitivity analysis, we tested the robustness of our results by using ethnicity-specific cutoff points for WC (≥80 cm for non-Caucasians) according to the International Diabetes Federation and Adult Treatment Panel III recommendations (25,26). For the cohort analyses, distributions of participant characteristics were assessed by t test for continuous variables and Pearson χ² test for categorical variables by GDM status. Univariable Poisson regression identified significant risk factors for GDM (Table 2), which were, overall, consistent with established risk factors (age ≥35 years, minority race/ethnicity, prepregnancy overweight/obesity, family history of diabetes, previous GDM, and preexisting hypertension) recommended by clinical guidelines for early GDM risk assessment. Multivariable risk estimates were slightly attenuated but remained significant for most established risk factors, except for family history of diabetes. In the multivariable model, WHR or WC in early pregnancy was significantly and positively associated with GDM risk; RRs comparing the highest versus lowest quartile for WHR and WC were 3.82 (95% CI: 1.90-7.68) and 2.84 (95% CI: 1.37-5.91), respectively.

Results
Among 1,750 singleton pregnancies, 186 (10.6%) had a GDM diagnosis (Table 1). Compared to women without GDM, women with GDM were more likely to be older and Asian/Pacific Islander and have BMI before pregnancy falling into the obesity category (≥27.5 or 30.0 for Asians or non-Asians, respectively), family history of diabetes, a previous pregnancy complicated by GDM, and preexisting hypertension, whereas smoking or physical activity in early pregnancy did not vary by GDM status.

Univariable Poisson regression identified significant risk factors for GDM (Table 2), which were, overall, consistent with established risk factors (age ≥35 years, minority race/ethnicity, prepregnancy overweight/obesity, family history of diabetes, previous GDM, and preexisting hypertension) recommended by clinical guidelines for early GDM risk assessment. Multivariable risk estimates were slightly attenuated but remained significant for most established risk factors, except for family history of diabetes. In the multivariable model, WHR or WC in early pregnancy was significantly and positively associated with GDM risk; RRs comparing the highest versus lowest quartile for WHR and WC were 3.82 (95% CI: 1.90-7.68) and 2.84 (95% CI: 1.37-5.91), respectively.
Furthermore, central obesity was significantly associated with greater risk of GDM, regardless of being at high risk (i.e., presence of at least one aforementioned established risk factor) or low risk (no risk factors). When central obesity was defined by WHR ≥ 0.85, compared with women at low risk without central obesity, women at high risk without central obesity had a 1.99-fold (95% CI: 0.99-4.02) increased risk of GDM, whereas women with central obesity among the low- and high-risk group had a 2.41-fold (95% CI: 1.14-5.06) and 6.22-fold (95% CI: 3.49-11.10) increased risk of GDM, respectively (Figure 1). When central obesity was defined by WC ≥ 88 cm, the corresponding risk estimates across groups were 2.96 (95% CI: 1.62-5.40), 2.83 (95% CI: 1.35-5.92), and 5.40 (95% CI: 3.20-9.12). Likewise, while assessing the incremental predictive ability of central obesity beyond overall obesity alone after adjusting for other established risk factors (Supporting Information Table S1), heterogeneous associations of central versus overall obesity with GDM risk were observed. There was a 3.36- or 1.91-fold significantly increased risk of GDM among women with overall overweight/obesity before pregnancy and central obesity in early pregnancy (WHR ≥ 0.85 or WC ≥ 88 cm). Furthermore, among women who had underweight or normal weight before pregnancy, there was a 2.16-fold (95% CI: 1.11-4.18) increased risk among women with WHR ≥ 0.85 but not WC ≥ 88 cm. Robust results were observed while using ethnicity-specific cutoff points for WC (≥ 80 cm for non-Caucasians), with slightly greater effect sizes (data not shown).

Furthermore, the receiver operating characteristic curve analyses illustrated significant incremental predictive value of WHR on a continuum scale beyond established risk factors (Figure 2A); leave-one-out cross-validated C statistics were 0.792 versus 0.737 (P < 0.001 for difference). Similar incremental predictive capacity was observed for WC on a continuum scale beyond established risk factors (C statistics 0.789 vs. 0.737; P < 0.001 for difference; Figure 2B).

| TABLE 1 | Participant characteristics at 10–13 weeks of gestation by subsequent gestational diabetes status, the prospective Pregnancy Environment and Lifestyle Study, 2013–2016 |
|---------|----------------------------------------------------------------------------------|
|          | Non-GDM (n = 1,564) | GDM (n = 186) | P value\(^a\) |
| Age (y), n (%) |                  |            |       |
| 18–24 | 301 (19.2) | 15 (8.1) | <0.001 |
| 25–29 | 404 (25.8) | 35 (18.8) |
| 30–34 | 564 (36.1) | 83 (44.6) |
| ≥35  | 295 (18.9) | 53 (28.5) |
| Race/ethnicity, n (%) |                  |            | <0.001 |
| Non-Hispanic White | 371 (23.7) | 37 (19.9) |
| Hispanic | 653 (41.8) | 66 (35.5) |
| African American | 166 (10.6) | 12 (6.5) |
| Asian/Pacific Islander | 320 (20.5) | 68 (36.6) |
| Other | 54 (3.5) | 3 (1.6) |
| Education, n (%) |                  |            | 0.64 |
| High school or less | 224 (14.3) | 25 (13.4) |
| Some college | 629 (40.2) | 70 (37.6) |
| College graduate or above | 711 (45.5) | 91 (48.9) |
| Nulliparity, n (%) |                  |            | 0.49 |
| Prepregnancy BMI categories, n (%)\(^b\) |                  |            | <0.001 |
| Underweight | 42 (2.7) | 1 (0.5) |
| Normal weight | 580 (37.1) | 26 (14.0) |
| Overweight | 510 (32.6) | 57 (30.6) |
| Obesity | 432 (27.6) | 102 (54.8) |
| Smoking before pregnancy, n (%) |                  |            | 0.26 |
| Smoking during early pregnancy, n (%) | 11 (0.7) | 1 (0.5) | 0.80 |
| Family history of diabetes, n (%) | 326 (22.5) | 62 (34.8) | <0.001 |
| Previous gestational diabetes, n (%) | 31 (2.0) | 29 (15.6) | <0.001 |
| Preexisting hypertension, n (%) | 55 (3.5) | 17 (9.1) | <0.001 |
| Physical inactivity in early pregnancy, n (%)\(^c\) | 726 (46.4) | 92 (49.9) | 0.43 |
| Waist to hip ratio, mean (SD) | 0.86 (0.07) | 0.91 (0.06) | <0.001 |
| Waist circumference (cm), mean (SD) | 90.3 (14.2) | 102.4 (18.5) | <0.001 |

\(^a\) Obtained by \(t\) test for continuous variables and Pearson \(\chi^2\) test for categorical variables.

\(^b\) BMI cutoffs for underweight, normal weight, overweight, and obesity were <18.5, 18.5–22.9, 23.0–27.4, and ≥27.5 kg/m\(^2\) or <18.5, 18.5–24.9, 25.0–29.9, and ≥30.0 kg/m\(^2\) for Asians or non-Asians, respectively, based on World Health Organization recommendations.

\(^c\) Defined as less than 150 min/wk of moderate-intensity physical activity.
| TABLE 2 Univariable and multivariable relative risk (95% CI) for gestational diabetes in association with waist circumference, waist to hip ratio, and established risk factors, the prospective Pregnancy Environment and Lifestyle Study, 2013-2016 |
|------------------------------|-------------------|-------------------|-------------------|
|                              | Univariable relative risk | Multivariable relative risk |
| Age (y)                      |                               |                               |
| <25                          | 1 (reference)                | 1 (reference)                |
| 25-29                        | 0.64 (0.35-1.15)             | 0.73 (0.41-1.31)             |
| 30-34                        | 1.63 (1.11-2.40)             | 1.23 (0.86-1.77)             |
| ≥35                          | 1.97 (1.30-2.97)             | 1.42 (0.97-2.07)             |
| \( P \) for trend\( ^a \)   | <0.001                        | 0.007                        |
| Race/ethnicity               |                               |                               |
| Non-Hispanic White           | 1 (reference)                | 1 (reference)                |
| African American             | 0.73 (0.38-1.39)             | 0.68 (0.37-1.26)             |
| Asian/Pacific Islander       | 1.99 (1.35-2.92)             | 1.72 (1.19-2.49)             |
| Hispanic                     | 1.04 (0.70-1.54)             | 0.90 (0.61-1.32)             |
| Other                        | 0.58 (0.19-1.83)             | 0.55 (0.19-1.61)             |
| Family history of diabetes   |                               |                               |
| No                           | 1 (reference)                | 1 (reference)                |
| Yes                          | 1.71 (1.28-2.27)             | 1.10 (0.83-1.46)             |
| Previous gestational diabetes|                               |                               |
| No                           | 1 (reference)                | 1 (reference)                |
| Yes                          | 5.27 (3.90-7.10)             | 3.29 (2.31-4.71)             |
| Preexisting hypertension     |                               |                               |
| No                           | 1 (reference)                | 1 (reference)                |
| Yes                          | 2.34 (1.49-3.67)             | 1.60 (1.04-2.47)             |
| Prepregnancy BMI categories, \( n \)\( ^b \) |                               |                               |
| Underweight                  | 0.54 (0.08-3.90)             | 0.65 (0.12-3.53)             |
| Normal weight                | 1 (reference)                | 1 (reference)                |
| Overweight                   | 2.34 (1.49-3.67)             | 1.69 (1.08-2.64)             |
| Obesity                      | 4.45 (2.94-6.74)             | 2.79 (1.78-4.37)             |
| \( P \) for trend\( ^c \)   | <0.001                        | 0.007                        |
| Waist to hip ratio\( ^c \)   |                               |                               |
| Quartile 1 (0.68-0.80)       | 1 (reference)                | 1 (reference)                |
| Quartile 2 (0.81-0.85)       | 2.98 (1.48-6.01)             | 2.03 (1.01-4.08)             |
| Quartile 3 (0.86-0.91)       | 4.55 (2.33-8.88)             | 2.61 (1.31-5.21)             |
| Quartile 4 (0.92-1.18)       | 8.94 (4.72-16.9)             | 3.82 (1.90-7.68)             |
| \( P \) for trend\( ^c \)   | <0.001                        | <0.001                       |
| Waist circumference (cm)\( ^c \) |                               |                               |
| Quartile 1 (61-80)           | 1 (reference)                | 1 (reference)                |
| Quartile 2 (81-88)           | 1.97 (1.07-3.60)             | 1.51 (0.81-2.81)             |
| Quartile 3 (89-99)           | 3.01 (1.71-5.31)             | 1.70 (0.89-3.25)             |
| Quartile 4 (100-166)         | 5.73 (3.37-9.74)             | 2.84 (1.37-5.91)             |
| \( P \) for trend\( ^c \)   | <0.001                        | 0.007                        |

\(^a\)Tests of linear trend conducted by using median value of each ordered category and fitting it as continuous variable.

\(^b\)BMI cutoffs for underweight, normal weight, overweight, and obesity were <18.5, 18.5-22.9, 23.0-27.4, and ≥27.5 kg/m\(^2\) or <18.5, 18.5-24.9, 25.0-29.9, and ≥30.0 kg/m\(^2\) for Asians or non-Asians, respectively.

\(^c\)Risk estimates adjusted for gestational age at waist and hip circumference measurement.
In the nested case-control analyses within the cohort, similar differences in major participant characteristics between GDM cases and controls were observed as in the PETALS cohort except for the matching variables, as expected (Supporting Information Table S2). Both WHR and WC at gestational weeks 10 to 13 were positively correlated with markers of impaired glucose tolerance or insulin resistance (fasting serum glucose, insulin, and HOMA-IR) and inversely correlated with adiponectin at gestational weeks 16 to 19; these significant associations persisted only among non-GDM controls after adjusting for covariates (Supporting Information Table S3). Comparing the highest versus lowest quartile, WHR and WC at gestational weeks 10 to 13 were both significantly associated with a sixfold increased risk of GDM.
after adjusting for covariates (Table 3). After additionally adjusting for markers of insulin resistance, the WHR–GDM association was slightly attenuated but remained significant, whereas the WC–GDM association did not persist. Significant partial mediation effect was observed through markers of insulin resistance on the WC–GDM association; the proportions mediated by insulin, HOMA-IR, and adiponectin were 40.0% (8.6%-71.5%), 41.4% (6.8%-75.3%), and 35.4% (7.4%-63.4%), respectively. Similar but smaller partial mediation effects were observed for the WHR–GDM association, ranging from 9.0% to 11.1% (all \( P < 0.05 \)). Sensitivity analyses additionally adjusting for diet, physical activity, and gestational weight gain up to visit 1 yielded robust, similar results (data not shown).

## Discussion

In this prospective study of a multiracial/multiethnic cohort, central obesity measures WHR and WC in early pregnancy were significant predictors of subsequent GDM risk, independent of overweight/obesity and other established risk factors recommended by existing clinical care guidelines for early GDM screening (17,18). Furthermore, WHR and WC illustrated significant incremental predictive ability for GDM risk, beyond aforementioned established risk factors. In the nested case-control analyses, markers of insulin resistance exhibited a significant mediating role in both the WC–GDM and WHR–GDM associations, although with a smaller magnitude for the latter.

### TABLE 3 Mediation analysis: adjusted odds ratio (95% CI) for risk of gestational diabetes in association with waist to hip ratio, waist circumference, and markers of insulin resistance, a nested case-control study within the Pregnancy Environment and Lifestyle Study, 2013-2016

| Quartile 1   | Quartile 2   | Quartile 3   | Quartile 4   | Proportion mediated, %a | \( P \) for indirect effect |
|--------------|--------------|--------------|--------------|--------------------------|-----------------------------|
| **Waist to hip ratio and markers of insulin resistance** | | | | | |
| Multivariable modelb | | | | | |
| Waist to hip ratio 1 (reference) | 1.72 (0.43-6.91) | 3.27 (0.83-12.9) | 6.59 (1.78-24.4) | - | - |
| Multivariable model + insulinc | | | | | |
| Waist to hip ratio 1 (reference) | 1.36 (0.31-5.95) | 2.21 (0.49-9.93) | 4.26 (1.06-17.2) | - | - |
| Waist to hip ratio 1 (reference) | 3.68 (0.71-19.0) | 3.69 (0.65-20.9) | 7.94 (1.44-43.8) | 9.0 (0.5-17.5) | 0.037 |
| Multivariable model + HOMA-IRc | | | | | |
| Waist to hip ratio 1 (reference) | 1.20 (0.28-5.24) | 2.39 (0.54-10.6) | 4.17 (1.03-16.9) | - | - |
| HOMA-IR 1 (reference) | 1.41 (0.32-6.33) | 3.02 (0.60-15.2) | 6.09 (1.30-28.4) | 9.6 (1.0-18.1) | 0.028 |
| Multivariable model + adiponectinc | | | | | |
| Waist to hip ratio 1 (reference) | 1.31 (0.28-6.04) | 2.72 (0.61-12.2) | 5.13 (1.21-21.7) | - | - |
| Adiponectin 3.35 (0.87-12.9) | 1.54 (0.42-5.63) | 0.53 (0.12-2.37) | 1 (reference) | 11.1 (0.7-21.6) | 0.037 |
| **Waist circumference and markers of insulin resistance** | | | | | |
| Multivariable modelb | | | | | |
| Waist circumference 1 (reference) | 1.85 (0.48-7.16) | 2.98 (0.71-12.6) | 6.35 (1.07-37.7) | - | - |
| Multivariable model + insulinc | | | | | |
| Waist circumference 1 (reference) | 0.82 (0.17-3.97) | 1.30 (0.24-6.92) | 2.43 (0.32-18.3) | - | - |
| Insulin 1 (reference) | 4.95 (0.96-25.7) | 5.38 (0.89-32.4) | 12.0 (2.03-71.4) | 40.0 (8.6-71.5) | 0.013 |
| Multivariable model + HOMA-IRc | | | | | |
| Waist circumference 1 (reference) | 0.79 (0.16-3.85) | 1.26 (0.23-6.77) | 2.06 (0.27-16.0) | - | - |
| HOMA-IR 1 (reference) | 2.22 (0.48-10.3) | 4.41 (0.79-24.6) | 9.93 (1.89-52.1) | 41.1 (6.8-75.3) | 0.019 |
| Multivariable model + adiponectinc | | | | | |
| Waist circumference 1 (reference) | 1.49 (0.36-6.26) | 2.68 (0.59-12.3) | 4.91 (0.77-31.4) | - | - |
| Adiponectin 5.51 (1.45-21.0) | 2.07 (0.59-7.24) | 0.76 (0.18-3.17) | 1 (reference) | 35.4 (7.4-63.4) | 0.013 |

Quartiles classified based on values among non-gestational diabetes controls.

aProportion mediated on risk difference scale calculated as indirect effect attributed to particular biomarker divided by total effect.
bAdjusted for prepregnancy BMI, family history of diabetes, previous gestational diabetes, and preexisting hypertension.
cAdjusted for covariates in multivariable model and insulin, HOMA-IR, or adiponectin at 16-19 weeks of gestation.

HOMA-IR, homeostatic model assessment of insulin resistance.
Taken together, our findings may have significant clinical implications, particularly considering that women with central obesity but a conventionally low-risk profile based on overweight/obesity and other established risk factors are not considered a target population for early GDM risk assessment or preventive management (17,37), highlighting the potential importance of considering heterogeneity in obesity phenotypes for GDM risk assessment. The observation that increased insulin resistance partially mediated the central obesity–GDM risk association may provide insights into potential prevention strategies to mitigate GDM risk by aiming at reducing central obesity and/or insulin resistance.

Outside of pregnancy, central obesity measures have been shown to be significant risk factors for diabetes, cardiovascular diseases, and mortality beyond overall obesity (8-10). Furthermore, as illustrated in a 2012 review and meta-analysis including data from more than 300,000 multiethnic individuals, WHR may serve as a better predictor than WC beyond BMI for cardiometabolic outcomes, including diabetes (38). This is in line with our findings of overall greater discriminative ability of WHR than WC for GDM risk, which may be partially attributable to the smaller intercorrelation of WHR than WC with BMI, as demonstrated previously (39) and herein.

To the best of our knowledge, this is the first large, contemporary prospective study of multiracial/multiethnic women demonstrating that central obesity in early pregnancy significantly increased subsequent risk of GDM, even with absence of established risk factors, including the most prominent factor of prepregnancy overweight or obesity. Interpretation of previous data was largely hindered by the cross-sectional design of central obesity measurement at the time of GDM diagnosis and also by limited data on WHR (40). Our findings are consistent with a few small-scale studies, including 10 to 45 GDM cases, which have linked ultrasonography measured visceral fat in early pregnancy to impaired glucose tolerance or GDM in the third trimester (12,41). However, these studies were not able to examine the joint association and incremental predictive value of visceral fat beyond a combination of established risk factors for GDM. In a recent study as a secondary analysis of an antioxidant supplementation trial to prevent gestational hypertensive disorders, Basraon et al. also reported positive associations between WHR in early pregnancy and GDM but no significant incremental predictive ability of WHR versus BMI for GDM risk (14).

Although the biological mechanisms underlying the central obesity–GDM association remain to be elucidated, our nested case-control analyses provide potential mechanistic insights by illustrating the mediating role of increased insulin resistance, as estimated by insulin, HOMA-IR, and adiponectin, which might have contributed to the later onset of GDM. These findings are consistent with data among nonpregnant women showing that central obesity measured by dual-energy x-ray absorptiometry was strongly associated with increased insulin resistance measured by euglycemic-hyperinsulinemic clamp (42). Furthermore, data in nonpregnant animal models demonstrated that the removal of visceral fat reversed insulin resistance and delayed the onset of diabetes (43). Interestingly, in our study, the mediation effect of insulin resistance markers was greater for WC compared with WHR in relation to GDM risk. It is plausible that WHR compared with WC may serve as an indicator of certain central obesity phenotypes more sensitive to pathways other than insulin resistance.

Major strengths of our study include a large racially/ethnically diverse population and the prospective cohort design along with a nested case-control study, which is uniquely suited to address the temporal sequence and to provide mechanistic insights into the central obesity–GDM association. Notably, we used a lower cutoff for overweight/obesity (BMI ≥ 23.0) for Asians based on the WHO recommendations to allow for ethnicity-specific at-risk BMI (27,37). Some potential limitations of the study merit discussion. We used WHR and WC as central obesity measures and did not have visceral fat assessment. However, WHR and WC were demonstrated as simple and reliable surrogate measures for intra-abdominal or visceral fat (16). Furthermore, these central obesity measures are clinically appealing, with the potential to serve as a simple and inexpensive tool for screening. To define central obesity, the WHO cutoff points for women in the general population were used (24), given the lack of recommendations tailored to pregnant women. Nonetheless, the study-specific median value of WHR or WC was equal to the respective WHO cutoffs. We also conducted sensitivity analysis using ethnicity-specific cutoff points for WC according to the International Diabetes Federation and Adult Treatment Panel III recommendations (25,26); results remained robust. Finally, we were not able to validate the incremental predictive value of WHR or WC beyond established risk factors for GDM in a separate cohort; however, we used the leave-one-out cross-validation approach to replicate the validation process and avoid model overfitting.

Conclusion

In summary, central obesity measures in early pregnancy were significantly and positively associated with risk of GDM, independent of established risk factors, including overweight/obesity prior to pregnancy. Our findings highlight that central obesity in early pregnancy, even with absence of overweight/obesity and other established risk factors, represented a high-risk phenotype for GDM and may help identify at-risk women for early screening and prevention. Furthermore, the significant association between central obesity in early pregnancy and GDM risk was partially mediated through increased insulin resistance in midpregnancy, providing insights into potential prevention strategies targeted reducing central obesity and/or insulin resistance to mitigate risk of GDM.

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