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Central obesity increases the risk of gestational diabetes partially through increasing insulin resistance

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Abstract

Objective: We 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 (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, waist and hip circumferences were measured at gestational weeks 10–13. In a nested case-control study within the cohort, 115 GDM cases and 230 controls had fasting serum insulin, HOMA-IR, and adiponectin measurements at gestational weeks 16–19. Poisson and conditional logistic regression models were used, adjusting for established risk factors for GDM including prepregnancy overweight/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 risks increased 2.41-fold (1.14–5.06), and with other risk factors, 6.22-fold (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 9511%; corresponding mediation proportions for the WC-GDM association were 35–41% (all *P*-values<0.04).

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

Keywords

Central obesity; gestational diabetes; insulin resistance; pregnancy; prediction

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Introduction

Gestational diabetes (GDM) has emerged as the most common pregnancy complication affecting 7–17% of pregnancies worldwide (1, 2), representing a growing, urgent public health concern (3). The increasing prevalence of GDM may be fueling the epidemic of adverse sequelae 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 high-risk women for GDM. Obesity is a major risk factor for GDM (6). Notably, data are mostly on overall obesity defined based on body mass index (BMI); however, GDM is also frequently observed in women with 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, 9, 10). However, evidence has been largely confined to non-pregnant 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 10–80 women with GDM (11, 12, 13, 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 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 multi-racial/ethnic 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). Further, 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 multi-racial/ethnic pregnant women, within which a nested case-control study of GDM etiology is underway. The study design and scope have been described in detail elsewhere (19). The source population was identified from the Kaiser Permanente Northern California, an integrated health care delivery system serving 4 million members, representing approximately 30% of the northern California population and is racially/ethnically and socio- economically diverse and representative of the population in the served geographic area (20, 21). Questionnaire data and fasting blood specimens were collected at gestational weeks 10–13 (clinic visit 1) and 16–19 (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 search of the electronic health records (EHR), pregnant women of all races/ethnicities, aged 18–45 years, and with a gestational age less than 11 weeks were approached by telephone calls to determine eligibility. Women with multiple gestations or recognized pre-existing diabetes, cancer, hepatitis C, or liver cirrhosis were excluded. Women are further excluded if termination of pregnancy, diagnosis of overt diabetes or gestational diabetes, 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 the PETALS and delivered as of August 2016, 1,759 (96%) were screened for GDM. Women with missing data on waist or hip circumference ($n = 9$) were excluded, 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, HOMA-IR, and adiponectin were available for 115 GDM cases and 230 matched controls. This subset of 115 cases was representative of the 186 GDM women in the entire cohort with regard to WHR and WC measures and established GDM risk factors.

Outcome ascertainment

In this clinical setting, pregnant women are universally screened for GDM by a 50-g, 1-h glucose challenge test around 24–28 weeks of gestation. Among pregnancies with glucose challenge test values above 7.8 mmol/L, a diagnostic 100-g, 3-h oral glucose tolerance test was performed after a 12-h 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-h 10.0 mmol/L, 2-h 8.6 mmol/L, and 3-h 7.8 mmol/L (22).

Exposure measures

At clinic visit 1 (10–13 gestational weeks), waist and hip circumferences were measured according to standard anthropometric protocols by trained study personnel who undergo yearly re-certification to ensure adherence to the standard protocol and quality control (23). Specifically, WC was measured by positioning a tape one 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 waist 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 ethnic 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, pre-existing hypertension, and family history of diabetes (all assessed by the study questionnaire and supplemented with EHR), as well as prepregnancy BMI calculated using prepregnancy weight (kg, measured closest to the last menstrual period within 12 weeks prior from the EHR) divided by squared height (m^2, measured at visit 1). Notably, overweight or obesity was defined as a BMI ≥25.0 kg/m^2 for non-Asians or ≥23.0 kg/m^2 for Asians according to the WHO recommendations on racial/ethnic specific BMI cutoffs (27). We also assessed the following variables as potential covariates: education, parity, and smoking before/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; physical inactivity defined as <150 minutes/week 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 last menstrual period (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 0.5–2 kg in the first trimester according to the Institute of Medicine guidelines on gestational weight gain (30), changes in central obesity measures are expected to be small, if not minimal, up to weeks 10–13 of gestation. Further, the effect sizes of Pearson's correlation between central obesity measures and the gestational age of measurements were small ($r = 0.12$ and 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 weeks10–13.

Markers of insulin resistance

Fasting blood samples were collected after an 8–12-hour overnight fast at clinic visit 1 (gestational weeks 10–13) and visit 2 (gestational weeks 16–19) in serum separator tube (SST). The SST was centrifuged within 30 minutes of blood collection at the medical center's clinical laboratory and 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 (KPRB). Once at the KPRB Biorepository, serum from the SST tube was aliquoted into four cryovials and stored at −80ºC until being thawed immediately before assay. Given the temporal sequence of central obesity measures at visit 1 and GDM diagnosis at 24–28 gestational weeks, we examined markers of insulin resistance

at gestational weeks 16–19 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, OH). Insulin was measured using the Millipore radioimmunoassay (St Charles, MO). HOMA-IR was calculated by the 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 Student's t test for continuous variables and Pearson's χ^2 test for categorical variables by GDM status. Univariable and multivariable Poisson regression with robust standard errors calculated crude and adjusted relative risks (RR) 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 kg/m^2 for Asians or ≥25.0 kg/m^2 for non-Asians), family history of diabetes, previous GDM, and pre-existing 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 presence of any of the *a priori* established 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 ethnic specific cutoff points for WC (≥80 cm for non-Caucasians) according to the International Diabetes Federation and Adult Treatment Panel III recommendations (25, 26). Further, we conducted leave-one-out cross validation of receiver-operating-characteristic curve analyses and compared C statistics for risk prediction of GDM using WHR or WC in addition to aforementioned established risk factors using DeLong's test (32, 33).

In the case-control analyses nested within the cohort, conditional logistic regression was used to calculate odds ratios of GDM associated with central obesity measures (WHR or WC) and markers of insulin resistance (insulin, HOMA-IR, or adiponectin), after adjusting for aforementioned established risk factors. We analyzed central obesity measures and insulin resistance markers by categorizing each measure into quartiles based on the distribution among controls (34). To gain insight into the underlying pathophysiologic processes involved in central obesity and GDM risk, we calculated crude and partial Spearman's correlation coefficients of WHR and WC at gestational weeks 10–13 with fasting serum glucose, insulin, HOMA-IR, and adiponectin at gestational weeks 16–19, respectively. We further conducted mediation analyses and calculated proportions of the

association between WHR or WC and GDM risk that was mediated through insulin, HOMA-IR, or adiponectin, respectively. Proportion mediated on a risk difference scale was calculated as the indirect effect divided by the total effect (35, 36). Specifically, the mediation proportion is the proportion of the association between central obesity measures (WHR or WC) and risk of GDM that can be attributed to elevated levels of insulin or HOMA-IR (relative to the lowest quartile as the reference) or decreased levels of adiponectin (relative to the highest quartile as the reference) as intermediate variables, respectively. Further, given that the mediation methods assume baseline covariates are sufficient to control for exposure-outcome, mediator-outcome, and exposure-mediator confounding, we tested robustness of our results against potential residual confounding due to physical activity during early pregnancy and gestational weight gain up to blood collection at visit 1. Analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC).

Results

Among 1,750 singleton pregnancies, 186 (10.6%) had GDM diagnosis (Table 1). Compared to women without GDM, GDM women were more likely to be older and Asian/Pacific Islander and have a BMI falling into the obesity category (≥27.5 or 30.0 kg/m^2 for Asians or non-Asians, respectively) before pregnancy, family history of diabetes, a previous pregnancy complicated by GDM, and pre-existing 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 pre-existing 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 were significantly and positively associated with GDM risk; RRs comparing the highest vs. lowest quartile for WHR and WC were 3.82 (95% CI 1.90–7.68) and 2.84 (1.37–5.91), respectively.

Further, 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 factors) or low-risk (no risk factors). When central obesity was defined by WHR ≥0.85, compared to 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 (1.14–5.06) and 6.22-fold (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 (1.35–5.92), and 5.40 (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 (Table S1), heterogeneous associations of central versus overall obesity with GDM risk were observed. There was a 3.365 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). Further, among women who were 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 ethnic specific cutoff points for WC (≥80 cm for non-Caucasians), with slightly greater effect sizes (data not shown).

Further, 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 vs. 0.737 (*P*-for-difference <0.001). Similar incremental predictive capacity was observed for WC on a continuum scale beyond established risk factors (C statistics 0.789 vs. 0.737, *P*-for-difference <0.001; Figure 2B).

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 (Table S2). Both WHR and WC at gestational weeks 105 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 16–19; these significant associations only persisted among non-GDM controls after adjusting for covariates (Table S3). Comparing the highest vs. lowest quartile, WHR and WC at gestational weeks 10–13 were both significantly associated with a 6-fold 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%511.1% (all P-values <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 multi-racial/ethnic 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). Further, 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.

Taken together, our findings may have significant clinical implications, particularly considering that women with central obesity but 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, 9, 10). Further, as illustrated in a recent 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 multi-racial/ethnic 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 limited data on WHR (40). Our findings are consistent with a few small-scale studies including 10–45 GDM cases, which 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). However, the participants in this trial were low-risk, nulliparous pregnant women free of major pre-existing diseases enrolled from 2003–2008, limiting the comparability against other studies of general pregnant populations. Our study extends the literature by illustrating the relative incremental predictive ability of central obesity measures WHR and WC for risk of GDM beyond overweight/obesity and other established risk factors in a relatively large, contemporary cohort of multi-racial/ethnic women representative of the population in the underlying geographic area.

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 non-pregnant 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). Further, data in non-pregnant 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 to WHR in relation to GDM risk. It is plausible that WHR compared to 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 racial/ethnic 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 kg/m^2) for Asians based on the WHO recommendations to allow for ethnic 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 have been demonstrated as simple and reliable surrogate measures for intra-abdominal or visceral fat (16). Further, these central obesity measures are clinically appealing with the potential of serving 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 ethnic 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.

Conclusions

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. Further, the significant association between central obesity in early pregnancy and GDM risk was partially mediated through increased insulin resistance in mid pregnancy, providing insights into potential prevention strategies targeting at reducing central obesity and/or insulin resistance to mitigate risk of GDM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes research and clinical practice 2014;103: 176–185. [PubMed: 24300020]
2. Ferrara A Increasing prevalence of gestational diabetes mellitus: a public health perspective. Diabetes Care 2007;30 Suppl 2: S141–146. [PubMed: 17596462]
3. Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. Curr Diab Rep 2016;16: 7. [PubMed: 26742932]
4. Ferrara A, Peng T, Kim C. Trends in postpartum diabetes screening and subsequent diabetes and impaired fasting glucose among women with histories of gestational diabetes mellitus: A report from the Translating Research Into Action for Diabetes (TRIAD) Study. Diabetes Care 2009;32: 269–274. [PubMed: 18984776]
5. Metzger BE. Long-term outcomes in mothers diagnosed with gestational diabetes mellitus and their offspring. Clin Obstet Gynecol 2007;50: 972–979. [PubMed: 17982340]
6. Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, et al. Maternal Obesity and Risk of Gestational Diabetes Mellitus. Diabetes Care 2007;30: 2070–2076. [PubMed: 17416786]
7. Hedderson M, Ehrlich S, Sridhar S, Darbinian J, Moore S, Ferrara A. Racial/ethnic disparities in the prevalence of gestational diabetes mellitus by BMI. Diabetes Care 2012;35: 1492–1498. [PubMed: 22619080]
8. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk—a review of the literature. European journal of clinical nutrition 2010;64: 16–22. [PubMed: 19654593]
9. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, et al. Normal-weight central obesity: Implications for total and cardiovascular mortality. Annals of Internal Medicine 2015;163: 827–835. [PubMed: 26551006]
10. Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study. Am J Clin Nutr 2006;84: 483–489. [PubMed: 16960160]
11. De Souza LR, Berger H, Retnakaran R, Vlachou PA, Maguire JL, Nathens AB, et al. Hepatic fat and abdominal adiposity in early pregnancy together predict impaired glucose homeostasis in mid-pregnancy. Nutr Diabetes 2016;6: e229. [PubMed: 27643724]
12. Gur EB, Ince O, Turan GA, Karadeniz M, Tatar S, Celik E, et al. Ultrasonographic visceral fat thickness in the first trimester can predict metabolic syndrome and gestational diabetes mellitus. Endocrine 2014;47: 478–484. [PubMed: 24452873]
13. Alptekin H, Cizmecioglu A, Isik H, Cengiz T, Yildiz M, Iyisoy MS. Predicting gestational diabetes mellitus during the first trimester using anthropometric measurements and HOMA-IR. J Endocrinol Invest 2016;39: 577–583. [PubMed: 26754418]
14. Basraon SK, Mele L, Myatt L, Roberts JM, Hauth JC, Leveno KJ, et al. Relationship of early pregnancy waist to hip ratio versus body mass index with gestational diabetes and insulin resistance. Am J Perinat 2016;33: 114.
15. Ashwell M, Cole TJ, Dixon AK. Obesity: new insight into the anthropometric classification of fat distribution shown by computed tomography. Br Med J (Clin Res Ed) 1985;290: 1692–1694.
16. Schreiner PJ, Terry JG, Evans GW, Hinson WH, Crouse JR, 3rd, Heiss G. Sex-specific associations of magnetic resonance imaging-derived intra-abdominal and subcutaneous fat areas with conventional anthropometric indices. The Atherosclerosis Risk in Communities Study. American journal of epidemiology 1996;144: 335–345. [PubMed: 8712190]
17. American College of Obstetricians and Gynecologists Committee on Practice Bulletins55 Obstetrics. Practice Bulletin No. 180: Gestational Diabetes Mellitus. Obstet Gynecol 2017;130: e17–e37. [PubMed: 28644336]

18. American Diabetes Association. Management of diabetes in pregnancy. Sec. 13. In Standards of Medical Care in Diabetes-2017. Diabetes Care 2017;40: S114–S119. [PubMed: 27979900]
19. Zhu Y, Hedderson MM, Feng J, Mevi AA, Ferrara A. The Pregnancy Environment and Lifestyle Study (PETALS): a population-based longitudinal multi-racial birth cohort. BMC pregnancy and childbirth 2017;17: 122. [PubMed: 28415965]
20. Gordon N, Lin T. The Kaiser Permanente Northern California Adult Member Health Survey. The Permanente Journal 2016;20.
21. Go AS, Lee WY, Yang J, Lo JC, Gurwitz JH. Statin therapy and risks for death and hospitalization in chronic heart failure. JAMA : the journal of the American Medical Association 2006;296: 2105–2111. [PubMed: 17077375]
22. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 1982;144: 768–773. [PubMed: 7148898]
23. Lohman T, Roche A, Martorell R. Anthropometric standardization reference manual. Human Kinetic Books: Champaign, IL, 1988.
24. World Health Organization. Waist circumference and waist-hip ratio: Report of a WHO expert consultation. World Health Organization: Geneva, Switzerland, 2011.
25. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA : the journal of the American Medical Association 2001;285: 2486–2497. [PubMed: 11368702]
26. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. Lancet 2005;366: 1059–1062. [PubMed: 16182882]
27. World Health Organization Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363: 157–163. [PubMed: 14726171]
28. US Department of Health Human Services. US Department of Health and Human Services 2008 physical activity guidelines for Americans. Washington, D.C., 2014.
29. Chasan-Taber L, Schmidt MD, Roberts DE, Hosmer D, Markenson G, Freedson PS. Development and validation of a Pregnancy Physical Activity Questionnaire. Med Sci Sports Exerc 2004;36: 1750–1760. [PubMed: 15595297]
30. Institute of Medicine. Weight Gain During Pregnancy: Reexamining the Guidelines. In: Rasmussen KM, Yaktine AL (eds). National Academies Press: Washington, DC, 2009.
31. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28: 412–419. [PubMed: 3899825]
32. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44: 837–845. [PubMed: 3203132]
33. Zhu Y, Mendola P, Albert PS, Bao W, Hinkle SN, Tsai MY, et al. Insulin-like growth factor axis and gestational diabetes: A longitudinal study in a multiracial cohort. Diabetes 2016.
34. Lacroix M, Battista MC, Doyon M, Menard J, Ardilouze JL, Perron P, et al. Lower adiponectin levels at first trimester of pregnancy are associated with increased insulin resistance and higher risk of developing gestational diabetes mellitus. Diabetes Care 2013;36: 1577–1583. [PubMed: 23300287]
35. VanderWeele TJ. Explanation in Causal Inference: Methods for Mediation and Interaction. Oxford University Press: New York, NY, 2015.
36. Vanderweele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. American journal of epidemiology 2010;172: 1339–1348. [PubMed: 21036955]
37. American Diabetes A Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33 Suppl 1: S62–69. [PubMed: 20042775]
38. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev 2012;13: 275–286. [PubMed: 22106927]

39. Vazquez G, Duval S, Jacobs DR, Jr., Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. Epidemiol Rev 2007;29: 115–128. [PubMed: 17494056]

40. Bolognani CV, de Sousa Moreira Reis LB, de Souza SS, Dias A, Rudge MV, de Mattos Paranhos Calderon I. Waist circumference in predicting gestational diabetes mellitus. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2014;27: 943–948.

41. De Souza LR, Berger H, Retnakaran R, Maguire JL, Nathens AB, Connelly PW, et al. First-Trimester Maternal Abdominal Adiposity Predicts Dysglycemia and Gestational Diabetes Mellitus in Midpregnancy. Diabetes Care 2016;39: 61–64. [PubMed: 26525976]

42. Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ. Abdominal fat and insulin resistance in normal and overweight women: Direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. Diabetes 1996;45: 633–638. [PubMed: 8621015]

43. Gabriely I, Ma XH, Yang XM, Atzmon G, Rajala MW, Berg AH, et al. Removal of Visceral Fat Prevents Insulin Resistance and Glucose Intolerance of Aging. Diabetes 2002;51: 2951. [PubMed: 12351432]

What is already known about this subject?

- Overweight or obesity is a major risk factor for gestational diabetes (GDM); however, GDM is also frequently observed in women with normal BMI.
- Central obesity has been linked to diabetes risk but data are limited among pregnant women.
- 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.

What does this study add?

- Waist-to-hip ratio and waist circumference in early pregnancy illustrated significant incremental predictive ability for GDM risk, beyond overweight/obesity prior to pregnancy and other established risk factors.
- Mediation analyses illustrated that markers of insulin resistance partially mediated the association between central obesity and GDM.
- Our findings may have significant clinical implications, particularly considering that women with central obesity but conventionally low-risk profile based on absence of established risk factors are not considered a target population for early GDM risk assessment or preventive management.

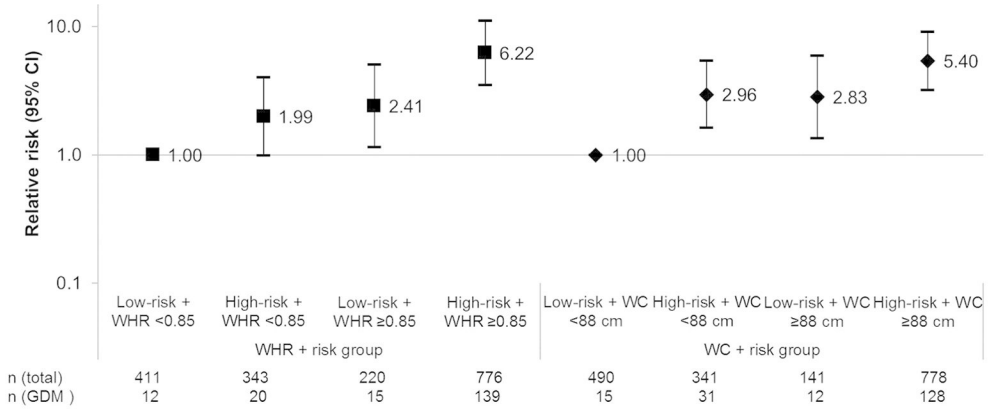

Fig. 1. Joint association of central obesity measures and established risk factors with risk of gestational diabetes

WC, waist circumference; WHR, waist-to-hip ratio.

High-risk group was defined as women having one or more of the following established risk factors for gestational diabetes: age ≥35 years, high-risk race/ethnicity (Asian/Pacific Islander, African American, Hispanic, or other), prepregnancy overweight/obesity (BMI ≥23.0 or 25.0 kg/m^2 for Asians or non-Asians, respectively), family history of diabetes, previous gestational diabetes, and pre-existing hypertension. Low-risk group was defined as women having none of the above listed risk factors for gestational diabetes.

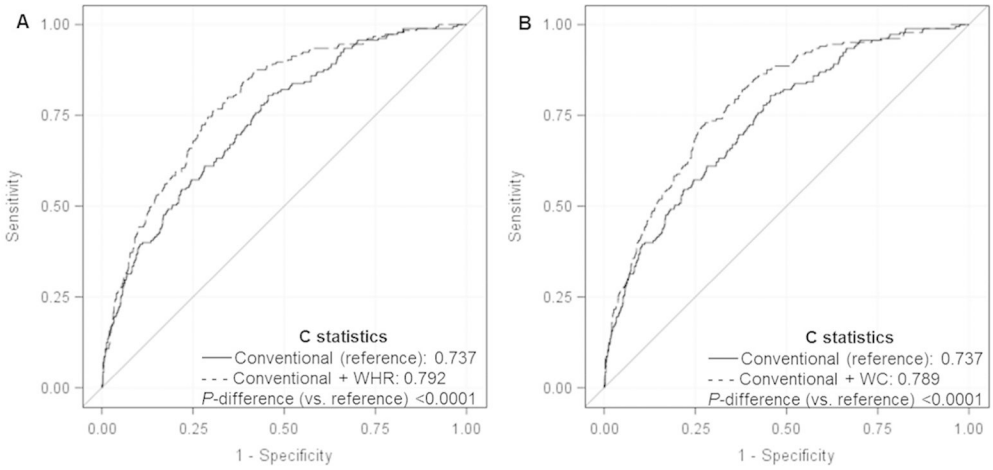

Fig. 2. Leave-one-out cross-validated incremental predictive value of waist-to-hip ratio (A) and waist circumference (B) in early pregnancy for subsequent risk of gestational diabetes

WC, waist circumference; WHR, waist-to-hip ratio. C statistics were estimated by leave-one-out cross validation for risk prediction of gestational diabetes using waist-to-hip ratio or waist circumference (red curve), in addition to the conventional model including established risk factors (age ≥35 years, high5risk race/ethnicity [Asian/Pacific Islander, African American, Hispanic, or other], prepregnancy overweight/obesity (BMI ≥23.0 or 25.0 kg/m^2 for Asians or non-Asians, respectively), family history of diabetes, previous gestational diabetes, and pre-existing hypertension; blue curve).

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, *n (%), years*			<0.001
18–24	301 (19.2)	15 (8.1)	
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 (%)*	664 (42.5)	74 (39.8)	0.49
Prepregnancy BMI categories,[b] *n (%)*			<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 (%)*	93 (5.9)	15 (8.1)	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
Pre-existing hypertension, *n (%)*	55 (3.5)	17 (9.1)	<0.001

	Non-GDM (n = 1,564)	GDM (n = 186)	*P* value[a]
Physical inactivity in early pregnancy,[c] *n (%)*	726 (46.4)	92 (49.5)	0.43
Mean waist-to-hip ratio (SD)	0.86 (0.07)	0.91 (0.06)	<0.001
Mean waist circumference (SD), *cm*	90.3 (14.2)	102.4 (18.5)	<0.001

[a]Obtained by Student's t test for continuous variables and Pearson's χ^2 test for categorical variables.

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

[c]Defined as less than 150 minutes/week 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	
		Waist-to-Hip Ratio	Waist Circumference
Age, years			
<25	1 (reference)	1 (reference)	1 (reference)
25–29	0.64 (0.35, 1.15)	0.73 (0.41, 1.31)	0.76 (0.43, 1.37)
30–34	1.63 (1.11, 2.40)	1.23 (0.86, 1.77)	1.25 (0.87, 1.79)
≥35	1.97 (1.30, 2.97)	1.42 (0.97, 2.07)	1.49 (1.01, 2.19)
P-for-trend	<0.001	0.007	0.005
Race/ethnicity			
Non-Hispanic White	1 (reference)	1 (reference)	1 (reference)
African American	0.73 (0.38, 1.39)	0.68 (0.37, 1.26)	0.73 (0.40, 1.35)
Asian/Pacific Islander	1.99 (1.35, 2.92)	1.72 (1.19, 2.49)	2.24 (1.54, 3.25)
Hispanic	1.04 (0.70, 1.54)	0.90 (0.61, 1.32)	0.98 (0.68, 1.43)
Other	0.58 (0.19, 1.83)	0.55 (0.19, 1.61)	0.56 (0.20, 1.58)
Family history of diabetes			
No	1 (reference)	1 (reference)	1 (reference)
Yes	1.71 (1.28, 2.27)	1.10 (0.83, 1.46)	1.10 (0.83, 1.46)
Previous gestational diabetes			
No	1 (reference)	1 (reference)	1 (reference)
Yes	5.27 (3.90, 7.10)	3.29 (2.31, 4.71)	3.55 (2.47, 5.11)
Pre-existing hypertension			
No	1 (reference)	1 (reference)	1 (reference)
Yes	2.34 (1.49, 3.67)	1.60 (1.04, 2.47)	1.74 (1.12, 2.71)
Prepregnancy BMI categories,[b] *n (%)*			
Underweight	0.54 (0.08, 3.90)	0.65 (0.12, 3.53)	0.53 (0.09, 3.10)
Normal weight	1 (reference)	1 (reference)	1 (reference)
Overweight	2.34 (1.49, 3.67)	1.69 (1.08, 2.64)	1.57 (0.97, 2.55)
Obesity	4.45 (2.94, 6.74)	2.79 (1.78, 4.37)	2.18 (1.22, 3.90)
P-for-trend	<0.001	0.007	0.005
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	<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)

	Univariable Relative Risk	Multivariable Relative Risk	
		Waist-to-Hip Ratio	Waist Circumference
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	<0.001		0.001

[a] Tests of linear trend were conducted by using the median value of each ordered category and fitting it as a continuous variable.

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

[c] Risk estimates were adjusted for gestational age at waist and hip circumference measurement.

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[a]	Quartile 2	Quartile 3	Quartile 4	Proportion mediated, %[b]	*P* for indirect effect
Waist-to-hip ratio and markers of insulin resistance						
Multivariable model[c]						
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 + insulin[d]						
Waist-to-hip ratio	1 (reference)	1.36 (0.31, 5.95)	2.21 (0.49, 9.93)	4.26 (1.06, 17.2)		
Insulin	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-IR[d]						
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 + Adiponectin[d]						
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 model[c]						
Waist circumference	1 (reference)	1.85 (0.48, 7.16)	2.98 (0.71, 12.6)	**6.35 (1.07, 37.7)**	-	-
Multivariable model + insulin[d]						
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-IR[d]						
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 + Adiponectin[d]						
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**

HOMA-IR, insulin and homeostasis model assessment of insulin resistance.

[a] Quartiles are classified based on values among non-gestational diabetes controls.

[b] Proportion mediated on a risk difference scale was calculated as the indirect effect attributed to the particular biomarker divided by the total effect.

[c] Adjusted for prepregnancy body mass index, family history of diabetes, previous gestational diabetes, and pre-existing hypertension.

[d] Adjusted for covariates in the multivariable model and insulin, HOMA-IR, or adiponectin at 16519 weeks of gestation, respectively.