Low Prepregnancy Adiponectin Concentrations Are Associated With a Marked Increase in Risk for Development of Gestational Diabetes Mellitus

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OBJECTIVE—To examine whether circulating total and high–molecular weight (HMW) adiponectin concentrations, measured before pregnancy, are associated with subsequent risk of gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS—This was a nested case-control study among women who participated in the Kaiser Permanente Northern California Multiphasic Health Check-up exam (1984–1996) with a serum sample obtained and who had a subsequent pregnancy (1984–2009). Eligible women were free of recognized diabetes. Case subjects were the 256 women who developed GDM. Two control subjects were selected for each case and matched for year of blood draw, age at exam, age at pregnancy, and number of intervening pregnancies.

RESULTS—Compared with the highest quartile of adiponectin, the risk of GDM increased with decreasing quartile (odds ratio [OR] 1.5 [95% CI 0.7–2.9], 3.7 [1.9–7.2], and 5.2 [2.6–10.1]; $P_{trend} < 0.001$) after adjustment for family history of diabetes, BMI, parity, race/ethnicity, cigarette smoking, and glucose and insulin concentrations. Similar estimates were observed for HMW ($P_{trend} < 0.001$). The combined effects of having total adiponectin levels below the median (<10.29 mg/mL) and being overweight or obese (BMI ≥25.0 kg/m^2) were associated with a sevenfold increased risk of GDM compared with normal-weight women with adiponectin levels above the median (OR 6.7 [95% CI 3.6–12.5]).

CONCLUSIONS—Prepregnancy low adiponectin concentrations, a marker of decreased insulin sensitivity and altered adipocyte endocrine function, is associated with reduced glucose tolerance during pregnancy and may identify women at high risk for GDM to target for early intervention.

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Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first diagnosis during pregnancy, is a common complication of pregnancy. Women with a history of GDM have a sevenfold increased risk of developing type 2 diabetes after delivery (1), and the children of women with GDM are more likely to be obese and develop diabetes (2,3). The underlying etiology of GDM appears to be similar to the physiological abnormalities that characterize diabetes outside of pregnancy and is thought to be due to an inability of the pancreatic β-cells to compensate for the increased insulin resistance induced by pregnancy (4,5). The extent to which insulin resistance or reduced insulin sensitivity leading to GDM occurs even years before pregnancy has not been determined in population-based studies. There is increasing interest in identifying prepregnancy risk factors and biomarkers for GDM to inform future preconception prevention strategies, given the proven success of specific prevention strategies for type 2 diabetes in high-risk populations (6).

Adiponectin is an abundant adipocyte-derived hormone demonstrated to have actions consistent with protection against insulin resistance, inflammation, and atherosclerosis (7). Total adiponectin circulates in the bloodstream as three discrete complexes: a lower–molecular weight trimer, a mid–molecular weight hexamer, and a high–molecular weight (HMW) complex (8). Some evidence suggests that HMW adiponectin is the isoform that mediates the insulin-sensitizing and antiatherogenic effects (9,10). Prospective studies examining adiponectin and incident type 2 diabetes reported that lower circulating total adiponectin concentrations were associated with a higher risk of type 2 diabetes in a dose-response relationship (11). Both total adiponectin (12) and HMW adiponectin (13) are known to decrease significantly in normal pregnancies in response to decreased insulin sensitivity; therefore, it is important to determine whether prepregnancy levels of adiponectin are related to subsequent risk of GDM in order to clarify the temporal sequence of the association. The aim of this study is to examine the association between prepregnancy total and HMW adiponectin concentrations and the risk of developing GDM and to determine whether these associations are independent of known metabolic risk factors for GDM.

RESEARCH DESIGN AND METHODS

—The setting was Kaiser Permanente Northern California (KPNC), an integrated health care delivery system

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that provides medical care for approximately one-third of the underlying population in the San Francisco Bay area. KPNC subscribers are representative of the region (14).

The source population consisted of women KPNC members who completed a voluntary Multiphasic Health Checkup (MHC) at the Kaiser Permanente Oakland Medical Center between 1984 and 1995. KPNC members at this facility were invited to complete a comprehensive health check-up upon enrollment. The MHC consisted of a clinic visit for the completion of questionnaires and clinical measurements, including blood pressure, weight, and serum glucose and cholesterol (measured in serum obtained from a random blood draw). An extra serum sample was collected and stored at −40°C for future use. The goal of the MHC was to provide health maintenance through early diagnosis (15). BMI was calculated as weight in kilograms divided by the square of height in meters; height was measured using a stadiometer and weight using a balance beam scale. Information on age, sex, race/ethnicity, education level, cigarette smoking, family history of diabetes, medical history, alcohol consumption, coffee consumption, and use of medications and hours since last food ingestion was collected using self-administered questionnaires (15). Serum glucose was measured on serum obtained from a random blood draw using the hexokinase method, and total cholesterol was assessed using a Kodak Ektachem Chemistry analyzer by the regional laboratory of KPNC at the time of the MHC exam. This laboratory participates in the College of American Pathologists' accreditation and monitoring program.

Among women 15–45 years of age who participated in the MHC from 1985 to 1996 (n = 27,743 with clinical and questionnaire data, as well as an extra serum sample), we identified 4,098 women who subsequently delivered an infant by 2010 by searching the KPNC hospitalization database and the Pregnancy Glucose Tolerance and GDM Registry (16), an active surveillance registry that annually identifies all pregnancies resulting in a live birth or stillbirth among KPNC members. Women with recognized pregravid diabetes (17) are excluded from the GDM Registry. It also captures the results of all screening and diagnostic tests for GDM from KPNC's electronic laboratory database (data available since 1994).

Table 1—*Characteristics of case and control subjects*

	GDM case subjects	Control subjects	*P*
N	256	497	
Age at MHC exam (years)	28.2 ± 5.5	28.4 ± 5.2	0.78[a]
Age at delivery (years)	35.4 ± 5.1	35.1 ± 4.9	0.43[b]
<30	39 (15.2)	80 (16.1)	
30–34	73 (28.5)	145 (29.2)	
35–39	102 (39.8)	183 (36.8)	
≥40	42 (16.4)	89 (17.9)	
Time between exam and delivery (years)	7.1 ± 4.4	6.7 ± 4.4	0.21[a]
Education (years)			0.24[b]
≤12	74 (28.9)	119 (23.9)	
13–15	85 (33.2)	157 (31.6)	
≥16	92 (35.9)	214 (43.1)	
Unknown	5 (2.0)	7 (1.4)	
Race/ethnicity			<0.001[b]
Non-Hispanic white	50 (19.5)	186 (37.4)	
African American	91 (35.5)	184 (37.0)	
Asian/Pacific Islander	80 (31.3)	84 (16.9)	
Hispanic	35 (13.7)	43 (8.7)	
Parity			<0.001[b]
0	142 (55.5)	278 (55.9)	
1	47 (18.4)	106 (21.3)	
≥2	44 (17.2)	70 (14.1)	
Unknown	23 (9.0)	43 (8.7)	
Gestational age at birth (weeks)			0.01[b]
≥37	218 (84.8)	460 (90.7)	
<37	39 (15.2)	39 (7.7)	
Large-for-gestational age at birth[c]			<0.01[b]
No	198 (81.1)	427 (89.5)	
Yes	46 (18.9)	50 (10.5)	
Alcohol			<0.001[b]
None	74 (28.9)	81 (16.3)	
Occasional or more drinks/day	149 (58.2)	346 (69.6)	
Unknown	33 (12.9)	70 (14.1)	
Smoking			0.40[b]
Never	150 (58.6)	277 (55.7)	
Former	37 (14.5)	92 (18.5)	
Current	38 (14.8)	61 (12.3)	
Unknown	31 (12.1)	67 (13.5)	
Hypertension status at index pregnancy			<0.001[b]
No hypertension	138 (53.9)	326 (65.5)	
Preexisting hypertension[d]	28 (10.9)	18 (3.6)	
Gestational hypertension	33 (12.9)	68 (13.7)	
Preeclampsia	42 (16.4)	37 (7.4)	
Family history of diabetes			<0.001[b]
Yes	151 (59.0)	192 (38.6)	
BMI (kg/m^2)	26.0 ± 6.5	23.7 ± 4.6	<0.001[b]
Weight change from MHC to pregnancy (kg)	8.9 ± 9.9	4.4 ± 8.2	<0.001[a]
Rate of gestational weight gain (kg/week)[e]	0.3 ± 0.2	0.4 ± 0.2	<0.05[b]
Serum glucose (mg/dL)	89.6 ± 13.5	83.6 ± 8.3	<0.001[a]
Serum cholesterol (mg/dL)	182.9 ± 33.2	176 ± 32.6	<0.01[a]
Systolic blood pressure (mmHg)	115.6 ± 14.7	113.3 ± 13.4	<0.05[a]
Diastolic blood pressure (mmHg)	69.9 ± 10.4	68.3 ± 9.0	<0.05[a]
White blood cell count (1,000 cells/mm^3)	6.9 ± 1.9	6.5 ± 1.9	<0.01[a]
HMW adiponectin (μg/mL)	2.8 ± 1.5	4.0 ± 2.0	<0.001[f]

Continued on p. 3932

Table 1—*Continued*

	GDM case subjects	Control subjects	*P*
Total adiponectin (μg/mL)	7.7 ± 3.5	10.6 ± 4.4	<0.001[f]
Insulin (μU/mL)	25.8 ± 28.6	17.5 ± 16.7	<0.001[f]
HOMA-IR index[g]	4.1 ± 3.5	2.9 ± 2.9	<0.001[f]

Data are *N* (%) or means ± SD unless otherwise indicated. [a]*t* test to compare differences in mean values of continuous variables except as noted below for Wilcoxon test. [b]χ^2 test for categorical variables. [c]Subset of women with singleton births; large-for-gestational age >90th percentile based on race and gestational age–specific quantiles. [d]Includes women who experienced preeclampsia superimposed on preexisting hypertension. [e]Weight change in kilograms per week from beginning of index pregnancy until screening glucose (measurement obtained 1 h after the 50-g oral challenge). Data were available for 226 case and 407 control subjects. [f]Wilcoxon test for differences in median values. [g]Subset of women fasting for >6 h at the time of MHC exam (case subjects, *n* = 149; control subjects, *n* = 269).

Study design

This is a nested case-control study within a cohort of 4,098 women who took part in an MHC exam, had an extra tube of serum stored for future use, and had a subsequent pregnancy—on average, 6 years after the MHC exam. All cohort members who went on to develop GDM were included as case subjects; two control subjects were selected for each case from among women not meeting the GDM case definition.

GDM case definition

We identified 267 women with GDM according to the KPNC electronic databases: case subjects had either *1*) glucose values obtained during a standard 100-g, 3-h oral glucose tolerance test that met the American College of Obstetricians and Gynecologists plasma glucose thresholds for GDM (18) in the laboratory database (*n* = 228) or *2*) a hospital discharge diagnosis of GDM in the electronic hospital discharge database for pregnancies occurring before the electronic laboratory data were available (prior to 1994; *n* = 39). Standardized medical chart review was conducted by trained abstractors to confirm that these 267 women had a 100-g, 3-h oral glucose tolerance test meeting the American College of Obstetricians and Gynecologists criteria (18) for GDM (plasma glucose thresholds: fasting 5.3 mmol [95 mg/dL], 1 h 10.0 mmol/L [180 mg/dL], 2 h 8.6 mmol/L [155 mg/dL], and 3 h 7.8 mmol/L [140 mg/dL]). Case subjects were excluded if at the time of the MHC exam they had a random glucose >200 mg/dL (*n* = 6), no indication of GDM during the index pregnancy (*n* = 4) or impaired glucose tolerance with insufficient follow-up testing (*n* = 1), leaving a total of 256 confirmed cases of GDM.

Control selection and matching criteria

From among those women without an indication of GDM, control subjects were randomly selected; two control subjects were individually matched to each case on year of MHC serum collection date (±3 months), age at MHC serum collection (±2 years), number of intervening pregnancies (0, 1, ≥2), and age at delivery of the index pregnancy (±2 years). We matched for the year of serum collection to account for any potential degradation in the quality of the serum over time, thereby assuring the sample storage time was approximately the same for case and control subjects. Since GDM is more common in older women, we matched on age at serum collection and age at delivery. We matched on number of pregnancies to account for any differences in pregnancies between the initial exam and the index pregnancy. Control subjects were excluded from the analysis if they had glucose values diagnostic of GDM found during medical chart abstraction (*n* = 5), had an abnormal screening glucose but no follow-up diagnostic glucose test (*n* = 5), or had one abnormal glucose value on the diagnostic glucose test (*n* = 5), suggestive of "mild" GDM. Of the 512 matched control subjects identified, 497 were eligible.

Exposure variables

Serum biomarker assays. Serum samples were thawed, aliquoted, and transported in batches on dry ice to the laboratory of P.J.H. at the University of California, Davis, for analysis. Serum adiponectin was measured with a commercially available radioimmunoassay (Millipore [formerly Linco Research]) using ^{125}I-labeled murine adiponectin and a multispecies anti-adiponectin antibody. The assay has a sensitivity of 1 ng/mL and a linearity of 200 ng/mL. The intra- and interassay coefficients of variation are <6.0% and <9.0%, respectively. HMW adiponectin was measured with a commercially available ELISA kit (cat. no. EZHMWA-64 K; Millipore), a method that has recently been validated against Western blot analysis (19). Insulin was measured with a radioimmunassay (Millipore); the intra-assay and interassay coefficients of variation are <4.0% and <10%, respectively.

Statistical analysis

Conditional logistic regression was used to obtain odds ratios (ORs) to estimate the relative risk of GDM in relation to prepregnancy adiponectin levels. Associations of prepregnancy adiponectin levels with prepregnancy BMI, age, and glucose, insulin, and cholesterol levels were estimated with Spearman correlation coefficients. Women were categorized by quartile of adiponectin levels as defined among control subjects. Variables evaluated for confounding included race/ethnicity, pregravid BMI, parity, cigarette smoking, and family history of diabetes—all assessed at the time of adiponectin measurement. To assess confounding, we entered covariates into a logistic regression model, one at a time, and compared the adjusted and unadjusted estimates. We first included covariates that altered unadjusted estimates by ≥10%. We then added potential intermediary variables of the effects of adiponectin on GDM: prepregnancy glucose and insulin levels (and further adjusted for hours since last food intake) for these models.

To assess the potential modifying effects of prepregnancy BMI (overweight or obese ≥25 kg/m^2 vs. not overweight or obese <25 kg/m^2), race/ethnicity (white, Asian, Hispanic, and African American), and median time since MHC exam (≥6.2 years vs. <6.2 years), we included appropriate cross-product (interaction) terms in regression models. To examine the effects of weight gain after the MHC exam, we added weight gain to the fully adjusted conditional logistic regression model (20). This study was approved by the human subjects committee of the Kaiser Foundation Research Institute.

RESULTS—Table 1 summarizes the demographic, anthropometric, reproductive, and metabolic characteristics of the study participants by case-control status.

Women who developed GDM were more likely to have <12 years of education, to be Asian or Hispanic, to be nulliparous at the time of the exam, to abstain from alcohol, and to have a family history of type 2 diabetes compared with women who did not develop GDM. Women who developed GDM also had higher levels of several cardiometabolic risk factors including BMI at the MHC exam, serum glucose, total cholesterol, systolic and diastolic blood pressure, serum insulin concentrations, and weight gain from the MHC exam to the index pregnancy. Mean prepregnancy HMW and total adiponectin concentrations were both significantly lower in women who developed GDM compared with those who did not develop GDM (2.8 vs. 4.0 and 7.7 vs. 10.6, respectively; *P* value <0.001). Table 2 shows the correlation of serum total and HMW adiponectin levels with several metabolic covariates separately for case and control subjects (Table 2).

As presented in Table 3, women in the lowest quartile of total adiponectin distribution (1.2–7.2 μg/mL) prior to pregnancy experienced a fivefold increased risk of GDM compared with women whose values fell within the highest quartile (13.1–25.2 μg/mL, OR 5.18 [95% CI 2.65–10.11]) after adjustment for race/ethnicity, BMI, parity, family history of diabetes, smoking status at time of MHC exam, insulin, glucose, and fasting status. Since gaining ≥5.0 kg from the time of MHC exam to pregnancy was associated with a 3.6-fold increased risk of GDM compared with women who maintained or lost weight (≤0.5 kg) (OR 3.6 [95% CI 2.15–6.03]), weight gain was added to the model and similar results were obtained (results not shown).

When the combined effects of adiponectin levels and maternal BMI were examined, among normal-weight women (BMI <25.0 kg/m^2), having low concentrations of total adiponectin (defined as <10.29 mg/mL) was associated with a 3.5-fold increased risk of GDM compared with high total adiponectin levels (defined as ≥10.29 mg/mL). Women who were overweight or obese (BMI ≥25.0 kg/m^2) and had high adiponectin concentrations had a twofold increased risk of GDM compared with normal-weight women with the same adiponectin concentrations. Women who both were overweight and had low total adiponectin had 6.8-fold increased risk of GDM. Similar results were observed with HMW adiponectin (Fig. 1).

The association remained also when women were stratified by median time since MHC exam. In a stratified analysis examining quartiles of total adiponectin and GDM risk, the ORs for the lowest compared with highest quartile of adiponectin were similar when the time since initial exam was years >6.2 years (the median time since exam), 5.0 (95% CI 2.0–12.0), compared with when it had been <6.2 years since the exam, 4.2 (2.0–9.1); there was no significant interaction by time since exam (*P* = 0.66). There was also no significant interaction by pregravid BMI or race/ethnicity. While the interaction with race was not statistically significant, we found some suggestion that the association between adiponectin and GDM risk may be stronger for Asians and Hispanics for continuous adiponectin: white OR 0.86 (95% CI 0.77–0.96), black 0.89 (0.82–0.98), Asian/Pacific Islander 0.77 (0.67–0.88), and Hispanic 0.62 (0.42–0.91).

A sensitivity analysis restricted to the 149 case and 269 control subjects who had fasted for >6 h found similar adjusted ORs associated with being in the lower two quartiles of adiponectin and GDM risk (quartile 2, 3.4 [95% CI 1.6–7.1], and quartile 1, 4.3 [95% CI 2.0–9.4]), compared with quartile 4. Among this subset, we further adjusted for homeostasis model assessment of insulin resistance (HOMA-IR) and found that the ORs associated with being in the lower two quartiles of adiponectin were slightly attenuated but remained significant (quartile 2, 3.2 [95% CI 1.5–6.9], and quartile 1, 3.7 [95% CI 1.7–8.1] compared with quartile 4).

Finally, we examined the association between adiponectin and GDM among a subset of women without the strongest risk factors for GDM: women who were normal weight (BMI <25.0 kg/m^2) and had no family history of GDM (*n* = 55 case and *n* = 224 control subjects). Among this subset of low-risk women, the OR associated with continuous adiponectin was 0.70 (95% CI 0.56–0.88) for HMW and 0.84 (95% CI 0.76–0.92) for total adiponectin after adjustment for matching variables, BMI (continuous), parity, and race.

CONCLUSIONS—In this nested case-control study, we found that lower adiponectin concentrations measured, on average, 6 years before pregnancy were associated with a 5.0-fold increased risk of developing GDM. We found similar associations between total and HMW adiponectin and GDM even when the measurement occurred ≥6 years before pregnancy, confirming the robustness of the association. Of note, these relationships were independent of known risk factors for GDM, including BMI, age, and race/ethnicity, as well as markers of insulin resistance (specifically, glucose and insulin) that have been associated with adiponectin (7) concentrations and the development

Table 2—*Pearson correlation coefficients of pregravid maternal plasma total and HMW adiponectin with selected (pregravid) maternal characteristics*

	Total adiponectin		HMW adiponectin	
	GDM case subjects	Control subjects	GDM case subjects	Control subjects
n	256	497	256	497
Maternal age at exam (years)	−0.17 (<0.01)	0.06 (0.16)	−0.16 (0.01)	0.09 (0.05)
BMI (kg/m^2)	−0.20 (<0.01)	−0.04 (0.41)	−0.19 (<0.01)	−0.01 (0.80)
Serum glucose (mg/dL)	−0.20 (<0.01)	−0.23 (<0.0001)	−0.23 (<0.001)	−0.23 (<0.0001)
Serum insulin (μU/mL)	−0.12 (<0.05)	−0.03 (0.45)	−0.12 (0.05)	−0.07 (0.12)
Serum cholesterol (mg/dL)	−0.25 (<0.0001)	−0.14 (<0.01)	−0.26 (<0.0001)	−0.16 (<0.001)
HOMA-IR index*	−0.36 (<0.0001)	−0.08 (0.17)	−0.37 (<0.0001)	−0.11 (0.07)

Data are *r* (*P*) unless otherwise indicated. *Subset of women fasting for >6 h at the time of MHC exam (case subjects, *n* = 149; control subjects, *n* = 269).

Table 3—*ORs (95% CI) for GDM associated with prepregnancy circulating adiponectin concentrations from conditional logistic regression models*

	Conditional logistic regression models		
Prepregnancy risk factor	Crude	Multivariable adjusted[a]	Multivariable adjusted[b]
Total adiponectin (μg/mL)			
Continuous	0.82 (0.78–0.86)	0.83 (0.78–0.88)	0.83 (0.78–0.88)
Quartile 1 (1.18–7.19)	5.61 (3.31–9.50)	4.69 (2.56–8.57)	5.18 (2.65–10.11)
Quartile 2 (7.20–10.28)	3.22 (1.89–5.50)	3.34 (1.82–6.13)	3.71 (1.90–7.24)
Quartile 3 (10.29–13.12)	1.18 (0.65–2.14)	1.16 (0.60–2.22)	1.45 (0.73–2.88)
Quartile 4 (13.13–25.22)	1.00	1.00	1.00
HMW adiponectin (μg/mL)			
Continuous	0.65 (0.58–0.73)	0.68 (0.60–0.78)	0.67 (0.58–0.78)
Quartile 1 (0.45–2.48)	5.88 (3.44–10.08)	4.74 (2.54–8.84)	5.25 (2.63–10.48)
Quartile 2 (2.49–3.70)	3.14 (1.83–5.40)	2.93 (1.60–5.38)	3.39 (1.73–6.63)
Quartile 3 (3.71–4.96)	1.37 (0.76–2.48)	1.20 (0.63–2.29)	1.46 (0.74–2.88)
Quartile 4 (4.97–11.31)	1.00	1.00	1.00

[a]Adjusted for race/ethnicity, BMI, parity, family history of diabetes, and smoking status at time of MHC exam.
[b]Further adjusted for insulin, glucose (as tertiles), and fasting status (defined as ≥6 h since last food at time of MHC exam).

of reduced glucose tolerance in both pregnant and nonpregnant populations (21,22). These associations were not mediated by subsequent weight gain. Our findings are among the first to suggest that low circulating adiponectin concentrations may predict GDM years prior to pregnancy and extend existing knowledge pertaining to pregravid risk factors for GDM. We found that the association between prepregnancy adiponectin and GDM risk remained a significant risk factor for GDM among the subset of women who were normal weight and had no family history of GDM: two strong risk factors for GDM. This finding is of clinical relevance because it suggests that adiponectin may help identify a group of high-risk women who may otherwise not be identified as being at high risk of developing GDM.

Our findings are consistent with previous studies of adiponectin and type 2 diabetes. A systematic review and meta-analysis of prospective studies examining adiponectin and incident type 2 diabetes found that higher adiponectin levels were associated with a 30% lower risk of type 2 diabetes (relative risk [RR] 0.72 [95% CI 0.67–0.78]) per 1 log μg/mL increment in adiponectin levels, consistent with a dose-response relationship (11). Less is known about the role of adiponectin in GDM risk. A couple of studies assessing the prospective association between adiponectin levels in the first trimester of pregnancy and the risk of GDM found that women with GDM had lower levels of adiponectin compared with women who did not develop GDM (23–25), which is consistent with the current study. Other previous studies (26) with a small sample size examined adiponectin levels during the third trimester and GDM (24,27). However, since both total adiponectin (12) and HMW adiponectin (13) have been shown to decrease significantly in normal pregnancies, the previous studies were not able to assess whether the association between adiponectin and increased risk of GDM was related only to the physiologic changes that accompany normal pregnancy. Pregnancy-induced changes such as rapid increases in body weight and fat, insulin resistance, inflammation, and lipids are related to both lower adiponectin and reduced glucose tolerance (7). The findings of our prospective study suggest that altered adiponectin levels in women with normal glucose metabolism years before pregnancy may lead to decreased glucose tolerance during pregnancy, such as GDM.

There is biologic plausibility for an important role of adiponectin in GDM risk. The underlying etiology of GDM is believed to be diminished insulin secretion prepregnancy coupled with pregnancy-induced insulin resistance (5). These results add more evidence to support this possible mechanism. Adiponectin has been shown to promote β-cell function and survival and decrease hepatic glucose output (thereby lowering systemic glucose levels) (28). Therefore, low adiponectin levels may lead to both reduced insulin secretion and increased insulin resistance. In human studies, adiponectin has been shown to be inversely related to visceral adiposity (29) and liver fat accumulation (30) and positively correlated with truncal fat, all of which have been shown to be associated with insulin resistance and diabetes risk independent of BMI (28).

We found no evidence that weight gain either before pregnancy affected the association between adiponectin and GDM regardless of baseline BMI. However, adiponectin levels have been shown to increase after significant weight loss either by caloric restriction or from weight loss surgery (gastric bypass) (28), and medications that increase the number of small adipocytes, such as thiazolidinediones, also increase adiponectin production (31). While this suggests that adiponectin can be modified, more information is needed to determine strategies for increasing circulating adiponectin concentrations to better inform possible prevention strategies for both GDM and type 2 diabetes.

Strengths of this study include our ability to exclude women with glucose values indicative of recognized, pregestational diabetes. We had the unique ability to look at adiponectin levels measured several years before pregnancy on a large number of GDM case and matched control subjects. We were able to control for markers of insulin resistance (HOMA-IR) among a subset, and our findings remained when adjusted for potential mediators. The study was limited by the lack of data on more informative measures of adiposity in addition to BMI, such as waist circumference or percent body fat, and we therefore were not able to assess whether the association between adiponectin and GDM was possibly mediated by increased visceral fat. We also lacked information on diet and physical activity changes that may have occurred from the baseline exam to the subsequent pregnancy; therefore, we were unable to assess the impact of lifestyle changes on GDM risk in this study. We only had a single measurement of adiponectin, which may be subject to variation; such misclassification would be nondifferential and bias our results toward the null hypothesis. Finally, our samples were nonfasting; however, the majority of studies have found either no or only a minor effect of

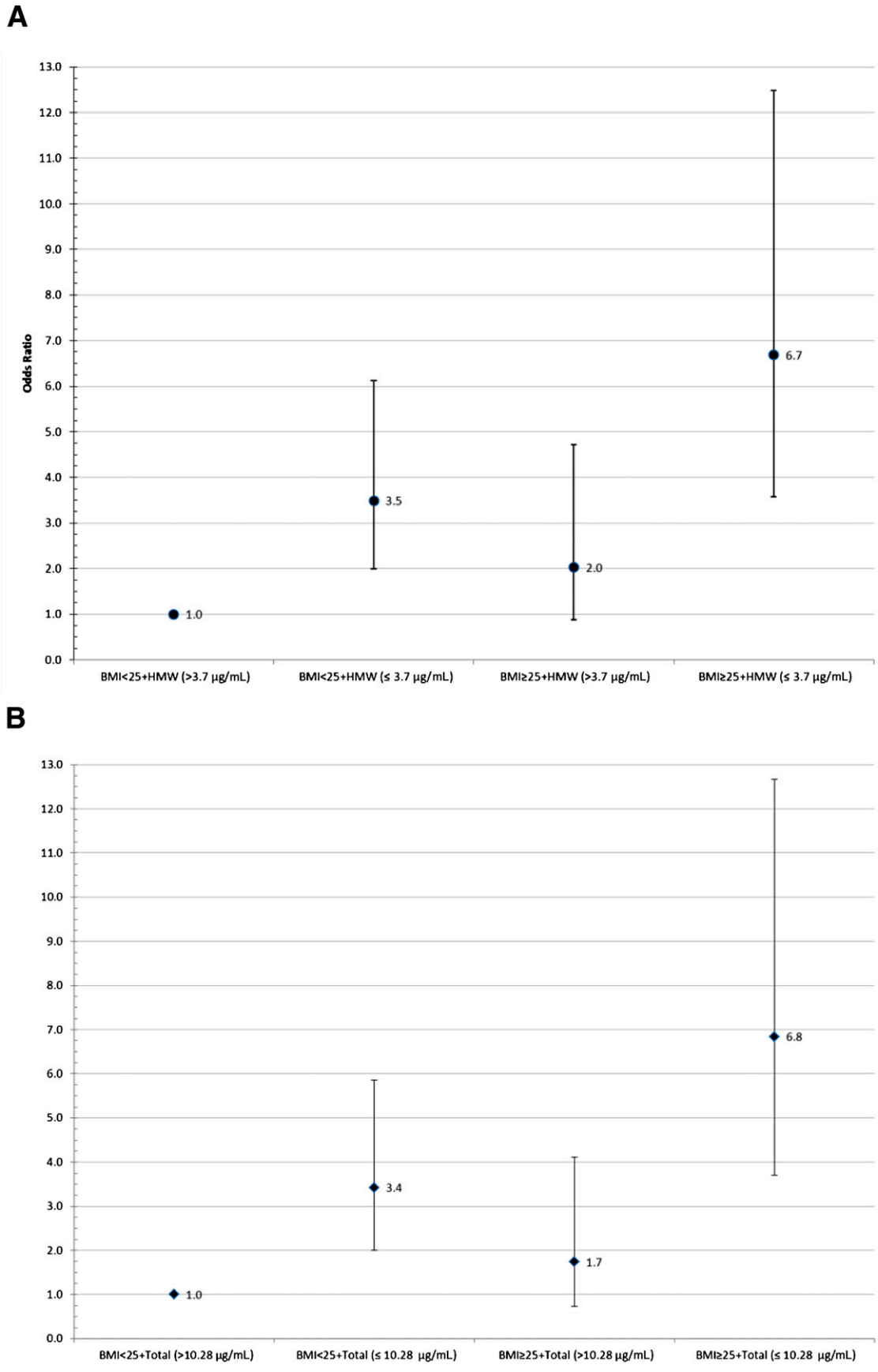

Figure 1—*ORs for association between joint effects of pregravid adiponectin and BMI and risk of GDM.* A*: Total adiponectin.* B*: HMW adiponectin.*

feeding/fasting on circulating adiponectin concentrations (7), and our findings were similar in the subanalysis restricted to women who fasted for ≥6 h.

In summary, after adjusting for potential confounding factors and clinical factors known to be related to insulin resistance, we found that low adiponectin concentrations, measured on average 6 years prior to pregnancy, were associated with a fivefold increased risk of GDM. Circulating concentrations of total and HMW adiponectin represent potentially useful new biomarkers regarding who is at risk for GDM beyond the currently established clinical and demographic risk factors. Future studies designed to be able to assess the sensitivity and specificity of adiponectin in predicting GDM will be valuable to help further clarify the clinical utility of these biomarkers.

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M.M.H. designed the study, oversaw data collection, and wrote the manuscript. J.D. conducted data analysis and contributed to writing the manuscript. P.J.H. performed the analyses of the biospecimens and contributed to the data analysis and writing the manuscript. C.P.Q. contributed to the study design, provided statistical expertise, and contributed to writing the manuscript. S.S. assisted with data collection and contributed to writing and editing the manuscript. S.E. contributed to writing and editing the manuscript. A.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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