

# History of Gestational Diabetes Mellitus and Future Risk of Atherosclerosis in Mid-life: The Coronary Artery Risk Development in Young Adults Study

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**Background**—History of gestational diabetes mellitus (GDM) increases lifetime risk of type 2 diabetes (DM) and the metabolic syndrome (MetS), which increase risk of cardiovascular disease. It is unclear, however, whether GDM increases risk of early atherosclerosis independent of pre-pregnancy obesity and subsequent metabolic disease.

**Methods and Results**—Of 2787 women (18 to 30 years) enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) study, we studied 898 (47% black) who were free of DM and heart disease at baseline (1985-1986), delivered  $\geq 1$  post-baseline births, reported GDM history, and had common carotid intima media thickness (ccIMT, mm) measured in 2005-2006. We used multivariable linear regression to assess associations between GDM and ccIMT adjusted for race, age, parity, and pre-pregnancy cardiometabolic risk factors. We assessed mediators (weight gain, insulin resistance, blood pressure), and effect modification by incident DM or MetS during the 20-year period. Of the 898 women, 119 (13%) reported GDM (7.6 per 100 deliveries). Average age was 31 at last birth and 44 at ccIMT measurement for GDM and non-GDM groups. Unadjusted mean ccIMT was 0.023 mm higher for GDM than non-GDM groups ( $P=0.029$ ), but pre-pregnancy BMI attenuated the difference to 0.016 mm ( $P=0.109$ ). In 777 women without subsequent DM or the MetS, mean ccIMT was 0.023 mm higher for GDM versus non-GDM groups controlling for race, age, parity, and pre-pregnancy BMI (0.784 versus 0.761,  $P=0.039$ ). Addition of pre-pregnancy insulin resistance index had minimal impact on adjusted mean net ccIMT difference (0.22 mm). Mean ccIMT did not differ by GDM status among 121 women who developed DM or the MetS ( $P=0.58$ ).

**Conclusions**—History of GDM may be a marker for early atherosclerosis independent of pre-pregnancy obesity among women who have not developed type 2 diabetes or the metabolic syndrome. (*J Am Heart Assoc.* 2014;3:e000490 doi: 10.1161/JAHA.113.000490)

**Key Words:** atherosclerosis • gestational diabetes mellitus • pregnancy • prospective cohort studies • women

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Failure to adapt to the greater physiological demands<sup>1</sup> of pregnancy may lead to complications that signify increased cardiovascular disease (CVD) risk in women. Gestational diabetes mellitus (GDM), defined as glucose intolerance that is first recognized during pregnancy, is associated with maternal obesity and confers a 4- to 7-fold greater risk of incident type 2 diabetes (DM),<sup>2,3</sup> and increased risk of developing the metabolic syndrome (MetS) in mid-life.<sup>4,5</sup> In addition, a history of GDM among nondiabetic women is characterized by elevations in fasting glucose and insulin concentrations,<sup>6</sup> as well as dyslipidemia and greater inflammation in the absence of the MetS.<sup>7-9</sup>

Previous history of GDM not only increases a woman's risk of future metabolic disease, but has been linked to excess heart disease risk in women.<sup>10</sup> Studies have reported a 66% to 85% higher risk of CVD,<sup>11</sup> including coronary artery disease, myocardial infarction, and/or stroke,<sup>7,12</sup> as well as a 56% higher risk of self-reported CVD.<sup>13</sup> However, these findings

are based on administrative or clinical databases with retrospective or cross-sectional study designs that have limited ability to distinguish whether the GDM and CVD association was due to pre-pregnancy obesity or the GDM pregnancy itself, rather than future onset of type 2 diabetes<sup>12</sup> and/or the metabolic syndrome. It is unclear whether a history of GDM increases CVD risk independent of these subsequent metabolic disorders because previous studies have lacked biochemical screening for metabolic diseases before and after pregnancy to assess risk preceding CVD events.

Carotid artery intima-media thickness (cIMT) is a subclinical measure of early atherosclerosis that strongly predicts heart disease and stroke, particularly in women.<sup>14</sup> Cross-sectional studies that measured cIMT during pregnancy reported higher<sup>15–17</sup> or similar<sup>18</sup> levels for GDM and non-GDM pregnancies. However, these studies did not measure cIMT again post-delivery to ascertain if differences persisted. Retrospective studies have measured carotid artery IMT up to several years post-delivery, but have been unable to shed light on the temporality of type 2 diabetes or cardiometabolic disease onset to endothelial changes after GDM pregnancy.<sup>19–23</sup> Thus, longitudinal study designs with frequent metabolic screening during the reproductive years (before and after pregnancies) are essential to the evaluation of a history of GDM as an independent risk factor for early atherosclerosis prior to the onset of metabolic diseases.

In the CARDIA Study biracial cohort of black women and white women (1986–2006), we sought to conduct a longitudinal analysis of women without prior heart disease or diabetes mellitus before pregnancies to examine where GDM pregnancy leads to greater carotid artery IMT in women in midlife at age 38 to 50 years. CARDIA prospectively measured CVD risk factors before and after pregnancy as well as having women to report GDM pregnancies at exams within 1 to 5 years post-delivery. We hypothesize that pregnancy GDM status will be related to subsequent measures of early atherosclerosis, and that this association depends on the onset of DM or the MetS during follow-up.

## Materials and Methods

The CARDIA Study is a population-based, multi-center, longitudinal, observational study examining the trends and determinants of coronary heart disease risk factors in young black and white men and women.<sup>24,25</sup> In 1985–1986, a total of 5115 subjects (2787 women) aged 18 to 30 years (52% black) were recruited from 4 geographic areas in the United States: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Retention rates at follow-up exams 7, 10, 15, and 20 years later (2005–2006) were

81%, 79%, 74%, and 72% of the surviving cohort, respectively.<sup>26</sup> Institutional review boards at each participating study center approved the study. Written, informed consent was obtained from subjects.

## Sample Selection

From 2787 women enrolled at baseline (1985–1986), we selected women who had cIMT measured 20 years later (2005–2006), delivered one or more post-baseline births, and had no prior heart disease or diabetes before pregnancies. Of 2062 women who attended the year 20 exam, we excluded 790 women without any post-baseline births, 212 missing cIMT measurements, and 129 with history of heart disease, 17 recently or currently pregnant, and 9 with previous hysterectomy at baseline. We also excluded women with clinically relevant diabetes at baseline and those who developed diabetes before the first post-baseline birth (n=7). The analytic sample included 898 women (delivered 1572 births), of whom 119 (13%) reported a history of GDM during the 20-year follow-up (1986–2006). Women excluded from the analysis were more likely to be of black race, have fewer years of education, and higher BMI at baseline.

## Data Collection

Participant characteristics, including lifestyle, sociodemographic, medical conditions, medication use, family history of diabetes, post-baseline diabetes diagnosis, reproductive events (pregnancies and births), and GDM status, as well as clinical assessments, anthropometric measurements, and blood specimens were obtained at baseline and follow-up exams using standardized research methodologies that included self- and interviewer-administered questionnaires.<sup>24</sup>

## Common Carotid Artery Intima-Media Thickness Measurements

Carotid Artery intima-media thickness is an early measure of subclinical atherosclerosis, and predicts myocardial infarction and stroke in women. Measurements were obtained from 3 anatomic locations in the carotid arteries: the internal (1 to 8), Bulb (1 to 8), and the Common (1 to 4) sections at the year 20 exam in 2005–2006. The common carotid artery maximum intima-media thickness has the strongest correlation with CVD risk factors in the CARDIA cohort.<sup>27</sup> Therefore, we selected the maximum cIMT measure, which is defined as the mean of the maximum wall thickness obtained from ultrasound studies via standard protocol using a GE-Logiq-700. We used a high-resolution M12L transducer operating at a frequency of 13 MHz to image the common carotid artery

(CCA). Four measurements were obtained for the common carotid arteries from the left and right sides to calculate the mean near and far wall maximum thickness.<sup>27</sup>

## Pregnancies and GDM Status

Pregnancies and deliveries were assessed at each exam. Participants reported current pregnancy or lactation status, the number of pregnancies and births since the previous exam and how they ended (abortion, miscarriage, and live or stillbirths), as well as the length(s) of gestation, multi-fetal gestation, dates of delivery(ies), gestational hypertensive disorders, and diabetes only during pregnancy (GDM pregnancy). Post-baseline births were defined as delivery of a live infant >20 weeks gestation that was conceived after the baseline CARDIA exam, and delivered within subsequent exam intervals (0 to 2, 2 to 5, 5 to 7, 7 to 10, 10 to 15, 15 to 20). Parity at year 20 signifies the total number of live births. We calculated time from baseline to the first post-baseline birth, and the time from the last birth to the year 20 exam (years), as well as maternal age at each birth. We validated self-report of GDM history by abstraction of glucose tolerance test results from prenatal records for a subsample of 165 women who delivered 200 births after CARDIA baseline to determine whether blood glucose during pregnancy was elevated to levels meeting GDM diagnostic criteria.<sup>28</sup> Sensitivity for classification by self-report as ever having GDM was 100% (20 of 20) and specificity was 92% (134 of 145).<sup>3</sup>

## Cardiometabolic Risk Factor Measurements

All biochemical measurements were obtained in the non-pregnant and non-lactating state in years 0, 7, 10, 15, and/or 20, and were used to classify women with incident DM and the MetS before pregnancy and after pregnancies during follow-up. The baseline exam (1985-1986) measurements were used to assess pre-pregnancy cardiometabolic risk factors because our objective was to distinguish the pre-pregnancy effects from the long-term effects of pregnancy on maternal risk factors across successive pregnancies.<sup>29</sup> Venous blood samples were drawn in the morning after an overnight fast of  $\geq 8$  hours. Procedures for blood specimen collection and methodologies to assay plasma concentrations of triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) including the Friedewald equation with TG  $>400$  mg/dL, total cholesterol (TC), glucose, and insulin are reported elsewhere.<sup>30,31</sup> Diagnosis of DM was ascertained based on fasting serum glucose values at exams in years 0, 7, 10, 15, and 20, 2-hour glucose from the 75 g oral glucose tolerance test at exams in years 10, 15, and 20, glycosylated hemoglobin (HbA1c) at year 20, as well as the use of diabetes medications and self-report of

diabetes at all exams.<sup>3</sup> Classification of incident DM was determined by criteria from the American Diabetes Association,<sup>32</sup> and the Metabolic Syndrome by the NCEP-ATP III criteria.<sup>33</sup> Homeostasis model assessment index (HOMA-IR) was derived for insulin resistance using the equation: [fasting glucose (mmol/L)  $\times$  fasting insulin (mU/L)]/22.5.<sup>34</sup>

At each exam, blood pressure was measured 3 times at 1-minute intervals after an initial 5-minute rest using the Hawksley random-zero (RZ) sphygmomanometer from baseline through year 15; the first and fifth phase Korotkoff sounds were recorded with second and third measurements averaged.<sup>25</sup> The OmRON HEM907XL oscillometer was used at year 20. The appropriate cuff size (small, medium, large, extra-large) was based on the upper arm circumference, as the midpoint between the acromion and the olecranon. Systolic (SBP) and diastolic blood pressure (DBP) measurements in year 20 were calibrated to random-zero sphygmomanometers from prior CARDIA exams.<sup>35</sup> Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg or self-reported anti-hypertensive medication use.

Certified technicians measured weight, height, and waist circumference using standardized protocol to the nearest 0.1 kg or 0.5 cm in participants wearing light clothing and without shoes. Waist circumference was measured midway between the iliac crest and bottom of the rib cage.<sup>36</sup> Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared.

## Covariates

Sociodemographic, medical treatment, and other characteristics were assessed before and after pregnancy including race, age, medication use (anti-hypertensive, diabetes, lipid-lowering), and cigarette smoking status (current, past, or never) and smoking quantity in pack-years. Categorical variables were race (black, white), smoking (never, current, or past), BMI ( $<25$ , 25 to 29.9,  $\geq 30$ ), menopausal status during follow-up (ever), use of lipid lowering medications, gestational hypertensive disorders, incident DM, onset of the MetS, Center, family history of heart disease, and family history of diabetes. Family history of diabetes was based on report of one or more first-degree relatives (father, mother, or siblings) with diabetes at exam years 0, 5, 10, 15, and 20. Family history of heart disease was similarly obtained via self-report.

## Statistical Analysis

Baseline and follow-up differences in characteristics of participants were described by GDM history using chi-square statistics for categorical variables (clinic site, race, education, BMI, family history of diabetes, parity) and by comparison of

means for continuous variables using *t*-tests (fasting plasma lipids, age, BMI, HOMA-IR, systolic and diastolic blood pressure). Bivariate associations between GDM group characteristics at baseline and at the 20-year follow-up were also examined using *t*-tests and chi-square statistics. Median and interquartile ranges were reported for age at first birth and time since last birth to the year 20 exam. All *P*-values presented are for 2-sided tests; statistical significance was defined as  $<0.05$ .

Unadjusted and multivariable adjusted means (95% CI) and mean net group differences (95% CI) for cclMT by race and GDM history were estimated from linear regression models using procedures from SAS for Windows 9.1.3 (SAS Institute Inc). Covariates evaluated as potential confounders based on a priori hypotheses included pre-pregnancy BMI, age, parity, smoking status, and education level. Covariates were excluded as confounders if they were not associated with the dependent variables independent of the other covariates. Adjusted models were devised by stepwise addition of covariates as confounders, and then addition of pre-pregnancy BMI, cardiometabolic risk factors (fasting glucose, HOMA-IR) and weight gain (BMI at year 20), and incident DM, and/or the MetS. Weight gain, HOMA-IR, and blood pressure at year 20 were also examined as mediators (ie, on the causal pathway) of the GDM and cclMT association. Effect modification for the association between GDM status and cclMT by race, age, pre-pregnancy BMI, and DM or MetS (combined) was evaluated by introduction of cross-product terms for additive interaction into the models (significance  $P<0.10$ ). The interaction for DM or MetS reached statistical significance at  $P=0.01$ . We also estimated adjusted least square means for cclMT among GDM and non-GDM groups stratified by DM and/or the MetS groups.

## Results

The analytic sample of 898 women (47% black) were an average age of 24 (range 18 to 30 years) and free of diabetes and heart disease at baseline (1985-1986). They delivered one or more live post-baseline births (total of 1572 births) from 1986 to 2006, and had cclMT measured at 20 years after baseline in 2005-2006. Of 898 women, 119 (13%) reported GDM (7.6 per 100 deliveries), and were heavier and slightly older, and had higher mean fasting glucose and HOMA-IR at baseline ( $P<0.05$ ) than the non-GDM group (Table 1). At follow-up (Table 2), the GDM group had higher mean fasting serum triglycerides ( $P=0.04$ ), mean fasting serum glucose ( $P<0.001$ ), diastolic blood pressure ( $P=0.03$ ), and BMI ( $P<0.001$ ) than the non-GDM group. The GDM group was more likely to have developed DM (25% versus 6%,  $P<0.001$ ) and to have the MetS (13% versus 7%,  $P=0.03$ ) during the 20-year period.

**Table 1.** Baseline Characteristics for Women With One or More Post-baseline Births and Carotid Artery IMT Measurements in 2005–2006 by History of GDM (n=898)

Baseline Characteristics	GDM (n=119)	Non-GDM (n=779)	<i>P</i> Value
	n (%)		
Race (black)	51 (43)	364 (47)	0.43
Center			
Alabama	35 (29)	178 (23)	0.23
Chicago	25 (21)	224 (29)	
Minneapolis	23 (19)	137 (18)	
Oakland	36 (30)	239 (31)	
Pre-pregnancy BMI, kg/m <sup>2</sup>			
Normal (<25)	76 (64)	582 (75)	0.02
Overweight (25 to <30)	24 (20)	128 (16)	
Obese (≥30)	19 (16)	69 (9)	
Parity (number of births)	0.42 (0.67)	0.42 (0.81)	0.96
	Mean (SD)		
Age, y	24.7 (3.9)	24.1 (3.7)	0.10
Pre-pregnancy (baseline) BMI, kg/m <sup>2</sup>	24.8 (5.6)	23.3 (4.3)	0.001
Waist circumference, cm	74.4 (11.1)	71.7 (8.8)	0.004
Blood pressure, mm Hg			
Systolic	106.1 (8.9)	105.3 (9.0)	0.39
Diastolic	66.4 (8.5)	66.0 (8.6)	0.61
Fasting plasma lipids, mg/dL			
Triglycerides	68.8 (32.4)	64.6 (37.1)	0.24
HDL-C	54.9 (13.0)	56.5 (12.4)	0.19
LDL-C	106.2 (28.9)	108.3 (29.0)	0.46
Total cholesterol	174.9 (30.4)	177.7 (31.4)	0.36
Fasting serum glucose, mg/dL	81.0 (9.8)	79.1 (7.3)	0.02
HOMA-IR	2.4 (1.9)	2.0 (1.6)	0.02

Missing fasting glucose and insulin: n=2 women in GDM and n=27 women in non-GDM group. Missing fasting blood lipids: n=1 women in GDM and n=21 women in non-GDM group. BMI indicates body mass index; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment index of insulin resistance; IMT, intima media thickness; LDL-C, low-density lipoprotein cholesterol.

Racial differences in cclMT were apparent with black women having higher unadjusted mean (SD) for cclMT than white women (0.800 [0.115] versus 0.729 [0.091],  $P<0.001$ ). Pre-pregnancy BMI and weight gain largely explained the mean cclMT race-differences (data not shown). In linear regression models (Table 3), mean (95% CI) cclMT (mm) was higher for GDM than non-GDM groups; unadjusted ( $P=0.029$ ), and adjusted models with covariates (age, race, parity);  $P=0.020$ . Addition of pre-pregnancy BMI attenuated cclMT

**Table 2.** Follow-up Characteristics for Women With One or More Post-baseline Births and Carotid Artery IMT Measurements in 2005–2006 by History of GDM

Reproductive Characteristics (1986–2006) and At Year 20 Exam (2005–2006)	GDM (n=119)	Non-GDM (n=779)	P Value
	n (%)		
Maximum education (high school or less)	13 (11)	90 (12)	0.90
Smoker (ever)	56 (47)	338 (43)	0.45
Hypertension (outside of pregnancy)	30 (25)	165 (21)	0.32
Gestational hypertension (ever)	46 (39)	257 (33)	0.22
Lipid-lowering medication (ever)	7 (6)	32 (4)	0.38
Postmenopausal (baseline to 20)	26 (22)	143 (18)	0.36
Family history of heart disease	26 (22)	155 (20)	0.62
Incident diabetes (post-delivery to year 20)	30 (25)	49 (6)	<0.001
Metabolic syndrome (baseline to year 20)	16 (13)	58 (7)	0.03
Incident diabetes or the metabolic syndrome	35 (29)	86 (11)	<0.001
Age (years) at:	Mean (SD)		
First birth post-baseline	30.7 (4.7)	30.8 (4.8)	0.81
Last birth post-baseline	33.7 (4.6)	33.4 (4.8)	0.52
Exam year 20	44.8 (4.1)	44.3 (3.7)	0.14
Blood pressure, mm Hg			
Systolic	114.2 (16.0)	112.1 (14.9)	0.15
Diastolic	72.5 (12.4)	70.1 (10.9)	0.03
Fasting plasma lipids, mg/dL			
Triglycerides	100.3 (48.3)	89.5 (51.0)	0.04
HDL-C	56.5 (15.1)	59.9 (16.6)	0.08
LDL-C	108.7 (29.2)	107.1 (28.6)	0.60
Total cholesterol	185.6 (31.8)	184.9 (31.6)	0.82
Fasting serum glucose, mg/dL	104.2 (29.3)	92.4 (18.8)	<0.001
HOMA-IR	4.7 (2.9)	3.6 (2.8)	<0.001
BMI, kg/m <sup>2</sup>	31.3 (7.6)	28.9 (7.4)	<0.001
Waist circumference, cm	91.8 (15.3)	86.3 (14.7)	<0.001
Smoking pack-years (life-time)	3.6 (6.7)	3.3 (7.0)	0.72
Weight gain (kg) per year to 1st birth	0.9 (1.9)	0.7 (1.8)	0.20
Total parity at year 20	2.3 (0.95)	2.2 (1.1)	0.25

Continued

**Table 2.** Continued

Reproductive Characteristics (1986–2006) and At Year 20 Exam (2005–2006)	GDM (n=119)	Non-GDM (n=779)	P Value
	Median (IQR)*		
Time baseline to first post-baseline birth, y	4.9 (5.1)	5.3 (5.9)	0.10
Time from last birth to year 20, y	12.5 (7.3)	11.6 (7.1)	0.52

Missing fasting glucose, lipids, or insulin: n=15 in GDM and n=63 in non-GDM. BMI indicates body mass index; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment index of insulin resistance; IMT, intima media thickness; LDL-C, low-density lipoprotein cholesterol. \*Kruskal-Wallis test.

mean differences by GDM status to non-significant levels ( $P=0.109$ ) but addition of pre-pregnancy HOMA-IR had no impact on mean cclMT.

Two-way interactions for the GDM-cclMT association by race ( $P=0.29$ ), age ( $P=0.22$ ) were not statistically significant. However, incident DM or MetS status modified the GDM-cclMT association in models adjusted for race, age, and parity (interaction  $P=0.01$ ). Among 777 women without DM or the MetS during the 20-year follow-up (Table 4), mean (95% CI) net difference in cclMT was 0.023 mm higher for GDM compared with non-GDM groups in adjusted models (age, race, parity, pre-pregnancy BMI;  $P=0.039$ ). Addition of pre-pregnancy HOMA-IR had minimal impact on adjusted mean cclMT. Weight gain during the 20-year period partially attenuated these differences to 0.019 (−0.003, 0.041);  $P=0.089$ , and addition of HOMA-IR and diastolic blood pressure measured at the year 20 exam modestly attenuated the association. Among 121 women who developed incident DM or MetS during the 20-year follow-up, unadjusted and fully adjusted mean cclMT did not differ by GDM history (Table 4).

### Discussion

Our findings demonstrate that a history of GDM is associated with early subclinical atherosclerosis before the onset of diabetes and the metabolic syndrome during the intervening years after delivery independent of pre-pregnancy obesity, race, parity, and age. Among women who developed type 2 diabetes mellitus or the metabolic syndrome prior to the assessment of carotid artery IMT, a history of GDM was not associated with carotid artery IMT. Thus, GDM history may be considered a risk factor for atherosclerosis before the onset of diabetes or metabolic disease. Weight gain, insulin resistance, and blood pressure increases during the study period partially accounted for the GDM-cclMT association. Our findings suggest that body size, blood pressure control,

**Table 3.** Unadjusted and Adjusted Means (95% CI) for Carotid Artery IMT by GDM History for the Entire Sample (n=898) of CARDIA Women With One or More Post-baseline Births by Year 20 (2005–2006)

Model	Carotid Artery IMT (mm)		P Value	GDM vs Non-GDM Mean Net Difference (95% CI)
	GDM (n=119)	Non-GDM (n=779)		
	Mean (95% CI)			
Unadjusted	0.782 (0.763, 0.802)	0.759 (0.751, 0.766)	0.029	0.023 (0.002, 0.044)
<i>Model 1:</i> covariates: age, race, parity	0.785 (0.767, 0.803)	0.762 (0.755, 0.769)	0.020	0.023 (0.004, 0.042)
<i>Model 2:</i> Model 1+pre-pregnancy BMI	0.778 (0.760, 0.796)	0.763 (0.756, 0.769)	0.109	0.016 (–0.003, 0.034)
<i>Model 3:</i> Model 2+pre-pregnancy HOMA-IR	0.777 (0.759, 0.795)	0.761 (0.754, 0.768)	0.100	0.016 (–0.003, 0.035)
<i>Model 4:</i> Model 3+weight gain (mediator)	0.774 (0.755, 0.794)	0.763 (0.756, 0.770)	0.283	0.011 (–0.009, 0.032)
<i>Model 5:</i> Model 4+year 20 (HOMA-IR+DBP) (mediators)	0.771 (0.752, 0.790)	0.763 (0.756, 0.770)	0.430	0.008 (–0.012, 0.029)
<i>Model 6:</i> Model 4+incident diabetes or metabolic syndrome in 20 years	0.773 (0.754, 0.791)	0.760 (0.748, 0.771)	0.188	0.013 (–0.006, 0.032)

P-values for 2-way interaction terms in *Model 1:* age=0.12; race=0.52; incident diabetes or metabolic syndrome=0.01. P-values for 2-way interaction terms in *Model 2:* age=0.22; race=0.29; pre-pregnancy BMI=0.42; incident diabetes or metabolic syndrome=0.29. Missing fasting glucose and insulin: n=2 women in GDM and n=27 women in non-GDM group. Note: Weight gain covariate is represented by BMI at year 20 independent of BMI at Year 0 in the same model. BMI indicates body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; HOMA-IR, homeostatic model assessment index of insulin resistance; IMT, intima media thickness.

**Table 4.** Unadjusted and Adjusted Means (95% CI) for Carotid Artery IMT (2005–2006) by GDM History Within the Strata of Women Who Had Incident Diabetes or Metabolic Syndrome Status (n=121) at Year 20 (2005–2006) and Women Who Did Not (n=777)

Model	Carotid Artery IMT (mm)		P Value	GDM vs Non-GDM Mean Net Difference (95% CI)
	GDM	Non-GDM		
	Mean (95% CI)			
Incident diabetes or metabolic syndrome present at year 20				
	n=35	n=86		
Unadjusted	0.804 (0.768, 0.841)	0.812 (0.788, 0.837)	0.732	–0.008 (–0.052, 0.036)
<i>Model 1:</i> covariates: age, race, parity	0.791 (0.757, 0.825)	0.794 (0.772, 0.817)	0.853	–0.004 (–0.045, 0.037)
<i>Model 2:</i> Model 1+pre-pregnancy BMI	0.764 (0.730, 0.799)	0.776 (0.753, 0.800)	0.549	–0.012 (–0.052, 0.028)
<i>Model 3:</i> Model 2+pre-pregnancy HOMA-IR	0.767 (0.732, 0.801)	0.774 (0.750, 0.798)	0.731	–0.007 (–0.048, 0.034)
<i>Model 4:</i> Model 3+weight gain (mediator)	0.761 (0.726, 0.795)	0.762 (0.738, 0.786)	0.941	–0.002 (–0.042, 0.038)
<i>Model 5:</i> Model 4+year 20 (HOMA-IR+DBP) (mediators)	0.751 (0.713, 0.789)	0.757 (0.731, 0.784)	0.776	–0.006 (–0.049, 0.037)
Incident diabetes or metabolic syndrome not present at year 20				
	n=84	n=693		
Unadjusted	0.773 (0.750, 0.796)	0.753 (0.745, 0.761)	0.106	0.020 (–0.004, 0.044)
<i>Model 1:</i> covariates: age, race, parity	0.783 (0.761, 0.804)	0.758 (0.751, 0.766)	0.035	0.024 (0.001, 0.047)
<i>Model 2:</i> Model 1+pre-pregnancy BMI	0.784 (0.763, 0.806)	0.761 (0.754, 0.769)	0.039	0.023 (0.001, 0.045)
<i>Model 3:</i> Model 2+pre-pregnancy HOMA-IR	0.783 (0.761, 0.803)	0.761 (0.752, 0.767)	0.054	0.022 (0.000, 0.044)
<i>Model 4:</i> Model 3+weight gain (mediator)	0.778 (0.758, 0.799)	0.761 (0.754, 0.769)	0.123	0.017 (–0.005, 0.039)
<i>Model 5:</i> Model 4+year 20 (HOMA-IR+DBP) (mediators)	0.778 (0.756, 0.800)	0.764 (0.756, 0.772)	0.241	0.014 (–0.009, 0.037)

Covariates: age at year 20, parity at year 20. Missing fasting glucose and insulin: n=2 women in GDM and n=27 women in non-GDM group. Note: Weight gain covariate is represented by BMI at year 20 independent of BMI at Year 0 in the same model. BMI indicates body mass index; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; HOMA-IR, homeostatic model assessment index of insulin resistance; IMT, intima media thickness.

and insulin resistance may be important modifiable risk factors that may influence progression of atherosclerosis during midlife in women with a history of GDM.

An important question that previous studies were unable to answer is whether a history of GDM influenced early atherosclerosis risk before progression to overt diabetes or

the metabolic syndrome. These studies were unable to assess pre-pregnancy risk factors and thus, could not determine whether diabetes and cardiometabolic risk factors were present before pregnancy. Findings from cross-sectional studies are mixed; reporting higher IMT or no differences in cIMT by GDM status during the third trimester of pregnancy.<sup>15–17</sup> Retrospective studies that assessed cIMT within one to several years postpartum are also mixed. Higher carotid artery IMT has been associated with history of GDM, but have shown no consistent relationship with concurrent metabolic status. One study found that the association was independent of concurrent cardiometabolic risk factors,<sup>37</sup> while others reported that cIMT was higher only among those without metabolic abnormalities,<sup>21</sup> or only among those with impaired glucose tolerance.<sup>20</sup> Studies with null associations found a tendency for the presence of hyperglycemia (HbA1c above 6.0%),<sup>18</sup> or GDM severity (ie, insulin-treated versus diet-treated GDM)<sup>38</sup> to correlate with higher IMT. These previous findings suggest that impaired glucose metabolism post-delivery may influence development of atherosclerosis among women with a history of GDM, but the cross-sectional designs limit the findings.

The CARDIA prospective, longitudinal design focused on women of reproductive age by measuring biochemical and clinical risk factors (ie, maternal obesity, fasting glucose, HOMA-IR, weight) both before and after pregnancies, as well as screened for diabetes and metabolic diseases every 5 years during the 20-year follow-up period. Therefore, we were able to exclude pre-gestational diabetes<sup>39</sup> as distinct from “true” GDM unlike other studies. In addition, GDM was reported reliably in CARDIA women, given our 100% sensitivity from the chart validation study.<sup>28</sup> Another strength of CARDIA is that women delivered pregnancies during the period (1986–2006) of routine universal screening and treatment for GDM. The rates of GDM deliveries (7.6 per 100) in CARDIA are comparable to rates reported within the US population. Most epidemiologic studies enrolled older women for whom GDM history is unknown or incompletely ascertained because their pregnancies occurred prior to the mid 1980s, when screening for glucose tolerance was limited.

In our study, the GDM association with early atherosclerosis was independent of pre-pregnancy BMI, a predictor of GDM as well as CVD risk among women without diabetes or metabolic disease at follow-up. Pre-pregnancy obesity is related to higher insulin resistance, but control for pre-pregnancy insulin resistance did not attenuate the group differences. GDM history apparently increases progression to subclinical atherosclerosis, even in the absence of overt metabolic disease. Weight gain, progressive insulin resistance (ie, higher mean HOMA-IR), and elevated blood pressure, may mediate the increase in IMT before onset of type 2 diabetes and the metabolic syndrome during midlife. A previous follow-up study

that examined women once during 18 years after delivery, reported a borderline significant 26% higher Framingham CVD risk score for GDM, but the prevalence of GDM was very low (0.4%), and no subclinical measures of cardiometabolic risk factors, or measures of early atherosclerosis were reported.<sup>40</sup>

Women who develop GDM exhibit pancreatic beta cell defects resulting in insufficient insulin secretion to meet the demands of pregnancy.<sup>41,42</sup> Obesity before pregnancy contributes to the greater insulin resistance and lower HDL-cholesterol levels during gestation, as well as post-delivery.<sup>9,43</sup> Higher risk of type 2 diabetes or the metabolic syndrome after pregnancy has been purported to explain most of the excess CVD risk associated with previous history of GDM.<sup>44</sup> Our findings challenge this evidence, and further indicate that GDM history may be an early marker of CVD risk apart from pre-pregnancy obesity, older maternal age, and parity that predispose women to higher GDM risk. Weight gain only modestly attenuated the GDM-association with IMT in women who had not developed DM or the MetS (mean net difference of 0.023 versus 0.019 after controlling for weight gain during follow-up).

Limitations of our study include the lack of IMT measurements before or during pregnancy to establish whether higher IMT preceded the onset of GDM. However, major strengths of our design include the young age of the cohort, our ability to exclude women with overt diabetes before pregnancies, control for pre-pregnancy BMI, and our ability to assess several pre-pregnancy cardiometabolic risk factors (glycemia, insulin resistance, blood pressure, and dyslipidemia). Our longitudinal study design enabled us to delineate the elevations in carotid artery IMT due to GDM separately from effects of progression to diabetes or metabolic diseases. Furthermore, pre-pregnancy biochemical risk factors were similar at baseline for GDM and non-GDM groups, except that women with GDM were more likely to have been overweight or obese, and more insulin resistant before pregnancy than non-GDM groups. Ever having a history of gestational hypertension did not differ between GDM and non-GDM groups, and adjustment for this condition did not affect our results, but subsequent increases in diastolic blood pressure and HOMA-IR influenced the IMT levels similar to weight gain.

Based on our findings, GDM history appears to be an independent risk factor for early atherosclerosis and signifies increased CVD risk apart from greater pre-pregnancy obesity that characterizes women predisposed to develop GDM. For both nondiabetic as well as diabetic adults, hyperglycemia and dyslipidemia are independent risk factors for coronary heart disease and early atherosclerosis in women.<sup>45–47</sup> Persistent insulin resistance and dyslipidemia (ie, lower HDL-C) may be present before,<sup>48</sup> during, and/or after GDM pregnancy,<sup>49</sup> and damage the endothelium to promote inflammatory processes leading to early atherosclerosis.

Nonfatal or fatal cardiovascular disease (coronary heart disease, stroke, heart failure) events occurred in 13 women (1 in GDM group) as expected in our cohort, given their relatively young age of 38-50 years at follow-up. CVD is the leading cause of death in US women.<sup>50</sup> Women have a higher excess risk of CVD mortality attributable to diabetes as compared with men, accounting for age differences, because women develop CVD at older ages.<sup>46</sup> Older women with both diabetes and the metabolic syndrome have a 2- to 3-fold higher mortality from heart disease than women without these conditions.<sup>51</sup> Elevated glucose and dyslipidemia are believed to mediate the association of diabetes with higher CVD risk. A majority of women with a history of GDM may exhibit persistent mild or moderate insulin resistance and dyslipidemia without conversion to diabetes in midlife. Thus, a history of GDM may serve as an additional early indicator of elevated CVD risk before the onset of type 2 diabetes mellitus or overt metabolic disease in women.

The concept that reproductive complications unmask future disease risk is relatively new. In 2011, the American Heart Association Recommendations for Prevention of Heart Disease in Women added pregnancy complications (ie, gestational diabetes, gestational hypertension, and pre-eclampsia) to the evidence-based recommendations for risk assessment in prevention of heart disease in women.<sup>52</sup> For women with a history of GDM, this new recommendation on CVD risk was based on the higher risk of type 2 diabetes mellitus. Our finding that GDM history is associated with risk of early atherosclerosis before overt metabolic disease is important to primary prevention efforts, particularly for weight and blood pressure control.

To our knowledge, ours is the first longitudinal study to examine subclinical or clinical measures of cardiovascular disease, such as carotid artery intima media thickness, in relation to a history of GDM, and to establish the temporality of development of metabolic diseases in relation to pregnancy and subclinical atherosclerosis. Our findings provide strong evidence that women with a history of GDM are at greater risk of early subclinical atherosclerosis in women before the onset of diabetes and metabolic diseases. The American Diabetes Association and American College of Obstetrics and Gynecology recommend early postpartum screening for diabetes after GDM delivery, and annual repeat screening for diabetes for women with impaired glucose values. Our findings support the addition of postpartum screening for CVD risk factors among women with a history of GDM, to identify women at highest risk for early CVD and related morbidity or mortality during mid-life. Further investigation is required to determine the efficacy as well as the public health impact of carotid artery IMT as a screening tool for risk stratification of women with a history of GDM, and early prediction of heart disease risk. Women with a history of GDM display atherosclerotic

changes to the endothelium at much earlier ages than most women, and therefore effective early prevention efforts should be focused on these women during the postpartum period, including those who have not yet developed overt diabetes or metabolic diseases.

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## Disclosure

None.

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