HHS Public Access

Author manuscript

Circulation. Author manuscript; available in PMC 2022 March 09.

Published in final edited form as:

Circulation. 2021 March 09; 143(10): 974–987. doi:10.1161/CIRCULATIONAHA.120.047320.

Gestational Diabetes History and Glucose Tolerance After Pregnancy Associated with Coronary Artery Calcium in Women During Mid-life: The CARDIA Study.

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Abstract

Background: Gestational diabetes (GD) leads to earlier onset and heightened risk of type 2 diabetes, a strong risk factor for cardiovascular disease (CVD). However, it is unclear whether attaining normoglycemia can ameliorate the excess CVD risk associated with GD history. This study sought to evaluate GD history and glucose tolerance after pregnancy associated with coronary artery calcification (CAC) in women, a manifestation of atherosclerotic CVD (ASCVD), and predictor of CVD clinical events.

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Contributors: Dr. Gunderson had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Gunderson designed the study, developed that analytic plan, directed the data analysis, and led the ancillary studies for additional data collection and evaluation in CARDIA women. Ms. Baiyang Sun was responsible for the configuration of the variables, and conducted the statistical analysis. Dr. Catov contributed to the data analysis, and provided critical review of the manuscript content. Drs. Lewis, Sidney, and Carr were responsible for the data collection, and provided critical review of the manuscript content. Drs. Rana, Hou, Wellons, and Allen critically reviewed the manuscript content and/or statistical methodology. This manuscript has been reviewed and approved by the CARDIA Study for scientific content, including the statistical power and analysis.

Institutional Review Boards and the Study Approval numbers

CARDIA Field Centers:

University of Alabama at Birmingham Institutional Review Board. # IRB0000726

Northwestern University Biomedical Institutional Review Board, #STU00024971-CR0001

University of Minnesota Institutional Review Board, Human Subjects #8304M00575

Kaiser Permanente Northern California Institutional Review Board #CN-98SSidn-03-H

Pending patent unrelated to the current research project on Metabolite Biomarkers Predicting Type 2 Diabetes. (Gunderson, EP).

Supplemental Materials

Supplemental Online Tables I to V

Methods: Data from the Coronary Artery Risk Development in Young Adults Study, a U.S. multicenter, community-based prospective cohort of young Black (50%) and White adults aged 18–30 years at baseline (1985–1986). The sample included 1,133 women without diabetes at baseline, who had one or more singleton births (n=2,066) during follow up, glucose tolerance testing at baseline and up to 5 times during 25 years (1986–2011), GD status, and CAC measurements at follow up exam at years 15, 20, and/or 25 (2001–2011). CAC was measured by non-contrast cardiac computed tomography; dichotomized as Any CAC (score>0) or No CAC (score=0). Complementary log-log models for interval-censored data estimated adjusted hazard ratios of CAC and 95% confidence intervals for GD history and subsequent glucose tolerance groups (normoglycemia, prediabetes, or incident diabetes) on average 14.7 years after the last birth adjusted for pre-pregnancy and follow up covariates.

Results: Of 1,133 women, 139 (12.3%) reported GD and were aged 47.6 years (4.8 SD) at follow up. CAC was present in 25% (34/139) of women with GD and 15% (149/994) of women with no GD. Compared to no GD/normoglycemia, adjusted hazard ratios (95% confidence intervals) were 1.54 (1.06, 2.24) for no GD/prediabetes and 2.17 (1.30, 3.62) for no GD/incident diabetes, and 2.34 (1.34, 4.09), 2.13 (1.09, 4.17) and 2.02 (0.98, 4.19) for GD/normoglycemia, GD/prediabetes, and GD/incident diabetes, respectively (overall p-value=0.003).

Conclusions: Women without previous GD showed a graded increase in the risk of CAC associated with worsening glucose tolerance. Women with a history of GD had a 2-fold higher risk of CAC across all subsequent levels of glucose tolerance. Mid-life ASCVD risk among women with previous GD is not diminished by attaining normoglycemia.

Keywords

cardiovascular; imaging; glucose tolerance; coronary artery calcium; gestational diabetes; type 2 diabetes; prediabetes; atherosclerosis; cardiovascular disease; women; prospective cohort; African American; hyperglycemia

Journal Subject Heads

Gestational diabetes mellitus; Type 2 Diabetes Mellitus; Atherosclerotic Cardiovascular Disease

Introduction

Gestational diabetes (GD), glucose intolerance first recognized during pregnancy, affects 8–9% (n~250,000) of U.S. pregnancies,[1, 2] and up to 17–20% worldwide.[3] Before pregnancy, women who develop GD may have impaired glucose tolerance (i.e., prediabetes) and/or dyslipidemia.[4] After pregnancy, they are 4 to 7 times more likely to develop type 2 diabetes (T2D).[5–7] T2D is a contributing factor to the 1.7- to 3-fold higher risk of cardiovascular disease (CVD) and/or coronary artery disease (CAD) in women with a history of GD.[8–12] Yet, evidence is mixed about whether GD history increases CVD risk independent of subsequent T2D; with relative risks ranging from a null association among older European women,[13] to a 1.25- to 2-fold higher risk among younger women.[12, 14] Women with a history of GD who do not develop T2D have a 30% [15, 16] to 56% higher CVD risk based on a pooled-risk estimate from a meta-analysis.[12] Yet, current evidence, based on retrospective

study designs utilizing self-report or administrative hospital data sources to ascertain new onset diabetes after pregnancy may underestimate the risks. The misclassification of T2D, particularly among young women and minority groups, is likely because routine diabetes testing is not recommended in adults under age 45 years, except with obesity and other risk factors (e.g., history of GD). Further, previous studies could not distinguish prediabetes from normoglycemia, which represents the lowest risk group with highest relevance as the referent group for younger populations. Thus, what is the risk of CVD in women with a history of GD in the context of sustained postpartum normoglycemia?

Prediabetes is a strong predictor of T2D,[17] and a risk factor for coronary heart disease (CHD), especially in women.[18–20] About 24% of U.S. adults aged 18 to 44 years have prediabetes,[21] but almost 75% are unaware they have the condition.[22] Prediabetes is more common in women with a history of GD, affecting about 40%.[23] Yet, the low uptake of post-delivery diabetes testing,[24, 25] and lack of routine screening for CVD risk factors in young women are barriers to detection.[26] Prediabetes is rarely available by self-report, or from administrative and hospital databases. Thus, our understanding of transitions in clinical glucose tolerance related to the development CVD outcomes after GD pregnancy is incomplete.

This study sought to evaluate the relationship of GD history and subsequent transitions in glucose tolerance across the reproductive years to the presence of coronary artery calcium (CAC) in women during mid-life, a strong predictor of atherosclerotic CVD (ASCVD).[27, 28] We hypothesized that worsening glucose tolerance, including prediabetes, after pregnancy will increase the risk of CAC independent of other CVD risk factors, and a history of GD will be associated with higher risk of CAC, even among subsequently normoglycemic women. This research fills a major gap in the evidence base for clinical practice recommendations regarding traditional CVD risk factor screening among young women in general as well as those with a history of GD.

RESEARCH DESIGN AND METHODS

The CARDIA Study is a U.S. multi-center, longitudinal observational study examining the determinants of coronary heart disease risk factors in young black and white men and women. In 1985–1986 (baseline), 5,115 participants (2,787 women) aged 18–30 years (52% black) were recruited from four U.S. geographic areas: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Retention at exams in follow-up years 15, 20, 25 was 74%, 72% and 72% of the surviving cohort. Written informed consent was obtained at enrollment and each subsequent exam. Institutional review boards at each study site granted study approvals.

Anonymized data have been made publicly available at the [BioLINCC] and can be accessed at [https://biolincc.nhlbi.nih.gov/home/]. Access to biospecimen samples may be requested from the CARDIA Study with information available at [https://www.cardia.dopm.uab.edu/].

Sample Selection

Among 2,787 women at baseline (1985–1986), we included 1,392 who had ≥1 post-baseline birth(s). We excluded women with (n=58) multi-fetal gestations, (n=12), overt diabetes at baseline, (n=2) diabetes before a first post-baseline birth, (n=180) with no CAC measurements, or (n=7) CAC measured only before post-baseline births. The analytic sample included 1,133 parous women who had 2,066 births after baseline, and metabolic risk factors measured before the first pregnancy (Figure 1). Parous women excluded were slightly younger at the first post-baseline birth, more likely to be Black race and to have educational level at high school or lower and had higher level of pre-pregnancy HOMA-IR than those included (Supplemental Table I).

Blood Pressure, Anthropometry, and Biochemical Measurements

Trained and certified staff assessed medical and clinical attributes, sociodemographic factors and lifestyle behaviors at in-person exams using standardized methodologies, anthropometry using calibrated equipment, and interviewer and self-administered questionnaires. Research protocol for blood pressure (BP) measurements, venipuncture, laboratory quality control, and biochemical assays are detailed elsewhere.[2928] Hypertension was defined as systolic BP (SBP) ≥140 and/or diastolic BP (DBP) ≥90 mmHg, and/or self-report of antihypertensive medication using criteria during the study period. Body mass index (BMI) was calculated as weight divided by height (kg/m^2). Blood was drawn after an overnight fast to measure plasma total cholesterol and triglycerides, high-density lipoprotein cholesterol (HDL-C),[30] and low-density lipoprotein cholesterol (LDL-C) calculated using the Friedewald equation.[31, 32] Serum glucose and insulin were measured at fasting in years 0, 7, 10, 15, 20, 25, and 2 hours after a 75 g oral glucose load (2-h OGTT) in years 10, 20, 25. Glycosylated hemoglobin (HbA1C) was measured in years 20 and 25. The homeostasis model assessment index (HOMA-IR) was calculated as fasting glucose (mmol/l) multiplied by fasting insulin (mU/l) and divided by 22.5 to estimate insulin resistance.[33] High sensitivity C-reactive protein (hs-CRP) was measured at exam years 15 and 20 using a nephelometry-based high throughput assay (BNII nephelometer) and at exam year 25 using a Roche latex-particle enhanced immunoturbidimetric assay kit.[34, 35] The metabolic syndrome was diagnosed for having any three of five factors using the National Cholesterol Education Program/Adult Treatment Panel III (NCEP-ATP III) criteria: (1) waist circumference >88 cm; (2) triglycerides ≥150 mg/dL; (3) HDL-C <50 mg/dL; (4) SBP ≥130 and/or DBP ≥85 mmHg, and/or self-reported use of antihypertensive medication; and (5) fasting glucose ≥100 mg/dL and/or self-reported use of diabetes medication.[36]

Measurement of Coronary Artery Calcium by Computed Tomography

Non-contrast cardiac computed tomography (CT) was performed using standard protocol at years 15 (2000–01), 20 (2005–06), and 25 (2010–11) following the baseline exam. At years 15 and 20, CAC scores were averaged from two sequential scans. At year 25 a single scan was used based on the reproducibility of the CAC score observed for prior exams and to reduce radiation exposure. Technical details of the CT systems, protocol, and observed radiation exposure are previously reported.[27] CAC was estimated using the FDA approved calcium scoring software (Aquarius Workstation, TeraRecon, Foster City, CA) and reported

as the Agatston score, corrected for slice thickness with a minimum lesion size of 4 adjacent pixels (minimum calcification area of 1.87 mm^2) and attenuation threshold of ≥130 Hounsfield units.[28] The year 15 CAC scores were reanalyzed to ensure longitudinal standardization. A physician adjudicated the CAC scores under the following conditions: discordant for CAC presence within paired scans at years 15 and 20, a score change of >200, a change in CAC status from positive to negative, or a potential surgical intervention identified by the analyst. CAC was categorized as Any CAC (Score >0; range 0.93 to 4428) or No CAC (Score=0). The first exam (years 15, 20, or 25) with CAC>0, or the last exam with CAC=0 after the last birth was defined as the end-of-follow-up for each participant.

Glucose Tolerance Categories (Normoglycemia, Prediabetes and Diabetes)

Biochemical testing of glucose tolerance was performed at baseline and at subsequent exam years (7, 10, 15, 20, and 25). We classified women into glucose tolerance categories (normoglycemia, prediabetes, and incident diabetes) based on fasting glucose at exam years 0, 7, 10, 15, 20, and 25; 2-hour 75-gram post-load glucose in years 10, 20, and 25; and/or glycosylated hemoglobin (HbA1C) in years 20 and 25 using the American Diabetes Association diagnostic criteria.[37] Diabetes was classified by fasting glucose ≥126 mg/dL, 2-hour glucose ≥ 200 mg/dL, or HbA1C ≥ 6.5%, and/or self-report of diabetes and diabetes medication use. Prediabetes was classified by fasting glucose 100 to 125 mg/dL, 2-hour glucose 140 to 199 mg/dL, or HbA1C 5.7% to 6.4%.[37] Diabetes could also be classified based on self-report of medications prescribed to treat diabetes.

Pregnancies and Gestational Diabetes Status:

At each exam, women reported current pregnancy status, number of pregnancies, and births (≥20 weeks' gestation), dates of deliveries, and perinatal outcomes [e.g., gestational diabetes (GD) hypertensive disorders of pregnancy (HDP)]. We calculated the age at the first birth after baseline (post-baseline) and at the last post-baseline birth for each woman based on the delivery dates. GD status based on report of "diabetes only during pregnancy", and no diabetes prior to pregnancy based on biochemical testing, or self-report of diabetes as described above.[6] We validated self-report of GD using the 3-hr 100 g OGTT results abstracted from prenatal medical records among 165 CARDIA women who delivered 200 births. GD classification had a sensitivity of 100% (20/20), and specificity of 92% (134/145).[6] Women delivered pregnancies between consecutive exams. Parity (total number of births) and GD status were updated at each exam, but women remained in the GD category once classified.

Women were classified into time-varying GD status and glucose tolerance categories from the first post-baseline birth through the end of follow up as: 1) No GD/normoglycemia (referent group), 2) No GD/prediabetes, 3) No GD/incident diabetes, 4) GD/normoglycemia, 5) GD/prediabetes, or 6) GD/incident diabetes. Women transitioned across the six groups as their GD and glucose tolerance status was updated at exam years 15, 20 and/or 25 through the end of follow up that corresponded to the same exam years for available CAC measurements. Once a woman transitioned into a higher glucose intolerance and/or the GD group, the classification was maintained through the end of follow up (i.e., normoglycemia to incident prediabetes or incident diabetes, or prediabetes to incident diabetes).

Covariates:

Structured questionnaires at up to 8 exams assessed socio-demographics, reproductive history, medical history, medication use (e.g., anti-hypertensive, diabetes, and lipid-lowering medications, oral contraceptives, and other hormones) and lifestyle behaviors (tobacco use, alcohol consumption, dietary intake and physical activity). Menopausal status and menopausal hormone therapy were assessed at years 15, 20 and 25. The Diet History questionnaire assessed dietary intake at baseline (year 0) and years 7 and 20.[38] We calculated the *a priori* diet quality score (the average of years 0, 7 and 20), as an index of plant-based food patterns detailed elsewhere.[39] The CARDIA Physical Activity History questionnaire estimated a physical activity score (race-specific quartiles), which is correlated with the symptom-limited graded treadmill exercise test duration.[40] Family history of diabetes and heart disease was classified by report of diseases for primary relatives.

Statistical Analysis

Pre-pregnancy and the end of follow up characteristics were assessed among glucose tolerance groups and by CAC status using chi-square statistics, analysis of variance methods, and the Kruskal-Wallis test of the equality of medians for variables with skewed distributions. CAC status for each woman was classified for up to three exams at years 15, 20 and/or 25. The association between the proportion of women with Any CAC (score>0) at the end of follow up was evaluated among worsening glucose tolerance within the GD and no GD groups using the Cochran–Armitage test for trend (p-value trend).

We estimated the hazard ratio (HR) and 95% confidence interval (95%CI) of CAC associated with GD status, and by GD status stratified by Incident Diabetes (yes or no), and then by GD status and the subsequent glucose tolerance categories (normoglycemia, prediabetes, or incident diabetes). We used the complementary log-log model,[41, 42] an analogue to the Cox proportional hazards model to handle interval-censored time to event (CAC>0) and time-dependent covariates. Examination years (time) and an indicator variable for the length of each interval were included in all models to account for the unequal intervals between the consecutive exams. Participants entered the analysis at the first post-baseline birth and exited at the first presence of CAC>0, or the last follow up exam in years 15, 20 or 25 (censoring). We adjusted for age at first post-baseline birth to account for differences in time at entry into the analysis.

Potential confounders were evaluated based on a priori hypotheses and statistical significance (p-value <0.05) for the association with main effects and/or risk of CAC. These included race, lifestyle behaviors, pre-pregnancy (closest exam preceding the first post-baseline birth) systolic BP, BMI, and blood lipids, HDP, and other CVD risk factors. We also evaluated the average *a priori* diet quality score, and time-varying covariates during follow up (i.e., cigarette smoking habit (pack-years), hypertension, parity, lipid-lowering medication, hormone use, and change in BMI). All p-values are for two-sided tests with statistical significance <0.05. All analyses used Statistical Analysis Software (SAS) for Windows 9.4 (SAS Institute Inc, Cary, NC, USA).

Multivariate models evaluated the covariates' impact on HRs of CAC in a stepwise manner. Model 1 included race, age at first birth, and pre-pregnancy Systolic BP. Model 2 (fully adjusted) included Model 1 covariates plus pre-pregnancy BMI, and time-varying smoking in pack-years. Models 3 and 4 sequentially added time-varying hypertension status and BMI change, respectively, as intervening risk factors during follow up. Addition of CVD risk factors (i.e., pre-pregnancy LDL-C, HDL-C, HOMA-IR, physical activity score, *a priori* diet quality score, HDP, parity, lipid-lowering medication, hormonal contraception, menopausal hormone therapy, and change in BMI) had minimal impact on HRs (data not shown). Sensitivity analyses excluded women with history of HDP (analysis of n=891 women with no reported HDP), and women parous at baseline (analysis of n=782 nulliparas).

We also estimated the probability of a woman being free of CAC as a survival curve for each of the six GD status and glucose tolerance groups based on results from the unadjusted model. For calculation of the survival curves, the average length of time interval between the first post-baseline birth and the year 15 exam is 9.4 years, and each of the later intervals are 5.0 years.

RESULTS

The sample of 1,133 parous women (49% Black, 51% White) had 2,066 births after baseline and up through year 25. Of these, 92% of births occurred before year 15, 6.6% between years 15 and 20, and 1.4% between years 20 and 25. There were 139 women (12.3%) who reported GD during pregnancy (6.7 per 100 pregnancies). The mean (SD) age at first post-baseline birth was 30.1 (4.9) years, and at end of follow up was 47.6 (4.8) years (range 33–56). The mean (SD) time since the last birth to end of follow up was 14.7 (5.9) years.

Women with previous GD were more likely to develop prediabetes or incident diabetes than maintain normoglycemia after pregnancy (36%, 25.9%, or 38.1%) compared to women with No GD (35%, 9%, or 56%); overall p-value<0.001. Of the 125 incident diabetes cases, women with previous GD had earlier onset compared to the no GD group; 16.7% and 10.1% had onset before year 15 (p-value=0.36), and 69.5% and 47.2% had onset between years 15 and 20 (p-value=0.009), respectively.

Overall, CAC (score >0) was present in 16.2% (183/1133) of women. About 24.5% (34/139) with previous GD had CAC compared to 15.0% (149/994) with No GD (p-value=0.005). The proportion with CAC (Figure 2) did not vary by glucose tolerance categories among women with GD (p-value=0.65), but increased with worsening glucose intolerance among women with No GD (p-value=0.003). Among women who were normoglycemic at end of follow up, 12.9% (72/557) and 28.3% (15/53), respectively, were classified with CAC among no GD and GD groups; p-value=0.002. Within the prediabetes and incident diabetes groups, there were no significant differences in CAC prevalence by GD status.

Higher levels of CAC scores were associated with worsening glucose tolerance among women with no GD (p-value=0.003), but women with GD showed more similar proportions across the glucose tolerance groups (Table 1). The overall CAC levels increased over time, with higher proportions having scores above 10 at exam year 25 than years 15 and 20. The

distribution of overall CAC scores of >0 to 10, >10 to 50, >50 to 99, and ≥100 were 8.3, 4.4, 2.0, and 1.4 percent of women, respectively, as expected for their young age (Supplemental Table II).

Glucose intolerance at follow up was associated with higher pre-pregnancy BMI, waist circumference, fasting glucose, insulin and HOMA-IR, and lower HDL-C, as well as characteristics at follow up, including higher BMI, waist circumference, fasting triglycerides, glucose, and insulin, hs-CRP, and HOMA-IR, higher percentages of women with obesity, the metabolic syndrome, hypertension, and lipid-lowering medication use, as well as longer time since last birth to end of follow up, regardless of GD status; all p-values<0.01 (Tables 2 and 3). Among women with No GD, worse glucose tolerance after pregnancy was associated with lower HDL-C and physical activity, higher pre-pregnancy BP, fasting triglycerides, and waist girth, higher percentages with post-menopausal status, family history of diabetes and heart disease, and higher weight change and HOMA-IR at follow up, as well as lower average a priori dietary quality score (all p-values <0.01). Among women with GD, HOMA-IR increased among all glucose tolerance groups (p-value=0.07), including those with normoglycemia, despite no differences in weight change (p-value=0.68). Among women with normoglycemia at follow up (Table 3), median hs-CRP was higher for women with previous GD compared to women with no GD (p-value=0.05). There was no significant difference in mean HOMA-IR change between these groups.

Characteristics associated with CAC included older age, smoking, the metabolic syndrome, and hypertension, as well as higher pre-pregnancy BMI, waist circumference, SBP, DBP, fasting glucose, insulin, HOMA-IR, triglycerides, total cholesterol and LDL-C (Supplemental Table III). During follow up, CAC was associated with incident diabetes, the metabolic syndrome, hypertension, pregnancy complications (GD and hypertensive disorders), and lipid-lowering medication use. Any CAC was also associated with higher BMI, fasting insulin, HOMA-IR, hs-CRP, LDL-C, and triglycerides, and lower HDL-C at follow up.

In multivariate models, GD status was associated with higher risk of CAC; HR (95%CI) of 1.85 (1.28, 2.69) adjusted for age, race and pre-pregnancy SBP (Model 1) (Table 4). Addition of pre-pregnancy BMI, and time-varying smoking in pack-years (Model 2) slightly attenuated the HR to 1.73 (1.18, 2.52), but hypertension during follow-up (Model 3) had minimal impact. In models stratified by diabetes status after pregnancy, GD was not associated with CAC in women with incident diabetes, but GD was associated with a twofold higher risk of CAC in women with No diabetes; adjusted HR (95%CI) of 2.02 (1.31, 3.11) from Model 1 that was attenuated to 1.95 (1.27, 3.01) with the addition of other covariates; pre-pregnancy BMI, time-varying smoking (Model 2), and time-varying hypertension during follow up (Model 3).

For GD status and subsequent glucose tolerance groups (Table 4), HRs (95%CIs) of CAC adjusted for race, age at first birth and pre-pregnancy SBP (Model 1) were 1.69 (1.17, 2.46) and 2.68 (1.62, 4.44) for prediabetes, and incident diabetes among women with No GD, respectively, and were 2.30 (1.32, 4.02), 2.46 (1.26, 4.78), and 2.65 (1.31, 5.37) among women with GD and normoglycemia, prediabetes, and incident diabetes, respectively,

compared to women with No GD and normoglycemia. In Model 2 (fully adjusted), addition of pre-pregnancy BMI and time-varying smoking in pack-years covariates slightly attenuated the HRs that remained statistically significant, except for the GD/incident diabetes group [2.02 (0.98, 4.19)]. In Models 3 and 4, addition of time-varying hypertension during follow up and time-varying BMI change (intervening risk factors), respectively, resulted in modest attenuation of the HRs that remained statistically significant with the exception of the GD/Incident diabetes group. Inclusion of other lifestyle behaviors, lipid-lowering medication use, time-varying hs-CRP, or change in HOMA-IR had minimal impact on model estimates.

The sensitivity analyses using stage 1 cut-points (SBP ≥130 and/or DBP ≥80 mm Hg) to define hypertension, or defining Any CAC as scores >10 yielded similar results. Other sensitivity analyses limiting the sample to nulliparas at baseline, or women with no previous HDP showed consistent or stronger associations for GD and glucose tolerance groups with risk of CAC (Supplemental Tables IV and V). We show curves for the probability of being free of CAC among GD status and glucose tolerance groups at follow up. The probability is lower for women with GD subgroups, including normoglycemic group, and for incident diabetes among women no GD (Figure 3).

DISCUSSION

Importantly, the findings show that even sustained normoglycemia after pregnancy was associated with increased risk of CAC among women with a history of GD. Compared to women without GD and with normoglycemia, the risk of CAC was about two times higher for women with a history of GD across all levels of glucose tolerance, independent of sociodemographic, clinical and lifestyle behavioral risk factors. The risk associations were not confounded by use of lipid-lowering medications in our study. This indicates that GD history may adversely affect CVD risk apart from glucose tolerance. To our knowledge, ours is the first study to differentiate normoglycemia from prediabetes as well as overt diabetes in estimating the association of GD history and subsequent glucose tolerance with the risk of subclinical coronary artery disease. In contrast, others found much weaker relative risks of 1.30 to 1.56 for future CVD outcomes among women with GD and no T2D.[12, 15, 16] Previous estimates may be biased toward the null from a higher prevalence of prediabetes and/or undiagnosed overt diabetes in the referent group of women without prior GD due to a lack of routine testing in clinical population settings (i.e., detection bias).[15, 16] As expected, the risk of CAC increased with worsening glucose tolerance (prediabetes, or incident diabetes) compared to normoglycemia among women with no previous GD.

In CARDIA, a history of GD was associated with larger carotid artery intima media thickness (cIMT), representing a 6-year increase in vascular aging, among women without T2D or the metabolic syndrome.[32] Other studies found a 26% higher risk of hypertension associated with GD history independent of pregnancy hypertensive disorders, and T2D.[43] Thus, a history of GD may entail underlying vascular changes or other mechanisms that adversely affect cardiovascular health independent of hyperglycemia.[44] The pathways could include common metabolic derangements that women with GD experience including heightened insulin resistance, delayed insulin secretion, endothelial dysfunction, systemic

inflammation, dyslipidemia, and/or other vascular changes such as hypertension.[43, 45, 46] In a longitudinal study of women with previous GD, women with normal glucose tolerance and no obesity also exhibited both insulin resistance and reduced insulin secretion.[47] Insulin resistance is an independent predictor of cardiovascular disease and coronary artery atherosclerotic plaque progression in adults, regardless of dysglycemia.[48] Evidence from Hannukainen et al. showed these same metabolic features in patients with ischemic coronary artery disease; i.e., enhanced glucose oxidation with lower insulin sensitivity, and a blunting of insulin secretion in response to a glucose load in the absence of hyperglycemia. The study findings were independent of traditional cardiometabolic risk factors (cholesterol, blood pressure, age, race, and BMI).[49] Thus, impaired insulin secretion and insulin resistance, the hallmarks of GD dysmetabolism, may explain the increased coronary artery atherogenesis in the absence of glucose intolerance. Further, in our study, traditional risk factors (i.e., total and LDL-C, and smoking) for atherosclerosis did not vary by glucose tolerance status among the GD groups. Of note, average weight gain was inversely correlated with glucose tolerance in women with no GD, but not in women with previous GD. Thus, a history of GD may confer additional underlying risk for ASCVD through obesity-related cardiometabolic pathways without apparent clinical manifestations. Our findings add to evidence that women with previous GD may need additional screening beyond the testing of glycemia, and that a history of GD may need incorporation into women's CVD risk calculations.[50]

Strengths of this study are the systematic biochemical testing of glucose tolerance across the childbearing years to distinguish all levels of glucose tolerance including normoglycemia from prediabetes and incident diabetes, and measurements of CVD risk factors (BMI, blood lipid profiles, and blood pressure) up to 6 times during 25 years with high retention (72%).[6] All previous studies relied on self-report or administrative data to dichotomize glucose tolerance as T2D versus no T2D, which combines prediabetes and normoglycemia into a single referent group. Thus, previous estimates may underestimate excess CVD risks in young to middle aged women,[14] especially for Black women who are seldom tested, and for women with GD, in whom uptake of post-delivery testing is low.[25, 51] Most importantly, our study estimated relative risks of CAC compared to a normoglycemic group without GD. Also, CARDIA women delivered pregnancies from 1986–2011 during a period of universal screening for GD. The 6.7 GD pregnancies per 100 deliveries in CARDIA is comparable to overall rates in the U.S.[2, 52]

There were also some limitations, including no CAC measurements before pregnancy to establish whether higher CAC preceded the onset of GD or overt diabetes before year 15. This concern is mitigated by the extremely low prevalence of CAC prior to age 35 years in women. We used a surrogate measure, CAC score, since the young age at follow-up in our parous sample limited our ability to evaluate clinical CHD or CVD events (n=26). However, CAC measured in younger to middle aged adults is a strong risk factor for subsequent CVD outcomes. Using CAC measurements at ages 32 to 56 years, CARDIA previously found a 3-fold increase in CVD events (n=108) and 5-fold increase in CHD events (n=56), both fatal and nonfatal, with 12.5 years of follow-up in the sample of 3043 men and women.[28] CAC scores of 1–19, 20–99, and ≥100 were associated with increased risk of premature CHD (HRs =2.6, 5.8, and 9.8), and CAC scores ≥100 were associated with early death (HR=22.4).

[28] Thus, even low CAC scores were associated with later CHD and CVD events, and CAC increased exponentially during 10 years men and women through mid-life.

Heart disease is the leading cause of death for women worldwide. In 2018, the American Heart Association Guidelines specified history of GD as an important ASCVD risk-enhancing factor for women.[8, 53] Yet, the evidence basis to screen younger women for CVD risk has been starkly lacking. For example, few CVD risk prediction models have evaluated pregnancy complications because of limited data sources, particularly for young women.[54] A study of northern European women found a borderline significant 26% higher Framingham CVD risk score with a history of GD, but GD prevalence in the sample was extremely low (0.5%) compared to contemporary cohorts (8%).[55] Another study evaluated reproductive risk factors, including breastfeeding, age at first birth, and stillbirths, and found slight improvements in CVD risk prediction for women,[56] but they did not evaluate any pregnancy complications (e.g., GD history, and preeclampsia). Other studies included hypertensive disorders, size at birth and preterm birth in CVD risk prediction models with none, or only minimal improvement in risk prediction, but they did not evaluate GD in any models.[57–59]

In summary, development of coronary calcified plaque as measured by CAC is present in some women in midlife. In our study, relative risk of such coronary plaque was about two times higher in women with previous GD for all subsequent glucose tolerance levels, including normoglycemia, compared to women without GD and normoglycemia. Thus, GD history may represent a constellation of risk factors (e.g., dyslipidemia, cumulative BP increases, mounting insulin resistance, endothelial dysfunction or inflammatory responses), [60] that promote development of atherosclerotic plaque in the absence of hyperglycemia. Insulin resistance and possibly higher inflammation (hs-CRP) among women with prior gestational diabetes who remained normoglycemic at follow up in our study is consistent with this hypothesis. Gestational diabetes[61] may be an especially vulnerable condition of dysmetabolism leading to initiation and/or propagation of coronary atherogenesis[32] from early lesions to the advanced calcified coronary plaque in younger women.

Higher ASCVD risk among women with GD history has been primarily attributed to their younger age at T2D onset, and several fold higher risk of progression to T2D.[10, 14] It is well-known that onset of T2D under age 40 increases (3.6 to 6.2-fold higher) cardiovascular-related mortality and outcomes in women.[62] Our findings represent a shift in this paradigm by showing that normoglycemia after GD pregnancy was still related to higher CAC risk. The risk did not further increase with transition to prediabetes and T2D. By contrast, women with no prior GD who subsequently developed prediabetes, or overt diabetes had a 1.5-fold and 2.1-fold higher risk of CAC, respectively, compared to those with normoglycemia. The clinical implications of our findings are that women with previous GD may benefit from enhanced traditional CVD risk factor testing (i.e., blood pressure, dyslipidemia, hyperinsulinemia), and perhaps incorporation of GD into risk calculators to improve CVD risk stratification and prevention.[63]

Better characterization of the GD phenotypes is also needed to assess CVD risk, because GD diagnostic criteria differ between the U.S. and other countries.[64] In CARDIA, 25.9% of

women with GD progressed to diabetes on average 15 years later, which is similar to the 16% to 29% cumulative incidence after 10 to 20 years of follow up in contemporary meta-analyses,[65, 66] and the U.S. population.[2]

Life course epidemiologic studies are challenging to undertake in population-based clinical settings because of extended time between pregnancy complications and onset of CVD events. A major limitation of this research in general is the lack of routine biochemical testing for diabetes or CVD risk factors among young women of childbearing age. The importance of modifiable lifestyle behaviors with the highest relevance to reduce both diabetes and CVD risk during the first year postpartum (i.e., lactation, and sleep) merit increased attention.[67, 68] Furthermore, more accurate clinical prediction tools are needed for women that take into account a history of GD as well as other pregnancy complications. Finally, this study adds to the mounting evidence that enhanced CVD risk factor screening among women with a history of GD is needed to better risk stratify women for early ASCVD prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

Dr. Gunderson is the guarantor of the manuscript and takes full responsibility for the work as a whole, including (if applicable) the study design, access to data, and the decision to submit and publish the manuscript. The authors thank the participants of the CARDIA study for their long-term commitment and important contributions to the study.

Funding Sources: The analyses were supported by grants from R01 DK106201 (Gunderson, PI), R01 DK090047 (Gunderson, PI) and K01 DK059944 (Gunderson, PI) from the National Institute of Diabetes, Digestive and Kidney Diseases. The Coronary Artery Risk Development in Young Adults Study (CARDIA) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201800005I & HHSN268201800007I), Northwestern University (HHSN268201800003I), University of Minnesota (HHSN268201800006I), and Kaiser Foundation Research Institute (HHSN268201800004I).

Study Sponsors: The study sponsor provided funding. The National Heart, Lung, and Blood Institute program official served on the study steering committee and publications subcommittee with one vote on each. The sponsor did not otherwise influence the analyses or decisions to publish this manuscript.

Disclosures:

Funding unrelated to the current research project from Janssen Pharmaceuticals, Inc., in 06/01017-12/31/2018 (Gunderson, EP)

Non-standard Abbreviations and Acronyms

2-h OGTT	Two-hour oral glucose tolerance test
95%CI	95% confidence interval
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
BP	Blood pressure

CAC	Coronary artery calcification/calcium
CAD	Coronary artery disease
CARDIA	The Coronary Artery Risk Development in Young Adults
CHD	Coronary heart disease
cIMT	Carotid artery intima media thickness
CT	Computed tomography
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
GD	Gestational diabetes
HbA1C	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HDP	Hypertensive Disorders of Pregnancy
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HR	Hazard ratio
hs-CRP	high sensitivity C-reactive protein
LDL-C	Low-density lipoprotein cholesterol
NCEP-ATP III	National Cholesterol Education Program/Adult Treatment Panel III
SAS	Statistical Analysis Software
SBP	Systolic blood pressure
T2D	Type 2 diabetes

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Clinical Perspective

What is new?

- Among black and white women with no history of gestational diabetes, progression to impaired glucose tolerance, or overt diabetes within 15 years after pregnancy was associated with a graded increase in the relative risk (1.5 to 2.2-fold) of coronary artery calcification in mid-life compared to women who maintained normoglycemia.
- Among black and white women with a history of gestational diabetes, the relative risk of coronary artery calcification in mid-life was twofold higher for those with normoglycemia, impaired glucose tolerance (prediabetes), or overt diabetes within 15 years after pregnancy compared to women with no history of gestational diabetes who maintained normoglycemia.

What are the clinical implications?

- Sustained normoglycemia among women with previous gestational diabetes may not diminish future atherosclerotic cardiovascular disease risk in women during mid-life.
- A history of gestational diabetes may entail underlying vascular changes, and/or adversely affect development of cardiovascular disease through pathways such as insulin resistance and impaired insulin secretion that promote atherogenic plaques independent of dysglycemia.
- These findings add to the mounting evidence that enhanced cardiovascular disease risk factor screening among women with a history of gestational diabetes is needed to better risk stratify women for early atherosclerotic cardiovascular disease prevention.

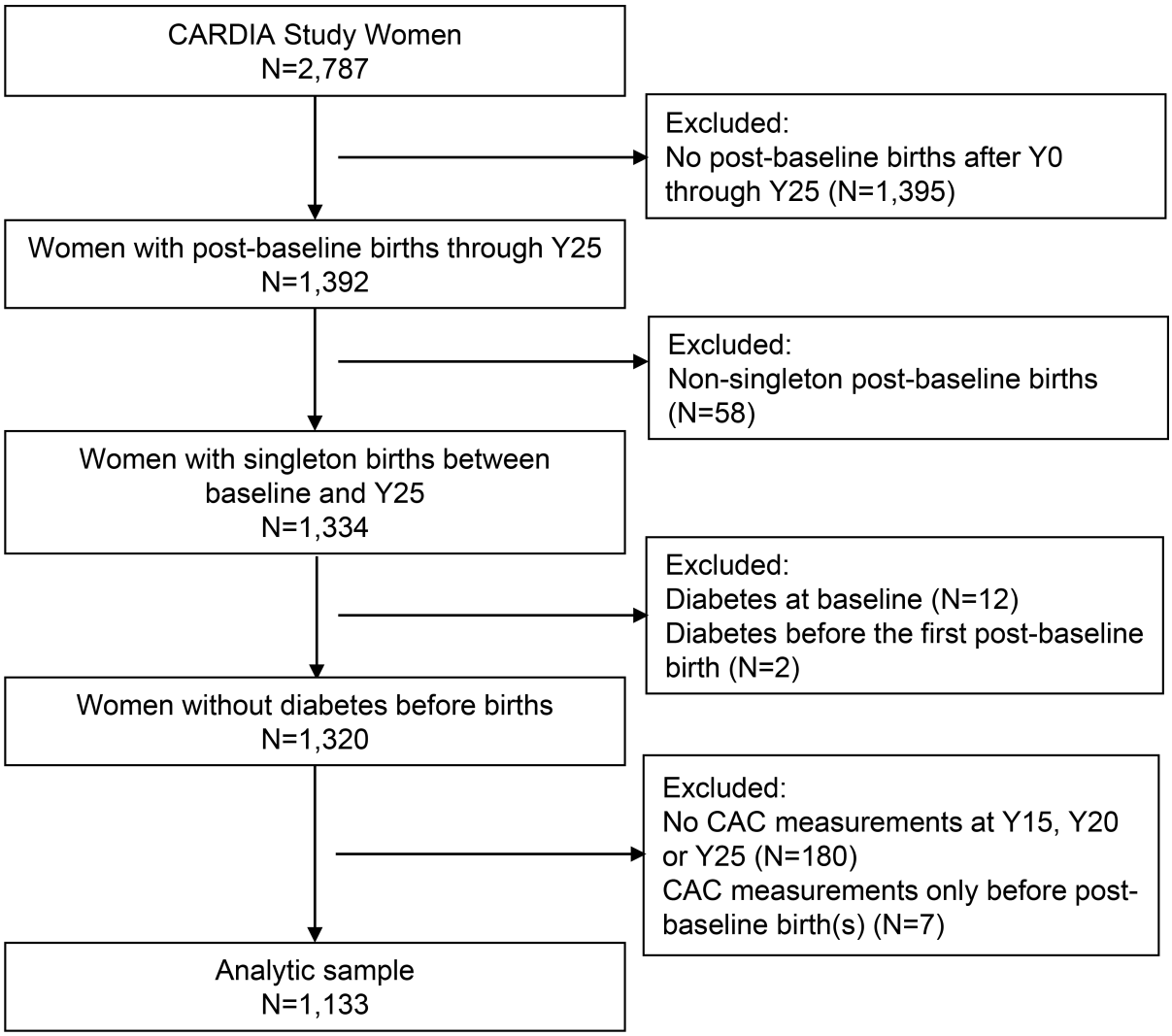

Figure 1.

Selection Flow Chart: CARDIA Women who reported one or more post-baseline births and had Coronary Artery Calcification (CAC) measurements at exams in years 15, 20 and/or 25 since baseline (Y0); (1985–1986 through 2010–2011).

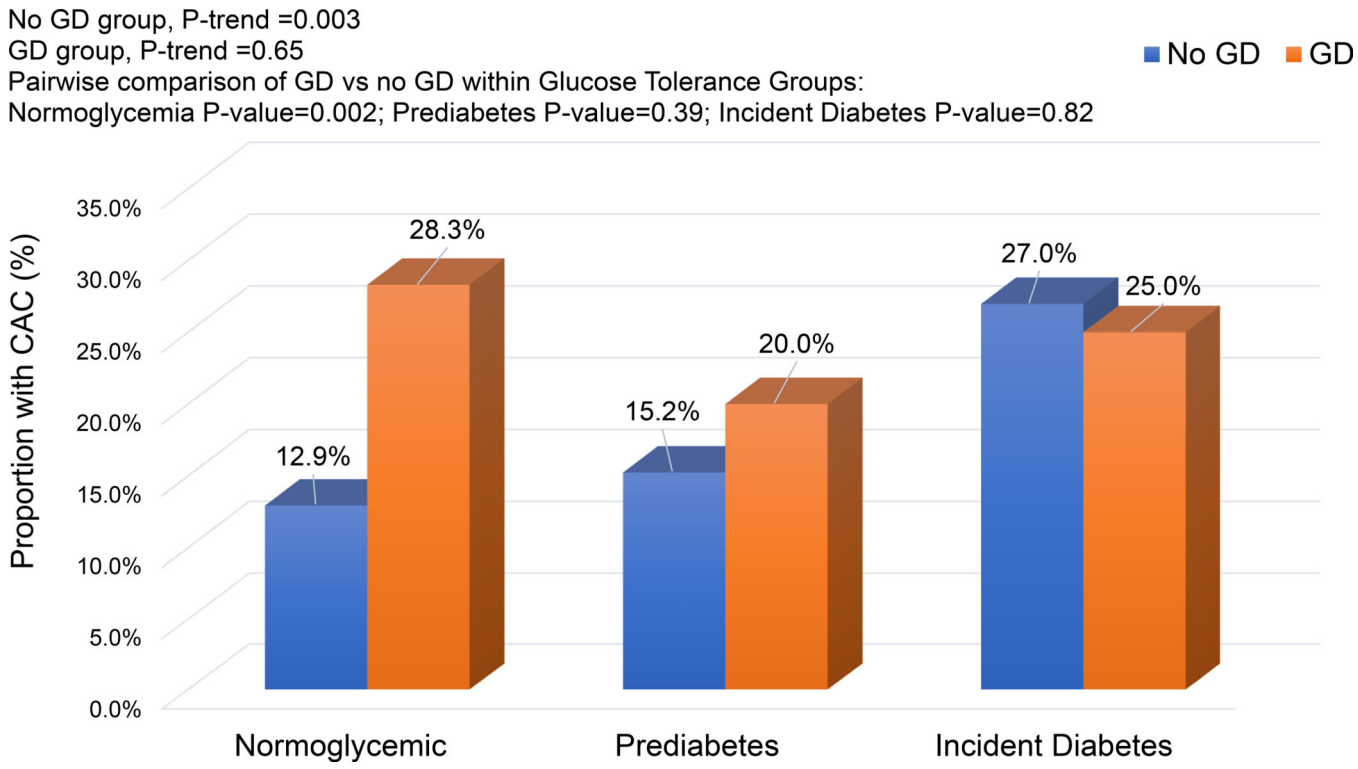

Figure 2.

No.(%) of Women with Any CAC At the End of Follow Up (Years 15, 20 or 25) by GD Status and Subsequent Glucose Tolerance Groups.

GD Status:		No GD				GD			
Subsequent Glucose Tolerance Groups	Total	**Normoglycemia**	**Prediabetes**	**Incident Diabetes**	trend p-value†	**Normoglycemia**	**Prediabetes**	**Incident Diabetes**	trend p-value†
Entire Sample, N	1133	557	348	89		53	50	36	
Any CAC, N (%)	183 (16.2)	72 (12.9)	53 (15.2)	24 (27.0)	0.003	15 (28.3)	10 (20.0)	9 (25.0)	0.65

Pairwise comparisons chi-square test for GD vs no GD within each Glucose Tolerance Group: Normoglycemia, p-value=0.002; Prediabetes p-value=0.39; Incident Diabetes p-value =0.82,
† Cochran–Armitage test for trend.

Figure 3.

Probability of Being CAC Free by GD Status and Subsequent Glucose Tolerance Groups During Follow Up.

Note: Estimates are based on the models unadjusted for covariates. On average, the length of the time interval between the first post-baseline birth and Year 15 is 9.4 years, and the length of each of the following two intervals is 5.0 years. Births after baseline occurred between 1986 and 2010.

Table 1.

Distribution of CAC Scores at End of Follow Up Among Women by GD Status and Subsequent Glucose Tolerance Groups After Pregnancy.

Categories of CAC score	No GD (N=994)				GD (N=139)			
	Glucose Tolerance After Pregnancy				Glucose Tolerance After Pregnancy			
N (%)	Normoglycemia	Prediabetes	Incident Diabetes	p-value*	Normoglycemia	Prediabetes	Incident Diabetes	p-value*
	(N=557)	(N=348)	(N=89)		(N=53)	(N=50)	(N=36)	
End of follow up				0.003				0.051
CAC = 0	485 (87.1)	295 (84.8)	65 (73.0)		38 (71.7)	40 (80.0)	27 (75.0)	
CAC >0 to 10	42 (7.5)	25 (7.2)	9 (10.1)		10 (18.9)	3 (6.0)	5 (13.9)	
CAC >10 to 50	18 (3.2)	16 (4.6)	6 (6.7)		1 (1.9)	7 (14.0)	2 (5.6)	
CAC >50	12 (2.2)	12 (3.5)	9 (10.1)		4 (7.6)	0	2 (5.6)	

*Based on the chi-square test.

Table 2.

Pre-pregnancy Characteristics (1985–2006) by GD Status and Subsequent Glucose Tolerance Groups After Pregnancy (2000–2011).

Pre-pregnancy Characteristics	No GD (N=994)				GD (N=139)			
	Glucose Tolerance After Pregnancy				Glucose Tolerance After Pregnancy			
Mean (SD) † or N (%)	Normoglycemia (N=557)	Prediabetes (N=348)	Incident Diabetes (N=89)	p-value	Normoglycemia (N=53)	Prediabetes (N=50)	Incident Diabetes (N=36)	p-value
Age at first post-baseline birth, *y	30.2 (4.7)	30.1 (5.2)	29.2 (4.6)	0.25	30.1 (4.9)	29.7 (5.2)	30.7 (4.4)	0.68
Black, n (%)	218 (39)	204 (59)	66 (74)	<.001	23 (43)	18 (36)	22 (61)	0.07
Nulliparous, n (%)	405 (73)	235 (68)	49 (55)	0.002	36 (68)	33 (66)	24 (67)	0.98
Education, n (%)				0.001				0.43
High school or less	136 (24)	94 (27)	30 (34)		14 (26)	11 (22)	4 (11)	
College education	280 (50)	202 (58)	46 (52)		31 (58)	28 (56)	23 (64)	
Graduate/ professional degree	141 (25)	52 (15)	13 (15)		8 (15)	11 (22)	9 (25)	
Weight status, n (%)				<.001				<.001
Normal (BMI <25)	408 (73)	207 (59)	30 (34)		36 (68)	27 (54)	10 (28)	
Overweight (BMI: 25–29.9)	95 (17)	75 (22)	21 (24)		14 (26)	11 (22)	5 (14)	
Obese (BMI ≥30)	54 (10)	66 (19)	38 (43)		3 (6)	12 (24)	21 (58)	
BMI, kg/m^2	23.7 (4.7)	25.1 (5.5)	29.1 (7.1)	<.001	23.8 (4.5)	26.0 (6.2)	30.9 (7.7)	<.001
Waist circumference, cm	72.6 (9.6)	76.2 (11.6)	84.5 (15.1)	<.001	72.9 (9.3)	77.5 (13.3)	87.9 (16.1)	<.001
Systolic BP, mm Hg	103 (9)	105 (10)	109 (12)	<.001	104 (9)	104 (10)	105 (9)	0.88
Diastolic BP, mm Hg	65 (9)	66 (10)	69 (12)	<.001	66 (7)	65 (13)	67 (9)	0.67
Total cholesterol, mg/dL	179 (35)	180 (36)	182 (39)	0.69	184 (36)	183 (39)	178 (25)	0.69
LDL-cholesterol, mg/dL	105 (30)	108 (33)	111 (35)	0.17	110 (29)	109 (37)	109 (24)	0.98
HDL-cholesterol, mg/dL	60 (14)	57 (13)	55 (16)	0.007	59 (12)	59 (15)	52 (13)	0.01
Fasting Triglycerides, mg/dL †	57 (41, 78)	60 (45, 84)	68 (54, 97)	<.001	61 (46, 86)	63 (50, 89)	76 (57, 105)	0.08
Fasting glucose, mg/dL	79 (7)	82 (8)	83 (10)	<.001	79 (8)	82 (9)	88 (13)	<.001
Fasting insulin, μU/mL †	8.6 (6.1, 12.0)	10.0 (6.8, 14.0)	14.5 (9.2, 19.0)	<.001	8.3 (6.6, 14.3)	10.0 (6.3, 17.0)	13.9 (9.4, 22.0)	0.008
HOMA-IR †	1.6 (1.2, 2.3)	2.0 (1.3, 2.8)	3.1 (1.7, 4.1)	<.001	1.7 (1.3, 2.7)	2.1 (1.4, 3.7)	3.1 (1.8, 5.2)	<.001

Pre-pregnancy Characteristics	No GD (N=994)				GD (N=139)			
	Glucose Tolerance After Pregnancy				Glucose Tolerance After Pregnancy			
Mean (SD) † or N (%)	Normoglycemia (N=557)	Prediabetes (N=348)	Incident Diabetes (N=89)	p-value	Normoglycemia (N=53)	Prediabetes (N=50)	Incident Diabetes (N=36)	p-value
Prediabetes, n (%)	0	12 (3)	8 (9)	<.001	0	4 (8)	5 (14)	0.03
Physical activity score †	276 (133, 459)	255 (139, 442)	191 (84, 278)	<.001	236 (146, 406)	269 (148, 378)	329 (148, 558)	0.51
Smoking, lifetime pack-years	1.9 (4.1)	2.4 (4.9)	2.4 (4.1)	0.20	2.2 (3.8)	2.8 (5.8)	2.0 (4.3)	0.68
A priori diet quality score *, Year 0	65 (14)	64 (13)	60 (12)	0.001	65 (13)	66 (12)	65 (14)	0.95

Abbreviations: BMI, body mass index; BP, blood pressure; GD, gestational diabetes; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; SD, standard deviation.

Pre-pregnancy measurements from the closest exam before the first post-baseline birth,

* *a priori* diet quality score was obtained from the CARDIA baseline exam (Year 0; 1985–86).

* Age at first post-baseline birth is calculated from the date of the delivery of first pregnancy >20 weeks gestation after CARDIA baseline (>1985 to 2009).

† Median (25th, 75th percentiles)

Table 3.

Characteristics at the End of Follow Up by GD Status and Subsequent Glucose Tolerance Groups After Pregnancy (2000–2011).

End of Follow Up Characteristics*	No GD (N=994)				GD (N=139)			
	Glucose Tolerance After Pregnancy				Glucose Tolerance After Pregnancy			
Mean (SD) † or N (%)	Normoglycemia (N=557)	Prediabetes (N=348)	Incident Diabetes (N=89)	p-value	Normoglycemia (N=53)	Prediabetes (N=50)	Incident Diabetes (N=36)	p-value
Age, years	47.0 (4.9)	48.4 (4.3)	48.7 (4.1)	<.001	46.5 (6.0)	47.7 (5.1)	48.2 (4.9)	0.31
Weight status, n (%)				<.001				<.001
Normal (BMI <25)	226 (41)	82 (24)	6 (7)		18 (34)	13 (26)	4 (11)	
Overweight (BMI: 25–29.9)	161 (29)	83 (24)	17 (19)		22 (42)	11 (22)	4 (11)	
Obese (BMI ≥30)	170 (31)	183 (53)	66 (74)		13 (25)	26 (52)	28 (78)	
BMI, kg/m^2	27.6 (6.3)	31.4 (7.6)	36.1 (8.4)	<.001	28.0 (5.9)	31.1 (7.4)	35.0 (7.8)	<.001
Waist circumference, cm	83.6 (13.0)	92.7 (15.3)	103.7 (17.8)	<.001	85.2 (12.5)	91.4 (15.5)	102.2 (17.6)	<.001
Systolic BP, mm Hg	113 (16)	118 (16)	123 (21)	<.001	121 (19)	115 (18)	116 (14)	0.22
Diastolic BP, mm Hg	72 (12)	75 (11)	78 (11)	<.001	76 (13)	73 (12)	74 (9)	0.46
Total cholesterol, mg/dL	192 (32)	191 (36)	190 (42)	0.95	191 (34)	195 (41)	183 (35)	0.35
LDL-cholesterol, mg/dL	109 (28)	112 (31)	110 (37)	0.36	113 (27)	111 (38)	101 (30)	0.21
HDL-cholesterol, mg/dL	65 (18)	59 (16)	53 (16)	<.001	61 (17)	61 (21)	58 (25)	0.74
Fasting Triglycerides, mg/dL †	74 (56, 100)	89 (67, 123)	118 (84, 163)	<.001	72 (53, 102)	91 (73, 138)	98 (74, 133)	0.01
Fasting glucose, mg/dL	86 (7)	95 (9)	130 (55)	<.001	86 (7)	97 (10)	122 (39)	<.001
Fasting insulin, μU/mL †	8.0 (5.0, 11.0)	11.3 (7.0, 16.9)	15.7 (9.3, 23.8)	<.001	9.8 (5.8, 15.0)	10.9 (7.2, 15.7)	14.0 (8.2, 26.7)	0.05
HOMA-IR †	1.7 (1.0, 2.4)	2.7 (1.6, 4.0)	4.8 (2.6, 8.6)	<.001	1.8 (1.2, 3.1)	2.5 (1.8, 4.0)	4.0 (2.9, 7.0)	<.001
Metabolic syndrome, n (%)	59 (11)	138 (40)	69 (78)	<.001	5 (9)	19 (38)	28 (78)	<.001
hs-CRP, μg/mL †	1.0 (0.4, 2.8)	2.2 (0.7, 5.1)	4.8 (1.6, 8.7)	<.001	1.6 (0.6, 4.3)	1.9 (0.7, 5.8)	4.0 (1.1, 8.8)	0.03
hs-CRP (>3 μg/mL), n (%)	123 (23)	151 (44)	53 (60)	<.001	15 (28)	17 (34)	20 (56)	0.03
Hypertension, n (%)	99 (18)	120 (34)	61 (69)	<.001	13 (25)	14 (28)	20 (56)	0.006
Lipid-lowering medication, n (%)	29 (5)	29 (8)	30 (34)	<.001	4 (8)	5 (10)	14 (39)	<.001
Physical activity score †	244 (111, 450)	214 (95, 383)	147 (62, 294)	<.001	256 (144, 504)	210 (80, 344)	231 (61, 406)	0.25
Smoking, lifetime pack-years	3.2 (6.7)	4.3 (9.1)	4.6 (7.6)	0.07	3.8 (6.7)	3.9 (6.9)	3.3 (6.8)	0.93

End of Follow Up Characteristics*	No GD (N=994)				GD (N=139)			
	Glucose Tolerance After Pregnancy				Glucose Tolerance After Pregnancy			
Mean (SD) † or N (%)	Normoglycemia (N=557)	Prediabetes (N=348)	Incident Diabetes (N=89)	p-value	Normoglycemia (N=53)	Prediabetes (N=50)	Incident Diabetes (N=36)	p-value
Average *a priori* diet quality score (Years 0, 7 and 20)	69 (12)	66 (11)	64 (9)	<.001	67 (11)	69 (11)	68 (11)	0.77
Oral contraceptive use, n (%)	521 (94)	335 (96)	86 (97)	0.14	50 (94)	48 (96)	33 (92)	0.70
Post-menopausal status, n (%)	157 (28)	139 (40)	41 (46)	<.001	17 (32)	18 (36)	18 (50)	0.22
Menopausal hormone therapy, n (%)	32 (6)	22 (6)	6 (7)	0.90	4 (8)	5 (10)	4 (11)	0.84
Family history of diabetes, n (%)	186 (34)	180 (52)	66 (74)	<.001	27 (51)	27 (54)	19 (53)	0.95
Family history of heart disease, n (%)	273 (49)	209 (60)	57 (64)	0.001	26 (49)	30 (60)	19 (53)	0.53
Weight change, kg	10.6 (11.9)	17.1 (14.1)	19.4 (17.7)	<.001	11.4 (11.1)	13.5 (11.2)	11.5 (17.9)	0.68
HOMA-IR change	0.0 (1.4)	0.9 (2.7)	2.8 (4.3)	<.001	0.3 (1.7)	0.5 (2.4)	2.7 (8.7)	0.07
Time from first birth to CAC, y	10.7 (4.9)	11.2 (5.0)	12.2 (5.0)	0.02	10.9 (4.5)	11.9 (5.8)	10.7 (4.0)	0.47
Time from last birth to EFU, y	13.8 (5.9)	15.7 (5.8)	17.5 (4.5)	<.001	12.7 (6.0)	14.3 (5.6)	15.8 (5.5)	0.04

Abbreviations: BMI, body mass index; BP, blood pressure; GD, gestational diabetes; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; SD, standard deviation.

"End of follow up" (EFU) is defined as the first exam with CAC >0, or the last exam with CAC=0 measurement at exam years 15, 20 or 25.

Change in weight and HOMA-IR from the nearest exam preceding the first birth to the end of follow up.

*Based on measurements from the last exam, or the first exam when the women had CAC>0.

†Median (25th, 75th percentiles)

Note: n=15 women were missing hs-CRP in exam years 10, 15 and 20.

Table 4.

Unadjusted and Adjusted Hazard Ratios (HR) and (95%CI) of CAC Associated with GD Status and Subsequent Glucose Tolerance Status (normoglycemia, prediabetes or incident diabetes) in Women During Mid-life (1986–2011).

GD and Glucose Tolerance Groups	% Any CAC (n/N)†	Model 1 HR (95%CI)		Model 2 HR (95%CI)		Model 3 HR (95%CI)		Model 4 HR (95%CI)	
GD Status									
No GD	15.0 (149/994)	1	Referent	1	Referent	1	Referent	1	Referent
GD	24.5 (34/139)	1.85	(1.28, 2.69)	1.73	(1.18, 2.52)	1.66	(1.13, 2.43)	1.66	(1.13, 2.42)
GD Status Stratified by Incident Diabetes									
Incident diabetes									
No GD	27.0 (24/89)	1	Referent	1	Referent	1	Referent	1	Referent
GD	25.0 (9/36)	1.10	(0.50, 2.42)	0.97	(0.43, 2.19)	1.03	(0.45, 2.33)	1.06	(0.46, 2.44)
No diabetes (prediabetes & normoglycemia)									
No GD	13.8 (125/905)	1	Referent	1	Referent	1	Referent	1	Referent
GD	24.3 (25/103)	2.02	(1.31, 3.11)	2.01	(1.30, 3.09)	1.95	(1.27, 3.01)	1.96	(1.27, 3.02)
GD and Subsequent Glucose Tolerance									
No GD/Normoglycemia	12.9 (72/557)	1	Referent	1	Referent	1	Referent	1	Referent
No GD/Prediabetes	15.2 (53/348)	1.69	(1.17, 2.46)	1.54	(1.06, 2.24)	1.50	(1.03, 2.17)	1.52	(1.04, 2.22)
No GD/Incident diabetes	27.0 (24/89)	2.68	(1.62, 4.44)	2.17	(1.30, 3.62)	1.79	(1.06, 3.01)	1.82	(1.08, 3.09)
GD/Normoglycemia	28.3 (15/53)	2.30	(1.32, 4.02)	2.34	(1.34, 4.09)	2.24	(1.28, 3.92)	2.25	(1.29, 3.94)
GD/Prediabetes	20.0 (10/50)	2.46	(1.26, 4.78)	2.13	(1.09, 4.17)	2.08	(1.06, 4.07)	2.11	(1.07, 4.14)
GD/Incident diabetes	25.0 (9/36)	2.65	(1.31, 5.37)	2.02	(0.98, 4.19)	1.76	(0.85, 3.67)	1.76	(0.84, 3.66)

Model 1: adjusted for race, age at the first birth and pre-pregnancy systolic BP.

Model 2: Model 1 + adjusted for pre-pregnancy BMI and time-varying lifetime smoking exposure (pack-years). (Fully adjusted model)

Model 3: Model 2 + adjusted for time-varying hypertension during follow up (intervening variable).

Model 4: Model 3 + adjusted for time-varying BMI change during follow up (intervening variable).

n = number of women with Any CAC, and N = number of women within the group strata.

† At the end of follow up