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Association Between Gestational Diabetes and Incident Maternal CKD: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Supplementary Material

Supplementary Material Descriptive Text for Online Delivery

Supplementary Table S1 (PDF). Exam year 0 characteristics compared for CARDIA women included and excluded from this analysis.

Supplementary Table S2 (PDF). Cumulative incidence of CKD by history of GDM among all CARDIA women reporting interim births at exam years 0, 10, 15, 20, and 25.

Supplementary Table S3 (PDF). HRs for CKD by history of exposure to GDM among all CARDIA women reporting interim births during mean 20.8 y of follow-up.

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Abstract

Background—Gestational diabetes mellitus (GDM) is associated with increased risk for diabetes mellitus, metabolic syndrome, and cardiovascular disease. We evaluated whether GDM is associated with incident chronic kidney disease (CKD), controlling for pre-pregnancy risk factors for both conditions.

Study Design—Prospective cohort

Setting & Participants—Of 2,747 women (aged 18–30 years) enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study in 1985–86, we studied 820 who were nulliparous at enrollment, delivered at least one pregnancy > 20 weeks' gestation and had kidney function measures during 25 years of follow-up.

Predictor—GDM was self-reported by women for each pregnancy.

Outcomes—CKD was defined as development of estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or urine albumin-creatinine ratio ≥ 25 mg/g at any one CARDIA examination in years 10, 15, 20 or 25.

Measurements—HRs for developing CKD were estimated for women who developed GDM versus women without GDM using complementary log-log models, adjusting for pre-pregnancy age, systolic blood pressure, dyslipidemia, body mass index, smoking, education, eGFR, fasting glucose, physical activity level (all measured at the CARDIA examination prior to first pregnancy), race, and family history of diabetes. We explored for an interaction between race and GDM.

Results—Over a mean follow-up of 20.8 years, 105 of 820 (12.8%) women developed CKD, predominantly increased urine albumin excretion (98 albuminuria only, 4 decreased eGFR only, 3 both). There was evidence of a GDM-race interaction on CKD risk (p=0.06). Among black women, the adjusted HR for CKD was 1.96 (95% CI, 1.04–3.67) in GDM compared to those without GDM. Among white women, the HR was 0.65 (95% CI, 0.23–1.83).

Limitations—Albuminuria was assessed by single untimed measurements of urine albumin and creatinine.

Conclusions—GDM is associated with subsequent development of albuminuria among black women in CARDIA.

Index words

gestational diabetes mellitus (GDM); chronic kidney disease (CKD); incident CKD; albuminuria; pregnancy; diabetes mellitus; race/ethnicity; African American; CKD risk factor

Introduction

Gestational diabetes mellitus (GDM), i.e., glucose intolerance with onset or first recognition during pregnancy, affects about 6% of pregnancies in the United States, where the prevalence of GDM has been increasing over time.[1,2] GDM is known to be associated with subsequent development of cardiovascular risk factors including type 2 diabetes mellitus[3–6] and metabolic syndrome[7,8] as well as subclinical atherosclerosis[8,9] and manifest

cardiovascular disease.[10–12] Chronic kidney disease (CKD), defined by increased urine albumin excretion (albuminuria) and/or reduced estimated glomerular filtration rate (eGFR), affects approximately 13.6% of US adults (2007–2012).[13] Reduced eGFR and albuminuria are independent risk factors for all-cause mortality, cardiovascular mortality and end-stage renal disease in the general population.[14,15]

The relationship between GDM and subsequent CKD is unclear. Studies have reported an association between GDM and early stage CKD[16], increased albuminuria among women with a history of GDM compared to those without GDM history,[17,18] and a higher prevalence of albuminuria among women with GDM history who later developed diabetes compared to normoglycemic women.[19] Other studies have not found differences in albuminuria between women with and without GDM history,[20,21] although the cross-sectional nature, lack of pre-pregnancy measurement of shared risk factors for GDM and CKD, or short duration of follow-up time since pregnancy constrained several studies. The aim of this study was to estimate the association between GDM and CKD in a longitudinal, prospective population-based study of young adults that includes pre-pregnancy assessments of kidney function and shared risk factors for GDM and CKD.

Methods

Study Design

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a prospective, population-based cohort study that enrolled 5,115 black and white participants aged 18–30 years in 1985–1986.[22] Follow-up examinations occurred at 2, 5, 7, 10, 15, 20 and 25 years (2010–2011) after the initial examination. Participants were recruited from Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. All participants gave informed consent, and the appropriate institutional review boards approved this study.

Sample Selection Criteria

Women were asked at each cohort examination whether they were currently pregnant or breastfeeding, and about the number of pregnancies, abortions, miscarriages, stillbirths and live births since the last exam. The first reported pregnancy > 20 weeks' gestation was treated as the "index" pregnancy. Women were included in our analytic cohort at the examination prior to the index pregnancy, and all covariates were selected from that examination. For example, for a woman who reported her first birth at CARDIA examination year 15, pre-pregnancy covariates were selected from the prior examination in year 10. Urine specimens used to define our outcome were collected at CARDIA years 10, 15, 20 and 25. Women who reported a first birth prior to the 10-year follow-up examination had their covariates assessed at the first CARDIA examination. As shown in Figure 1, we excluded women who were parous at the initial CARDIA examination (n=1008), women with zero births at the end of CARDIA follow-up (examination year 25, n=862), women with CKD prior to or at the baseline examination (n=7), women with diabetes mellitus prior to any pregnancy (n=3), women missing measurement of baseline CKD or missing measures of both albuminuria and eGFR at all four examinations where the outcome was measured

(n=25), and women missing data for covariates of interest (n=30). Baseline CKD was defined as GFR < 60 ml/min/1.73m^2 or self-reported kidney disease other than nephrolithiasis or pyelonephritis or a urine albumin-creatinine ratio (ACR) ≥ 25 mg/g adjusted for race and gender (urine ACR was not measured at the year 0 examination). Compared to the women included in these analyses, women excluded from this study were more likely to be older, black, with higher systolic blood pressure, body mass index (BMI), LDL (low density lipoprotein)-cholesterol levels, eGFR, and fasting plasma glucose at enrollment into CARDIA (Table S1, available as online supplementary material). The women excluded also were more likely to be smokers and have less education, while being more likely to have metabolic syndrome and family history of CKD compared with the included study population.

Parity and Gestational Diabetes Mellitus

At each examination, women were asked if they had diabetes and whether they had diabetes only during pregnancy. Self-report of GDM was validated for 200 births between baseline and year 10 in 165 CARDIA women by medical record abstraction of laboratory data. The sensitivity of reports of ever having GDM was 100% (20 of 20) and specificity was 92% (134 of 145).[3]

Women were included if nulliparous (no live births of > 20 weeks' gestation) at baseline, and transitioned across follow-up time intervals (0–10, >10–15, >15–20, and >20–25) in which the number of births (parity) and GDM status were updated. The number of births was cumulative to the end of follow up (i.e. examination year of development of CKD or year 25). Once women developed GDM, they were classified as having GDM for all subsequent follow-up time (which may have included additional pregnancies).

Chronic Kidney Disease

Single, untimed urine specimens were collected for measurement of urine albumin and creatinine at the years 10, 15, 20 and 25 examinations. Urine albumin was measured by nephelometry with a specific anti-albumin monoclonal antibody. In years 10, 15, and 20, urine creatinine was measured by the Jaffe method. In year 25, urine creatinine was measured by the Roche enzymatic method. Based on creatinine excretion across 3 days of 24-hour urine collections obtained in a CARDIA subsample (n=839),[23] calibration constants were used in our study to adjust for gender and race-specific differences in urinary creatinine excretion as in Murtaugh et al[24] using the formula albumin/(k*creatinine) where k=0.88 in black women (no adjustment needed for female gender).

Blood samples were drawn from seated participants after at least 8 hours of fasting. Serum creatinine was measured at years 0, 10, 15, and 20 by the modified-rate Jaffe method. In year 25, creatinine was measured by the Roche enzymatic method. Samples from years 10, 15, 20 and 25 have been calibrated to National Institute of Standards and Technology Standards as recommended by the National Kidney Disease Education Program Laboratory Working Group.[25] The eGFR was calculated using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[26] The accuracy of the CKD-EPI equation over a range of kidney function, clinical characteristics and racial backgrounds has been documented. [26, 27]

Incident CKD was defined in this study as the development of eGFR < 60 ml/min/1.73 m^2, or urine ACR ≥ 25 mg/g after one or more births during follow up, at any one CARDIA examination in years 10, 15, 20 and 25. In examination years where only one CKD measure was available for an individual, either eGFR or ACR was used to define the outcome.

Other Covariates

Information on race, sex, and age was self-reported, and trained interviewers assessed sociodemographic information including highest level of education completed, medical history, family history and medication use. Education level, measured at each examination, was used as a measure of socioeconomic status, and categorized as high school or less or more than high school. Physical activity was assessed using the interviewer-administered CARDIA Physical Activity History assessment at each examination.[28] Family history of diabetes mellitus was defined by a report of one or more first-degree relatives having diabetes mellitus at one or more examinations, and family history of CKD was defined as report of one or more first-degree relatives with kidney disease.

Sitting blood pressure was measured by trained technicians who chose the cuff size appropriate to the arm circumference. After an initial 5-minute rest, blood pressure was measured three times at 1-minute intervals using the Hawksley (Lancing, Sussex, UK) random-zero sphygmomanometer through year 15 and the oscillometric Omron (Omron Corp., Schaumberg, IL) HEM907XL in years 20 and 25. Calibration equations were established to calibrate the Omron measurements to the random-zero device.[29] The average of the second and third measurements were used. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg or use of antihypertensive medications.

Weight and height were measured at each examination, to the nearest 0.5 cm and nearest 0.2 kg, respectively.[30] BMI was computed as weight in kilograms divided by height in meters squared.

Glucose was measured using the hexokinase ultraviolet method at years 0, 10, 15 and 20 using hexokinase coupled to glucose-6-phosphate dehydrogenase.[31] At year 25 fasting glucose was measured by the Roche Modular P hexokinase method. Blood lipids and lipoproteins were measured at each examination.[32] Total cholesterol and triglycerides (TG) were measured enzymatically, high-density lipoprotein (HDL) cholesterol was determined by precipitation with dextran sulfate-magnesium chloride, and low-density lipoprotein cholesterol was calculated using the Friedewald equation.[32] Diabetes mellitus was defined as a fasting glucose ≥ 126 mg/dl, hemoglobin A1c ≥ 6.5%, 2 hour oral glucose tolerance test (OGTT) ≥ 200 mg/dl and/or use of diabetes medications. Glucose intolerance was defined as fasting plasma glucose ≥ 100 mg/dl, 2 hour OGTT ≥ 140 mg/dl or use of diabetes medications. Insulin resistance was defined as TG-HDL cholesterol ratio ≥ 1.7 for black women and TG-HDL cholesterol ratio ≥ 2.2 for white women[33] or by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).[34,35] Metabolic syndrome was defined as any 3 of waist girth > 88 cm, TG ≥ 150 mg/dl, HDL cholesterol < 50 mg/dl, SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg or use of antihypertensive medications, and fasting glucose ≥ 100 mg/dl.

Statistical Analysis

Baseline characteristics were compared between women with and without reported GDM pregnancies. Pre-pregnancy characteristics correspond to the examination at the beginning of the interval during which a woman first reports a birth, where the intervals are CARDIA examination years 0–10, 10–15, 15–20, 20–25. The probability of not having CKD at each time interval was calculated by product limit estimation, and cumulative incidence of CKD within each time interval was calculated as 1 minus survival, for parous women with and without exposure to GDM. To account for interval censored data, complementary log-log models were used to estimate hazard ratios (HRs) of CKD by the method of Prentice and Gloecker,[36] comparing women with and without a history of GDM. Confounders were chosen a priori based on a directed acyclic graph.[37] DAGgitty[38] was used to determine the minimally sufficient set, which included baseline (from the CARDIA examination prior to first pregnancy) age, race, smoking, dyslipidemia, SBP, BMI, physical activity score, and education level (for socioeconomic status) as well as any report of family history of diabetes. Additionally, baseline fasting glucose and eGFR were included in the adjusted model. Effect measure modification between race and the exposure was calculated by the addition of an interaction term to each model and considered significant for likelihood ratio tests with p-values less than 0.1. To analyze change in eGFR over time, percent annualized decline in eGFR was calculated for each interval and used as the outcome measure in linear mixed models. Linear mixed models were chosen to account for within-subject correlation of repeated measure using the autoregressive (1) correlation structure based on corrected Akaike Information Criterion. The same minimally sufficient set of baseline confounders was included in the adjusted model, as well as baseline fasting glucose and eGFR. Analyses were conducted using SAS version 9.4 (Cary, NC) and type 1 error was set at 5% level of significance for two-sided tests.

Results

Study Participants

A total of 101/820 (12.3%) of the women in the analytic sample reported a GDM pregnancy. Women with GDM were more likely to have family history of diabetes, they more frequently had a family history of CKD, and they had higher pre-pregnancy BMI (Table 1). There was no difference between those with and without GDM for pre-pregnancy age, race, education, eGFR, smoking status, fasting glucose, waist circumference, HDL-C levels, systolic blood pressure, diastolic blood pressure and total physical activity score.

A total of N=105 incident cases of CKD accrued over mean follow-up time of 20.8 years. Of those, 98 had albuminuria only, 4 had decreased eGFR only, and 3 met both CKD criteria. Overall, among women with GDM, 17/101 (16.8%) developed CKD compared to 88/719 (12.2%) without GDM (p=0.2). Among black women with GDM, 13/42 (31.0%) developed CKD compared to 45/289 (15.6%) without GDM (p=0.03). Among white women who reported GDM, 4/59 (6.8%) developed CKD compared to 43/430 (10.0%) without GDM (p=0.6). The cumulative incidence of CKD at each examination interval was greater among those with GDM compared to those without although this result was not statistically significant (Table 2). The relative hazard of incident CKD was higher among women with

GDM compared to parous women without a history of GDM, although not statistically significant in the crude model (Table 3). Adjustment for confounders did not significantly change the result. There was evidence of interaction between GDM and race (likelihood ratio test interaction p=0.06). Among black women, the HR for CKD was 1.96 (95% CI, 1.04–3.67) for those with GDM versus parous women without GDM. Among white women, the HR was 0.65 (95% CI, 0.23–1.83). The incidence curves by race and GDM status are presented in Figure 2.

We examined whether the development of glucose intolerance, insulin resistance, diabetes mellitus, metabolic syndrome, or hypertension contributed to explain the association between GDM and CKD. Black women were more likely than white women to develop insulin resistance as defined by HOMA-IR, metabolic syndrome, hypertension and diabetes mellitus (Table 4). However, there was no evidence of effect measure modification between interval development of those factors and the association between CKD and GDM in parous black women (Table 5).

No differences were seen in percent-annualized eGFR change between parous women with and without GDM (Table 6), nor was there evidence of an interaction between race and GDM (Wald p for interaction ≥ 0.2).

Sensitivity Analysis

Normal pregnancy affects renal physiology, resulting in an increase in eGFR and a small increase in albuminuria.[39] As a sensitivity analysis, measures of CKD were set to missing for any examination year when a woman was pregnant, and complementary log-log models were again used to estimate HRs of CKD. Results did not differ from the initial analysis. Among black women, the HR was 1.96 (95% CI, 1.04–3.67) for those with GDM compared to those without GDM, while among white women the HR was 0.64 (95% CI, 0.23–1.81).

Women with pregnancies before the initial CARDIA examination who also reported interim births during follow-up (n=387) were included in a sensitivity analysis with the main study sample (total N=1207 for this analysis). Only births occurring after the initial CARDIA examination were considered, and covariates were taken from the CARDIA examination at the beginning of the interval during which women reported their first interim birth. Overall, results did not differ significantly from the main analysis (Tables S2 and S3). In addition, the analysis was repeated considering only women with albuminuria as the outcome. Results were not different from the main analysis.

Discussion

GDM was associated with development of CKD, predominantly albuminuria, among black women, but not white women in this study of parous women. The association was similar after adjusting for pre-pregnancy risk factors for GDM and CKD, including age, SBP, dyslipidemia, BMI, smoking, socioeconomic status, eGFR, fasting glucose, and physical activity level as well as race and family history of diabetes.

Biomarkers of endothelial dysfunction are elevated in women with recent GDM compared to controls[40] and have been shown to predict the development of diabetes independent of other known risk factors.[41,42] Elevated levels of these biomarkers have also been associated with onset and progression of albuminuria as well as increased risk of death among patients with type 2 diabetes.[43] Given the increased cardiovascular and mortality risk associated with albuminuria even in the general population,[14,44] several authors have proposed that endothelial dysfunction, at least in part, may explain the link between albuminuria, cardiovascular disease and mortality.[45,46]

Only a small number of women in this cohort developed eGFR < 60 ml/min/1.73 m^2, and no association was seen between GDM and eGFR decline. Glomerular hyperfiltration, or abnormally high eGFR, is seen in early diabetic kidney disease along with albuminuria, and may predict progressive diabetic nephropathy.[47–49] Although we used the CKD-EPI equation in our study, as it was developed to be more accurate at higher eGFRs,[26] among diabetics this equation and other estimation formulas may fail to detect hyperfiltration and underestimate eGFR decline when compared to measured GFR.[50]

A prior, although cross-sectional, analysis reported results similar to ours. Women in the National Kidney Foundation's Kidney Early Evaluation Program (KEEP) with self-reported GDM, but without subsequent diabetes, had higher odds of microalbuminuria compared to women without any diabetes history.[16] An interaction with race and GDM was also seen in the KEEP population, with the association between GDM and albuminuria found in black women, but not white women. Another cross-sectional analysis of women with GDM but not subsequent diabetes in the NHANES (National Health and Nutrition Examination Survey) was equivocal in relating moderately increased albuminuria to GDM.[18] The divergent results in the latter two studies may reflect differences in age of the women with GDM history (mean ages, 32.2 years in NHANES and 51.5 years in KEEP), and the population-based design of NHANES and the kidney disease risk setting in KEEP.

Several studies have shown greater risk for incident type 2 diabetes among black women with GDM history compared to white women with GDM history.[5,6] Diabetes is a well-established risk factor for CKD,[51,52] and development of type 2 diabetes mellitus after a GDM pregnancy could explain the association between GDM and incident CKD. Go et al[19] evaluated a cohort of 289 black women with GDM a median of 11 years after delivery and reported a prevalence of moderately increased albuminuria of 11% in normoglycemic women versus 36% in women who had overt DM after GDM. Kew et al[21] tested women who were 3 years postpartum, and found an association between current glucose intolerance and elevated urine ACR, but not GDM and moderaltely increased albuminuria, although glucose intolerance was treated as a confounder of the association between GDM and moderately increased albuminuria. We consider post-partum development of glucose intolerance and type 2 diabetes mellitus to be an intermediate on the causal pathway between GDM and CKD, and did not adjust for it to avoid introducing bias.[53,54] The presence of glucose intolerance, insulin resistance, diabetes mellitus, and metabolic syndrome prior to albuminuria onset did not explain the association between incident albuminuria and GDM seen among black women in our study. Other potential explanations for the association between GDM and CKD in black women include genetic variation, blood

pressure elevation following GDM, differences in lactation practices, or differences in the severity of GDM. At least one study reported that genes flanking the major histocompatibility complex are associated with diabetes mellitus, insulin resistance, hypertension and moderately increased albuminuria in black women with a history of GDM.[55] Black women have been shown to develop hypertension, a risk factor for CKD, more often and more rapidly following a GDM pregnancy compared to white women.[56] In our cohort, black women were more likely than white women to develop hypertension prior to onset of albuminuria, however the presence of hypertension did not seem to account for the association between incident albuminuria and GDM seen among black women. Higher lactation intensity and longer duration are associated with lower incidence of type 2 diabetes 2 years after a GDM pregnancy,[57] and longer lactation duration was associated with lower metabolic syndrome incidence years after a GDM delivery.[31] Failure to initiate breastfeeding was reported to be higher among black women,[58] including a failure to initiate breastfeeding after GDM pregnancy.[59] The severity of GDM may be greater in black than in white women, as they may be more likely to require incident insulin treatment for GDM[60] and may have more severe complications of GDM.[61]

Among the limitations of this study is that GDM was self-reported, although the validity of self-reported GDM in CARDIA was high versus medical record review[3], similar to other validation studies of self-reported GDM.[62,63] Urine specimens were not obtained at the initial CARDIA examination, so urine ACR ≥ 25 mg/g at year 0 could not be used as exclusion criteria for women who entered the cohort during the interval from year 0 to year 10. Although some women with underlying kidney disease may have been included in the cohort, a high prevalence of albuminuria is unlikely in women aged 18–30 years old. Albuminuria was assessed by untimed measurements of urinary albumin and creatinine and thus associated with significant within-person variability,[64] although this practice is supported by strong associations of albuminuria using single ACR measurements with cardiovascular and kidney outcomes documented in the literature. [15,65,66] Few women developed reduced eGFR, but results were similar when reduced eGFR was removed from the outcome definition. The strengths of this study include the racially diverse study population, long duration of follow-up and the availability of longitudinal measures of CKD and pre-pregnancy risk factors for both CKD and GDM.

We conclude that black women in CARDIA with a history of GDM are at risk for subsequent albuminuria, independent of traditional risk factors for CKD. Early detection of albuminuria allows for both lifestyle and medical interventions, which slow progression of disease and reduce cardiovascular risk, yet early stages of CKD are asymptomatic.[67] Other pregnancy complications, including preeclampsia and gestational hypertension, have been associated with incident maternal CKD.[68–70] Pregnancy may present a window of opportunity to identify women at risk of CKD and implement prevention strategies. Replication of our results would suggest that following a GDM pregnancy, black women may benefit from counseling about the need for screening for albuminuria and risk modification strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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This manuscript has been reviewed by CARDIA for scientific content and consistency of data interpretation with previous CARDIA publications.

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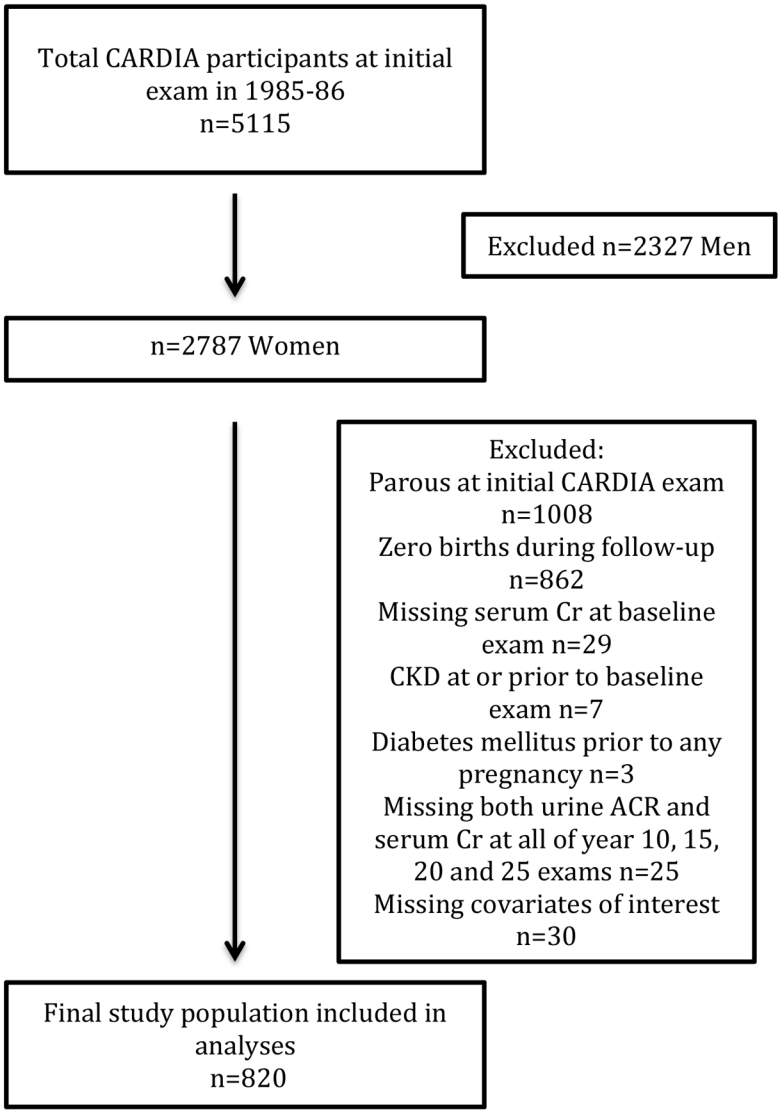

Figure 1.

Study population selection. Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; Cr, creatinine; CKD, chronic kidney disease; ACR, albumin-creatinine ratio.

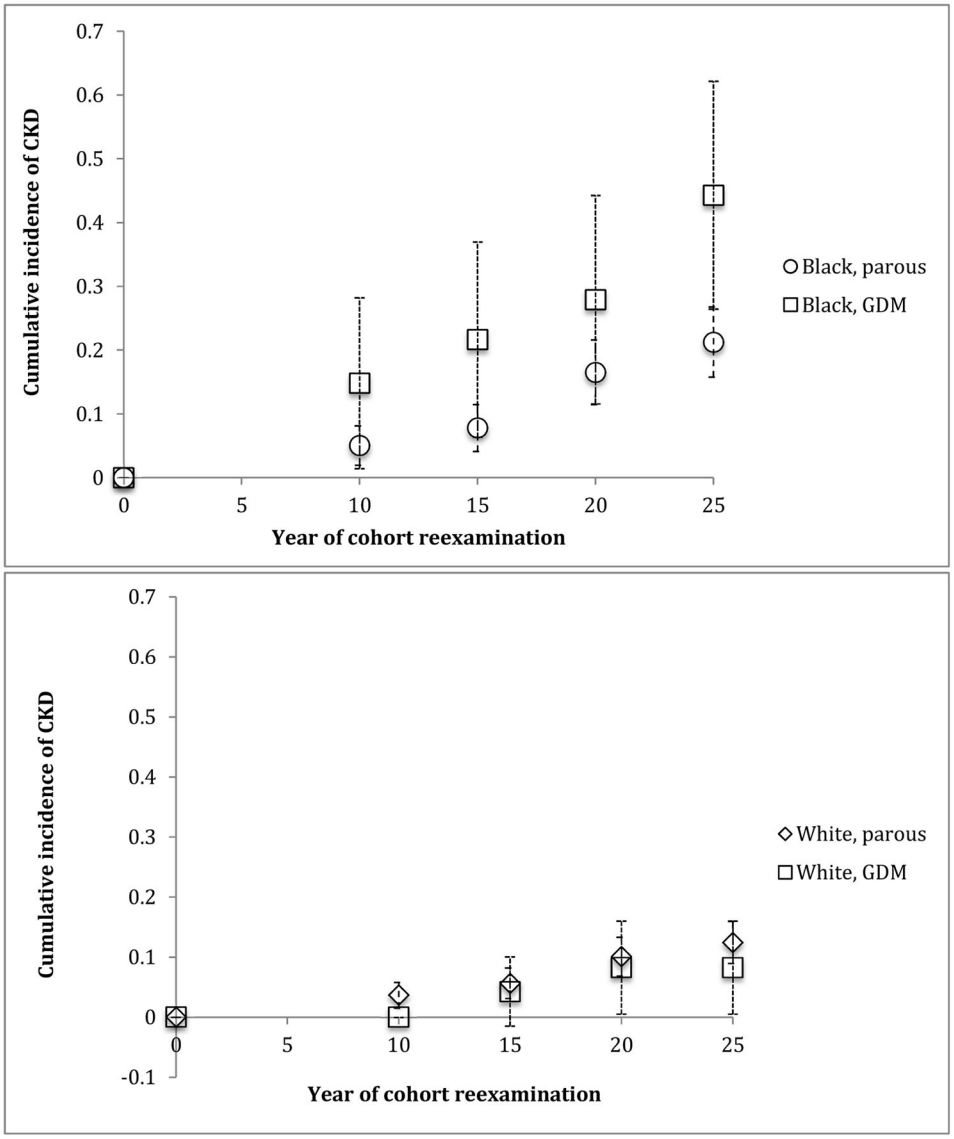

Figure 2.

Incident CKD in parous women with and without GDM, by race. Abbreviations: CKD, chronic kidney disease, GDM gestational diabetes mellitus.

Table 1

Baseline characteristics by GDM status

Variable	Parous, no GDM N=719	GDM N=101	p-value
Age[a] (years)	25.8 ± 5.1	25.3 ± 5.1	0.3
Race			0.8
Black	289 (40.2)	42 (41.6)	
White	430 (59.8)	59 (58.4)	
Education			0.5
≤High school	179 (24.9)	21 (20.8)	
>High school	540 (75.1)	80 (79.2)	
eGFR (ml/min/1.73 m^2)	119.2 ± 17.8)	118.4 ± 16.7	0.7
Smoking status			0.3
Never	474 (65.9)	62 (61.4)	
Former	101 (14.1)	12 (11.9)	
Current	144 (20.0)	27 (26.7)	
BMI (kg/m^2)	23.5 ± 4.9	24.7 ± 5.6	0.03
Waist circumference (cm)	71.9 ± 9.9	74.3 ± 11.5	0.05
Fasting glucose (mg/100 ml)	80.5 ± 7.3	81.6 ± 9.2	0.3
HDL cholesterol (mg/dl)	57.5 ± 12.8	55.5 ± 13.0	0.1
SBP (mmHg)	105.4 ± 9.1	106.2 ± 9.4	0.4
DBP (mmHg)	66.2 ± 8.9	67.6 ± 8.6	0.2
Family history of diabetes			0.002
Yes	291 (40.5)	58 (57.4)	
No	428 (59.5)	43 (42.6)	
Family history of CKD			0.02
Yes	54 (9.0)	15 (17.7)	
No	548 (91.0)	70 (82.4)	
Total physical activity score[b]	316 [174–504]	258 [182–476]	0.3

Note: Characteristics are for the sample of 820 CARDIA women who were nulliparous at baseline examination and delivered ≥1 births during follow-up (mean, 20.8 years) and had measures of CKD. Values for categorical variables are given as count (percentage); for continuous variables, as median [interquartile range]. P-values were calculated using t-test for continuous variables and by Fisher's Exact Test or chi-square where appropriate for categorical variables except where noted.

Baseline characteristics were taken from the examination at the beginning of interval during which participants reported their first pregnancy, except family history of diabetes which could be reported at any examination, and family history of CKD which was only collected at examination year 25. Conversion factors for units: glucose in mg/dl to mmol/L, x0.05551, cholesterol in mg/dl to mmol/L, x0.02586.

Abbreviations: BP, blood pressure; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CKD, chronic kidney disease; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SBP, systolic blood pressure

[a] Age at CARDIA examination prior to first reported pregnancy

[b] p-value was calculated using Kruskal-Wallis test.

Table 2

Cumulative incidence of CKD at examination years 0 to 25 by GDM status among parous CARDIA women with follow-up births

Exam year	No. of events	No. at risk	Cumulative Incidence (95% CI)
GDM			
0	0	66	0 (0–0)
10	4	62	0.065 (0.003–0.126) at year 10
15	4	72	0.116 (0.040–0.193) at year 15
20	4	73	0.165 (0.079–0.250) at year 20
25	5	69	0.225 (0.131–0.320) at year 25
Parous, no GDM			
0	0	520	0 (0–0)
10	21	499	0.042 (0.024,–0.060) at year 10
15	13	547	0.065 (0.044–0.086) at year 15
20	34	531	0.125 (0.097–0.152) at year 20
25	20	534	0.158 (0.127–0.188) at year 25

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; CKD, chronic kidney disease; GDM, gestational diabetes mellitus

Table 3

Hazard ratios for CKD by GDM status among CARDIA women nulliparous at baseline who self-reported interim births during mean 20.8 years of CARDIA follow-up

	HR (95% CI)		
Model	**Parous, no GDM**	**GDM**	**p for interaction**
Crude model	1.00 (reference)	1.46 (0.87–2.45)	
Model 1[a]	1.00 (reference)	1.33 (0.78–2.26)	
Model 2[b]			0.06
Black women	1.00 (reference)	1.96 (1.04–2.67)	
White women	1.00 (reference)	0.65 (0.23–1.83)	

Note: 820 subjects contributed 2407 observations to each model. Each subject can contribute one observation for each CARDIA examination year she has data available for the outcome.

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; CKD, chronic kidney disease; GDM, gestational diabetes mellitus; HR, hazard ratio.

[a]Model 1 includes variables for age, race, body mass index, smoking, family history of diabetes, fasting glucose, baseline estimated glomerular filtration rate, education, high-density lipoprotein cholesterol, systolic blood pressure and physical activity score.

[b]Model 2 is model 1 + interaction term for race and GDM.

Table 4

Cumulative incidence of metabolic dysfunction in parous CARDIA women by race

Variable	Black n=331	White n=489	p-value
Glucose intolerance[a]			0.08
Yes	121 (36.6)	150 (30.7)	
No	210 (63.4)	339 (69.33)	
Insulin resistance[b]			0.6
Yes	141 (42.6)	198 (40.5)	
No	190 (57.4)	291 (59.5)	
HOMA-IR			<0.001
>4	114 (34.4)	63 (12.9)	
≤4	217 (65.6)	426 (87.1)	
HOMA-IR			<0.001
≥ 2.73	192 (58.0)	145 (29.7)	
<2.73	139 (42.0)	344 (70.4)	
Metabolic syndrome[c]			<0.001
Yes	72 (21.8)	60 (12.3)	
No	259 (78.3)	429 (87.7)	
Diabetes mellitus			<0.001
Yes	41 (12.4)	22 (4.5)	
No	290 (87.6)	467 (95.5)	
Hypertension			<0.001
Yes	115 (34.7)	69 (14.1)	
No	216 (65.3)	420 (85.9)	
GDM			0.8
Yes	42 (12.7)	59 (12.1)	
No	289 (87.3)	430 (87.9)	
CKD			0.001
Yes	58 (17.5)	47 (9.6)	
No	273 (82.5)	442 (90.4)	

Notes: Values presented are number (percentage). P-values obtained from Fisher's exact test.

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CKD, chronic kidney disease; GDM, gestational diabetes mellitus; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance.

Table 5

Association between CKD and GDM by presence of glucose intolerance, insulin resistance, metabolic syndrome, diabetes, and hypertension in parous black CARDIA women

	HR (95% CI)		
Variable	**no GDM**	**GDM**	**LRT p for interaction of GDM & variable**
Glucose intolerance[a]			0.4
Yes	1.00 (reference)	1.70 (0.71–4.07)	
No	1.00 (reference)	2.98 (1.23–7.26)	
Insulin resistance[b]			0.1
Yes	1.00 (reference)	1.23 (0.47–3.23)	
No	1.00 (reference)	3.80 (1.69–8.55)	
HOMA-IR			0.6
>4	1.00 (reference)	1.83 (0.75–4.44)	
≤4	1.00 (reference)	2.60 (1.08–6.28)	
HOMA-IR			0.3
≥2.73	1.00 (reference)	1.77 (0.89–3.91)	
<2.73	1.00 (reference)	3.77 (1.41–10.13)	
Metabolic syndrome[c]			0.5
Yes	1.00 (reference)	1.55 (0.55–4.35	
No	1.00 (reference)	2.50 (1.15–5.43)	
Diabetes mellitus			0.9
Yes	1.00 (reference)	2.05 (0.66–6.36)	
No	1.00 (reference)	1.95 (0.87–4.37)	
Hypertension			0.3
Yes	1.00 (reference)	1.39 (0.47–4.10)	
No	1.00 (reference)	2.94 (1.38–6.26)	

Note: 331 subjects contributed 948 observations to each model. Each subject can contribute one observation for each CARDIA exam year she has data available for the outcome.

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; CKD, chronic kidney disease; GDM, gestational diabetes mellitus; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HR, hazard ratio; LRT, likelihood ratio test

Table 6

Differences in percent annualized decline in eGFR for parous CARDIA women by GDM history

Model	no GDM	GDM[a]
Crude	1.00 (reference)	0.064 (−0.16 to 0.29)
Model 1[b]	1.00 (reference)	0.013 (−0.21to 0.24)

Note: 820 subjects contributed 2407 observations to each model. Each subject can contribute an observation for each CARDIA.

examination year she has data available for the outcome measurement.

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; eGFR, estimated glomerular filtration rate; GDM, gestational diabetes mellitus.

[a]Result may be interpreted as the difference in percent annual decline in eGFR (% ml/min/1.73 m^2); values in parenthese are 95% confidence interval.

[b]Model 1 is adjusted for race, age, body mass index, smoking, family history of diabetes, fasting glucose, baseline eGFR, education, high-density lipoprotein cholesterol, systolic blood pressure, and physical activity score.