

ORIGINAL CONTRIBUTION

Gestational Diabetes and Risk of Stroke Among US Black Women

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BACKGROUND: There is a paucity of evidence on whether gestational diabetes (GDM) is a risk factor for cerebral vascular disease for Black women and lack of data on incident stroke as end point.

METHODS: We conducted a large prospective cohort study of Black women across the United States and assessed the association between self-reported history of GDM and incident stroke. The study began when participants became parous or enrolled in 1995. We followed up 41 143 parous Black women who were free of cerebral vascular disease or cancer and followed up until incident stroke, death, or the end of 2021. Our exposure was self-reported history of GDM, and outcome was incident stroke. Multivariable Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% CIs, adjusting for major known risk factors for stroke.

RESULTS: A total of 1495 incident stroke cases were identified among 41 143 Black women from 1995 until 2021 (881 505 person-years of follow-up). Black women with a history of GDM had a consistent 1.4-fold increased risk of stroke compared with those with a healthy pregnancy (age-adjusted HR, 1.44 [95% CI, 1.14–1.82]; multivariable HR, 1.41 [95% CI, 1.11–1.79]). Compared with healthy parous women with neither GDM nor type 2 diabetes, women with a history of both had a 2.6-fold increased stroke risk (multivariable HR, 2.59 [95% CI, 1.88–3.57]); women with only type 2 diabetes have 2-fold increased stroke risk (multivariable HR, 2.04 [95% CI, 1.79–2.32]); women with a history of GDM but no progression to type 2 diabetes do not have an increased risk of stroke (multivariable HR, 1.22 [95% CI, 0.86–1.73]).

CONCLUSIONS: In this large prospective study of Black women, a vulnerable population at high risk for stroke, a history of GDM increased stroke incidence by 41%. There was no elevated risk of stroke for Black women with a history of GDM and no progression to type 2 diabetes, while the stroke risk increased by 2.6-fold for Black women with GDM and progression to type 2 diabetes. Our results highlight the importance of consideration of history of GDM for stroke early prevention, especially Black women with progression to T2DM after GDM.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: diabetes, gestational ■ incidence ■ risk factors ■ stroke ■ vulnerable populations

Black women are particularly vulnerable and experience stroke and stroke-related mortality at higher rates and earlier onset,^{1,2} compared with women from other racial groups.^{3,4} A major risk factor for stroke is diabetes. Gestational diabetes (GDM) is a glucose intolerance condition first onset or first recognition during pregnancy.^{5–7} Worldwide, GDM affects 6% to 13% of pregnancies and is the most common

pregnancy-associated metabolic disease.⁸ It is well known that women with a history of GDM have higher risk of type 2 diabetes. Black women, in particular, have the highest rate of subsequent progression to type 2 diabetes after GDM⁹: 10-fold risk of progression to type 2 diabetes for Black women versus 7-fold risk for White women as compared with their counterparts without GDM.

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Nonstandard Abbreviations and Acronyms

BMI	body mass index
BWHS	Black Women's Health Study
GDM	gestational diabetes
HR	hazard ratio

Pregnancy is a unique time period for women, and the risk of stroke is high during the third trimester and postpartum period due to cardiometabolic physiological changes.^{10,11} Pregnancy itself is also a stress test for women, with hemodynamic changes (systemic vascular resistance decreases, hypercoagulability, higher risk of thrombosis), vascular changes (changes in aortic vessel wall), and metabolic changes (increase maternal glucose production and insulin resistance).¹² GDM shares some common underlying pathological mechanisms with stroke involving underlying subclinical metabolic dysfunction, inflammation, and oxidative stress, which may lead to later increased stroke risk. Evidence from predominantly White participants showed that GDM is a risk factor for subsequent atherosclerotic cardiovascular disease.^{3,13–17} However, there is a paucity of data on the association of history of GDM with cerebral vascular disease for Black Americans and in particular, lack of data on incident stroke as end point. The American Heart Association called for more research on risk of stroke in women across the lifespan and more research, especially in diverse populations, is needed because the potential link between GDM and subsequent stroke risk has not been studied.^{3,14}

We hypothesize that a history of GDM is associated with stroke risk for Black women. To test this hypothesis, we utilized a longitudinal study of 59 000 Black women, BWHS (Black Women's Health Study), in progress for almost 25 years, with 1495 incident strokes cases, and with information available for GDM and development of type 2 diabetes.

METHODS

BWHS data and methods will be available to researchers upon request to the principle investigators of BWHS study. This article follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.¹⁸

Study Population

BWHS is a prospective cohort study of Black women enrolled in 1995^{19–21} across the continent of United States. At enrollment, participants' median age was 38 years (age range, 21–69 years). Black women were recruited mainly from 17 states and follow-up rate was >80% for each questionnaire cycle. Every 2 years, self-administrated questionnaires were sent out collecting information regarding participants' demographic

characteristics, socioeconomic factors, medical conditions, reproductive history, lifestyle factors, and behavior.

The analytic sample for this analysis consisted of 41 143 parous women (Figure S1). Participants with missing or contradictory information on GDM history were excluded (eg, in the same questionnaire, participants reported have a GDM diagnosis, but parity status was listed as nulliparous). For women who were parous at 1995 (enrollment of BWHS), they started contributing person time at 1995 and those with a stroke diagnosis or a diagnosis of coronary heart disease²² before 1995 were excluded. For women who became parous during 1995 to 2021, they started contributing person time at the time of first pregnancy. Participants were free of cerebral vascular disease or cancer and followed up until onset of incident stroke, loss to follow-up, or the end of follow-up (December 2021), whichever came first. The Boston University Medical Campus institutional review board approved the study.

Exposure

Our exposure of interest is self-reported history of GDM. During 1995 to 2013, BWHS participants answered detailed questions regarding their reproductive and medical history, including parity, age at first birth, age at last birth, and history of GDM. Because most BWHS participants were past reproductive age by 2013, we stopped collecting information about reproductive history at that time. History of GDM and year of diagnosis were collected.^{23,24} Question was specifically asked if participant ever had a physician-diagnosed diabetes during pregnancy. If yes, year of diagnosis was collected. In BWHS, GDM status on each pregnancy across a participant's reproductive years was not collected. We were unable to differentiate which pregnancy was complicated by GDM and to differentiate first versus recurrent GDM. Therefore, we defined history of GDM status as never versus ever.

Outcome

The primary outcome was incident stroke including nonfatal and fatal strokes.^{25,26} Fatal strokes were strokes reported as underlying cause of death in the National Death Index (*International Classification of Diseases* code: I60–I69). Nonfatal strokes were those ascertained through medical record adjudication or through biennial BWHS questionnaires, in which we asked participants to self-report occurrences of physician-diagnosed stroke. Stroke medical record review was led by an independent team of neurologists using the World Health Organization definition with a confirmation rate of 72% among the subset of strokes for which we obtained medical records.^{25–27} For sensitivity analyses, we defined incident stroke as cases were confirmed through neurologists' adjudications or through National Death Index linkages only.

Covariates

We adjusted for the following confounders selected a priori based on subject knowledge: age, questionnaire cycle, parity (1, 2, and ≥3), age at first birth (<20, 20–24, 25–29, and ≥30 years), body mass index (BMI) at age 18 years (weight in kilograms divided by height in meters squared: continuous, as well as a categorical variable <20, 20–24, 25–29, and ≥30 kg/m²), family history of cerebral vascular disease (yes, no), and family

history of type 2 diabetes (yes, no). In additional analyses, we also controlled for 1995 baseline covariates that included neighborhood socioeconomic status (quintiles),^{28–30} education level (<12, 12–15, 16, and ≥17 years), and years since last birth (<10 and ≥10 years).

For the majority of participants (88%), we used BMI at age 18 years as a proxy for prepregnancy BMI because they already had pregnancies before 1995 enrollment. Current height was assessed in the 1995 questionnaire at baseline. Weight was assessed every 2 years. In validation studies, spearman correlations for self-reported weight and height were 0.93 and 0.97, respectively.

For type 2 diabetes, a separate question was asked if a participant had a physician-diagnosed diabetes not during pregnancy. Self-reported type 2 diabetes has been assessed on BWHS biennial questionnaires with a confirmation rate of 96% when compared with medical record review.³¹ We also estimated prevalence of undiagnosed diabetes based on a sample of 1873 participants.³² Based on the glycated hemoglobin A1c (HbA1c) level measured from blood samples provided from 1873 BWHS participants in 2013 to 2016, 6.1% (120/1873) had HbA1c levels ≥6.5% but not self-reported type 2 diabetes.³² For BWHS, no more than 6% of participants had undiagnosed type 2 diabetes.³³

Statistical Analyses

Cox proportional hazards model was used to estimate multivariable hazard ratios (HRs) and 95% CIs. Given the particularly high rate of progression to type 2 diabetes after GDM for Black women, we estimated HRs based on participants' joint history of GDM and type 2 diabetes and tested effect modification by type 2 diabetes. We categorized our participants based on their history of GDM and type 2 diabetes: (1) women with neither, (2) women with type 2 diabetes only, (3) women with GDM only, and (4) women with both. By definition, women who had type 2 diabetes before reported GDM diagnosis were defined as “no” to history of GDM. For 4, women with both were those with a history of GDM and subsequently progressed to type 2 diabetes. Relative excess risk due to interaction was calculated ($RR_{11}-RR_{10}-RR_{01}+1$). For sensitivity analysis, we restricted to stroke cases confirmed through medical record adjudication (Figure S1). We conducted stratified analysis by age (<55 and ≥55 years), BMI at age 18 years (<30 and ≥30 kg/cm²), and stroke belt (yes, no). We tested effect modification by creating interaction terms between GDM and the stratified terms and tested interaction using the Wald test.

RESULTS

During a median of 21 years (841 505 person-years) of follow-up of 41 143 parous women, we identified a total of 1495 incident strokes, among which 484 were adjudicated and confirmed by neurologists. Compared with women without a GDM history (n=39 456), Black women with a history of GDM (n=1687) were similar in terms of living in a stroke belt, neighborhood socioeconomic status, and family history of cerebral vascular disease. However, they were more likely have a family history of type 2 diabetes, were more likely to have first

birth at age ≥25 years, and more likely to have BMI at age 18 years ≥25 kg/m² (Table 1).

In an age-adjusted model, compared with women without a history of GDM, women with a history of GDM had a 1.4-fold increased risk of stroke (HR, 1.44 [95% CI, 1.14–1.82]; Table 2). This elevated stroke risk persisted and remained the same after multivariable adjustments (multivariable adjusted HR, 1.41 [95% CI, 1.11–1.78]). The results remained similar after further adjustment for neighborhood socioeconomic status, participant's education level, and years since last birth.

We further examined this association by 4 categories based on participant's history of GDM and type 2 diabetes: (1) neither; (2) with type 2 diabetes only; (3) with GDM only; and (4) both. compared with the reference group (parous women with neither), women with a history of GDM and progression to type 2 diabetes had

Table 1. Baseline Characteristics of 41 143 Parous Women by History of GDM

	History of GDM	No history of GDM
	n=1687	n=39 456
Age in 1995, y; mean (SD)	36.26 (8.58)	40.06 (10.83)
Age at first birth, y (%)		
<20	23	29
20–24	27	31
≥25	31	25
BMI at age 18 y, kg/m ² (%)		
<25	83	87
25–30	11	9
≥30	4	3
Neighborhood SES, %		
Q1	19	19
Q2	17	18
Q3	18	18
Q4	19	18
Q5	18	18
Education, y (%)		
<12	2	3
12–15	51	56
16	25	21
≥17	20	20
Parity, %		
1	20	30
2	29	31
≥3	33	26
Family history of cerebral vascular disease, %	66	68
Family history of type 2 diabetes, %	38	27
Stroke belt, %	27	25

BMI indicates body mass index; GDM, gestational diabetes; and SES, socioeconomic status.

Table 2. Association Between History of GDM and Incident Stroke

	Cases/person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
No GDM	1420/839 865	1.00 (reference)	1.00 (reference)	1.00 (reference)
GDM	75/41 640	1.44 (1.14–1.82)	1.41 (1.11–1.78)	1.41 (1.11–1.79)

Model 1 stratified by age and questionnaire cycle. Model 2 further adjusted for parity (1, 2, and ≥ 3), age at first birth (<20, 20–24, 25–29, and ≥ 30), BMI at age 18 years (continuous, kg/m²), family history of cerebral vascular disease (yes, no), and family history of diabetes (yes, no). Model 3 further adjusted for neighborhood socioeconomic status (quintiles), education level (<12, 12–15, 16, and ≥ 17), and years since last birth (<10 and ≥ 10). BMI indicates body mass index; GDM, gestational diabetes; and HR, hazard ratio.

the highest stroke risk (multivariable adjusted HR, 2.59 [95% CI, 1.88–3.57]; Table 3), while the multivariable adjusted HR was 1.22 (95% CI, 0.86–1.73) for women with GDM with no progression to type 2 diabetes. Relative excess risk due to interaction was 0.33 (95% CI, 0.23–0.52) and *P* for interaction <0.05.

As sensitivity analyses, we repeated our analyses among a subset of participants whose medical records were collected and reviewed (18 incident strokes among the GDM group and 466 incident strokes among the no-GDM group), results attenuated and reduced to null (Table 4). The observed association reduced from an HR of 1.4 to 1.1 with wide CI. No significant interaction was found in our stratified analyses by different subgroups. Among the subgroup with participants aged <55 years, the multivariable HR for incident stroke was 1.65 (1.23–2.22; Table S1), while HR was 1.09 (0.72–1.64) for subgroup with age ≥ 55 years.

DISCUSSION

In this prospective cohort study of 41 143 parous Black women of whom 1495 developed incident strokes, women with a history of GDM had an estimated 41% increased stroke risk compared with those without GDM. There was no elevated stroke risk for Black women with GDM and no progression to type 2 diabetes, while the stroke risk increased by 2.6-fold for Black women with GDM who subsequently progressed to type 2 diabetes.

Compared with other racial groups, Black women have a lower prevalence of GDM but the highest risk of developing subsequent type 2 diabetes, a risk factor for stroke⁹ (10-fold higher risk of diabetes for Black women versus

7-fold higher risk for Whites). GDM history is associated with higher risk of subclinical atherosclerosis and risk of cardiovascular disease (relative risk, 1.7 [95% CI, 1.1–2.5]).^{14,34,35} Only a few studies have examined GDM as a risk factor for stroke, specifically 3 studies were among White women^{36–38} and 1 study included an unknown number of Black women.³⁹ Results of GDM with stroke were inconsistent with 3 null associations^{36,37,39} and 1 positive association³⁸: the number of stroke cases in these studies were 24,³⁷ 68,³⁹ 520,³⁶ and 80.³⁸ Our study (41 143 Black women with 1495 incident stroke cases) showed that GDM predisposes Black women to a 41% increased stroke risk. Our observed association was null among the subset of participants with neurologists' adjudicated stroke cases. However, statistical power for this association was limited with only 18 incident stroke cases among women with a history of GDM.

Given the disproportional high burden of stroke, there is a need for evidence specifically for Black women. Strengths of our study include large sample size of Black women, wide geographic distribution with participants came across the United States, large number of incident strokes, and long-term follow-up.

Our study has some limitations. First, BWHS medical records were collected only among a limited subset ($\approx 30\%$) of participants who self-reported having a physician-diagnosed stroke. We were unable to collect medical records from participants with self-reported stroke but did not provide consent. It is also possible that a Black woman had a stroke onset but was not aware of this diagnosis and, therefore, did not report on the questionnaire. Medical records were not collected for these participants, and, therefore, we were

Table 3. Association Between History of GDM, History of T2DM, and Incident Stroke

	Cases/person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Neither history	875/670 434	1.00 (reference)	1.00 (reference)	1.00 (reference)
T2DM only	408/92 293	2.24 (1.97–2.53)	2.10 (1.84–2.39)	2.04 (1.79–2.32)
GDM only	34/26 915	1.24 (0.88–1.75)	1.22 (0.86–1.73)	1.22 (0.86–1.73)
GDM and progression to T2DM	40/12 317	2.65 (1.92–3.65)	2.61 (1.89–3.60)	2.59 (1.88–3.57)

Model 1 stratified by age and questionnaire cycle. Model 2 further adjusted for parity (1, 2, and ≥ 3), age at first birth (<20, 20–24, 25–29, and ≥ 30), BMI at age 18 years (continuous, kg/m²), family history of cerebral vascular disease (yes, no), and family history of diabetes (yes, no). Model 3 further adjusted for neighborhood socioeconomic status (quintiles) and education level (<12, 12–15, 16, and ≥ 17). BMI indicates body mass index; GDM, gestational diabetes; HR, hazard ratio; and T2DM, type 2 diabetes.

Table 4. Association Between GDM and Incident Cases of Medical Records Adjudicated Stroke

	Cases/person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
No GDM	466/850 225	1.00 (reference)	1.00 (reference)	1.00 (reference)
GDM	18/42 277	1.13 (0.70–1.82)	1.15 (0.72–1.85)	1.14 (0.71–1.83)

Model 1 stratified by age and questionnaire cycle. Model 2 further adjusted for parity (1, 2, and ≥3), age at first birth (<20, 20–24, 25–29, and ≥30), BMI at age 18 years (continuous, kg/m²), family history of cerebral vascular disease (yes, no), and family history of diabetes (yes, no). Model 3 further adjusted for neighborhood socioeconomic status (quintiles), education level (<12, 12–15, 16, and ≥17), and years since last birth (<10 and ≥10). BMI indicates body mass index; GDM, gestational diabetes; and HR, hazard ratio.

not able to estimate the negative predictive value. Second, information on GDM is self-reported and subject to exposure misclassification and underreporting. No validation study has been done in BWHS to estimate the validity of self-reported GDM history. GDM history may be incompletely ascertained in pregnancies before the mid-1980s, a time period when screening test for glucose tolerance was not widely used. However, prior studies suggested moderate validity of maternal self-reported history of GDM,⁴⁰ birth,⁴¹ and pregnancy characteristics.^{42–44} A recent validation study including Black women found women can accurately recall a history of GDM.⁴⁵ In BWHS, we did not collect information on each pregnancy, were unable to differentiate which pregnancy was complicated by GDM and differentiate first versus recurrent GDM. We also did not have information on GDM diagnosis criteria, types of GDM treatment (eg, medication, insulin), and the extent of glycemic control. Third, hypertensive disorders of pregnancy are a significant complication related to stroke risk and GDM and should be considered in the multivariable adjusted model. However, BWHS did not collect detailed complication information on each pregnancy. We did not have information on the detailed complications for each pregnancy, when it occurred, and at which pregnancies. We were unable to separate whether hypertensive disorders of pregnancy occurred at the same pregnancy complicated with GDM, before, or after onset of GDM pregnancy. BWHS did not collect information on prepregnancy diet, physical activity, and smoking, and we were unable to adjust for these known stroke risk factors. Therefore, our study may subject to some residual confounding. Our study consists of Black women only and precluded the ability to examine racial difference. Our results may not generalize to women from other racial/ethnic background. Further studies focus on women from other racial/ethnic groups are greatly needed.

To date, there has been a particular knowledge gap on specific risk factors for stroke in Black women.⁴⁶ Our study provided important evidence that history of GDM is associated with higher long-term stroke risk for Black women, particularly those women who have progressed to type 2 diabetes.

CONCLUSIONS

In this large prospective study of Black women, a vulnerable population at high risk for stroke, a history of GDM increased stroke incidence by 41%. There was no elevated risk of stroke for Black women with a history of GDM and no progression to type 2 diabetes, while the stroke risk increased by 2.6-fold for Black women with GDM and subsequently progressed to type 2 diabetes. Our results highlight the importance of consideration of history of GDM for stroke early prevention, especially for Black women with progression to type 2 diabetes after GDM.

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Disclosures

None.

Supplemental Material

Table S1
Figure S1

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