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Racial differences in the association between parity and incident stroke: Results from the REGARDS Study

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Abstract

Background—Circulatory and vascular changes across consecutive pregnancies may increase the risk of later-life cerebrovascular health outcomes.

Methods—The association between parity and incident stroke was assessed among 7674 white and 6280 black women, aged 45+, enrolled in the REGARDS Study from 2003–2007. Parity was assessed at baseline, and incident stroke was ascertained from physician-adjudicated medical records through September 2014. Cox proportional hazards models were used to estimate hazard ratios (HR) for the association between parity and stroke, adjusting for baseline measures.

Results—At baseline, 12.7% of white women and 16.2% of black women reported 1 live birth, while 8.2% and 19.0%, respectively, reported 5 live births. Mean follow-up time was 7.5 years (SD=2.8); there were 447 incident strokes. A significant interaction between race and parity was detected ($p=0.05$). Among white women, those with 5 live births had a higher stroke risk than

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those with 1 live birth (HR=1.57; 95% CI 0.93-2.65). However, the association was eliminated after adjustment for baseline characteristics (HR=1.00, 95% CI 0.59-1.71). For black women, those with 5 live births had the highest stroke risk compared to those with 1 live birth (HR=1.91, 95% CI 1.25-2.93), but the association was attenuated and no longer statistically significant after adjustment for confounders (HR=1.40, 95% CI 0.89-2.18).

Conclusion—In adjusted models, no statistically significant associations were observed between parity and stroke risk in a diverse cohort of U.S. women. Further studies are needed to elucidate the role of lifestyle and psychosocial factors in the race-specific associations that were observed.

Keywords

women; parity; pregnancy; stroke; race; cohort; prospective

Introduction

Cerebrovascular disease is a leading cause of morbidity and mortality among women in the United States (U.S.). Each year, approximately 425,000 U.S. women experience a new or recurrent stroke,[1] and 77,600 die from stroke.[2] Women have a higher lifetime risk of stroke than men, which is likely due to their longer life expectancy.[3] They also have a higher prevalence of selected stroke risk factors, such as hypertension, diabetes, migraine, atrial fibrillation, depression, and psychosocial stress.[4]

There are several factors unique to women that may be associated with stroke, including lactation,[5] menopause,[4] postmenopausal hormonal use,[4] and oral contraceptive use.[4] Pregnancy has also been found to impact the prevalence and characteristics of cerebrovascular disease.[4] Women experience several changes during pregnancy, including decreased vascular resistance, insulin resistance, dyslipidemia, weight gain, and inflammation.[1-3] While most of these changes are temporary, some could persist[4] and accumulate across successive pregnancies.[1,5,6] Women are also at risk of developing pregnancy complications, such as preeclampsia, that are associated with a higher risk of stroke during pregnancy and the postpartum period[6-8] as well as adverse cerebrovascular health outcomes in later life.[9-11] Physiologic adaptations and complications occurring across consecutive pregnancies may be associated with an even higher risk of later-life adverse cerebrovascular events.[12-14]

Only a handful of previous studies have examined the association between number of pregnancies (i.e. gravidity) or live births (i.e. parity) and stroke, and the results are inconsistent.[12-16] In addition, these studies have been limited by study populations that were predominantly of Asian[12, 13] or Swedish[15, 16] descent and a lack of information on stroke subtypes (i.e. ischemic and hemorrhagic).[13, 16] Only one prior study published nearly twenty years ago has been conducted in the U.S.[14] To our knowledge, no studies have examined racial differences in these associations. However, racial differences may exist as black women in the U.S. have a higher incidence of stroke,[17] and they report higher birth rates and larger family sizes than their white counterparts.[18]

Understanding racial differences in the impact of parity on the risk of stroke in a large and biracial population is important for informing preventive efforts to reduce the incidence of stroke among women. Our objective was to examine the association between parity and incident stroke among women enrolled in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Based on findings from previous studies suggesting that parity may be associated with CVD outcomes, including stroke, in a J-shaped fashion,[19, 20] we hypothesized that women with no live births and those with multiple live births would have a higher incidence of stroke than women with one live birth. We also aimed to explore racial differences in this association.

Materials and Methods

Study Population

The REGARDS Study is a population-based, longitudinal cohort study with oversampling of blacks and residents from the stroke belt region of the U.S., the southeastern part of the U.S., because these two groups have the highest rates of stroke mortality in the U.S.[21] Between January 2003 and October 2007, men and women aged 45 years and older were recruited for participation (n=30,239). Participants completed a baseline telephone interview and self-administered questionnaires with information collected about demographics, behavioral characteristics, and medical history. An in-home examination was conducted to collect physical measurements, blood and urine samples, resting electrocardiogram, and medication information. After baseline, participants were contacted biannually by telephone to identify stroke symptoms, hospitalizations, and general health status. More detailed information about the REGARDS study is published elsewhere.[22] This study was approved by the University of Alabama at Birmingham Institutional Review Board, and each participant provided informed consent.

For this analysis, individuals were excluded if they were male (n=13,551), missing baseline in-home visit forms (n=56), or missing data for parity (n=31), follow-up time (n=269), or covariates included in the models (n=1,426). We further excluded individuals who reported at baseline that they had a history of stroke (n=952). The final sample included 13,954 women without a history of stroke and with complete data on all measures pertinent to the study.

Measures

Parity—Parity was defined as the number of prior live births as reported by women on a self-administered questionnaire at baseline. For this analysis, parity was categorized as: 0, 1, 2, 3, 4, 5 live births.

Stroke Ascertainment—Biannual follow-up interviews were conducted in which participants or their proxy reported suspected stroke events that required hospitalization, emergency department visits, overnight stays in nursing home or rehabilitation centers, or deaths in the previous six months. For proxy-reported deaths, interviews were conducted with the next of kin. Medical records were retrieved for reported events and reviewed by clinicians who verified stroke occurrence and classified stroke subtypes as ischemic or

hemorrhagic. Stroke was defined as focal neurological symptoms lasting for >24 hours or non-focal neurological symptoms with positive imaging for stroke. More details have been previously described.[17] This analysis included incident stroke cases occurring after baseline through September 2014.

Covariates—At baseline, women reported their age, race, years of education (categorized as less than high school, high school graduate, some college, and college graduate), marital status, annual family income (categorized as <\$20,000, \$20,000-\$34,000, \$35,000-\$74,000, \$75,000), smoking status (categorized as current, past, and never), alcohol consumption (categorized as current, past, and never), menopausal status, use of oral contraceptives, use of hormone replacement therapy, and history of stroke risk factors (hypertension, diabetes, and heart disease). State of residence was categorized as the stroke belt region (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee) or non-stroke belt region (all remaining states and the District of Columbia).[21]

Statistical Analysis

Descriptive analyses were conducted to examine baseline participant characteristics by parity and to estimate frequencies of stroke subtypes by race. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between parity and incident stroke. The associations were investigated in three models with different adjustments, including Model 1 (unadjusted), Model 2 (adjusted for age at baseline), and Model 3 (adjusted for age, race, education, marital status, family income, geographic region, smoking status, alcohol consumption, menopause status, oral contraceptive use, hormone replacement therapy). An interaction term was included in the fully adjusted model to assess variations by race (a priori, $p < 0.1$ was considered statistically significant). A type III test was conducted with 5 degrees of freedom and a statistically significant interaction was detected ($p = 0.05$), thus the models were stratified by race and results were reported separately for blacks and whites. We conducted secondary analyses to further estimate the direct effect of parity on stroke independent of stroke risk factors by adjusting for all covariates in Model 3 plus history of hypertension, diabetes and heart disease. These risk factors were not included in primary analyses since they are likely on the causal pathway between pregnancy and stroke.

Women with one live birth were chosen as the referent group rather than women with 0 births to assess the possibility of a J-shaped association between nulliparity (0 live births) and incident stroke. In addition to women who did not intend to have children, nulliparous women include those with a history of infertility or other reproductive issues. Conditions that contribute to infertility may be associated with stroke risk factors and could increase the incidence of stroke among nulliparous women. Analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC).

Results

Study Population

A total of 13,954 women (7674 white, 6280 black) aged 45+ years met the eligibility criteria for this analysis. At baseline, the mean number of live births per woman was 2.6 (SD=1.9) and ranged from 0-16. High proportions of women with 5 live births were aged 60+ years, black, did not have a college education, had a low family income, never consumed alcohol, had a history of hypertension, and never used oral contraceptives or hormone therapy (Table 1). Conversely, high proportions of women with 1 live birth were aged <60 years, white, college graduates, had a high family income, were current alcohol consumers, and used oral contraceptives or hormone therapy.

Frequency of Stroke Subtypes by Parity and Race

There were 447 incident strokes that occurred over a mean follow-up time of 7.5 years (SD=2.8) among women in the REGARDS cohort. There were 380 ischemic strokes, 34 hemorrhagic strokes, and 33 strokes with unknown subtypes. Although white women had a slightly higher number of stroke events overall (n=211), black women with 5 live births had the highest number of stroke events (n=59), including hemorrhagic stroke, among all race and parity groups (Supplemental Table 1).

Parity and Stroke Events by Race

For white women, higher parity groups had an increased risk of stroke in unadjusted analyses, but none of the associations were statistically significant. In particular, those with 5 live births had a higher risk of stroke than those with 1 live birth (HR=1.57; 95% CI 0.93-2.65), but the association was not statistically significant (Table 2). Adjustment for age eliminated the positive associations that were observed and the estimates did not change after further adjustment for other baseline characteristics. Among black women, those with 5 live births had nearly twice the risk of stroke (HR=1.91; 95% CI 1.25-2.93) in unadjusted analyses. After adjustment for baseline measures, the association was attenuated and no longer statistically significant (HR=1.40; 95% CI 0.89-2.18).

For both white and black women, further adjustment for history of hypertension, diabetes and heart disease did not change the estimates (data not shown).

Discussion

In this cohort of U.S. women, black and white women differed in the association between parity and stroke risk. For black women with 5 live births, the risk of stroke was nearly twice that of black women with 1 live birth, but for the same comparison in white women, there was no association. None of the other associations across the parity categories were statistically significant for either black or white women. In addition, for black women in this highest parity group, much of the association observed in the unadjusted model was attenuated by adjustment for age, suggesting that secular trends in the number of live births over time contributed to the unadjusted association.

Previous studies of the association between parity and stroke have mixed results. Although our study was conducted in the U.S. and included white and black women from the 48 contiguous states, our results for black women are similar to those from studies among Chinese and Korean populations that found an association between high parity and both an increased risk of any stroke (5 vs. 1 live birth: HR=1.27, 95% CI 1.03-1.55)[12] and an increased risk of hemorrhagic stroke (4 vs. 0-1 live births: odds ratio, OR=2.97, 95% CI 1.71-5.16).[13] However, our findings are in contrast to two studies among Swedish populations where parity 1 (vs. 0; relative risk, RR=0.5, 95% CI 0.2-1.1)[15] and 4 (vs. 1; OR=0.45, 95% CI 0.16-1.32)[16] was associated with the lowest risk of hemorrhagic stroke. Prior studies that assessed the association between gravidity and stroke found that women with 6 pregnancies had a 30% [14] and 38% [12] increased risk of stroke, as compared to those with 0 and 1 pregnancies, respectively.

The inconsistent results across prior studies may be partly explained by methodological limitations as well as variations in the risk for stroke and stroke subtypes across populations. Overall, while our study does not provide strong evidence for an association between parity and stroke, results from the collective body of studies suggest that an association may exist, although the direction of the association is unclear and it may differ for blacks and whites. Physiologic adaptations and lifestyle factors associated with childbearing may partly explain the observed associations between parity and stroke in prior studies. Adverse metabolic changes occurring across consecutive pregnancies have been found to be associated with later-life cardiovascular health outcomes such as coronary heart disease [7] and type II diabetes [8] that share risk factors for cerebrovascular disease. Physical activity and diet as well as other behavioral and emotional changes associated with childrearing (e.g., sleep deprivation, stress, anxiety) have also been found to impact the incidence of stroke.[12]

In this study, adjustment for age attenuated the estimates of the association between parity and stroke, especially in the highest parity group. Women with the highest parity were, on average, 68 years old at the time of enrollment in 2003 and were likely to have been in their prime childbearing years during the late 1950s and early 1960s when the number of children per family peaked at 3.7 in the U.S.[23] Oral contraceptives were first introduced in 1960 and federal funding for family planning services was not established until 1970.[23] Older women in our study, particularly those with lower socioeconomic status, thus may have had more difficulty controlling their fertility than younger women whose peak childbearing years occurred later on. When explaining the association between parity and stroke among populations with wide variations in age at enrollment, future studies should consider secular trends in fertility, including the age at childbearing and the availability of contraception during the prime childbearing years.

The racial difference observed in the association between parity and stroke in the highest parity group may be partly explained by race-specific variations in the determinants of parity. In the U.S., black women have more children and larger families than white women. [18] They are also more likely to live in poverty,[24] less likely to have access to contraception,[25] and have a higher rate of unintended pregnancies.[26] Among women with low socioeconomic status and limited access to contraception, high parity may be associated with an increased stroke risk; in contrast, in a cultural context that encourages and

values large families, high parity may be a marker for greater resources and reduced stroke risk. These considerations underscore the complexity of measuring parity as an epidemiological exposure, in that parity is both a biological exposure and a function of a woman's psychosocial circumstances. Further studies are needed to elucidate the role of lifestyle and psychosocial factors in the race-specific associations that were observed.

Strengths and limitations

Overall, this study expands upon prior studies and fills an important gap in the literature by examining racial differences in the association of parity and incident stroke in a U.S. population. To our knowledge, this is the first study to suggest a racial difference in the association between parity and stroke. The strengths of this study include the large cohort of white and black women recruited from throughout the U.S. with a high proportion in the stroke belt region, which is an area with high stroke mortality. This prospective cohort study has collected detailed information on stroke and hospitalizations biannually for more than ten years. Additionally, all medical records for stroke events are adjudicated by clinicians.

Although there are many strengths of this study, some limitations exist. The exclusion of women with a history of stroke at baseline may have limited our assessment of those whose prior strokes were related to pregnancy. In addition, the small number of stroke events, particularly hemorrhagic strokes, prevented further assessment of the association between parity and stroke subtypes. The sample size may have also limited our ability to detect statistically significant associations between parity and stroke in adjusted analyses. The REGARDS study lacked information on pregnancy-related complications, including gestational hypertension and preeclampsia, which have been found to be associated with adverse cerebrovascular health outcomes in later life[9-11] and may contribute to the associations that were observed. These complications may accelerate the progression to future cardiovascular disease, thus functioning as mediators for the association between parity and incident stroke. Such complications may also motivate women to limit the number of additional pregnancies. This study also lacked information on history of miscarriages or still births and infertility that prevented further refinement of the nulliparous group for assessing their risk of stroke. Although we adjusted for stroke risk factors and several socio-demographic, behavioral, and reproductive characteristics, there may be additional unmeasured risk factors associated with multi-parity and stroke (e.g., stress and other social factors). Residual confounding by these factors may have weakened the associations that were observed. Similar to previous studies,[12, 13, 16] this study did not adjust for other intermediates on the causal pathway between parity and stroke (e.g., blood pressure, cholesterol) as this may result in overadjustment and increase bias when estimating total effects.[27] Similar to all other cohort studies, those who agreed to participate in REGARDS may not be representative of the general population, potentially reducing generalizability.

Conclusion

This study highlights the importance of multi-parity as a potential risk factor for stroke in later life. Although the observed associations were not statistically significant, there was a

significant race-by-parity interaction, suggesting that parity may play a larger role among black than white women. The 2014 AHA/ASA's Guidelines for the Prevention of Stroke in Women provides recommendations for preventing hypertensive disorders of pregnancy and stroke among women with a history of these complications, but parity is not included.[4] Further assessment of how race may modify these associations will allow for better tailoring of stroke prevention efforts for women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of women in the REGARDS Study, by parity (N=13,954), 2003-2014.

	0 live births (n=1654)	1 live birth (n=1993)	2 live births (n=3900)	3 live births (n=2964)	4 live births (n=1616)	5 live births (n=1827)
Overall, %	11.9	14.3	27.9	21.2	11.6	13.1
Years of follow-up (mean $\pm$ SD)	7.7 $\pm$ 2.8	7.6 $\pm$ 2.8	7.6 $\pm$ 2.8	7.6 $\pm$ 2.8	7.5 $\pm$ 2.8	7.2 $\pm$ 3.1
Age at baseline (mean $\pm$ SD)	63.3 $\pm$ 10.3	62.6 $\pm$ 9.8	62.5 $\pm$ 9.3	64.1 $\pm$ 9.1	66.1 $\pm$ 8.7	68.3 $\pm$ 7.9
Age at baseline, %						
<50	8.2	7.9	7.2	5.5	3.2	1.7
50-59	33.4	35.9	35.2	27.5	19.5	11.4
60-69	31.1	32.6	35.1	39.3	43.6	43.2
70+	27.3	23.6	22.5	27.7	33.7	43.6
Black, %	43.9	51.1	36.4	40.2	45.1	65.5
Education, %						
Less than high school	7.3	10.8	6.7	9.8	16.2	32.6
High school graduate	18.8	24.3	28.3	29.1	34.7	31.4
Some college	25.3	28.7	29.1	30.9	26.4	23.9
College graduate	48.6	36.2	35.9	30.2	22.8	12.1
Married, %	32.4	39.6	54.7	50.9	43.7	34.5
Annual family income, %						
<\$20,000	18.4	21.6	15.3	18.3	26.4	41.7
\$20,000-\$34,000	24.4	23.0	22.9	26.7	29.2	25.5
\$35,000-\$74,000	31.4	29.8	30.4	27.9	22.5	14.4
\$75,000	13.2	13.5	17.1	12.6	7.0	3.0
Refused	12.6	12.2	14.3	14.6	14.9	15.4
Stroke belt, %	49.2	56.7	60.8	59.2	59.5	56.3
Smoking status, %						
Current	14.4	17.0	14.6	12.9	14.0	12.3
Past	33.3	33.5	31.1	32.5	31.5	30.3
Never	52.4	49.6	54.3	54.6	54.5	57.4
Alcohol consumption, %						
Current	53.9	51.1	53.1	47.1	42.6	31.0

	0 live births (n=1654)	1 live birth (n=1993)	2 live births (n=3900)	3 live births (n=2964)	4 live births (n=1616)	5 live births (n=1827)
Past	15.2	14.0	11.2	13.2	14.4	18.2
Never	30.9	34.9	35.7	39.7	43.0	50.8
Postmenopausal, %	86.9	88.9	88.8	90.8	91.7	94.4
Ever used oral contraceptives, %	45.7	59.5	65.1	60.0	53.7	44.1
Ever used hormone therapy, %	53.5	57.2	60.3	59.2	56.1	46.6
History of hypertension, %	53.4	57.4	53.6	57.7	65.0	70.6
History of diabetes, %	19.7	20.2	16.7	18.0	22.3	27.6
History of heart disease, %	9.4	11.4	9.7	12.5	14.2	16.4

Abbreviations: SD, standard deviation

Table 2

Hazard ratios for the association between parity and incident stroke, by race, (N=13,954), 2003-2014.

	No. of subjects	Stroke cases	Model 1 [*]		Model 2 [†]		Model 3 [‡]	
			HR	95% CI	HR	95% CI	HR	95% CI
			White women (n=7,674)					
Number of live births								
0	928	21	0.76	0.43-1.35	0.73	0.41-1.28	0.73	0.41-1.29
1	975	28	1.00	Ref	1.00	Ref	1.00	Ref
2	2481	51	0.71	0.45-1.12	0.69	0.43-1.09	0.74	0.47-1.17
3	1772	60	1.17	0.75-1.84	0.96	0.61-1.51	1.01	0.64-1.59
4	887	40	1.60	0.99-2.60	1.10	0.68-1.79	1.11	0.68-1.81
5	631	28	1.57	0.93-2.65	1.00	0.59-1.69	1.00	0.59-1.71
Black women (n=6,280)								
Number of live births								
0	726	24	1.09	0.64-1.86	1.06	0.62-1.80	0.97	0.57-1.67
1	1018	31	1.00	Ref	1.00	Ref	1.00	Ref
2	1419	50	1.18	0.75-1.85	1.21	0.77-1.90	1.24	0.79-1.95
3	1192	25	0.68	0.40-1.16	0.67	0.40-1.14	0.67	0.40-1.14
4	729	24	1.09	0.64-1.86	1.01	0.59-1.72	0.99	0.58-1.69
5	1196	65	1.91	1.25-2.93	1.50	0.97-2.31	1.40	0.89-2.18

Abbreviations: HR, hazard ratio; CI, confidence interval

^{*} Unadjusted

[†] Adjusted for age

[‡] Adjusted for socio-demographics (race, education, marital status, income, region) + behavioral characteristics (smoking, alcohol) + reproductive history (menopause, oral contraceptive use, hormone replacement therapy)