Title

Sex and Race Differences in the Risk of Ischemic Stroke Associated With Fasting Blood Glucose in REGARDS.

Journal

Neurology, 97(7)

Authors

Madsen, Tracy

Long, D

Carson, April

et al.

Publication Date

2021-08-17

DOI

10.1212/WNL.0000000000012296

Peer reviewed

RESEARCH ARTICLE

Sex and Race Differences in the Risk of Ischemic Stroke Associated With Fasting Blood Glucose in REGARDS

Tracy E. Madsen, MD, PhD, D. Leann Long, PhD, April P. Carson, PhD, MSPH, George Howard, DrPH, Dawn O. Kleindorfer, MD, Karen L. Furie, MD, MPH, JoAnn E. Manson, MD, DrPH, Simin Liu, MD, ScD, and Virginia J. Howard, PhD

Correspondence
Dr. Madsen
tracy_madsen@brown.edu

Neurology® 2021;97:e684-e694. doi:10.1212/WNL.0000000000012296

Abstract

Objective

To investigate sex and race differences in the association between fasting blood glucose (FBG) and risk of ischemic stroke (IS).

Methods

This prospective longitudinal cohort study included adults age ≥45 years at baseline in the Reasons for Geographic And Racial Differences in Stroke Study, followed for a median of 11.4 years. The exposure was baseline FBG (mg/dL); suspected IS events were ascertained by phone every 6 months and were physician-adjudicated. Cox proportional hazards were used to assess the adjusted sex/race-specific associations between FBG (by category and as a restricted cubic spline) and incident IS.

Results

Of 20,338 participants, mean age was 64.5 (SD 9.3) years, 38.7% were Black, 55.4% were women, 16.2% were using diabetes medications, and 954 IS events occurred. Compared to FBG <100, FBG ≥150 was associated with 59% higher hazards of IS (95% confidence interval [CI] 1.21–2.08) and 61% higher hazards of IS among those on diabetes medications (95% CI 1.12–2.31). The association between FBG and IS varied by race/sex (hazard ratio, FBG ≥150 vs FBG <100: White women 2.05 [95% CI 1.23–3.42], Black women 1.71 [95% CI 1.10–2.66], Black men 1.24 [95% CI 0.75–2.06], White men 1.46 [95% CI 0.93–2.28], $p_{\text{FBG×race/sex}} = 0.004$). Analyses using FBG splines suggest that sex was the major contributor to differences by race/sex subgroups.

Conclusions

Sex differences in the strength and shape of the association between FBG and IS are likely driving the significant differences in the association between FBG and IS across race/sex subgroups. These findings should be explored further and may inform tailored stroke prevention guidelines.

From the Departments of Emergency Medicine (T.E.M.), Neurology (K.L.F.), Epidemiology (S.L.), Medicine (S.L.), and Surgery (S.L.), and Center for Global Cardiometabolic Health, Brown University School of Public Health (S.L.), Alpert Medical School of Brown University, Providence, RI; Departments of Biostatistics (D.L.L., G.H.) and Epidemiology (A.P.C., V.J.H.), School of Public Health, University of Alabama at Birmingham; Department of Neurology (D.O.K.), University of Michigan Medical School, Ann Arbor; and Department of Medicine, Division of Preventive Medicine (J.E.M.), Brigham and Women's Hospital/Harvard Medical School, Boston, MA.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

BMI = body mass index; **CI** = confidence interval; **FBG** = fasting blood glucose; **HR** = hazard ratio; **IS** = ischemic stroke; **PAF** = population attributable fractions; **REGARDS** = Reasons for Geographic and Racial Differences in Stroke; **SBP** = systolic blood pressure.

Elevated fasting blood glucose (FBG), a marker of the severity of abnormal glucose metabolism and diabetes control, is associated with an increased risk of cardiovascular disease (including stroke), although the relationship may be nonlinear, and data conflict as to whether this relationship varies by sex.[1-3] Data have consistently shown a stronger association between a diagnosis of clinical diabetes and incident stroke in women than men,[4,5] suggesting the possibility of a similar sex difference in the relationship between FBG and stroke. Data are also lacking on sex differences in absolute measures of stroke risk associated with diabetes or FBG.

Although less is known about the association between diabetes and stroke by race, data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study demonstrated that the stroke risk associated with diabetes varies by sex in White but not Black participants.[6,7] Contributors to such race-based differences are not clear, although disparities in the treatment of diabetes, prevalence of uncontrolled FBG, and overall stroke risk and mortality are a possibility.[8]

Studies evaluating sex- and race-based differences in stroke risk associated with diabetes have not consistently accounted for the use of diabetes medications or demonstrated whether differences in stroke risk persist across varying levels of FBG.[4,5] We investigated the severity of hyperglycemia by race/sex subgroups and differences in the risk of incident IS across increasing levels of FBG between race and sex subgroups, accounting for the use of diabetes medications as well as other stroke risk factors.

Methods

Study Population/Participants

The REGARDS study is a national longitudinal cohort study into which 30,239 adults ≥45 years of age were enrolled between 2003 and 2007; individuals who identified as Black or living in 1 of the 8 stroke belt states were oversampled. Detailed study methodology has been published.[9] A structured telephone interview plus a home visit was conducted at the time of enrollment to collect data on demographics, medical history, and medications, including those for diabetes. Vital signs, an electrocardiogram, and a blood draw were also performed during the initial home visit. For this analysis, participants were excluded if they had prevalent stroke at baseline, did not have a FBG performed, or had missing data on any of the covariates used in the primary analysis (figure 1).

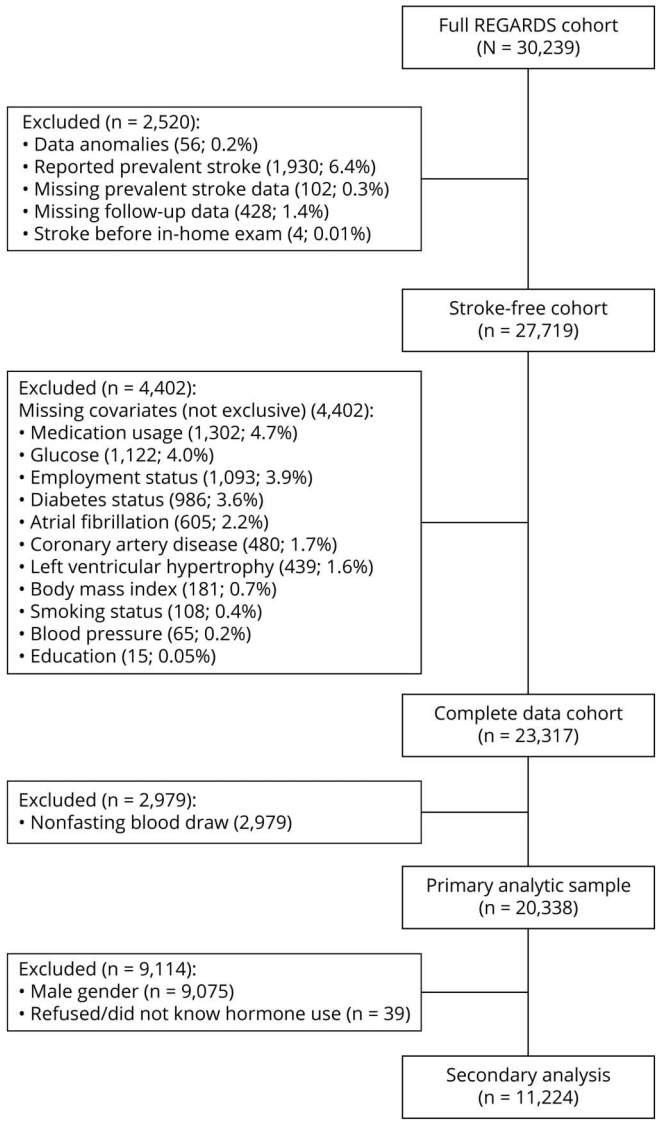
Standard Protocol Approvals, Registrations, and Patient Consents

The REGARDS study was approved by institutional review boards at all participating sites. All participants provided written informed consent.

Exposure

The primary exposure variable was FBG measured during the initial home visit. Participants were asked to fast overnight for

Figure 1 Flowchart of Study Sample



REGARDS = Reasons for Geographic and Racial Differences in Stroke.

10–12 hours, and blood glucose was measured using colorimetric reflectance spectrophotometry on the Ortho Vitros 950 IRC Clinical Analyzer (Johnson & Johnson Clinical Diagnostics) at the University of Vermont.

Outcome

The outcome was incident ischemic stroke (IS), defined as a sudden onset, neurologic deficit lasting ≥24 hours or imaging evidence of a stroke with accompanying appropriate symptoms, and without evidence of intracranial hemorrhage as the primary stroke subtype. Potential cases of IS are initially identified via computer-assisted telephone interviews that occur every 6 months. Medical records associated with self- or proxy-reported medical encounters suspected to be stroke events are then adjudicated by trained study physicians using medical records and results of brain imaging. For this analysis, events through September 2018 were included. Details of case ascertainment and adjudication have been published previously.[10]

Covariates

Data on the primary independent variables (biologic sex [male/female] and race [Black/White]) were collected during interviews occurring at the time of study enrollment. Other demographic variables collected at baseline include age, education, and annual household income. Clinical variables included body mass index (BMI) as well as factors included in the Framingham Stroke Risk Score (baseline systolic blood pressure [SBP], use of antihypertensive medications, history of atrial fibrillation, left ventricular hypertrophy, history of heart disease, smoking status, and diabetes). Finally, whether women had ever used menopausal hormone therapy (MHT) was obtained by self-report.

Statistical Analyses

Baseline characteristics of the sample by categorical FBG level were analyzed using descriptive statistics (frequencies with proportions or means with SDs as appropriate). Next, prevalence of hyperglycemia (defined here as FBG ≥150 or ≥200 mg/dL) was described by race/sex subgroup using frequencies and proportions.

Cox proportional hazard models were used to assess the association between FBG and incident IS, both with FBG as a categorical variable (to account for clinically meaningful categories) and then as a restricted cubic spline, to explore a potential nonlinear relationship between FBG and incident IS. Analyses were performed for the entire study sample, followed by analyses stratified by use of diabetes medication (oral medications or insulin vs no diabetes medication use). All time-to-IS analyses used cause-specific proportional hazard models to account for the competing risk of death.[11]

FBG as a Categorical Variable

For analyses with FBG as a categorical variable, the 4 categories of FBG were chosen a priori based on established clinical thresholds for impaired glucose metabolism: euglycemia (<100 mg/dL), prediabetes (100–125 mg/dL), clinical diabetes (≥126 mg/dL), and FBG ≥150 mg/dL, to capture those with more severe disease. In each of the above models, in addition to including FBG and a race/sex by FBG interaction term, we adjusted for demographic variables (age and a interaction term for age by race/sex subgroup), variables corresponding to the Framingham Stroke Risk Score,[12] BMI, education level, and annual household income. In the model with the entire study sample, we also adjusted for use of diabetes medications (insulin, oral medication, or none). Pooled hazard ratios (HRs) (overall HRs across all race/sex subgroups) followed by HRs with 95% confidence intervals (CIs) representing the risk of IS specific to each race/sex subgroup (White women, Black women, White men, and Black men) across increasing FBG levels were reported with FBG <100 as the reference group. We also reported the results of joint tests for the race/sex by FBG interaction term; specifically, we treated both race/sex and FBG category as 4-level variables, and the Wald χ^2 tests of multiplicative interaction each had 9 *df*.

In a sensitivity analysis, to account for MHT as a potential confounding variable, we then restricted our analysis to women and adjusted our model for ever vs never use of MHT, in addition to the Framingham stroke risk factors, BMI, use of diabetes medications (no diabetes medication, oral diabetes medication, insulin use), education level, and household income. Finally, w that the association between FBG and IS may also differ between women who have never used MHT and those who have (i.e., effect modification), we restricted our analysis to women who reported never using MHT and repeated the analysis. *p* Values for the interaction terms for race by FBG were reported.

FBG as a Restricted Cubic Spline

For FBG as a restricted cubic spline, we again performed Cox proportional hazards regression with incident IS as the outcome. The relative hazards of incident IS (with FBG of 100 mg/dL as reference) were graphed, stratified by race/sex category. The restricted cubic spline functions had 5 knots with the outer quantiles located at 0.05 and 0.95 and the others equally spaced on the quantile scale (27.5th, 50th, and 72.5th percentiles). Robustness to the number of knots was visually assessed, and Wald statistics were used to test FBG*race/sex interaction terms.[13] Based on observed sex differences of the shapes of the race/sex spline curve, we then performed ad hoc analyses, stratifying by sex only. Spline models were adjusted for the same variables as described for models with FBG as a categorical term.

Secondary Analyses: Predicted Risk, Risk Differences, and Population Attributable Fractions of Stroke Risk by FBG and Race/Sex Subgroup

In preplanned secondary analyses, we calculated the 5- and 10-year race- and sex-specific predicted marginal risks of IS from Cox proportional hazards models along with associated risk differences by FBG level to better understand the changes

in absolute stroke risk by sex and race across increasing FBG. Methods used to calculate predicted marginal risks from the Cox proportional hazards model follow Austin et al.[14] To obtain the predicted risk of IS events for each category of FBG in each race/sex subgroup, the predicted marginal probabilities of incident IS for each designated subgroup were estimated from Cox proportional hazard models at 2 time points, 5 years and 10 years, adjusted for age, age × race/sex, medication use (no diabetes medication, oral diabetes medication, insulin use), BMI, SBP, use of antihypertensive medications, left ventricular hypertrophy, atrial fibrillation, history of coronary artery disease, smoking, education, and annual household income. Individual probabilities of IS occurring before 5 and 10 years were estimated assuming each participant had a specific FBG category; these predicted probabilities were then averaged within each designated race/sex subgroup to obtain predicted marginal IS risk. For each race/sex subgroup, risk differences were calculated by subtracting the predicted marginal risk in the <100 mg/dL group from the predicted marginal risk in each of the other FBG categories. Both absolute predicted marginal risks and risk differences were multiplied by 100 by obtain percentages.

An additional method of assessing the excess risk associated with elevated FBG is the calculation of population attributable fractions (PAF), or the reduction in incidence that would occur if all participants in the study population had FBG <100, compared to the actual exposure pattern.[15] The PAF was calculated for each race/sex subgroup by first calculating the difference between the cumulative incidence of stroke among all those included in the designated subgroup and the cumulative incidence of stroke in those with FBG <100, then dividing by the cumulative incidence of stroke in the subgroup study population.[16] The cumulative incidence is defined as the number of events in each race/sex subgroup divided by the total number of individuals in that subgroup at the start of the study.[16]

For all main effects, an α value less than 0.05 was considered to be statistically significant; for interaction terms, an α value less than 0.10 was chosen a priori. Statistical analyses were performed using SAS 9.4 (SAS Institute) and R Studio, version 3.6.1.[17]

Data Availability

Deidentified data can be requested by qualified investigators through the REGARDS presentations and publications committee.

Results

In total, 20,338 participants (200,586 person years) were included in our analyses with a median follow-up time of 11.4 years and 954 IS events. The mean age of participants was 64.5 (SD 9.3) years; 38.7% of participants were Black, 55.4% were women, and 16.2% were using diabetes medications at baseline (table 1). The proportion of Black participants increased with increasing FBG level; 34.9% of participants with FBG <100 were Black compared with 63.6% of participants with FBG ≥200 mg/dL. The distribution of income and education levels also varied across FBG levels (table 1). For example, of those with FBG <100, 14.2% were in the <$20,000 income bracket, while 29.3% of those in the ≥200 mg/dL category were in this lowest income bracket. With regard to the prevalence of hyperglycemia in our sample within race/sex subgroups, 7.7% of Black women (n = 380), 8.6% of Black men (n = 253), 3.3% of White women (n = 206), and 4.5% of White men (n = 278) had FBG levels ≥150.

Estimates for HRs of IS associated with FBG, both pooled and sex/race-specific, are displayed in table 2 and figure 2. Overall, compared to FBG <100 mg/dL, FBG ≥150 mg/dL was associated with 59% higher hazards of IS (95% CI 1.21–2.08) and 61% higher hazards of IS when only those on diabetes medications were included (95% CI 1.12–2.31). In the full sample (model 1), the association between FBG and IS varied by race/sex (HR for FBG ≥150 mg/dL compared to FBG <100 mg/dL: White women 2.05 [95% CI 1.23–3.42], Black women 1.71 [95% CI 1.10–2.66], Black men 1.24 [95% CI 0.75–2.06], White men 1.46 [95% CI 0.93–2.28], $p_{FBG\times race/sex} = 0.004$). Effect estimates for the middle FBG categories can be found in table 2 and figure 2. The race/sex differences were also present when restricting to participants on medications for diabetes at baseline (model 2). The adjusted HR of IS for FBG ≥150 compared to FBG <100 was 3.30 (95% CI 1.20–9.10) for White women, 2.02 (95% CI 1.06–3.87) for Black women, 1.24 (95% CI 0.63–2.46) for Black men, and 1.08 (95% CI 0.53–2.17) for White men ($p_{FBG*race/sex} = 0.08$). Among those not on diabetes medications (eTable 1 available from Dryad, doi.org/10.5061/dryad.rjdfn2zbb), IS risk across FBG did not vary significantly by race and sex ($p_{FBG\times race/sex} = 0.36$).

eTable 2 (available from Dryad, doi.org/10.5061/dryad.rjdfn2zbb) displays the results of analyses restricted to women only. From model 4, adjusted for history of ever using MHT in addition to all other covariates, White women with FBG ≥150 mg/dL had 1.84 times the hazard of IS (95% CI 1.06–3.17) compared to those with FBG <100, slightly higher than for Black women (HR 1.54, 95% CI 0.96–2.48) and slightly attenuated from effect estimates in models 1 and 2. Findings from model 5, restricting the sample to only women reporting no previous use of MHT, are also displayed in eTable 2.

Figure 3 displays spline figures that assess FBG with a restricted cubic spline rather than as a categorical variable. The figure displays the HRs of IS relative to a FBG of 100 by race/sex subgroups for all participants (panel A), by race/sex subgroups among only participants on diabetes medications (panel B), by sex subgroups for all participants (panel C), and by sex subgroups among only participants on diabetes medications (panel D). Panel A demonstrates a difference in the association between FBG and IS by race/sex (p value 0.01), with the highest HR for White women, similar to the results in table 2. Among participants on diabetes medications (panel B), the interaction term between race/sex and FBG was not significant

Table 1 Baseline Characteristics of 20,338 Women and Men in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study by Fasting Blood Glucose

		Fasting blood glucose category, mg/dL				
Characteristics	**Total**	**<100**	**100–125**	**126–149**	**150–199**	**≥200**
Overall	20,338	13,547 (66.6)	4,707 (23.1)	967 (4.8)	735 (3.6)	382 (1.9)
Female sex	11,263 (55.4)	7,768 (57.3)	2,411 (51.2)	498 (51.5)	384 (52.2)	202 (52.9)
Race						
Black	7,880 (38.7)	4,734 (34.9)	2,009 (42.7)	504 (52.1)	390 (53.1)	243 (63.6)
White	12,458 (61.3)	8,813 (65.1)	2,698 (57.3)	463 (47.9)	345 (46.9)	139 (36.4)
Age, y	64.5 (9.3)	64.3 (9.5)	64.9 (9.0)	65.7 (8.8)	64.4 (8.5)	62.7 (8.5)
Education						
< High school	2,190 (10.8)	1,250 (9.2)	538 (11.4)	172 (17.8)	142 (19.3)	88 (23.0)
High school	5,176 (25.4)	3,325 (24.5)	1,270 (27.0)	269 (27.8)	210 (28.6)	102 (26.7)
Some college	5,471 (26.9)	3,667 (27.1)	1,251 (26.6)	260 (26.9)	190 (25.9)	103 (27.0)
≥ College graduate	7,501 (36.9)	5,305 (39.2)	1,648 (35)	266 (27.5)	193 (26.3)	89 (23.3)
Income						
<$20K	3,216 (15.8)	1,924 (14.2)	782 (16.6)	225 (23.3)	173 (23.5)	112 (29.3)
$20K–$34K	4,865 (23.9)	3,182 (23.5)	1,111 (23.6)	275 (28.4)	201 (27.3)	96 (25.1)
$35K–$74K	6,356 (31.3)	4,305 (31.8)	1,511 (32.1)	250 (25.9)	187 (25.4)	103 (27.0)
≥$75K	3,540 (17.4)	2,527 (18.7)	777 (16.5)	118 (12.2)	81 (11.0)	37 (9.7)
Refused	2,361 (11.6)	1,609 (11.9)	526 (11.2)	99 (10.2)	93 (12.7)	34 (8.9)
BMI	29.1 (6.1)	28.0 (5.6)	30.7 (6.1)	32.5 (6.5)	33.1 (6.7)	32.3 (6.4)
SBP	126.9 (16.4)	125.1 (16.1)	129.4 (16.1)	132.0 (17.1)	132.9 (17.0)	133.4 (17.5)
Use of blood pressure medications	10,198 (50.1)	5,970 (44.1)	2,770 (58.8)	673 (69.6)	530 (72.1)	255 (66.8)
LVH	1,851 (9.1)	1,094 (8.1)	484 (10.3)	130 (13.4)	89 (12.1)	54 (14.1)
Atrial fibrillation	1,540 (7.6)	971 (7.2)	376 (8.0)	91 (9.4)	66 (9.0)	36 (9.4)
History of heart disease	3,225 (15.9)	1,889 (13.9)	826 (17.5)	230 (23.8)	177 (24.1)	103 (27.0)
Smoking status						
Current	2,831 (13.9)	1,837 (13.6)	687 (14.6)	146 (15.1)	98 (13.3)	63 (16.5)
Past	8,103 (39.8)	5,187 (38.3)	2,028 (43.1)	423 (43.7)	301 (41.0)	164 (42.9)
Never	9,404 (46.2)	6,523 (48.2)	1,992 (42.3)	398 (41.2)	336 (45.7)	155 (40.6)
Documented history of diabetes at baseline	3,842 (18.9)	779 (5.8)	979 (20.8)	967 (100)	735 (100)	382 (100)
Ever MHT use[a]	6,363 (56.7)	4,488 (58.0)	1,369 (56.9)	249 (50.2)	168 (43.9)	89 (44.5)

Abbreviations: BMI = body mass index; LVH = left ventricular hypertrophy; MHT = menopausal hormone therapy; SBP = systolic blood pressure.
[a] Sample size for ever MHT use = 11,224.
Values are n (%) or mean (SD).

(p = 0.17), although the curves for White women and Black women appear again to be separated from the curves for men. In terms of sex-specific estimates, among all participants (panel C) and only those on diabetes medications (panel D), women have higher HRs than men (p = 0.01, all participants, and p = 0.03, restricted to those on diabetes medications) across most of the FBG continuum. Shapes of the spline curves differ by sex as well, with HRs for women tending to peak and plateau at lower levels of FBG compared with men. Findings from the model restricted to those individuals not on diabetes

Table 2 Estimates for Risk of Ischemic Stroke Associated With Increasing Fasting Blood Glucose by Race/Sex Group

	Model 1: All participants (n = 20,338)		Model 2: Participants on diabetes medications (n = 3,293)	
Fasting blood glucose	**Stroke events/N**	**Adjusted HRs (95% CI)**	**Stroke events/N**	**Adjusted HRs (95% CI)**
<100 (Ref)				
Black women	110/3,004	1.0	14/291	1.0
White women	167/4,764	1.0[b]	5/118	1.0[b]
Black men	84/1,730	1.0	15/191	1.0
White men	194/4,049	1.0	15/179	1.0
Overall HR		1.0[b]		1.0
100–125				
Black women	60/1,252	1.17 (0.85–1.60)	15/323	0.94 (0.45–1.95)
White women	62/1,159	1.39 (1.04–1.87)	19/187	2.66 (0.98–7.18)
Black men	45/757	1.18 (0.82–1.71)	16/199	1.06 (0.52–2.15)
White men	82/1,539	1.00 (0.77–1.30)	14/270	0.60 (0.29–1.24)
Overall HR		1.17 (1.00–1.37)		1.03 (0.71–1.50)
126–149				
Black women	17/298	1.23 (0.73–2.08)	13/195	1.38 (0.65–2.94)
White women	24/200	2.72 (1.74–4.25)	17/115	4.17 (1.52–11.42)
Black men	10/206	0.80 (0.41–1.56)	6/138	0.56 (0.22–1.45)
White men	8/263	0.45 (0.22–0.93)	7/171	0.48 (0.20–1.19)
Overall HR		1.14 (0.85–1.53)		1.13 (0.75–1.70)
≥150				
Black women	29/380	1.71 (1.10–2.66)	28/338	2.02 (1.06–3.87)
White women	18/206	2.05 (1.23–3.42)	17/159	3.30 (1.20–9.10)
Black men	20/253	1.24 (0.75–2.06)	19/206	1.24 (0.63–2.46)
White men	24/278	1.46 (0.93–2.28)	17/213	1.08 (0.53–2.17)
Overall HR		1.59 (1.21–2.08)		1.61 (1.12–2.31)
***p* Value for race/sex by FBG interaction term**	0.0036[a]		0.08[a]	

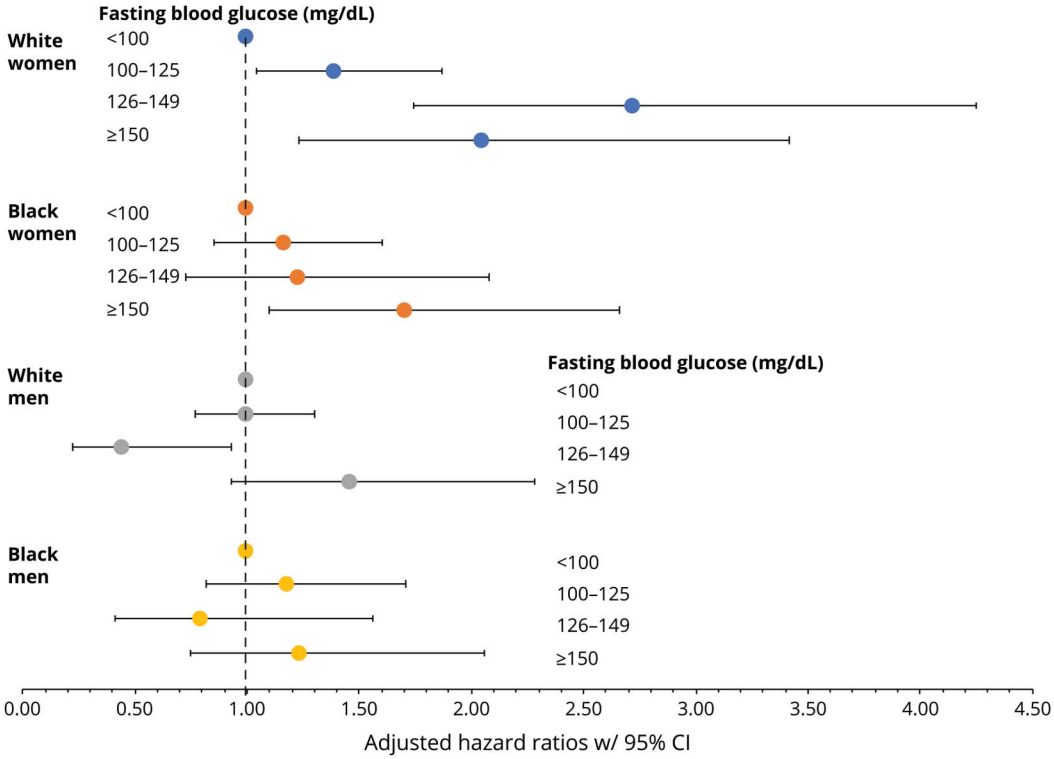
Abbreviations: CI = confidence interval; HR = hazard ratio.
Models are adjusted for age, age by race/sex, fasting blood glucose, race/sex by fasting blood glucose, body mass index, systolic blood pressure, use of antihypertensive medications, left ventricular hypertrophy, atrial fibrillation, history of coronary artery disease, smoking, education, and annual household income. Model 1 is also adjusted for use of diabetes medications (insulin use, oral medication, or none).
[a] Prespecified $p < 0.10$ considered statistically significant for interaction terms.
[b] p Value <0.05 for linear trend.

medications are displayed in eFigure 1 (available from Dryad, doi.org/10.5061/dryad.rjdfn2zbb). In this figure, the association between FBG and incident stroke does not differ by race/sex subgroup ($p = 0.71$) or by sex subgroup ($p = 0.39$).

Marginal predicted risks of IS specific to race/sex subgroups and FBG categories along with risk differences by FBG categories are displayed in table 3 and parallel the findings from our relative effect estimates already described. For example, at 10 years, in the referent groups for each race/sex subgroup where FBG <100, the predicted absolute risk of IS is lowest for White women, followed by Black women, White men, and Black men. However, due to larger FBG-associated risk differences among White women and Black women compared with White men and Black men, the absolute risk of IS at 10 years for those in the ≥150 group is similar across all 4 race/sex groups (with ranges between 7.06% for Black women to 7.66% for White men).

Finally, PAFs also indicate differences in the risk associated with elevated FBG across race/sex subgroups. Among all

Figure 2 Adjusted Relative Hazards of Incident Ischemic Stroke by Fasting Blood Glucose (FBG) Level by Sex/Race Subgroups



This model includes full study sample and is adjusted for age, age × race/sex, race/sex, diabetes medication use (no diabetes medication, oral diabetes medication, insulin use), body mass index, systolic blood pressure, use of antihypertensive medications, left ventricular hypertrophy, atrial fibrillation, history of coronary artery disease, smoking, education, and annual household income. CI = confidence interval.

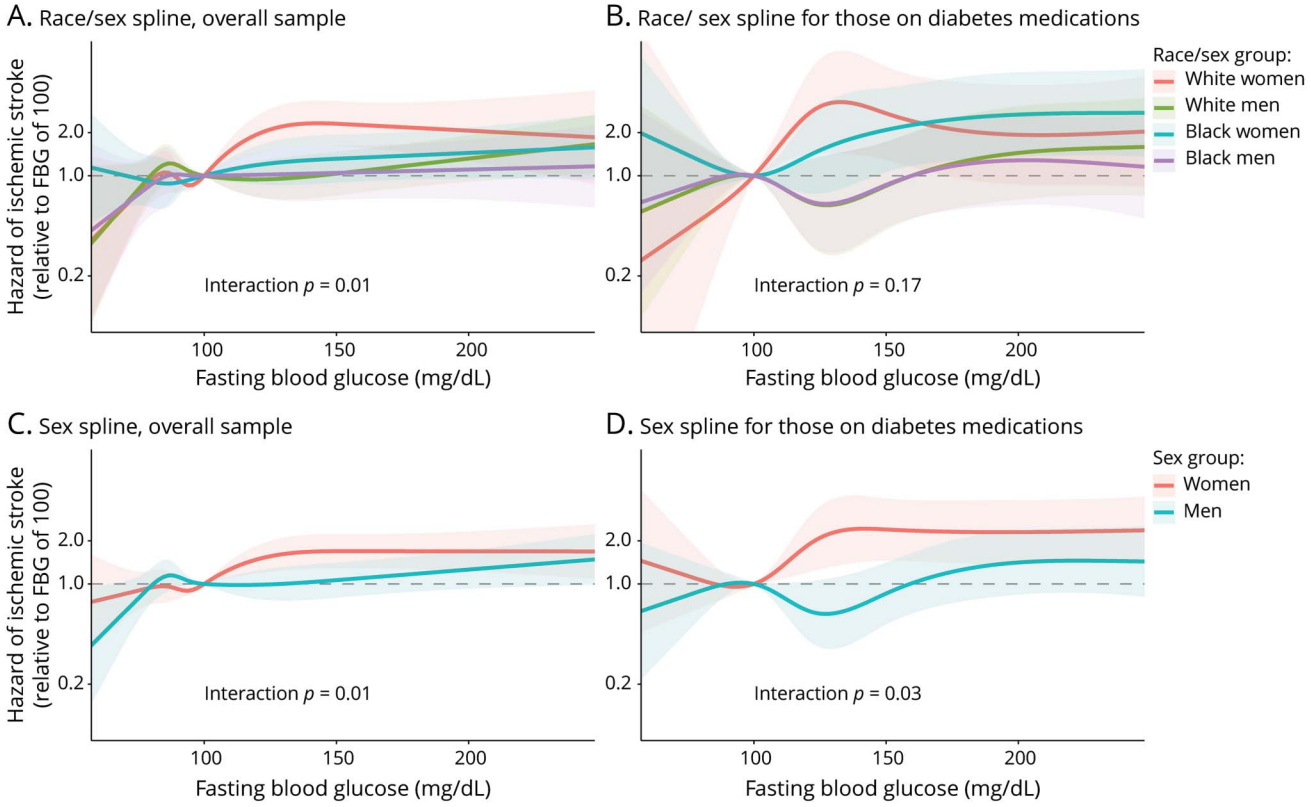
individuals, the PAFs are 16.3% for Black women, 18.1% for White women, 10.0% for Black men, and 4.6% for White men, indicating the proportion of stroke cases in each race/sex population that is attributable to having a blood glucose >100.

Discussion

We investigated the sex- and race-specific risks of incident IS across increasing levels of FBG, a key glycemic maker in the diagnosis and management of diabetes mellitus. Based on clinically relevant categories of FBG, our findings demonstrated the strongest associations between increasing FBG and IS among White women and Black women and weaker associations among White men and Black men. When treating FBG as a restricted cubic spline term, our findings again demonstrated stronger associations between FBG and IS in the female subgroups as well as differing nonlinear shapes of the relationship between FBG and IS; the risk for White women and Black women appears to increase at lower FBG levels when compared with White men and Black men. Although participants were a priori grouped by race and sex in our primary analyses based on known disparities in stroke risk factors, incidence, and mortality, our findings do not demonstrate any clear differences in the association between FBG and IS by race specifically. Further, findings with FBG as a spline term suggest that sex is likely the main driver of our findings of a significant race/sex by FBG interaction term in primary analyses. In addition, differences in stroke risk by FBG across race/sex subgroups appeared to be driven by participants who reported taking medications for diabetes and less so by those participants who either did not have diabetes or did not require medications for diabetes, though stratified analyses are limited by small subgroups and thus a wide degree of variability. Overall, our findings add to previously demonstrated sex differences in diabetes-associated stroke by demonstrating a similar sex difference between FBG, a more granular marker of control and severity of disordered glucose metabolism, and incident IS.[3]

A major strength of our study is the report of both relative estimates of the association between elevated FBG and IS in race/sex subgroups as well as absolute stroke risks according to race, sex, and specific FBG levels. Subgroup-specific measurements of the relative increase in IS risk are critical to understanding potential sex and race differences in the relative contribution of disordered glucose metabolism to stroke risk. Furthermore, sex differences in the relative risk of IS could be used to support consideration of targeted stroke prevention strategies. Our reported absolute estimates of predicted stroke

Figure 3 Relative Hazard of Ischemic Stroke by Fasting Blood Glucose (FBG) as a Restricted Cubic Spline



For all models, hazard ratios were obtained from a race/sex × FBG or sex × FBG interaction term as appropriate and also adjusted for age, body mass index, systolic blood pressure, use of antihypertensive medications, left ventricular hypertrophy, atrial fibrillation, history of coronary artery disease, smoking, education, and income. (A) FBG as restricted cubic spline by race/sex subgroups, in addition adjusted for age × race/sex and medication use (no diabetes medication, oral diabetes medication, insulin use). (B) FBG as restricted cubic spline by race/sex subgroups, in addition adjusted for age × race/sex. (C) FBG as restricted cubic spline by sex subgroups, adjusted for race, age × race, and medication use (no diabetes medication, oral diabetes medication, insulin use). (D) FBG as restricted cubic spline by sex subgroups, adjusted for race and age × race.

risk across increasing FBG by race and sex subgroups provide additional valuable information, especially with respect to the translation of these findings to clinical populations with similar demographic characteristics. For example, the predicted risks of IS demonstrate that despite lower predicted baseline stroke risk in women than men, when FBG levels were in the range of clinical diabetes (≥126 mg/dL), the predicted stroke risk in women was equal to or exceeded stroke risk in men. In other words, at the same level of disordered glucose metabolism as measured by FBG, women are no longer at lower risk of stroke than their male counterparts, a novel finding from this study.

Our findings of a higher stroke risk associated with increasing FBG in women compared with men point to possible mechanistic differences in the pathophysiologic process by which clinical diabetes is related to cerebrovascular disease. Similar to prior literature demonstrating that sex differences in the stroke risk associated with diabetes were not explained by other vascular risk factors such as hypertension and obesity,[5] our findings remained despite adjustment for all the Framingham stroke risk factors along with obesity, income, and education. These data further support a sex difference in the mechanism by which impaired glucose metabolism leads to vascular dysfunction and support the idea that impaired glucose metabolism essentially eliminates any protective effect related to biologic sex. Further research is needed to investigate sex-specific contributors to vascular dysfunction related to disordered glucose metabolism such as insulin resistance, inflammation, coagulation, and the role of sex hormones. We were able to demonstrate that effect estimates for stroke risk were slightly attenuated when we adjusted for use of MHT and remained significant in White women when only those who had never used MHT were included, but we were not able to account for other hormone-related factors (i.e., history of preeclampsia) that may affect circulating active sex hormones and in turn, participants' vascular risk profiles (i.e., hyperandrogenism).

Although the magnitude of the association between FBG and stroke risk was higher for both Black and White women than their male counterparts, whether there were true differences in the strength of association between FBG and stroke between Black and White participants is not clear. There were, however, differences in the distribution of FBG levels between Black and White participants, suggesting potential disparities

Table 3 Sex- and Race-Specific Predicted Risk of Incident Ischemic Stroke at 5 and 10 Years by Increasing Fasting Blood Glucose in Reasons for Geographic and Racial Differences in Stroke (REGARDS)

	At 5 years, %		At 10 years, %	
Fasting blood glucose, mg/dL	Predicted risk	Risk difference	Predicted risk	Risk difference
Black women				
<100	2.00	0 (ref)	4.23	0 (ref)
100–125	2.33	0.33	4.91	0.67
126–150	2.46	0.46	5.17	0.94
150+	3.39	1.38	7.06	2.83
Black men				
<100	2.73	0 (ref)	5.75	0 (ref)
100–125	3.22	0.49	6.75	1.00
126–150	2.19	−0.54	4.64	−1.11
150+	3.37	0.64	7.06	1.31
White women				
<100	1.78	0 (ref)	3.76	0 (ref)
100–125	2.46	0.68	5.15	1.39
126–150	4.70	2.92	9.61	5.85
150+	3.59	1.80	7.42	3.65
White men				
<100	2.56	0 (ref)	5.38	0 (ref)
100–125	2.57	0.01	5.39	0.02
126–150	1.17	−1.39	2.50	−2.88
150+	3.69	1.13	7.66	2.28

Predicted stroke risks are averages of predicted probabilities of stroke events across all individuals in a given race/sex subgroup, estimated from Cox proportional hazards model and adjusted for age, age × race/sex, race/sex, medication use (no diabetes medication, oral diabetes medication, insulin use), body mass index, systolic blood pressure, use of antihypertensive medications, left ventricular hypertrophy, atrial fibrillation, history of coronary artery disease, smoking, education, and income. Predicted risks and risk differences were then multiplied by 100 to obtain the percentages.

in the control of diabetes by race. Further investigation of diabetes control by race is needed in order to understand the potential relationship with BMI as well as social determinants of health (i.e., lower income, access to healthy foods) that are more common in Black participants and likely directly result from inequities present in the health care system. Our data are consistent with previous data demonstrating poorer glycemic control among underrepresented minorities with diabetes[18,19] along with higher stroke incidence and mortality in Black participants compared with White participants.[20]

The relationship between FBG levels below 100 mg/dL and stroke risk is also somewhat unclear, although the multimodel relationship we demonstrated among White women is consistent with prior data demonstrating a nonlinear relationship between increasing FBG and vascular disease, defined by a composite outcome of coronary heart disease and IS.[2] This nonlinear relationship may also contribute to the lack of dose response in our findings when FBG is treated as a categorical variable, although low event rates may also be contributing. Our findings are also similar to prior data showing a significant association between FBG and vascular disease among persons with diabetes but not those without diabetes.[2] In our analysis, we chose to include participants not on diabetes medications in order to be able to assess risk by sex and race across the full spectrum of fasting glucose, including those with undiagnosed diabetes or prediabetes not yet on medications, although the analysis of participants not on diabetes medications was limited due to small frequencies of stroke events.

Our findings have clinical implications related to the management of diabetes and suggest the need for future studies to further explore such sex differences. The sex differences in stroke risk in our study not only point to the need for strict adherence to current guidelines for stroke prevention among those with diabetes but also to the need for prospective research studies to determine whether following sex-specific treatment guidelines for people with diabetes would result in reduced rates of stroke, especially given the steeper rise of IS risk at lower FBG levels. In addition, it is possible that diabetes should be more heavily weighted for women than men in clinical risk scores for stroke. Finally, our findings point to the need for increased attention to management of diabetes among Black participants, who we know have higher stroke incidence and mortality from stroke.[20]

Our study has several limitations. First, our primary analysis used FBG measured at baseline. Because FBG changes over time, the use of this single measurement may not accurately reflect the long-term glucose control of participants. In future studies, it would be important to consider other glycemic markers (e.g., hemoglobin A1C or insulin resistance) that are more reflective of long-term glucose control or better approximate the body's underlying ability to respond to insulin. Second, although REGARDS has so far accumulated >200,000 person-years of follow-up, small numbers of incident events occurred among some subgroups defined by race, sex, and FBG categories and limited the conclusions based on analyses stratified by use of diabetes medications. There may also be nuances related to intensity of treatment of diabetes (i.e., dosing of insulin or number of medications used to achieve FBG control) affecting the lack of dose response that we were not able to capture in our study. Finally, we did not have data on other vascular risk factors that may affect both the degree of disordered metabolism and stroke risk in women; these include preeclampsia, gestational diabetes, and markers of hyperandrogenism.

Our data demonstrated sex differences in the association between impaired glucose metabolism and risk of IS, adding to

existing knowledge that sex-specific stroke risk associated with diabetes is higher among women than men. Further research is needed to identify how such differences might be incorporated into clinical care guidelines including the use of sex-specific treatment recommendations across the spectrum of FBG. Finally, disparities in glycemic control by race point to the need for further intervention to prevent stroke in racial minorities.

Acknowledgment

The authors thank the other investigators, the staff, and the participants of the REGARDS study for their contributions.

Study Funding

This research project is supported by cooperative agreement U01 NS041588 co-funded by the National Institute of Neurologic Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), NIH, Department of Health and Human Services. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NINDS or the NIA. Representatives of the NINDS were involved in the review of the manuscript but were not directly involved in the collection, management, analysis, or interpretation of the data. A full list of participating REGARDS investigators and institutions can be found at uab.edu/soph/regardsstudy/. T.E. Madsen is supported by a research grant from the *National Heart, Lung, and Blood Institute* (*NHLBI*) (K23HL140081). J.E. Manson is supported by research grants from NHLBI (HL34594 and HL145386) and NCI (CA138962). S. Liu is supported by research grants from NIH (ES031391, ES029082, DK125403, and DK103699).

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* December 23, 2020. Accepted in final form May 7, 2021.

Appendix Authors

Name	Location	Contribution
Tracy E. Madsen, MD, PhD	Alpert Medical School of Brown University, Providence, RI	Designed and conceptualized study, drafted and revised the manuscript for intellectual content, data acquisition
D. Leann Long, PhD	School of Public Health, University of Alabama at Birmingham	Analyzed the data, study design, revised the manuscript for intellectual content
April P. Carson, PhD, MSPH	School of Public Health, University of Alabama at Birmingham	Designed and conceptualized study, revised the manuscript for intellectual content
George Howard, DrPH	School of Public Health, University of Alabama at Birmingham	Major role in the acquisition of data, revised the manuscript for intellectual content
Dawn O. Kleindorfer, MD	University of Michigan Medical School; previous affiliation: University of Cincinnati College of Medicine, University of Cincinnati Gardner Neuroscience Institute, OH	Major role in the acquisition of data, revised the manuscript for intellectual content
Karen L. Furie, MD, MPH	Alpert Medical School of Brown University, Providence, RI	Revised the manuscript for intellectual content
JoAnn E. Manson, MD, DrPH	Brigham and Women's Hospital/Harvard Medical School, Boston, MA	Designed and conceptualized study, revised the manuscript for intellectual content
Simin Liu, MD, ScD	Brown University School of Public Health, Alpert Medical School of Brown University, Providence, RI	Designed and conceptualized study, revised the manuscript for intellectual content
Virginia J. Howard, PhD	School of Public Health, University of Alabama at Birmingham	Major role in the acquisition of data, designed and conceptualized study, revised the manuscript for intellectual content

References

1. Park C, Guallar E, Linton JA, et al. Fasting glucose level and the risk of incident atherosclerotic cardiovascular diseases. *Diabetes Care.* 2013;36(7):1988-1993.
2. Sarwar N, Gao P, Kondapally Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet.* 2010;375(9733):2215-2222.
3. Zhao W, Katzmarzyk PT, Horswell R, Wang Y, Johnson J, Hu G. Sex differences in the risk of stroke and HbA1c among diabetic patients. *Diabetologia.* 2014;57(5):918-926.
4. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. *Lancet.* 2014;383(9933):1973-1980.
5. Gnatiuc L, Herrington WG, Halsey J, et al. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies. *Lancet Diabetes Endocrinol.* 2018;6(7):538-546.
6. Howard VJ, Madsen TE, Kleindorfer DO, et al. Sex and race differences in the association of incident ischemic stroke with risk factors. *JAMA Neurol.* 2019;76(2):179-186.
7. Malla G, Long DL, Judd SE, et al. Does the association of diabetes with stroke risk differ by age, race, and sex? Results from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Diabetes Care.* 2019;42(10):1966-1972.
8. Winston GJ, Barr RG, Carrasquillo O, Bertoni AG, Shea S. Sex and racial/ethnic differences in cardiovascular disease risk factor treatment and control among individuals with diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care.* 2009;32(8):1467-1469.
9. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology.* 2005;25(3):135-143.
10. Howard VJ, Kleindorfer DO, Judd SE, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. *Ann Neurol.* 2011;69(4):619-627.
11. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation.* 2016;133(6):601-609.
12. Wolf PA, D'Agostino RB, Belanger AJ, et al. Probability of stroke: a risk profile from the Framingham Study. *Stroke.* 1991;22(3):312-318.
13. Harrell FE Jr. *Regression Modeling Strategies: With Application to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*, 2nd ed. Springer; 2015.

14. Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. *J Clin Epidemiol.* 2010;63(1):46-55.
15. Greenland S, Rothmah KJ, Lash TL. Measures of effect and measures of association (ch 4). In: Rothmah KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*, 3rd ed. Lippincott Williams & Wilkins; 2008:51-70.
16. Gordis L. *More on risk: estimating the potential for prevention (ch 12)*. In: Gordis L, ed. Epidemiology, 4th ed. Saunders; 2009:215-222.
17. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2019.
18. Saydah S, Cowie C, Eberhardt MS, De Rekeneire N, Narayan KMV. Race and ethnic differences in glycemic control among adults with diagnosed diabetes in the United States. *Ethn Dis.* 2007;17(3):529-535.
19. Smalls BL, Ritchwood TD, Bishu KG, Egede LE. Racial/Ethnic differences in glycemic control in older adults with type 2 diabetes: United States 2003-2014. *Int J Environ Res Public Health.* 2020;17(3):E950.
20. Howard G, Moy CS, Howard VJ, et al. Where to focus efforts to reduce the black-white disparity in stroke mortality: incidence versus case fatality? *Stroke.* 2016;47(7):1893-1898.