Racial Differences in the Association of Insulin Resistance With Stroke Risk

The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

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Background and Purpose—Insulin resistance is associated with increased stroke risk, but the effect has not been adequately examined separately in white and black populations.

Methods—The association of baseline insulin resistance with risk of cerebral infarction (CI) and intracerebral hemorrhage (ICH) was assessed in 12,366 white and 6,782 black participants from the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort, recruited between 2003 and 2007 and followed for an average of 5.7 years. Insulin resistance was measured with the homeostasis model assessment-insulin resistance.

Results—There were 364 incident CI and 41 incident ICH events. The risk for CI increased with the log of insulin resistance in whites (hazards ratio [HR]_{\text{ln(IR)}}=1.17; 95% confidence interval [CI], 1.00–1.38) but was largely attenuated by adjustment for stroke risk factors (HR_{\text{ln(IR)}}=1.05; 95% CI, 0.88–1.26). There was no association in blacks (HR_{\text{ln(IR)}}=1.01; 95% CI, 0.81–1.25). After adjustment for demographic factors and risk factors, there was a significant difference by race in the association of insulin resistance with risk of ICH (P=0.07), with a decrease in the risk of ICH in whites (HR_{\text{ln(IR)}}=0.61; 95% CI, 0.35–1.04) but a nonsignificant increase in blacks (HR_{\text{ln(IR)}}=1.20; 95% CI, 0.60–2.39).

Conclusions—These data support the growing evidence that insulin resistance may play a more important role in stroke risk among white than black individuals and suggest a potentially discordant relationship of insulin resistance on CI and ICH among whites. (Stroke. 2014;45:00-00.)

Key Words: hemorrhage ■ infarction ■ insulin resistance ■ stroke

There is growing evidence that the impact of insulin resistance on cardiovascular health may differ by race, with a lesser impact in the black population. In the Insulin Resistance Atherosclerosis Study (IRAS) study, insulin resistance (indexed by Bergman’s S_{p}) was related to carotid intimal-media thickness in white and Hispanic participants but not in blacks. Similarly, in the Multi-Ethnic Study of Atherosclerosis (MESA), the difference in carotid intimal-media thickness between first and fifth quintiles of insulin resistance (by the homeostasis model assessment-insulin resistance [HOMA-IR] model) was twice as large for whites (0.08 mm) as for blacks (0.04 mm), with tests for trends stronger in whites (P<0.0001) than in blacks (P=0.01). In addition, there was a consistent increased risk for coronary calcium with increased insulin resistance in whites (P<0.001) but not in blacks (P=0.1); and insulin resistance remained associated with both coronary calcium and carotid intimal-media thickness after adjustment for the metabolic syndrome in whites but not in blacks (P=0.1). Hence, insulin resistance may be a more important risk factor contributing to vascular disease in whites than blacks.

An association between insulin resistance and stroke risk was demonstrated in the Atherosclerosis Risk in Communities (ARIC) study (using fasting insulin levels); the Cardiovascular Health Study (CHS; using the Gutt insulin sensitivity index); National Health and Nutrition Examination Survey (NHANES; using the HOMA-IR model); the Northern Manhattan Study (NOMAS; using HOMA-IR, but only a marginal effect with a threshold in the highest quartile); and the Uppsala Longitudinal Study of Adult
Men (using serum insulin, fasting proinsulin, and insulin sensitivity by the euglycemic clamp), and a study in the general Japanese population (using the HOMA-IR model). In contrast, no statistically significant association was observed in the Rotterdam Study (using the HOMA-IR model) or the Bezafibrate Infarction Prevention Study (BIP) of patients with stable coronary heart disease.

Of these studies, only the ARIC and NOMAS reports explicitly discussed a potential differential association by race/ethnicity. In ARIC, higher insulin levels were associated with stroke risk among whites but not blacks ($P_{interaction}=0.036$). In NOMAS, there was no differential association by race; however, the analysis diluted the opportunity for detection by the use of an undirected alternative hypothesis across 3 ethnic groups (ie, only testing racial differences rather than specifically testing whether the relationship is less in blacks compared with whites plus Hispanics) and was limited by a relatively small number of white and black participants (only ≈317 of each). Only ARIC examined racial differences in the association of insulin resistance with heart disease, failing to find a difference in the magnitude of the association between whites and blacks.

The currently active Insulin Resistance Intervention after Stroke (IRIS) trial assesses the potential benefit of insulin sensitization using pioglitazone and has a stated secondary aim of assessing racial differences in treatment efficacy. Currently, 11% of the IRIS patients are black (W. Kernan, MD, personal communication, 2014). The growing body of literature (including this report) of a weaker association of insulin resistance and stroke risk in the black population will make assessing effect modification by race important; however, the number of blacks in the trial imply that IRIS will have marginal statistical power to assess interaction.

Some risk factors have a differential association with cerebral infarction (CI) and intracerebral hemorrhage (ICH). For example, total cholesterol is positively associated with CI16–18 but negatively associated with ICH. Although it is likely that the positive association of lipid levels with CI is based on atherosclerosis, the mechanism for the protective association of hemorrhagic stroke is not well understood. Most of the studies of the association of insulin resistance and stroke risk focused on CI outcomes, and to our knowledge, only 2 studies have assessed the association of insulin resistance and ICH risk, both failing to find an association.

Herein, we assess the relationship of insulin resistance with CI and ICH risk in a longitudinal cohort study of black and white participants.

Methods

The overall goal of the REasons for Geographic And Racial Differences in Stroke (REGARDS) study is to advance the understanding of racial and geographic differences in stroke mortality, including differences in the impact of risk factors. REGARDS recruited 30,239 community-dwelling black and white participants between 2003 and 2007, oversampling black participants (42%). A cardiovascular risk survey was completed by telephone and an in-home physical assessment (including fasting sample collection and ECG) conducted at 6-month intervals by telephone, and medical records were retrieved for adjudication of outcome events. Details of the study methods are provided elsewhere. Of the eligible participants contacted, the cooperation rate was 49%.

Suspected strokes were identified by hospitalization for stroke or stroke-like symptoms solicited during telephone interviews conducted at 6-month intervals. Medical records were retrieved for suspected strokes, and stroke end points (including the determination of stroke subtype) were determined by physician review.

Fasting insulin was measured for all participants not self-reporting diabetes mellitus using an electrochemiluminescence immunoassay using the Roche Elecsys 2010 system (Roche Diagnostics, Indianapolis, IN). The primary exposure variable, insulin resistance, was assessed using the homeostasis model (HOMA-IR=(insulin [mg/dL]×glucose [mg/dL])/405).

Risk factors included in the Framingham Stroke Risk Profile were considered as potential confounders of the relationships of insulin resistance with CI and ICH. During the in-home assessment, 2 blood pressure measures were taken and average systolic blood pressure was used for analyses. Use of antihypertensive medications was defined by self-report. Because of the challenges in assessing insulin resistance among patients with diabetes mellitus, we excluded all participants who self-reported having diabetes mellitus or who were on treatment for diabetes mellitus. However, there were a small number of participants with a fasting glucose ≥126 mg/dL, who reported being nondiabetic, and these participants were retained in the study and are referred to as undiagnosed diabetic. Smoking was defined by self-report. Atrial fibrillation was defined as self-reported physician diagnosis or ECG evidence. Left ventricular hypertrophy was defined from the ECG. History of heart disease was defined as self-reported myocardial infarction, ECG evidence of myocardial infarction, or self-reported coronary artery bypass, angioplasty, or stent.

Proportional hazards analysis was used to assess associations between risk factors and incident CI and ICH events through April 1, 2012. A priori, main effects were assessed at $\alpha=0.05$ and interactions at $\alpha=0.10$. Models were fit to assess the relationship between HOMA-IR and stroke risk both after adjustment for demographic factors (age and sex) and after further adjustment for risk factors. The risk factor adjustment included all Framingham Stroke Risk Profile variables except diabetes mellitus. Because the HOMA-IR includes the glucose level used to define undiagnosed diabetes mellitus, a final separate adjustment was done for this factor. For ICH, there were 41 events (28 in whites+13 in blacks), and subsequent to the adjustment for demographic factors (age, race and sex), because of the small number of events the risk factor adjustment included only systolic blood pressure and use of antihypertensive medications (factors previously shown predictive of ICH events). Because some medical records could not be retrieved and other records remained in the adjudication process at the time of analysis ($\approx10\%$ each), multiple imputation techniques were used in the analysis to reduce the potential bias arising from unconfirmed stroke events. Details of the multiple imputation approach used are provided elsewhere.

Results

Of the 30,239 REGARDS participants, 56 (0.2%) participants had data anomalies requiring exclusion, 6,527 (22%) self-reported being diabetic, 402 (1%) did not have follow-up data, 2,873 (10%) were not fasting at the baseline visit, 986 (3%) reported stroke at baseline, and 247 (0.8%) did not have glucose data for calculation of the HOMA-IR model, collectively reducing the cohort to 19,148 participants. Among these, 12,366 were white with 71,683 person-years of exposure, during which 240 CI events and 28 ICH events occurred. The remaining 6,782 were black with 36,986 person-years of exposure, during which 124 CI events and 13 ICH events occurred.

Those with higher levels of HOMA-IR had higher blood pressure, were more likely to be on antihypertensive treatment, and had undiagnosed diabetes mellitus, left ventricular hypertrophy, and history of heart disease (Table 1). A total of 366 were white with 71,683 person-years of exposure, during which 240 CI events and 28 ICH events occurred. The remaining 6,782 were black with 36,986 person-years of exposure, during which 124 CI events and 13 ICH events occurred.
808 participants reported no diabetes mellitus but had a fasting glucose >126 mg/dL.

For whites, there was an increasing risk (hazards ratio [HR]_ln(IR)=1.17; 95% confidence interval [CI], 1.00–1.68) of CI with increasing levels of insulin resistance (Table 2); however, much of this association was attenuated by adjustment for risk factors (HR_ln(IR)=1.09; 95% CI, 0.92–1.29) and subsequent adjustment for diabetes mellitus (HR_ln(IR)=1.05; 95% CI, 0.88–1.26). Much of the association present in the demographic model seemed to be associated with higher risk in the fourth quartile. In contrast, there was no evidence of an increasing stroke risk at higher levels of HOMA-IR for blacks in the demographic model (HR_ln(IR)=1.01; 95% CI, 0.81–1.25), with adjustment for risk factors resulting in a nonsignificant protective association. These differences between races should be interpreted with caution because a formal test of interaction failed in either the demographic model (P=0.19) or after adjustment for risk factors or diabetes mellitus (P=0.26 for both).

For ICH among whites, there was a trend for a decreased risk of ICH at higher levels of HOMA-IR (HR_ln(IR)=0.64; 95% CI, 0.37–1.11), with little effect after adjustment for systolic blood pressure and use of antihypertensive medications (HR_ln(IR)=0.61; 95% CI, 0.35–1.04). In contrast, for blacks there was no association, whether adjusted only for demographics (HR_ln(IR)=1.35; 95% CI, 0.69–2.63) or additionally adjusted for systolic blood pressure and use of antihypertensive medication (HR_ln(IR)=1.20; 95% CI, 0.60–2.39). Although the decrease in ICH risk at higher levels of insulin resistance for whites and the increase in ICH risk with insulin resistance in blacks were both nonsignificant, that they were in different directions contributed to evidence of interaction in the risk factor model (P=0.07) and borderline evidence in the demographic model (P=0.11).

The sensitivity analysis excluding undiagnosed patients with diabetes mellitus from the analysis is provided in Table I in the online-only Data Supplement and showed no substantial difference in interpretation.

### Discussion

These data support a potentially larger impact of insulin resistance on the risk of CI in the white population than in the black population; however, this finding should be interpreted with caution. First, much of the association present in the demographic model was attenuated by adjustment for cerebrovascular risk factors. This is to be expected because it is well known that individuals with high levels of insulin resistance are more likely to have the metabolic syndrome, and many of these factors are likely in the causal pathway of the action of insulin resistance. That is, many of components of the metabolic syndrome (ie, obesity, insulin resistance or hyperglycemia, hypertension, dyslipidemia) have a common pathogenesis, which primarily involves abnormal energy balance and inflammation. There are associations between elements of the metabolic syndrome, however, which are complex and important.

Insulin resistance, for example, is causally linked to abnormal lipid metabolism and hyperglycemia. In addition, it has been suggested that insulin resistance is causally related to hypertension, and this is the risk factor with the largest population attributable risk for stroke. If this is the case, because so many of the stroke risk factors are part of the metabolic syndrome, the attenuation of the association between insulin resistance and stroke risk with the adjustment for these risk factors underscores the truth of the observed association between insulin resistance and stroke risk.

Second, although the association between HOMA-IR and CI risk was significant for whites but not blacks, the formal assessment of whether the association was different for whites and blacks (ie, the interaction test between HOMA-IR and race) failed to reach a level of statistical significance for cerebral infarction (although it was marginally significant for hemorrhages in the demographic model and significant in the risk factor-adjusted model). Hence, although we saw precisely what we hypothesized (a significant association of insulin resistance with stroke risk in whites and no association...
in blacks), there is no clear evidence that the significant association in whites and the nonsignificant association in blacks differ in their magnitude.

Despite a relatively small number of ICH events, there was an inverse association of insulin resistance with risk of ICH events in whites, suggesting that the impact of insulin resistance on ICH risk differed in blacks and whites (P=0.07 in the risk factor model and P=0.11 in the demographic model). To our knowledge, only the Rotterdam study and the Uppsala Longitudinal Study of Adult Men have previously examined associations between insulin resistance and risk of ICH, finding virtually no evidence of an association (HR=1.03; 95% CI, 0.76–1.39 for the Rotterdam study; HR=0.95; 95% CI, 0.60–1.50 for Uppsala). The relationship of insulin resistance and stroke risk is similar to patterns observed between elevated lipids and stroke risk, whereas other studies showed increased stroke risk is similar to patterns observed between elevated lipids and stroke risk, whereas other studies showed increased risk of CI but lower risk of ICH with elevated lipids. Like lipids and stroke risk, whereas other studies showed increased risk of CI but lower risk of ICH with elevated lipids.

An additional challenge to understanding the association between insulin resistance and stroke risk is the quantification of insulin resistance. Although there are several approaches to measuring insulin resistance, the invasive and time-consuming euglycemic clamp is the generally recognized gold standard, with the marginally less invasive and time-consuming frequently sampled insulin/glucose test and the insulin suppression test being considered the best second-line measures. However, all of these approaches require infusion of glucose or insulin and require several hours for assessment; hence, these approaches may be impractical clinically and for epidemiological studies. Other diagnostic strategies involve measurement of insulin and glucose during an oral glucose tolerance test, which has seen limited use in epidemiological studies. Other diagnostic strategies involve measurement of insulin and glucose during an oral glucose tolerance test, which has been considered the best second-line measures.

Table 2. Hazard Ratio (and 95% Confidence Intervals) for Cerebral Infarction or ICH by Quartile of Insulin Resistance and as a Function of the Log of the Insulin Resistance Value

<table>
<thead>
<tr>
<th>Insulin quartile</th>
<th>White (n=14085)</th>
<th>Black (n=7984)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Demo</td>
<td>Demo+Risk Factor</td>
</tr>
<tr>
<td>Q1 (0.0–1.3 uU/mL)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Q2 (1.3–2.2 uU/mL)</td>
<td>0.94 (0.68–1.30)</td>
<td>0.87 (0.62–1.22)</td>
</tr>
<tr>
<td>Q3 (2.2–3.7 uU/mL)</td>
<td>0.94 (0.67–1.32)</td>
<td>0.86 (0.60–1.21)</td>
</tr>
<tr>
<td>Q4 (3.7–180.1 uU/mL)</td>
<td>1.19 (0.84–1.68)</td>
<td>0.97 (0.68–1.39)</td>
</tr>
<tr>
<td>1 U Ln(IR)</td>
<td>1.17 (1.00–1.38)</td>
<td>1.09 (0.92–1.29)</td>
</tr>
</tbody>
</table>

Demographic models included adjustment for age and sex. For analysis of infarction, adjustment for risk factors included systolic blood pressure, use of antihypertensive medications, diabetes mellitus, cigarette smoking, atrial fibrillation, left ventricular hypertrophy, and history of heart disease. Because of a smaller number of events for ICH, adjustment for risk factors included only systolic blood pressure and use of antihypertensive medications. For each outcome ewhite and eblack are the number of events in whites and blacks, respectively. ICH indicates intracerebral hemorrhage; and IR, insulin resistance.
Acknowledgments

We thank the investigators, staff, and participants of the REasons for Geographic And Racial Differences in Stroke (REGARDS) study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org.

Sources of Funding

This research project was supported by cooperative agreement U01-N0141588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Disclosures

None.

References


**SUPPLEMENTAL MATERIAL**

<table>
<thead>
<tr>
<th>Insulin Quartile</th>
<th>White (n = 14,085)</th>
<th>Black (n = 7,984)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Demo</td>
<td>Demo + RF</td>
</tr>
<tr>
<td>Infarction e &lt;sub&gt;white&lt;/sub&gt; = 225 e &lt;sub&gt;AA&lt;/sub&gt; = 118</td>
<td></td>
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</tr>
<tr>
<td>Q1 (0.0 – 1.3 uU/mL)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Q2 (1.3 – 2.2 uU/mL)</td>
<td>0.94 (0.68 – 1.31)</td>
<td>0.87 (0.62 – 1.22)</td>
</tr>
<tr>
<td>Q3 (2.2 – 3.7 uU/mL)</td>
<td>0.95 (0.68 – 1.34)</td>
<td>0.87 (0.61 – 1.24)</td>
</tr>
<tr>
<td>Q4 (3.7 – 180.1 uU/mL)</td>
<td>1.15 (0.79 – 1.68)</td>
<td>0.95 (0.64 – 1.39)</td>
</tr>
<tr>
<td>1 unit Log(IR)</td>
<td>1.13 (0.95 – 1.36)</td>
<td>1.05 (0.87 – 1.26)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insulin Quartile</th>
<th>White (n = 14,085)</th>
<th>Black (n = 7,984)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Demo</td>
<td>Demo + RF</td>
</tr>
<tr>
<td>ICH e &lt;sub&gt;white&lt;/sub&gt; = 28 e &lt;sub&gt;AA&lt;/sub&gt; = 8</td>
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<td>Q1 (0.0 – 1.3 uU/mL)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
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<tr>
<td>Q2 (1.3 – 2.2 uU/mL)</td>
<td>1.11 (0.47 – 2.62)</td>
<td>1.05 (0.44 – 2.49)</td>
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<tr>
<td>Q3 (2.2 – 3.7 uU/mL)</td>
<td>0.52 (0.15 – 1.76)</td>
<td>0.49 (0.15 – 1.62)</td>
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<tr>
<td>Q4 (3.7 – 180.1 uU/mL)</td>
<td>0.64 (0.20 – 2.12)</td>
<td>0.58 (0.18 – 1.89)</td>
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<tr>
<td>1 unit Log(IR)</td>
<td>0.66 (0.38 – 1.17)</td>
<td>0.63 (0.36 – 1.10)</td>
</tr>
</tbody>
</table>

Supplemental Table I: Excluding diabetics and re-estimating hazard ratio (and 95% confidence intervals) for cerebral infarction (infarction) or intracerebral hemorrhage (ICH) by quartile of insulin resistance and as a function of the log of the insulin resistance value. Demographic models included adjustment for age and sex. For analysis of infarction, adjustment for risk factors included systolic blood pressure, use of antihypertensive medications, diabetes, cigarette smoking, atrial fibrillation, left ventricular hypertrophy and history of heart disease. Because of a smaller number of events for ICH, adjustment for risk factors included only systolic blood pressure and use of antihypertensive medications (factors shown to be significantly related to risk in previous work). Race-by-LN(IR) interaction for infarctions in the demographic model p = 0.33, in the risk factor model p = 0.46; similar interactions for hemorrhages in the demographic model p = 0.10, in the risk factor model p = 0.092.