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 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]_{ln(IR)}=1.17; 95% confidence interval [CI], 1.00–1.38) but was largely attenuated by adjustment for stroke risk factors (HR_{ln(IR)}=1.05; 95% CI, 0.88–1.26). There was no association in blacks (HR_{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_{ln(IR)}=0.61; 95% CI, 0.35–1.04) but a nonsignificant increase in blacks (HR_{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;45:2257-2262.)

Key Words: hemorrhage ■ infarction ■ insulin resistance ■ stroke
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 \( \approx 317 \) 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 explicit discussion of this null interaction=0.036).6

Risk factors included in the Framingham Stroke Risk Profile\(^2\) 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 \( \geq 126 \text{ mg/dL} \), who reported being nondiabetic, and these participants were retained in the study and are referred to as undiagnosed diabetic.

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 \( \text{HOMA-IR} = \left( \frac{\text{insulin} \times \text{glucose}}{405} \right) \). Risk factors included in the Framingham Stroke Risk Profile\(^2\) 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 \( \geq 126 \text{ mg/dL} \), 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, ECG evidence of 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).\(^25\)

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).\(^25\)

Because some medical records could not be retrieved and other records remained in the adjudication process at the time of analysis \( (\approx 10\% \) each), multiple imputation\(^29\) 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.\(^27\)

**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 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
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 whites and blacks ($P=0.07$ in the risk factor model and $P=0.11$ in the demographic model). To our knowledge, only the Rotterdam study\textsuperscript{13} and the Uppsala Longitudinal Study of Adult Men\textsuperscript{11} 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 stroke risk.

Thus, we are also uncertain on the potential protective pathway of the observed protective association of lipids with ICH risk, which is important because peripheral insulin resistance may not be identified with the HOMA, which correlates more closely with adverse metabolic consequences of insulin resistance such as inflammation, hypertension, and dyslipidemia. There are other alternative simple measures of insulin resistance (including fasting insulin level),\textsuperscript{35} and part of the inconsistent association of insulin resistance and stroke risk is potentially attributable to limitations of fasting measures characterizing peripheral insulin resistance.

The strengths of this study include the large sample size of the cohort (particularly a large number of blacks) and a reasonable number of CI events (n=364). In addition, physician adjudication of medical records gives confidence in the

### 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></th>
<th>White (n=14085)</th>
<th></th>
<th>Black (n=7984)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Demo</td>
<td>Demo+Risk Factor</td>
<td>Demo</td>
<td>Demo+Risk Factor</td>
</tr>
<tr>
<td></td>
<td>Demo+Risk Factor</td>
<td>Demo+Diabetes Mellitus</td>
<td>Demo</td>
<td>Demo+Diabetes Mellitus</td>
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<tr>
<td>Infarction</td>
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<tr>
<td>$e_{wh}=240, e_{bb}=124$</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
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<tr>
<td>Insulin quartile</td>
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<tr>
<td>O1 (0.0–1.3 uU/mL)</td>
<td>0.94 (0.68–1.30)</td>
<td>0.87 (0.62–1.22)</td>
<td>0.87 (0.62–1.21)</td>
<td>1.03 (0.63–1.71)</td>
</tr>
<tr>
<td>O2 (1.3–2.2 uU/mL)</td>
<td>0.94 (0.67–1.32)</td>
<td>0.86 (0.60–1.21)</td>
<td>0.85 (0.60–1.21)</td>
<td>1.03 (0.64–1.68)</td>
</tr>
<tr>
<td>O3 (2.2–3.7 uU/mL)</td>
<td>1.19 (0.84–1.68)</td>
<td>0.97 (0.68–1.39)</td>
<td>0.92 (0.63–1.34)</td>
<td>1.09 (0.66–1.78)</td>
</tr>
<tr>
<td>O4 (3.7–180.1 uU/mL)</td>
<td>1.17 (1.00–1.38)</td>
<td>1.09 (0.92–1.29)</td>
<td>1.05 (0.88–1.26)</td>
<td>1.01 (0.81–1.25)</td>
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<tr>
<td>1 U Ln(IR)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
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<td>ICH</td>
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<tr>
<td>$e_{wh}=28, e_{bb}=13$</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
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<tr>
<td>Insulin quartile</td>
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<tr>
<td>O1 (0.0–1.3 uU/mL)</td>
<td>1.10 (0.46–2.61)</td>
<td>1.05 (0.44–2.49)</td>
<td>0.92 (0.13–6.80)</td>
<td>0.85 (0.11–6.29)</td>
</tr>
<tr>
<td>O2 (1.3–2.2 uU/mL)</td>
<td>0.51 (0.15–1.74)</td>
<td>0.48 (0.14–1.61)</td>
<td>1.33 (0.24–7.34)</td>
<td>1.09 (0.11–6.29)</td>
</tr>
<tr>
<td>O3 (2.2–3.7 uU/mL)</td>
<td>0.58 (0.17–1.97)</td>
<td>0.52 (0.16–1.77)</td>
<td>1.19 (0.21–6.80)</td>
<td>0.88 (0.15–6.23)</td>
</tr>
<tr>
<td>O4 (3.7–180.1 uU/mL)</td>
<td>0.64 (0.37–1.11)</td>
<td>0.61 (0.35–1.04)</td>
<td>1.35 (0.69–2.63)</td>
<td>1.20 (0.60–2.39)</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 $e_{wh}$ and $e_{bb}$ are the number of events in whites and blacks, respectively. ICH indicates intracerebral hemorrhage; and IR, insulin resistance.
stroke diagnosis and stroke subtype distinction between CI and ICH. Perhaps the greatest weakness is a relatively small number of ICH events (n=41); however, this number was sufficient to provide precision to detect a significant racial difference in the relationship between insulin resistance and ICH risk.

In conclusion, although there was an association between insulin resistance and increased risk for CI in white participants but not in black participants, the race-by-HOMA-IR interaction was nonsignificant. Although the association observed in white participants was attenuated by adjustment for cerebrovascular risk factors, it could be argued that many of these risk factors are in the pathway of action for insulin resistance (specifically hypertension and diabetes mellitus), and as such, the model may be overadjusting for risk factors. We also provide the first evidence of a racial difference in the relationship between insulin resistance and risk of ICH. As such, these data suggest that insulin resistance, as measured by the HOMA, may be playing a larger role in white than black populations. The reasons for these racial differences, and the pathway for a protective effect of insulin resistance on ICH, certainly require additional research.

Acknowledgments
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Disclosures
None.

References
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**SUPPLEMENTAL MATERIAL**

<table>
<thead>
<tr>
<th></th>
<th>White (n = 14,085)</th>
<th></th>
<th>Black (n = 7,984)</th>
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<tr>
<td></td>
<td>Demo</td>
<td>Demo + RF</td>
<td>Demo</td>
<td>Demo + RF</td>
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<td><strong>Infarction</strong></td>
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<tr>
<td>e&lt;sub&gt;white&lt;/sub&gt; = 225</td>
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<td></td>
<td>e&lt;sub&gt;AA&lt;/sub&gt; = 118</td>
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<tr>
<td><strong>Insulin Quartile</strong></td>
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<tr>
<td>Q1 (0.0 – 1.3 uU/mL)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</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>0.94 (0.68 – 1.31)</td>
<td>0.87 (0.62 – 1.22)</td>
<td>1.05 (0.63 – 1.75)</td>
<td>1.08 (0.64 – 1.83)</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>
<td>1.08 (0.63 – 1.75)</td>
<td>0.97 (0.58 – 1.62)</td>
</tr>
<tr>
<td>Q4 (3.7 – 180.1 uU/mL)</td>
<td>1.15 (0.79 – 1.68)</td>
<td>0.95 (0.604 – 1.39)</td>
<td>1.15 (0.68 – 1.93)</td>
<td>1.01 (0.59 – 1.73)</td>
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<td><strong>ICH</strong></td>
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<td></td>
<td>e&lt;sub&gt;AA&lt;/sub&gt; = 8</td>
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<tr>
<td><strong>Insulin Quartile</strong></td>
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<tr>
<td>Q1 (0.0 – 1.3 uU/mL)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<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>
<td>0.91 (0.13 – 3.12)</td>
<td>0.84 (0.12 – 5.94)</td>
</tr>
<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>
<td>1.35 (0.24 – 7.44)</td>
<td>1.11 (0.20 – 6.17)</td>
</tr>
<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>
<td>1.19 (0.24 – 7.04)</td>
<td>0.95 (0.17 – 5.33)</td>
</tr>
<tr>
<td><strong>1 unit Log(IR)</strong></td>
<td>1.13 (0.95 – 1.36)</td>
<td>1.05 (0.87 – 1.26)</td>
<td>1.01 (0.79 – 1.28)</td>
<td>0.93 (0.73 – 1.19)</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.