Self-Report of Stroke, Transient Ischemic Attack, or Stroke Symptoms and Risk of Future Stroke in the Reasons for Geographic And Racial Differences in Stroke (REGARDS) Study

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Background and Purpose—History of stroke and transient ischemic attack (TIA) are documented risk factors for subsequent stroke and all-cause mortality. Recent reports suggest increased risk among those reporting stroke symptoms absent stroke or TIA. However, the relative magnitude of increased stroke risk has not been described across the symptomatic spectrum: (1) asymptomatic, (2) stroke symptoms (SS) only, (3) TIA, (4) distant stroke (DS), and (5) recent stroke (RS).

Methods—Between 2003 and 2007, the REasons for Geographic And Racial Differences in Stroke (REGARDS) study enrolled 30,239 black and white Americans ≥45 years of age. DS and RS were defined as self-report of physician diagnosis of stroke >5 or <5 years before baseline, respectively. SS was defined as a history of any of 6 sudden onset stroke symptoms absent TIA/stroke diagnosis. Kaplan-Meier and proportional hazards analysis were used to contrast stroke risk differences.

Results—Over 5.0±1.72 years of follow-up, 737 strokes were validated. Compared with asymptomatic persons, those with SS, TIA, DS, and RS all had increased risk of future stroke. After adjustment for age, race, sex, income, education, alcohol intake, current smoking, and a history of diabetes mellitus, hypertension, myocardial infarction, atrial fibrillation, and dyslipidemia, there was 1.20-fold (not statistically significant) increased stroke risk for SS (95% CI, 0.96–1.51), 1.73-fold for TIA (95% CI, 1.27–2.36), 2.23-fold for DS (95% CI, 1.61–3.09), and 2.85-fold for RS (95% CI, 2.16–3.76).

Conclusions—Results suggest a spectrum of risk from stroke symptoms to TIA, DS, and RS, and imply a need for establishing these categories in health screenings to manage risk for future stroke, reinforcing the clinical importance of stroke history including the presence of stroke symptoms. (Stroke. 2013;44:00-00.)

Key Words: mortality ■ stroke ■ stroke symptoms ■ transient ischemic attack

Previous studies demonstrated that having a previous history of stroke or transient ischemic attack (TIA) confers a substantial risk for subsequent stroke. Pooled analyses from the Framingham Heart Study, the Atherosclerosis Risk in Communities Study, and the Cardiovascular Health Study demonstrated that between 13% and 32% of individuals experiencing a stroke will have a recurrent stroke within 5 years. Additional population-based studies demonstrated that the risk of stroke immediately after TIA is between 3% and 17.3%. However, many people who experience TIA or stroke were either never diagnosed with it or were not aware of a diagnosis they received. Consequently, in studies utilizing self-report of stroke/TIA diagnoses, misclassification in the outcome occurs (fewer outcomes will be observed than are actually occurring) and might lead to underestimation of associations. Queries to research subjects on self-report of stroke-like symptoms might help to improve classification of previous stroke and identify persons at increased risk of subsequent stroke.

The clinical importance of evaluating stroke symptoms in the absence of a stroke or TIA diagnosis is underscored by several recent observations in the REGARDS cohort. First, the prevalence of stroke-like symptoms is more than 18% in the general population ≥45 years of age, substantially higher than the 2.9% prevalence of stroke in the population ≥20 years of age. Second, presence of these stroke symptoms are associated with higher Framingham Stroke Risk Score, increased odds of cognitive impairment, and lower quality of life.
of life. Finally, in the REGARDS cohort, there was a 36% increased risk of future stroke after report of any stroke symptom (sudden onset of weakness, numbness, blindness, difficulty in communicating, or difficulty in understanding); a 46% increased risk for people reporting 2 symptoms, and a 77% increased risk for those reporting 3. Although the risk of stroke after self-reported symptoms is now well characterized, no study has been large enough to contrast the magnitude of increased risk of subsequent stroke or death in those with stroke symptoms, history of diagnosed stroke, or history of diagnosed TIA.

We sought to characterize the history of cerebrovascular events (CVA) across a spectrum utilizing self-report of diagnosed stroke/TIA and stroke symptoms as exposure variables. Understanding the association of self-report of cerebrovascular events/symptoms and risk of future stroke is clinically important to expand on the validity of self-reported history of CVA. The REGARDS cohort, a large, biracial, and nationally representative cohort of 30,239 subjects, provides a unique opportunity to study risk of stroke after a number of types of cerebrovascular events (including stroke and TIA) and cerebrovascular event symptoms.

Methods

The REGARDS cohort was assembled between 2003 and 2007 and included 30,239 black and white adults ≥45 years of age residing in the 48 continental United States. The study was designed to oversample in the Stroke Belt, a section of the Southeastern United States characterized by high stroke mortality (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana). Target recruitment was to have half of the cohort residing in the Southeast, half male, and half black.

The study methods have been described previously. Briefly, participants were recruited from commercially available lists (Genesys, Inc) similar to the methods used by the National Center for Health Statistics Behavioral Risk Factor Surveillance Study. After a letter was sent to each participant’s home describing the study and informing the individual that he/she would be receiving a phone call, the call center contacted the participant and invited him/her to be a part of the study. Participants provided verbal consent and completed a 45-minute phone interview to collect demographic, socioeconomic, risk factors, and history of disease information. The telephone response rate was 33% and cooperation rate was 49%, similar to other cohort studies. After the phone call, a trained health professional went to the participant’s home to collect blood and urine samples, blood pressure measurements, an ECG, and other key study variables. Blood was stored and analyzed at the central laboratory at the University of Vermont, and ECGs were centrally read at a Wake Forest University.

The study was approved by Institutional Review Boards at all participating institutions.

Self-reported history of stroke, TIA, and stroke symptoms were classified across a 4-level spectrum: recent stroke (RS), distant stroke (DS), TIA, and stroke symptoms (SS). If the participant answered yes to “Were you ever told by a physician that you had a stroke?” we then asked “How old were you when you had your first stroke?” If the participant could not remember the exact age at which he/she had the stroke, we asked him/her to estimate the decade in which the stroke occurred. We used this information to characterize DS as a stroke that occurred >5 years from baseline and an RS as one that occurred within 5 years of baseline. Time to previous stroke was calculated as the time from reported stroke date to baseline interview. In cases in which participants gave a range of years when the stroke may have occurred, we used the midpoint of the interval as the date at which first stroke occurred. In the case when a participant reported >1 stroke before baseline, we calculated time from most RS. For those not reporting a history of stroke, self-report of TIA was characterized using the question “Were you ever told by a physician that you had a mini-stroke or TIA, also known as a transient ischemic attack?” The time since diagnosis of TIA was not asked. For those not reporting a history of stroke or TIA, we then used the 6 questions from the Questionnaire for Verifying Stroke-Free Status. They include “Have you ever had sudden painless weakness on one side of your body?”, “Have you ever had sudden numbness or a dead feeling on one side of your body?”, “Have you ever had sudden painless loss of vision in one or both eyes?”, “Have you ever suddenly lost one half of your vision?”, “Have you ever suddenly lost the ability to express yourself verbally or in writing?”. We considered a yes to any of the 6 questions as a positive response to history of stroke symptoms.

Age, race, sex, region of residence, education, income, alcohol intake, and current smoking were all collected during the baseline telephone interview via self-report. History of diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, and dyslipidemia were collected from self-report and use of medical information from the in-home visit. Hypertension was defined as self-reported use of medications to lower blood pressure, or blood pressure at or above 140/90 mm Hg. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dL (or nonfasting glucose ≥200 mg/dL, if the participant was not fasting) or self-reported medication use for glucose control. Dyslipidemia was defined as triglycerides ≥240 mg/dL or low-density lipoprotein ≥160 mg/dL or high-density lipoprotein ≤40 mg/dL. Atrial fibrillation was defined as either self-report or ECG evidence. History of heart disease was defined as self-reported pre-baseline myocardial infarction/heart attack, coronary artery bypass surgery, coronary angioplasty/stenting, or evidence of myocardial infarction from ECG.

Stroke Event Ascertainment

Questions related to all hospitalizations were asked of participants or their proxies by interview at 6-month intervals, and medical records were pursued for all hospitalizations suspected to be related to stroke, TIA, or stroke symptoms. Medical records for strokes that occurred before baseline were not pursued. Upon receipt of medical records, they were first reviewed by a trained neurological nurse to verify the record was complete and to remove clear nonstroke cases; then suspected strokes were forwarded on to review by a team of stroke experts. A stroke is defined as focal neurological symptoms lasting >24 hours or nonfocal symptoms with imaging positive for stroke. For deaths in which medical records are not available (participant died at home or did not make it to the hospital), a proxy was interviewed to probe for information relating to the stroke. Stroke adjudicators then utilized the death certificate, National Death Index, and proxy interview to determine whether a stroke occurred. For this analysis, stroke events were available through February 1, 2011.

Death Ascertainment

In addition to stroke outcomes, the risk of all-cause mortality was assessed across the symptomatic spectrum. Notification of death was provided by proxies through the mail, during the routine 6-month telephone calls, or by telephone calls to a toll-free number for REGARDS participants. Searches using the Social Security Death Index death master file and the National Death Index were used to look for participants who possibly died for whom there was no proxy report of death and was also used to confirm the date of death given by proxies. For this analysis, death events were available through April 1, 2011.

Statistical Methods

Cox Proportional Hazards modeling was used to examine the association between the main exposure (the spectrum of cerebrovascular event history modeled as a 5-level categorical dummy variable) and both the stroke and death outcomes. We also...
used nonparametric Kaplan-Meier plots to visually display the data. Incremental models were fit to assess the influence of groups of covariates: (1) demographics, (2) then adding socioeconomic status (defined by highest education obtained and household income), and (3) adding stroke risk factors. Because there was some racial difference in terms of medical records obtained, we applied a mathematical correction for the final model to ensure that this bias did not alter our results. We included the following covariates in all final models: age, race, sex, region of residence, education, income, alcohol intake, current smoking, and a history of diabetes mellitus, hypertension, myocardial infarction, atrial fibrillation, and dyslipidemia.

**Results**

Participants were included if they had at least 1 follow-up phone call after the baseline interview (n=29846) and participants were excluded if they did not answer the stroke, TIA, or stroke symptom questions (n=431), resulting in a final sample of 29415 (95% of the study sample).

Compared with the asymptomatic group, participants with a self-report of previous stroke diagnosis were more likely to be male, black, and not have graduated college (Table 1). These trends were similar across exposure groups such that those with self-report of previous stroke were more likely to be male, black, and not have graduated college than those who reported a TIA or stroke symptom. In addition, those with an RS were more likely to have other concomitant diseases such as heart disease, diabetes mellitus, and atrial fibrillation. They were also less likely to consume alcohol and to be current smokers. Across the categories of self-reported stroke, TIA, or SS, the prevalence of hypertension declined, but in all cases was higher than those without any of the components of the symptomatic spectrum. Eighty-two percent of those with an RS had hypertension, compared with 77% of those with a distant stroke, 75% of those reporting a TIA, 65% of those reporting SS, and 56% of those without any history of stroke, TIA, or SS.

Compared with those not reporting stroke or SS, self-report of an RS (within the past 5 years) was most strongly associated with future stroke (hazard ratio [HR]=3.72; 95% CI=2.89 to 4.78; Table 2) after adjusting for age, race, and sex. Adding region of residence, education, income, alcohol intake, current smoking, and a history of diabetes mellitus, hypertension, heart disease, atrial fibrillation, and dyslipidemia to the model attenuated the association only modestly (HR, 2.85; 95% CI, 2.16–3.76). The Figure demonstrates a progressive relationship between no stroke, SS, TIA, DS, and RS in a Kaplan-Meier plot. Even after adjusting for the risk factors mentioned above, the strong graded association between no stroke and SS, TIA, DS, and RS persisted. The fully adjusted HRs increased from 1.20 (P<0.05) in those reporting SS to 1.73 (P<0.01) in those reporting TIA, to 2.23 (P<0.01) in those reporting DS, and finally to 2.85 (P<0.01) in those reporting RS. All HRs are relative to those not reporting SS, TIA, or stroke.

Over a median of 4.5 years, we observed a similar strong association across the stroke spectrum with risk of all-cause mortality (Table 3). In participants reporting a stroke within 5 years of baseline, the risk of death was >2-fold greater than those without a stroke, TIA, or SS at baseline (HR, 2.47; 95% CI, 2.14–2.85). This was only modestly attenuated in the fully adjusted model (HR, 1.79; 95% CI, 1.53–2.09). A

### Table 1. Demographic, Socioeconomic, and Health Characteristics in Those People Self-Reporting a History of Stroke, TIA, or Stroke Symptoms in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Reported History of Stroke, TIA, or Stroke Symptoms (n=22795)</th>
<th>Stroke Symptoms (n=3871)</th>
<th>Distant Stroke (n=807)</th>
<th>Recent Stroke (n=846)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>10194 (44.8)</td>
<td>1697 (44.0)</td>
<td>454 (41.5)</td>
<td>373 (46.5)</td>
<td>437 (52.0)</td>
</tr>
<tr>
<td>Blacks</td>
<td>8786 (38.6)</td>
<td>1957 (50.8)</td>
<td>429 (39.3)</td>
<td>439 (54.7)</td>
<td>414 (49.4)</td>
</tr>
<tr>
<td>Residence outside of stroke belt</td>
<td>10098 (44.4)</td>
<td>1663 (43.2)</td>
<td>511 (46.8)</td>
<td>377 (47.0)</td>
<td>370 (44.0)</td>
</tr>
<tr>
<td>College graduate</td>
<td>8539 (37.5)</td>
<td>1013 (26.3)</td>
<td>341 (31.2)</td>
<td>179 (22.5)</td>
<td>198 (23.7)</td>
</tr>
<tr>
<td>Income &lt;$20k</td>
<td>3506 (15.4)</td>
<td>1001 (26.0)</td>
<td>235 (21.5)</td>
<td>257 (32.0)</td>
<td>247 (29.4)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3045 (13.4)</td>
<td>675 (17.6)</td>
<td>173 (15.9)</td>
<td>153 (19.1)</td>
<td>161 (19.2)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>956 (4.3)</td>
<td>133 (3.6)</td>
<td>34 (3.2)</td>
<td>26 (3.3)</td>
<td>20 (2.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7900 (35.3)</td>
<td>1024 (27.4)</td>
<td>300 (28.0)</td>
<td>203 (26.0)</td>
<td>194 (23.4)</td>
</tr>
<tr>
<td>None</td>
<td>13506 (59.3)</td>
<td>2578 (69.0)</td>
<td>738 (68.8)</td>
<td>553 (70.7)</td>
<td>617 (74.3)</td>
</tr>
<tr>
<td>Concomitant disease history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>2366 (10.6)</td>
<td>602 (15.9)</td>
<td>242 (22.9)</td>
<td>191 (24.5)</td>
<td>229 (27.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4214 (19.2)</td>
<td>1063 (28.7)</td>
<td>316 (29.9)</td>
<td>265 (34.7)</td>
<td>330 (40.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12667 (55.8)</td>
<td>2487 (64.8)</td>
<td>819 (75.1)</td>
<td>624 (77.7)</td>
<td>687 (82.0)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1593 (7.1)</td>
<td>481 (12.9)</td>
<td>184 (17.4)</td>
<td>115 (14.9)</td>
<td>126 (15.6)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12618 (57.5)</td>
<td>2306 (62.5)</td>
<td>720 (67.2)</td>
<td>525 (68.7)</td>
<td>578 (71.9)</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack. A recent stroke is defined as a stroke within 5 years of the baseline interview. A distant stroke is defined as a stroke that occurred ≥5 years from baseline interview. Recent stroke, distant stroke, TIA, and stroke symptoms were all ascertained by self-report.

* P Values are for χ² test.
Figure. Risk of future stroke (Kaplan-Meier) after self-report stroke, transient ischemic attack (TIA), or stroke symptoms in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Self-report was obtained at baseline between 2003 and 2007. Participants have been followed up for stroke events which are confirmed by a physician (baseline strokes were not physician verified) for a mean of 5.0±1.72 years. An older stroke is defined as a stroke that occurred ≥5 years from baseline interview. Recent stroke, distant stroke, TIA, and stroke symptoms were all ascertained by self-report. Recent stroke, distant stroke, TIA, and stroke symptoms were all ascertained by self-report.

Table 2. Risk of Future Stroke After Self-Reported Stroke, TIA, or Stroke Symptoms in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

<table>
<thead>
<tr>
<th></th>
<th>No Report of Stroke</th>
<th>Stroke Symptoms</th>
<th>TIA</th>
<th>Distant Stroke*</th>
<th>Recent Stroke*</th>
<th>P Value (trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>22,795</td>
<td>3,871</td>
<td>1,096</td>
<td>807</td>
<td>846</td>
<td></td>
</tr>
<tr>
<td>Number of adjudicated strokes</td>
<td>456</td>
<td>104</td>
<td>56</td>
<td>50</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Adjusts for age, race, and sex</td>
<td>ref</td>
<td>1.32 (1.07–1.64)</td>
<td>2.15 (1.62–2.84)</td>
<td>2.74 (2.05–3.68)</td>
<td>3.72 (2.89–4.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusts for above plus region, income, and education</td>
<td>ref</td>
<td>1.26 (1.02–1.57)</td>
<td>2.11 (1.59–2.79)</td>
<td>2.61 (1.95–3.31)</td>
<td>3.49 (2.71–4.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusts for above plus comorbidities†</td>
<td>ref</td>
<td>1.20 (0.96–1.51)</td>
<td>1.73 (1.27–2.36)</td>
<td>2.23 (1.61–3.09)</td>
<td>2.85 (2.16–3.76)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.

*A recent stroke is defined as a stroke within 5 years of the baseline interview. A distant stroke is defined as a stroke that occurred ≥5 years from baseline interview. Recent stroke, distant stroke, TIA, and stroke symptoms were all ascertained by self-report.
†Comorbidities include alcohol intake, current smoking, and a history of diabetes mellitus, hypertension, history of coronary artery disease, atrial fibrillation, dyslipidemia, and the racial difference in retrieving medical records.

Dose–response association was present across the symptom spectrum (P<0.001). HRs of death for the other 3 stroke spectrum categories were: DS, 1.86 (95% CI, 1.58–2.20), TIA, 1.58 (95% CI, 1.35–1.85), and for SS, 1.33 (95% CI, 1.19–1.48). Contrary to the stroke findings, the differences between the RS group and the DS group were more modest. Although a linear trend was still present, the HRs for RS and DS were similar across all models.

Discussion

In the REGARDS cohort, a large population-based sample of US adults, relative to other types of cerebrovascular events, people who self-reported an RS have the largest risk for having a stroke in the future. In fact, this risk was nearly twice as high as the HRs of stroke for atrial fibrillation and hypertension in REGARDS. A strong dose response, as indicated by a P for trend <0.001, was observed across our 4 categories of SS, TIA, DS, and RS for both the stroke and mortality outcome. This suggests that the 8 questions asked of REGARDS participants (history of stroke, history of TIA, and 6 questions from the validated questionnaire for verifying stroke-free status) could help primary care doctors identify people at a high risk of stroke and death for targeted risk factor management.

Previous studies have not found self-report of stroke to be highly correlated with actual stroke when stroke neurologists have examined medical records and imaging results of those self-reporting stroke. In one study, the sensitivity for a self-report of stroke predicting actual stroke was 32.4%, and specificity was 78.9%. Interestingly, this study also found evidence for racial differences in the predictive value of self-report of stroke (in whites: sensitivity=26.5% and specificity=83.5%, and in blacks: sensitivity=37.3% and specificity=77.4%). This confirmed previous studies also showing high false-negative rates (low sensitivity) for diagnosis of stroke when relying solely on self-report of stroke. Although our study does not refute the findings of the previous work, it does provide some perspective about the potential health risks associated with perceived stroke. Although it is possible that as few as 26% of the strokes we identified through self-report were real strokes, these reported strokes were associated with a high rate of future stroke. From a public health perspective, whereas these events were not adjudicated as stroke, they may still provide a population that is at high risk for future stroke and may thereby benefit from interventional studies. It is also possible that REGARDS participants had better knowledge of previous stroke given their willingness to participate in the study.

The strong associations of history of TIA and SS with future stroke risk and death are also worth noting. It is possible these TIA and SS were undiagnosed stroke events, consistent with other findings that silent infarcts are associated with increased risk of stroke. It is not currently known whether these SS and TIA represent actual strokes, but future studies including brain imaging to document this would be helpful. In the meantime, that these symptoms are associated with up to a 20% greater risk of stroke and a 34% increased risk of death in people who have not reported having had a stroke or TIA is intriguing.
There are some limitations of the current study. First, as discussed above, misclassification of prebaseline stroke and TIA is likely; however, associations of these self-reports with future stroke were strong nonetheless. Although the exposure may be misclassified, the incident stroke outcome was adjudicated by stroke experts, providing a robust outcome measure. Second, ascertainment of stroke events in blacks was not as complete as in whites because of the racial difference in medical record retrieval. However, we were able to account for this using imputation.\textsuperscript{15}

In conclusion, we report a graded association of the spectrum of baseline stroke, from SS to TIA, to DS and RS, with the risk of future stroke. Further, these same conditions were associated with substantial mortality risk. Findings have potentially important public health importance if other studies can demonstrate that special interventions in these patient groups are beneficial at reducing stroke.

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Disclosures

None.

References

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