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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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Abstract

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 (Asx), 2) stroke symptoms only (SS), 3) TIA, 4) stroke in the distant past (DS), and 5) recent stroke (RS).

Methods—Between 2003–2007 the REasons for Geographic And Racial Differences in Stroke (REGARDS) study enrolled 30,239 black and white Americans aged 45+. 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 six 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 to Asx 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, 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).

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Discussion—Results suggest a spectrum of risk from stroke symptoms to TIA, distant stroke, and recent stroke, 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.

Keywords

stroke; TIA; stroke symptoms; mortality

Introduction

Previous studies demonstrated that having a prior 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 years¹. Additional population based studies demonstrated that the risk of stroke immediately following a Transient Ischemic Attack (TIA) is between 3 and 17.3%²⁻⁴. However, many people who experience TIA or stroke either were never diagnosed with it or were not aware of a diagnosis they received⁵. 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 prior stroke and identify persons at increased risk of subsequent stroke⁵⁻⁷.

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 over 18% in the general population aged 45+,⁵ substantially higher than the 2.9% prevalence of stroke in the population aged 20+.¹ Second, presence of these stroke symptoms are associated with higher Framingham Stroke Risk Score⁵, increased odds of cognitive impairment⁸, and lower quality of life⁹. Finally, in the REGARDS cohort there was a 36% increased risk of future stroke following 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 two symptoms, and a 77% increased risk for those reporting three⁷. Although the risk of stroke following self-reported symptoms is now well characterized^{6, 7}, 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^{6, 10}.

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 upon the validity of self-reported history of CVA. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, a large, biracial and nationally representative cohort of 30,239 subjects, provides a unique opportunity to study risk of stroke following a number of types of cerebrovascular events (including stroke and TIA) and/or cerebrovascular event symptoms.

Methods

The REGARDS cohort was assembled between 2003 and 2007 and includes 30,239 black and white adults age 45 and over 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 African American.

The study methods have been described elsewhere¹¹. 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 (BRFSS). After a letter was sent to the 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, socio-economic, risk factors, and history of disease information. The telephone response rate was 33% and cooperation rate was 49%, similar to other cohort studies¹². Following the phone call, a trained health professional went to the participant's home to collect blood and urine samples, samples, blood pressure measurements, an electrocardiogram (ECG), and other key study variables. Blood was stored and analyzed at the central lab 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 four-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 them to estimate the decade in which the stroke occurred. We used this information to characterize DS as a stroke that occurred more than five years from baseline and a RS as one that occurred within five years of baseline. Time to previous stroke was calculated as the time from reported stroke date to baseline interview. In cases where participants gave a range of years when the stroke may have happened, we used the midpoint of the interval as the date at which first stroke occurred. In the case when a participant reported more than one stroke before baseline, we calculated time from most recent stroke. 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 six questions from the Questionnaire for Verifying Stroke-Free Status (QVSFS)¹³. 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 understand what people were saying?", and "Have you ever suddenly lost the ability to express yourself verbally or in writing?". We considered a yes to any of the six 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, 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 mmHg. Diabetes was defined as a fasting glucose level ≥ 126 mg/dL (or non-fasting glucose ≥ 200 mg/dL if the participant was not fasting) or self-reported medication use for glucose control. Dyslipidemia was defined as a triglycerides ≥ 240 mg/dL or LDL ≥ 160 mg/dL or HDL ≤ 40 mg/dL. Atrial fibrillation were defined as either self-report or ECG evidence¹⁴. History of heart disease was defined as self-reported

prebaseline 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 is complete and to remove clear non-stroke cases; then suspected strokes are forwarded on to review by a team of stroke experts. A stroke is defined as focal neurologic symptoms lasting greater than twenty-four hours or non-focal 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 if 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 either through the mail, during the routine six month telephone calls, or by telephone calls to a toll free number for REGARDS participants. Searches using the Social Security Death Index (SSDI) death master file and the National Death Index (NDI) were used to look for participants who may have 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 non-parametric 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. As 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 results¹⁵. 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, hypertension, myocardial infarction, atrial fibrillation, and dyslipidemia.

Results

Participants were included if they had at least one 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 to the Asx group, participants with a self-report of prior 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 prior 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 recent strokes were more likely to have other concomitant disease like heart disease, diabetes and atrial fibrillation. They were also less likely to consume alcohol and to be a current smoker. 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. 82% of those with a recent stroke had hypertension, compared to 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 a recent stroke (within the past five years) was most strongly associated with future stroke, HR = 3.72; 95% CI=2.89-4.78 (Table 2) after adjusting for age, race and sex. Adding region of residence, education, income, alcohol intake, current smoking, and a history of diabetes, hypertension, heart disease, atrial fibrillation, and dyslipidemia to the model attenuated the association only modestly (HR=2.85; 95% CI=2.16-3.76). Figure 1 demonstrates a progressive relationship between no stroke, SS, TIA, distant stroke and recent stroke 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 recent stroke persisted. The fully adjusted hazard ratios 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 a DS, and finally to 2.85 ($p<0.01$) in those reporting an RS. All hazard ratios 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 five years of baseline the risk of death was over two-fold greater than in 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 dose response association was present across the symptomatic spectrum ($p<0.001$). Hazard ratios of death for the other three stroke spectrum categories were: DS (HR=1.86; 95% CI=1.58, 2.20), TIA (HR=1.58; 95% CI=1.35, 1.85), and for SS (HR=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 a recent stroke have the largest risk for having a stroke in the future. In fact, this risk was nearly twice as high as the hazard ratios of stroke for atrial fibrillation and hypertension in REGARDS¹⁶. A strong dose response, as indicated by a p for trend less than 0.001, was observed across our four categories of SS, TIA, DS and RS for both the stroke and mortality outcome. This suggests that the eight questions asked of REGARDS participants (history of stroke, history of TIA, and six questions from the validated questionnaire for verifying stroke-free status QVSFS) could help primary care doctors identify people at a high risk of stroke and death for targeted risk factor management^{13, 17, 18}.

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%¹⁹. 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 stroke²⁰. 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. Even though 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, while 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^{21, 22}. It is also possible that REGARDS participants had better knowledge of prior 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 TIAs and SS were undiagnosed stroke events, consistent with other findings that “silent infarcts” are associated with increased risk of stroke^{23, 24}. It is not currently known whether these SS and TIAs 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 intriguing.

There are some limitations of the current study. As discussed above, misclassification of prebaseline stroke and/or TIA are 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 the whites due to the racial difference in medical record retrieval. We were however able to account for this using imputation²⁵.

In conclusion, we report a graded association of the spectrum of baseline stroke, from SS to TIA, to distant stroke and recent stroke, 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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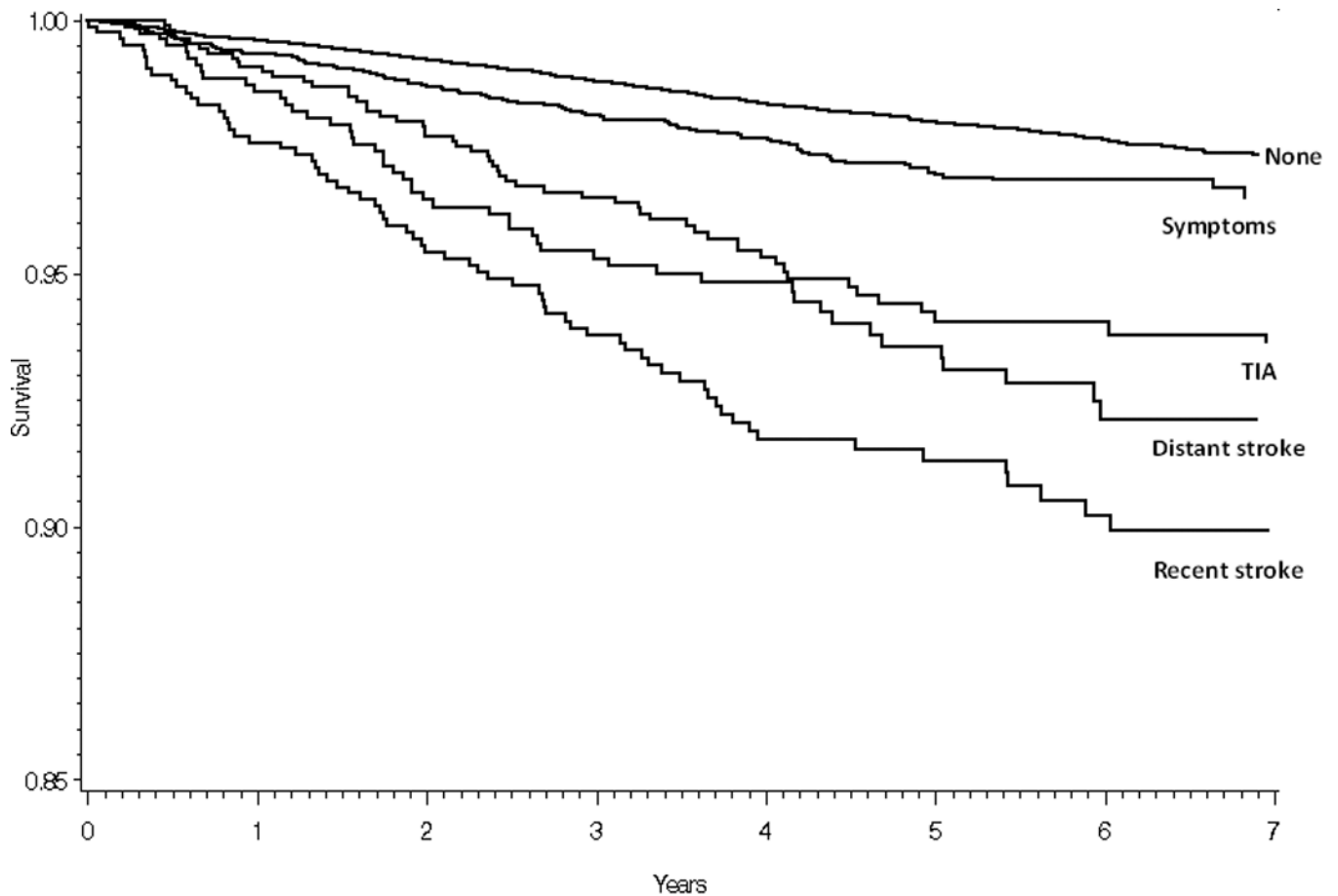


Figure 1.

Risk of future stroke (Kaplan-Meier) following self-report stroke, 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 for stroke events which are confirmed by a physician (baseline strokes were not physician verified) for a mean of 5.0 ± 1.72 years. A older stroke is defined as a stroke that occurred 5 years or further from baseline interview. Recent stroke, distant stroke, TIA and stroke symptoms were all ascertained by self-report.

Table 1

Demographic, socio-economic and health characteristics in those people self-reporting a history of stroke, TIA or stroke symptom in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.

	No reported history of stroke, TIA, or stroke symptoms N=22795	Stroke symptom N=3871	TIA N=1096	Distant stroke N=807	Recent stroke N=846	p ^a
	n (%)	n (%)	n (%)	n (%)	n (%)	
Males	10194 (44.8)	1697 (44.0)	454 (41.5)	373 (46.5)	437 (52.0)	<0.001
Blacks	8786 (38.6)	1957 (50.8)	429 (39.3)	439 (54.7)	414 (49.4)	<0.001
Residence outside of stroke belt	10098 (44.4)	1663 (43.2)	511 (46.8)	377 (47.0)	370 (44.0)	0.17
College graduate	8539 (37.5)	1013 (26.3)	341 (31.2)	179 (22.5)	198 (23.7)	<0.001
Income less than \$20k	3506 (15.4)	1001 (26.0)	235 (21.5)	257 (32.0)	247 (29.4)	<0.001
Current Smoker	3045(13.4)	675 (17.6)	173 (15.9)	153 (19.1)	161 (19.2)	<0.001
Alcohol intake						
Heavy	956(4.3)	133 (3.6)	34 (3.2)	26 (3.3)	20 (2.4)	
Moderate	7900 (35.3)	1024 (27.4)	300 (28.0)	203 (26.0)	194 (23.4)	
None	13506 (59.3)	2578 (69.0)	738 (68.8)	553 (70.7)	617 (74.3)	<0.001
Concomitant disease history						
Heart disease	2366 (10.6)	602 (15.9)	242 (22.9)	191 (24.5)	229 (27.8)	<0.001
Diabetes	4214 (19.2)	1063 (28.7)	316 (29.9)	263 (34.7)	330 (40.7)	<0.001
Hypertension	12667 (55.8)	2487 (64.8)	819 (75.1)	624 (77.7)	687 (82.0)	<0.001
Atrial Fibrillation	1593 (7.1)	481 (12.9)	184 (17.4)	115 (14.9)	126 (15.6)	<0.001
Dyslipidemia	12618 (57.5)	2306 (62.5)	720 (67.2)	525 (68.7)	578 (71.9)	<0.001

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 or further from baseline interview. Recent stroke, distant stroke, TIA and stroke symptoms were all ascertained by self-report.

^a p values are for chi-squared test

Risk of future stroke following self-reported stroke, TIA or stroke symptoms in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.

Table 2

N	No report of stroke symptom, TIA or stroke	Stroke symptom	TIA	Distant stroke [†]	Recent stroke [†]	P (trend)
22795	456	3871	1096	807	846	
Number of adjudicated strokes	456	104	56	50	71	
Adjusts for age, race, and sex	ref	1.32 (1.07, 1.64)	2.15 (1.62, 2.84)	2.74 (2.05, 3.68)	3.72 (2.89, 4.78)	<0.001
Adjusts for above plus region, income and education	ref	1.26 (1.02, 1.57)	2.11 (1.59, 2.79)	2.61 (1.95, 3.51)	3.49 (2.71, 4.50)	<0.001
Adjusts for above plus comorbidities [‡]	ref	1.20 (0.96, 1.51)	1.73 (1.27, 2.36)	2.23 (1.61, 3.09)	2.85 (2.16, 3.76)	<0.001

[†] 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 or further 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, hypertension, history of coronary artery disease, atrial fibrillation, dyslipidemia, and the racial difference in retrieving medical records

Table 3

Risk of death following self-reported stroke, TIA or stroke symptoms in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.

	No report of stroke symptom, TIA or stroke	Stroke symptom	TIA	Distant stroke ^J	Recent stroke ^J	p (trend)
N	22795	3871	1096	807	846	
Number of deaths	1844	529	213	196	211	
Adjusts for age, race, and sex	ref	1.63 (1.47, 1.79)	2.01 (1.74, 02.32)	2.51 (2.16, 2.91)	2.47 (2.14, 2.85)	<0.001
Adjusts for above plus income and education	ref	1.45 (1.33, 1.60)	1.88 (1.63, 2.18)	2.07 (1.78, 2.42)	2.07 (1.78, 2.39)	<0.001
Adjusts for above plus comorbidities [‡]	ref	1.33 (1.19, 1.48)	1.58 (1.35, 1.85)	1.86 (1.58, 2.20)	1.79 (1.53, 2.09)	<0.001

^J 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 or further 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, hypertension, myocardial infarction, atrial fibrillation, and dyslipidemia