Original Investigation

Trajectory of Cognitive Decline After Incident Stroke

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IMPORTANCE Cognitive decline is a major cause of disability in stroke survivors. The magnitude of survivors' cognitive changes after stroke is uncertain.

OBJECTIVE To measure changes in cognitive function among survivors of incident stroke, controlling for their prestroke cognitive trajectories.

DESIGN, SETTING, AND PARTICIPANTS Prospective study of 23 572 participants 45 years or older without baseline cognitive impairment from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, residing in the continental United States, enrolled 2003-2007 and followed up through March 31, 2013. Over a median follow-up of 6.1 years (interquartile range, 5.0-7.1 years), 515 participants survived expert-adjudicated incident stroke and 23 057 remained stroke free.

EXPOSURE Time-dependent incident stroke.

MAIN OUTCOMES AND MEASURES The primary outcome was change in global cognition (Six-Item Screener [SIS], range, 0-6). Secondary outcomes were change in new learning (Consortium to Establish a Registry for Alzheimer Disease Word-List Learning; range, 0-30), verbal memory (Word-List Delayed Recall; range, 0-10), and executive function (Animal Fluency Test; range, ≥0), and cognitive impairment (SIS score <5 [impaired] vs ≥5 [unimpaired]). For all tests, higher scores indicate better performance.

RESULTS Stroke was associated with acute decline in global cognition (0.10 points [95% CI, 0.04 to 0.17]), new learning (1.80 points [95% CI, 0.73 to 2.86]), and verbal memory (0.60 points [95% CI, 0.13 to 1.07]). Participants with stroke, compared with those without stroke, demonstrated faster declines in global cognition (0.06 points per year faster [95% CI, 0.03 to 0.08]) and executive function (0.63 points per year faster [95% CI, 0.12 to 1.15]), but not in new learning and verbal memory, compared with prestroke slopes. Among survivors, the difference in risk of cognitive impairment acutely after stroke, compared with immediately before stroke, was not statistically significant (odds ratio, 1.32 [95% CI, 0.95 to 1.83]; $P = .10$); however, there was a significantly faster poststroke rate of incident cognitive impairment compared with the prestroke rate (odds ratio, 1.23 per year [95% CI, 1.10 to 1.38]; $P < .001$). For a 70-year-old black woman with average values for all covariates at baseline, stroke at year 3 was associated with greater incident cognitive impairment: absolute difference of 4.0% (95% CI, −1.2% to 9.2%) at year 3 and 12.4% (95% CI, 7.7% to 17.1%) at year 6.

CONCLUSIONS AND RELEVANCE Incident stroke was associated with an acute decline in cognitive function and also accelerated and persistent cognitive decline over 6 years.

Editorial page 29

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Each year, 795 000 US residents experience a stroke.[1] In 2010, almost 7 million adults were stroke survivors.[1] Over the last 2 decades, age-standardized years lived with disability rates increased by 40% for stroke—the only major disease to show a significant increase in this important disability measure.[2] Disability due to stroke is a major driver of health burden and costs for families, health care systems, and public programs such as Medicare and Medicaid.[2] Cognitive impairment after stroke is a major contributor to this disability,[3,4] and its prevalence has increased sharply in older adults.[5,6] Despite its enormous social and economic burden, poststroke cognitive impairment has been called a "neglected consequence of stroke."[7]

Although stroke is associated with acute cognitive decline,[3] it is unclear whether stroke survivors acquire a faster rate of cognitive decline over the years following the event (ie, slope) compared with the prestroke rate of cognitive decline, after accounting for the acute cognitive decline at the time of the event.[8] While cognitive decline over the years before stroke is common[9] and is associated with poststroke cognitive decline,[10] most studies of stroke cannot measure actual changes in the rate of cognitive decline associated with stroke because they lack measures of patients' prestroke cognitive changes or use proxy-reported measures.[10-14] Moreover, most studies of stroke have not measured both the acute decline in cognitive function at the time of the stroke and the change in the rate of cognitive decline over the years after stroke simultaneously.[15] One study[9] suggests that stroke causes an acute decline in cognitive function at the time of the event but does not cause faster cognitive decline over the years following the event.

We hypothesized that stroke causes an acute decline in cognitive function at the time of the event and also faster cognitive decline during the years following the event.

Methods

Study Design, Participants, and Measurements

The Reasons for Geographic and Racial Differencs in Stroke (REGARDS) study is a prospective cohort study of 30 239 non-Hispanic black and white individuals examining regional and racial influences on stroke mortality.[16] Details are described elsewhere.[16] Briefly, participants were enrolled between 2003 and 2007 using commercially available lists and a combination of mail and telephone contacts to recruit English-speaking, community-dwelling adults 45 years or older who were living in the continental United States. Race and sex were balanced by design, with oversampling of the Southeastern United States. Race was self-reported. Baseline data collection included computer-assisted telephone interviews gathering demographic information, medical history, and health status. In-home examinations by trained health care professionals following standardized, quality-controlled protocols collected blood and urine samples, electrocardiograms, blood pressure, height and weight measurements, and medication use by pill bottle review. Blood and urine samples were centrally analyzed at the University of Vermont.

Participants or their proxies were followed up every 6 months by telephone with retrieval of medical records for reported hospitalizations. For this study, we followed up participants through March 31, 2013. To control for prestroke cognition, we required all participants to have a baseline measurement of each outcome. We excluded participants with baseline cognitive impairment, defined as a Six-Item Screener (SIS) score less than 5. This cut point is a valid measure of cognitive impairment in community-dwelling black and white adults.[17] We required that participants with incident stroke have 1 or more cognitive measurement after stroke.

The study was approved by the institutional review boards of all participating institutions, and all participants provided written informed consent.

Cognitive Function Assessments

REGARDS technicians who underwent formal training and certification administered cognitive function tests longitudinally by telephone including: the SIS beginning in 2003 and measured annually and a battery of 3 cognitive tests measured biannually starting in 2006 that included the Consortium to Establish a Registry for Alzheimer Disease (CERAD) Word List Learning (WLL), Word List Delayed Recall (WLD), and Animal Fluency Test (AFT).[18,19] Research demonstrates that global cognition, word list, and verbal fluency can be measured reliably and precisely over the telephone in middle-aged and older adults, with scores virtually identical to those obtained in person.[20-22] These cognitive measures are consistent with the Vascular Cognitive Impairment Harmonization Standards[23] and have been validated for black and white individuals.[17,24,25]

The SIS assesses global cognitive function and can detect cognitive dysfunction in older patients experiencing acute medical illness.[26] The SIS consists of 3-item recall and 3-item temporal orientation (score range, 0-6).[17] The CERAD WLL measures new learning (score range, 0-30) and the WLD measures verbal memory (score range, 0-10). The AFT assesses executive function (complex cognitive processing used in problem-solving or complex action sequences), with scores representing number of animals generated in 1 minute. For all cognitive tests, higher scores indicate better performance. Cognitive data were provided only by self-respondents.

Measurement of Incident Stroke

Incident strokes were adjudicated by a team of experts who used published guidelines and reviewed medical records.[27,28] Stroke events were defined as "rapidly developing clinical signs of focal, at times global, disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin" (World Health Organization).[27,29] Events not meeting this definition but characterized by symptoms lasting less than 24 hours and with neuroimaging consistent with acute ischemia or hemorrhage were classified as "clinical strokes." For fatal strokes, the medical history, hospital records, interviews with next of kin or proxies, and death certificate or National Death Index data were reviewed to adjudicate the cause of death.[30] Strokes were further classified as ischemic or hemorrhagic. Cases were as-

signed to 2 physician adjudicators and disagreements were resolved by full committee review. To maintain high interrater reliability, an adjudicator underwent retraining if disagreement with other adjudicators was greater than 20% in ongoing review.[27]

Covariates

Covariates were factors that could influence stroke and cognition and were measured at baseline. Demographics were age, sex, race, education, marital status, income, urban/rural residence, and region of residence. Vascular risk factors were systolic blood pressure, diabetes status, hyperlipidemia, atrial fibrillation, waist circumference, body mass index, alcohol intake, cigarette smoking, and physical activity. Clinical risk factors were baseline cognitive score for each cognitive outcome, glomerular filtration rate,[31] history of stroke, history of myocardial infarction, self-reported health status, and depression symptoms.[32]

Statistical Analysis

The primary outcome was global cognition measured by the SIS; secondary outcomes were new learning as measured by the WLL, verbal memory as measured by the WLD, and executive function as measured by the AFT. Each outcome measure was treated as a continuous variable. Continuous variables may better detect average intraindividual change and heterogeneity in intraindividual change in cognitive function.[33] An additional secondary outcome was cognitive impairment as measured by SIS score (<5 [impaired] vs ≥5 [unimpaired])[17] and allowing a participant's status of cognitive impairment to vary over time. Incident stroke was treated as a time-dependent covariate that affects a participant's cognitive test performance in all years after the stroke.[15] The eFigure in the Supplement shows the conceptual model.

Descriptive characteristics were compared between participants who did and did not have an incident stroke during follow-up using 2-sample *t* test with equal variance or χ^2 tests as appropriate. The association of baseline covariates with cognitive function was assessed using linear mixed-effects models that adjusted for baseline cognitive score and years since baseline.

We fit linear mixed-effects models to measure changes in cognitive function over time after adjusting for participant factors including baseline cognitive score. The models included random effects for intercept and slope to accommodate correlation of cognitive measures within participants over time and to allow participant-specific rates of cognitive change.[34,35] We analyzed each dependent variable separately. Cognition was censored at the time of second incident stroke, death, loss to follow-up, or the end of follow-up. Time was expressed as the years from the date of the first measurement of the cognitive outcome. Generalized linear mixed-effects models for a binary outcome were used for estimating the odds of incident cognitive impairment (SIS score <5).

Model A included a time-varying incident stroke variable to estimate the effect of incident stroke on the acute decline in cognitive function at the time of the event (the value changes from 0 to 1 on the date of the incident stroke) because stroke is associated with an acute decline in cognitive function. The acute decline in cognitive function at the time of stroke was estimated based on the fitted model, which included the first set of routinely administered cognitive function tests after a stroke event as well as all other cognitive function tests administered before and after stroke.[9,36] For this study, the first cognitive assessment after stroke is considered the acute component or early/mid-stage recovery.

Model B included the variables from Model A and added a time after stroke covariate to estimate the effect of incident stroke on the decline in cognitive function over the years following the event. This variable indicates the rate of change in cognitive function (slope) after incident stroke. Models included demographics, vascular risk factors, and clinical factors. Age, sex, race, education, region, and baseline cognitive score were retained in all models regardless of statistical significance. Other variables that did not reach statistical significance (defined as $P < .05$) were removed from the final models; these were marital status, urban/rural residence, hyperlipidemia, atrial fibrillation, body mass index, physical activity, and diastolic blood pressure.

After selecting the final, parsimonious model, we calculated participant-specific (conditional) predicted values for each cognitive score and participant-specific predicted probabilities of incident cognitive impairment (SIS score <5) over time for a 70-year-old black woman with the average values of all covariates at baseline (high school education, stroke belt residence, income <$20 000, never smoker, no alcohol use, systolic blood pressure 135 mm Hg, diabetes present, waist circumference 95 cm, no self-reported stroke, 4-item Center for Epidemiologic Studies Depression Scale score of 0.9 points, fair health status, and SIS score of 5 points) conditional on her experiencing or not experiencing an incident stroke midway through the follow-up period (at year 3). For our exemplar individual, we chose covariate values that were representative for the stroke belt population because it had a higher risk of cognitive decline relative to the remaining population. Random effects for this prediction were set to zero.

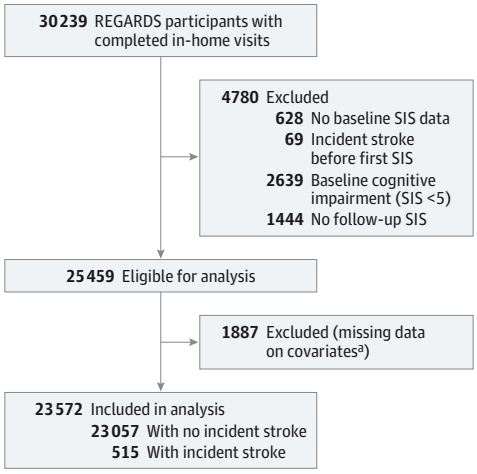
We included participants who self-reported a baseline history of stroke in the main analysis to allow comparison with a study[15] that included adults with a self-reported history of physician-diagnosed stroke at baseline. We repeated analyses excluding participants who reported a stroke history at baseline and using multiple imputation for missing baseline values of covariates (eMethods in the Supplement).[37]

Statistical significance for all analyses was set as $P < .05$ (2-sided). All analyses were performed using Stata version 13.1 (StataCorp).

Results

After excluding the 2639 individuals with baseline cognitive impairment, the 2072 with insufficient information on the primary outcome, the 1887 with missing covariate data, and the 69 with incident stroke before baseline outcome measurement, the study sample included 23 572 participants, 515

Figure 1. Participant Cohort, REGARDS Study, 2003-2013



REGARDS indicates Reasons for Geographic and Racial Differences in Stroke; SIS, Six-Item Screener test of global cognitive function.

[a] Categories for missing data for covariates are not mutually exclusive. Missing data for covariates included diabetes (n = 909), alcohol use (n = 459), 4-item Center for Epidemiologic Studies Depression Scale (n = 191), waist circumference (n = 184), smoking (n = 98), baseline history of self-reported stroke (n = 80), blood pressure (n = 74), health status (n = 43), and education (n = 15).

of whom experienced incident stroke (470 ischemic, 43 hemorrhagic, and 2 of undeterminable type) over a median follow-up of 6.1 years (interquartile range, 5.0-7.1 years) (**Figure 1**). There were 306 strokes in 14 632 white participants (2.1%) and 209 strokes in 8940 black participants (2.3%) (absolute difference, 0.2% [95% CI, 0.1% to 0.6%]; *P* = .2). Stroke incidence was stable over the duration of follow-up (eTable 1 in the Supplement). Excluded participants were more likely than included participants to be older, black, less educated, and current smokers and nondrinkers; excluded participants also were more likely to have lower incomes; diabetes; a history of stroke at baseline; fair or poor health status; higher baseline values of systolic blood pressure, waist circumference, and depressive symptoms; and lower baseline cognitive scores.

Table 1 presents baseline characteristics of study participants. Compared with participants who did not experience an incident stroke, those who did were more likely to be older, men, and current smokers and to have diabetes, less education, lower income, and worse health status. Adults who had incident stroke had higher baseline values of systolic blood pressure, waist circumference, and depressive symptom scores and more frequently reported a history of stroke at baseline than those who did not. Baseline prestroke SIS scores were slightly lower among those with than without incident stroke (5.7 vs 5.8 points; absolute difference, 0.04 points [95% CI, 0.002 to 0.08]; *P* = .04).

There were 61 deaths among the 515 individuals with incident stroke (11.8%) and 1812 deaths among the 23 056 without incident stroke (7.9%) (absolute difference, 4.0% [95% CI, 1.6% to 6.3%]; *P* = .001). Participants had undergone

Table 1. Baseline Characteristics Between Participants Who Did and Did Not Have an Incident Stroke During Follow-up: REGARDS Study, 2003-2013

Characteristic	Stroke, No. (%)		*P* Value
	No Incident (n = 23 057)	Incident (n = 515)	
Sociodemographics			
Age, mean (SD), y	64.2 (9.2)	68.3 (8.4)	<.001
Women	12 902 (56)	261 (51)	.02
Black race	8731 (38)	209 (41)	.21
Education			
<High school	2386 (10)	62 (12)	.01
High school graduate	5836 (25)	155 (30)	
Some college	6268 (27)	138 (27)	
≥College graduate	8567 (37)	160 (31)	
Region[a]			
Nonbelt	10 202 (44)	238 (46)	.43
Stroke buckle	4918 (21)	98 (19)	
Stroke belt	7937 (34)	179 (35)	
Urban/rural residence			
Mixed	2349 (10)	58 (11)	.70
Rural	2360 (10)	47 (9)	
Urban	16 154 (70)	359 (70)	
Missing	2194 (10)	51 (10)	
Income, $			
<20 000	3659 (16)	105 (20)	<.001
20 000-34 999	5441 (24)	147 (29)	
35 000-74 999	7243 (31)	152 (30)	
≥75 000	4043 (18)	47 (9)	
Refused to report/missing	2671 (12)	64 (12)	
Married	14 067 (61)	281 (55)	.003
Vascular Risk Factors			
Cigarette smoking			
Never	10 660 (46)	220 (43)	.02
Past	9229 (40)	203 (39)	
Current	3168 (14)	92 (18)	
Alcohol use[b]			
None	14 090 (61)	339 (66)	.09
Moderate	8019 (35)	158 (31)	
Heavy	948 (4)	18 (4)	
Physical activity			
None	8474 (37)	186 (37)	.40
1-3 d/wk	6781 (30)	139 (28)	
≥4 d/wk	7509 (33)	181 (36)	
Blood pressure, mm Hg, mean (SD)			
Systolic	126.9 (16.3)	133.3 (17.9)	<.001
Diastolic	76.4 (9.6)	77.0 (9.9)	.18
Diabetes	4658 (20)	160 (31)	<.001
Waist circumference, mean (SD), cm	95.9 (15.3)	97.5 (13.5)	.02
Body mass index[c]			
<18.5	204 (1)	3 (1)	.18
18.5-24.9	5419 (24)	116 (23)	
25-29.9	8509 (37)	214 (42)	
≥30	8828 (38)	181 (35)	
Hyperlipidemia	13 297 (59)	339 (67)	<.001
Atrial fibrillation	1835 (8)	61 (12)	.001

(continued)

Table 1. Baseline Characteristics Between Participants Who Did and Did Not Have an Incident Stroke During Follow-up: REGARDS Study, 2003-2013 (continued)

Characteristic	Stroke, No. (%)		*P* Value
	No Incident (n = 23 057)	Incident (n = 515)	
Clinical Factors			
Self-reported stroke before enrollment	1172 (5)	76 (15)	<.001
4-Item CES-D score, mean (SD)[d]	1.06 (2.0)	1.30 (2.2)	.006
Percentile			
25	0	0	
50	0	0	
75	1	2	
Self-reported health status			
Excellent	3893 (17)	61 (12)	<.001
Very good	7380 (32)	134 (26)	
Good	7987 (35)	199 (39)	
Fair	3153 (14)	95 (18)	
Poor	644 (3)	26 (5)	
Glomerular filtration rate, mean (SD), mL/min/1.73 m^2	85.7 (19.4)	80.4 (21.5)	<.001
History of MI	2626 (12)	108 (22)	<.001
Baseline cognitive scores, mean (SD)[e]			
Six-Item Screener	5.8 (0.4)	5.7 (0.4)	.04
Word List Learning	17.9 (4.9)	16.0 (4.8)	<.001
Word List Delayed Recall	6.7(2.0)	5.8 (2.0)	<.001
Animal Fluency Test	17.6 (5.8)	15.9 (4.8)	.002

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; MI, myocardial infarction; REGARDS, Reasons for Geographic and Racial Differences in Stroke.

[a] REGARDS oversampled residents of the stroke belt (defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina, and Georgia) and the stroke buckle (defined as the coastal regions within the states of North Carolina, South Carolina, and Georgia).

[b] Alcohol use was defined as heavy (≥7 drinks per week for women and ≥14 drinks per week for men), moderate (0-7 drinks per week for women and 0-14 drinks per week for men), and none (0 drinks per week).

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Measures depressive symptoms on a scale from 0 to 12. Higher scores indicate greater depressive symptoms.

[e] Six-Item Screener scores range from 0 to 6. Word List Learning scores range from 0 to 30. Word List Delayed Recall scores range from 0 to 10. Animal Fluency Test scores can be 0 or greater. For all cognitive tests, higher scores indicate better performance.

a mean of 3.0 (SD, 1.8) SIS tests and 1.4 (SD, 0.6) 3-test batteries before stroke. Stroke survivors had undergone a mean of 2.8 (SD, 1.8) SIS tests and 1.3 (SD, 0.5) 3-test batteries after stroke and a median follow-up of 2.5 years (interquartile range, 1.2 to 4.2 years). eTable 2 in the Supplement presents the time from incident stroke to the first poststroke measurement of each cognitive test.

Because the secondary outcome measures were introduced during follow-up and performed less frequently, the WLL analysis included 10 321 participants, 107 of whom had incident stroke; the WLD analysis included 10 053 participants, 102 of whom had incident stroke; and the AFT analysis included 11 214 participants, 120 of whom had incident stroke. eTable 3 in the Supplement presents the scores for each cognitive test at the end of follow-up by incident stroke status.

Change in Global Cognition After Stroke

Incident stroke was associated with a significant decline in global cognition acutely after stroke and also faster decline in global cognition over the years following the event. **Table 2** and **Figure 2** show that there was a slight increase in global cognition over time before stroke. Stroke survivors experienced an acute decline in global cognition after stroke (adjusted decline in SIS score, 0.10 points [95% CI, 0.04 to 0.17]; $P = .001$). In the years following stroke, global cognition declined significantly faster than it did before the stroke (decrease in slope after incident stroke, 0.06 points per year [95% CI, 0.03 to 0.08]; $P < .001$), resulting in a net negative slope after stroke (prestroke slope: 0.021; poststroke slope: −0.035). eTable 4 in the Supplement presents the unadjusted model.

We also assessed SIS as a binary outcome. Among survivors, the difference in risk of cognitive impairment acutely after stroke, compared with immediately before stroke, was not statistically significant (odds ratio, 1.32 [95% CI, 0.95 to 1.83]); however, there was a significantly faster rate of incident cognitive impairment after stroke compared with the prestroke rate (odds ratio, 1.23 per year [95% CI, 1.10 to 1.38]). For the exemplar individual, a 70-year-old black woman with average values of all covariates at baseline, stroke at year 3 was associated with a greater predicted probability of incident cognitive impairment compared with no stroke at year 3 (19.8% vs 15.7%; absolute difference, 4.0% [95% CI, −1.2% to 9.2%]; $P < .10$) and at year 6 (23.5% vs 11.1%; absolute difference, 12.4% [95% CI, 7.7% to 17.1%]; $P < .001$). At the end of follow-up, the frequency of incident cognitive impairment (noncumulative) was greater in stroke survivors than those without stroke (19.2% vs 8.7%; $P < .001$) (absolute difference, 10.6% [95% CI, 8.1% to 13.0%]; $P < .001$).

Changes in New Learning and Verbal Memory After Stroke

Table 3 and Figure 2 show that incident stroke was associated with significant acute declines in new learning and verbal memory after the event (WLL, 1.80 points [95% CI, 0.73 to 2.86]; $P = .001$; WLD, 0.60 points [95% CI, 0.13 to 1.07]; $P = .01$). New learning and verbal memory scores increased slightly over time before stroke but less so in black participants ($P = .01$ for WLL and $P = .02$ for WLD for race × time interaction term). We did not detect significant changes in the slopes of new learning or verbal memory after incident stroke compared with prestroke slopes ($P = .91$ for WLL and $P = .70$ for WLD for change in slope after incident stroke).

Changes in Executive Function After Stroke

Executive function declined significantly over time before stroke (0.31 points per year [95% CI, 0.27 to 0.35]; $P < .001$) (Table 3). Stroke was associated with an acute decline in executive function (0.90 points [95% CI, 0.23 to 1.57]; $P = .009$) in Model A but not in Model B (Table 3). In the

Table 2. Adjusted Changes in Global Cognitive Function Over Time Among All Participants: REGARDS Study, 2003 to 2013[a]

	SIS Score[b] (n = 23 572)				Incident Cognitive Impairment SIS <5 (n = 23 572)			
	Model A		Model B[c]		Model A		Model B[c]	
Variable	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
No. of incident strokes	515		515		515		515	
Baseline cognitive score per 1-point increase	0.18 (0.16 to 0 .19)	<.001	0.18 (0.16 to 0.19)	<.001	0.53 (0.49 to 0.57)	<.001	0.53 (0.49 to 0.57)	<.001
Baseline slope without incident stroke, per y	0.02 (0.02 to 0.02)	<.001	0.02 (0.02 to 0.02)	<.001	0.88 (0.86 to 0.90)	<.001	0.88 (0.85 to 0.90)	<.001
Acute change after incident stroke vs before stroke	−0.21 (−0.25 to −0.16)	<.001	−0.10 (−0.17 to −0.04)	.001	1.98 (1.58 to 2.48)	<.001	1.32 (0.95 to 1.83)	.10
Change in slope after incident stroke, per y	Not included		−0.06 (−0.08 to −0.03)	<.001	Not included		1.23 (1.10 to 1.38)	<.001
Age, per y	−0.02 (−0.02 to −0.01)	<.001	−0.02 (−0.02 to −0.01)	<.001	1.07 (1.07 to 1.08)	<.001	1.07 (1.07 to 1.08)	<.001
Intercept	5.3 (5.16 to 5.41)	<.001	5.28 (5.15 to 5.40)	<.001	NA		NA	
Log likelihood	−113 758.2		−11 3747.1		−25 151.4		−25 146.2	

Abbreviations: OR, odds ratio; REGARDS, Reasons for Geographic and Racial Differences in Stroke; SIS, Six-Item Screener.

[a] Interpretative example for the SIS score as a continuous measure: An average participant had been gaining 0.02 points per year on the SIS of global cognition (95% CI, 0.02 to 0.02; *P* < .001) before having a stroke. An average stroke survivor's SIS score decreased 0.10 points at the time of the stroke (95% CI, 0.04 to 0.17; *P* = .001). During the years following stroke, survivors experienced a significant annual decrease in SIS scores. The average stroke survivor's SIS score decreased 0.06 points per year compared with the baseline (prestroke) slope (95% CI, 0.03 to 0.08; *P* < .001). Interpretative example for incident cognitive impairment as a binary measure (SIS <5 [impaired] vs ≥5 [unimpaired]): The odds ratio is the odds of developing cognitive impairment compared with the odds of not developing cognitive impairment. Before stroke, participants experienced a significant annual decrease in the odds of developing cognitive impairment. The odds of participants developing cognitive impairment in a given prestroke year were 0.88 times lower than the odds of developing cognitive impairment during the previous year (OR, 0.88 per year [95% CI, 0.85 to 0.90]; *P* < .001). The risk of cognitive impairment acutely after stroke was not significantly different than the risk of cognitive impairment before stroke. The odds of developing cognitive impairment acutely after stroke were a nonsignificant 1.32 times greater than the odds of developing cognitive impairment immediately before stroke (OR, 1.32 [95% CI, 0.95 to 1.83]; *P* = .10). However, stroke survivors experienced a significant annual increase in odds of developing cognitive impairment, representing a significantly faster rate of incident cognitive impairment after stroke compared with the prestroke rate (OR, 1.23 per year [95% CI, 1.10 to 1.38]; *P* < .001), controlling for the odds of developing cognitive impairment before or acutely after the event. The odds of survivors developing cognitive impairment in a given poststroke year were 1.23 times greater than the odds of developing cognitive impairment during the previous year.

[b] The SIS measures global cognition (range, 0-6). Higher scores indicate better performance. The screener was analyzed as a continuous measure and as a binary measure of incident cognitive impairment (<5 [impaired] vs ≥5 [unimpaired]). Linear mixed-effects models included a random intercept, calendar time, and adjustment for time-varying incident stroke, time since incident stroke, and baseline values of cognitive scores, age, sex, race, education, region, systolic blood pressure, cigarette smoking, waist circumference, diabetes, self-reported stroke, depressive symptoms, income, alcohol use, self-reported health status, and a random effect for slope.

[c] Generalized linear mixed-effects models for a binary outcome were used for estimating the odds of incident cognitive impairment.

years following an incident stroke, executive function declined significantly faster than it did before the stroke (change in slope after incident stroke, 0.63 points per year [95% CI, 0.12 to 1.15]; *P* = 0.02) (Figure 2) (prestroke slope, −0.312; poststroke slope, −0.944).

Sensitivity Analyses

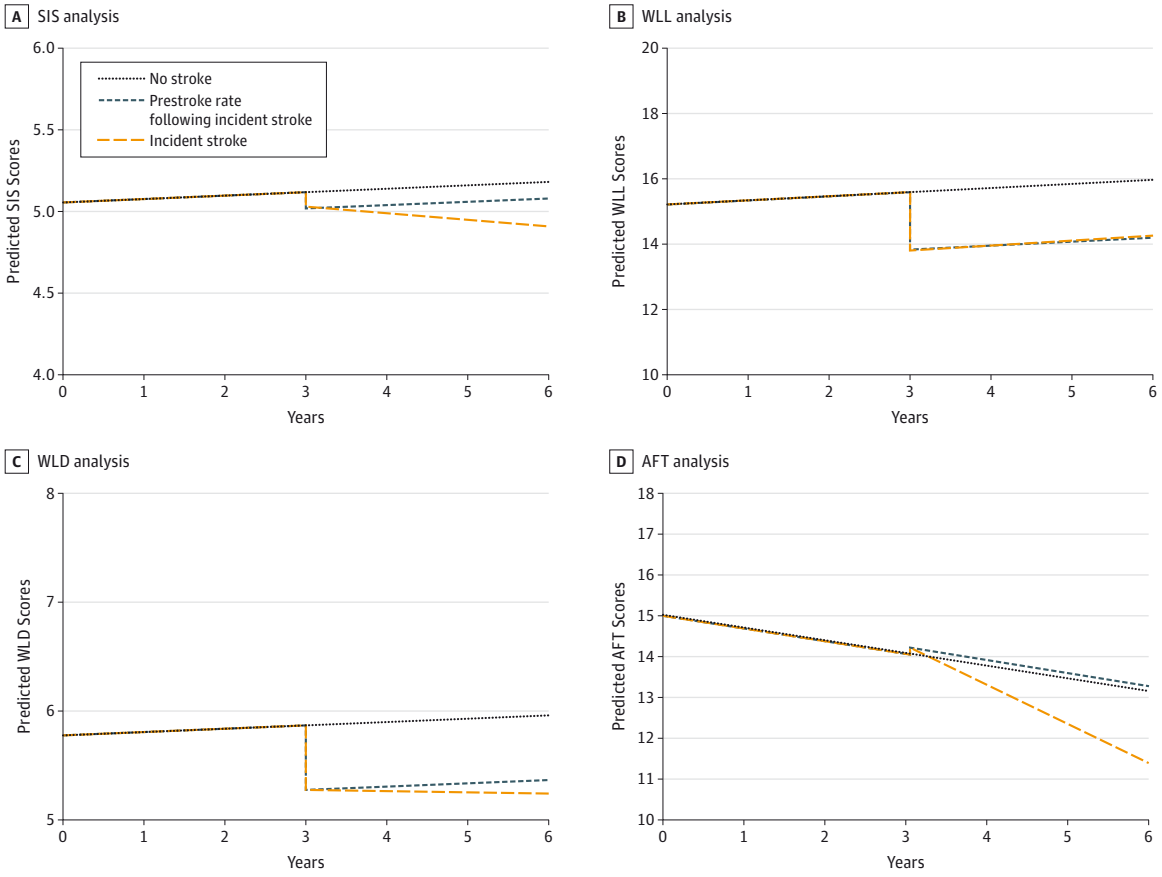
Results were similar in analyses excluding individuals with baseline history of stroke, imputing missing values of baseline covariates, adjusting for baseline renal function and history of myocardial infarction, and adjusting for death (eTables 5-8 in the Supplement). Cognitive changes after stroke persisted if participants were required to have 2 or more follow-up cognitive measures, but some changes in secondary outcomes were no longer statistically significant (eTable 9 in the Supplement). In analyses including stroke type, results for ischemic stroke were similar; results for hemorrhagic stroke were consistent, although some were no longer statistically significant (eTable 10 in the Supplement).

Discussion

In this national cohort of black and white US residents 45 years or older, incident stroke was associated with accelerated and persistent declines in global cognition and executive function, after accounting for individuals' cognitive changes before and acutely after the event. Stroke survivors had a significantly faster rate of incident cognitive impairment after stroke compared with the prestroke rate (odds ratio, 1.23 per year [95% CI, 1.10 to 1.38]; *P* < .001), controlling for the odds of developing cognitive impairment before or acutely after the event. We found significant, acute declines in new learning and verbal memory after stroke but no acceleration of prestroke rates of change in these functions.

Our data suggest that cognitive function declines both acutely and over the long term after incident stroke. Several studies[9,13,14] have suggested that cognitive decline does not accelerate after stroke, unless a recurrent stroke occurs. Our re-

Figure 2. Predicted Mean Change in Cognitive Function Test Scores Before and After Acute Stroke at Year 3: REGARDS Study, 2003-2013



Participant-specific (conditional) predicted values of cognition were calculated for a 70-year-old black woman with the average values of all covariates at baseline (high school education, stroke belt residence, income <$20 000, never smoker, no alcohol use, systolic blood pressure 135 mm Hg, diabetes present, waist circumference 95 cm, no self-reported stroke, Center for Epidemiologic Studies Depression Scale score of 0.9 points, fair health status, and Six-Item Screener [SIS] score of 5 points). Random effects for this prediction were set to zero. Linear mixed-effects models included a random intercept, random slope, and calendar time and adjust for time-varying incident stroke, time since incident stroke, and baseline values of cognitive scores, age, sex, race, race × time (Word List Learning [WLL] and Word List Delayed Recall [WLD] only), education, region, systolic blood pressure, cigarette smoking, waist circumference, diabetes, self-reported stroke, depressive symptoms, income, alcohol use, and self-reported health status. Black dotted line indicates the trajectory for stroke-free adults; orange dashed line, the trajectory for adults with incident stroke; blue dashed line, the prestroke rate of cognitive decline attributable to cognitive aging. A, The SIS analysis included 515 participants with incident stroke and 23 057 participants without incident stroke during follow-up. The prestroke slope was 0.02 points per year ($P < .001$); the acute decline after stroke was 0.01 points ($P = .001$). B, The WLL analysis included 107 participants with incident stroke and 10 214 participants without incident stroke during follow-up. The prestroke slope was 0.22 points per year ($P < .001$); the acute decline after stroke was 1.80 points ($P = .001$); there was no change in slope after stroke ($P = .91$). C, The WLD analysis included 102 participants with incident stroke and 9951 participants without incident stroke during follow-up. The prestroke slope was 0.08 points per year ($P < .001$); the acute decline after stroke was 0.60 points ($P = .01$); there was no change in slope after stroke ($P = .70$). D, The Animal Fluency Test (AFT) analysis included 120 participants with incident stroke and 11 093 participants without incident stroke during follow-up. The prestroke slope was −0.31 points per year ($P < .001$); there was no acute decline after stroke (the small increase in AFT scores at the time of stroke was not significant [$P = .78$]); the change in slope after stroke was −0.63 points per year ($P = .02$).

sults may differ because we had actual patient measures of prestroke cognition (not proxy-reported measures[13,14]), used expert-adjudicated strokes and dates (not self-report[9]), and used different cognitive measures.

The acute declines in global cognition, new learning, and verbal memory associated with stroke are likely clinically meaningful. A decline of 0.5 or more standard deviations from baseline has been defined as clinically meaningful decline,[38] has been correlated with clinically meaningful decline in global cognition in a cohort of cognitively normal adults 50 years or older,[39] and, for the CERAD battery, has been correlated with other established measures of cognitive decline in older adults with dementia.[40] A 0.5-SD decrease from the baseline score for each outcome is approximately 0.2 points for the SIS, 2.4 points for the WLL, 1.0 points for the WLD, and 2.4 points for the AFT. The 95% confidence intervals for the acute cognitive declines in global cognition, new learning, and verbal memory after stroke include declines of this magnitude. Acute cognitive decline after stroke increases survivors' risk of mortality,[41] disability,[3,4] and dependent living[3,4] and decreases their quality of life.[42] The long-term declines in global cognition and executive function parallel the long-term functional decline seen

Table 3. Adjusted Changes in New Learning, Verbal Memory, and Executive Function Over Time Among All Participants: REGARDS Study, 2003 to 2013

	Word List Learning Score (n = 10 321)[a]				Word List Delayed Recall Score (n = 10 053)[a]				Animal Fluency Test Score (n = 11 214)[a]			
	Model A		Model B[b]		Model A		Model B[b]		Model A		Model B[b]	
Variable	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
No. of incident strokes	107		107		102		102		120		120	
Baseline cognitive score per 1-unit increase	0.41 (0.39 to 0.43)	<.001	0.41 (0.39 to 0.43)	<.001	0.34 (0.33 to 0.36)	<.001	0.34 (0.33 to 0.36)	<.001	0.54 (0.52 to 0.55)	<.001	0.54 (0.52 to 0.55)	<.001
Baseline slope without incident stroke, per y	0.22 (0.17 to 0.28)	<.001	0.22 (0.17 to 0.28)	<.001	0.08 (0.06 to 0.10)	<.001	0.08 (0.06 to 0.10)	<.001	−0.31 (−0.35 to −0.27)	<.001	−0.31 (−0.35 to −0.27)	<.001
Acute change after incident stroke vs before stroke	−1.75 (−2.45 to −1.05)	<.001	−1.80 (−2.86 to −0.73)	.001	−0.67 (−0.97 to −0.37)	<.001	−0.60 (−1.07 to −0.13)	.012	−0.90 (−1.57 to −0.23)	.009	0.15 (−0.94 to 1.24)	.78
Change in slope after incident stroke, per y	Not included		0.03 (−0.45 to 0.51)	.91	Not included		−0.04 (−0.25 to 0.17)	.70	Not included		−0.63 (−1.15 to −0.12)	.017
Age, per y	−0.14 (−0.15 to −0.13)	<.001	−0.14 (−0.15 to −0.13)	<.001	−0.06 (−0.06 to −0.06)	<.001	−0.06 (−0.06 to −0.06)	<.001	−0.12 (−0.13 to −0.11)	<.001	−0.12 (−0.13 to −0.11)	<.001
Intercept	18.17 (17.06 to 19.28)	<.001	18.17 (17.06 to 19.29)	<.001	7.91 (7.45 to 8.38)	<.001	7.91 (7.45 to 8.38)	<.001	16.58 (15.52 to 17.65)	<.001	16.57 (15.50 to 17.63)	<.001
Log likelihood	−41 683.4		−41 683.3		−27 920.2		−27 920.1		−44 213.4		−44 210.5	

Abbreviation: REGARDS, Reasons for Geographic and Racial Differences in Stroke.

[a] The Consortium to Establish a Registry for Alzheimer Disease Word List Learning assesses new learning (range, 0-30); the Word List Delayed Recall assesses verbal memory (range, 0-10); and the Animal Fluency Test assesses executive function with scores representing number of animals generated in 1 minute. For all cognitive tests, higher scores indicate better performance.

[b] Linear mixed-effects models (Model B) included a random intercept, calendar time, and adjust for time-varying incident stroke, time since incident stroke, and baseline values of cognitive scores, age, sex, race, race × time (for Word List Learning and Word List Delayed Recall only), education, region, systolic blood pressure, cigarette smoking, waist circumference, diabetes, self-reported stroke, depressive symptoms, income, alcohol use, and self-reported health status. Interpretative example: An average participant gained 0.22 points per year on the Word List Learning test of new learning (95% CI, 0.17 to 0.28; $P < .001$) before having a stroke. An average stroke survivor's Word List Learning score decreased 1.80 points at the time of the stroke (95% CI, 0.73 to 2.86; $P = .001$). During the years following stroke, survivors experienced no significant annual change in Word List Learning scores (point estimate, 0.03 points [95% CI, −0.45 to 0.51]; $P = .91$) compared with the baseline (prestroke) slope.

in stroke survivors.[43] Moreover, declines in global cognition and executive function significantly increase the risk of mortality,[44] dementia,[17,45] depression,[46] and accelerated functional decline,[47,48] which in turn is associated with institutionalization and caregiver burden.

Incident stroke or its risk factors may cause long-term cognitive decline through several mechanisms. Stroke may induce or exacerbate neurodegenerative disease,[49,50] or neurodegenerative disease may amplify brain injury and cognitive deficits after stroke.[51] Vascular risk factors[52] or an immune response[53] may cause ongoing cerebrovascular injury, inflammation, and oxidative stress. Moreover, stroke survivors may experience incident comorbidity (eg, cardiac disease).[54] It is unlikely that clinically apparent recurrent strokes or baseline atrial fibrillation explain the long-term cognitive declines that we observed, because we censored cognitive information for participants at the time of recurrent stroke and adjusting for atrial fibrillation did not change our results. Still, stroke survivors may have had subclinical infarcts after their index stroke that contributed to subsequent cognitive decline.[55] We did not have brain imaging data subsequent to the incident stroke. Our findings suggest a scientific need to determine whether the acute and also accelerated long-term cognitive decline are the result of incomplete rehabilitation from the initial stroke, subsequent vascular injury attributable to uncontrolled risk factors,[56] behavioral changes, or other mechanisms.

Our study has several strengths. We had longitudinal cognitive assessments in a cohort and stroke subset of sufficient size to estimate before and after differences (and the acute change) in cognitive decline. Incident strokes were expert-adjudicated based on medical record review. REGARDS systematically measured cognitive domains commonly affected by stroke: global cognition, learning, memory, and executive function.[3,57] We accounted for prestroke cognitive decline and acute cognitive declines after stroke to disentangle the association between stroke and longitudinal cognitive decline.

Our study has limitations. Results are generalizable only to community-dwelling stroke survivors not requiring a proxy respondent (eg, without aphasia). Although excluded participants had higher prevalence of stroke and dementia risk factors than included participants, these differences would reduce the ability to detect the cognitive effects of stroke. We were unable to control for stroke features (location, laterality, severity[13]), acute stroke treatments, or heart failure because these data were unavailable. Selective attrition may lead to underestimation of cognitive decline because participants with worse cognition at baseline or after stroke die, drop out, or require a proxy.[58] Analyses that accounted for loss to follow-up or death did not change our results, consistent with research from Salthouse.[59]

Fewer incident strokes and cognitive observations potentially limited statistical power to detect changes in the secondary outcomes (eg, verbal memory[14,15]). The linear mixed-effects models perform well for sparse data with small numbers of repeated measures; still, the results of the secondary outcomes may require confirmatory analysis with more observations of cognition and incident stroke. Although stroke may exacerbate depression, we did not adjust for time-dependent depressive symptom scores because depressive symptoms are often comorbid with cognitive decline and therefore on the causal pathway. The slight increases in global cognition, new learning, and verbal memory over time before stroke may be attributable to practice effects.[39,60] We did not have data on functional impairments or incident dementia. The approach taken to defining clinically meaningful changes, by using a threshold of change exceeding 0.5 or greater SD, is a common approach, but it does not provide a clear intuition of actual clinical impact, and a clinically meaningful change may vary by an individual's age, education, sex, and baseline cognition.[60] Measurement of poststroke cognition during the early to mid-stage recovery phase may lead to underestimation of acute cognitive decline.

Our study has potential implications for clinical practice, research, and health care policy. Although clinical practice guidelines and quality improvement programs recommend cognitive assessments be performed for patients with stroke before hospital discharge and also in the postacute settings,[61,62] our results suggest that stroke survivors also warrant monitoring for mounting cognitive impairment over the years after the event. Moreover, our results suggest that long-term cognitive dysfunction is a potential domain for evaluating acute stroke therapies. As adults increasingly survive stroke,[63] cases of poststroke cognitive impairment will multiply.[5] Given that poststroke cognitive impairment increases mortality, morbidity, and health care costs,[64] health systems and payers will need to develop cost-effective systems of care that will best manage the long-term needs and cognitive problems of this increasing and vulnerable stroke survivor population.

Conclusions

Incident stroke was associated with acute decline in cognitive function and also accelerated and persistent cognitive decline over 6 years.

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