JAMA Neurology | Original Investigation

Cognitive Decline After First-Time Transient Ischemic Attack

Victor A. Del Bene, PhD; George Howard, DrPH; Toby I. Gropen, MD; Michael J. Lyerly, MD; Virginia J. Howard, PhD; Russell P. Sawyer, MD; Ronald M. Lazar, PhD

IMPORTANCE Prior research suggests reduced cognitive function after transient ischemic attack (TIA). Whether this is directly related to the TIA, a function of preexisting risk factors, or prior cognitive decline remains unclear.

OBJECTIVE To study if a single, diffusion-weighted image–negative, adjudicated TIA is associated with longitudinal declines in cognition, independent of preexisting risk factors.

DESIGN, SETTING, AND PARTICIPANTS This was a secondary data analysis from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a population-based cohort following up 30 239 Black and White participants for incident cerebrovascular events. The setting consisted of telephone cognitive assessments. Participants were individuals with first-time TIA, first-time stroke, and asymptomatic community control groups with neuroimaging used for adjudication.

EXPOSURES First-time TIA and stroke.

MAIN OUTCOMES AND MEASURES Verbal fluency and memory measures administered biannually. Primary outcome was a composite standardized *z* score, with secondary outcomes individual test performances. Adjusted segmented regression models characterized pre-event and postevent cognition and annual cognitive change.

RESULTS Included in the study were 356 individuals with first-time TIA (mean [SD] age, 66.6 [8.7]; 188 female [53%]) and 965 individuals with first-time stroke (mean [SD] age, 66.8 [8.2]; 494 male [51%]). A total of 14 882 individuals (mean [SD] age, 63.2 [8.6] years; 8439 female [57%]) were included in the asymptomatic control group. Overall cognitive composite before index event was lower in the stroke (−0.25; 95% CI, −0.32 to −0.17) than TIA (−0.05; 95% CI: −0.17 to 0.07; $P = .005$) and asymptomatic (0; 95% CI, −0.03 to 0.03; $P < .001$) groups. After the index event, the cognitive composite of the group with stroke significantly declined (−0.14; 95% CI, −0.21 to −0.07) compared with that of the group with TIA (0.01; 95% CI, −0.10 to 0.12; $P = .02$) and controls (−0.03; 95% CI, −0.05 to −0.01; $P = .003$). The annual decline after the index event was faster ($P = .001$) in the group with TIA (−0.05; 95% CI, −0.06 to −0.03) than that for asymptomatic controls (−0.02; 95% CI, −0.02 to −0.02) but not different from the group with stroke (−0.04; 95% CI, −0.05 to −0.03; $P = .43$).

CONCLUSIONS AND RELEVANCE Results of this cohort study suggest that despite the quick resolution of stroke symptoms in TIA, there was apparently sufficient impact to be associated with long-term cognitive decline. Whether the underlying mechanisms are by direct or secondary injury and/or interaction with concomitant neurodegenerative factors remains to be elucidated.

JAMA Neurol. doi:10.1001/jamaneurol.2024.5082
Published online February 10, 2025.

Editorial
Supplemental content

Author Affiliations: Department of Neurology, The University of Alabama at Birmingham Heersink School of Medicine, Birmingham (Del Bene, Gropen, Lyerly, Lazar); The Evelyn F. McKnight Brain Institute, The University of Alabama at Birmingham Heersink School of Medicine, Birmingham (Del Bene, Lazar); Department of Biostatistics, School of Public Health, The University of Alabama at Birmingham, Birmingham (G. Howard); Department of Epidemiology, School of Public Health, The University of Alabama at Birmingham, Birmingham (V. J. Howard); Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, Ohio (Sawyer).

Corresponding Author: Victor A Del Bene, PhD, Department of Neurology, The University of Alabama at Birmingham Heersink School of Medicine, EFH 500C, 1720 2nd Ave South, Birmingham, AL 35233 (victordelbene@uabmc.edu).

Transient ischemic attack (TIA) is an acute ischemic event in the brain that typically resolves within 2 to 15 minutes, with negative diffusion-weighted imaging (DWI). TIA typically exists on the milder end of the cerebrovascular continuum, increasing risk for future stroke, disability, morbidity, and mortality.[1] Stroke increases the risk of cognitive decline and dementia[2-4]; however, compared with stroke, the relationship between TIA and vascular cognitive impairment is less well understood.[5]

Data from the Oxford Vascular Study showed that TIA increases the risk of postevent dementia over 5 years, but approximately 5% had dementia before their TIA.[3] Also, cardiovascular risk is often elevated in people with TIA,[6] and these risk factors (ie, diabetes, hypertension, atrial fibrillation) are associated with increased risk of dementia and cognitive decline.[7,8] Whether TIA is associated with cognitive decline independently of risk factors remains unknown.

It is reasonable to suppose that if TIAs are associated with long-term changes in cognition, there should be persistent injury despite the absence of radiological evidence of an ischemic lesion. We found that administration of the γ-aminobutyric acid (GABA)-A agonist midazolam in patients after stroke was associated with recrudescence of former stroke symptoms.[9,10] Similarly, we showed that midazolam given to neurologically normal patients 24 to 72 hours after a DWI-negative TIA also experienced reemergence of their TIA deficits.[11] The persistent clinical effects of a possible injury related to a first-time TIA, however, remained to be demonstrated.

To address these questions, we probed the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, which is a population-based cohort of Black and White participants recruited from the 48 contiguous US states who are followed up for cerebrovascular events and periodically administered a telephone-based cognitive test battery.[12-14] A major advantage of studying this cohort is that we could identify a subgroup who were stroke and TIA free and had undergone cognitive testing, then determine the long-term cognitive trajectory after a first-time ischemic event. We hypothesized that after controlling for risk factors of cognitive decline, no baseline difference would be observed in the groups with TIA or stroke compared with an asymptomatic community control group. The index event will then be associated with long-term cognitive decline in both clinical groups, with those with stroke having a steeper rate of decline relative to those with TIA, and the group with TIA showing steeper cognitive decline than the asymptomatic control group.

Key Points

Question When controlling for vascular and demographic factors, does transient ischemic attack confer an independent risk for cognitive decline?

Findings In this longitudinal cohort study (Reasons for Geographic and Racial Differences in Stroke [REGARDS]), pre-event and postevent cognitive trajectories were compared in 356 individuals with TIA, 965 individuals with stroke, and 14 882 asymptomatic controls. A single, diffusion-weighted image–negative, adjudicated TIA was a risk factor for cognitive decline, independent of vascular and demographic risk factors, with an estimated annual decline similar to a single ischemic stroke.

Meaning TIA-associated cognitive decline suggests a need to reevaluate post-TIA management and to screen regularly for cognitive change.

Methods

Between 2003 and 2007, the REGARDS study enrolled 30 239, English-speaking, non-Hispanic Black and White community-dwelling adults, 45 years and older, living in the US. The primary purpose of the REGARDS study is to examine geographical and race relationships with risk factors and stroke incidence, prioritizing the oversampling of people living in the southeastern US and Black participants.[12] The REGARDS study was restricted to only non-Hispanic Black and White participants to (1) give the most precise estimates of risk in the Black population, (2) provide a more homogeneous comparison group of White participants, and (3) avoid the confounding of race and ethnicity with geography for Asian, Hispanic, and Indigenous populations, who were disproportionately in a relatively small subset of states at the time of the study design. Hence, this secondary data analysis of the REGARDS study only includes non-Hispanic Black and White participants. A computer-assisted telephone interview (CATI) was used to collect baseline demographic and medical data, and to administer the cognitive test battery. A standardized in-home examination collected biosamples (blood, urine), electrocardiogram (ECG), blood pressure, height, weight, and medications. Six-month follow-up visits are completed by CATI for surveillance of potential cerebrovascular events. Medical records for all suspected events are adjudicated by a committee of stroke experts.[13] The REGARDS study and this secondary analysis were approved by the institutional review boards of all participating institutions. Written informed consent was obtained for all participants. This secondary analysis of the REGARDS study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Cognitive Assessments

Starting in 2006, the REGARDS study cognitive battery was first administered. The battery includes the Consortium to Establish a Registry for Alzheimer Disease (CERAD)[15] Word List Learning as a measure of verbal learning and Word List Delayed Recall as an index of verbal recall memory. Processing speed and executive function were assessed by rapid word-list generation for words beginning with the letter *F* and for the names of animals.[16] The telephone administration of these auditory-verbal tests is reliable and consistent with traditional in-person assessments.[17]

Our primary outcome was a standardized (*z* score) mean of the 4 tests (composite cognitive outcome). Secondary outcomes were individual test performances. Before 2008, the 4 cognitive tests were not performed at the same telephone

contact; however, subsequently they were assessed at the same telephone contact at a 2-year interval. Because enrollment and data collection were staggered, the times for cognitive assessments are also distributed serially over time. Because our primary outcome was the mean of the 4 measures, we only used cognitive assessments beginning in 2008. In some cases, all 4 tests could not be administered, and when this occurred, the mean of the available instruments was used as the outcome. For the standardization process for each test, the mean and SD was calculated for 40 strata defined by age (10-year age strata: 45-54, 55-64, 65-74, 75-84, and ≥85 years), education (<high school, high school graduate, some college, and ≥college graduate), and race (Black or White). Performance for each cognitive test was standardized by subtracting the test mean from the mean of the asymptomatic community control group and dividing by the SD of the control group, yielding a *z* score. The composite *z* score was the mean of *z* scores of the 4 tests. The composite score was restandardized to have a mean of 0 and SD of 1 to allow the interpretation of the mean level differences of cognitive performance and annual change in terms of SDs.

Participants

We excluded any participant with a known or suspected history of stroke or TIA at enrollment. Participants were followed up for incident cerebrovascular events. Adjudicated events defined 3 subgroups: (1) incident TIA, (2) incident stroke, and (3) those without a confirmed adjudicated TIA/stroke, termed the *asymptomatic community control* group. For the clinical groups, we further restricted incident stroke and TIA cases to those with neuroimaging included as part of the adjudication process. We defined TIA as an acute ischemic event that resolved in less than 24 hours and was DWI negative. The timing of an index event for the groups with TIA and stroke was defined by the date of their TIA or stroke, with the cognitive assessment occurring at their next scheduled study visit, which occurs in 2-year intervals, regardless of whether there was a cerebrovascular event. The index event for asymptomatic community control participants was defined as an arbitrary time point during follow-up, allowing a comparison of the differences in cognitive change at the index event and changes in the cognitive trajectory associated with an index stroke or TIA event to normal variation expected in the general population. For the groups with stroke and TIA, if the participant had a second cerebrovascular event, cognitive assessments after the recurrent event were censored. Finally, we excluded participants with missing covariates and those with less than 3 cognitive assessments.

Statistical Analysis

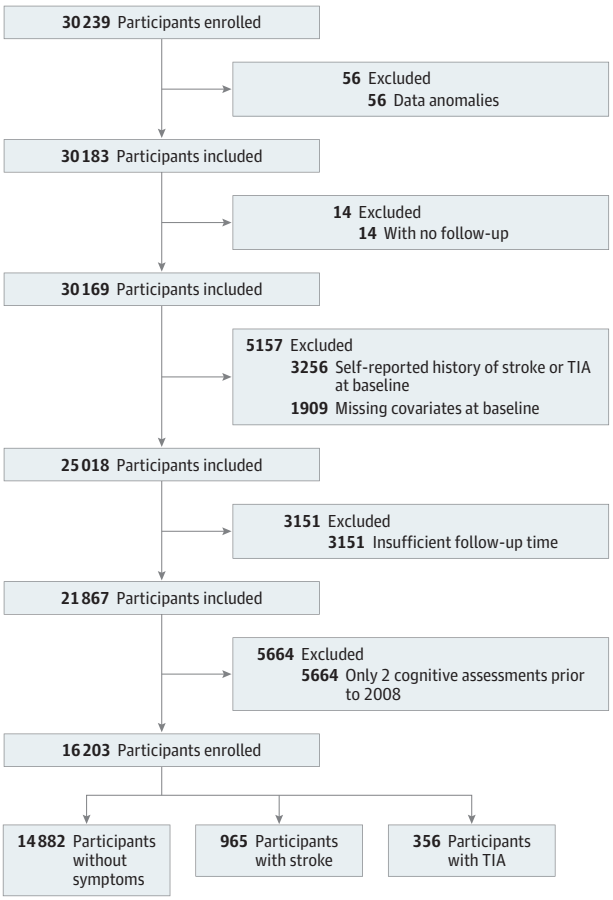
Demographic and clinical baseline data were described as mean (SD) or proportions, as appropriate. For primary and secondary cognitive outcomes, we used a segmented regression model, an approach that estimates the regression relationship between cognitive performance and time separately, before and after the index event. By setting the intercept term of both regression lines at the time of the index event, the intercept term from the regression before the index event provides an estimate of the cognitive performance immediately before the event and the intercept term from the regression immediately after the index event. This approach allows us to model (1) the overall level and rate of temporal change in cognitive functioning both before and after the index event, (2) the comparison of the change in rate of temporal decline of cognitive performance before vs after the index event, and (3) the magnitude of any abrupt change occurring at the time of the index event.

Group differences in mean cognitive levels or annual rate of cognitive change were estimated after adjustment for sex and major cerebrovascular risk factors. Further adjustments for age, race, and education were not necessary because they were accounted for in the cognitive *z* score standardization process. Adjustments were made for potential confounders selected for a known association with both the exposure (development of cerebrovascular disease) and outcome (cognitive performance). Because there is a growing appreciation that cerebrovascular disease and cognitive decline share many of the same risk factors,[8,18-20] the primary analysis adjusted for the well-accepted Framingham stroke risk factors of hypertension, diabetes, smoking, atrial fibrillation, left ventricular hypertrophy, and heart disease.[21] These risk factors were defined as follows: (1) hypertension, systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or self-reported use of antihypertensive medications; (2) diabetes, fasting glucose level of 126 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0555), or nonfasting glucose level of 200 mg/dL or greater, or self-reported use of diabetic medications; (3) atrial fibrillation, self-report of physician diagnosis or ECG evidence, (4), left ventricular hypertrophy, ECG evidence using Sokolow-Lyon criteria[22]; (5) smoking, self-report; and (6) heart disease, self-reported myocardial infarction, electrocardiogram evidence of myocardial infarction, or self-reported coronary artery bypass, angioplasty, or stenting. In order to assess the potential residual confounding, secondary analysis provided in supplemental material further adjusted for low-density lipoprotein cholesterol, obesity, low exercise levels, statin use, anticoagulant use, and depressive symptoms. The definition and distribution of these factors, along with the assessment of the patterns of cognitive decline in the TIA, stroke, and asymptomatic control groups, are provided in supplemental material (eMethods and eTable in Supplement 1). All *P* values were 2-sided, and a *P* value <.05 was considered statistically significant. Data were analyzed using SAS software, version 15.3 (SAS Institute).

Results

As seen in the CONSORT diagram (**Figure 1**), of the 30 239 REGARDS participants, 56 (<1%) were removed because of data anomalies. Of the remaining 30 183 participants, follow-up was available for 30 169 (≥99%). Of these participants, 3256 (11%) self-reported a physician diagnosis of stroke or TIA at baseline, and 1 or more covariates were missing for 1909 participants (7%), whose data were excluded from analysis. Of the remaining 25 018 participants, there was sufficient follow-up

Figure 1. Consolidated Standards of Reporting Trials Participant Exclusion Flowchart



to establish the presence or absence of a stroke or TIA or to have sufficient follow-up to declare a participant free of stroke and TIA during follow-up in 21 867 (87%) participants. These participants were followed up for a median (IQR) of 14.1 (9.3-16.9) years, and on or after 2008, 3 or more cognitive assessments were available for 16 203 participants (75%). There were 1678 assessments in 356 participants (mean [SD] age, 66.6 [8.7]; 188 female [53%]; 168 male [47%]; 104 Black race [29%]; 252 White race [71%]) with incident TIA, 4.223 assessments in 965 participants (mean [SD] age, 66.8 [8.2]; 471 female [49%]; 494 male [51%]; 354 Black race [37%]; 611 White race [63%]) with incident stroke, and 71 089 assessments in 14 882 asymptomatic community control participants (mean [SD] age, 63.2 [8.6] years; 8439 female [57%]; 6443 male [43%]; 5415 Black race [36%]; 9467 White race 64%]), totaling 76 990. Of these, all 4 cognitive tests were available in 46 615 participants (61%), 3 available in 7992 participants (10%), 2 in 19 691 participants (29%), and 1 in 2692 participants (4%). Baseline demographic and clinical variables are described in **Table 1**. Those with stroke and TIA were older, more likely to be male, and had a heavier risk factor burden compared with asymptomatic community control participants.

Figure 2 shows the mean overall cognitive composite performance at baseline and at the index event (ie, closest assessment postevent), the magnitude of the change in the mean cognitive performance linked to the index event, and the degree of annual cognitive change before and subsequent to the index event. **Table 2** provides the numeric estimates of these parameters.

The mean preindex event level of cognitive function for the group with stroke (−0.25; 95% CI, −0.32 to −0.17) reflected lower cognitive performance than the group with TIA (−0.05; 95% CI, −0.02 to 0.07; $P = .005$) and asymptomatic community control participants (0; 95% CI, −0.03 to 0.03; $P < .001$). The mean preindex event level of cognitive function of asymptomatic community control participants did not differ from that of the group with TIA.

Before the index event, the annual rate of cognitive decline (ie, slope) for the group with TIA (−0.03; 95% CI, −0.05 to −0.01) and asymptomatic community control participants (−0.02; 95% CI, −0.03 to −0.02) did not differ. In contrast, the slope of cognitive decline for the group with stroke (−0.04; 95% CI, −0.05 to −0.03) was more rapid compared to the asymptomatic community control participants ($P = .001$). There was no difference in preindex event rate of cognitive decline between the groups with TIA and stroke.

At the index event, the group with stroke showed the largest decline in cognition (−0.14; 95% CI, −0.21 to −0.07) compared with both the group with TIA (0.01; 95% CI, −0.10 to 0.12; $P = .02$) and the asymptomatic community control group (−0.03; 95% CI, −0.05 to −0.01; $P = .003$). The asymptomatic community control group did not differ from the group with TIA.

The postindex event annual rate of cognitive decline (ie, slope) was steeper for the group with TIA (−0.05; 95% CI, −0.06 to −0.03; $P = .001$) than for the asymptomatic community control group (−0.02; 95% CI, = −0.02 to −0.02), but the cognitive decline slope did not differ from the group with stroke (−0.04; 95% CI, = −0.05 to −0.03; $P = .43$). The rate of cognitive decline after the index event was more rapid for participants with stroke compared with that of asymptomatic community control participants.

The secondary analysis showed that further covariate adjustment for low-density lipoprotein cholesterol, obesity, low exercise, use of statins or anticoagulants, and depression had little impact on the pattern of cognitive change for any of the 3 groups of participants (eResults and eFigures 1 and 2 in Supplement 1).

Secondary Cognitive Analyses

Cognitive trajectories for CERAD Word List Learning, Word List Delayed Recall, and both letter *F* fluency and animal fluency are presented in Table 2 and **Figure 3**. The postindex event annual rate of cognitive decline for the group with TIA was driven largely by declines in immediate and delayed auditory-verbal recall rather than verbal fluency.

Discussion

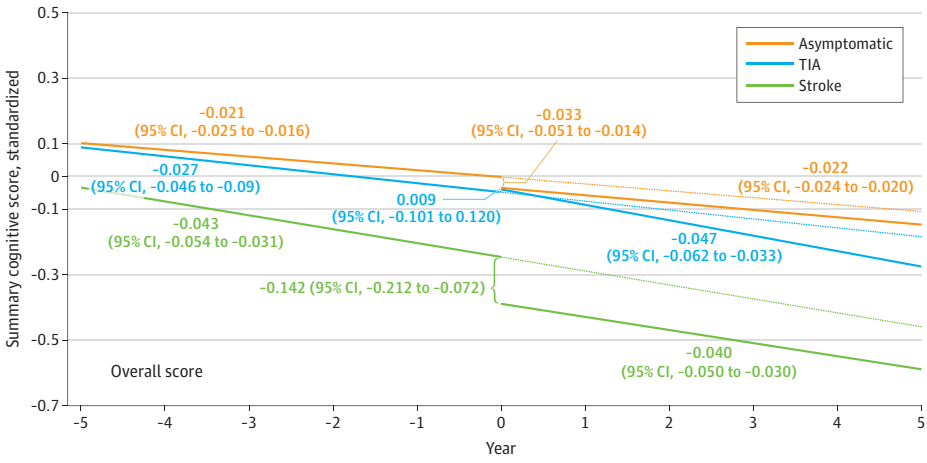
Our data showed that an incident stroke was associated with a large decline in cognitive performance over time, replicat-

Table 1. Clinical and Demographic Factors of Participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study Who Were Included in this Analysis by Incident Transient Ischemic Attack (TIA)/Stroke Status During Follow-Up (N = 16 203)

Factor type	Group		
	ASY	TIA	Stroke
No.	14 882	356	965
Demographic factors			
Age, mean (SD), y	63.2 (8.6)	66.6 (8.7)	66.8 (8.2)
Race, No. (%)			
Black	5415 (36.4)	104 (29.2)	354 (36.7)
White	9467 (63.6)	252 (70.8)	611 (63.3)
Education, No. (%)			
Less than high school	1193 (8.0)	30 (8.4)	93 (9.6)
High school graduate	3562 (23.9)	87 (24.4)	254 (26.3)
Some college	3949 (26.5)	97 (27.2)	261 (27.0)
College graduate or higher	6178 (41.5)	142 (39.9)	357 (37.0)
Cerebrovascular risk factors			
Sex, No. (%)			
Female	8439 (56.7)	188 (52.8)	471 (48.8)
Male	6443 (43.3)	168 (47.2)	494 (51.2)
Hypertension, No. (%)	7936 (53.3)	217 (61.0)	628 (65.1)
Diabetes, No. (%)	2470 (16.6)	73 (20.5)	249 (25.8)
Current smoking, No. (%)	1727 (11.6)	27 (7.6)	118 (12.2)
Atrial fibrillation, No. (%)	947 (6.4)	46 (12.9)	93 (9.6)
Left ventricular hypertrophy, No. (%)	1247 (8.4)	34 (9.6)	105 (10.9)
Heart disease, No. (%)	1870 (12.6)	69 (19.4)	210 (21.8)

Abbreviation: ASY, asymptomatic community control participant.

Figure 2. Overall Cognitive Composite Standardized Score Over Time for Participants Who Had a Transient Ischemic Attack (TIA) or Stroke and Remained Event Free Over Median Follow-Up of 14.1 Years



Time 0 is the time of the index event, with an arbitrary time selected for comparison to the asymptomatic community control group. Numeric estimates are provided for the following: (1) the annual rate of decline before the index event, (2) the magnitude of the abrupt decline associated with the index event, and (3) the annual rate of decline subsequent to the index event. All estimates are after multivariable adjustment for sex, hypertension, diabetes, smoking, atrial fibrillation, left ventricular hypertrophy, and heart disease.

ing prior findings,[2] but not an increase in the annual rate of cognitive decline. Cases of TIA that were adjudicated by a vascular neurologist were not associated with an immediate change in cognitive performance after the index event but were associated with an increase in the annual rate of decline, comparable with that after a stroke. These findings suggest that despite the quick resolution of symptoms and no radiological evidence of injury, TIA appears to be sufficient either directly or indirectly to initiate a pathological process leading to long-term changes in cognition.

We also found faster rates of overall cognitive decline in people previously free of cognitive impairment who experience a first-time TIA, compared with asymptomatic community controls. These findings appeared largely driven by immediate and delayed memory recall declines rather than verbal fluency declines. Our findings are consistent with a systematic review[23] showing elevated rates of clinically defined MCI (29% to 68%) and dementia (8% to 22%) after TIA, although it was acknowledged that none of the studies included DWI imaging or precerebrovascular event baseline cognitive func-

Table 2. Regression Models for Overall Cognitive Composite Individual Cognitive Test Outcomes with 95% CIs[a]

Outcome	Parameter	ASY	TIA	Stroke	*P* value for contrasts
Overall	Mean preindex event cognition level	0 (−0.03 to 0.03)	−0.05 (−0.02 to −0.07)	−0.25 (−0.32 to −0.17)	ASY vs TIA: .46 ASY vs stroke: <.001 TIA vs stroke: .005
	Pre- vs postdifference in mean cognition level	−0.03 (−0.05 to −0.01)	0.01 (−0.10 to 0.12)	−0.14 (−0.21 to −0.07)	ASY vs TIA: .46 ASY vs stroke: .003 TIA vs stroke: .02
	Annual cognitive change before index event	−0.02 (−0.03 to −0.02)	−0.03 (−0.05 to −0.01)	−0.04 (−0.05 to −0.03)	ASY vs TIA: .51 ASY vs stroke: .001 TIA vs stroke: .17
	Annual cognitive change after index event	−0.02 (−0.02 to −0.02)	−0.05 (−0.06 to −0.03)	−0.04 (−0.05 to −0.03)	ASY vs TIA: .001 ASY vs stroke: .001 TIA vs stroke: .43
	Pre- vs postannual cognitive change	0 (0)	−0.02 (−0.04 to 0)	0 (−0.01 to 0.02)	ASY vs TIA: .12 ASY vs stroke: .62 TIA vs stroke: .11
Letter fluency	Mean preindex event cognition level	−0.01 (−0.05 to 0.02)	0 (−0.12 to 0.13)	−0.15 (−0.23 to −0.07)	ASY vs TIA: .79 ASY vs stroke: .001 TIA vs stroke: .04
	Pre- vs postdifference in mean cognition level	0 (−0.01 to 0.03)	0.03 (−0.08 to 0.15)	−0.09 (−0.16 to −0.01)	ASY vs TIA: .67 ASY vs stroke: .02 TIA vs stroke: .09
	Annual cognitive change before index event	−0.02 (−0.02 to −0.01)	−0.02 (−0.04 to 0)	−0.02 (−0.04 to −0.01)	ASY vs TIA: .97 ASY vs stroke: .57 TIA vs stroke: .72
	Annual cognitive change after index event	−0.01 (−0.01 to −0.01)	−0.02 (−0.03 to 0)	−0.02 (−0.03 to 0)	ASY vs TIA: .40 ASY vs stroke: .45 TIA vs stroke: .81
	Pre- vs postannual cognitive change	0 (0 to 0.01)	0 (−0.02 to 0.03)	0.01 (−0.01 to 0.02)	ASY vs TIA: .57 ASY vs stroke: .95 TIA vs stroke: .66
Animal fluency	Mean preindex event cognition level	0.08 (0.05 to 0.12)	0.02 (−0.10 to 0.14)	−0.13 (−0.21 to −0.05)	ASY vs TIA: .35 ASY vs stroke: <.001 TIA vs stroke: .04
	Pre- vs postdifference in mean cognition level	−0.01 (−0.03 to 0.01)	0.03 (−0.08 to 0.15)	−0.14 (−0.21 to −0.06)	ASY vs TIA: .46 ASY vs stroke: .001 TIA vs stroke: .01
	Annual cognitive change before index event	−0.04 (−0.05 to −0.04)	−0.06 (−0.07 to −0.04)	−0.06 (−0.08 to −0.05)	ASY vs TIA: .17 ASY vs stroke: .001 TIA vs stroke: .53
	Annual cognitive change after index event	−0.04 (−0.04 to −0.04)	−0.05 (−0.06 to −0.03)	−0.05 (−0.06 to −0.04)	ASY vs TIA: .12 ASY vs stroke: .06 TIA vs stroke: .84
	Pre- vs postannual cognitive change	0 (0 to 0.01)	0.01 (−0.02 to 0.03)	0.02 (0 to 0.03)	ASY vs TIA: .91 ASY vs stroke: .22 TIA vs stroke: .54
Word list learning	Mean preindex event cognition level	−0.08 (−0.12 to −0.05)	−0.13 (−0.26 to 0)	−0.32 (−0.40 to −0.23)	ASY vs TIA: .49 ASY vs stroke: <.001 TIA vs stroke: .02
	Pre- vs postdifference in mean cognition level	−0.05 (−0.08 to −0.03)	0.07 (−0.06 to 0.20)	−0.15 (−0.24 to −0.07)	ASY vs TIA: .07 ASY vs stroke: .02 TIA vs stroke: .005
	Annual cognitive change before index event	0.01 (0 to 0.01)	0 (−0.03 to 0.02)	−0.01 (−0.03 to 0)	ASY vs TIA: .46 ASY vs stroke: .01 TIA vs stroke: .42
	Annual cognitive change after index event	0 (−0.01 to 0)	−0.04 (−0.06 to −0.03)	−0.01 (−0.02 to 0)	ASY vs TIA: <.001 ASY vs stroke: .14 TIA vs stroke: .002
	Pre- vs postannual cognitive change	−0.01 (−0.01 to 0)	−0.04 (−0.07 to −0.01)	0 (−0.02 to 0.02)	ASY vs TIA: .02 ASY vs stroke: .28 TIA vs stroke: .009

(continued)

tioning. The high variability in diagnostic estimates may be due to several factors, including the following: measurement of cognition (neuropsychological assessment vs cognitive screening), time duration between TIA and the cognitive assessment (days to years), and whether people with cognitive impairment at baseline were excluded. Over the course of 5 years after TIA, there is epidemiological evidence of increased risk of developing dementia.[3] After TIA, there is reduced white matter integrity[24] and subcortical gray matter volume loss,[25] but without pre-TIA scans, it is difficult to ascertain whether cerebrovascular disease observed on imaging predates the event.

The lower baseline level and the more rapid decline in cognitive performance in the group with stroke could be related to greater prestroke cerebrovascular disease burden (ie, leukoaraiosis, chronic subclinical ischemic lesions, or cortical and

Table 2. Regression Models for Overall Cognitive Composite Individual Cognitive Test Outcomes with 95% CIs[a] (continued)

Outcome	Parameter	ASY	TIA	Stroke	*P* value for contrasts
Word list recall	Mean preindex event cognition level	−0.08 (−0.11 to −0.04)	−0.12 (−0.26 to 0.01)	−0.31 (−0.39 to −0.22)	ASY vs TIA: .49 ASY vs stroke: <.001 TIA vs stroke: .02
	Pre- vs postdifference in mean cognition level	−0.04 (−0.06 to −0.02)	0.05 (−0.09 to 0.18)	−0.07 (−0.16 to 0.02)	ASY vs TIA: .23 ASY vs stroke: .46 TIA vs stroke: .15
	Annual cognitive change before index event	0 (−0.01 to 0)	−0.01 (−0.03 to 0.01)	−0.02 (−0.04 to −0.01)	ASY vs TIA: .48 ASY vs stroke: .02 TIA vs stroke: .46
	Annual cognitive change after index event	−0.01 (−0.01 to −0.01)	−0.06 (−0.08 to −0.04)	−0.02 (−0.03 to −0.01)	ASY vs TIA: <.001 ASY vs stroke: .09 TIA vs stroke: .001
	Pre- vs postannual cognitive change	−0.01 (−0.02 to 0)	−0.05 (−0.08 to −0.02)	0 (−0.02 to 0.02)	ASY vs TIA: .01 ASY vs stroke: .45 TIA vs stroke: .009

Abbreviations: ASY, asymptomatic community control participant; TIA, transient ischemic attack.

[a] Adjusted for age, race, and education in the standardization process. Differences between groups were further adjusted for sex and major cerebrovascular risk factors of hypertension, diabetes, current smoking, atrial fibrillation, left ventricular hypertrophy, and heart disease.

subcortical atrophy).[26] That those participants experiencing a TIA were similar to the asymptomatic population before the index event suggests a smaller cerebrovascular burden. Unfortunately, we do not have pre-event neuroimaging to confirm this assertion.

As expected, the group with stroke had the largest cognitive decline immediately after their index event, whereas there was no acute post-TIA cognitive change. Unlike the groups with TIA and stroke, the participants in the asymptomatic community control group were not linked to a specific clinical event. We note that the estimated abrupt change in the asymptomatic control group at the randomly selected time proved to be statistically significant. As there is no reason for a difference at this point in the asymptomatic group, and the change is quite small (−0.03), we feel that this jump is likely a spurious finding arising among the large number of estimates in our model. The preindex and postindex event slopes for the asymptomatic community control group did not differ, reflecting a similar rate of annual change.

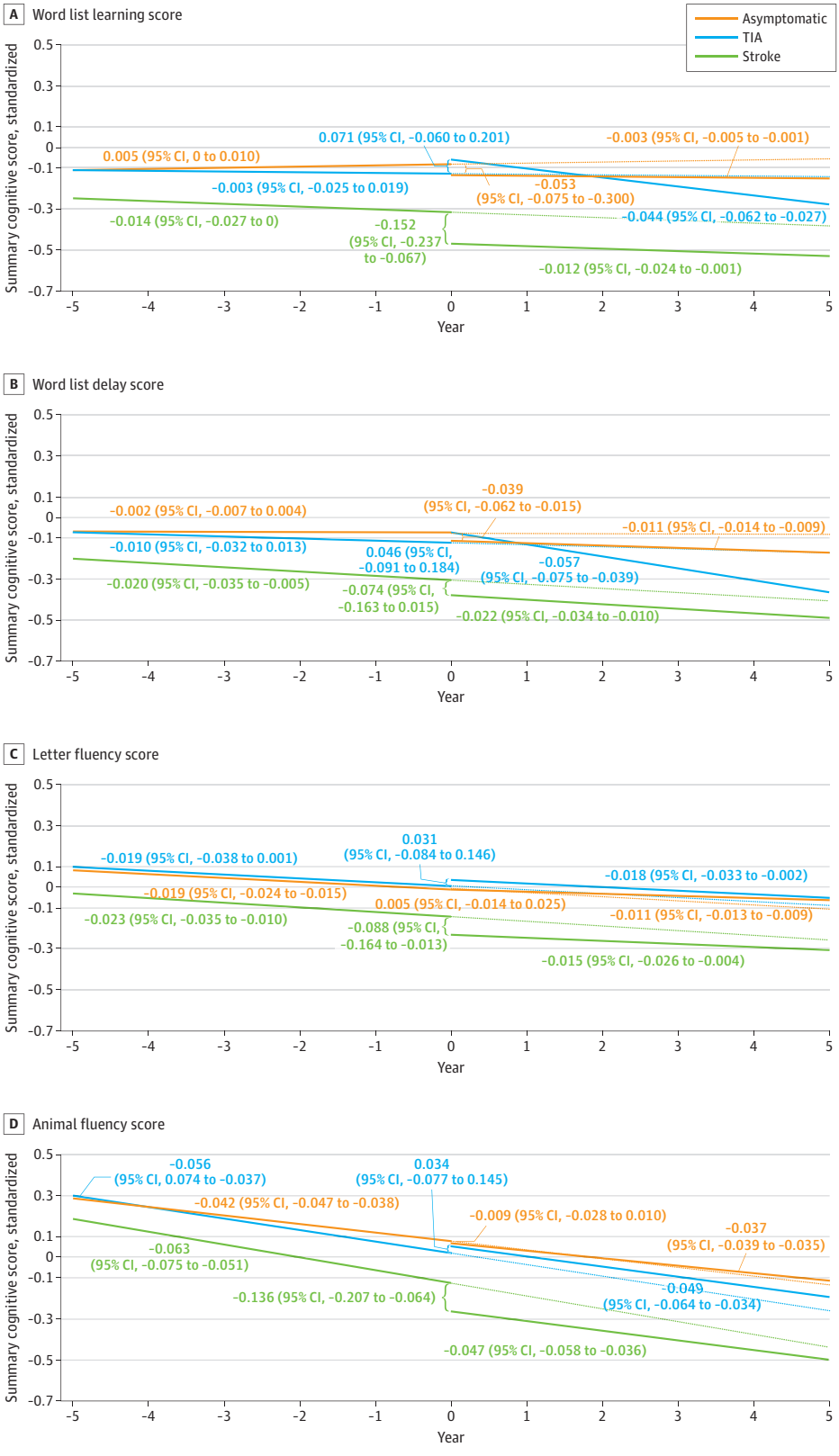
Because TIA is an ischemic event, one possible mechanism of TIA-related cognitive decline is the relationship with vascular risk factors. In our study, we controlled for vascular risk factors, indicating that the observed cognitive effects were independently related to the TIA. Nevertheless, we acknowledge that there may have been concurrent underlying pathology, such as cerebral amyloid angiopathy or markers of neurodegeneration. That all participants had comparable trajectories at least 5 years before the occurrence of their index event suggests that in the instances of concurrent but asymptomatic disease, a TIA was sufficient to initiate the cascade of decline. Previous research has shown that severe small vessel disease (>3 lacunar infarcts and confluent white matter changes) contributes to a delayed onset of dementia post-TIA.[27] Additionally, homozygous apolipoprotein E ε4 genotype positivity has been associated with increased risk of dementia after TIA.[4] Elevated cardiovascular risk is associated with hyperphosphorylated tau and β-amyloid pathology.[28] In people with elevated β amyloid who have a TIA or stroke, a faster rate of decline is observed when compared with participants who are negative for β amyloid.[29] It is possible that TIA may be a useful model for studying the vascular contributions to Alzheimer disease.

GABAergic disruption after TIA is another possible mechanism. The administration of midazolam has resulted in the recrudescence of stroke and TIA symptoms,[10,11] with this effect specific to GABAergic properties and not sedation.[9] In patients with TIA, there is preliminary magnetic resonance spectroscopy evidence of lower GABA levels in the symptomatic hemisphere.[30] Using single- and paired-pulse transcranial magnetic stimulation and motor evoked potentials in individuals with TIA, there is reduced intracortical inhibition in the affected hemisphere,[31] with this electrophysiological marker reflecting GABAergic processes.

Blood brain barrier (BBB) disruption occurs after an ischemic event,[32] and neuroinflammation occurs within the context of biological repair.[33] BBB dysfunction affects the transportation of cytokines and immune cells, resulting in cognitive impairment. In a diabetic rat model, BBB disruption is at least in part related to the increased inflammatory cytokines (tumor necrosis factor α and interleukin-6 messenger RNA expression).[34] Stroke damages endothelial cells, increasing the proliferation of free radicals and cytokines, with microglia activated in the acute stage of recovery.[32] Similarly, there is evidence of BBB breakdown in humans after TIA and minor acute ischemic stroke[35] but because these 2 groups were pooled together, it remains unknown if a TIA, per se, is capable of producing such an inflammatory response.

It has been traditionally believed that cerebrovascular disease largely affects frontal, executive function, resulting in definitions of vascular cognitive impairment that minimize the impact on memory.[36] More recent studies, however, suggest that episodic memory is more commonly affected than previously thought, in part because of more in-depth cognitive assessments and correlative findings on imaging made possible by advancements in the mapping of networks[37] and positron emission tomography scanning with ligands sensitive to microglial activation as a marker for neuroinflammation. There is also a new appreciation of how vascular risk factors in-

Figure 3. Individual Standardized Test Performance Over Time for Participants Who Had a Transient Ischemic Attack (TIA) or Stroke and Remained Event Free Over Median Follow-Up of 14.1 Years



Time 0 is the time of the index event, with an arbitrary time selected for comparison to the asymptomatic community control group. Numeric estimates are provided for the following: (1) the annual rate of decline before the index event, (2) the magnitude of the abrupt decline associated with the index event, and (3) the annual rate of decline subsequent to the index event. All estimates are after multivariable adjustment for sex, hypertension, diabetes, smoking, atrial fibrillation, left ventricular hypertrophy, and heart disease.

crease the brain's vulnerability to the deleterious effects of β amyloid.[38]

Strengths and Limitations

A significant strength of our analysis is the presence of preevent baseline cognitive data, missing from most other TIA studies. Similarly, participants are well characterized at baseline and with greater than 15 years of longitudinal data. Finally, all TIA cases were DWI negative, and all TIA and stroke cases were adjudicated by vascular neurologists.

This study also has some limitations, which include a telephone cognitive test battery that was somewhat limited in scope. Although the approach used by the REGARDS study has been demonstrated to be sensitive and have predictive validity,[14] the approach precludes administration of cognitive tests with a visual-spatial or motor component. Thus, it is possible that unmeasured cognitive domains could also be affected or remain unaffected by a TIA. Nevertheless, our approach was sufficiently sensitive to detect cognitive decline after TIA. Another limitation of the REGARDS dataset is the absence of National Institutes of Health Stroke Scale scores, precluding measurement of stroke severity, although these stroke cases were likely to be mild because participants are community-dwelling individuals who were able to complete cognitive testing remotely and continued in follow-up after the stroke event. This limitation, however, does not pertain to the TIA events. A differential pattern of temporal changes in cognition between the participants with TIA and stroke and asymptomatic participants could be attributable to potential confounding factors. We attempted to mitigate this possibility by adjusting for the Framingham stroke risk factors that are well known to be related to both the development of cerebrovascular disease and cognitive decline and attempted to address the potential for residual confounding by adjusting for 6 additional factors in the supplemental analysis. Although there is always the possibility for additional residual confounding from other factors or from our approach for quantification of the factors we considered, we believe the magnitude of this additional confounding is likely small. Because the REGARDS study examinations are performed in the participants' home, there was no opportunity to assess carotid stenosis by ultrasound or other methods. The REGARDS study has a measure of prevalent heart failure; however, heart failure generally does not present with an acute event to define a prevalent condition and heart failure can have an extended latent period, limiting our confidence in the measure of prevalent heart failure. This variable was, therefore, not included in the statistical models. At this point, we cannot determine whether the association with memory, which was not seen in verbal fluency, was the result of an interaction with neurodegenerative factors or that the pathological impact of a TIA is not sufficient to affect verbal fluency. We did not present sex differences here because the loss of power in the TIA group precluded a meaningful comparison. Furthermore, we did not adjust for sex during the standardization of neuropsychological scores but controlled for it as a covariate. We nevertheless agree with the importance of sex differences and acknowledged this weakness in our study. Finally, there is always the possibility that some asymptomatic community control participants could have had a TIA or mild ischemic stroke but never sought medical attention. However, if this occurred, it was likely a rare event that did not exert a bias on the group-level cognitive performance of the asymptomatic community control group because the preindex and postindex event slopes were not statistically different.

Conclusions

In this cohort study, results suggest that the rate of cognitive decline after a first-time, DWI-negative TIA was similar to the rate of decline observed in individuals after a first-time ischemic stroke. This pattern of overall cognitive decline was primarily due to immediate and delayed memory declines. Our findings suggest that TIA was an independent risk factor for cognitive decline, suggesting more aggressive treatment to minimize cognitive risk. Cognitive decline after TIA is likely multifactorial in origin and may involve the interaction with vascular risk factors, the presence of preexisting β amyloid and hyperphosphorylated tau deposition, post-TIA disruption of the GABAergic system, BBB permeability, and increased neuroinflammation, among other pathophysiological processes.

ARTICLE INFORMATION

Accepted for Publication: December 5, 2024.

Published Online: February 10, 2025. doi:10.1001/jamaneurol.2024.5082

Author Contributions: Drs Del Bene and G. Howard had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Del Bene, G. Howard, Gropen, Lyerly, Lazar.
Acquisition, analysis, or interpretation of data: Del Bene, G. Howard, Gropen, V. Howard, Sawyer, Lazar.
Drafting of the manuscript: Del Bene, V. Howard, Lazar.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: G. Howard.
Obtained funding: G. Howard, Gropen, V. Howard.
Administrative, technical, or material support: Del Bene, G. Howard, V. Howard, Sawyer, Lazar.
Supervision: Gropen, Lyerly, Lazar.

Conflict of Interest Disclosures: Dr Gropen reported receiving grants from the National Institute of Neurological Disorders and Stroke during the conduct of the study. Dr Lyerly reported receiving grants from the National Institutes of Health StrokeNet during the conduct of the study. Dr V. Howard reported receiving grants from the National Institutes of Health during the conduct of the study. No other disclosures were reported.

Funding/Support: This research project was supported in part by cooperative agreement U01 NS041588 cofunded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Service; NINDS grant U24 NS107223-06 (Drs Gropen and Lazar), and the McKnight Brain Research Foundation.

Role of the Funder/Sponsor: Representatives of the National Institute of Neurological Disorders and Stroke were involved in the review of the manuscript but were not directly involved in the collection, management, analysis or interpretation of the data.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institute on Aging.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions.

Beyond usual salary, no one received financial compensation for these contributions. A full list of participating REGARDS investigators and institutions can be found at: https://www.uab.edu/soph/regardsstudy/.

REFERENCES

1. Easton JD, Johnston SC. Time to retire the concept of transient ischemic attack. *JAMA*. 2022;327(9):813-814. doi:10.1001/jama.2022.0300

2. Levine DA, Galecki AT, Langa KM, et al. Trajectory of cognitive decline after incident stroke. *JAMA*. 2015;314(1):41-51. doi:10.1001/jama.2015.6968

3. Pendlebury ST, Rothwell PM; Oxford Vascular Study. Incidence and prevalence of dementia associated with transient ischemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol*. 2019;18(3):248-258. doi:10.1016/S1474-4422(18)30442-3

4. Pendlebury ST, Poole D, Burgess A, Duerden J, Rothwell PM; Oxford Vascular Study. APOE-ε4 genotype and dementia before and after transient ischemic attack and stroke: population-based cohort study. *Stroke*. 2020;51(3):751-758. doi:10.1161/STROKEAHA.119.026927

5. Dichgans M. Dementia risk after transient ischemic attack and stroke. *Lancet Neurol*. 2019;18(3):223-225. doi:10.1016/S1474-4422(18)30497-6

6. Janssen AW, de Leeuw FE, Janssen MC. Risk factors for ischemic stroke and transient ischemic attack in patients under age 50. *J Thromb Thrombolysis*. 2011;31(1):85-91. doi:10.1007/s11239-010-0491-3

7. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers Dement*. 2015;11(6):718-726. doi:10.1016/j.jalz.2015.05.016

8. Unverzagt FW, McClure LA, Wadley VG, et al. Vascular risk factors and cognitive impairment in a stroke-free cohort. *Neurology*. 2011;77(19):1729-1736. doi:10.1212/WNL.0b013e318236ef23

9. Lazar RM, Berman MF, Festa JR, Geller AE, Matejovsky TG, Marshall RS. GABAergic but not anticholinergic agents re-induce clinical deficits after stroke. *J Neurol Sci*. 2010;292(1-2):72-76. doi:10.1016/j.jns.2010.01.024

10. Lazar RM, Fitzsimmons BF, Marshall RS, et al. Reemergence of stroke deficits with midazolam challenge. *Stroke*. 2002;33(1):283-285. doi:10.1161/hs0102.101222

11. Lazar RM, Fitzsimmons BF, Marshall RS, Mohr JP, Berman MF. Midazolam challenge reinduces neurological deficits after transient ischemic attack. *Stroke*. 2003;34(3):794-796. doi:10.1161/01.STR.0000056540.04159.F3

12. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology*. 2005;25(3):135-143. doi:10.1159/000086678

13. Howard VJ, Kleindorfer DO, Judd SE, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. *Ann Neurol*. 2011;69(4):619-627. doi:10.1002/ana.22385

14. Levine DA, Wadley VG, Langa KM, et al. Risk factors for poststroke cognitive decline: the REGARDS study (Reasons for Geographic and Racial Differences in Stroke). *Stroke*. 2018;49(4):987-994. doi:10.1161/STROKEAHA.117.018529

15. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD): part II. standardization of the neuropathologic assessment of Alzheimer disease. *Neurology*. 1991;41(4):479-486. doi:10.1212/WNL.41.4.479

16. Marceaux JC, Prosje MA, McClure LA, et al. Verbal fluency in a national sample: telephone administration methods. *Int J Geriatr Psychiatry*. 2019;34(4):578-587. doi:10.1002/gps.5054

17. Hunter MB, Jenkins N, Dolan C, Pullen H, Ritchie C, Muniz-Terrera G. Reliability of telephone and videoconference methods of cognitive assessment in older adults with and without dementia. *J Alzheimers Dis*. 2021;81(4):1625-1647. doi:10.3233/JAD-210088

18. Elkins JS, O'Meara ES, Longstreth WT Jr, Carlson MC, Manolio TA, Johnston SC. Stroke risk factors and loss of high cognitive function. *Neurology*. 2004;63(5):793-799. doi:10.1212/01.WNL.0000137014.36689.7F

19. Khedr EM, Hamed SA, El-Shereef HK, et al. Cognitive impairment after cerebrovascular stroke: relationship to vascular risk factors. *Neuropsychiatr Dis Treat*. 2009;5:103-116. doi:10.2147/NDT.S4184

20. Llewellyn DJ, Lang IA, Xie J, Huppert FA, Melzer D, Langa KM. Framingham Stroke Risk Profile and poor cognitive function: a population-based study. *BMC Neurol*. 2008;8:12. doi:10.1186/1471-2377-8-12

21. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22(3):312-318. doi:10.1161/01.STR.22.3.312

22. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J*. 1949;37(2):161-186. doi:10.1016/0002-8703(49)90562-1

23. van Rooij FG, Kessels RP, Richard E, De Leeuw FE, van Dijk EJ. Cognitive impairment in transient ischemic attack patients: a systematic review. *Cerebrovasc Dis*. 2016;42(1-2):1-9. doi:10.1159/000444282

24. Tariq S, Tsang A, Wang M, et al. White matter tract microstructure and cognitive performance after transient ischemic attack. *PLoS One*. 2020;15(10):e0239116. doi:10.1371/journal.pone.0239116

25. Bivard A, Lillicrap T, Maréchal B, et al. Transient ischemic attack results in delayed brain atrophy and cognitive decline. *Stroke*. 2018;49(2):384-390. doi:10.1161/STROKEAHA.117.019276

26. Schellhorn T, Zucknick M, Askim T, et al. Prestroke cognitive impairment is associated with vascular imaging pathology: a prospective observational study. *BMC Geriatr*. 2021;21(1):362. doi:10.1186/s12877-021-02327-2

27. Mok VCT, Lam BYK, Wang Z, et al. Delayed-onset dementia after stroke or transient ischemic attack. *Alzheimers Dement*. 2016;12(11):1167-1176. doi:10.1016/j.jalz.2016.05.007

28. Rabin JS, Yang HS, Schultz AP, et al. Vascular risk and β-amyloid are synergistically associated with cortical tau. *Ann Neurol*. 2019;85(2):272-279. doi:10.1002/ana.25399

29. Liu W, Wong A, Au L, et al. Influence of amyloid-β on cognitive decline after stroke/transient ischemic attack: 3-year longitudinal study. *Stroke*. 2015;46(11):3074-3080. doi:10.1161/STROKEAHA.115.010449

30. Figlewski K, Andersen H, Stærmose T, von Weitzel-Mudersbach P, Nielsen JF, Blicher JU. Decreased GABA levels in the symptomatic hemisphere in patients with transient ischemic attack. *Heliyon*. 2018;4(9):e00790. doi:10.1016/j.heliyon.2018.e00790

31. Koerner C, Meinck HM. Long-lasting motor cortex disinhibition after short transient ischemic attacks (TIAs) in humans. *Neurosci Lett*. 2004;361(1-3):21-24. doi:10.1016/j.neulet.2003.12.074

32. Mathias K, Machado RS, Stork S, et al. Blood-brain barrier permeability in the ischemic stroke: An update. *Microvasc Res*. 2024;151:104621. doi:10.1016/j.mvr.2023.104621

33. Candelario-Jalil E, Dijkhuizen RM, Magnus T. Neuroinflammation, stroke, blood-brain barrier dysfunction, and imaging modalities. *Stroke*. 2022;53(5):1473-1486. doi:10.1161/STROKEAHA.122.036946

34. Geng J, Wang L, Zhang L, et al. Blood-brain barrier disruption induced cognitive impairment is associated with increase of inflammatory cytokine. *Front Aging Neurosci*. 2018;10:129. doi:10.3389/fnagi.2018.00129

35. Serlin Y, Ofer J, Ben-Arie G, et al. Blood-brain barrier leakage: a new biomarker in transient ischemic attacks. *Stroke*. 2019;50(5):1266-1269. doi:10.1161/STROKEAHA.119.025247

36. Gorelick PB, Scuteri A, Black SE, et al; American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(9):2672-2713. doi:10.1161/STR.0b013e3182299496

37. O'Sullivan MJ, Li X, Galligan D, Pendlebury ST. Cognitive recovery after stroke: memory. *Stroke*. 2023;54(1):44-54. doi:10.1161/STROKEAHA.122.041497

38. Ballard C, Rowan E, Stephens S, Kalaria R, Kenny RA. Prospective follow-up study between 3 and 15 months after stroke: improvements and decline in cognitive function among dementia-free stroke survivors >75 years of age. *Stroke*. 2003;34(10):2440-2444. doi:10.1161/01.STR.0000089923.29724.CE