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The Influence of Vascular Risk Factors and Stroke on Cognition in Late-life : Analysis of the NACC cohort

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Abstract

Objective—Vascular risk factors in mid-life predict late life cognitive decline in previously normal populations. We sought to investigate the contribution of vascular risk factors in late life to cognitive decline in a cohort of normal elderly individuals.

Methods—Cognitively normal subjects were identified from the longitudinal cohort of participants in the National Alzheimer Coordinating Center (NACC) database (n=2975). The association between a composite score of vascular risk factors (based on the Framingham Stroke

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Statement of Contribution

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Risk Profile) and cognitive function was tested at baseline visit and estimated in longitudinal analyses using linear mixed-effects models.

Results—Total vascular risk factor burden was associated with worse cognitive performance at baseline and faster decline longitudinally in univariate analyses but only with worse WAIS digit symbol performance in cross-sectional (estimate=−0.266 units/1 unit of Framingham Stroke Risk Profile Score, 95%CI −0.380 to −0.153, $p<0.001$) and longitudinal (estimate=−0.034 units/1 unit of Framingham Stroke Risk Profile Score/yr, 95%CI −0.055, to −0.012, $p=0.002$) analyses after adjusting for age, education and *APOE* genotype. Individuals with history of stroke performed significantly worse on the Trails B, category fluency, and Boston naming tests in cross-sectional analyses and in delayed logical memory and digit span backwards in longitudinal analyses.

Conclusions—Although the modified Framingham Stroke Risk Profile in late-life predicts rate of decline on selective neurocognitive measures in previously normal elderly individuals, age appears to be the strongest risk factor for cognitive impairment in this population. History of stroke independently influences rate of cognitive decline in these individuals.

INTRODUCTION

In recent years, a growing body of evidence has accumulated supporting the influence of vascular risk factors and cerebrovascular disease on cognitive impairment and dementia in the elderly^{1–6}. In Alzheimer's disease (AD), cross-sectional analyses have suggested associations between certain vascular risk factors such as atherosclerosis² or atrial fibrillation⁷ and AD. Longitudinal studies have suggested that diabetes, hypertension, heart disease, and current smoking are associated with increased risk of developing AD^{5, 8–11}, and that having numerous vascular risk factors further increases risk⁹. Atrial fibrillation, hypertension, and angina have been associated with a faster rate of decline in patients with AD³, and treatment of vascular risk factors with a slower rate¹². In normal elderly individuals, atrial fibrillation¹³, diabetes^{14–16}, smoking¹⁷, and hypertension¹⁶ have been separately associated with an increased risk of cognitive impairment in various studies.

The Framingham Stroke Risk Profile provides a global measure of an individual's vascular risk factor severity and has been used to estimate long-term stroke risk.^{18, 19} Its elements include age, gender, systolic blood pressure, use of anti-hypertension therapy, diabetes, cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, and cigarette smoking.¹⁹ In cognitively normal individuals, the Framingham Heart Study has reported an association between the Framingham Stroke Risk Profile and decreased cognitive performance in cross-sectional analyses¹. Several longitudinal studies have shown that total vascular risk factor burden, the presence of hypertension or diabetes, history of stroke, and *APOE* $\epsilon 4$ genotype are implicated in the progression of cognitive impairment in previously normal middle-aged individuals^{20–23}. In cognitively normal individuals homozygous for *APOE* $\epsilon 4$, a small study has suggested that hypertension, diabetes, cardiovascular disease and cigarette smoking affect rate of decline⁴.

However, several important questions remain unanswered. Although the influence of certain vascular risk factors and cognitive decline has been shown in middle-aged populations^{4, 20, 21}, the contribution of these risk factors to cognitive decline in previously

normal elderly individuals has been explored in relatively few studies. The influence of these factors in late-life may have importance in clinical practice as detailed information regarding mid-life vascular risk factors is often unavailable when elderly patients present for evaluation in memory clinics. Furthermore, though many studies have examined the effect of specific vascular risk factors on cognition, relatively few have examined the influence of overall vascular risk factor burden on cognitive dysfunction. Shedding light on these relationships could help to identify vascular-based preventive and therapeutic strategies for cognitively asymptomatic elderly patients. Using the elements of the Framingham Stroke Risk profile as a measure of global vascular risk factor burden, we sought to investigate these questions in the large multicenter prospective National Alzheimer Coordinating Center (NACC) cohort.

METHODS

Dataset

The NACC-based Uniform dataset (UDS) has been previously described in detail.^{24, 25} In brief, it is a prospective, longitudinal cohort that enrolls cognitively intact subjects, subjects with mild cognitive impairment (MCI), and subjects with dementia. It combines enrollment from 28 federally funded Alzheimer's Disease Centers (ADCs) collected since 2005.

Enrolled subjects undergo a standardized evaluation which includes collection of demographic information and medical history, including the presence of vascular risk factors and medication use; physical examination with measurement of blood pressure and neurologic evaluation; and detailed neurocognitive testing. Full description of these tests and standardization have been previously described.²⁴ The protocol requires annual, longitudinal follow-up as long as the subject is able and willing to participate. Subject death and drop-out are also documented. Trained clinicians collect data from subjects and their designated informants (usually a family member or close friend). Diagnoses are assigned either by a consensus team or a single physician who conducts the examination following the specific ADC protocol. Data are prospectively recorded on standardized UDS forms (hard copy or electronic) during the evaluation process and subsequently submitted centrally to NACC for data management. The method for recruitment of cognitively normal subjects varies by ADC, and includes community advertising, recruitment of spouses of cognitive impaired subjects, and recruitment of subjects from related ADC studies. The study has been approved by local institution review boards at all participating ADCs, and written informed consent is obtained from all participants.

Sample selection

The analysis cohort was drawn from individuals in the NACC UDS dataset as of Sept 2011 who were rated as CDR = 0 and non-demented at their initial visit (n= 8497). Subjects were included if they had at least one follow-up visit and they had sufficient data to calculate a composite score of vascular risk factors based on the Framingham Stroke Risk Profile¹⁹, and had *APOE* genotype data available. History of transient ischemic attack (TIA) and history of ischemic stroke were also analyzed. Number of exclusions by reason were as follows (note that some subjects were excluded for more than one reason): (1) no follow-up visits

(n=2201), (2) inability to calculate a modified Framingham risk score at baseline due to missing or out-of-range age (<54 years or >86 years) or systolic blood pressure (<95 mm Hg or >213 mm Hg for men and <95 mm Hg or >204 mm Hg for women; n=2017), and (3) lack of *APOE* genotype (n=1304). The final analysis sample included 2975 subjects.

For these subjects, we obtained baseline demographic, medical, neurologic data, *APOE* genotype, as well as neuropsychological and diagnostic variables at baseline and at subsequent visits, from the NACC database. Cognitive test data included mini-mental status examination (MMSE), measures of memory (Wechsler-III immediate and delayed logical memory), attention (Digit span forward and digit span backward), language function (Boston naming test), measures of executive function (Trails B [corrected for Trails A performance] and Category Fluency), and a measure of processing speed (WAIS-R digit symbol). A description of these tests has been previously published.²⁴ These tests had been specifically selected for their sensitivity to age-related change in cognition and their utility in studying the risk of conversion to cognitive impairment and dementia.²⁴ The Framingham Stroke Risk Profile score was calculated using information on age, gender, systolic blood pressure, use of anti-hypertension therapy, diabetes, cardiovascular disease (characterized as having one or more of the following: history of MI, angioplasty, CABG, or pacemaker), atrial fibrillation, and cigarette smoking.¹⁹ Because left ventricular hypertrophy was not collected in the NACC UDS dataset, a modified Framingham Stroke Risk Profile (modified Framingham risk score) was constructed omitting left ventricular hypertrophy. Values ranged from 0 to 30.

Statistical Analysis

Unadjusted associations between baseline characteristics of the cohort and modified Framingham risk score stratified into tertiles (0 to 10, 11 to 15, and 16 to 30) were assessed by one-way analysis of variance and Pearson chi-square tests. The effect of baseline Framingham risk score on global cognition and seven cognitive tests described above was tested in a series of linear mixed-effects models. For each cognitive measure, total modified Framingham risk score was tested as a predictor in these models. The relative contribution of individual components of the modified Framingham risk score, including age, were also examined. Models controlling for education (measured as years of schooling), age, number of *APOE* ϵ 4 alleles, history of TIA (but not stroke) and clinical stroke were constructed. As age is one of the components of the Framingham risk score, models that adjusted for age first separated this component from the modified Framingham risk score. To avoid bias due to any systematic differences in cognitive evaluation among NACC centers, NACC center was included as a random effect in all models. Secondary analyses explored the effect of age alone and linear interactions between age, Framingham risk score, and individual vascular risk factors.

Linear mixed-effects models were used to model the effect of baseline vascular risk factors on rate of change over time in global and domain-specific cognitive performance and in CDR sum-of-boxes, using the same predictors as the baseline analyses and their interactions with time since baseline as fixed effects. Participant-specific intercepts and slopes over time were included as random effects. The effect of baseline vascular risk factors on hazard of

conversion to cognitive impairment or dementia (defined as CDR 0.5 or CDR 1.0) was estimated by Cox regression. Models that included Framingham risk score with and without adjustment for age and number of *APOE* ϵ 4 alleles were tested. All analyses were performed with SAS version 9.2 (SAS Institute, Cary, North Carolina). All significance tests were 2-tailed. Nominal p-values are reported without adjustment for multiple comparisons; however the interpretation of results emphasizes findings where $p < 0.005$, based on a Bonferroni correction for 8 or 9 outcome measures evaluated for any given model.

RESULTS

Overall baseline characteristics of the cohort and characteristics stratified by modified Framingham risk score tertile are presented in Table 1. Individuals in higher risk score tertiles tended to be older and less educated and to have fewer copies of the *APOE* ϵ 4 allele. As expected, these individuals were also significantly more likely to have had a history of stroke or TIA. Furthermore, these individuals had significantly lower scores for both global cognitive function (MMSE) and domain-specific measures (Trails B, immediate and delayed logical memory, digit span, and WAIS).

In baseline analyses adjusting for education, modified Framingham risk score was significantly associated with worse performance on both global and domain-specific cognitive measures (Table 2, model 1). In models that adjusted for age, education, and *APOE* genotype (Table 2, model 2), modified Framingham risk score was significantly associated with worse WAIS digit symbol performance, but not other cognitive measures. These results did not significantly change in models adjusting only for age and education (data not shown). Framingham risk score remained significantly associated with WAIS digit symbol performance after adjustment for a history of stroke or TIA, (Table 2, model 3).

In longitudinal analyses adjusting for education, baseline modified Framingham risk score was significantly associated with worse performance over time on both global and domain-specific cognitive measures with the exception of digit span forward (Table 3, model 1). In models that adjusted for age, education, and *APOE* genotype, modified Framingham risk score was significantly associated with worse performance on the WAIS digit symbol over time and with worse performance on the Boston Naming Test over time (Table 3, model 2). These results did not significantly change in models adjusting only for age and education (data not shown). Moreover, the higher modified Framingham risk scores were associated with incrementally faster declines in WAIS digit symbol scores across age categories (54–70 yrs = -0.029 [95% CI $-0.066, 0.008$], 70–80 yrs = -0.035 [$-0.065, -0.005$], 80–86 yrs = -0.041 [$-0.092, 0.009$], time $\times$ modified Framingham Stroke Risk Profile score $\times$ age-group $p = 0.017$). Inclusion of a history of stroke or TIA in the model did not change these results (Table 3, model 3). We did not find a significant interaction between *APOE* genotype and Framingham risk score nor with specific vascular risk factors (data not shown). We also determined whether specific components of the modified Framingham Stroke Risk Profile score beside age influenced cognitive decline in these subjects. We found that no other components were independent predictors of differential rates of decline in cognitive scores. Finally, we observed no interaction between baseline scores for WAIS digit symbol or

baseline Boston Naming Test and modified Framingham Stroke Risk Profile score in predicting rates of change in these two cognitive tests ($p = 0.19$ and 0.90 , respectively).

Individuals with a previous history of stroke performed significantly worse on a subset of cognitive tests, both in cross-sectional and in longitudinal analyses. In adjusted baseline analyses, these individuals had significantly worse performance on Trails B and category fluency (vegetables), and a weaker association with Boston naming (Table 4). In adjusted longitudinal analyses, individuals with history of stroke had worse performance on delayed memory tests and digit span backwards over time (Table 4). In the individuals with no prior history of stroke at baseline ($n=2901$), 25 individuals developed a stroke during the follow-up period (total follow-up 9192 person-years). Assuming constant hazard, the rate of first ever stroke was 2.7/1000 person-years (95% CI 1.8 to 4.0). Individuals with incident stroke during the follow-up period had significantly lower MMSE score on subsequent follow-up visit compared to those without stroke after adjustment for age, education and *APOE* genotype (estimate = -0.419 , 95% CI -0.789 to -0.049 , $p=0.026$). We were unable to detect a difference in rate of cognitive decline between individuals with and without incident stroke (data not shown).

Finally, the effect of baseline variables on conversion to cognitive impairment or dementia (e.g. CDR 0.5 or CDR 1.0) at follow-up was examined using Cox-regression analyses. The hazard of transition from CDR 0 to CDR 0.5 or 1 increased 88% for a 10-unit increase in baseline modified Framingham risk score (HR = 1.88, 95% CI 1.36 to 2.59, $p < 0.001$). However, modified Framingham risk score was not associated with increased risk of conversion after adjustment for age (HR = 0.73, 95% CI 0.47 to 1.13, $p = 0.15$).

DISCUSSION

The major findings from this prospective longitudinal cohort are that late-life vascular risk factor burden (measured by Framingham Stroke Risk Profile) and stroke influence rate of cognitive decline in selective neurocognitive domains, however, age appears to play the predominant role in decline for most of these measures. Overall, it appears that age is the most important risk factor for cognitive decline in previously normal elderly individuals (mean age 72.1 years). History of stroke independently influences baseline cognitive function and rate of cognitive decline in specific domains in these individuals, independent of age.

Previous findings from cross-sectional analyses suggest an association between burden of vascular risk factors and cognitive function in older adults.^{1, 6, 22} Previous longitudinal analyses in middle-aged individuals have shown associations between vascular risk factors such as hypertension, diabetes, cholesterol, or smoking and cognitive decline^{26, 27} or dementia^{28, 29} in later life. However, the effect of these factors on predicting cognitive decline in older individuals has been less well studied. The average age of our cohort was 72.1 years with 9460 person-years of follow-up. Our results suggest that vascular risk factors may play a role in cognitive dysfunction in late life and extend the accumulating body of evidence^{9, 30} implicating these factors in the mechanisms underlying dementia. However, in contrast to the previous literature demonstrating that vascular risk factors in

mid-life strongly predict late life cognitive impairment^{20, 26, 27}, our results show considerably more modest effects independent of age. This may reflect more uniform vascular risk factor burden among older individuals and thus less independent variation available to assess associations separate from age. It may also suggest that the impact of vascular risk factor burden on cognition is attenuated by age effects in late-life or that compared to mid-life, some vascular risk factors may have inverse effects in late-life.^{31–33}

This study's primary strength is the large multicenter cohort of cognitively normal individuals with detailed clinical and neuropsychological assessments followed over time. Indeed, as cognitive trajectories likely differ among individuals identified as cognitively normal, those with the diagnosis of mild cognitive impairment, and those with AD^{34, 35}, considerable bias may be introduced in longitudinal analyses with heterogeneous groups of subjects.

Our results show that the age component of the Framingham Stroke Risk profile is the strongest predictor of decline in numerous cognitive domains, consistent with prior literature showing that age is strongly associated with risk of cognitive decline and dementia.^{36, 37} After controlling for age, many associations between the Framingham Stroke Risk profile and cognitive decline disappeared. However, we found strong evidence that vascular risk factors contribute independently to decline in processing speed in our cohort, after controlling for age. Vascular risk factors may contribute to impairment in these areas by causing lesions of small vessel disease that disrupt frontal connections implicated in executive function and processing speed. Indeed, previous studies have shown that lesions of small vessel disease, including white matter hyperintensities, contribute to impaired executive function and processing speed in population-based cohorts.³⁸ This has been shown to be related to the effect of these lesions on frontocortical connections^{39–41} and global brain network measures.⁴²

We had insufficient power to assess whether vascular risk factors independently affect the transition to dementia due to the small number of individuals who developed dementia over the relatively short follow-up time, although we cannot fully exclude bias due to possible selective drop-out of these individuals.⁴³ In contrast to a previous study which suggested that vascular risk factors may influence decline in cognitively normal individuals homozygous for the *APOE* $\epsilon 4$ allele⁴, we found no interaction between *APOE* genotype and vascular risk factors. Other larger studies will be needed to determine whether older individuals with higher Framingham risk score are at increased risk of developing dementia independent of age and *APOE* genotype.

Although our study demonstrates that vascular risk factor burden influences decline in specific areas of cognitive functioning as measured by a standard neuropsychological test battery, the precise mechanism through which this occurs requires further study. Brain ischemia, either symptomatic or silent, is more prevalent in persons with vascular risk factors and is one plausible mechanism by which vascular risk factors could cause cognitive impairment. Indeed, in our study we found an association between previous history of stroke and worse performance in several cognitive domains. Additionally, in the small subgroup of subjects with incident stroke during follow-up, we observed an association between incident

stroke and worse performance on subsequent MMSE testing. Although the incident stroke rate observed in our study is consistent with incidence rates in previous population-based studies^{44, 45}, we lacked sufficient power to determine whether incident stroke influences rate of cognitive decline or conversion from mild cognitive impairment to dementia (CDR 0.5 or CDR 1.0) during follow-up. Beyond symptomatic stroke, silent ischemic brain lesions and lower brain volumes identified on MRI have been associated with the Framingham Stroke Risk Profile in a previous population-based study.^{46, 47} Unfortunately, neuroimaging data are not available in the NACC database, therefore we were unable to determine whether silent brain lesions were a mechanism by which vascular risk factors were associated with cognitive decline. Future studies investigating the role of vascular factors in cognitive worsening should include detailed structural neuroimaging to better understand these relationships.

Our study has limitations. This study does not represent a true population-based cohort and thus considerable caution is warranted in generalizing our results to all older individuals. Cognitively normal individuals in our cohort may differ considerably from population-based samples in terms of vascular risk factors, stroke history, education and socioeconomic status. Only subjects with *APOE* genotyping were included in these analyses, but this is unlikely to have biased our results appreciatively because subjects with and without *APOE* genotype information were very similar (data not shown). Due to limited length of follow-up, we had low statistical power to assess the impact of vascular risk factor burden on conversion to AD in this cohort. Future studies from the NACC cohort with longer length of follow-up may be able to better address this issue. Finally, as routine detailed structural neuroimaging was not performed in the NACC cohort, we were unable to assess the precise impact of Framingham Stroke Risk profile on brain atrophy⁴⁶ or on cerebral small vessel disease.

In summary, this analysis of multicenter prospective longitudinal cohort data shows that late-life vascular risk factor burden in normal older adults plays a less important role in cognitive decline compared to the effects of age. Previous history of stroke appears to have independent effects on cognition in these individuals. Future studies should aim to further define the precise relationship between vascular risk factor burden, stroke, and cognitive dysfunction.

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Table 1
Baseline characteristics of the study cohort overall and stratified by Framingham risk score tertile.

Characteristic	Overall n=2975	0 – 10 n=955	11 – 15 n=1182	16 – 30 n=838	P-value
Age (years)	72.1±7.31	66.2±5.99	72.9±5.94	77.8±5.09	<.001
Male sex	33.9% (1008)	31.9% (305)	35.0% (414)	34.5% (289)	0.30
Years of Education	15.6±2.96	16.0±2.93	15.5±2.89	15.3±3.05	<.001
Number of APOE ε4 alleles					0.001
0	70.0% (2083)	68.4% (653)	68.6% (811)	73.9% (619)	
1	27.2% (810)	27.7% (265)	28.3% (335)	25.1% (210)	
2	2.8% (82)	3.9% (37)	3.0% (36)	1.1% (9)	
History of Stroke	2.4% (70)	0.5% (5)	1.9% (23)	5.0% (42)	<.001
History of transient ischemic attack	4.6% (136)	2.0% (19)	3.9% (46)	8.5% (71)	<.001
Use of anti-hypertensive agents [†]	56.2% (1671)	18.3% (175)	63.4% (749)	89.1% (747)	<.001
Systolic blood pressure [†]	133±17.7	124±14.1	135±15.9	141±18.6	<.001
Diastolic blood pressure [†]	74.0±10.1	73.2±9.77	74.6±9.91	73.8±10.8	0.004
CDR-sum of boxes					0.175
0	96.8% (2881)	97.0% (926)	97.5% (1152)	95.8% (803)	
0.5	3.1% (93)	3.0% (29)	2.5% (29)	4.2% (35)	
1	0.0% (1)	0.0% (0)	0.1% (1)	0.0% (0)	
Number of visits	3.77±1.30	3.61±1.30	3.81±1.29	3.89±1.29	<.001
Follow-up (years)	3.18±1.35	3.03±1.34	3.23±1.34	3.28±1.34	<.001
MMSE	29.0±1.29	29.2±1.16	29.0±1.21	28.8±1.48	<.001
Trails B test	84.8±38.9	72.9±32.3	86.3±38.7	96.8±42.2	<.001
Logical memory, immediate recall	13.7±3.91	14.3±3.73	13.4±3.97	13.5±3.98	<.001
Logical memory, delayed recall	12.4±4.26	13.0±4.07	12.2±4.30	12.1±4.36	<.001
Digit-span forward	6.78±1.07	6.85±1.05	6.78±1.06	6.71±1.10	0.018
Digit-span backward	4.95±1.23	5.10±1.25	4.89±1.21	4.86±1.22	<.001
WAIS Digit Symbol	48.0±11.9	52.9±11.4	47.1±11.7	43.6±10.7	<.001

[†] components of the Framingham Stroke Risk profile

Baseline analyses. Regression coefficients for modified Framingham risk score from mixed-effect models testing associations with global and domain-specific cognitive measures.

Outcome	Model 1		Model 2		Model 3	
	Adjusted for Education only		Adjusted for Education, Age, APOE		Adjusted for Education, Age, APOE, history of stroke/TIA	
	Est [95% CI]	P	Est [95% CI]	P	Est [95% CI]	P
MMSE	-0.025 [-0.035 -0.016]	<.001	-0.011 [-0.024 0.002]	0.098	-0.010[-0.023 0.003]	0.135
Trails B test	0.904 [0.650 1.158]	<.001	0.336 [0.003 0.669]	0.048	0.286 [-0.048 0.619]	0.093
Logical memory, immediate recall	-0.046 [-0.076 -0.016]	0.003	-0.007 [-0.048 0.033]	0.718	-0.007 [-0.048 0.033]	0.733
Logical memory, delayed recall	-0.063 [-0.096 -0.030]	<.001	-0.018 [-0.062 0.026]	0.428	-0.017 [-0.061 0.027]	0.451
Digit-span forward	-0.009 [-0.017 -0.001]	<.030	-0.003 [-0.014 0.008]	0.576	-0.002 [-0.013 0.009]	0.695
Digit-span backward	-0.015 [-0.025 -0.006]	<.002	-0.009 [-0.022 0.003]	0.149	-0.010 [-0.022 0.003]	0.142
WAIS Digit Symbol	-0.719 [-0.807 -0.631]	<.001	-0.265 [-0.378 -0.151]	<.001	-0.254 [-0.368 -0.140]	<.001
Boston Naming test	-0.048 [-0.071 -0.026]	<.001	0.015 [-0.015 0.045]	0.325	0.018 [-0.012 0.049]	0.236

Table 3

Longitudinal analyses. Regression coefficients for the modified Framingham risk score $\times$ time (in years) interaction terms from mixed-effect models testing associations with global and domain-specific cognitive measures and CDR sum-of-boxes.

Outcome	Model 1		Model 2		Model 3	
	Adjusted for Education only	P	Adjusted for Education, Age, APOE	P	Adjusted for Education, Age, APOE, history of stroke/TIA	P
	Est [95%CI]		Est [95%CI]		Est [95% CI]	
MMSE	-0.008 [-0.012 -0.004]	<.001	0.000 [-0.006 0.006]	0.977	0.000 [-0.006 0.006]	0.988
Trails B test	0.122 [0.042 0.201]	0.003	-0.029 [-0.133 0.075]	0.583	-0.019 [-0.123 0.085]	0.718
Logical Memory, immediate recall	-0.015 [-0.023 -0.007]	<.001	0.003 [-0.008 0.014]	0.614	0.004 [-0.007 0.015]	0.520
Logical Memory, delayed recall	-0.019 [-0.028 -0.010]	<.001	0.004 [-0.008 0.016]	0.500	0.005 [-0.007 0.017]	0.398
Digit-span forward	-0.001 [-0.003 0.001]	0.325	0.001 [-0.002 0.004]	0.589	0.001 [-0.002 0.004]	0.571
Digit-span backward	-0.004 [-0.006 -0.001]	0.003	-0.001 [-0.005 0.002]	0.430	-0.001 [-0.004 0.002]	0.571
WAIS Digit Symbol	-0.060 [-0.076 -0.045]	<.001	-0.032 [-0.053 -0.011]	0.002	-0.032 [-0.053 -0.010]	0.004
Boston Naming Test	-0.013 [-0.018 -0.008]	<.001	-0.008 [-0.015 -0.000]	0.038	-0.007 [-0.014 -0.000]	0.046
CDRSUM	0.008 [0.005 0.011]	<.001	0.001 [-0.002 0.005]	0.497	0.001 [-0.003 0.005]	0.554

Table 4

Individuals with history of stroke had worse performance on selective cognitive tests in baseline and longitudinal mixed-effect models.

Cognitive Test	Model		Model	
	Baseline Analyses		Longitudinal Analysis	
	Adjusted for modified Framingham score, education, APOE, history of TIA		Adjusted for modified Framingham score, education, APOE, history of TIA	
	Est [95% CI]	P	Est [95% CI]	P
MMSE	-0.124 [-0.289 0.040]	0.139	-0.059 [-0.188 0.069]	0.364
Trails B test	6.706 [2.434 10.979]	0.002	-1.596 [-3.993 0.802]	0.192
Category fluency (vegetables)	-0.958 [-1.551 0.365]	0.002	-0.056 [-0.327 0.215]	0.685
Logical Memory, immediate recall	0.083 [-0.426 0.591]	0.750	-0.214 [-0.463 0.035]	0.093
Logical Memory, delayed recall	0.092 [-0.462 0.646]	0.744	-0.292 [-0.560 -0.023]	0.033
Digit span forward	-0.090 [-0.229 0.049]	0.206	-0.020 [-0.087 0.047]	0.557
Digit span backwards	-0.014 [-0.176 0.147]	0.862	-0.089 [-0.163 -0.014]	0.019
Boston Naming Test	-0.387 [-0.772 0.002]	0.049	-0.078 [-0.240 0.083]	0.382
WAIS Digit Symbol	-1.097 [-2.595 0.401]	0.151	-0.219 [-0.702 0.264]	0.374