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Apoe E4 Carrier Status And Prestroke Cognitive Function In A Case/Cohort Sample Of Incident Stroke From The Reasons For Geographic And Racial Differences In Stroke (Regards) Study

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ABSTRACT

This study explores the role of ApoE e4 in cognitive function and incident stroke to better understand the risk of cognitive decline associated with both normal aging and dementia. ApoE e4 is a genetic risk factor for mild cognitive impairment and dementia, and may have detrimental effects on cerebrovascular integrity by increasing the risk of acquiring cerebrovascular abnormalities such as white matter lesions (WMLs), infarcts, and cerebral microbleeds. Subtle cognitive impairments may reflect these clinically undetected brain vascular pathologies that also are associated with increased likelihood of incident stroke. Results of the study revealed that ApoE e4 was associated with poorer performance on select domains of cognitive function, memory and learning. In addition, there was a significant interaction between stroke risk factors and ApoE e4 in regression models of memory performance, suggesting that the risk of ApoE e4 on cognition is greater at in the presence of a high number of stroke risk factors. It is possible that the interplay of these factors (ApoE e4, stroke risk factors) may help identify populations that are more vulnerable to cognitive impairment and the associated personal and public health burden.

The results also identify potential targets for interventions that may reduce the personal, caregiver, and public health burden associated with cognitive decline including

treatment of comorbid cerebrovascular risk factors to reduce the risk conferred by ApoE e4 on cognition; and assessment and intervention for psychological symptoms associated with cognitive decline. We believe that the current findings contribute to efforts to identify at risk patients and provide services and care that reduce risk and promote independence and quality of life in our aging population.

Keywords: ApoE e4, aging, cognitive function, psychology

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Hypothesis 1.2: This association will remain after adjustment for demographic variables (sex, race, education, region of residence) and time to event.

Hypothesis 1.3: The association between ApoE status and incident stroke and will be attenuated after adjustment for cardiovascular risk factors (hypertension, dyslipidemia, heart disease, diabetes, and smoking).

Aim 2: Evaluate the relationship between ApoE e4 status and prestroke cognitive function.

Hypothesis 2.1: ApoE e4 carrier status will be associated with lower scores on prestroke assessments of learning, memory, and executive function in the combined sample of incident stroke cases and cohort random sample members, *in a model* adjusting for demographics and Framingham stroke risk factors.

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ApoE e4 CARRIER STATUS AND PRESTROKE COGNITIVE FUNCTION

The current study examined the associations between cognitive function, incident stroke, cerebrovascular risk factors, and apolipoprotein E (ApoE) e4 carrier status in a population based, stroke case-cohort sample from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. ApoE e4, a genetic risk factor for mild cognitive impairment and dementia, may have detrimental effects on lipid metabolism and cholesterol clearance that increases the risk of acquiring cerebrovascular abnormalities such as white matter lesions (WMLs), infarcts, and cerebral microbleeds. Such cerebrovascular pathologies resulting from e4 carrier susceptibility as well as stroke risk factors may lower the threshold for detectable cognitive impairment and incident dementia. Numerous studies have found that individuals with cognitive impairments have high loads of white matter lesions, infarcts, and cerebral microbleeds (e.g., Pantoni, 2010) in addition to cardiovascular and cerebrovascular risk factors (Unverzagt et al, 2011). Consequently, even subtle cognitive impairments or changes may reflect clinically undetected brain vascular pathologies that also are associated with increased likelihood of incident stroke. Furthermore, it is possible that the interplay of these factors (ApoE e4, cerebrovascular risk factors, lower cognitive function) may help identify populations that are more vulnerable to stroke and cognitive impairment and the associated personal and public health burden.

I will review how ApoE e4 status may predispose individuals to acquiring the cerebrovascular risk factors and underlying cerebral abnormalities that could explain both

cognitive impairments and incident stroke by reviewing and integrating the current literature on ApoE e4 status and cognitive impairment, and ApoE e4 status and incident stroke. I will provide background on ApoE and some of the proposed physiological mechanisms associated with it that may link ApoE with cognitive function. I also will discuss hypotheses explaining the relationship between cognitive function and incident stroke, including the conceptualization of prestroke cognitive function as a manifestation of underlying cerebral abnormalities, and the contribution of cerebrovascular risk factors to cognitive function.

ApoE Genotype

Apolipoprotein E (ApoE) genotype—in particular, the presence of one or two ApoE e4 alleles—is associated with cognitive function and dementia in older adults, hippocampal volume reduction, and cardiovascular risk factors (Boyle, Buchman, Wilson, Kelly, & Bennett, 2010; Hostage, Choudhury, Doraiswamy, & Petrella, 2013; Yasuno et al., 2012). More recent literature has also examined the role of ApoE e4 in the relationship of poor and impaired cognitive function and incident stroke. The ApoE gene has two common polymorphisms, rs429358 and rs7412, which yield three ApoE alleles (e2, e3, e4) which are then expressed as six possible genotypes (e2/e3, e2/e2, e2/e4, e3/e3, e3/e4, and e4/e4) (Mahley & Rall, 2000). The distribution of ApoE genotypes varies across populations. The estimated gene frequencies in the general population for e2, e3, and e4 in African Americans are 13.1%, 66.8%, and 20.1%, respectively. In Caucasian Americans, the frequencies of e2, e3, and e4 are estimated to be 8.3%, 78.7%, and 13.3%, respectively (Eichner et al, 2002).

The exact mechanism by which ApoE may contribute to dementia, vascular risk factors, and possibly stroke are not yet clear. However, evidence suggests that one's ApoE genotype may affect stroke risk and cognitive functioning by coding for protein involved in lipid metabolism and clearing of cholesterol from blood (Sing & Davignon, 1985; Yasuno, Tanimukai, Sasaki, Ikejima, Yamashita et al, 2012). This function of ApoE may be implicated in stroke risk factors such as dyslipidemia, diabetes, and hypertension that are also known to affect cognitive function (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Yasuno et al, 2012). ApoE has also been shown to bind to amyloid beta (Aβ) protein and facilitate neuronal uptake, increase production of Aβ, and relate to Aβ toxicity (Yang, Mehta, Bates, Sun et al, 2011). E4 carriers may be less efficient at clearing beta amyloid than other genotypes. In effect, these mechanisms contribute to increased risk of cognitive impairment and dementia in e4 carriers. ApoE may be implicated in neuronal injury and repair (Yang, Mehta, Bates, Sun et al., 2011) as well as molecular changes in brain structures related to memory including the hippocampus and caudoputamen. Perhaps the most recognized theory is the vascular hypothesis with a strong relationship between ApoE e4 and cerebral hypoperfusion in the Baltimore Longitudinal Study of Aging (Thambisetty, Beason-Held, An, Kraut, Resknick, 2010). Although the exact mechanisms remain unclear, research has suggested multiple pathways through which ApoE e4 may impact cognitive function.

ApoE e4 and Cerebral Abnormalities

Cerebral abnormalities, which may underlie reduced performance on measures of cognitive function in non-demented adults, are highly prevalent and often under-diagnosed in the general population, even in the absence of TIA or stroke (de Groot et al., 2000; Longstreth et al., 2000; Mosley et al., 2005). Cerebrovascular risk factors such as hypertension increase the risk for developing cerebral abnormalities, although not everyone with these risk factors will develop such abnormalities, suggesting the possibility of mediating factors, such as ApoE genotype (de Leeuw, Richard, de Groot, van Duijn & Hofman, 2004; Espeseth, Westly, Fjell, Walhovd, & Rootwelt, 2006). Espeseth and colleagues (2006) found that ApoE e4 significantly accelerated aging trajectories of cortical thinning in the medial prefrontal and pericentral cortex, regions typically vulnerable to age-related neural changes. Steeper rates of cortical thinning also were evident in the occipito-temporal and basal temporal cortex, regions often implicated in AD and Aβ pathology.

ApoE genotype, particularly in e4 carriers, may be a determinant of the development of cerebral abnormalities in those with cardiovascular risk factors. For example, De Leeuw and colleagues investigated ApoE genotype and blood pressure in relation to subcortical and periventricular WMLs in 971 participants from the Rotterdam Scan Study. They found that ApoE e4 carriers had significantly higher subcortical WML volume than non-carriers (e3/e3 genotype). In addition, results of linear regression analyses illustrated that individuals with at least one ApoE e4 allele in addition to hypertension had significantly greater subcortical white matter lesion volumes in

comparison to e3 carriers when controlling for age, sex, body mass index (BMI), peripheral arterial disease, diabetes, and study site. Not only may ApoE e4 contribute to higher incidence of WMLs, but also, the effect of ApoE on the development of WMLs may be enhanced when in combination with cardiovascular risk factors.

A twin study on ApoE e4, vascular disease, and brain morphology by DeCarli, Reed, Miller et al (1999) provided evidence that ApoE e4 status may increase the occurrence of brain abnormalities, particularly in the presence of vascular disease. The study included 396 twins with concordant ApoE genotyping with a mean age of 72.3 years (*SD* = 2.8) and 72.7 (*SD* = 3.0) for e4 carriers and non-carriers, respectively. Participants were further classified by the presence or absence of cardiovascular disease. Results of the study showed that e4 carriers had significantly smaller average brain volumes than noncarriers when accounting for age and head size. In individuals without cardiovascular disease (CVD), there were no differences in measures of brain parenchyma, intracranial fluid, or white matter hyperintensities between e4 carriers and noncarriers. However, in the presence of CVD, ApoE e4 carriers showed greater reduction in brain volume and larger white matter hyperintensity volumes. The presence of ApoE e4, alone, may not be a risk factor for cerebral abnormalities underlying cognitive impairment. Rather, the moderation of CVD and ApoE e4 could contribute to declining cerebral integrity and cognitive function in non-demented elderly adults.

ApoE Genotype and Stroke Risk

Given the underlying pathology, it is no surprise that ApoE e4 genotype may be a risk factor for numerous biomarkers of cerebrovascular and cardiovascular disease. For example, results from the same twin study of ApoE genotype, vascular disease, and brain morphology revealed that e4 carriers have significantly higher rates of coronary heart disease in comparison to noncarriers (40.7% versus 29.8%; $p = .03$) and marginally higher rates of peripheral arterial disease (12.7% versus 7.4%; $p = .07$), consistent with the hypothesis that effects of ApoE e4 on atherosclerosis may contribute to cardiovascular disease (DeCarli, Reed, Miller et al., 1999). Several studies have suggested a dose-response relationship between ApoE genotype and cerebrovascular risk factors. For example, there may be a positive dose-response relationship between ApoE genotype (i.e., carriers of 0, 1, or two e4 alleles) and low-density lipoprotein cholesterol (LDL-C), triglycerides, and total cholesterol, with e4 carriers having higher levels in comparison to all other ApoE genotypes (Khan et al., 2013). With respect to cognitive function, Haan and colleagues (1999) found evidence of gene-environment interactions in which individuals with the ApoE e4 allele in combination with atherosclerosis, peripheral vascular disease, or diabetes are at substantially higher risk of cognitive decline than those without the ApoE e4 allele or the symptoms of subclinical cardiovascular disease (Haan et al, 1999). The intricacies of such possible gene-environment interactions are not fully understood, and this remains an active area of research with ongoing studies on the associations between ApoE genotype and an array of cardiovascular biomarkers.

Associations between ApoE genotype, cerebrovascular risk factors and cerebral abnormalities are only indirect evidence for a relationship between ApoE genotype and

incident stroke. There is less consensus and understanding on the role of ApoE genotype in clinically defined stroke events (Sudlow, Gonzalez, Kim, Clark, 2006). Results from the Kungsholmen project showed an increased risk of incident stroke for individuals with mild cognitive impairment and dementia, suggesting that ApoE status, which is implicated in these conditions, may be particularly important in a sample of incident stroke cases (Zhu et al., 2000). A review of 41 studies with 14,015 stroke cases and 77,888 controls found that the ORs for ischemic stroke were significantly elevated for e3/e4 and e4/e4 genotypes in comparison to the reference genotype e3/e3 with ORs = 1.15 (95% CI = 1.09, 1.21) and 1.22 (95% CI =1.05, 1.41), respectively (Khan, Shah, Prieto, et al., 2013). A study of 322 first-ever stroke patients and 1126 controls, mean age 67.9 years (*SD = 11*) and 64.3 years (*SD* = 10) in a Japanese rural population found that ApoE e4 carriers had a 2.5 fold risk of subarachnoid hemorrhage (OR = 2.5, 95% CI = 1.1 to 5.4) (Kokubo, Chowdhury, Date, Yokoyama et al., 2000). In contrast, a population based study of 1810 person aged 75 years and older from the Kungsholmen Project failed to find an association between ApoE genotype and incident stroke, although risk of hemorrhagic stroke was associated with e3/e4 genotype in subjects who survived a prior stroke. This finding may lend itself to the hypothesis that the relationship between ApoE genotype and stroke risk is more meaningful in high-risk populations. Additional studies on the associations of ApoE genotypes and stroke have yielded inconsistent findings and warrant further investigation of the relationship (Basun et al., 1996; Gu et al., 2013; Kokubo et al., 2000). To date, there is substantial evidence to warrant further investigation of the relationships between ApoE genotype, cardiovascular risk factors, cognitive function, and stroke

ApoE e4 and Cognition

Given the possible effect of ApoE on cerebrovascular risk factors and cerebral abnormalities, it is not surprising that studies demonstrate that ApoE e4 is also associated with poorer cognitive function. ApoE e4 is a well-documented risk factor for Alzheimer's disease (AD). In fact, one study reported that the risk of AD increases from 20 percent to 90 percent in those with two e4 alleles (Corder, Saunders, Strittmatter, 1993). However, there is less evidence that ApoE e4 contributes to poorer cognitive function in elderly individuals who are not demented but have poorer functional status and lower cognitive performance (Brayne, Harrington, Wischik et al, 1996; Helkala, Koivisto, Hanninen, et al, 1996). One study demonstrated that ApoE e4 genotype independently contributes to cognitive decline in middle age and elderly adults even after controlling for cardiovascular conditions and lipid profiles (e.g., Knopman, Mosley, Catellier, & Coker, 2009), while other large population-based studies have failed to find a significant effect of ApoE genotype on cognitive function in non-demented elderly (e.g., Jorm et al., 2007).

Bretsky, Guralni, Launer, Albert, and Seeman (2003) analyzed longitudinal data from the MacArthur Study of Successful Aging to examine the effect of ApoE-e4 genotype on cognitive decline at three and seven years following baseline assessments. The MacArthur Study of Successful Aging was a population-based prospective study of relatively high-functioning men and women between the ages of 70 and 79 years. The 965 eligible participants completed assessments of physical and cognitive function, and ApoE genotyping. Cognitive tests included a modified version of the Similarities subtest from the WAIS-R, delayed spatial recognition, a modified 18-item version of

the Boston Naming Test, and a "figures" task to assess spatial ability. Results of the study showed that ApoE e4 carriers were 2.9 times more likely to have declined in their performance on the naming tests and 2.0 times more likely to have declined performance on the figure-copy test in comparison to non-e4 carriers when controlling for demographic variables (age, education, gender, ethnicity), health status factors (BMI, self-rated health), and health behaviors (smoking, alcohol consumption, activity level). At the seven-year follow-up, individuals who were ApoE e4 carriers were twice as likely to have decline on the global cognitive summary score than non-carriers. In addition, e4 carriers had a significantly elevated risk of decline on four of the individual measures of cognitive function (naming, figures, similarity, spatial recognition). Also of importance, Bretsky and colleagues did not find that the effect of ApoE e4 on cognition differed by age, in contrast to many studies that have suggested the risk of cognitive decline associated with e4 peaks in the 7th but often diminishes by the 8th decade of life (Letter et al, unpublished manuscript; Smith, Bohac, Waring et al, 1998). This study by Bretsky and colleagues is limited by its inclusion of only "high-functioning" individuals between the ages of 70 and 79 years. This likely resulted in a biased sample; therefore, the findings may have limited generalizability.

It is also unclear whether ApoE e4 status is differentially associated with individual domains of cognitive function. Caselli, Reiman, Locke, et al (2007) concluded that e4 homozygotes (those with two e4 alleles) had a higher proportion of cognitive domain decline than e4 heterozygotes (those with one e4 allele) or non-carriers in a sample of 214 participants aged 50 to 69 years. Results of the study illustrated that declines in memory performance occurred more frequently in e4

homozygotes in comparison to e4 heterozygotes and non-carriers (15.2 versus 8.6 percent), although the study lacked the power to test the statistical significance of this difference. Caselli, Reiman, Osborne, et al (1990) completed an earlier study with a more comprehensive neuropsychological test battery. The study included 180 participants with a mean age of 60 years (SD = 6.2). There were no significant differences in performance on measures of any of the cognitive domains assessed (memory-verbal, language-naming, spatial skills-perceptual, executive function-problem solving) at baseline. In longitudinal analyses, e4 carriers had steeper rates of decline in memory performance and higher depression scores than non-carriers over 33 months. There were no differences between e4 carriers and noncarriers on measures of general intelligence, language, spatial skills, or executive function.

Cognitive Function as a Marker of Stroke Risk

Converging evidence indicates that cognitive impairment is associated with a higher risk of stroke in older adults (Lee, Saver, Hong, Wu, et al., 2014; Rostamian, Mahinrad, Stijnen, Sabayan, & de Craen, 2014). Additionally, studies have estimated that approximately ten percent of stroke patients may have pre-existing dementia (Pendlebury & Rothwell, 2009; Henon, Pasquier, Durieu, et al., 1997; Zhu, Fratiglioni, Guo, et al., 2000). Meta-analyses of published studies on cognitive impairment and stroke as of 2014, found that one standard deviation (SD) lower performance in cognitive tests was associated with 15% higher risk of incident stroke (Rostamian et al., 2014). Furthermore, impairments in different cognitive domains (executive function, memory, and language) were independently associated with elevated stroke risks, with a *trend* for higher stroke risks with executive function and attention impairments in

comparison to memory and language impairments. This finding is consistent with the clinical presentation of vascular cognitive impairment, which includes hallmark executive function and attention impairments (O'Brien et al., 2003). The following studies also support a robust relationship between cognitive impairment and higher stroke risk.

In cross-sectional studies, Pavlik and colleagues (2005) examined the association of HTN, DM, and other CVD risk factors with cognitive function in a sample of 3,385 men and women between the ages of 30 and 59 from the Third National Health and Nutrition Examination Survey (NHANES III). The combination of HTN and DM was significantly associated with worse performance on both the Simple Reaction Time Test (SRTT) and the Symbol Digit Substitution Test (SDST). Interesting, neither HTN nor DM, alone, was associated with performance on any measure of cognitive function. Results from the Framingham Heart Study indicated that a higher stroke risk score was associated with performance deficits on measures of multiple cognitive domains including abstract reasoning, visual spatial memory, visual organization, concentration, visual scanning, and tracking **(**Elias et al., 2004).

Elkins, O'Meara, Longstreath, Carlson, Maolio, & Johnston (2004) extended the research on cognitive function and stroke risk by examining how modifiable stroke risk factors may contribute to longitudinal, age-related declines in cognitive function in 5,264 individuals from the Cardiovascular Health Study (CHS), a population based, longitudinal study of cardiovascular disease in adults over the age of 65 years. All participants in the study completed cognitive assessments including an annual Modified Mini-Mental State Examination (3MS), a modified Mini-Mental State Examination

(MMSE) with delayed recall and verbal fluency tests, and the Digit-Symbol Substitution test (DSST). Longitudinal analyses included logistic regression models to estimate OR for cognitive decline as a function of baseline cognitive function and stroke risk quartiles. Elkins and colleagues hypothesized that individuals with high levels of baseline cognitive function may be less susceptible to the effects of stroke risk factors on cognition. Results supported their hypothesis. The risk of decline in 3MS and DSST scores at follow-up an average of 4.9 years later (SD = 1.6 years) significantly increased with quartile of stroke risk scores. However, the authors found support for their theory that individuals with high levels of cognitive function may be less susceptible to risk factors (such as cardiovascular risk factors) for cognitive decline. Furthermore, this apparent resilience may not be a function of merely less exposure to such risk factors because individuals with high baseline cognitive function but with high stroke risk scores did not have increased risk of cognitive decline.

Elias, Sullivan, D'Agostino, and colleagues (2004) evaluated the relationship between 10-year risk for stroke and multiple measures of cognitive performance in 1,011 men and 1,164 women with a mean age of 60.7 years (SD = 9.4 years, range = 33 - 89 years) from the Framingham Offspring Study using a cross-sectional design. Framingham stroke risk profiles (FSRPs) were calculated for each participant based on age, systolic blood pressure, antihypertensive medication, diabetes, cigarette smoking, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. In comparison to other studies of stroke risk reviewed, Elias et al used a more comprehensive battery of cognitive tests, that included the Similarities subtest from the Wechsler Adult Intelligence Scale (WAIS); the Paired Associates, Logical Memory, and Visual

Reproduction subtests from the Wechsler Memory Scale (WMS); Trail-making tests A & B, and the Hooper Visual Organization test**.**

Multiple multivariate linear regression models analyzed the relationship between FSRP, the independent variable, and cognitive performance on individual tests as well as cognitive composite scores. Results showed that each 10% increase in 10-year risk for stroke was associated with a -0.15 SD decrease in Visual-Spatial Memory and Organization composite scores and a -0.14 SD decrease in Concentration, Visual Scanning, and Tracking composite scores; and a -.011 SD decrease in scores on the Similarities subtest. These results remained after adjustment for alcohol consumption, BMI, total cholesterol, and depressed mood.

Similarly, the relationship between cardiovascular risk factors indicative of stroke risk and incidence of cognitive impairment was examined in sample of 23,752 participants, mean age of 64.3 years (SD = 9.2), from the REGARDS study (Unverzagt, McClure, Wadley et al, 2011). Results from this study suggested that stroke risk (FSRP score) was linearly related to rate of incident cognitive impairment in participants free of cognitive impairment and stroke at enrollment. In addition, all of the variables of the FSRP were significant univariate predictors of cognitive impairment.

Importantly, the findings from Elias and colleagues (2004) and Unverzagt and colleagues (2011) highlight that even in the absence of stroke, stroke risk factors are associated with impairments in cognitive function. In addition, in contrast to comparable studies in the field, these associations were significant for a wider range of cognitive domains including abstract reasoning, visual-spatial memory, visual organization, concentration, visual scanning, and tracking, as defined by Elias et al

(2004). However, stroke risk was not significantly associated with verbal memory. The authors concluded that the pattern of results -- deficits in motor performance, visuospatial, visual organizational and visual constructional abilities -- was similar to that seen in vascular dementia and vascular cognitive impairment. Overall, these studies provide further evidence that stroke risk factors may be related to poorer performance on a wide range of cognitive tests.

Interestingly, some studies have yielded conflicting results on the role of cardiovascular risk factors as contributors to the predictive value of cognitive impairment or performance levels for incident stroke. Early studies on the relationship of blood pressure, antihypertensive medications and cognitive performance in a sample of 1,993 men and women, aged 55-89 years, from the Framingham Study concluded that neither blood pressure nor antihypertensive medications was associated with cognitive performance (Farmer et al., 1987). In addition, Ferrucci, Guralnik, Salive, Pahor, Corti and colleagues (1996) found that neither hypertension nor diabetes mediated the association between cognitive impairment and incident stroke.

Stroke Risk, Cognition, and Age

It is possible that the variable relationship between stroke risk and cognitive impairment may relate to age. Sabayan and colleagues (2013) studied the predictive value of Framingham stroke risk score and cognitive impairment for incident stroke in a sample of 480 subjects, all aged 85 years and followed for five years. In this age group, individuals with higher Framingham risk scores did not have higher risk of stroke in comparison to those with low Framingham risk scores. However, cognitive function (MMSE scores) had discriminative power to predict stroke. The results of Sabayan and colleagues suggest that the predictive power of cardiovascular risk factors and cognitive impairments in stroke risk may be age-dependent, and that in "oldest old" cardiovascular risk factors may be less predictive of incident stroke. However, cognitive function remained a strong predictor of incident stroke even in this age group.

Elias et al (2004) found that each of the individual risk factors of the FSRP (age, systolic blood pressure --SBP, antihypertensive medication, diabetes, cigarette smoking, CVD, atrial fibrillation--AFib, and left ventricular hypertrophy--LVH) was inversely related to performance on cognitive tests of concentration, visual scanning, and visual tracking when adjusting for age, education, sex, depression, alcohol consumption, smoking, and total cholesterol. With adjustment for only age, education, and occupation all risk factors were also inversely related to Visual-Spatial performance. Similarly, Elkins and colleagues (2004) found a robust decrease in odds of having high cognitive function with each quartile increase in stroke risk score (Cardiovascular Health Study [CHS] stroke risk score) after adjustment for both demographic factors and ApoE genotype. However, only two (systolic blood pressure

and gait speed) of the nine individual risk factors comprising the CHS stroke risk score were significantly associated with cognitive function.

Prestroke Cognitive Function and Cerebral Abnormalities

The relationship between cognitive impairment and stroke often remains even when controlling for cardiovascular risk factors, suggesting that additional factors may contributeto the relationship between cognition and stroke risk (Rostamian et al., 2014). Prestroke cognitive impairments or lowered performance may also reflect underlying cerebral abnormalities such as small cerebral infarcts and white matter hyperintensities that are often undetected in routine clinical settings (de Groot et al., 2000; Longstreth et al., 2000; Vermeer et al., 2003; Zhu et al., 2000). Such cerebral abnormalities may not only explain cognitive impairments, but also, may develop into clinical stroke over time (Zhu et al., 2000). These cerebrovascular abnormalities (disease) may underlie the association between ApoE e4, stroke risk factors, cognition, and incident stroke.

Subtle neuroimaging abnormalities may be related to cognitive function in elderly adults without diagnoses of dementia (Inzitari, Pozzi, Ferrucci et al., 2008). Studies have shown that there is an association between imaging findings on MRI, including WML and reduced brain volumes, and lower performance of several cognitive tests (Au, Mascara, Wolf et al., 2006; de Groot et al., 1998; Mosley, Knopman, Catellier et al., 2005). Mosley and colleagues investigated ventricular size, white matter hyperintensities (microangiopathy), and sulcal size in relation to performance on delayed word recall test (DWRT), Digit Symbol Substitution test (DSST), and Word Fluency test (WFT). The study sample included 1,538 participants from the ARIC study with a mean age of 62.5 years (SD = 4.5) with no known history

of stroke or TIA. The study showed that high ventricular grade was associated with lower scores on the DWRT and DSST, and high sulcal grade was associated with lower scores on the DWRT. In addition, white matter hyperintensities and silent infarcts were related to significantly worse performance on all cognitive tests and greater risk of impaired performance on the DSST, in longitudinal analyses. These findings were important in that they illustrated how changes in brain morphology are associated with cognitive function in "neurologically healthy" adults.

Cognitive Function and Incident Stroke

Ferrucci and colleagues (1996) provided foundational research on cognitive impairment and the risk of incident stroke, as opposed to 10-year stroke risk calculations. Their work was driven by the theory that a large proportion of dementia in old age is an early marker of cerebrovascular disease that later becomes clinically evident as acute cerebrovascular events, such as stroke. The study included 5,024 individuals, ages 65 to 103 years, from the Established Populations for Epidemiologic Studies of the Elderly with no baseline history of stroke. Cognitive function was assessed using the Short Portable Mental Status Questionnaire (SPMSQ), and stroke occurrence was ascertained by hospital discharge diagnoses and death certificates. Results revealed that stroke incidence reflected prior performance level on the SPMSQ. Stroke incidence was lowest for those with scores within the "normal" range on the SPMSQ (12.1/1000 person-years), intermediate for those with scores suggesting moderate impairment (16.3/1000 person-years), and highest for those with scores suggesting severe impairment (30.9/1000 person-years). The relative risks of stroke for those with moderate and severe cognitive impairment were 1.2 (95% CI = 0.9, 1.6) and

2.2 (95% CI = 1.2, 3.8), respectively, when controlling for age, education, smoking, hypertension, blood pressure, heart attack, diabetes, and disability; however, neither hypertension nor diabetes mediated the association between cognitive impairment and incident stroke. Although the study lacked a comprehensive assessment of cognitive function, it provided evidence for a robust relationship between cognitive function and incident stroke that may prove independent of the contribution of cardiovascular risk factors, such as hypertension and diabetes.

Zhu and colleagues (2000) contributed to the investigation of cognitive function and incident stroke by examining the association in a community-based cohort of individuals over the age of 75 years. The study used data from the Kungsholmen Project, a longitudinal study of aging and dementia in the Kungsholmen district of Stockholm. A total of 1,551 participants were included in the study. Baseline interviews were conducted between October 1987 and April 1989 and participants were followed through the Stockholm inpatient register until the date of the first stroke event or death or until three years post-baseline. Dementia was detected using a screening phase and a clinical examination phase. All participants completed the Mini-Mental State Examination (MMSE) at baseline to screen for dementia. Scores on the MMSE range from 0 (worst) to 30 (best), and individuals who scored at or below 23 or 24 were considered to be at risk for dementia and further evaluated using clinical evaluation and diagnostic criteria for dementia from the Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised (DSM-III-R).

Those with scores lower than 23 or 24 on the MMSE who did not meet criteria for a diagnosis of dementia were defined as having cognitive impairment. The rest of the participants were defined as having "good cognition."

The group used Cox proportional hazards regression analyses to estimate the relative risk (RR) of stroke from dementia status and baseline MMSE score. Covariates included age, gender, education, disability, systolic blood pressure, antihypertensive drug use, heart disease, and diabetes mellitus. Based on MMSE score only, there was a clear dose-response relationship between MMSE score and incident stroke ($p = .01$) with lower scores on the MMSE associated with higher risk of stroke. Participants with MMSE scores of 0 to 17 and 18 to 23 had significantly higher incidence of stroke in comparison to participants with MMSE scores of 28 to 30. Cox proportional hazards regression analyses showed that individuals with mild dementia had more than a twofold higher risk of stroke than those with "good cognition" or cognitive impairment. There was also a trend for individuals with cognitive impairment to have a higher relative risk for stroke than those with "good cognition." Similarly, unpublished results of analyses using data from the REGARDS study concluded that lower executive function and memory scores were associated with significantly elevated hazards ratios for incident stroke (Letter et al., unpublished manuscript).

The results of the study by Zhu and colleagues (2000) leave the role of cardiovascular risk factors poorly understood. Individuals with cognitive impairment who developed stroke had higher frequencies of vascular factors (heart disease, diabetes, hypertension) in comparison to individuals with cognitive impairment who did not develop stroke (41.8% versus 33.2%). However, this difference was not statistically

significant. In addition, the MMSE is a brief cognitive test that may not have been sensitive enough to detect more subtle cognitive impairments. Overall, Zhu and colleagues concluded that their findings were in agreement with those of Ferrucci and colleagues (1996), further supporting the notion that cognitive impairment may be a manifestation of clinically unrecognized cerebrovascular disease.

Elkins, Knopman, Yaffe, and Johnston (2005) tested the hypothesis that poorer cognitive function is an early manifestation of vascular injury that predicts stroke and heart disease in a middle-aged cohort from the Atherosclerosis Risk in Communities (ARIC) Study. The ARIC study is a population-based prospective cohort study of cardiovascular disease in Forsyth County, NC, Jackson, MS, suburban Minneapolis, MN, and Washington County, MD. The study included 15,792 men and women, ages 45 to 64, who were recruited from 1987 to 1989. Participants completed a clinical examination at baseline, annual telephone-interview follow-ups and in-person clinic visits every three years. Incident cardiovascular events included a combined endpoint of definite or probable stroke, myocardial infarction (MI), or definite coronary heart disease (CHD) death that occurred after cognitive testing. Baseline cognitive assessments included Digit-Symbol Substitution Subtest of the Wechsler Adult Intelligence Scale-Revised (DSST), the Delayed Word Recall (DWR) Test, and the Word Fluency (WF) Test. Vascular risk factors, including hypertension, dyslipidemia, LVH, diabetes, and tobacco use were assessed at the time of baseline cognitive assessments. In addition, the Framingham coronary risk score was calculated for each participant (Wilson, D'Agostino, Levy, Belanger, Silbershatz, & Kannel, 1998).

Elkins and colleagues (2005) used Cox proportional hazards ratio analyses to estimate hazard ratios (HRs) with 95% CIs and likelihood ratio tests to assess linear trends by quartiles of cognitive test performance while adjusting for demographic variables. As expected, individuals with incident cardiovascular events had higher baseline Framingham coronary risk scores in comparison to those who did not experience an incident cardiovascular event. The results found that the HRs for incident cardiovascular events for individuals in the lowest quartile in comparison to the highest quartiles of performance on the DSST, DWR, and WF were 1.78 (95% CI = 1.41, 2.26, $p < .001$), 1.46 (95% CI = 1.15, 1.85, $p < .001$), and 1.47 (95% CI = 1.15, 1.87, $p < .001$). Furthermore, Elkins and colleagues noted a significant interaction between cardiovascular risk factors and cognitive test performance such that DSST scores predicted incident cardiovascular events in those with highest quartile of Framingham risk scores but not in those with the lowest quartile of Framingham risk scores. These results not only emphasize the relationship between cognitive function and incident stroke (considered as one of the endpoint events), but they also highlight significant interactions between cognitive function and cardiovascular risk factors that will be further explored in the proposed study.

In summary, studies have drawn variable conclusions about the nature of the relationship between cardio- and cerebrovascular risk factors and cognitive function. The proposed study hopes to further evaluate the associations between these risk factors and cognitive function by considering the role of ApoE genotype in a population-based incident stroke case/ cohort sample.

METHODS

Participants

Participants for the proposed study were drawn from the REGARDS study, which aims to identify factors related to excess stroke mortality in black individuals and in the Southeastern United States. REGARDS is a population-based cohort study of individuals 45 years and older with a sample size of 30,239 participants enrolled from January 2003 through October 2007 using mail and telephone contact. Twenty percent of participants were recruited from the coastal plain of North Carolina, South Carolina, and Georgia. Thirty percent of participants were recruited from the remaining areas of North Carolina, South Carolina, Georgia, and Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. The other 50 percent of participants were recruited from the remaining 42 contiguous states. Exclusion criteria for the cohort included race other than black or white, medical conditions preventing long-term participation, active cancer or active treatment for cancer, resident in or waiting placement in a nursing home, or inability to communicate in English.

Data Collection

Verbal informed consent was obtained during an initial telephone contact. Trained interviewers conducted computer-assisted telephone interviews (CATI) to gather demographic information and self-reported medical history of diabetes, hypertension, myocardial infarction, stroke, and cigarette smoking and a six-item screener of global

cognitive function. The CATI was used to collect data because of the high level of quality of control and standardization when using trained, certified, and monitored staff at the Survey Research Unit (SRU) at the University of Alabama at Birmingham. Baseline in-home assessments were scheduled to obtain written informed consent and collect BP, height, weight, electrocardiogram, and anthropometric measurements, urine and blood samples, and medication history. Participants were contacted at six-month intervals for follow-up assessments stroke events. Every twelve months, participants completed a measure of global cognitive function, the Six-item Screener. In addition, between 2006 and 2009, participants were asked to complete a short battery assessing cognitive function that included animal fluency, word list learning and delayed recall, and the NINDS-CSN 5-minute protocol, every eighteen months to two years.

Assessment of cognitive function. All measures of cognitive function were adapted for telephone administration using standardized scripts, narrated recordings for word lists, and customized scoring programs used by staff, who were monitored routinely for quality assurance. Participants were asked to complete a Six-item Screener (SIS) of global cognitive status at baseline and every twelve months thereafter during telephone interview. All participants were asked to complete a brief cognitive assessment of learning, memory, and executive function over the telephone at intervals of eighteen months to two years. Learning and memory were assessed with Word List Learning (WLL) and Word List Delayed Recall (WLD). Semantic fluency (animals) and the NINDS-CSN Letter Fluency (Letter F) were administered as measures of executive function (See Table 1). Theses cognitive data were obtained at various stages of follow-up depending on when the participant was enrolled in the study and their availability for

follow-up assessments. Participants' first cognitive assessments were used in analyses to capture the greatest number of participants with no repeated exposures to cognitive tests.

To obtain data from the REGARDS study, a manuscript proposal was submitted to the REGARDS executive committee to conduct the current study of ApoE e4 carrier status and prestroke cognitive function in the stroke case/cohort sample. The committee approved the proposed study on November 11, 2013.

Identification of stroke cases and cohort random sample. The current study utilized a subsample of the REGARDS participants who were selected as a part of the stroke case and cohort randomized sample for whom ApoE assays were planned. The cohort random sample of 1104 participants was drawn from the REGARDS sample of 29,653 participants with at least one follow-up contact and an initial assessment with the REGARDS additional cognitive measures. All REGARDS participants were given a random number to be used in assignment to the random cohort. The cohort random sample was selected using stratified sampling based on age, race, and sex. The target distribution included 50 percent black, white, male and female strata. The distribution for age was 20 percent from ages 45-54 years, 20 percent for ages 55-64 years, 25 percent for ages 65-74 years, 25 percent for ages 75-84, and ten percent for ages 85 years and older.

Stroke cases include all participants who developed an incident stroke through November 2011. To determine incident stroke cases, participants (or designated proxies) were asked via telephone contact at each six-month follow-up if they had been hospitalized for any reason, visited the emergency department, stayed overnight in nursing homes or rehabilitation centers, or if death had occurred. Interviewers queried participants for the reasons causing these incidents and requested medical records from

participant-reported locations for stroke, TIA, death, unknown reasons for hospitalizations, brain hemorrhage, or symptoms of stroke including sudden weakness, numbness, trouble speaking, sudden loss of vision, and headache. Medical records were screened by a stroke nurse to exclude events that were not stroke before the records were collected for annual review by the Adjudication Committee, a committee of stroke experts who validate and classify potential strokes. The process requires at least two physicians from the committee to agree on the event to validate stroke occurrence and classify stroke subtype (ischemic or hemorrhagic). Disagreement over stroke cases was resolved by a full committee review. Stroke events were identified if the event met the World Health Organization (WHO) definition or clinical stroke criteria. As defined by the WHO, a stroke is a "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." (Stroke, 1989). Clinical strokes included events characterized by symptoms lasting less than 24 hours with neuroimaging consistent with acute ischemia or hemorrhage. Probable strokes included cases in which adjudicators agreed that the event was a stroke or a death related to stroke but the information was incomplete for classification according to WHO or clinical stroke criteria. The approximate number of stroke cases considered for analyses is 619.

Inclusion/exclusion criteria. Participants from the stroke case/cohort sample who had initial cognitive assessments of learning, memory, and executive function and ApoE genotyping were eligible for inclusion in the study. Participants with prevalent stroke at enrollment were excluded. All cognitive assessments that occurred after the adjudicated

stroke events will be excluded from analyses. Participants who did not have sufficient data for determining their case status were excluded.

Measures

Six-item Screener. The SIS consists of 3-item recall and 3-item temporal orientation. Before the recall task, we instructed participants not to write anything down, and before the items of temporal orientation, we said, "Without looking at a calendar or watch," "what [year/month/day of the week] is this?" Scores on the SIS range from 0-6 with scores less than or equal to four suggesting cognitive impairment. The SIS was validated in community and clinical samples of Black and White adults with sensitivity and specificity to dementia and all-cause mild cognitive impairment of 74 and 80 percent, respectively, in community samples (Callahan, Unverzaft, Hui, Perkins & Hendrie, 2002).

NINDS-CSN 5-minute Battery. The NINDS-CSN 5 minute battery includes subtests of the Montreal Cognitive Assessment (MoCA): 5-word memory registration, 5-word delayed memory recall, 6-item orientation, and 1-letter (F) phonemic fluency (Nasreddine, Phillips, Bedirian, Charbonneau, Whitehead, Collin, Cummings, & Chertow, 2005). The spatial orientation items (place and city) were modified for telephone administration by asking the participant his/her home address and city. The full MoCA instrument was designed to identify individuals with mild degrees of cognitive impairment, who may otherwise score within the normal range on other cognitive screening tests. Scores on the 5-minute battery are positively correlated with performance on WLL, the SIS, and animal fluency are sensitive to cerebrovascular risk (Kennedy, Wadley, McClure, et al., 2014).

Word List Learning and Delayed Recall. Word List Learning (WLL) and Delayed Recall (WLD) were drawn from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Morris, Heyman, Mohs, Hughes, van Belle, et al., 1989) battery. The list learning task consists of three learning trials of a list of 10 semantically-unrelated words which are presented in a fixed order that varies across the three trials, followed by a free recall trial after a 5-minute delay filled with non-cognitive interview questions. For this study, the measure was administered according to the standard protocol, with two modifications for telephone administration: (1) no simultaneous visual presentation of the word list and (2) participants were instructed not to write anything down. In addition, a recognition trial was not administered. The instructions for each learning trial, including the oral presentations of the word list, were administered via a recording so that all participants were exposed to the same narration to avoid any differences in dialect, tone, gender, or volume that might affect participants' performance. For list learning, the scores from the three trials were summed, yielding a score ranging from 0-30, after excluding repetitions (repeating the same word more than once) and intrusions (including a word not on the list). For delayed recall, participants were asked to freely recall as many of the ten words as possible after the 5-minute delay during which non-cognitive interview questions were asked. Scores range from 0 to 10 after excluding repetitions and intrusions.

Phonemic and Semantic Fluency. The NINDS CSN Letter fluency and Semantic (Animal) Fluency Test (AFT) prompt participants to name as many words as they can that begin with the letter 'F' in one minute, and subsequently, to name as many animals as they can in one minute. Raw scores on each consist of the total number of valid

responses produced by each participant in 60 seconds, after subtracting repetition and intrusion errors. With explicit verbal permission from the study participants, the assessments were recorded in digital WAV files and then played back later for scoring following standard scoring protocols.

Z-score Transformations of Cognitive Scores. We converted all scores on measures of cognitive function to z-scores, adjusted for age. Raw scores (χ) were converted to Z scores using the mean (μ) and standard deviation (σ) for age stratified subsamples (less than 55, 55 to 64, 65 to 74, and 75 and above years of age) for each test where $z = {\chi - \mu}/{\sigma}$.

ApoE Genotyping

ApoE genotyping was performed at the REGARDS central blood repository at the University of Vermont using the Taqman system (Stephens, Smith & Donnelly, 2001; Stephens & Scheet, 2005). DNA was extracted from frozen buffy coat cells, and the Taqman system determined allele status at the two SNPs that are used to determine ApoE genotype: rs429358 (C/T) and rs7412 (T/C). Lab personnel were blinded to participants' identities, medical histories, cognitive testing results, and case/cohort status. Haplotype reconstruction was completed using a statistical method and software (PHASE v2.1.1) by Stephens and colleagues (2001) which utilizes expected patterns of haplotypes in natural populations to infer phase and linked loci from genotypes.

Covariates of Interest

Age at time of cognitive assessment, education at baseline (<HS, HS, some college, college graduate), sex (male, female), race (black, white), region of residence (stroke belt or not), smoking and depressive symptoms were considered as descriptive

characteristics and covariates. Age, race, sex, education, and smoking history were measured by self-report. We administered the Center for Epidemiological Studies-Depression Scale—4-item version (CES-D-4) during the baseline CATI. (Melchior, Huba, Brown, & Reback, 1993).

The CES-D-4 was derived from the full CES-D, and scores correlate acceptably (.87) with the full CES-D measure. Each of the four items in this instrument assesses *emotional,* but not somatic*,* symptoms of depression. Each item response is assigned a value of 0, 1, 2 or 3: "Rarely or none of the time (less than 1 day)" = 0; "Some or a little of the time (1-2 days)" = 1; "Occasionally or a more moderate amount of the time (3-4 days)" = 2; "More or all of the time (5-7 days)" = 3. Total scores range from 0 to 12; a score $\geq$ 4 suggests a clinically significant level of psychological distress. In a general population, about 20% would be expected to score in this range. We used the raw scores on the CES-D in our analyses.

Additional cardiovascular risk factors assessed at baseline included hypertension, dyslipidemia, heart disease, and diabetes. Hypertension was defined as a measured systolic pressure $\geq$ 140, measured diastolic pressure $\geq$90, or use of antihypertensive medication. Dyslipidemia was defined as total cholesterol >240ml/dl or use of lipid lowering medication. Heart disease was defined by evidence of myocardial infarction (MI), left ventricular hypertrophy (LVH), or atrial fibrillation (aFib) on baseline ECG; self-reported MI or afib; or self-reported history of coronary artery bypass graft, angioplasty or stenting. Diabetes was defined as having a fasting glucose greater than or equal to 126 mL/dL, non-fasting glucose greater than or equal to 200 mL/dL, or self-reported use of diabetes medications.

The Framingham Stroke Risk Profile (FSRP) was used as an estimate of the 10-year risk of stroke in regression models of cognitive function (Wolf, D'Agostino, Belanger, Kannel, 1991; D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB, 1994). The FSRP is calculated from age, measured systolic blood pressure (in mm Hg recoded into 10 groupings from 95 to 204 mm Hg), presence of diabetes mellitus, current cigarette smoking, history of heart disease, atrial fibrillation, LVH, and the use of antihypertensive medication. Diabetes was defined as fasting glucose greater than or equal to 126 mL/dL, nonfasting glucose greater than or equal to 200 mL/dL, or self-reported use of diabetes medications. Current cigarette smoking (at baseline) and current use of antihypertension medications (at the baseline) were determined by interview. History of heart disease was determined by self-reported myocardial infarction (MI), coronary artery bypass graft, angioplasty or stenting, or evidence of MI from baseline ECG. Atrial fibrillation was defined as self-reported or via ECG evidence. LVH was defined as presence on ECG (12 lead or 7 lead). FSRP was natural log transformed and centered to normalize the distribution and reduce multicollinearity for inclusion in regression models and interaction terms (Elias et al, 2004).

ANALYSES

Preliminary Analyses

We first examined data distributions, rates of missing data and presence of outlying scores. We evaluated the fit of our data with assumptions underlying multiple regression and cox proportional hazards models. We compared descriptive characteristics between included and excluded participants using two-sample t-tests or χ^2 tests.

We characterized the presentation of cardiovascular risk factors, distribution of ApoE e4 carrier status, demographic variables, and cognitive function in incident stroke cases and the cohort random sample. Descriptive statistics of group means for demographic variables, cardiovascular risk factors, and cognitive performance were displayed by ApoE e4 carrier status. We used t-tests and x^2 to evaluate univariate group differences in mean cognitive performance, cerebrovascular risk factors, and sociodemographic variables.

Aim 1. Examine the relationship between ApoE e4 status and incident stroke in a population based case-cohort sample from the REGARDS study.

Sequential cox regression models for case-cohort studies were used to estimate the hazard ratio of incident stroke as a function of ApoE e4 carrier status in sequential models (Barlow et al., 1999; Onland-Moret NC, van der AD, van der Schouw YT, Buschers W, Elias SG, van Gils et al., 2007). First, we confirmed the proportionality of hazards for Cox regression models. Covariates included in the models were determined a priori. Three-way and two-way interactions between age, race, and ApoE e4 status were

tested to determine inclusion in the models. Model 1 was adjusted for ApoE e4 status. Model 2 was additionally adjusted for age at baseline, sex, race, age by race interaction, region of residence, and education. Model 3 was adjusted for all variables in Model 1 and Model 2 and cardiovascular risk factors (hypertension, dyslipidemia, history of heart disease, atrial fibrillation, left ventricular hypertrophy, diabetes, smoking, and age by race interaction. The final model was stratified on age groups (less than 55, 55 to 64, 65 to 74, and 75 and above years of age). All models accounted for time to stroke event. For cases, time to event was the time between baseline assessments and incident stroke. For cohort members, time to event was the time (in years) between baseline assessments and the last available follow-up assessment.

Aim 1 analyses were weighted back to all REGARDS participants who would have been eligible for inclusion in the cohort random sample to account for oversampling of stroke cases. Weights were stratified by race, gender, and geographic region to account for the sampling scheme described in the Methods section. Weights for all analyses were derived using a weighting scheme proposed by Barlow, Ichikawa, Rosner et al (1999). The weight for control participants from the cohort random sample were equal to the inverse of their age/sex/race stratum-specific sampling probability. Weights for incident stroke cases that occurred within the cohort random sample were equal to the inverse of their age/sex/race stratum-specific sampling probability before their stroke and a weight of 1 at the time of incident stroke. Incident stroke cases that were not a part of the cohort random sample had a weight of 0 before their failure time and a weight of 1 at the time of stroke.

Aim 2. Evaluate the relationship between ApoE e4 status and prestroke cognitive function.

We examined the association of ApoE e4 carrier status with prestroke cognitive performance in the full case-cohort sample with available cognitive data using multiple linear regression with the age adjusted-Z-scores on word list learning, word list delayed recall, semantic fluency, and phonemic (letter) fluency. The regression models were adjusted for demographic variables (sex, race, education, region of residence), Framingham stroke risk profile scores, depression, and ApoE e4 carrier status. Age was not included in models as cognitive scores were age adjusted and FSRP scores included age at time of assessment. Manual backward model selection was used to exclude nonsignificant predictors at $p > .5$. Analyses were stratified by incident stroke status to further evaluate the relationship of ApoE e4 status and cognitive performance across subsamples.

Aim 3. Evaluate the interactions among ApoE e4, stroke, and stroke risk factors on cognition.

We evaluated the interactions among ApoE e4 carrier status and Framingham Stroke Risk Profile scores across incident stroke status on prestroke cognitive function. We included an interaction term for ApoE e4 x FSRP in regression models for stratified samples of stroke cases and cohort members to evaluate interactions among ApoE E4, stroke, and stroke risk factors.

Aim 4. Explore the relationship between age and e4 carrier status on prestroke cognitive function.

Due to evidence that age modifies both the effect of ApoE e4 on cognitive function and the risk for incident stroke, we evaluated the relationship between age and e4 carrier status by testing the interaction of ApoE x Age and ApoE x Age x Stroke. Selected exploratory analyses were conducted to further examine the effect of ApoE on cognitive function across age groups, using age of 75 years as cutoff, which has been used in other REGARDS analyses examining ApoE and cognitive function.

Sensitivity Analyses

We performed sensitivity analyses by excluding participants with baseline cognitive impairment (Six-item Screener <5) in order to minimize the presence of dementia and hemorrhagic stroke cases because pathways may differ from those implicated in ischemic stroke.

RESULTS

Baseline Characteristics of Study Participants

The study included 619 participants who developed a stroke during follow-up and 1104 participants randomly selected from the REGARDS study cohort. Participants with a history of stroke at baseline (N=87) or missing ApoE genotyping (N=80) were excluded from analyses, leaving a total of 1549 participants (588 cases and 961 participants from the cohort random sample) available for analysis. Additional participants were excluded due to missing data on medical comorbidities including atrial fibrillation, CHD, diabetes, dyslipidemia, left ventricular hypertrophy. See Figure 3. Excluded participants differed from included participants in that among excluded participants there was a greater proportion of women, had fewer years of education, greater percentage from the "non-stroke belt" United States, higher history of smoking, greater rates of atrial fibrillation, CAD, Diabetes; and lower rates of dyslipidemia. See Table 2.

Tables 3 and 4 display the baseline characteristics of the study sample by ApoE e4 carrier status and incident stroke status. In comparison to e4 noncarriers, ApoE E4 carriers included a greater number of black participants, current smokers and participants with heart disease, diabetes, dyslipidemia, left ventricular hypertrophy, and incident stroke. Those who experienced an incident stroke included a greater proportion of black and male participants, from the nonstroke belt region of the US. In addition, in comparison to cohort members only, those who experienced an incident stroke were more

likely to be past smokers, have atrial fibrillation, heart disease, diabetes, hypertension, and left ventricular hypertrophy.

Table 5 presents descriptive statistics for the REGARDS sample included in analyses by ApoE e4 carrier status. In comparison to ApoE e4 noncarriers, ApoE e4 carriers had a higher proportion of back participants and fewer participants from the stroke belt or buckle of the US. ApoE e4 carriers also had lower scores on WLL, WLD, and AF although these differences were not statistically significant. Table 6 presents additional descriptive statistics for each sample used in regression analyses for WLL, WLD, AF, and LF.

Aim 1. Examine the relationship between ApoE e4 status and incident stroke

Three-way and two-way interactions between ApoE e4 carrier status, race, and age were tested. Only the age by race interaction was significant and included in subsequent models. See Table 7.

Table 8 displays the model fit statistics for the three sequential cox regression models of ApoE e4 carrier status and incident stroke. Models 2 (ApoE e4 status and sociodemographics) and Model 3 (all covariates in Model 2 plus medical covariates) significantly predict time to stroke. The addition of sociodemographic predictors to the model significantly improved model fit in comparison the Model 1, which included only ApoE e4 carrier status, $X^2 = (11, N = 1549) = 161.04$, $p < .001$. The addition of medical covariates in Model 3 significantly improved the model fit in comparison to the model with sociodemographics covariates only, $X^2 = (8, N = 1451) = 124.88$, $p < .001$.

The hazard ratios (HR) of incident stroke as a function of ApoE e4 carrier status are displayed in Tables 9 and 10. ApoE e4 carrier status was not significantly associated

with stroke risk in any of the models. In the model controlling for ApoE e4 status and sociodemographics, male gender and education level of high school or less was significantly associated with increased risk of incident stroke (HR 1.35, 95% confidence interval [CI] 1.08, 1.70; HR 1.37, 95% CI 1.07, 1.75) while income greater than or equal to $75,000 was significantly associated with reduced stroke risk (HR .733, 95% CI 0.57, 0.94). The association of male gender with higher incident stroke risk was completely attenuated in the full model accounting for medical comorbidities. In the full model including sociodemographic and medical risk factors, education level of high school or less, being a current smoker, atrial fibrillation, coronary artery disease, hypertension, and left ventricular hyptertrophy were associated with higher risk of incident stroke, respectively (HR 1.38, 95% confidence interval [CI] 1.05, 1.82; HR 1.96, 95%CI 1.34, 2.85; HR 1.49, 95%CI 1.01, 2.19; HR 1.72, 95%CI 1.26, 2.36; HR 1.75, 95%CI 1.32, 2.33; HR 1.70, 95% CI 1.17, 2.47). Neither region of residence, gender, diabetes, nor dyslipidemia was significantly associated with incident stroke in the fully adjusted model.

The association of race with stroke risk was modified by age (*p* interaction = .002) in the full model. Table 10 includes the hazard ratios (HR) of incident stroke stratified by age (less than 55, 55 to 64, 65 to 74, and 75 and above years of age). The HR for black versus white participants was highest in the youngest age group (less than 55 years of age) (HR 3.25, 95%CI 0.48, 21.88). However, the association of race with incident stroke was reversed in the highest age group (75 years of age and above), suggesting that black versus white race was associated with a reduced risk of stroke in individuals 75 years of age and older (HR 0.42, 95%CI 0.24, 0.75).

Aim 2. Evaluate the relationship between ApoE e4 and cognitive function.

The interaction of Age x ApoE e4 carrier status was tested for inclusion in the models of WLL, WLD, AF, LF performance but was not significant, and therefore not included in subsequent models (WLL β = -.036, t = .275, p = *0*.784; WLD B= .144, β = .105, t = 1.023, p = .306; AF β = -.036, t = .275, p = .784; LF β = .002, t = .088, p = .930). The interaction of race with ApoE e4 was also tested for inclusion in the model of WLL, WLD, AF, LF but was not significant; and, therefore, it was not included in subsequent models (WLL, WLD, AF, LF, respectively), β = .144, β = .105, t = 1.023, p = .306; B=-.001, β = -.036, t = .275, p = .784; β = .043 t = .416, p = .678; β = -.056, t = -.486 , p = .627; WLD: β= 0.076, t =0.963, p =.336.

Results of the sequential regression models for WLL performance for the combined case-cohort, cohort only, and stroke cases are displayed in Table 12, 13, and 14. In the combined case-cohort sample, the initial model including only ApoE e4 carrier status was trending toward significance, F (1,899) = 3.55, p = .06. The addition of sociodemographic variables and FSRP scores significantly improved the model fit (sociodemographics R^2 change = .032, F (7, 892) = 4.246, p < .001; FSRP R^2 change = .006, F (1, 891) = 5.65, p < .05. The final model explained more, albeit a small amount, of the variance in WLL performance (adjusted R squared = .03). In all three sequential regression models for the full case-cohort sample, the presence of at least one ApoE e4 allele was associated with lower WLL performance *(*β = -.063, t = -1.916, p = .056), *(*β = -.062, t = -1.85, p = .064), *(*β = -.062, t = -1.87, p = .062), providing support for the hypothesis that ApoE e4 would be associated with poorer cognitive performance.

Results of the hierarchical regression models for WLD for the combined case-cohort, cohort only, and stroke cases are displayed in Tables 16, 17 and 18. In the combined case-cohort sample, the initial model including only ApoE e4 carrier was nonsignificant, F (1,868) = 0.046, p = 0.830. The addition of sociodemographic variables, but not FSRP scores significantly improved the model fit (sociodemographics R^2 change = .027, F (7, 861) = 3.448, p < .001; FSRP R^2 change = .003, F (1, 860) = 2.983, p = .085. The final model explained a small but significant amount of the variance in WLD performance (adjusted R squared = .02). The effect of FSRP was trending toward significance, such that higher FSRP scores were associated with lower WLD scores (B = -0.062, t = -1.727, p = 0.085). In all three regression models for the full case-cohort sample, the association of ApoE e4 carrier status with WLD performance was nonsignificant, contrary to the hypothesis that ApoE e4 carrier status would be associated with poorer performance on delayed recall.

Results of the hierarchical regression models for AF performance for the combined case-cohort, cohort, and stroke cases are displayed in Tables 20, 21, and 22. In the combined case-cohort sample, the initial model including only ApoE e4 carrier status was nonsignificant, F (1,916) = .626, p = .429. The addition of sociodemographic variables, but not FSRP scores, significantly improved the model fit (sociodemographics R^2 change = .021, F (7, 909) = 2.728, p < .01; adjusted R^2*= 0.013;* FSRP R^2 change = .000, F (1, 908) = .243, p *=.622,* adjusted R^2*= .012)*. Both models were of poor fit and explained a small amount of variance in AF performance. Contrary to the hypothesis that ApoE e4 carriers would be associated with poorer semantic fluency performance, in all three sequential regression models for the full case-cohort sample, the association of

ApoE e4 carrier status with AF performance was nonsignificant, β = -.026, t = -.79, p = .429; β = -.022, t = -.65, p = .515; β = -.022, t = -.657, p = .511.

Results of the hierarchical regression models for LF performance for the combined case-cohort sample are displayed in Tables 24, 25, and 26. ApoE e4 status was not significantly associated with LF performance in any of the sequential regression models for the combined case-cohort. None of the regression models explained a significant amount of variance in LF performance for the combined case-cohort sample.

Manual backward model selection was used to eliminate predictors with significance levels of $p > 0.5$. The resulting models for WLL and WLD performance excluded region and education. The resulting model for AF performance excluded region and gender from analyses. The resulting model for LF performance excluded gender and depressive symptoms, with improved overall model fit for the combined case-cohort, cohort, and stroke cases. Results of backward elimination model selection WLL, WLD, AF, and LF are displayed in Tables 15, 19, 23, and 27, respectively.

Hypothesis 2.2. ApoE e4 status will be more strongly predictive of lower prestroke cognitive scores in the incident stroke cases than in the cohort random sample.

Results from the sequential regression models for WLL for stroke cases and cohort sample members alone are presented in Table 13 and 14. ApoE e4 carrier status was associated with decreased performance on WLL in fully adjusted regression models for stroke cases, β = -.154, t = -2.072, p = .040. However, overall models were not significant for stroke cases, limiting the interpretability of this association, F (8, 173) = 1.40, p = .198. In the cohort sample, ApoE e4 carrier status was not significantly associated with WLL performance in any of the three sequential regression models (β = -.141, t =-1.91, p

=.058), (β = -.039, t = -1.05, p = .293), (β = -.039, t = -1.06, p = .298). This provides partial support that ApoE e4 status is more strongly associated with lower prestroke word list learning performance in the incident stroke cases than in the cohort random sample.

ApoE e4 carrier status was not significantly associated with WLD performance in the stratified samples of cohort members or stroke cases. The addition of sociodemographic variables, but not FSRP, to the model significantly improved the model fit for cohort members, R^2 change = .025, F (6, 690) = 2.993, $p < .01$. The full model including sociodemographic variables and FSRP scores was significantly associated with WLD performance for cohort members but not stroke cases; F (8, 689) = 2.479, $p < .05$, adjusted R^2 = .02. Neither the addition of sociodemographic variables nor FSRP scores improved the models of WLD performance for stroke cases. See Tables 17 and 18.

Similarly, ApoE e4 carrier status was not associated with performance on AF in adjusted or unadjusted regression models for stratified samples of stroke cases or cohort members. See Tables 21 and 22. Fully adjusted regression models of AF which included sociodemographic variables and FSRP were significant for cohort members, but not for stroke cases, F (8, 742) = 2.372, p = .016; Adjusted R^2 = .014; F (8, 158) = 0.339, p = .950; Adjusted R^2 = -.033. These results do not support the hypothesis that ApoE e4 carrier status would be associated with semantic fluency performance.

ApoE e4 status was not significantly associated with LF performance in regression models including stratified samples of stroke cases and cohort members, failing to confirm the hypothesis that ApoE e4 would show a stronger relationship with executive function as assessed with letter fluency performance for stroke cases. In

addition, there was a nonsignificant ApoE x Stroke interaction, (β = -.018, t = -0.069, p = .4824). See Tables 25 and 26. In summary, regression models of WLL provide limited support that ApoE is associated with poorer performance on list learning but no other cognitive tasks.

Hypothesis 2.3: ApoE e4 status will be more strongly predictive of memory function than other cognitive domains (i.e., executive function). ApoE e4 carriers had lower WLL scores in regression models including sociodemographic variables and FSRP scores. However, ApoE e4 was not associated with performance on WLD, AF, and LF in adjusted regression models. This provides partial support for a stronger association between ApoE e4 and memory function than other cognitive domains.

Aim 3: Evaluate the interactions among ApoE e4 carrier status, incident stroke status, and Framingham stroke risk profile scores on prestroke cognitive performance.

Table 28 displays the parameter estimates for regression models of WLL when including the interaction ApoE e4 x FSRP. The interaction was not significantly associated with word list learning age-adjusted z-scores in regression models for the full sample, cohort only, or stroke cases, β = -.023, t = -.593, p = .554; β = -.023, t = -.520, p = .603; β = .037, t = .436, p = .663, respectively. FSRP scores were associated with lower age adjusted z-scores on WLL in regression models for the combined case-cohort and cohort samples, β = -.088, t = -2.245, p = .025; β = -.099, t = -2.571, p = .01.

Due to substantial differences when running sensitivity analyses for WLD regression models, results presented in Table 29 reflect a sample excluding those with baseline cognitive impairment and hemorrhagic stroke cases. The interaction of ApoE x

FSRP was trending toward significance and significant in regression models of WLD for the combined stroke case-cohort and cohort samples, respectively; β = -.159, *t* = -1.82, *p* = 0.070; β = -.210, *t* = -2.22, *p* = 0.027. Results show a positive association between ApoE e4 and WLD performance at low FSRP scores; but a negative association of ApoE e4 with WLD at medium and high FSRP scores. See Figure 6. Results for regression models of WLD including the sample of cases of cognitive impairment at baseline and hemorrhagic stroke cases are presented in Supplemental Table 1 and 2.

Table 30 displays parameter estimates and model fit statistics for AF performance when including ApoE e4 x FSRP interaction. The interaction was not significantly associated with animal fluency performance in regression models for the full sample, cohort only, or stroke cases, β = -.036, *t* = -.909, *p* = .364; β = -.054, *t* = -1.25, *p* = .212 (cohort); β = .007, *t* = .076, *p* = .940.

The interaction of ApoE x FSRP was trending significance in the regression model of LF performance for cohort members only *(*β = -.085, *t* = -0.069, *p* = 0.071; *F* (7, 638) =1.336, p = 0.230, adjusted R^2 = 0.004. The addition of an interaction for ApoE e4 carrier status with FSRP scores did not significantly improve the model fit for the full sample, stroke cases, or non-stroke cohort members. See Table 31 for parameter estimates and model fit statistics for regression models of LF performance, including ApoE x FSRP interaction.

In summary, results did not support the hypothesis that the interaction ApoE e4 x FSRP would be significant for stroke cases. Rather, ApoE x FSRP was significant in regression models of WLD for combined case-cohort and cohort only samples.

Aim 4. Explore the relationship between age and e4 on cognitive function

Three-way and two-way interactions for Age x ApoE x Stroke and ApoE x Age were tested to assess whether the effect of ApoE on cognitive function varied across age. Three-way and two-way interactions were nonsignificant in regression models for WLL, WLD, AF, and LF. See Table 32 for interaction testing. However, exploratory analyses of WLD performance in a subsample of only those greater than 75 years of age, show that ApoE e4 carrier status was negatively associated with WLD performance in a model including sociodemographic risk factors and FSRP in samples of the combined case-cohort and cohort only, (case-cohort, β = -.349, t = -1.997, p = 0.048; Cohort β = -.311, t = -1.943, p = 0.053). However, the effect of ApoE was attenuated and no longer significant with the addition of the interaction ApoE x FSRP in models of WLD. For stroke cases over the age of 75 years, the interaction ApoE x FSRP was trending significance, β = 0.383, t = 1.758, p = 0.085, reflecting an association that was not evident across both age groups or those less than 75 years of age. See Supplemental Table 2. In addition, in a subsample of only those greater than 75 years of age, ApoE was a significant predictor of AF performance in the combined case-cohort, and cohort only sample (β = -.219, t = -2.837, p = .005; β = -.237, t = -2.812, p = .005) in regression models in which model fit was trending and significant, respectively, F (7, 357) = 1.877, p = .072, adjusted R^2= *.017; F* (7, 293) = 2.728, p = .051; adjusted R^2= *.024.* Having at least one ApoE e4 allele was associated with -.237 standard deviations lower on the animal fluency task in cohort members over 75 years of age. See Table 33.

Sensitivity Analyses.

The association between ApoE e4 and prestroke cognitive function will not significantly change when excluding participants with baseline cognitive impairment, or when excluding hemorrhagic stroke cases.

A sensitivity analyses excluding those with baseline cognitive impairment on the global Six-item Screener from regression models of WLL with all predictors and ApoE e4 x FSRP interaction was conducted. The associations between ApoE e4 status and WLL, AF and LF remained relatively stable when excluding those with baseline cognitive impairment. Similarly, while excluding baseline cognitive impairment cases did improve the overall model fit for full sample and cohort members in age stratified analyses, there was no difference in the relationship between ApoE e4 carrier status and cognitive performance in the combined samples or stratified case cohort samples.

However, sensitivity analyses for models of WLD results in improved model fit as well as significant ApoE x FSRP interaction; as such, regression models for WLD excluded those with baseline cognitive impairment and hemorrhagic stroke. Regression models for the full sample are presented in Supplemental Tables 1 and 2.

When excluding those with baseline cognitive impairment from regression models for AF, model fit improved for the combined stroke-case cohort sample and cohort subsample, F (7, 213) = 2.40, p = .022, Adjusted R^2= .04; F (7, 168) = 2.91, p = .007, Adjusted R^2= .071. ApoE e4, FSRP scores, and the interaction ApoE x FSRP were significantly associated with AF performance in the combined case-cohort (β = -.239, t = -2.402, p = .017; β = -.182, t = -2.31, p = .022, β = .315, t = 2.90, p = .004) and cohort only (β = -.260, t = -2.345, p = .020; β = -.188, t = -2.119, p = .036, β = .363, t = 2.959,

p = .004). However, ApoE and FSRP were not significant in models without interactions and high correlations between these variables warrant caution in interpreting these results. See Table 34.

There were no appreciable differences in the significance of parameter estimates or model fit statistics of regression models of cognitive performance on WLL, AF, or LF when excluding hemorrhagic stroke cases.

DISCUSSION

ApoE e4 and Stroke

We examined the association of ApoE e4 with incident stroke in a population based case-cohort from the REGARDS study. ApoE e4 was not independently associated with incident stroke in this population based case-cohort sample of older adults without dementia when adjusting for sociodemographic variables and cerebrovascular risk factors (see Tables 9 and 10). These results are consistent with those of a population based study of 1810 person aged 75 years and older from the Kungsholmen Project, which failed to find an association between ApoE genotype and incident stroke, despite a significantly greater proportion of e4 carriers in stroke cases, and significant associations between ApoE and cognitive decline. However, ApoE e4 carriers with prior stroke in that study were more likely to have a subsequent hemorrhagic stroke than non-carriers. (Basun et al., 1996; Greenberg, Rebeck, Vonsattel et al., 1995; Alberts, Graffagnino, McClenny et al., 1999).

It is also possible that ApoE indirectly affects risk of incident stroke through its association with cerebrovascular risk factors (see Table 9). Consistent with existing literature, we found that smoking, atrial fibrillation, coronary artery disease, hypertension, and left ventricular hypertrophy were associated with incident stroke, and were significantly more prevalent in e4 carriers than non-carriers (Table 10), concordant with the posited vascular damage conferred by ApoE e4. Another possible explanation

for the nonsignificant association between ApoE e4 and incident stroke is the theory that ApoE e4 is related to the degree of injury or recovery from stroke rather than stroke incidence (Marin, Breuer, Marin, 1998; Horsburgh, McCarron, White, Nicoll., 2000). Lastly, the lack of ApoE e4 association with incident stroke points to the possibility of a path between ApoE and cognitive function that is independent of the effect of cerebrovascular risk factors, further discussed below.

ApoE E4 and Cognitive Function

When examining the association of ApoE e4 with cognitive function, ApoE e4 was associated with poorer performance on select measures of cognitive function. ApoE e4 was most strongly associated with performance on measures of learning/memory in stroke cases (see Tables 13 and 14), consistent with existing evidence of significant associations between ApoE and AD as well as the association between ApoE e4 and cognitive function in older adults without dementia (Boyle, Buchman, Wilson, Kelly, & Bennett, 2010; Hostage, Choudhury, Doraiswamy, & Petrella, 2013; Yasuno et al., 2012). Current findings contribute to the relatively small body of research on ApoE e4 and cognitive function in older adults without dementia, which has not yet consistently identified the cognitive domains most affected by ApoE e4. Our results, as well as others that identify memory and learning as the most sensitive cognitive domains to the effect of ApoE e4, follow a model of pathoanatomic relationships in which AD-risk factors contribute to memory function and may reflect the neuropathological mechanisms associated with ApoE e4 including increased Aβ uptake, Aβ toxicity, increased tau deposition, and molecular changes in brain structures associated with memory function (hippocampus and caudoputamen); (Cho, Choi, Hwang, Lee, Kim, 2016; Shi, Yamada,

Liddelow, Smith, Zhao et al, 2017; Yang et al., 2011). Our finding is consistent with theories of AD in which memory deficits are related to learning and encoding of information, and is consistent with reduced hippocampal activation during encoding in ApoE e4 carriers (Trivedi, Schmitz, Ries, Torgerson, Sager et al., 2006). The fact that e4 was significantly related to lower memory performance in incident stroke cases, only, suggests that memory function may serve as a marker for brain changes that increase the risk for stroke and hints that AD pathology and vascular changes interact to increase risk of stroke.

Higher FSRP scores indicative of cerebrovascular risk were also significantly associated with poorer performance on measures of learning. This relationship may reflect underlying cerebral abnormalities such as small cerebral infarcts, white matter hyperintensities, brain volume reductions associated with stroke risk factors but often undetected in routine clinical settings. However, FSRP scores were not associated with performance on measures of executive function, inconsistent with vascular hypothesis that cerebrovascular risk factors are more likely to impact executive function and attentional processes than memory in a pattern comparable to that seen in vascular cognitive impairment. The selective association of FSRP with memory performance may reflect the cumulative influence of ApoE e4 and cerebrovascular pathology on cognitive function.

It is possible that the study sample included individuals with high levels of cognitive reserve and resilience to neurological insults secondary to stroke risk factors. Although the study sample included individuals with high FSRP, participants with a previous history of stroke were excluded, suggesting the possibility of a selection bias of

relatively neurologically resilient participants. This is not inconsistent with the findings of Elkins et al (2004) who found that those with high baseline cognitive function did not have an elevated risk for cognitive decline associated with cerebrovascular risk factors.

Nonetheless, previous studies have demonstrated that up to 50% of dementia risk is associated with vascular risk factors (Bergmann & Sano, 2018; Bink, Ritz, Aronica, et al., 2013), and the inverse association of cerebrovascular risk factors with memory and learning performance in the current study highlight the importance of such risk factors in cognitive dysfunction.

The results also show that depressive symptoms were inversely related to learning, memory, and semantic fluency performance, but not phonemic fluency (see Tables 15, 19, and 23). While the association of depressed mood with decreased cognitive performance is widely recognized, the direction of this relationship is not yet fully understood. Depressive symptoms may emerge, in part, due to the frustration, perceived and real limitations of those with cognitive difficulties; but it may also reflect degradation of neuronal processes involved in emotion regulation and shared neuropathology (Panza et al., 2010). In a study of community-dwelling older adults, depressive symptoms were significantly associated with memory, executive function, processing speed, and everyday functional performance. There is also support that cognitive function mediated the path between depressive symptoms and functional decline (Brewster, Peterson, Roker, Ellis, & Edwards, 2017). Although not a primary focus of this paper, the relationship between depressive symptoms and cognitive function is meaningful as depression may contribute to faster rates of cognitive decline and loss of function and independence (Yen, Rebok, Gallo, Jones, & Tennestedt, 2011).

Interaction of ApoE e4 and Cerebrovascular Risk Factors

Results did not support the hypothesis that the interaction ApoE e4 x FSRP would be significant for stroke cases, a subgroup with higher levels of cerebrovascular risk factors, in comparison to cohort members. Rather, ApoE x FSRP was significant in regression models of delayed list recall for combined case-cohort and cohort only samples (see Table 29). Nonetheless, this interaction suggests that there is a negative association between ApoE e4 and memory for those with a high level of cerebrovascular risk factors, even in the absence of incident stroke (see Figure 7). Our findings suggest that those with a higher number of cerebrovascular risk factors may experience a greater vulnerability to the detrimental effects of ApoE e4 on cognitive function, consistent with our findings and conclusions above regarding the significant association between FSRP and memory. These findings converge with existing literature that cerebrovascular disease and ApoE e4 may have a synergistic effect on cognitive decline (Kalmijn, Feskens, Launder, Kromhout, 1996; Haan et al., 1999; Frisoni et al., 1999), such that the presence of ApoE e4 alleles may potentiate the effect of cerebrovascular disease on cognitive decline. Specifically, hypercholesterolemia, prior tobacco use, diabetes mellitus, and hypertension were related to longitudinal declines in memory in cognitively normal individuals who were ApoE e4 carriers, but not ApoE e4 noncarriers (Casselli, 2011). One possible explanation for this relationship is that β-amyloid increases neurotoxicity and induces vascular insufficiency which makes the brain more vulnerable to protein deposits. At the same time, stroke risk factors contribute to vascular insufficiency and increase the amount of β-amyloid. Together, these processes may combine to promote neuronal dysfunction and cell death contributing to cognitive

impairment (Iadecola & Gorelick, 2003). Notably, although the interaction of ApoE e4 and FSRP was significant for delayed recall, this interaction was not significant in models of list learning across trials.

The Effect of ApoE across Age

Results of the interaction testing for Age x ApoE e4 interaction did not support that hypothesis that ApoE e4 would be more strongly associated with cognitive function in older individuals, over the age of 75 years. This is in contrast to multiple studies which have found that the effect of ApoE e4 on cognitive function varies across age, with greater effect at older ages. However, exploratory analyses provide some evidence that the association of ApoE with cognitive function is greater in those over the age of 75 years, as the presence of at least one ApoE e4 allele was associated with lower scores on a task of semantic fluency in those over the age of 75 years.

Impaired performance on measures of semantic fluency, rather than phonemic fluency, can be indicative of underlying Alzheimer's disease related pathology, as it is more dependent upon the integrity of semantic memory (Henry, Crawford, Phillips, 2004). As such, the association of ApoE e4 with poorer performance on semantic fluency may reflect the changes to the medial temporal lobe suspected in ApoE e4 pathophysiology.

The fact that the effect of ApoE on learning, memory, and phonemic fluency did not significantly vary across age may be related to the use of cross-sectional analyses. Prior studies point to the possibility of ApoE e4 contributing to a cumulative process across age which is best identified through longitudinal analyses, rather than cross-sectional, as used in the current study. It is possible that the negative association of ApoE

e4 would become more pronounced over time. For example, Rawle, Davis, Bendayan, Wong, Kuh, Richards (2018) illustrated that while baseline difference in memory function across ApoE e4 carriers were not evident, ApoE e4 carriers showed greater rates of cognitive decline in longitudinal analyses of a population-based birth cohort.

Because those with previous stroke were excluded from analyses, it is possible that the subsample of those over the age of 75 years represents a resilient and healthy subgroup of participants, which might obscure differences in ApoE e4 across age. Lastly, an age cut-off of 75 years was used given that this age was previously identified as an inflection point for age stratified analyses involving ApoE in the Regards cohort. However, it is possible that a lower age cut-off would have been more fruitful given previous findings that the effect of ApoE may be greatest in the 7th decade of life (Smith, Bohac, Waring et al,1998).

Sensitivity Results Summary

Exclusion of those with baseline cognitive impairment resulted in improved model fit, particularly for regression models including the full case-cohort and cohort only samples. These sensitivity analyses suggest that the current models were of particularly poor fit for those with baseline cognitive impairment, who may have included individuals who experienced incident dementia. The inclusion of those with baseline cognitive impairment may have masked the more subtle associations expected between ApoE and FSRP in older adults without dementia.

When excluding hemorrhagic stroke cases from regression models, model fit statistics and parameter estimates were largely comparable to models including

hemorrhagic stroke cases. As only 19 individuals with cognitive data experienced hemorrhagic stroke, this finding is not unexpected.

Strengths

The current study utilized a case-cohort sample of the general population with a greater age range, sample size, and inclusion of greater proportion of Black participants than most comparable studies to date. The greater age range allowed us to examine possible, and underexplored, effects of age on the relationship of ApoE genotype and cognitive function. We also included a more comprehensive assessment of cognitive function than most studies on ApoE genotype and cognitive function, allowing us to explore effects of ApoE on independent cognitive domains. The inclusion of adults without dementia is also a unique strength of the current analyses. The current study is one of few studies that examined ApoE genotype and incident stroke, rather than stroke risk factors. The prospective case-cohort study design of REGARDS provided the opportunity to consider the temporal sequence of risk factors (ApoE, cerebrovascular risk factors) and first stroke.

Limitations

Limitations of the proposed study include the lack of brain MRI data, which restricts our ability to draw conclusions about the mechanisms by which ApoE and cerebrovascular risk factors impact cognitive function in adults without dementia. The current analyses included only cross-sectional assessments of cognitive function which limits our ability to draw conclusions about the effect of ApoE and vascular risk factors on cognitive change over time. In general, poor model fit may have biased our results. Lastly, the stroke case cohort sample is not representative of the US population, with

oversampling of Black race and those in the stroke belt; which should be taken into when considering the generalizability of our findings.

Future Directions

Current results suggest that the ApoE may moderate the effect of cerebrovascular disease on cognition, which pinpoints cerebrovascular risk factors as possible targets for clinical interventions to reduce the risk of cognitive decline in aging populations. To further refine which risk factors may be driving this effect, future studies may look at the interaction of ApoE with individual risk factors.

There is evidence that ApoE e4 homozygotes may experience faster rates of cognitive decline than heterozygotes or noncarriers, yet the current study did not examine the effect of ApoE e4 homozygotes versus heterozygotes. Given the small effect size of ApoE on cognitive function in adults without dementia, future studies may benefit from evaluating the possible dose-response relationship between ApoE e4 and cognitive function. It is not clear if the negative association of ApoE e4 with cognition represents a prodromal state prior to vascular cognitive impairment, MCI or AD, as some studies have suggested. Longitudinal analyses could clarify whether the current findings reflect a pre-MCI or pre-dementia state.

Although we chose not to weight analyses for Aim 2 through Aim 4 to the full REGARDS sample on whom genotype was not performed, future research might consider such an approach. One also might consider weighting analyses to the US population to generalize beyond the stroke case-cohort sample, and the full REGARDS sample, with a higher degree of confidence.

Conclusion

Although ApoE e4 was not associated with incident stroke, ApoE e4 was associated with select measures of cognitive function in older adults without dementia; and this association was strongest in stroke cases. It appears to be more strongly associated with measures of memory, but the relationship between ApoE e4 and language and executive functioning cannot be ruled out given the significant association in subsamples less than and greater than 75 years of age. The effect of ApoE e4 may vary with the presence of cerebrovascular risk factors and across age. Overall, the current findings help fill substantial gaps in the existing literature on ApoE and cognition in adults without dementia. Results indicate that ApoE e4 is associated with poorer performance on measures of cognitive function that are reliant on the integrity of the medial temporal lobe, a region suspected to be vulnerable to the detrimental effects of ApoE e4 through increased tau deposition and Aβ toxicity. While ApoE e4 was independently related to learning, it was also indirectly related to memory function via interactions with stroke risk factors. ApoE- related cognitive decline in adults without dementia may reflect a pre-MCI or pre-dementia state associated with increased risk of subsequent dementia (Caselli et al., 2007). As such, identifying individuals during this pre-clinical state would increase the window for early interventions to reduce the risk of incident cognitive decline and its associated burden.

Brief cognitive assessments in addition to routine screening of cerebrovascular risk factors are a potentially feasible method for identifying at-risk individuals in routine clinical settings such as primary care. Individuals may or may not be aware of subtle

cognitive changes, and cognitive screening tools may help identify difficulties prior to potential development of dementia or substantial functional difficulties. However, given the sometimes subtle neuropsychological declines associated with preclinical dementia, normal aging, and cerebrovascular disease, the use of cognitive screening assessment may not have adequate sensitivity to detect cognitive change. A comprehensive evaluation of comorbid risk factors and cognitive function is likely to result in greater classification of at-risk individuals.

The results reveal multiple potential targets for interventions that may reduce the personal, caregiver, and public health burden associated with cognitive decline. Of note, the association of ApoE e4 and memory was moderated by the severity of comorbid stroke risk factors, highlighting the importance of managing comorbid health conditions to reduce the increased risk conferred by ApoE on cognition. Cognitive impairment can impact quality of life and contribute to reduced functional independence. Those with cognitive impairment may have a higher risk of comorbid conditions because they are less likely to adhere to medication regimens and/or routinely choose health-promoting behaviors, such as healthy diets and physical exercise. Providing instructions on compensatory strategies and accessible medical resources to aging individuals that accommodate cognitive difficulties would be prudent in minimizing the downstream impact of cognitive decline, including medical adherence difficulties and loss of functional independence. Lastly, the results urge monitoring of mood and providing psychological and psychiatric interventions, as appropriate, for aging individuals as depression may contribute to cognitive difficulties, and vice versa.

In summary, identifying individuals at high risk of cognitive decline may help reduce individual disability and the public health burden associated with cognitive impairment (Norrving & Kissela, 2013). As life expectancy increases and the elderly population of the US grows, the number of individuals with cognitive impairment is expected to rise, with an estimated 13.2 million cases of Alzheimer's disease by 2050 (Herbert, Scherr, Bienias, Bennett, Evans, 2003). Cognitive impairment can take a significant financial, functional, emotional toll on patients and caregivers. The need to identify at risk patients and provide services and care that reduce risk and promote independence is critical in maintaining quality of life in our aging population.

REFERENCES

Addison-Brown, K.J., Letter, A.J., Yaggi, K., McClure, L.A., Unverzagt, F.W., Howard, V.J., Lichtman, J.H., Wadley, V.G. (2014). Age differences in the association of obstructive sleep apnea risk with cognition and quality of life. *J Sleep Res, 23,* 69-76.

Alberts, M.J., Graffagnino, C., McClenny, C., DeLong, D., Strittmatter, W., Saunders, A.M., Roses, A.D. (1995). ApoE genotype and survival from intracerebral hemorrhage. *Lancet*, *346*, 575.

Barlow, W.E., Ichikawa, L., Rosner, D., Izumi, S. (1999). Analysis of case-cohort designs. *J Clin Epidemiol, 52*, 1165-1172.

Basun, H., Corder, E.H., Guo, Z., Lannfelt, L., Corder, L.S., Manton. K.G., Winblad, B., Vitanen, M. (1996). Apolipoprotein E polymorphism and stroke in a population sample aged 75 years or more. *Stroke*, *27,* 1310-1315.

Boyle, P.A., Buchman, A.S., Wilson, R.S., Kelly, J.F., Bennett, D.A. (2010). The ApoE e4 allele is associated with incident mild cognitive impairment among community-dwelling older persons. *Neuroepidemiology, 34,* 43-49.

Brayne, C., Harrington, C.R., Wischik, C.M., Huppert, F.A., Chi, L.Y., Xuereb, J.H., O'Connor, D.W., Paykel, E.S. (1996). Apolipoprotein E genotype in the prediction of cognitive decline and dementia in a prospectively studied elderly population. *Dementia, 7(*3): 169-74.

Brewster, G. S., Peterson, L., Roker, R., Ellis, M. L., & Edwards, J. D. (2017). Depressive Symptoms, Cognition and Everyday Function among Community-Residing Older Adults HHS Public Access. *J Aging H, 29(3): 367-388.*

Callahan, C.M., Unverzagt, F.W., Hui, S.L., Perkins, A.J., & Hendrie, H.C. (2002). Six-item Screener to identify cognitive impairment among potential subjects for clinical research. *Med Care;* 40, 771-781.

Caselli, R.J., Dueck, A.C., Locke, D.E.C., Sabbagh, M.N., Ahern, G. L., Rapcsak, S. Z., … Reiman, B.E.M. (2011). Cerebrovascular risk factors and preclinical memory decline in healthy ApoE 4 homozygotes. *Neurology*, (76), 1078–1084.

Cho, H., Choi, J. Y., Hwang, M. S., Lee, J. H., Kim, Y. J., Lee, H. M., … Lee, M. S. (2016). Tau PET in Alzheimer disease and mild cognitive impairment. *Neurology*, *87*(4), 375–383.

Corder, E.H., Saunders, A.M., Strittmatter, W.J. et al (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, 261, 921-923.

Cushman, M., Judd, L.A., Howard, V.J., Kissela, B., Guitterrez, O.M., Jenny, N.S. et al. (2014). N-terminal pro-B-type natriuretic peptide and stroke risk; the reasons for geographic and racial differences in stroke cohort. *Stroke*, *45*, 1646-1650.

DeFries, T., Avendaño, M., & Glymour, M.M. (2009). Level and change in cognitive test scores predict risk of first stroke. *Journal of the American Geriatrics Society*, *57*(3), 499–505.

De Groot, J. C., de Leeuw, F. E., Oudkerk, M., van Gijn, J., Hofman, A, Jolles, J., & Breteler, M.M. (2000). Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Annals of Neurology*, *47*(2), 145–51.

De Leeuw, F.E., Richard, F., de Groot, J. C., van Duijn, C. M., Hofman, A., Van Gijn, J., & Breteler, M.M.B. (2004). Interaction between hypertension, ApoE, and cerebral white matter lesions. *Stroke; a Journal of Cerebral Circulation*, *35*(5), 1057–60.

Eichner, J. E., Dunn, S. T., Perveen, G., Thompson, D. M., Stewart, K. E., & Stroehla, B. C. (2002). Apolipoprotein E polymorphism and cardiovascular disease: A HuGE review. *American Journal of Epidemiology*, *155*(6), 487–495.

Elias, M.F., Sullivan, L. M., D'Agostino, R.B., Elias, P. K., Beiser, A., Au, R., … Wolf, P. (2004). Framingham stroke risk profile and lowered cognitive performance. *Stroke; a Journal of Cerebral Circulation*, *35*(2), 404–409.

Elkins, J. S., Knopman, D. S., Yaffe, K., & Johnston, S. C. (2005). Cognitive function predicts first-time stroke and heart disease. *Neurology*, *64* (10), 1750–5.

Elkins, J. S., O'Meara, E. S., Longstreth, W. T., Carlson, M. C., Manolio, T. a, & Johnston, S. C. (2004). Stroke risk factors and loss of high cognitive function. *Neurology*, *63*(5), 793–9.

Espeseth, T., Westlye, L.T., Fjell, A.M., Walhovd, K.B., Rootwelt, H., Reinvang, I. (2008). Accelerated age-related cortical thinning in healthy carriers of apolipoprotein E epsilon 4.*Neurobiology of Aging*, *29*, 329–40.

Frisoni, G.B., Laakso, M.P., Beltramello, A., Geroldi, C., Bianchetti, A., Soininen, H., Trabucchi, M. (1999). Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease. *Neurology* 52, 91–100.

Greenberg, S.M., Rebeck, G.W., Vonsattel, J.P., Gomez-Islaq, T., Hyman, B.T. (1995). Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloidangiopathy. *AnnNeurol, 38,* 254-259.

Gu, L., Su, L., Chen, Q., Liang, B., Qin, Y., Xie, J., … Wang, J. (2013). Association between the apolipoprotein E gene polymorphism and ischemic stroke in Chinese populations: New data and meta-analysis. *Experimental and Therapeutic Medicine*, *5*(3), 853–859.

Haan, M. N., Shemanski, L., Jagust, W. J., Manolio, T.A., & Kuller, L. (1999). The role of ApoE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA : The Journal of the American Medical Association*, *282*(1), 40–6.

Hachinski, V., Iadecola, C., Peterson, R.C., Breteler, M.B., Nyenhuis, D.L., Black, S.E., Powers, W.J., Decarli, C., Merino, J.G., Kalaria, R., Vinters, H., Holtzman, D., Hostage C.A.,Choudhury K., Doraiswamy, P.M., Petrella, J.R. (2013). Dissecting the gene dose-effects of the ApoE ε4 and ε2 alleles on hippocampal volumes in aging and Alzheimer's disease. PloS one; 8:e54483.

Henry, J.D., Crawford, J.R. (2004). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology 18,* 284–295.

Horsburgh, K., McCarron, M.O., White, F., Nicoll, J.A.R. (2000). The role of apolipoprotein E in Alzheimer's disease, acute brain injury and cerebrovascular disease: evidence of common mechanisms and utility of animal models. *Neurobiol Aging, 21*: 245–255.

Howard, V.J., Cushman, M., Pulley, L., Gomez, C.R., Go, R.C., Prinea, R.J., Graham,

A., Moy C.S., Howard, G. (2005). The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology*, 25, 135-143.

Helkala, E.L., Koivisto, K., Hanninen, T., Vanhanen, M., Kervinen, K., Kuusisto, J., Riekkinen, P. (1996). Memory functions in human subjects with different apolipoprotein E phenotypes during a 3-year population-based follow-up study. *Neurosci Lett*, *204*(3), 177–180.

Iadecola, C., & Gorelick, P.B. (2003). Converging pathogenic mechanisms in vascular and neurodegenerative dementia. *Stroke, 34*: 335-337

Jin, Y.P., Ostybe, T., Feightner, J.W., et al (2008). Joint effect of stroke and ApoE 4 on dementia risk: the Canadian Study of Health and Aging, *Neurology*, 70, 9-16.

Jorm, A. F., Mather, K.A., Butterworth, P., Anstey, K.J., Christensen, H., & Easteal, S. (2007). ApoE genotype and cognitive functioning in a large age-stratified population sample. *Neuropsychology*, *21*(1), 1–8.

Kalaria, R.N., Premkumar D.R.D. (1995). Apolipoprotein E genotype and cerebral amyloid angiopathy. *Lancet*, *346*, 1424.

Kalmijn, S., Feskens, E.J.M., Launer, L.J., Kromhout, D. (1996). Cerebrovascular Disease, the Apolipoprotein e4 Allele, and Cognitive Decline in a Community-Based Study of Elderly Men, *Stroke, 27*, 2230-2235.

Knopman, D.S., Mosley, T.H., Catellier, D.J., & Coker, L.H. (2009). Fourteen-year longitudinal study of vascular risk factors, ApoE genotype, and cognition: the ARIC MRI Study. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *5*(3), 207–14.

Kokubo, Y., Chowdhury, A.H., Date, C., Yokoyama, T., Sobue, H., & Tanaka, H. (2000). Age-Dependent Association of Apolipoprotein E Genotypes with Stroke Subtypes in a Japanese Rural Population. *Stroke*, *31*(6), 1299–1306.

Kuller, L.H., Shemanski, L., Manolio, T., Haan, M., Fried, L., Bryan, N., Burke, G.L., Tracy, R., Bhadelia, R. (1998). Relationship Between ApoE, MRI Findings, and Cognitive Function in the Cardiovascular Health Study. *Stroke*. *29*, 388–398.

Letter, A.J., Unverzagt, F.W., McClure, L.A., Howard, G., Howard, V., Cushman, M., Kelley, B.J., Moy, C., Kissela. B., Wadley, V.G. Lower executive function and memory predict risk of first stroke in the national REGARDS cohort. Unpublished manuscript.

Longstreth, W. T., Arnold, A.M., Manolio, T.A., Burke, G. L., Bryan, N., Jungreis, C. A., Fried, L. (2000). Clinical correlates of ventricular and sulcal size on cranial magnetic resonance imaging of 3,301 elderly people. The Cardiovascular Health Study. Collaborative Research Group. *Neuroepidemiology*, *19*(1), 30–42.

Mahley, R.W., Rall, S.C. (2000). Apolipoprotein E: far more than a lipid transport protein. *Annu Review Genomics Human Genetics,* 1, 507-37.

Mai, L.M., Oczkowski, W., Mackenzie, G., Shuster, A., Wasielesky, L., Franchetto, A., Sahlas, D. J. (2013). Screening for cognitive impairment in a stroke prevention clinic using the MoCA. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques*, *40*(2), 192–7.

Marin, D.B., Breuer, B., Marin, M. (1998). The relationship between apolipoprotein E, dementia, and vascular illness. *Atherosclerosis,* 140: 173–180.

Morris, J.C., Heyman, A., Mohs, R.C., Hughes, J.P., van Belle, G., Fillenbaum, G., Mellits, E.D., Clark, C. (1989). The consortium to establish a registry for Alzheimer's disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*, 39(9), 1159-65.

Mosley, T.H., Knopman, D.S., Catellier, D.J., Bryan, N., Hutchinson, R.G., Grothues, C.A., Folsom, A.R., Cooper LS, Burke GL, Liao D, Szklo M. (2005). Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities study. *Neurology*, *64,* 2056–62.

Melchior, L.A., Huba, G.J., Brown, V.B., Reback, C.J. (1993). A short depression index for women. *Educational and Psychological Measurement*, *53,* 1117-1125.

Nasreddine, Z.S., Phillips, N.A., Bedirian,, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc, 53,* 695-699.

Norrving, B., Kissela, B. (2013). The global burden of stroke and need for a continuum of care. Neurology, *80*, S5-S12.

O'Brien, J.T., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L., et al (2003). Vascular cognitive impairment. *Lancet Neurology. 2*, 89-98.

Pantoni, L. (2010). Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurology:* 9, 689-701.

Panza, F., Frisardi, V., Capurso, C., D'Introno, A., Colacicco, A.M., Imbimbo, B.P., Solfrizzi, V. (2010). Late-life depression, mild cognitive impairment, and

dementia: Possible continuum? *American Journal of Geriatric Psychiatry*, *18(2),* 98–116.

Pendlebury, S.T., Rothwell, P.M. (2009). Prevalence, incidence, and factors associated with prestroke and post stroke dementia: a systematic review and meta-analysis. *Lancet Neurology*, 69, 640-650.

Rawle, M. J., Davis, D., Bendayan, R., Wong, A., Kuh, D., & Richards, M. (2018). Apolipoprotein-E (ApoE) ε4 and cognitive decline over the adult life course. *Translational Psychiatry, 8(1*), 18.

Rosenberg, G.A., Dichgans, M., Marler, J., Leblanc, G.G. (2006). NINDS-CSN vascular cognitive impairment harmonization standards. *Stroke*, 37, 2220-2241.

Seshadri, S., Wolf, P.A., Beiser, A., Elias, M.F., Au, R., Kase, C.S., D'Agostino, R.B., DeCarli, C. (2004). Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. *Neurology,* 63, 1591-1599.

Shi, Y., Yamada, K., Liddelow, S. A., Smith, S.T., Zhao, L., Luo, W., et al. (2017). ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. *Nature,* 549, 523–527.

Smith, G.E., Bohac, D.L., Waring, S.C., et al. **(**1998). Apolipoprotein E genotype influences cognitive 'phenotype' in patients with Alzheimer's disease but not in healthy control subjects. *Neurology,* 50, 355-62.

Sing, C. F., & Davignon, J. (1985). Role of the apolipoprotein E polymorphism in determining normal plasma lipid and lipoprotein variation. *American Journal of Human Genetics*, *37*(2), 268–85.

Stephens, M., Smith, N., & Donnelly, P. (2001). A new statistical method for haplotype

reconstruction from population data. *American Journal of Human Genetics,* 68, 978-989.

Stephens, M., & Scheet, P. (2005). Accounting for Decay of Linkage Disequilibrium in Haplotype Inference and Missing-Data Imputation. *American Journal of Human Genetics,* 76, 449-46

Stroke (1989). Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO task force on stroke and other cerebrovascular disorders. *Stroke*, 20, 1407 -1431.

Sudlow, C., Gonzalez, M., Kim, J., & Clark, C. (2006). Does apolipoprotein E genotype influence the risk of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage? Systematic review and meta-analysis of 31 studies among 5,961 cases and 17965 controls. *Stroke*, 37, 364-70.

Tatemichi,T.K., Saktor, N., Dementia associated with cerebrovascular disease, other degenerative diseases, and metabolic disorders. In: Terry RD, Katzman R, Bick KL, eds. Alzheimer ’s disease. New York, NY: Raven Press, Ltd; 1994: 123-166.

Thambisetty, M., Beason-Held, L., An, Y, Kraut, M.A., Resnick, S.M. (2010). ApoE ε4 genotype and longitudinal changes in cerebral blood flow in normal aging. *Arch Neurology,* 67, 93-98.

Unverzagt, F. W., McClure, L.A., Wadley, V. G., Jenny, N. S., Go, R. C., Cushman, M., … Howard, G. (2011). Vascular risk factors and cognitive impairment in a stroke-free cohort. *Neurology*, *77*(19), 1729–1736.

Verghese, P.B., Castellano, J.M., Holtzman, D.M. (2011). Roles of apolipoprotein E on Alzheimer’s disease and other neurological disorders. *Lancet Neurology, 10(3),*

241-252.

Vermeer, S.E., Prins, N.D., den Heijer, T., Hofman, A., Koudstaal, P. J., & Breteler, M. M. B. (2003). Silent brain infarcts and the risk of dementia and cognitive decline. *The New England Journal of Medicine*, *348*(13), 1215–22.

Wiberg, B., Lin, L., Kilander, L., Zethelius, B., Sundelof, J.E., Sundstrom, J. (2010). Cognitive function and risk of stroke in elderly men. *Neurology*, 74, 380 – 385.

Wilson, D'Agostino, Levy, Belanger, Silbershatz, & Kannel. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation* 97, 1837-1847.

Wisdom, N. M., Callahan, J. L. & Hawkins, K. A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. *Neurobiol. Aging*, 32, 63–74.

Wolf, P.A, D'Agostino, R.B., Belanger, A.J., Kannel, W.B. (1991). Probability of stroke: a risk profile from the Framingham Study. *Stroke*; *22,* 312–318.

Yang, J., Ji, Y., Mehta, P., Bates, K.A., Sun, Y., et al. (2011). Blocking the apolipoprotein E/amyloid b interaction reduces fibrillar vascular amyloid deposition and cerebral microhemorrhages in TgSwDI mice. *Journal of Alzheimers Disease, 24*, 269-285.

Yasuno, F., Tanimukai, S., Sasaki, M., Ikejima, C., Yamashita, F., Kodama, C., Hidaka, S., Mizukami, K., Asada, T. (2012). Effect of plasma lipids, hypertension and ApoE genotype on cognitive decline. *Neurobiology of Aging*, 33(11), 2633-2640.

Yen, Y., Rebok, G.W., Gallo, J.J., Jones, R.N., Tennestedt, S.L. (2011). Depressive symptoms impaired everyday problem-solving ability through cognitive abilities in late life. *American Journal of Geriatric Psychiatry*; 19(2), 142–150.

Zhu, L., Fratiglioni, L., Guo, Z., Winblad, B., Viitanen, M. (2000). Incidence of stroke in relation to cognitive function and dementia in the Kungsholmen Project. *Neurology*, 54, 2103–2107.

Table 1

Cognitive Assessment Measures

Domain	Measures	Score
Memory	Word List Delayed Recall (WLD)	Number correct (0-10), Age Adjusted z-scores
Learning	Word List Learning (WLL)	Sum of 3 learning trials (0-30), Age adjusted z-scores
Executive	Animal Fluency Letter Fluency	Number correct in 60 seconds, Age-adjusted z scores

Table 2

Baseline characteristics between participants who were and were not included in Aim 1 analysis: REGARDS, 2003-2015, *(weighted to full REGARDS sample)*

Variable	Included (*n*=1549)	Excluded (*n*=174)	p value
Sociodemographics			
Age, *years*, *M (SD*)	68.09 (10.90)	69.03 (11.50)	.550
Women, *n* (%)	13727.20 (54.29)	1835.71 (61.10)	<.001
Black, *n* (%)	15026.20 (59.40)	1751.50 (58.30)	.218
Education, *n* (%)			<.001
< High school	2968.19 (11.70)	295.84 (9.80)	
High school graduate	5721.77 (22.60)	1106.51 (36.80)	
Some college	7215.24 (28.50)	660.98 (22.00)	
≥ College graduate	9381.92 (37.10)	943.28 (31.40)	
Region, *n* (%)			<.001
Non-Belt	11848.40 (46.90)	1539.25 (51.20)	
Stroke Buckle	4694.11 (18.60)	527.36 (17.50)	
Stroke Belt	8744.64 (34.60)	940.00 (31.30)	
Income, n (%)			<.001
<$20,000	3841.18 (15.20)	601.24 (20.00)	

$20,000-$34,999	5843.96 (23.11)	675.74 (22.50)	
$35,000-$74,999	7983.88 (31.60)	765.57 (25.50)	
≥$75,000	4294.04 (17.00)	511.66 (17.02)	
refused/missing	3324.07 (13.20)	452.40 (15.10)	
Vascular Risk Factors			
Cigarette smoking, *n* (%)			<.001
Never	12316.10 (48.70)	1221.69 (42.70)	
Past	9558.32 (37.80)	1246.21 (43.60)	
Current	3412.68 (13.50)	391.56 (13.70)	
Atrial fibrillation, *n* (%)	2224.92 (8.90)	308.71 (12.10)	<.001
CAD, *n* (%)	3906.28 (15.60)	670.86 (24.40)	<.001
Diabetes, *n* (%)	5243.06 (20.90)	818.46 (38.40)	<.001
Dyslipidemia, *n* (%)	15186.90 (60.10)	1196.29 (39.79)	<.001
Hypertension, *n* (%)	14330.80 (57.20)	1707.50 (55.60)	.096
Incident Stroke, *n* (%)	1084.21 (4.30)	130.26 (4.30)	.909
LVH, *n* (%)	2097.87 (8.40)	226.04 (8.70)	.632

Notes. Analyses weighted to the full REGARDS sample.
Abbreviations: CAD, Coronary Artery Disease; LVH, Left Ventricular Hypertrophy

Table 3

Baseline Descriptive Statistics for Stroke Cases and Cohort Participants Included in Aim 1 Analyses: REGARDS, 2003-2015, *(weighted to full REGARDS sample)*

	Incident Stroke				
Characteristic	No Stroke		Stroke		
	n	%	*n*	%	*p*
ApoE e4	8661	33.8	273	23.7	< .001
Age (*M, SD*)	64.57	9.27	69.92	8.60	< .001
Age at Event (*M, SD*)	72.25	9.53	72.74	8.31	.087
Black	10391	40.50	505	43.80	.025
Women	14251	55.60	455	39.50	< .001
Region					< .001
Stroke belt	8831	34.40	311	26.90	
Stroke buckle	4754	18.50	219	19.00	
Non stroke belt	12068	47.00	623	54.00	
Education					< .001
< High school	3046	11.90	104	9.00	
High school graduate	5985	23.30	246	21.30	
Some college	7183	28.00	403	34.90	
College graduate and above	9439	36.80	401	34.70	
Income					< .001
less than $20k	4027	15.70	178	15.50	

$20k-$34k	5851	22.80	326	28.30	
$35k-$74k	7871	30.70	360	31.20	
$75k and above	4393	17.10	191	16.60	
Refused	3512	13.70	98	8.50	
Smoking					< .001
Never	12404	48.40	433	37.50	
Past	9580	37.30	562	48.80	
Current	3526	13.70	155	13.50	
Atrial Fibrillation	2130	8.50	233	20.50	< .001
CAD	3818	15.20	366	32.00	< .001
Diabetes	5108	20.30	420	36.80	< .001
Hypertension	14534	57.00	814	70.70	< .001
LVH	2026	8.10	118	10.30	.007

Notes. Analyses weighted to the full REGARDS sample.
Abbreviations: CAD, Coronary Artery Disease; LVH, Left Ventricular Hypertrophy

Table 4

Baseline Descriptive Statistics by ApoE e4 Carrier Status of Participants Included in Aim 1 Analyses: REGARDS, 2003-2015, (weighted to full REGARDS sample)

	ApoE e4 Carrier Status				
	Noncarriers		Carriers		
Characteristic	*n*	%	*n*	%	*p*
Age (*M, SD*)	65.07	9.50	64.27	8.87	< .001
Age at Stroke	73.40	8.65	71.62	8.69	< .05
Black	6493	36.30	4403	49.30	< .05
Female	9460	52.90	5246	58.70	
Region					< .001
Stroke belt	6264	35.00	2878	32.20	
Stroke buckle	3431	19.20	1542	17.30	
Non stroke belt	8178	45.80	4514	50.50	
Education					> .001
< High school	1977	11.10	1173	13.10	
High school graduate	4381	24.50	1850	20.70	
Some college	5013	28.00	2573	28.80	
College graduate and above	6501	36.40	3338	37.40	

Income					< .001
less than $20k	2773	15.50	1433	16.00	
$20k-$34k	4310	24.10	1867	20.90	
$35k-$74k	5566	31.10	2665	29.80	
$75k and above	2958	16.60	1626	18.20	
Refused	2266	12.70	1343	15.00	
Smoking					< .001
Never	8536	47.80	4301	48.10	
Past	7083	39.60	3059	34.20	<.05
Current	2108	11.80	1574	17.60	<.05
Atrial Fibrillation	1614	9.20	749	8.70	.196
CAD	2557	14.50	1627	18.80	< .001
Diabetes	3490	19.90	2038	23.20	< .001
Dyslipidemia	10288	58.70	5540	62.80	< .001
Hypertension	10314	57.80	5034	57.30	.514
LVH	1328	7.60	816	9.30	< .001

Notes. Analyses weighted to the full REGARDS sample.
Abbreviations: CAD, Coronary Artery Disease; LVH, Left Ventricular Hypertrophy;

Table 5

Descriptive Statistics for Key Study Variables by ApoE Status for Regression Models of Cognitive Function (age-adjusted Z-scores) in Regards Stroke Case-Cohort Sample

	ApoE Carriers		ApoE Noncarriers		
Characteristic	*M or n*	*SD* or %	*M or n*	*SD* or %	*p*
Cognitive Score					
WLL	-0.09	1.02	0.03	0.97	.060
WLD	-0.04	1.04	0.03	0.97	.660
AF	-0.05	1.02	0.00	1.00	.423
LF	0.05	1.04	-0.01	0.96	.387
Incident Stroke	52	17.70	133	20.84	.150
Race, % black	165	56.12	272	42.60	< .001
Age, *years*	66.27	10.88	67.57	11.53	.103
Education, % High School or Less	112	38.09	237	37.15	.827
Gender, % female	162	55.10	321	50.30	.098

Region, % Belt or Buckle	134	45.58	346	54.23	< .05
Cognitive Impairment	25	8.50	38	5.90	.098
Hemorrhagic Stroke	6	2.00	13	3.60	.412
FSRP	12.09	12.03	12.33	11.67	.780
CES-D	1.22	2.05	1.15	2.03	.665

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years; WLL, World List Learning; WLD, Word List Delayed Recall; AF, Animal Fluency; LF, Letter Fluency
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 6

Descriptive Statistics for Key Variables for Regression Models of Cognitive Function in REGARDS Stroke Case-Cohort Sample

	WLL		WLD		AF		LF	
Characteristic	*M or n*	*SD* or %	*M or n*	*SD* or %	*M or n*	*SD* or %	*M or n*	*SD* or %
Cognitive Score	16.67	5.33	6.21	2.26	16.17	5.68	10.46	4.89
ApoE e4 Carriers	294	31.5	208	31.00	289	31.60	130	28.70
Incident Stroke	185	19.80	131	19.60	171	18.20	40	8.30
Race, % black	437	46.90	301	44.90	454	48.20	237	49.10
Age, *years*	67.16	11.34	65.62	11.38	67.45	11.65	77.91	6.03
Time to Assessment, *years*	2.73	2.54	2.19	2.19	3.11	2.96	5.39	2.61
Education, % high school or Less	349	37.40	231	34.50	354	37.60	205	42.40

Gender, % female	449	51.80	386	57.60	475	50.40	244	50.50
Region, % Belt or Buckle	480	51.50	358	53.40	498	52.90	236	48.90
Cognitive Impairment	63	6.80	60	6.70	63	6.70	53	11.00
Hemorrhagic Stroke	19	2.00	19	2.10	19	2.00	3	0.60
FSRP	12.26	11.78	11.36	11.32	12.81	12.74	19.50	14.23
CES-D	1.17	2.03	1.22	2.10	1.23	2.13	1.06	1.77

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years; WLL, World List Learning (range 0 – 30); WLD, Word List Delayed Recall (range 0 – 10); AF, Animal Fluency; LF, Letter Fluency;
Notes. Means are raw scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 7

Interaction Testing for Cox Regression Models of Incident Stroke by ApoE e4 Carrier Status, Age, and Race

Interaction	*df*	*Wald Chi-Square*	*p value*
ApoE e4 x Race	1	0.62	.433
ApoE e4 x Age	1	0.01	.908
Age x Race	1	5.73	.017
ApoE e4 x Age x Race	1	0.08	.782

Table 8

Model Fit Statistics for Cox Regression Models of Incident Stroke

	-2 Log Likelihood	$\chi 2$	Likelihood Ratio	df	*p*
Model 1[a]	9535.37		1.23	1	.268
Model 2[b]	9374.34	161.04	162.27	12	< .0001
Model 3[c]	8593.64	124.88	287.15	20	< .0001

Notes. [a] ApoE e4 carrier status
[b]ApoE e4 carrier status, race, education, sex, income, region of residence (Stroke Belt, Stroke Buckle, Remaining U.S.)
[c]ApoE e4 carrier status, sociodemographics, atrial fibrillation, coronary artery disease, diabetes, dyslipidemia, hypertension, left ventricular hypertrophy, and smoking status

Table 9

Cox Regression Model for Incident Stroke by ApoE e4 Carrier Status and Sociodemographic Factors

Parameter	DF	Estimate	SE	ChiSq	p-value	Hazard Ratio	95% Confidence Interval
ApoE e4	1	0.01	0.12	0.01	.925	1.01	(0.80 - 1.29)
Black	1	1.84	0.63	8.47	.004	0.72	(0.55 - 0.95)
Age	1	0.05	0.01	52.05	< .0001	.	.
Age*Race	1	-0.03	0.01	10.14	.002	.	.
Region of Residence							
Stroke Buckle	1	0.09	0.15	0.36	.550	1.10	(0.81 - 1.48)
Stroke Belt	1	0.04	0.13	0.09	.768	1.04	(0.81 - 1.34)

Male	1	0.30	0.12	6.70	.010	1.35	(1.08 - 1.70)
Income							
$20,000-$34,999	1	0.05	0.17	0.10	.755	1.05	(0.76 - 1.47)
$35,000-$74,999	1	-0.12	0.18	0.41	.524	0.89	(0.63 - 1.27)
≥$75,000	1	-0.69	0.24	8.49	.004	0.50	(0.32 - 0.80)
Refused/missing	1	-0.30	0.20	2.24	.134	0.74	(0.50 - 1.10)
Education	1	0.31	0.12	6.16	.010	1.37	(1.07 - 1.75)

Notes. [a]Cognitively normal peers were the reference group., education greater than high school, income less than 20,000, female gender, nonstroke belt/buckle US, White race, ApoE e4 noncarriers were the reference groups

Table 10

Cox Regression Model for Incident Stroke by ApoE e4 Carrier Status, Sociodemographic and Vascular Risk Factors

Parameter	df	Estimate	SE	ChiSq	p	Hazard Ratio	95% Confidence Interval
ApoE E4 Carrier	1	0.03	0.14	0.04	.849	1.03	(0.78- 1.34)
Black	1	1.82	0.71	6.55	.011	0.72	(0.55 - 0.95)
Age		0.04	0.01	30.49	< .0001		
Age*Race	1	-0.03	0.01	9.49	.002	.	.
Region of Residence							
Stroke Buckle		-0.07	0.17	0.18	.673	0.93	(0.67 - 1.30)
Stroke Belt		-0.13	0.15	0.75	.385	0.88	(0.66 - 1.17)
Male	1	0.09	0.13	0.46	.500	1.10	(0.84 - 1.43)
Income							

$20,000-$34,999	1	0.15	0.19	0.64	.423	1.17	(0.80 - 1.69)
$35,000-$74,999	1	-0.01	0.20	0.00	.945	0.99	(0.67 - 1.46)
≥$75,000	1	-0.51	0.26	3.73	.054	0.60	(0.36 - .1.01)
Refused/missing	1	-0.21	0.23	0.84	.360	0.81	(0.52 - 1.27)
High School or Less	1	0.32	0.14	5.40	.020	1.38	(1.05 - 1.82)
Smoking							
Past	1	0.26	0.14	3.71	.054	1.30	(0.99 - 1.69)
Current	1	0.67	0.19	12.19	.001	1.96	(1.34 - 2.85)
Atrial Fibrillation	1	0.40	0.20	4.12	.042	1.49	(1.01 - 2.19)
CAD	1	0.54	0.16	11.59	.001	1.72	(1.26 - 2.36)
Diabetes	1	0.10	0.15	0.42	.520	1.10	(0.82 - 1.49)
Dyslipidemia	1	-0.05	0.13	0.12	.730	0.95	(0.74 - 1.24)
Hypertension	1	0.56	0.14	15.24	< .0001	1.75	(1.32 - 2.33)
LVH	1	0.53	0.19	7.67	.006	1.70	(1.17 - 2.47)

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; CAD, Coronary Artery Disease; LVH, Left Ventricular Hypertrophy; Afib, Atrial Fibrillation
Notes. education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 11

Hazard Ratios and 95% CI for Association of Race with Odds of Incident Stroke, Stratified by Age

Age, *years*		Demographics[a]	Full Model[b]
	p value for age by race interaction	.001	.002
<55		4.37 (1.20 – 15.82)	3.25 (0.48-21.88)
55-64		1.05 (0.63 – 1.76)	0.91 (.48 – 1.73)
65-75		0.96 (0.61 – 1.51)	1.00 (0.57 – 1.74)
>75		0.61 (0.40 – 0.95)	0.42 (0.24 – 0.75)

Notes. [a]ApoE E4 carrier status, race, education, sex, income, region of residence (Stroke Belt, Stroke Buckle, Remaining U.S.)
[b]ApoE E4 carrier status, sociodemographics, and atrial fibrillation, coronary artery disease, diabetes, dyslipidemia, hypertension, left ventricular hypertrophy, and smoking; White race was the reference group

Table 12

Summary of Regression Models for Word List Learning Performance (N=900)

Variable	Model 1			Model 2			Model 3		
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.135	.070	.070[a]	-.132	.071	-.062[a]	-.133	.071	-.062[a]
Incident Stroke				-.169	.085	-.068*	-.127	.086	-.051
Time				.032	.014	.081*	.037	.014	.093**
CES-D				-.042	.016	-.089**	-.041	.016	-.087*
Education				.100	.069	.049	.074	.070	.036
Gender				.148	.067	.074*	.121	.068	.060[a]
Race				.143	.068	.072*	.130	.068	.065[a]
Region of Residence				-.023	.067	-.011	-.022	.066	-.011
FSRP							-.085	.036	-.083*
R^2		.004			.036			.042	
Adjusted R^2		.003			.027			.032	

F for change in R^2	3.55[a]	4.25***	5.65***
Model *F*	3.55[a]	4.17***	4.35***

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed; [a] p < .08, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years; WLL, World List Learning (score range 0 – 30);

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 13

Summary of Regression Models for Word List Learning Performance for Cohort Members without Incident Stroke (N=718)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.329	.172	-.141	-.082	.078	-.039	-.083	.078	-.039
Time				.032	.014	.086*	.037	.014	.099**
CES-D				-.045	.018	-.096*	-.043	.018	-.093*
Education				.107	.077	.053	.075	.078	.037
Gender				.091	.074	.046	.059	.075	.030
Race				.155	.075	.079*	.137	.075	.070[a]
Region				-.055	.074	-.028	-.054	.074	-.027
FSRP							-.089	.038	-.091*
R^2		.002			.031			.031	

Adjusted R^2	.001	.022	.028
F for change in R^2	1.66	3.56**	5.49*
Model *F*	1.66	3.29**	3.59***

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years;

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 14

Summary of Regression Models for Word List Learning Performance for Incident Stroke Cases (N=182)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.101	.078	-.048[a]	-.355	.172	-.152*	-.358	.173	-.154*
Time				.042	.064	.050	.042	.064	.050
CES-D				-.031	.036	-.064	-.031	.036	-.064
Education				.102	.159	.049	.100	.160	.048
Gender				.393	.159	.189*	.386	.160	.186*
Race				.136	.161	.064	.136	.162	.064
Region				.100	.158	.048	.102	.159	.049
FSRP							-.039	.110	-.026
R^2		.002			.060			.061	

Adjusted R^2	.001	.022	.017
F for change in R^2	3.65[a]	1.25	0.13
Model *F*	3.65[a]	1.60	1.40

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed ; [a] p < .08, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years;

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 15

Regression Model using Backward Elimination Model Selection for Word List Learning Performance by Incident Stroke Status

	Full Sample (N = 900)			No Stroke (N =718)			Stroke (N = 182)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.126	.071	-.059[a]	-.078	.078	-.037	-.359	.172	-.154*
Time	.041	.013	.104**	.036	.014	.097*	.034	.062	.040
CES-D	-.043	.016	-.091**	-.047	.018	-.100**	-.032	.036	-.067
Gender	.113	.068	.057	.051	.075	.026	.388	.159	.187*
Race	.129	.067	.065[a]	.141	.074	.072[a]	.148	.159	.070
FSRP	-.103	.035	-.100**	-.096	.037	-.099**	-.038	.109	-.026
R^2		.038			.037			.057	
Adjusted R^2		.032			.029			.025	
Model *F*		5.933 ***			4.514***			1.770	

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed ; [a] p < .08, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years; WLL, World List Learning
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 16

Summary of Regression Models for Word List Delay Age-Adjusted Z Scores in REGARDS to Full Sample (N=870)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.016	.073	-.007	-.020	.073	-.009	-.020	.073	-.009
Stroke				-.075	.087	-.030	-.044	.088	-.018
Time				.034*	.014	.087	.038**	.014	.096
CES-D				-.051**	.016	-.108	-.050**	.016	-.107
Education				.046	.071	.022	.027	.072	.013
Gender				.193**	.069	.097	.173*	.070	.087
Race				.051	.070	.025	.040	.070	.020
Region				.036	.068	.018	.037	.068	.018
FSRP							-.064	.037	-.062
R^2	.000			.027			.031		

Adjusted R^2	-.001	.018	.021
F for change in R^2	.05	3.45**	2.98
Model *F*	.05	3.02**	3.03**

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed; [a] p < .08, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLD assessment in years; WLD, Word List Delayed Recall;

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, White race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 17

Summary of Regression Models for Word List Delay Age-Adjusted Z Scores in REGARDS Cohort Sample without Incident Stroke (N=698)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.001	.080	-.001	.004	.081	.002	.004	.081	.002
Time				.033*	.014	.089	.036*	.014	.097
CES-D				-.057**	.018	-.120	-.056**	.018	-.119
Education				.061	.080	.030	.041	.081	.020
Gender				.130	.077	.065	.111	.078	.056
Race				.032	.078	.016	.021	.078	.011
Region				.038	.076	.019	.039	.076	.019
FSRP							-.054	.039	-.054

R^2	.000	.025	.028
Adjusted R^2	-.001	.015	.017
F for change in R^2	.00	2.99**	1.85
Model *F*	.00	2.57*	2.48*

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLD assessment in years; WLD, Word List Delayed Recall
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 18

Summary of Regression Models for Word List Delay Age-Adjusted Z Scores in REGARDS Cohort Sample with Incident Stroke (N=172)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.108	.173	-.048	-.141	.172	-.063	-.149	.172	-.066
Time				.037	.063	.045	.037	.063	.045
CES-D				-.034	.036	-.073	-.034	.036	-.074
Education				-.019	.159	-.009	-.024	.159	-.012
Gender				.486**	.158	.242	.470**	.159	.234
Race				.149	.161	.072	.148	.161	.072
Region				.036	.158	.018	.043	.158	.021
FSRP							-.093	.109	-.065
R^2	.002			.059			.063		

Adjusted R^2	-.004	.019	.017
F for change in R^2	.39	1.65	.73
Model *F*	.39	1.47	1.38

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLD assessment in years; WLD, Word List Delayed Recall
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 19

Summary of WLD Regression Models using Backward Elimination Model Selection

	Case Cohort (*N*=627)			Cohort (*N=502*)			Stroke Cases(*N=125)*		
Variable	*B*	*SE B*	*t*	*B*	*SE B*	*t*	*B*	*SE B*	*t*
ApoE e4	-.018	.085	-.008	.002	.094	.001	-.122	.204	-.053
Time	.022	.018	.047	.020	.019	.045	.026	.082	.028
CES-D	-.071	.019	-.149***	-.079	.021	-.164***	-.052	.042	-.110
Gender	.231	.080	.114**	.161	.090	.080[a]	.563	.186	.274**
Race	.115	.079	.057	.103	.088	.051	.210	.187	.099
FSRP	-.087	.039	-.087*	-.077	.043	-.080[a]	-.120	.127	-.083
R^2	.048			.045			.091		
Adjusted R^2	.039			.034			.045		
Model *F*	5.34***			4.08**			1.99[a]		

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed; [a] p < .08, two-tailed
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and AF assessment in years; AF, Animal Fluency
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 20

Summary of Regression Models for Animal Fluency Age-Adjusted Z Scores in REGARDS Stroke Case Cohort Sample (N=917)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.057	.072	-.026	-.047	.072	-.022	-.047	.072	-.022
Stroke				-.075	.086	-.030	-.066	.087	-.026
Time				.014	.012	.038	.014	.012	.040
CES-D				-.034	.016	-.070	-.034	.016	-.070*
Education				.151	.070	.073	.146	.071	.070*
Gender				-.002	.068	-.001	-.008	.069	-.004
Race				.104	.069	.051	.101	.069	.050
Region				-.067	.068	-.033	-.067	.068	-.033
FSRP							-.018	.036	-.017

R^2	.001	.015	.016
Adjusted R^2	.001	.004	.004
F for change in R^2	.63	2.73*	.24
Model *F*	.63	2.47*	2.22*

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and AF assessment in years; AF, Animal Fluency
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 21

Summary of Regression Models for Animal Fluency Performance in REGARDS Cohort Sample without Incident Stroke (N=750)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.094	.079	-.043	-.075	.079	-.035	-.075	.079	-.035
Stroke				.014	.013	.040	.014	.013	.041
Time				-.041	.018	-.084	-.041	.018	-.084
CES-D				.138	.078	.066*	.132	.080	.063*
Education				-.025	.076	-.013	-.031	.077	-.015
Gender				.115	.076	.057	.112	.077	.055
Race				-.072	.075	-.036	-.072	.075	-.035
Region				-.075	.079	-.035	-.016	.038	-.016
FSRP							-.075	.079	-.035

R^2	.002	.025	.025
Adjusted R^2	.001	.016	.025
F for change in R^2	1.41	2.90**	.17
Model *F*	1.41	2.47**	2.74*

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and AF assessment in years; AF, Animal Fluency
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 22

Summary of Regression Models for Animal Fluency Performance in REGARDS Incident Stroke Cases (N=166)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	.112	.172	.050	.111	.175	.050	.107	.177	.048
Stroke				.003	.055	.005	.002	.055	.004
Time				-.001	.038	-.002	-.001	.038	-.003
CES-D				.212	.165	.105	.210	.166	.104
Education				.083	.161	.042	.079	.163	.040
Gender				.043	.168	.021	.045	.169	.022
Race				-.045	.158	-.023	-.044	.159	-.022
Region				.111	.175	.050	-.022	.112	-.016
FSRP							.107	.177	.048

R^2	.003	.017	.017
Adjusted R^2	-.003	-.027	-.033
F for change in R^2	.42	.38	.04
Model *F*	.42	.38	.34

*$p < .05$, two-tailed; **$p < .01$., two-tailed; ***$p < .001$, two-tailed; [a] $p < .08$, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and AF assessment in years; AF, Animal Fluency

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 23

Regression Model using Backward Elimination Model Selection for Animal Fluency Performance by Incident Stroke Status

	Full Sample (N = 917)			No Stroke (N =750)			Stroke (N = 166)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.043	.072	-.020	-.074	.079	-.034	.112	.175	.050
Time	.018	.012	.050	.016	.013	.046	.001	.054	.002
CES-D	-.035	.016	-.072*	-.043	.018	-.089*	.000	.038	.001
Education	.154	.071	.074*	.143	.079	.068	.211	.164	.104
Race	.090	.068	.045	.104	.076	.051	.029	.166	.014
FSRP	-.023	.035	-.022	-.013	.038	-.013	-.029	.111	-.021
R^2	.020			.023			.015		
Adjusted R^2	.013			.016			-.022		
Model *F*	3.07**			2.98**			.40		

*$p < .05$, two-tailed; **$p < .01$., two-tailed; ***$p < .001$, two-tailed; [a] $p < .08$, two-tailed
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and AF assessment in years; AF, Animal Fluency
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 24

Summary of Regression Models for Letter Fluency Performance in REGARDS Stroke Case Cohort Sample (N=728)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	.013	.023	.063	0.063	0.078	0.03	.063	.079	.030
Stroke				-.017	.134	-.005	-.002	.137	-.001
Time				.008	.015	.021	.010	.015	.025
CES-D				-.012	.018	-.024	-.011	.018	-.024
Education				.164	.077	.080*	.151	.079	.074
Gender				.011	.074	.005	-.002	.076	-.001
Region				-.132	.074	-.067[a]	-.132	.075	-.066
Race				.014	.075	.007	.007	.076	.004
FSRP							-.035	.039	-.035

R^2	.001	.015	.016
Adjusted R^2	.000	.004	.004
F for change in R^2	.73	.11	.37
Model *F*	.73	1.47	.80

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed, [a] p < .08, two-tailed.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and LF assessment in years; LF, Letter Fluency
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 25
Summary of Regression Models for Letter Fluency Performance in REGARDS Cohort Members (N=645)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	.062	.084	.029	.065	.085	.030	.065	.085	.030
Time				.003	.016	.008	.005	.016	.013
CES-D				-.013	.019	-.028	-.013	.019	-.026
Education				.105	.084	.051	.088	.085	.043
Gender				.000	.080	.000	-.017	.082	-.008
Region				-.093	.080	-.047	-.093	.080	-.046
Race				.041	.082	.021	.032	.082	.016
FSRP							-.045	.041	-.045

R^2	.001	.008	.010
Adjusted R^2	-.001	-.003	-.002
F for change in R^2	.54	.80	1.20
Model *F*	.54	.77	.82

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and LF assessment in years; LF, Letter Fluency
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 26

Summary of Regression Models for Letter Fluency in REGARDS Stroke Cases (N=81)

	Model 1			Model 2			Model 3		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	.112	.235	.053	.143	.223	.068	.136	.223	.065
Time				.042	.058	.078	.056	.060	.105
CES-D				-.008	.056	-.015	.002	.057	.004
Education				.552	.215	.282*	.566	.215	.289*
Gender				.082	.202	.044	.117	.205	.063
Region				-.413	.205	-.223*	-.419	.205	-.226*
Race				-.232	.211	-.118	-.234	.211	-.119
FSRP							.139	.143	.108

R^2	.003	.198	.208
Adjusted R^2	-.010	.122	.121
F for change in R^2	.23	2.99*	.95
Model *F*	.23	2.61*	2.40*

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and LF assessment in years; LF, Letter Fluency
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 27

Regression Model using Backward Elimination Model Selection for Letter F Fluency Performance by Incident Stroke Status

	Full Sample (N=791)			No Stroke (N=705)			Stroke (N=86)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	.062	.079	.029	.063	.085	.029	.144	.220	.069
Time	.010	.014	.026	.006	.016	.015	.048	.058	.090
Education	.157	.078	.077*	.096	.084	.047	.557	.211	.285*
Region	-.135	.074	-.068[a]	.038	.082	.019	-.255	.206	-.129*
Race	.011	.076	.006	-.098	.080	-.049	-.416	.203	-.225
FSRP	-.035	.038	-.035	-.044	.040	-.044	.122	.136	.095
R^2		.016			.009			.204	
Adjusted R^2		.007			.000			.141	
Model *F*		1.91[a]			1.01			3.21**	

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed; [a] p < .08, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and LF assessment in years; LF, Letter Fluency
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 28

Summary of Interaction of ApoE e4 Carrier Status and Stroke Risk Scores in Regression Models for Word List Learning in REGARDS Stroke Case Cohort Sample

	Full Sample (*N=900*)			Stroke-Free Cohort (*N = 718*)			Stroke Cases (*N = 181*)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.120	.062	-.064[a]	-.069	.069	-.038	-.404	.154	-.199*
Time	.041	.013	.104**	.036	.014	.097*	.034	.062	.041
CES-D	-.044	.016	-.092**	-.047	.018	-.101**	-.035	.036	-.072
Gender	.114	.068	.057	.051	.075	.026	.393	.159	.190*
Race	.126	.067	.063[a]	.139	.075	.071[a]	.133	.158	.062
FSRP	-.091	.040	-.088*	-.085	.044	-.087[a]	-.069	.125	-.047
ApoE e4 x FSRP	-.040	.067	-.023	-.036	.070	-.023	.104	.238	.037
R^2		.039			.037			.071	
Adjusted R^2		.032			.027			.033	

F for change in R^2	.35	.60	.66
Model *F*	5.18**	3.88 ***	1.89[a]

*$p < .05$, **$p < .01$., ***$p < .001$, [a] $p < .08$, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years;

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 29

Summary of ApoE x FSRP Interaction in Regression Models for Word List Delay in REGARDS

	Case Cohort (*N=870)*			Cohort (*N=698*)			Stroke Cases (*N=172*)		
Variable	*B*	*SE B*	*t*	*B*	*SE B*	*t*	*B*	*SE B*	*t*
ApoE e4	-.013	.084	-0.15	-.009	.094	-.10	-.030	.192	-.16
Time	.018	.018	0.99	.008	.019	.40	.081	.079	1.03
CES-D	-.074**	.020	-3.71	-.079**	.023	-3.48	-.071[a]	.041	-1.73
Gender	.204*	.081	2.52	.106	.091	1.17	.619**	.183	3.39
Race	.108	.080	1.36	.052	.090	.58	.343[a]	.181	1.89
FSRP	-.041	.048	-0.86	-.021	.053	-.40	-.132	.148	-.89
ApoE x FSRP	-.159[a]	.087	-1.82	-.209*	.094	-2.22	.051	.305	.17
R^2		.049			.046			.134	
MSE		.941			.943			.909	

Model *F*	4.55**	3.44**	2.59*

*$p < .05$, two-tailed; **$p < .01$., two-tailed; ***$p < .001$, two-tailed; [a] $p < .08$, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLD assessment in years

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups; analyses excluded those with baseline cognitive impairment and hemorrhagic stroke

Table 30

Summary of Interaction of ApoE e4 Carrier Status and Stroke Risk Scores in Regression Models for Animal Fluency Scores in REGARDS Stroke Case Cohort Sample

	Full Sample			Stroke-Free Cohort			Stroke Cases		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.045	.072	-.021	-.084	.080	-.039	.107	.186	.048
Time	.018	.012	.049	.015	.013	.044	.001	.054	.002
CES-D	-.035	.016	-.073	-.044	.018	-.091	.000	.038	.001
Education	.152	.071	.073	.139	.079	.067*	.211	.165	.104
Race	.088	.069	.043	.099	.076	.049	.029	.166	.014
FSRP	-.003	.041	-.003	.016	.045	.016	-.035	.131	-.025
ApoE e4 x FSRP	-.070	.077	-.036	-.102	.082	-.054	.019	.254	.007
R^2	.020			.026			.015		

Adjusted R^2	.013	.016	-.028
F for change in R^2	.83	1.56	.01
Model *F*	2.75**	2.78**	.35

*$p < .05$, two-tailed; **$p < .01$., two-tailed; ***$p < .001$, two-tailed; [a] $p < .08$, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and AF assessment in years

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 31

Interaction of ApoE e4 Carrier Status with Framingham Stroke Risk Profile Scores in Regression Models of Letter F Fluency Performance

	Full Sample (n=791)			Cohort (n=705)			Stroke Cases (n=86)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	.060	.079	.028	.057	.085	.027	.050	.231	.024
Time	.010	.014	.025	.005	.016	.013	.051	.058	.096
Education	.007	.076	.003*	.092	.084	.044	.517	.212	.264*
Race	-.138	.074	-.070	.031	.082	.015	-.280	.206	-.142
Region	.155	.078	.076[a]	-.102	.080	-.051	-.416	.202	-.225*
FSRP	.002	.045	.003	.002	.048	.002	.029	.154	.022
ApoE x FSRP	-.122	.083	-.065	-.158	.087	-.085[a]	.416	.323	.159
R^2		.019			.014			.222	
Adjusted R^2		.009			.004			.148	

F for Change in R^2	.14	.07	.20
Model *F*	1.95[a]	1.34	3.01**

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed, [a]*p* < .08.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and LF assessment in years.
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups.

Table 32

Summary of Interaction Testing ApoE x Stroke x Age in Regression Models of Cognitive Function

			ApoE x Age x Stroke		ApoE x Age	
Dependent Variable	*df*	*df error*	*MS*	*F*	*MS*	*F*
Word List Learning	1	855	0.00	0.00	0.00	0.00
Word List Delay	1	826	0.09	0.10	0.98	1.03
Animal Fluency	1	872	1.03	1.02	0.66	0.66
Letter F Fluency	1	690	1.45	1.46	0.69	0.64

Table 33

Summary of Regression Models for Animal Fluency Scores in REGARDS Stroke Case Cohort over the Age of 75 years

	Full Sample (n = 364)			Stroke-Free Cohort (n = 300)			Stroke Cases (n = 64)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.483	.170	-.219**	-.521	.185	-.237**	-.293	.485	-.127
Time	.024	.017	.075	.031	.018	.096	-.087	.090	-.131
CES-D	-.008	.029	-.015	-.012	.034	-.020	.010	.061	.022
Education	.027	.108	.013	.023	.120	.011	.045	.262	.023
Race	.084	.110	.042	.113	.122	.056	-.141	.272	-.069
FSRP	-.182	.100	-.114[a]	-.170	.113	-.106	-.263	.235	-.164
ApoE e4 x FSRP	.330	.188	.145[a]	.325	.201	.148	.518	.604	.181
R^2		.035			.046			.042	

Adjusted R^2	.017	.024	-.078
Model *F*	1.88[a]	2.06***	.35

*$p < .05$, two-tailed; **$p < .01$., two-tailed; ***$p < .001$, two-tailed; [a] $p < .08$, two-tailed.
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and Animal Fluency assessment in years.
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups.

Table 34

Sensitivity Analyses of Regression Models for Animal Fluency Scores in REGARDS Stroke Case Cohort Sample over the Age of 75 years without Baseline Cognitive Impairment

	Full Sample (*n* = *364*)			Stroke-Free Cohort (*n* = 300)			Stroke Cases (*n* = 64)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.484	.170	-.219**	-.522	.184	-.237**	-.314	.469	-.136
Time	.024	.017	.076	.031	.018	.098[a]	-.090	.088	-.135
Race	.093	.107	.046	.123	.119	.061	-.135	.265	-.066
FSRP	-.188	.099	-.117[a]	-.176	.111	-.110	-.267	.228	-.167
ApoE e4 x FSRP	.330	.188	.145[a]	.326	.200	.149	.540	.587	.189
R^2		.035			.026			.041	
Adjusted R^2		.022			.016			-.042	
Model *F*		2.61*			2.83*			.50	

*$p < .05$, two-tailed; **$p < .01$., two-tailed; ***$p < .001$, two-tailed; [a] $p < .08$, two-tailed
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and AF assessment in years;
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups

Table 35

Sensitivity Analyses excluding Cases of Baseline Cognitive Impairment from Regression Models of Word List Learning in REGARDS Stroke Case Cohort Sample

	Full Sample (n=691)			Cohort (n = 539)			Stroke Cases (n= 151)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.136	.073	-.071[a]	-.071	.081	-.039	-.397	.176	-.186*
Time	.031	.018	.067[a]	.027	.018	.062	.059	.077	.062
CES-D	-.056	.018	-.115**	-.065	.020	-.138***	-.022	.042	-.043
Gender	.156	.078	.077*	.103	.086	.052	.350	.182	.161[a]
Race	.211	.077	.104**	.243	.085	.123**	.118	.185	.053
FSRP	-.135	.045	-.133**	-.140	.048	-.147**	-.070	.138	-.046
ApoE e4 x FSRP	-.039	.074	-.023	-.033	.077	-.022	.199	.293	.061
R^2		.064			.075			.061	
Adjusted R^2		.054			.063			.015	
F for change in R^2		.28			.19			.46	

Model *F*	6.65***	6.15 ***	1.34

*$p < .05$, two-tailed; **$p < .01$., two-tailed; ***$p < .001$, two-tailed; [a] $p < .08$, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years.

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups.

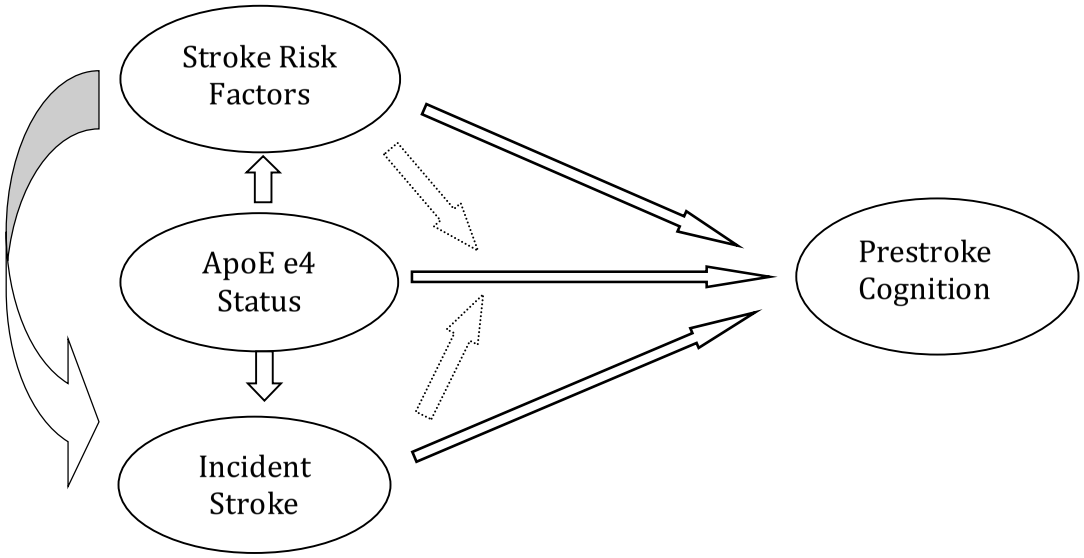


Figure 1. Hypothetical model of prestroke cognitive function with ApoE e4 carrier status, cardiovascular risk factors, and incident stroke status

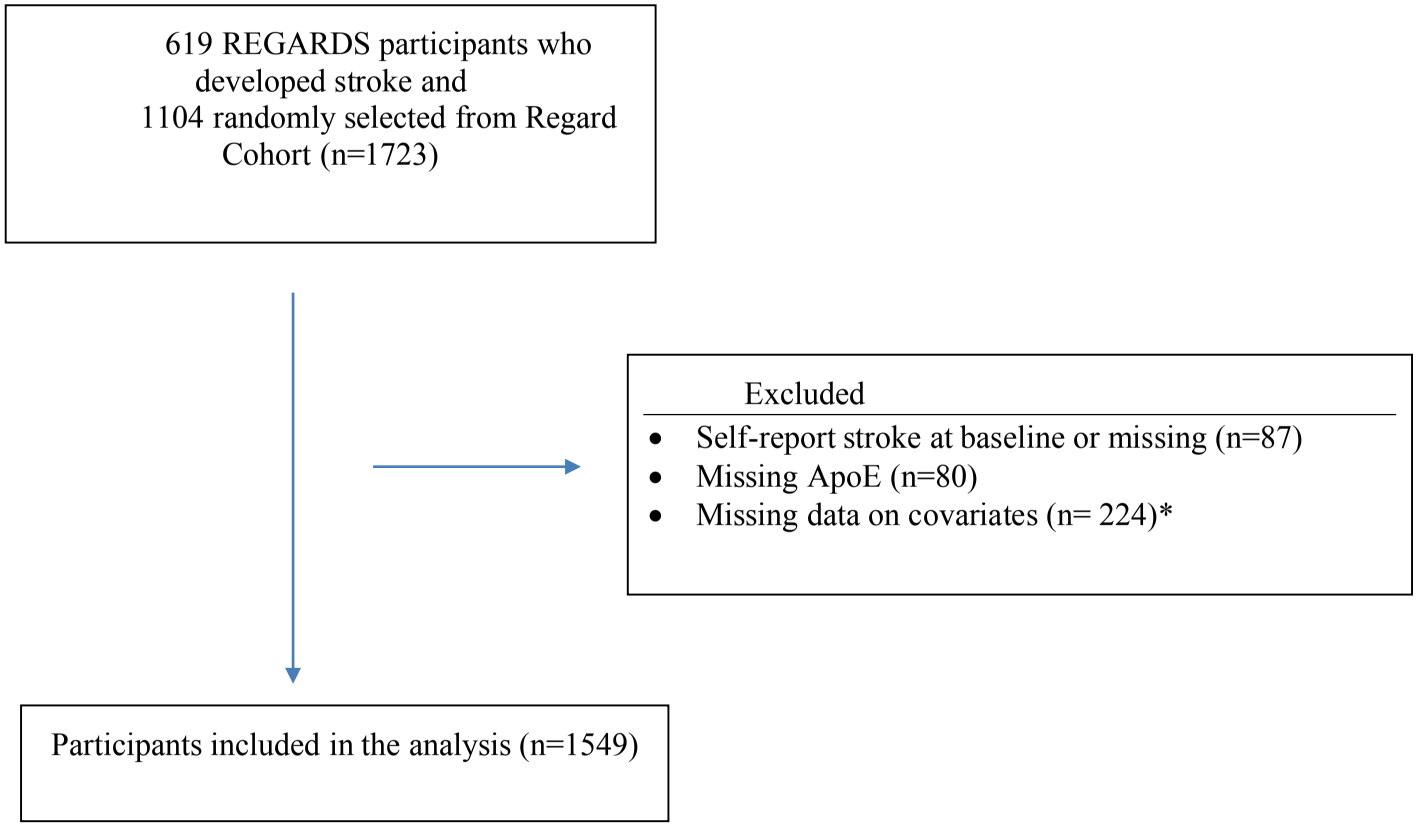


Figure 2. Study Sample for Aim 1 Analyses from the REGARDS Stroke Case Cohort

*Categories for missing data on covariates are not mutually exclusive. Missing data are for hypertension (n=7), diabetes (n=60), smoking (n=7), dyslipidemia (n=54), atrial fibrillation (n=42), left ventricular hypertrophy (n=26), coronary heart disease (n=28)

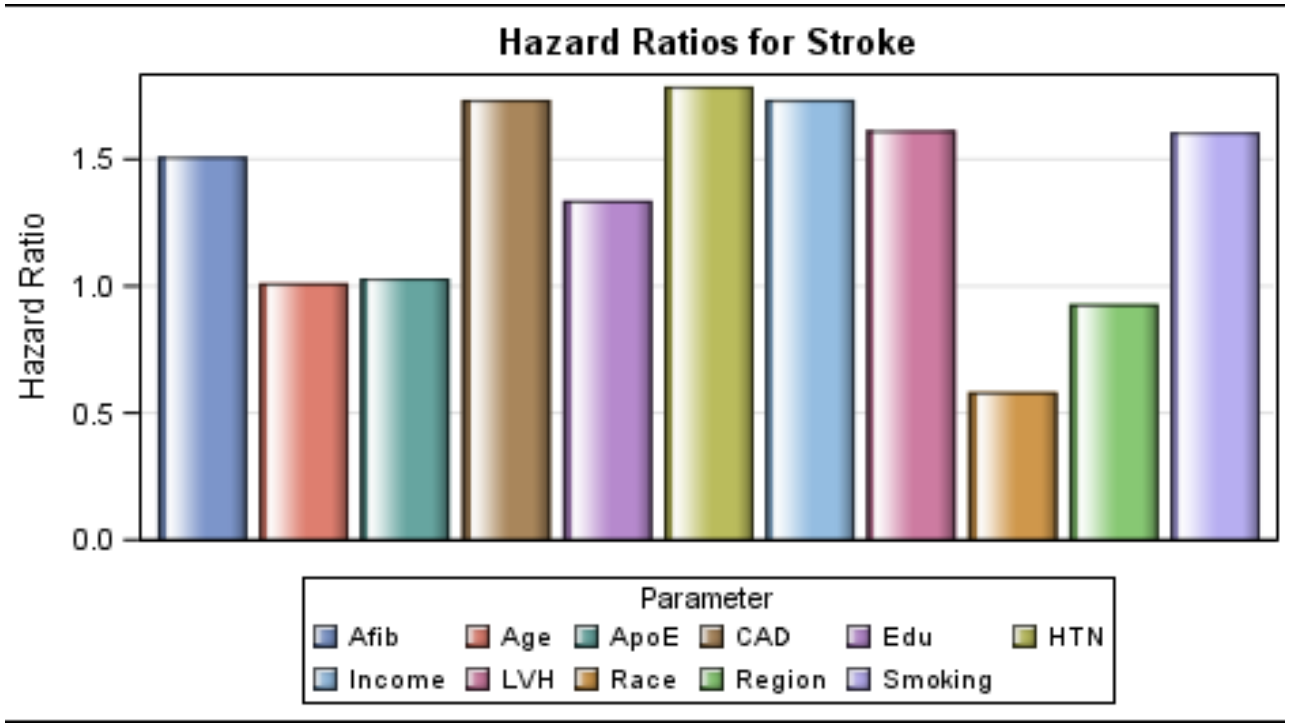


Figure 3. Bar graph of hazards ratios from Cox regression model for incident strok

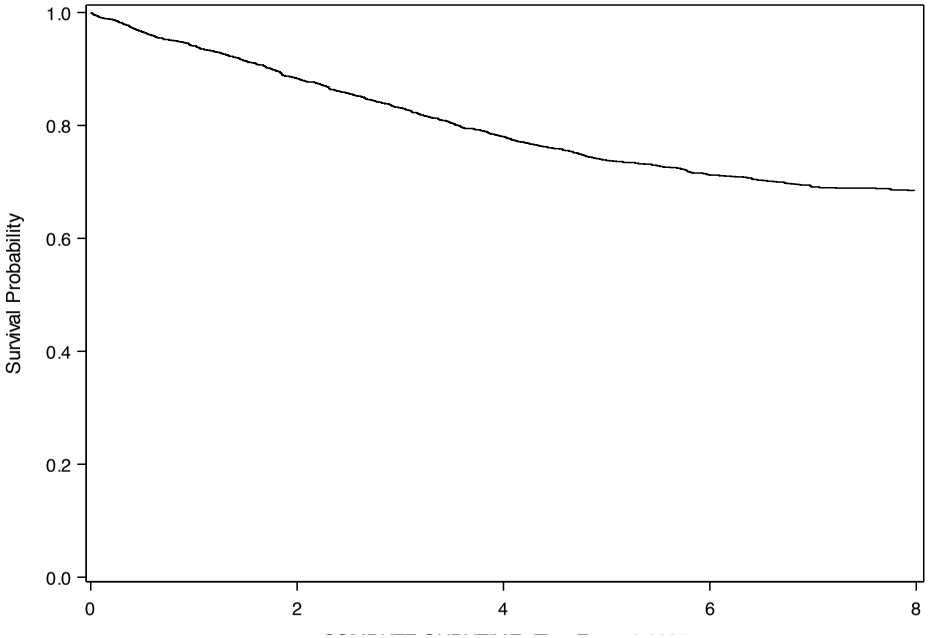


Figure 4. Survival Plot for Incident Stroke in the Absence of Stroke Risk Factors

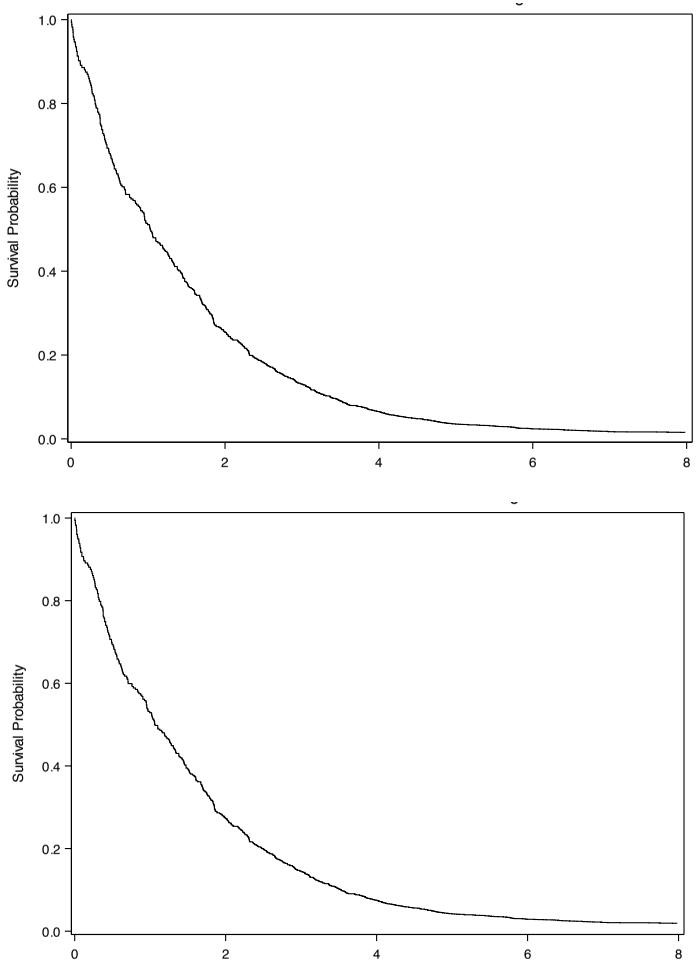


Figure 5. Survival Plot for Stroke for Stroke Cases that were ApoE e4 Carriers (above) and ApoE e4 Noncarriers (below)

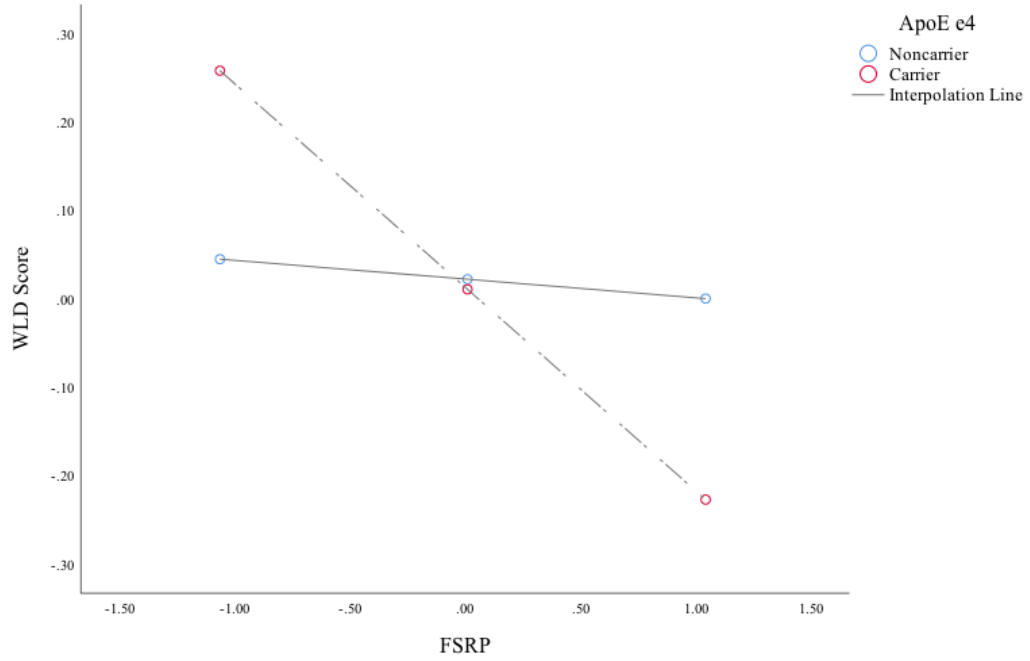


Figure 6. Line Chart Depicting Interaction Testing for WLD Performance for Case-Cohort and Cohort

Notes. FSRP scores were log transformed and centered for computing interaction terms

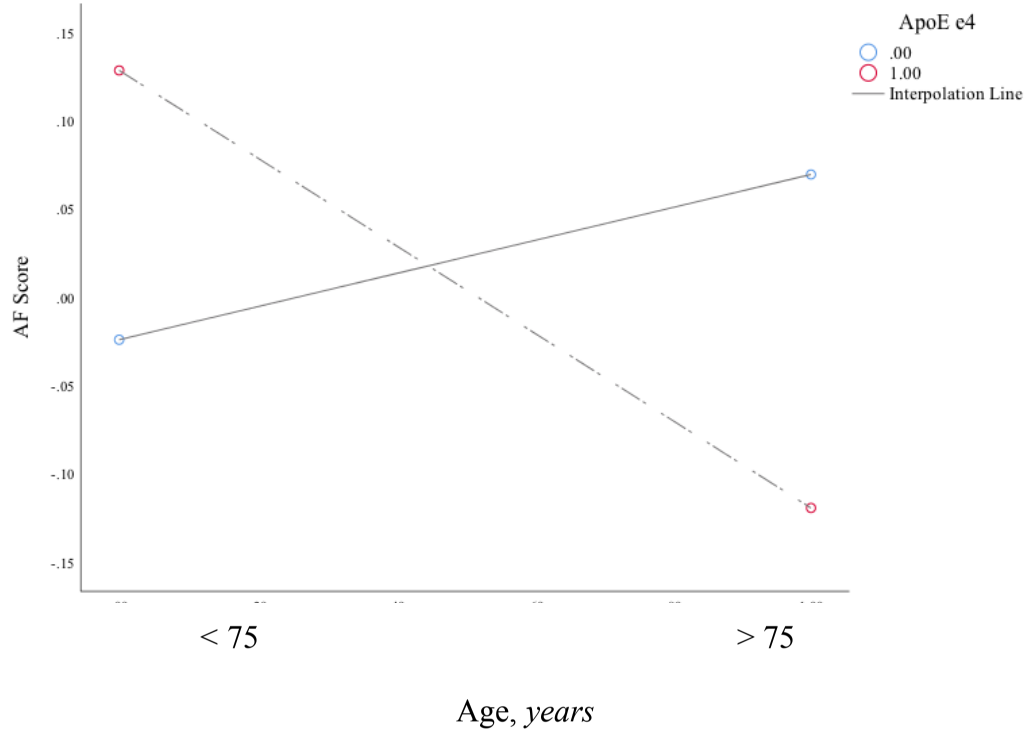


Figure 7. Line Chart for Exploratory Analyses for Animal Fluency Performance for Case Cohort by Age and ApoE e4 Carrier Status.
Notes. AF, Animal Fluency; scores were age-adjusted z-scores; ApoE e4 value of 0, e4 noncarriers; ApoE e4 value of 1, e4 carriers

APPENDIX

Supplemental Materials

Supplemental Table 1

Regression Model for WLD using Manual Model Selection for the Full Sample

	Full Sample			Cohort			Stroke Cases		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.019	.073	-.009	.004	.080	.002	-.151	.171	-.067
Time	.039**	.014	.099	.036*	.014	.096	.034	.062	.042
CES-D	-.050**	.016	-.106	-.056**	.018	-.119	-.034	.036	-.073
Gender	.172*	.069	.086	.109	.077	.055	.470**	.158	.234
Race	.044	.068	.022	.031	.077	.015	.141	.158	.068
FSRP	-.069	.035	-.067	-.057	.039	-.057	-.091	.108	.064
R^2	.030			.027			.063		

Adjusted R^2	.023	.019	.029
F for change in R^2	4.44**	3.23**	1.84
Model *F*	4.44**	3.23**	1.84

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed; [a]p < .08, two-tailed
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLD assessment in years; WLD, Word List Delayed Recall (score range 0 -10);
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups;

Supplemental Table 2

Regression Model for WLD including ApoE e4 x FSRP Interaction for full Regards Case-cohort Sample

	Full Sample			Cohort			Stroke Cases		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.022	.073	-.010	-.008	.081	-.004	-.193	.185	-.086
Time	.039**	.014	.099	.036*	.014	.096	.035	.062	.043
Depression	-.051**	.016	-.108	-.058**	.018	-.122	-.034	.036	-.072
Gender	.174*	.069	.087	.111	.077	.056	.465**	.159	.232
Race	.040	.068	.020	.023	.077	.012	.137	.158	.066
FSRP	-.042	.042	-.041	-.020	.046	-.020	-.129	.126	-.091
ApoE x FSRP	-.093	.078	-.048	-.126	.083	-.069	.155	.257	.056
R^2	.032			.031			.065		
Adjusted R^2	.024			.021			.025		
F for change in R^2	2.40			2.33			.36		

Model *F*	4.02**	3.11**	1.62

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed; [a]*p* < .08, two-tailed
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLD assessment in years; WLD, Word List Delayed Recall;
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups; full sample included those with baseline cognitive impairment and hemorrhagic stroke cases.

Supplemental Table 3

Summary of Regression Models for Word List Learning Age-Adjusted Z Scores in REGARDS Stroke Case Cohort Sample over the Age of 75 years

	Full Sample (n=350)			Stroke-Free Cohort (n = 277)			Stroke Cases (n= 72)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.032	.143	-.017	.009	.161	.005	-.376	.326	-.180
Time	.047	.019	.133*	.049	.021	.146*	-.025	.100	-.031
CES-D	-.030	.030	-.054	-.050	.034	-.089	.010	.065	.020
Gender	-.091	.110	-.045	-.193	.121	-.097	.317	.261	.155
Race	-.028	.111	-.014	-.009	.124	-.004	-.110	.264	-.051
FSRP	-.047	.103	-.029	-.022	.109	-.014	-.230	.303	-.112
ApoE e4 x FSRP	-.105	.176	-.048	-.112	.194	-.054	.088	.444	.033
R^2		.033			.052			.060	
Adjusted R^2		.013			.028			.041	

Model *F*	1.68	2.12*	0.76

*$p < .05$, two tailed; ** $p < .01$, two tailed; ***$p < .001$, two tailed; [a]$p < .08$, two-tailed

Notes. Education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups.
Abbreviations. FSRP, Framingham Stroke Risk Profile, CES-D, Center for Epidemiologic Studies-Depression Scale; Time; time between baseline assessment and WLL assessment in years.

Supplemental Table 4

Summary of Regression Models for Word List Learning Age-Adjusted Z Scores in REGARDS Stroke Case Cohort Sample under the Age of 75 years

	Full Sample (N=549)			Stroke-Free Cohort (n = 440)			Stroke Cases (n= 108)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.164	.091	-.089[a]	-.084	.108	-.047	-.420	.190	-.212*
Time	.030	.019	.065	.021	.020	.050	.066	.084	.076
CES-D	-.048	.018	-.109**	-.045	.020	-.106*	-.055	.045	-.118
Gender	.232	.088	.116**	.198	.097	.101*	.418	.216	.200[a]
Race	.224	.085	.112**	.232	.094	.119*	.250	.208	.118
FSRP	-.108	.058	-.095	-.106	.066	-.094	-.038	.166	-.026
ApoE e4 x FSRP	-.074	.092	-.045	-.038	.101	-.025	.067	.323	.023
R^2		.067			.058			.093	
Adjusted R^2		.054			.043			.039	
Model *F*		5.52**			3.83**			1.48	

*$p<.05$, two tailed; **$p<.01$, two tailed; ***$p<.001$, two tailed; [a]$p < .08$, two-tailed
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years; WLL, World List Learning, scores range from 0 to 30;
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups; full sample included those with baseline cognitive impairment and hemorrhagic stroke cases.

Supplemental Table 5

Summary of Regression Models for Word List Delay Age-Adjusted Z Scores in REGARDS Stroke Case Cohort Sample under the Age of 75 years

	Full Sample (N=441)			Stroke-Free Cohort (n = 369)			Stroke Cases (n= 71)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	.038	.116	.018	.047	.136	.022	-.111	.238	-.054
Time	.028	.024	.055	.023	.025	.047	.039	.109	.041
CES-D	-.063	.022	-.136**	-.067	.024	-.145	-.044	.052	-.098
Gender	.238	.100	.117*	.191	.112	.093	.559	.233	.298*
Race	.135	.096	.067	.102	.108	.050	.359	.227	.186
FSRP	-.080	.065	-.071	-.045	.075	-.039	-.218	.183	-.164
ApoE e4 x FSRP	-.100	.116	-.053	-.121	.129	-.066	-.023	.385	-.008
R^2		0.054			0.045			0.159	
Adjusted R^2		0.039			0.026			0.067	

Model *F*	3.55***	2.43*	1.73

*$p<.05$, two tailed; **$p<.01$, two tailed; ***$p<.001$, two tailed; [a]$p < .08$, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years; WLL, World List Learning; WLD, Word List Delayed Recall;

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups; full sample included those with baseline cognitive impairment and hemorrhagic stroke cases.

Supplemental Table 6

Summary of Regression Models for Word List Delay Age-Adjusted Z Scores in REGARDS Stroke Case Cohort Sample over the Age of 75 years

	Full Sample (N=207)			Stroke-Free Cohort (n = 153)			Stroke Cases (n= 54)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.341	.243	-.149	-.257	.265	-.120	-.840	.592	-.312
Time	.001	.029	.003	.006	.029	.016	-.006	.132	-.006
CES-D	-.093	.037	-.177*	-.121	.044	-.227*	-.047	.073	-.093
Gender	.185	.143	.093	.088	.156	.046	.448	.335	.197
Race	.002	.144	.001	.010	.160	.005	-.177	.331	-.076
FSRP	-.113	.135	-.070	-.078	.142	-.053	-.273	.358	-.125
ApoE e4 x FSRP	.043	.258	.019	-.125	.268	-.063	1.405	.799	.383[a]
R^2		.062			.099			.106	
Adjusted R^2		.030			.060			-.027	

Model *F*	2.23*	2.29**	0.79

*$p<.05$, two tailed; **$p<.01$, two tailed; ***$p<.001$, two tailed; [a] $p < .08$, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLD assessment in years; WLD, Word List Delayed Recall

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups; full sample included those with baseline cognitive impairment and hemorrhagic stroke cases.

Supplemental Table 7

Summary of Regression Models for Animal Fluency Age-Adjusted Z Scores in REGARDS Stroke Case Cohort under the Age of 75 years

	Full Sample (n = 552)			Stroke-Free Cohort (n=449)			Stroke Cases (n = 102)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	.059	.103	.027	.022	.122	.010	.158	.222	.072
Time	.012	.017	.029	.005	.018	.013	.038	.070	.055
Depressive Symptoms	-.044	.019	-.096*	-.054	.021	-.120*	.005	.050	.010
Education	.250	.093	.117**	.241	.104	.112*	.293	.220	.142
Race	.098	.088	.048	.116	.098	.057	.052	.216	.026
FSRP	.027	.060	.023	.070	.068	.060	.006	.186	.004
ApoE e4 x FSRP	-.046	.108	-.023	-.073	.121	-.039	-.073	.326	-.028
R^2		.033			.038			.033	
Adjusted R^2		.020			.022			-.038	

Model *F*	2.64*	2.47*	.47

*$p < .05$. **$p < .01$., [a] $p < .08$

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and AF assessment in years; AF, Animal Fluency

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups; full sample included those with baseline cognitive impairment and hemorrhagic stroke cases.

Supplemental Table 8

Regression Models for Phonemic (Letter F Fluency) Performance for Participants over 75 Years of Age

	Full Sample (n = 307)			No Stroke (n = 269)			Stroke (n = 38)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.082	.181	-.038	-.116	.194	-.052	.599	.520	.264
Time	.034	.022	.089	.037	.025	.093	.122	.083	.244
Education	.153	.118	.076	.099	.128	.049	.400	.287	.227
Region	-.094	.116	-.048	.048	.131	.024	-.082	.282	-.044*
Race	.066	.120	.033	-.028	.127	-.014	-.568	.256	-.342
FSRP	-.085	.104	-.056	-.090	.112	-.059	.110	.264	.077
ApoE e4 x FSRP	.136	.194	.063	--	--	--	.140	.582	.062
R^2		.020			.016			.376	
Adjusted R^2		.003			.010			.221	
Model *F*		.52			.61			2.42*	

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed; [a]$p < .08$, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and LF assessment in years;
Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups; full sample included those with baseline cognitive impairment and hemorrhagic stroke cases.

Supplemental Table 9

Regression Models for Phonemic (Letter F Fluency) Performance for Participants under 75 Years of Age

	Full Sample (n = 420)			No Stroke (n = 373)			Stroke (n = 45)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.030	.119	-.014	-.026	.130	-.013	-.026	.130	-.013
Time	-.017	.020	-.042	-.026	.021	-.063	-.026	.021	-.063
Education	.156	.106	.074	.091	.112	.043	.091	.112	.043
Region	-.055	.099	-.028[a]	-.150	.104	-.075	-.362	.324	-.183
Race	-.172	.098	-.086	-.012	.106	-.006	-.428	.314	-.209
FSRP	.024	.070	.021	.038	.075	.033	-.096	.270	-.064
ApoE e4 x FSRP	-.278	.122	-.148*	-.303	.129	-.165*	.307	.516	.105
R^2		.036			.035			.195	
Adjusted R^2		.020			.017			.047	

Model *F*	2.23*	1.90[a]	1.32

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed; [a]*p* < .08, two-tailed

Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and LF assessment in years

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups; full sample included those with baseline cognitive impairment and hemorrhagic stroke cases.

Supplemental Table 10

Interaction Testing for Regression Models of Letter Fluency for Case Cohort under 75 Years of Age

Interaction	Effect	SE	t	p	95% Confidence Interval
Low FSRP	0.339	0.127	2.67	.008	(0.89, 0.59)
Medium FSRP	0.249	0.109	2.28	.023	(0.35, 0.46)
High FSRP	0.066	0.115	0.57	.568	(0.16, 0.29)

Notes. Model adjusted for time between baseline and assessment, education, region, and race, FSRP scores were centered at the mean;

Supplemental Table 11

Sensitivity Analyses excluding Baseline Cognitive Impairment from Regression Models of Word List Learning Age-Adjusted Z Scores in REGARDS Stroke Case Cohort Sample

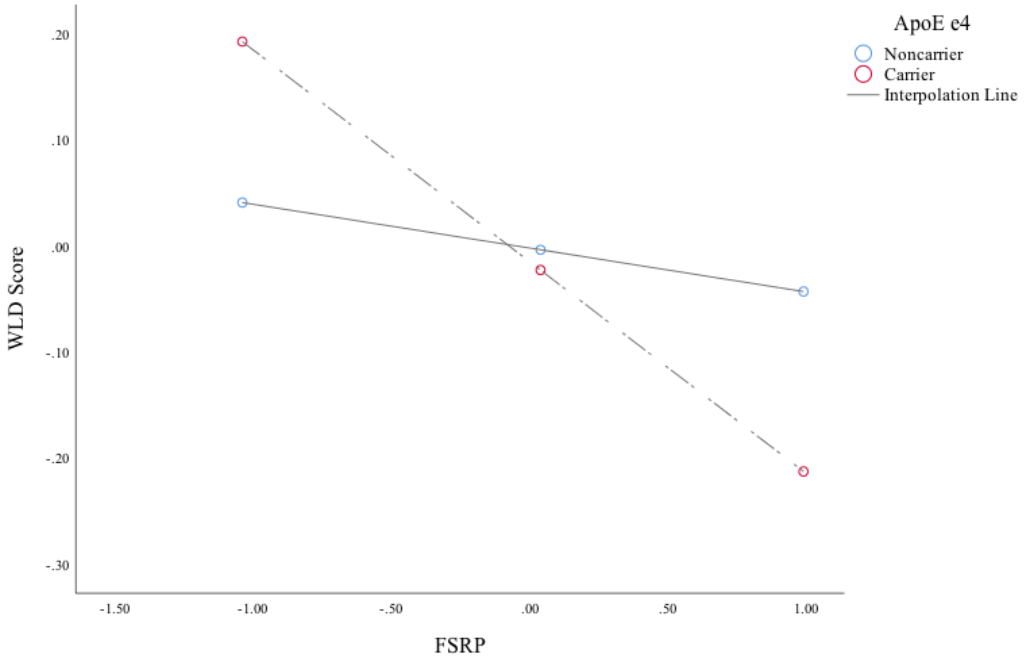
	Full Sample (N=691)			Stroke-Free Cohort (n = 539)			Stroke Cases (n= 151)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
ApoE e4	-.136	.073	-.071[a]	-.071	.081	-.039	-.397	.176	-.186*
Time	.031	.018	.067[a]	.027	.018	.062	.059	.077	.062
CES-D	-.056	.018	-.115**	-.065	.020	-.138***	-.022	.042	-.043
Gender	.156	.078	.077*	.103	.086	.052	.350	.182	.161[a]
Race	.211	.077	.104**	.243	.085	.123**	.118	.185	.053
FSRP	-.135	.045	-.133**	-.140	.048	-.147**	-.070	.138	-.046
ApoE e4 x FSRP	-.039	.074	-.023	-.033	.077	-.022	.199	.293	.061
R^2		.064			.075			.061	
Adjusted R^2		.054			.063			.015	
F for change in R^2		.279			.190			.460	

Model *F*	6.65***	6.15***	1.34

*p<.05, two tailed; **p<.01, two tailed; ***p<.001, two tailed; [a]*p* < .08, two-tailed

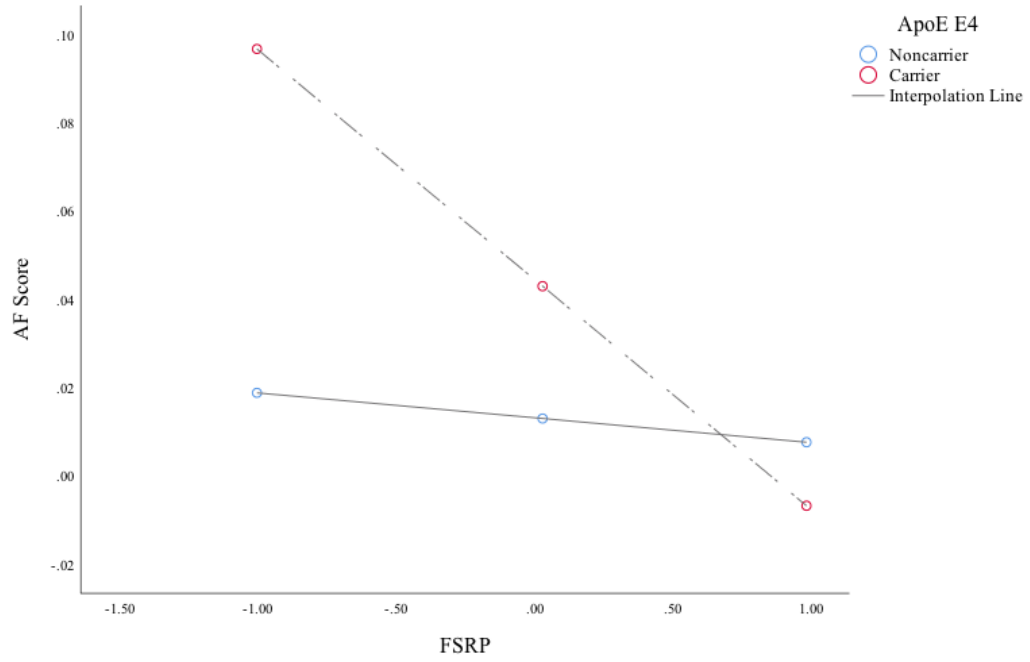
Abbreviations. FSRP, Framingham Stroke Risk Profile; CES-D, Center for Epidemiologic Studies-Depression Scale; Time, time between baseline assessment and WLL assessment in years; WLL

Notes. Means are age-adjusted z-scores; education less than high school, female gender, nonstroke Belt/Buckle United States, white race, ApoE e4 noncarriers, and those without incident stroke were the reference groups; full sample included those with baseline cognitive impairment and hemorrhagic stroke cases.



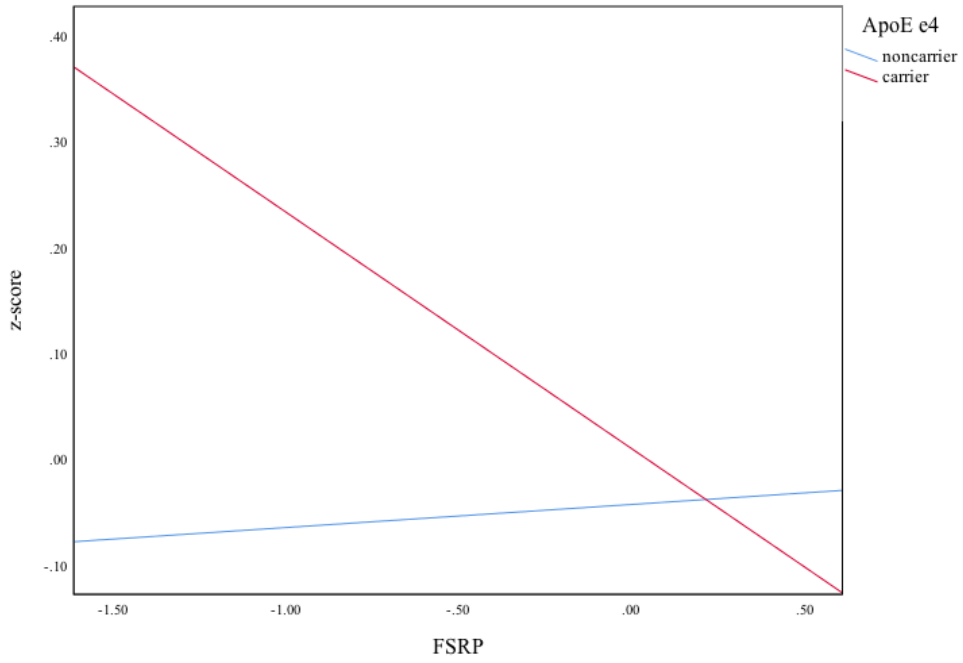
Supplemental Figure 1. Line Chart for Regression Models of Word List Learning including ApoE x FSRP in Stroke Case-Cohort

Notes. FSRP scores were log transformed and centered at the mean, tertile score cut-offs were used to generate interaction plots



Supplemental Figure 2. Line Chart for Exploratory Analyses of ApoE x FSRP interaction in Regression Models of Animal Fluency Performance

Notes. FSRP scores were log transformed and centered at the mean, tertile score cut-offs were used to generate interaction plots



Supplemental Figure 3. Exploratory analyses for Letter Fluency Performance for FSRP and ApoE e4 Carrier Status in Regards Case-Cohort under the age of 75.

Notes. FSRP scores were log transformed and centered at the mean, tertile score cut-offs were used to generate interaction plots