APOE Genotype Modifies the Relationship between Midlife Vascular Risk Factors and Later Cognitive Decline

Katherine J. Bangen, PhD,* Alexa Beiser, PhD,†‡§ Lisa Delano-Wood, PhD,*‖ Daniel A. Nation, PhD,¶ Melissa Lamar, PhD,# David J. Libon, PhD,** Mark W. Bondi, PhD,*¶ Sudha Seshadri, MD,†‡ Philip A. Wolf, MD,†‡ and Rhoda Au, PhD†‡

Background: Vascular risk factors have been associated with cognitive decline; however, it remains unclear whether apolipoprotein E (APOE) genotype modifies this relationship. We aimed to further elucidate these relationships and extend previous findings by examining data from a more comprehensive cognitive assessment than used in prior studies. *Methods:* In all, 1436 participants from the prospective Framingham Offspring Cohort Study underwent health examination from 1991 to 1995, followed by a baseline neuropsychological assessment (1999-2003) and a repeat neuropsychological assessment approximately 8 years later (2004-2009). Multivariate linear regression analyses were performed to examine the relationship among midlife vascular risk factors, presence of the APOE ε4 allele, and cognitive change. *Results:* APOE genotype significantly modified the associations between both midlife hypertension and cardiovascular disease and decline in language abilities and midlife diabetes and decline in verbal memory, attention, and visuospatial abilities. Associations between increased midlife vascular risk burden and greater cognitive decline were observed among APOE ε4 carriers but not noncarriers. *Conclusions:* The present findings revealed a subgroup at increased risk for cognitive decline (APOE ε4 carriers with midlife exposure to vascular risk factors) and suggest that treatment of vascular risk factors during midlife may reduce the risk of cognitive impairment later in life, particularly among APOE ε4 carriers. **Key Words:** Apolipoprotein E—cognition—vascular risk—aging—diabetes—hypertension—cardiovascular disease.

Introduction

The presence of vascular risk factors in midlife is associated with greater cognitive decline[1] and the development of dementia later in life.[2,3] Among nondemented older adults, some studies report that greater vascular risk burden is associated with cognitive

From the *Department of Psychiatry, University of California, San Diego School of Medicine, La Jolla, California; †Department of Neurology, Boston University School of Medicine, Boston, Massachusetts; ‡The Framingham Heart Study, Framingham, Massachusetts; §Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts; ‖Research Service, Veterans Affairs San Diego Healthcare System, San Diego, California; ¶Psychology Service, Veterans Affairs San Diego Healthcare System, San Diego, California; #Department of Psychiatry, University of Illinois, Chicago, Chicago, Illinois; and **Department of Neurology, Drexel University, Philadelphia, Pennsylvania.

Received February 21, 2013; accepted March 12, 2013.

Grant support: This research was made possible by the Framingham Heart Study's National Heart, Lung, and Blood Institute contract (NIH/NHLBI contract #N01-HC-25195) and grants from the National Institutes of Health (K24 AG26431, T32 MH 19934-17, P30 AG013846, R01 AG12674, AG08122, AG16495, AG033193, and AG031287).

Address correspondence to Katherine J. Bangen, PhD, 9500 Gilman Drive, Mail Code 151B, La Jolla, CA 92093. E-mail: kbangen@ucsd.edu.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.03.013

decline restricted to a particular domain such as executive functioning[1] or language,[4] whereas other studies have found associations with poorer performance across multiple additional domains including processing speed, visuospatial abilities,[5] and memory.[6]

The presence of the apolipoprotein E (APOE) ε4 allele is a well-established susceptibility gene for Alzheimer's disease (AD).[7] APOE genotype also influences susceptibility to atherosclerosis[8] and may increase risk of vascular dementia.[9] In terms of the role of the APOE ε4 allele as a risk factor for cognitive decline in normal aging, findings have been somewhat mixed. Some studies demonstrate poorer cognitive performance or greater decline among APOE ε4 carriers relative to noncarriers that is restricted to episodic memory,[1] whereas other studies show poorer performance across a variety of additional abilities, including global cognitive functioning and executive functioning.[10] Further, several previously published reports show no association between APOE genotype and cognitive functioning in nondemented older adults,[11] particularly when those with preclinical AD are removed from the sample.[12]

There are few published reports examining whether APOE genotype influences the relationship between vascular risk burden and cognitive impairment, and even fewer have investigated these associations in a longitudinal context. Generally, findings across such studies have been inconsistent with some results demonstrating that the APOE ε4 allele in combination with vascular risk factors imparts increased risk of cognitive decline,[6,13,14] whereas other studies have reported no such interaction.[1,15] Notably, these studies have differed in terms of participant characteristics (e.g., mean age at baseline cognitive evaluation) and methodology (e.g., length of follow-up, vascular risk factors assessed, cognitive measures administered). Further, in general, a caveat of existing longitudinal studies involves the limited nature of the cognitive domains and measures examined.

Given the potential significant public health impact of identification of risk factors for preclinical cognitive decline[16] and the limitations of existing studies examining the influence of vascular risk burden and APOE genotype on cognition in older adults, we aimed to further elucidate whether APOE genotype modifies the relationship between midlife vascular risk burden and later cognitive decline. In particular, we sought to extend findings of existing published reports by examining data from a more comprehensive cognitive assessment than used in previous studies. We hypothesized that APOE genotype would modify the relationship between vascular risk and cognitive decline across a variety of cognitive domains including memory, attention, executive functioning, visuospatial skills, and language. Specifically, we expected that the association between midlife vascular risk exposure and later cognitive decline would be stronger among APOE ε4 carriers relative to noncarriers. Further, given the possibility that vascular risk factors may interact with genetic risk to lead to cognitive decline through multiple divergent and convergent physiologic pathways, we examined each vascular risk factor and cognitive domain to determine whether these individual risk factors show differential relationships with the various cognitive domains.

Materials and Methods

Participants

The Framingham Heart Study is a community-based, prospective study that was initiated in 1948 to identify risk factors for cardiovascular disease (CVD). To date, the study has followed 3 generations of participants including (1) the Original Cohort, (2) the Offspring Cohort, which includes biological children of the Original Cohort and Offspring spouses, who have been followed since 1971, and (3) the Third Generation Cohort, which includes children from members of the Offspring Cohort, who have been followed since 2000. Participants in the current study were members of the Offspring Cohort who have undergone health examinations approximately every 4 years since 1971.[17] Of the 3799 participants from the Offspring Cohort who participated in the fifth examination (exam 5) between 1991 and 1995, 1602 individuals also underwent 2 neuropsychological assessments at least 5 years apart. The first assessment was administered between 1999 and 2003 and the second assessment was conducted between 2004 and 2009. Of the 1558 participants aged 45-84 years at the first neuropsychological assessment, individuals were excluded from the present study for the following reasons: documented clinical stroke, dementia, or other neurological disorders (e.g., multiple sclerosis, head trauma) at the first assessment (n = 38); neurological conditions at the second assessment (n = 17); missing APOE genotype data (n = 28); APOE ε2/ε4 genotype given the ambiguity associated with the presence of both an allele imparting increased risk (ε4) and an allele with a possible protective impact (n = 31), and missing covariate data (n = 8). Individuals with mild cognitive impairment at the first assessment were not excluded. These inclusion and exclusion criteria resulted in a final sample for the present analyses of 1436 participants.

Vascular Risk Factors

Vascular risk factors were assessed at exam 5. Hypertension was defined as systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or use of antihypertensive medications[18]; history of CVD was based on history of coronary heart disease (includes myocardial infarction, angina pectoris, and coronary insufficiency), cardiac failure, and intermittent claudication[19]; diabetes was defined as fasting glucose of 7 mmol/L or greater or use of an antidiabetic