The APOE-E4 Allele and the Risk of Functional Decline in a Community Sample of African American and White Older Adults

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Background. Given previous findings of adverse health outcomes associated with the E4 allele, data from a biracial community sample of older adults were used to determine whether functional decline is associated with the apolipoprotein E (APOE) E4 allele.

Methods. In 1986, a stratified random household sample of community residents 65 years of age and older (n = 4162) formed the Duke Established Populations for Epidemiologic Studies of the Elderly. Of those available 6 years later, 78.4% (n = 1999) were genotyped, providing “baseline” data at this time. The available survivors (n = 1529) provided longitudinal data 4 years later. Using longitudinal data from this sample, a combination of measures assessing self-care capability, instrumental activities of daily living (IADL), and mobility was obtained at baseline and 4 years later (n = 1529) to determine the extent to which the E4 allele affected change in functional status. Functional status was assessed using items from a modified Katz Activities of Daily Living (ADL) Scale, the Older American Resources and Services IADL scale, and the Rosow-Breslau physical health scale. Control measures included demographic characteristics, depression, health status, arthritis, and cognitive status. APOE was coded as E4 present versus absent.

Results. APOE E4 was not associated with decline in functional status in either bivariate or multivariate analyses as a main effect. There were, however, statistically significant interactions of the E4 allele with gender and baseline functional status, with greater functional decline in women with the E4 allele, whereas those with poorer baseline functioning who had the E4 allele were less likely to decline. No significant racial differences were found.

Conclusions. Despite the documented association of the E4 allele of APOE with adverse health outcomes, the E4 allele was not associated with a decline in functional status as a main effect. Interactions of E4 with gender (female) and baseline functional status, however, did predict functional decline.

The E4 allele of apolipoprotein E (APOE) on chromosome 19 has been associated with a number of adverse outcomes (1–6). E4 has been proposed as a susceptibility gene for late age onset of sporadic Alzheimer’s disease and subsequent cognitive decline (1,2). In addition, E4 has been associated with coronary artery disease (3), vascular disease in diabetes (6), stroke (4), and increased risk of mortality (7,8). The E4 allele has also been found to adversely affect rehabilitation outcome from trauma (9,10). Each of these outcomes can lead to or are in theory associated with a decline in overall functional status. However, no published studies to date document the association of the E4 allele and overall functional status over time, perhaps the most important factor in determining independence in, and the use of health services by, the elderly population (11). Although the E4 allele may lead to multiple susceptibilities, studies of the association of the E4 allele and Alzheimer’s disease have dominated research into this susceptibility gene, and studies into core factors in late life, such as functional status and functional decline, have lagged behind.

Previous studies of the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE) cohort of older adults found that the E4 allele is more frequent in African Americans than in whites (12). In addition, the E4 allele was significantly and uniquely related to lower scores on the Short Portable Mental Status Questionnaire (SPMSQ) (13) and increased the odds of cognitive decline over a period of 4 years. The E4 allele was associated with older age but not, in this sample, with other health conditions (e.g., history of heart disease, high blood pressure, stroke, diabetes, cancer, and arthritis) or with self-rated health. There was no cross-sectional relationship between the E4 allele and functional disability or depression.

Because the E4 allele has generally been found to be a risk factor for various health conditions that affect functional status (14–18), we would anticipate that elderly persons with the E4 allele would have a poorer functional status than those without this allele. Functional status, which encompasses mobility (both in the home and community), instrumental tasks (those required to remain a functioning member of society), and basic self-care (19–21), determines continued independence. As functional status deteriorates, an increasingly sheltered setting is necessary to maintain well being and eventually life itself. Thus, the hypothesis that the E4 allele affects functional status merits close attention because the consequences may have an impact on health services use and cost as well as on quality of life.

We hypothesized that the E4 allele of APOE would be associated with a decline in functional status over time, even...
when factors known to be associated with functional decline are controlled (e.g., baseline age, gender, prior functional status, health conditions, and cognitive status). This hypothesis is tested in a community sample of older adults, the Duke EPESE. APOE genotype in this sample was established during the third in-person interview in 1992-93 (and at later dates for a small percentage of the sample), and follow-up functional status was determined during the fourth in-person interview in 1996-97.

**METHODS**

Sample.—Data from this study derive from the Duke EPESE (22). This population survey was part of a multicenter, collaborative epidemiologic investigation of physical, psychological, and social function of persons 65 years of age and older living in East Boston, Massachusetts; Iowa and Washington Counties, Iowa; New Haven, Connecticut; and the north-central Piedmont of North Carolina (22–24). The North Carolina sample consisted of community residents selected from five contiguous Piedmont counties (one county was predominantly urban and the other four predominantly rural). The Duke EPESE is a 10-year prospective cohort study with a baseline interview (P1) conducted in 1986-87 and three additional in-person contacts with sample members in 1989-90 (P2), 1992-93 (P3), and 1996-97 (P4). Follow-up interviews were conducted by telephone in 1987-88, 1988-89, 1990-91, and 1991-92. All data collection and analyses were approved by the institutional review board of the Duke University Medical Center. The sampling design has been described previously (23).

Data Collection.—At initial evaluation (1986-87) and during the following three in-person follow-up interviews, data were gathered on age, gender, race, marital status, education, urban versus rural residence, presence of arthritis, heart attack, stroke, cancer, and diabetes) (26). Functional status was assessed by the SPMSQ (13). The Center for Epidemiological Studies-Depression Scale (CES-D) (25) was administered. Medical status was summarized on an index based on the summed weighted measure of five chronic conditions (hypertension, heart attack, stroke, cancer, and diabetes) (26). Functional status was assessed by a modified Katz Activities of Daily Living (ADL) scale (20), a modified Older American Resources and Services (OARS) instrumental ADL (IADL) scale (19), and an abbreviated Rosow-Breslau physical health scale (21).

Development of Functional Status Measures.—Separately, for the Katz scale, the OARS IADL scale, and the abbreviated Rosow-Breslau scale, we noted (i) the number of tasks that participants reported being unable to perform (a continuous measure) and (ii) whether participants reported inability on any task (a dichotomous measure). In addition, the three measures were summed to indicate (iii) the total number of tasks that could not be performed independently (a continuous measure) and (iv) whether any task could not be performed (a dichotomous variable).

Assessment of Genotype.—At the third in-person interview, 6 years after baseline, blood was drawn from all subjects who gave their personal consent. Approximately 4 years later (10 years after baseline), cheek swabs were sought from survivors who had been unable to give personal consent to the blood draw (e.g., the cognitively impaired) or who had been unwilling to undergo the blood draw. Apolipoprotein E genotype was determined as follows: high-molecular weight DNA was obtained from whole blood, and crude DNA extract was obtained from buccal cheek swabs. Genomic DNA was amplified by polymerase chain reaction. An initial denaturation was followed by 35 cycles of annealing in the final extension. After amplification, 5 U of HhaI were directly added to each well, and the plates were incubated for at least 3 hours at 37°C. Type III Stop dye was added to each well, and 3 μl of each reaction was loaded on a 6% nondenaturing polyacrylamide gel and electrophoresed for 1 hour under constant conditions (45 mA). After electrophoresis, the DNA was visualized by staining with SyberGold (FMC) followed by fluorography (Molecular Dynamics, Sunnyvale, CA). Each fluorogram was read independently by two observers (1,27).

Of the 2550 sample members who participated at P3, information on genotype was available for 1999 (78.4%). Four years later, by the time of the P4 interview, 399 sample members had died, and for 71 information on functional status was not available at both the P3 and P4 interviews because of refusal, shielding, or inability to locate. The resulting analysis sample therefore consisted of 1529 sample members.

**Results**

Table 1 presents the characteristics of the sample at the third in-person interview in 1992-93. The mean age of the entire sample at P3 was 77.8 years. As can be seen, the sample members who were genotyped were slightly younger and more likely to be white and male than the overall sample. Their education level was somewhat higher, and they were more likely to be married. Genotyped sample members also had a higher level of cognitive and physical health functioning and were more likely to survive to the next in-
The unadjusted odds ratios for functional status 4 years later are presented for a series of variables in Table 2. As would be expected, older age, female gender, African American race, lower education, poor health status, poor cognitive status, more depressive symptomatology, and functional disability at baseline were associated with functional status 4 years later (31). The presence of the E4 allele, however, was not so associated.

Initial multivariable models to assess decline in functional status were run (linear and logistic) in which age, gender, race, education, functional status at P3, and cognitive status were controlled. The factors found to be associated with functional status in bivariate analyses persisted, with the exception of race, which was no longer predictive. No association was found between the E4 allele and decline in functional status as a main effect. To create the full model, health status, depression, and arthritis were added, as well as the significant interactions with E4. Presence of the E4 allele alone did not predict functional decline; the interaction between E4 and gender and between E4 and functional status at P3 were significant. Specifically, the interaction of E4 and female gender increased the risk of functional decline. The interaction of E4 and functional status at P3 appeared to be protective against functional decline.

To clarify the latter finding, the analysis was repeated, looking separately at those without functional disability at P3 and those with functional disability at P3 to determine whether the E4 allele conferred a greater risk of functional decline in the functionally disabled compared with the functionally intact. No association was found between the E4 allele and functional decline in either group. We also ran analyses to determine whether the E4 allele predicted decline in any of the three components of the summed functional status measures (Katz ADL, OARS IADL, and abbreviated Rosow-Breslau). The presence of the E4 allele did not predict additional disabilities among those who already had at least one disability; however, it was predictive of the development of disability among those not previously disabled. In particular, it was a risk factor for the development of IADL disabilities ($p < .0004$) and, to a lesser extent, disability in physical health functioning ($p < .0465$). Urban/rural status was not predictive in any model and therefore was dropped from the full model. The linear and logistic models produced
almost identical results in terms of significant effects as did a model that excluded the Center for Epidemiologic Studies–Depression scale (which contained appreciable nonresponse), so virtually all sample members were included. We present only the full linear model in Table 3.

**DISCUSSION**

In this sample of community-dwelling elderly persons, the presence of the E4 allele was not associated with functional decline as a main effect. Despite previous findings in this sample that the E4 allele is associated with cognitive decline and that cognitive status is associated with functional decline, in this longitudinal analysis, E4 independently did not predict functional decline either in bivariate or in multivariable analyses. In a previous analysis, the E4 allele in this sample was not found to be associated with increased mortality at P4 (4 years later) (12). This is in contrast to previous studies (7,8). When interaction terms were included in the model, E4 interacted with female gender and functional status at P3 but in opposite directions. Women with the E4 allele had an increased risk of functional decline, but those with E4 and poorer functional status at P3 had a decreased risk of further decline. Further analysis indicated that the E4 allele was a risk factor for the development of disability in those not previously disabled, but it did not have a detrimental effect on those who already had a disability. Therefore, the hypothesis of a main effect of the E4 allele as a predictor of functional decline was not substantiated. Rather, the E4 allele appears to have more targeted, interactive effects.

The absence of a main effect for the E4 allele could be explained in a number of ways (none of which has been clarified by the extant literature). One possibility is selection bias. For example, compared with the entire sample participating at P3, the genotyped subjects were less likely to be cognitively impaired. Perhaps many subjects at risk for cognitive impair-
is also not easily explained. One possibility is that women are more sensitive to adverse biological status in terms of functional decline. Therefore, the biological risk for functional decline due to the E4 allele is more manifested in women than men. This argument, however, is to some extent counterintuitive. Although women exhibit a greater likelihood at any given age of being more functionally impaired and exhibit greater functional decline over time, they experience a greater life expectancy (36). In addition, conditions with an increased risk of mortality (e.g., heart disease), for which E4 has been associated, are more likely to cause death in men than in women.

In summary, the findings of this study raise more questions than they answer. Given the documented problems with which the E4 allele is associated, it is important to note the absence of a main effect of the E4 allele in predicting functional decline in a sample of older adults. Few doubt the adverse consequences of the E4 allele for some outcomes; nevertheless, the overall adverse consequences of the allele, especially those consequences that are most critical to geriatric health care, are not well documented to date.

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References


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