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 (being female) and baseline functional status, however, did predict functional decline.
Methods

Sample.—Data from this study derive from the Duke EPESE (22). This population survey was part of a multi-center, 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, health status, cognitive status, depressive symptomology, and functional status. Cognitive 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.

Statistical Procedures

The analyses proceeded in two phases. In the first phase, the data were summarized by percentages for all covariates at the P3 interview. Bivariate odds ratios for functional decline between P3 and P4 were calculated. In the second phase, a series of regression analyses (logistic regression when the dependent variable was dichotomized and ordinary least squares [OLS] regression when the dependent variable was continuous) were performed for each scale separately and for the aggregated scales to determine the risk from the E4 allele for functional decline at P4 with functional status at P3 controlled. Here we report only the results from the OLS analysis on the aggregated scale. Results of the other analyses were comparable. Variables were constructed representing the interaction between E4 and each variable. These were entered as a chunk. Because this chunk of interaction terms was significant, the model was rerun with the interaction terms entered stepwise and with the final model retaining only the two interaction terms significant at the p < .01 level.

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-
person interview 4 years later (data not shown). The distribution of the APOE genotype is comparable to that of other studies (28–30).

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 impairment secondary to the E4 allele had already developed cognitive impairment and therefore were not included. Because cognitively impaired persons are more likely to become functionally impaired, those who are functionally impaired would, in turn, be underrepresented. As evidence of this potential bias, we would note that the genotyped sample is somewhat skewed toward better functioning. Because overall health and functional status are higher in this group, the group may be protected to some extent from the adverse effects of E4. On the other hand, one might argue that persons at a higher level of functioning at P3 could exhibit a decline in performance by P4 because the floor effect would be less important.

This study has certain limitations. In particular, we combined information on elderly subjects who possessed one E4 allele with those who possessed two E4 alleles. Even in this relatively large sample, only 22 subjects were homozygous for E4. If a larger sample were studied, perhaps being homozygous for E4 would be predictive of functional decline. Studies of Alzheimer’s disease indicate that the impact of the E4 allele is modified both as a function of whether one or two E4 alleles are present and of whether the E2 or E3 allele is also present (2).

It is also possible that the genotyped sample may have already passed through much of the age of increased risk of decline in function secondary to E4. Perhaps those who experienced a decline in function in part associated with the E4 allele might be less likely to appear in the genotyped sample. Given that we have reported previously that this sample is not at increased risk for mortality (in contrast to other studies of younger samples), such a concern must be taken seriously (12). It has been reported that E4 is less of a risk factor for cognitive decline among the oldest old, and this may hold for functional decline as well (27,30).

Yet another reason for finding no main effect association between the E4 allele and functional decline may be that the sample is over one half African American. It has been suggested that African Americans are less likely to experience the adverse effects of the E4 allele than whites (32).

The association of E4 and adverse health outcomes (such as functional decline) in persons without specific illnesses may not be appreciable (33,34). Small and colleagues found that the presence of the E4 allele did not affect cognitive performance in older adults without dementia and thought that decline probably reflected impending dementia (34). Dik found no change in cognitive performance in normally functioning adults with E4 (33). The findings here are similar in that the effect of the E4 allele varies depending on whether a particular condition is present or not. Whereas the studies cited indicate that the E4 allele is a risk factor for continued cognitive decline, our study on change in functional status suggests that the E4 allele is a risk factor for the initial development of functional disability but not for increased disability in those already disabled. It is of interest that the tasks most likely to be affected are instrumental activities, which have been recognized as having a notable cognitive component (35), particularly when compared with physical health activities and basic ADLs. Thus, the effect of the E4 allele on functional status may be through its effect on cognitive function. Its effect on conditions less likely to be determined by cognitive function may be quite limited. It may be for this reason that the E4 allele is not a risk factor for further decline.

The significant increased risk of functional decline predicted by the interaction of the E4 allele and female gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Probability</th>
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<tr>
<td>Intercept</td>
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<td>1.261</td>
<td>0.0001</td>
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<td>Female</td>
<td>–0.030</td>
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<tr>
<td>Education</td>
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<td>0.040</td>
<td>0.0001</td>
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<td>Cognitive status</td>
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<td>0.064</td>
<td>0.0001</td>
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<td>Health status</td>
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<td>0.002</td>
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</tr>
<tr>
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<td>0.296</td>
<td>0.4731</td>
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<tr>
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<td>0.190</td>
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<td>E4 allele</td>
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<td>0.318</td>
<td>0.0950</td>
</tr>
<tr>
<td>E4 allele × gender</td>
<td>1.432</td>
<td>0.381</td>
<td>0.0002</td>
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<tr>
<td>E4 allele × functional status</td>
<td>–0.181</td>
<td>0.070</td>
<td>0.0099</td>
</tr>
</tbody>
</table>

Note: Adjusted $R^2$ for the model = 0.44.
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), with 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