Effects of Family History and Apolipoprotein E ε4 Status on Cognitive Decline in the Absence of Alzheimer Dementia

The Cache County Study

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Objective: To evaluate the influences of a family history of Alzheimer dementia (FHxAD) and the apolipoprotein E ε4 genotype (APOE ε4) on cognitive decline.

Design, Setting, and Participants: Residents of Cache County, Utah, aged 65 years or older, were invited to participate. At baseline, 2957 participants provided DNA for genotyping of APOE and a detailed FHxAD. They also completed the Modified Mini-Mental State Examination. Cognitive status was reexamined after 3 and 7 years. We used mixed-effects models to examine the association among FHxAD, APOE ε4, and cognitive trajectories.

Main Outcome Measure: Modified Mini-Mental State Examination score trajectories over time.

Results: Compared with participants who did not have APOE ε4 or an FHxAD, those with APOE ε4 scored lower on the Modified Mini-Mental State Examination at baseline (−0.70 points; 95% confidence interval [CI], −1.15 to −0.24). Participants with an FHxAD and APOE ε4 differed less, if at all, in baseline score (−0.46 points; 95% CI, −1.09 to 0.16) but declined faster during the 7-year study (−9.75 points [95% CI, −10.82 to −8.67] vs −2.91 points [95% CI, −3.37 to −2.44]). After exclusion of participants who developed prodromal AD or incident dementia, the group with an FHxAD and APOE ε4 declined much less during the 7-year study (−1.54; 95% CI, −2.59 to −0.50).

Conclusions: Much of the association among FHxAD, APOE ε4, and cognitive decline may be attributed to undetected incipient (latent) disease. In the absence of latent disease, the 2 factors do not appear individually to be associated with cognitive decline, although they may be additive.

ent AD cases in the samples.\textsuperscript{23,24,31} One very large study found no differences associated with APOE ε4 on cognitive tests. However, the participants were young, ranging in age from 20 to 64 years, and the study was cross-sectional.\textsuperscript{32} Few studies have evaluated the influences of both FHxAD and APOE ε4 status on cognitive trajectories in elderly populations. Herein we evaluate the combined effects of the presence or absence of an FHxAD and the APOE ε4 genetic variant on cognition over time.

**STUDY SAMPLE**

Research protocols for the study have been previously described in detail.\textsuperscript{17,33} Briefly, at the beginning of the study in early 1995, all residents of the county who were 65 years or older were invited to participate. A total of 5092 persons completed baseline screening and a risk factor questionnaire. Surviving members of the cohort who were willing to participate underwent screening again 3 and 7 years later (1999 and 2003). For the current evaluation, we set aside 357 cases of prevalent all-cause dementia. Another 491 individuals without complete family history reports were excluded, as were 95 individuals who did not provide DNA for APOE genotyping. Of 4149 individuals with the necessary information, a total of 2957 completed at least 1 subsequent evaluation and were eligible for inclusion in the analytic sample. Individuals who were excluded (n = 2135) tended to be older but did not differ regarding FHxAD. Of those who provided DNA for APOE genotyping, proportionally more individuals in the excluded group had APOE ε4. This difference was attributed to an overrepresentation of ε3/ε4 and ε4/ε4 genotypes among prevalent dementia cases (χ² = 93.70; P < .001).

**COGNITIVE ASSESSMENT**

At each evaluation point, a cognitive screening test, the Modified Mini-Mental State Examination (3MS)\textsuperscript{35} adapted for epidemiological studies\textsuperscript{39} was used to evaluate participants’ cognitive status. The 3MS is frequently used as a screening instrument to detect changes in global cognition. Based on the Mini-Mental State Examination, it was adapted for epidemiological studies by changing some questions and adjusting the scoring from a range of 1 to 30 to a range of 1 to 100. Demographic questions that are difficult to verify in fieldwork (ie, date and place of birth) were changed to questions about current and past presidents. With fewer ceiling effects than the Mini-Mental State Examination, the 3MS is more sensitive in the detection of dementia and milder cognitive syndromes.\textsuperscript{36} Previously, we reported the sensitivity, specificity,\textsuperscript{37,38} and normative data on the 3MS in this cohort.\textsuperscript{39} In the first 2 evaluations, we used the 3MS in combination with the Dementia Questionnaire\textsuperscript{40} (3MS cut point, 86/87); at the second follow-up, we combined the 3MS with a brief battery of neuropsychological tests (3MS cut point, 90/91). The sensitivities for the detection of dementia at each evaluation were 84.6%, 93.6%, and 96.7%, respectively. Individuals with screening results that were positive for a cognitive disorder received a full clinical assessment. At the second follow-up evaluation, all individuals 85 years or older underwent clinical assessments. Dementia cases were diagnosed using standard criteria\textsuperscript{41-43} as described previously.\textsuperscript{44,45} Cases of prodromal AD\textsuperscript{46} were diagnosed clinically on the basis of a history of mild symptomatic disease (eg, memory loss or changes in instrumental activities of daily living). Diagnoses were assigned if the participants’ history, medical evaluation, and clinical profile indicated subsyndromal AD after excluding competing causes.

**ASSESSMENT OF FHxAD**

An FHxAD was determined with a structured questionnaire that was administered at baseline and at the first follow-up evaluation. Participants were asked to list the names of biological parents and siblings and to provide information about whether they ever had memory problems. If memory problems were reported, further questions determined the age at which problems began, whether they began suddenly or slowly, if they progressed over time, if there were limitations with activities of daily living, and whether a physician’s diagnosis was received. In addition, a list of problems (AD, Parkinson disease, Down syndrome, hardening of the arteries, ministrokes or transient ischemic attacks, arteriosclerosis, and other neurological conditions) was presented as a cue for diagnoses that may have been given. Each relative was classified as having suspected AD if a physician had given a diagnosis of AD or, lacking a physician’s diagnosis, if the relative’s memory problems had worsened over time, causing limitations with daily activities. If a first-degree relative had died before 50 years of age but did not have dementia, that person’s information was coded as missing. Study participants were classified as having an FHxAD if at least 1 first-degree relative was categorized as having suspected AD.

**ANALYTIC APPROACH**

Initial comparisons were made between individuals who reported an FHxAD and those who reported no FHxAD. We compared categorical variables using χ² tests and evaluated continuous variables using 2-sample t tests. To assess the effects of an FHxAD and APOE ε4 genotype on cognition over time, we used the 3MS as a measure of global cognitive performance and applied mixed-effects modeling techniques using the SAS PROC MIXED procedure.\textsuperscript{45} This procedure accommodates fixed and random effects that account for individual differences in cognitive performance at baseline and at subsequent measurements. All mixed-effects models were adjusted for factors significantly associated with baseline 3MS scores, including age, sex, and education. Time was evaluated as a nominal variable (0, 3, and 7 years) corresponding with baseline and average time to each of 2 follow-up evaluations. A quadratic term for time (time²) was included to allow for nonlinear changes in cognition over time. For the main exposures of interest, we constructed a categorical variable classifying each participant into 1 of the following 4 mutually exclusive groups: those with no FHxAD and no APOE ε4; those with an FHxAD only, those with APOE ε4 only, and those with both risk factors. The variable was dummy coded with the no FHxAD and no APOE ε4 category as the reference group. To assess differences in cognitive trajectories over time, we included interaction terms for linear and quadratic time with each of the FHxAD × APOE ε4 groups. Parameterized in this way, main-effect terms for each of the 3 nonreference FHxAD × APOE ε4 groups provide estimates of mean differences in 3MS scores compared with the reference group at baseline, whereas the interaction terms rep-
Table 1. Demographic Characteristics of 2957 Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FHxAD−/APOE ε4− (n=1532)</th>
<th>FHxAD+/APOE ε4− (n=533)</th>
<th>FHxAD−/APOE ε4+ (n=585)</th>
<th>FHxAD+/APOE ε4+ (n=307)</th>
<th>Total (n=2957)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline age, mean (SD), y</td>
<td>74.3 (6.6)</td>
<td>74.6 (6.7)</td>
<td>73.0 (6.1)</td>
<td>73.1 (5.5)</td>
<td>74.0 (6.4)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>867 (56.6)</td>
<td>333 (62.5)</td>
<td>335 (57.3)</td>
<td>175 (57.0)</td>
<td>1710 (57.8)</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>13.4 (2.9)</td>
<td>13.4 (2.9)</td>
<td>13.5 (2.8)</td>
<td>13.6 (2.9)</td>
<td>13.4 (2.9)</td>
</tr>
<tr>
<td>Baseline 3MS score, mean (SD)</td>
<td>92.1 (5.7)</td>
<td>92.2 (5.7)</td>
<td>91.9 (5.8)</td>
<td>92.2 (5.1)</td>
<td>92.1 (5.7)</td>
</tr>
</tbody>
</table>

Abbreviations: APOE ε4, apolipoprotein E ε4 genotype; FHxAD, family history of Alzheimer dementia; 3MS, Modified Mini-Mental State Examination; −, absent; +, present.

Table 2. Means and Cumulative Declines in 3MS Scores During 7 Years of Observation

<table>
<thead>
<tr>
<th>Model No.</th>
<th>Baseline</th>
<th>3-y Follow-up</th>
<th>7-y Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 FHxAD−/APOE ε4−</td>
<td>1 [Reference]</td>
<td>−0.32 (−0.62 to −0.03)</td>
<td>−2.91 (−3.37 to −2.44)</td>
</tr>
<tr>
<td>FHxAD+/APOE ε4−</td>
<td>0.02 (−0.49 to 0.53)</td>
<td>−0.25 (−0.81 to 0.31)</td>
<td>−2.69 (−3.55 to −1.83)</td>
</tr>
<tr>
<td>FHxAD−/APOE ε4+</td>
<td>−0.70 (−1.15 to −0.24)</td>
<td>−2.21 (−2.69 to −1.72)</td>
<td>−6.64 (−7.38 to −5.90)</td>
</tr>
<tr>
<td>FHxAD+/APOE ε4+</td>
<td>−0.46 (−1.09 to 0.16)</td>
<td>−2.37 (−3.09 to −1.66)</td>
<td>−9.75 (−10.82 to −8.67)</td>
</tr>
<tr>
<td>2 FHxAD−/APOE ε4−</td>
<td>1 [Reference]</td>
<td>0.37 (0.09 to 0.66)</td>
<td>−1.03 (−1.43 to −0.63)</td>
</tr>
<tr>
<td>FHxAD+/APOE ε4−</td>
<td>−0.26 (−0.80 to 0.28)</td>
<td>0.19 (−0.36 to 0.74)</td>
<td>−1.30 (−2.06 to −0.55)</td>
</tr>
<tr>
<td>FHxAD−/APOE ε4+</td>
<td>−0.42 (−0.91 to 0.07)</td>
<td>0.44 (−0.05 to 0.92)</td>
<td>−0.82 (−1.46 to −0.19)</td>
</tr>
<tr>
<td>FHxAD+/APOE ε4+</td>
<td>−0.58 (−1.30 to 0.13)</td>
<td>1.37 (0.60 to 2.15)</td>
<td>−1.54 (−2.59 to −0.50)</td>
</tr>
</tbody>
</table>

Abbreviations: APOE ε4, apolipoprotein E ε4 genotype; FHxAD, family history of Alzheimer dementia; 3MS, Modified Mini-Mental State Examination; −, absent; +, present.

RESULTS

Demographic characteristics of the sample are reported in Table 1. From a total sample of 2957 individuals participating in at least 2 evaluations, 28.4% had an FHxAD and 30.2% had APOE ε4; 10.4% had both. Most participants were female (57.8%) (mean age, 74 years), and most had a high school education or more. The average baseline 3MS score was 92.1. Groups with APOE ε4 alone or an FHxAD plus APOE ε4 were significantly younger. The average follow-up time was 6 (SD, 2.1; range, 2-9) years.

Modeling cognitive trajectories based on 3MS scores showed that the inclusion of interaction terms between time (linear and quadratic components) and each of the FHxAD × APOE ε4 groups was significant (likelihood ratio test, χ² = 17.8, P = .007). In the model with these interactions (model 1 in Table 2), there was no evidence of differences in the rate of change in the 3MS score over time for those with an FHxAD only (multivariate Wald, P = .91). The presence of APOE ε4 was significantly associated with a lower baseline score (−0.70; 95% confidence interval [CI], −1.15 to −0.24) and a faster decline over time (−6.64; 95% CI, −7.38 to −5.90; multivariate Wald, P = <.001) than the reference group. Participants with both an FHxAD and APOE ε4 declined significantly faster than did those with neither risk factor (multivariate Wald, P < .001). We estimated that those with both an FHxAD and APOE ε4 declined on average 9.75 points on the 3MS score during the 7-year study (95% CI, −10.82 to −8.67) compared with a 2.91-point decline (95% CI, −3.37 to −2.44) for the reference group. Results shown in Figure 1 represent the average participant in each group after adjustment for baseline age (centered at 74 years of age), sex, and education (centered at 13.4 years). A separate model designed to test multiplicative interaction between an FHxAD and APOE ε4 revealed no significant interaction between these 2 risk factors (P = .59; data not shown).

We then undertook a second evaluation of cognitive trajectories after removing from the sample 348 individuals who eventually received a diagnosis of dementia (72.7% were AD cases) and 464 individuals who at their last observation point were diagnosed as having prodromal AD. A total of 2145 individuals at the first follow-up and 1369 at the second follow-up remained in the sample. These results are presented in model 2 in
Table 2. As a result of removing incident cases of dementia and prodromal AD, the slope of the curves decreased (Figure 2). A post hoc multivariate Wald test revealed that a statistically significant difference between the reference group and the group with an FHxAD and APOE ε4 remained (P = .007), although the change over time was not clinically meaningful (−1.54 points during the 7 years).

We evaluated the associations between an FHxAD and APOE ε4 and their combination on cognitive change over time compared with participants with neither risk factor. The cumulative decline during the 7-year study in the group with both risk factors roughly approximates the sum of the declines for the groups with an FHxAD alone and APOE ε4 alone, suggesting that the 2 factors are additive. A formal test for a multiplicative interaction between an FHxAD and APOE ε4 revealed none. After removing incident cases of dementia and prodromal AD, trajectories of the groups became more similar, but a significant effect remained for the group with an FHxAD and APOE ε4. These findings imply that the greater cognitive decline found in those with APOE ε4 reflects the known relation of APOE ε4 to AD and not to another independent phenotype of poor cognition.

These analyses may help explain the lack of consensus in the literature on the effects of APOE ε4 on cognitive change over time. Sources of variation in results have been attributed to different study designs, study populations, follow-up periods, and age distributions of the samples under study. In some instances, previous research did not take future dementia diagnoses into account. For example, in the MacArthur Studies of Successful Aging, a population-based multisite 7-year study of 965 individuals, incident dementia cases were not removed from the sample, and the authors concluded that the ε4 allele was related to cognitive decline.19 In studies in which incident cases were removed from the sample27,30 or groups were analyzed separately according to cognitive status,28,29 no decline has been found in cognitively normal individuals with APOE ε4. However, a careful study by Christensen et al20 found that individuals with APOE ε4 had poorer scores on the Mini-Mental State Examination and the Symbol Digit Modalities Test after controlling for other risk factors. When mild cases of cognitive disorder were set aside, the results were unchanged. Similarly, Hofer et al21 found a significant effect of APOE ε4 on cognitive decline during a 7-year study using latent growth curve modeling. In this study, dementia cases were identified only at the first 2 evaluations and not the third. Cases of mild impairment or FHxAD were not considered. Indeed, most studies of APOE ε4 and cognitive decline do not consider family history in their analyses.

In our study, the difference between groups was attenuated with the removal of prodromal AD and incident dementia cases, suggesting that much of the decline was due to incipient disease. Nonetheless, a clinically small but statistically significant difference remained. There are several possible explanations for this phenomenon. It may be that we did not identify all incident cases in the sample and that the resulting decline is the result of unidentified cases. We doubt this is the case, because the protocol of the Cache County Study of Memory, Health, and Aging called for close scrutiny of those with APOE ε4. A more likely explanation is that much of the residual decline represents early change that has not yet revealed itself as a recognizable cognitive syndrome. In our sample, once incident dementia and prodromal AD cases were removed, the group with APOE ε4 and no FHxAD did not show significantly greater decline over time than did the reference group. Finally, we note the effects of the combination of FHxAD and APOE ε4, suggesting that the former may act independently, possibly reflecting other genetic influences or shared environment, and these influences may result in cognitive decline that does not reflect incipient AD.

Very few studies have evaluated the combined effects of APOE ε4 and family history. In a 6-year follow-up of the Kungsholmen Project cohort, Huang et al16 concluded that a family history of dementia was associated only with an increased risk of dementia among APOE ε4 carriers. Duara et al35 evaluated the combined effects of
family history and APOE ε4 on time to AD onset in a sample of 197 individuals and concluded that APOE ε4 and family history of disease are independent risk factors that operate in an additive manner. Our results extend these findings and suggest a similar additive effect of APOE ε4 and FHxAD on cognitive decline.

Our study has several strengths and limitations. Our determination of FHxAD was based on self-reported data. We acknowledge that, with the advent of widespread genetic testing, self-reported family history information may soon become obsolete. However, the method of data collection applied herein was a structured, detailed interview similar to those commonly used in genetic studies. This method has been successfully used in numerous studies and found to be reasonably reliable albeit with some measurement error. In the present study, measurement error may bias our results in favor of those who have APOE ε4 because it is associated with earlier disease onset. Individuals with APOE ε4 and an FHxAD were younger than those with an FHxAD only (P < .01). Information about the FHxAD in the present analysis was updated through the second data point but was not available for the full cohort at the third evaluation. Therefore, it is possible that some individuals with an FHxAD were misclassified; however, the effect of such a misclassification would tend to make our results more conservative. Our measure of cognitive performance, the 3MS, mainly reflects global cognition rather than specific cognitive domains. For this reason it is possible that we were unable to detect subtle changes that may be specific to particular cognitive domains. The strengths of the study include the large sample size and long-term follow-up. We implemented a comprehensive evaluation of cognitive status at all 3 time points, although it is possible that some incident cases of cognitive decline may have been misclassified. This may explain the remaining observed decline among those with an FHxAD and APOE ε4 when incident cases were removed. Although this finding was statistically significant, the decline itself was not clinically significant.

There may appear to be some tautology inherent in this study in that the removal of individuals with cognitive impairment from the analysis yields a sample of individuals with little or no cognitive decline. Although this is true, the objective of the study was to evaluate the performance of individuals with an FHxAD and APOE ε4 compared with individuals with neither risk factor to see whether decline could be observed before any clinical manifestation of disease. We have shown that an FHxAD and APOE ε4 have deleterious effects on cognition over time. This effect is significant for those who have both risk factors and suggests, as we know, that genes beyond APOE have influences on AD risk and expression. When prodromal AD and incident dementia cases are removed from the sample, the effects of genes on cognitive decline are mitigated, implying that much of the decline can be attributed to early expression of disease. Observable decline in cognitive screening scores over time (among individuals classified as normal) may be a useful indicator for subgroups at risk for AD or already expressing mild symptomatic disease. Further work is needed to elucidate more fully the cognitive patterns that precede and predict cognitive decline for each of these groups.

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Author Contributions: Dr Hayden had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hayden, Zandi, West, Tschanz, Breitner, and Welsh-Bohmer. Acquisition of data: West, Tschanz, Norton, and Welsh-Bohmer. Analysis and interpretation of data: Hayden, Zandi, West, Corcoran, Breitner, and Welsh-Bohmer. Drafting of the manuscript: Hayden, Zandi, and Welsh-Bohmer. Critical revision of the manuscript for important intellectual content: Hayden, Zandi, West, Tschanz, Norton, and Welsh-Bohmer. Statistical analysis: Hayden, Zandi, and Corcoran. Obtained funding: Welsh-Bohmer. Administrative, technical, and material support: West, Tschanz, Norton, Breitner, and Welsh-Bohmer.

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Error in Figure. In the Observation article titled “Depletion of B Lymphocytes From Cerebral Perivascular Spaces by Rituximab” by del Pilar Martin et al, published in the August issue of the Archives (2009;66[8]:1016-1020), part B of the Figure on page 1018 was incorrect. The corrected figure appears here.

**Figure.** Rituximab depletes B cells from peripheral blood, cerebrospinal fluid, and cerebral perivascular spaces (CPVS). At 6.5 months after the last dose of rituximab, no mature CD19+B cells were identified by flow cytometry in peripheral blood (A) or cerebrospinal fluid (B) in a patient with gastrointestinal mantle-cell lymphoma who developed progressive multifocal leukoencephalopathy (PML) following rituximab therapy. C, A cerebral magnetic resonance image of the index patient obtained 6 months after the last rituximab dose. D and E, No CD20+B cells or CD19+B cells were detectable in CPVS of the index patient (indicated as PML with rituximab) (original magnification x40). In contrast, B cells were present in autopsy tissue of 1 patient with healthy brain tissue (D and F), 4 patients with a diagnosis of multiple sclerosis (MS) not treated with rituximab therapy (D and G), and 2 patients diagnosed with PML not associated with rituximab (indicated as PML) (D and H) (original magnification x40). D, The number of B cells in CPVS of patients who developed PML not associated with rituximab therapy was also significantly decreased compared with that in healthy cerebral tissue and tissue from patients with MS not treated with rituximab. VF indicates visual field; error bars, SEM. In E-H, an anti-CD19 monoclonal antibody (clone LE-CD19; Dako Corp, Glostrup, Denmark) was used to confirm the presence of B cells in CPVS. In F-H, arrows indicate B cells in CPVS.