Effects of Family History and *APOE* ε4 Status on Cognitive Decline in the Absence of AD: The Cache County Study

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Abstract

Context—Studies have shown that the *APOE* ε4 genotype is associated with cognitive decline and increased risk of Alzheimer's dementia (AD). Other genes are probably associated with both outcomes. Family history of AD (FhxAD) may represent genetic factors or shared environmental factors that increase the risk of cognitive decline.

Objective—To evaluate the influences of FhxAD and *APOE* ε4 on cognitive decline.

Design, Setting, and Participants—Residents of Cache County, Utah, aged 65+ were invited to participate. At baseline 2,957 participants provided DNA for genotyping at *APOE* and a detailed family history of AD. They also completed the Modified Mini-Mental State Examination (3MS). Cognitive status was re-examined after three and seven years. We used mixed models to examine the association between FhxAD, *APOE* ε4, and cognitive trajectories.

Main Outcome Measure—3MS score trajectories over time.

Results—Compared with participants who had neither *APOE* ε4 nor FhxAD, those with *APOE* ε4 scored lower at baseline (−0.70 points on 3MS, 95% confidence interval (CI) −1.15 to −0.24). Participants with both FhxAD and *APOE* ε4 differed less, if at all, in baseline score (−0.46, 95% CI −1.09 to 0.16) but declined faster over 7 years (− 9.75, CI −10.82 -- 8.67) vs.(−2.91, CI −3.37 to −2.44). After exclusion of participants who developed prodromal AD or incident dementia, the group with FhxAD and *APOE* ε4 declined much less over 7 years (−1.54, CI −2.59 to −0.50).

Conclusions—These results suggest that much of the association between FhxAD, *APOE* ε4, and cognitive decline is attributed to undetected incipient (latent) disease. Absent this association, the

two factors do not appear individually to be associated with cognitive decline although they may be additive.

Keywords

APOE; family history; Alzheimer's dementia; cognitive decline; cognitive trajectory

Introduction

Alzheimer dementia (AD) is a neurodegenerative condition that begins with mild memory loss and progresses to total memory loss, loss of independence,[1] and is a leading cause of death.[1,2] A report from the nationally representative Aging, Demographics, and Memory Study indicated that AD accounts for almost 70% of all dementias in the population.[3] Individuals with an expressed family history of AD have a 39% higher lifetime risk of disease by age 96.[4] When both parents develop the disease, the risk for offspring is higher still (41.8% by age 70; 54% by age 80).[4,5] Few studies have evaluated the effect of family history of AD (FhxAD) on cognitive trajectories over time. FhxAD may be viewed as an indicator for genetic contributions in the absence of confirmed associations with risk genes, although shared environment may account for a portion of the variance associated with family history.

There are three genes that predispose individuals to an early AD onset, however, these are rare in the general population.[6–9] Other, as yet unconfirmed genetic associations will likely account for a much greater proportion of disease.[10] The only non-Mendelian risk gene that has been firmly established is the ε4 variant of the apolipoprotein (*APOE*) gene.[11–15] The ε4 allele of this gene is a well known risk factor[16] thought to affect the timing of disease.[17,18] Interestingly, the association between *APOE* ε4 and cognitive decline is somewhat equivocal in the literature. Previous findings have suggested that *APOE* ε4 is associated with cognitive decline in many[19–26] but not all[27–30] studies. Some researchers theorize that the difference may be the inclusion of incipient AD cases in the samples.[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, and the study was cross sectional.[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 FhxAD and the *APOE* ε4 genetic variant on cognition over time.

Methods

The Cache County Memory Study (CCMS) is an epidemiological investigation of memory in aging in Cache County, Utah.[17] Protocols and procedures were approved by the Institutional Review Boards of Utah State University, Duke University, and the Johns Hopkins University. Informed consent was obtained from all study participants at each stage of the study. Spouses or next of kin gave consent when participants were unable to provide it.

Study Sample

Research protocols for the study have been previously described in detail.[17,33] Briefly, at the beginning of the study in early 1995, all residents of the county aged 65+ were invited to participate. A total of 5,092 persons completed baseline screening and a risk factor questionnaire. Surviving members of the cohort who were willing to participate were screened 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 4,149 individuals with the necessary information, a total of 2,957 completed at least one

subsequent evaluation and were eligible for inclusion in the analytic sample. Individuals who were excluded (n=2,135) 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 over-representation of ε3/4 and ε4/4 genotypes among prevalent dementia cases (χ^2 93.70; p-value <.0001).

Cognitive Assessment

At each evaluation point, a cognitive screening test, the Modified Mini-Mental State Examination (3MS)[34] adapted for epidemiological studies[35] 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 (MMSE), it was adapted for epidemiological studies by changing some questions and adjusting the scoring from a range of 1–30 to 1–100. Demographic questions that are difficult to verify in fieldwork (i.e., date and place of birth) were changed to questions about current and past presidents. With fewer ceiling effects than the MMSE, the 3MS is more sensitive in detection of dementia and milder cognitive syndromes.[36] Previously we reported the sensitivity, specificity,[37, 38] and normative data on the 3MS in this cohort.[39] In the first two evaluations we used the 3MS in combination with the Dementia Questionnaire[40] (3MS cutpoint: 86/87); at the second follow-up the 3MS was combined with a brief battery of neuropsychological tests (3MS cutpoint: 90/91). The sensitivities for the detection of dementia at each evaluation were 84.6%, 93.6%, and 96.7% respectively. Individuals who screened positive for cognitive disorder received a full clinical assessment. At the second follow-up evaluation, all individuals aged 85+ were clinically assessed. Dementia cases were diagnosed using standard criteria[41–43] as described previously. [17, 33] Cases of prodromal AD[44] were diagnosed clinically based on a history of mild symptomatic disease (e.g. memory loss or changes in instrumental activities of daily living). Diagnoses were assigned if participants' history, medical evaluation, and clinical profile indicated subsyndromal AD after excluding competing etiologies.

Assessment of Family History of Disease

FhxAD was determined with a structured questionnaire administered at baseline and the first follow-up evaluation. Participants were asked to list the names of biological parents and siblings and 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, progressed over time, if there were limitations with activities of daily living, and whether a doctor's diagnosis was received. Additionally, a list of problems (AD, Parkinson's disease, Down's Syndrome, hardening of the arteries, mini-strokes or TIA's, 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 doctor gave a diagnosis of AD or, lacking a doctor's diagnosis, the relative's memory problems worsened over time causing limitations with daily activities. If a first degree relative died prior to age 50 without dementia, their information was coded as missing. Study participants were classified as having a positive FhxAD if at least one first-degree relative was categorized with suspected AD.

Analytic Approach

Initial comparisons were made between individuals who reported a FhxAD to those who reported no FhxAD. Categorical variables were compared with χ^2 tests; continuous variables were evaluated with *t*-tests. To assess the effects of 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.[45] This procedure

accommodates both 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 two follow-up evaluations. A quadratic term for time (time^2) 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 one of four mutually exclusive groups: those with no FhxAD and no *APOE* ε4, those with only a FhxAD, those with only *APOE* ε4, 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-by-*APOE* ε4 groups. Parameterized in this way, main effect terms for each of the three non-reference FhxAD-by-*APOE* ε4 groups provide estimates of mean differences in 3MS scores compared with the reference group at baseline, while the interaction terms represent differences in the rate of change over time. We evaluated the significance of including the interaction terms with time using an omnibus likelihood ratio test to determine if there were any differences in the rate of change among the FhxAD-by-*APOE* ε4 groups. Post hoc comparisons of the differences in the rate of change between each individual group and the reference were made separately using multivariate Wald tests. An additional model was constructed with an alternate parameterization including separate dichotomous indicator terms for the presence/absence of FhxAD, of *APOE* ε4, and another term for the product between the two to test for multiplicative interaction.

Results

Demographic characteristics of the sample are reported in Table 1. From a total sample of 2,957 individuals participating in at least two evaluations, 28% had FhxAD and 30% had *APOE* ε4; 10% 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. Groups with *APOE* ε4 alone or FhxAD plus *APOE* ε4 were significantly younger. The average follow-up time was 6 years (standard deviation 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-by-*APOE* ε4 groups was significant (Likelihood ratio test χ^2=17.8, *df*=6, p-value=0.007). In the model with these interactions (Table 2, model 1), there was no evidence of differences in the rate of change on the 3MS over time for those with only FhxAD (multivariate Wald p-value = 0.91). *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 than the reference group (−6.64, 95% CI −7.38 to −5.89; multivariate Wald p-value <0.0001). Participants with both FhxAD and *APOE* ε4 declined significantly faster than those with neither risk factor (multivariate Wald p-value <0.0001). We estimated that those with both FhxAD and *APOE* ε4 declined on average 9.75 points on the 3MS over 7 years (95% CI −10.82 to −8.67) compared with 2.91 points (95% CI −3.37 to −2.44) for the reference group. Results presented in Figure 1 represent the average participant in each group after adjustment for baseline age (centered at age 74), sex, and education (centered at 13.4 years). A separate model designed to test multiplicative interaction between FhxAD and *APOE* ε4 revealed no significant interaction between these two risk factors (p-value =0.59; 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 with prodromal AD. A total of n=2,145 individuals at the first follow-up and n=1,369 at the second follow-up

remained in the sample. These results are presented in Table 2, model 2. As a result of removing both dementia and prodromal AD cases, 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 FxhAD and *APOE* ε4 remained (p=0.007) although the change over time was not clinically meaningful (1.54 points over 7 years).

Comment

We evaluated the associations between FhxAD, *APOE* ε4, and their combination on cognitive change over time as compared with participants with neither risk factor. The cumulative decline over 7 years in the group with both risk factors roughly approximates the sum of the declines for the groups with FhxAD alone and *APOE* ε4 alone, suggesting that the two factors are additive. A formal test for a multiplicative interaction between 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 FhxAD plus *APOE* ε4 group. 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, prior research did not take future dementia diagnoses into account. For example in the MacArthur Study of Successful Aging, a population based multi-cite study of 965 individuals over 7 years, incident dementia cases were not removed from the sample and the authors concluded that ε4 was related to cognitive decline.[19] In studies where incident cases are removed from the sample [27, 30] or groups are 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 al, [20] found that individuals with *APOE* ε4 had poorer scores on the MMSE 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 al found a significant effect of *APOE* ε4 on cognitive decline over 7 years using latent growth curve modeling.[21] In this study, dementia cases were identified only at the first two evaluations and not the third. Cases of mild impairment or family history of AD 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 the resulting decline is due to unidentified cases. We doubt this is the case, because the CCMS protocol 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. Yet another explanation, suggested by others, is that individuals with *APOE* ε4 decline at a faster rate in a way that is unrelated to development of symptomatic conditions. In our sample, once incident dementia and prodromal AD cases were removed, the group with *APOE* ε4 and no family history did not show significantly greater decline over time than the reference group. Finally, we note the effects of the combination of family history *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 six year follow-up of the Kungsholmen Project cohort, Huang et al,[46] concluded that a family history of dementia was only associated with an increased risk of dementia among *APOE* ε4 carriers. Duara et al,[47] 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.

This 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 here 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[40] albeit with some measurement error. In the current study, measurement error may bias our results in favor of those who have *APOE* ε4 as it is associated with earlier disease onset. Individuals with *APOE* ε4 and FhxAD were younger than those with FhxAD only (p<0.01). Information about FhxAD 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 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 a 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 three 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 FhxAD and *APOE* ε4 when incident cases were removed. While this finding was statistically significant, the decline itself was not clinically significant.[48]

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. While this is true, the objective of the study was to evaluate the performance of individuals with FhxAD and *APOE* ε4 compared with individuals with neither risk factor to see if decline could be observed prior to any clinical manifestation of disease. We have shown that both 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 is 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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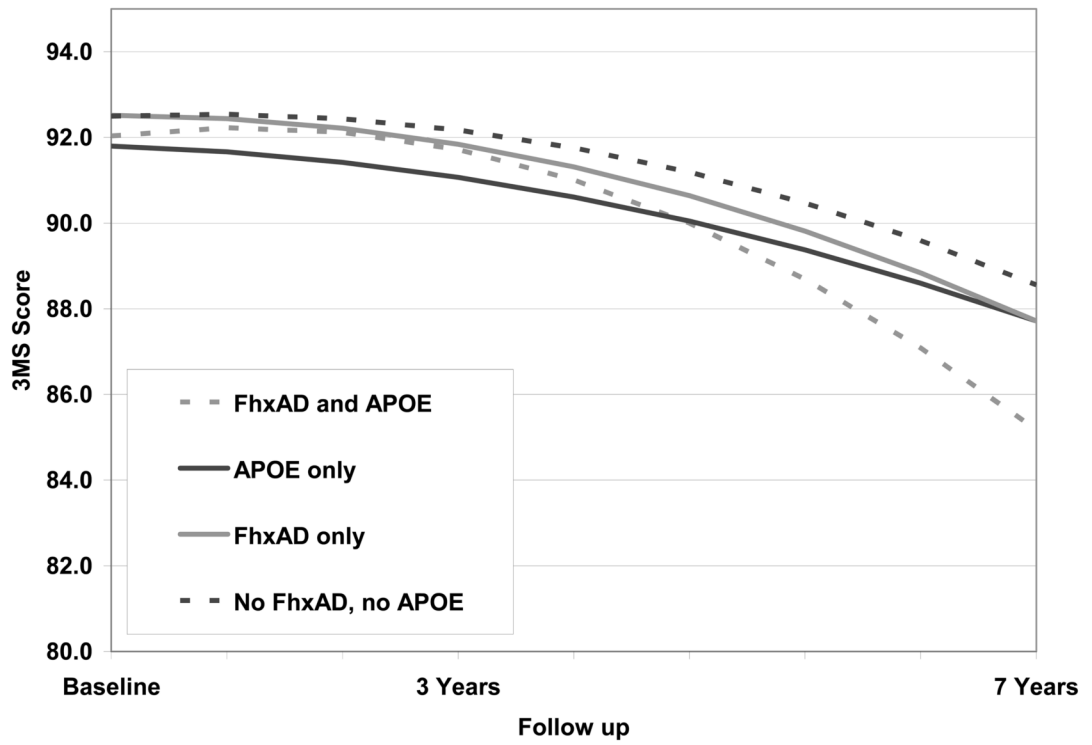
Figure 1.
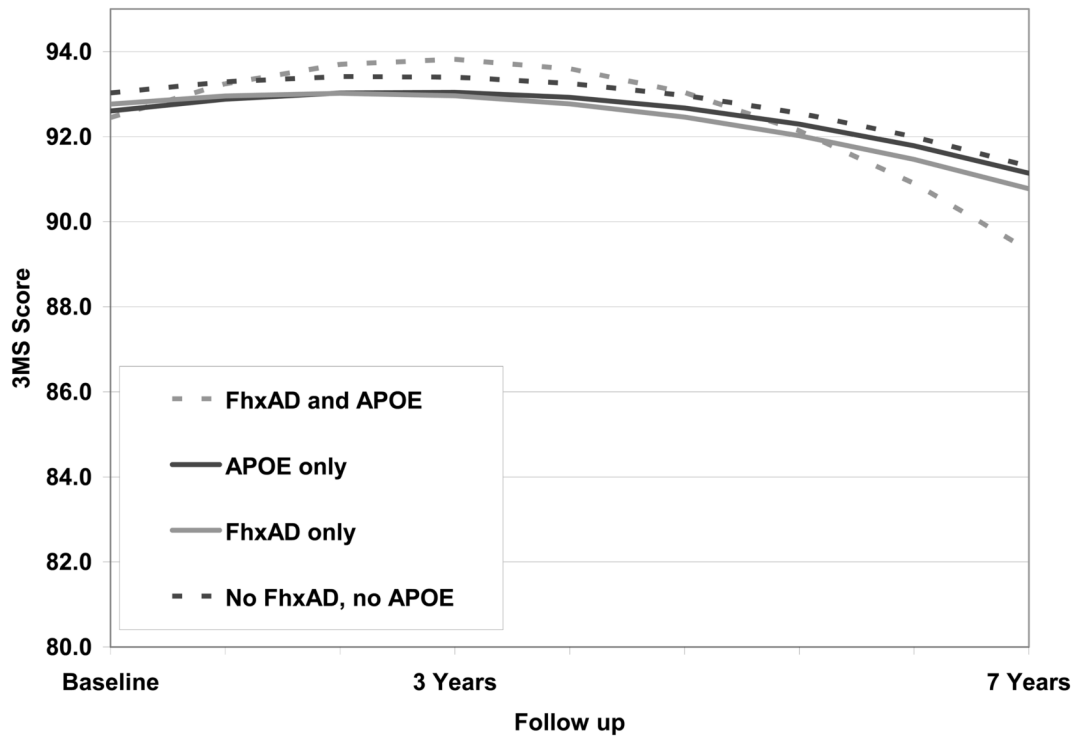Trajectories of cognitive change by FhxAD and *APOE* status

Figure 2.
Trajectories of cognitive change by FhxAD and *APOE* status among cognitively normal individuals

Table 1

Demographic Characteristics of 2,957 Study Participants

Characteristic	FhxAD(−) APOE(−) (n=1532)	FhxAD(+) APOE(−) (n=533)	FhxAD(−) APOE(+) (n=585)	FhxAD(+) APOE(+) (n=307)	Total (n=2,957)
Baseline Age, mean (SD) *	74.3 (6.6)	74.6 (6.7)	73.0 (6.1)	73.1 (5.5)	74.0 (6.4)
Female Sex, No. (%)	867 (56.6)	333 (62.5)	335 (57.3)	175 (57.0)	1,710 (57.8)
Education, mean (SD)	13.4 (2.9)	13.4 (2.9)	13.5 (2.8)	13.6 (2.9)	13.4 (2.9)
Baseline 3MS score, mean (SD)	92.1 (5.7)	92.2 (5.7)	91.9 (5.8)	92.2 (5.1)	92.1 (5.7)

*
$p<0.01$

Values are presented as means and standard deviations (SD) unless indicated as number and percent (%).

Table 2

Means and Cumulative Declines in 3MS scores over 7 years of Observation[*]

Model 1	Baseline (n=2,957)	3 years (n=2,957)	7 years (n=1,936)
FhxAD (−), APOE(−)	(reference)	−0.32 (−0.62 to −0.03)	−2.91 (−3.37 to −2.44)
FhxAD (+), APOE(−)	0.02 (−0.49 to 0.53)	−0.25 (−0.81 to 0.31)	−2.69 (−3.55 to −1.83)
FhxAD (−), APOE(+)	−0.70 (−1.15 to −0.24)[a]	−2.21 (−2.69 to −1.72)	−6.64 (−7.38 to −5.90)[b]
FhxAD (+), APOE(+)	−0.46 (−1.09 to 0.16)	−2.37 (−3.09 to −1.66)	−9.75 (−10.82 to −8.67)[b]
Model 2	**Baseline (n=2,145)**	**3 years (n=2,145)**	**7 years (n=1,369)**
FhxAD (−), APOE(−)	(reference)	0.37 (0.09 to 0.66)	−1.03 (−1.43 to −0.63)
FhxAD (+), APOE(−)	−0.26 (−0.80 to 0.28)	0.19 (−0.36 to 0.74)	−1.30 (−2.06 to −0.55)
FhxAD (−), APOE(+)	−0.42 (−0.91 to 0.07)	0.44 (−0.05 to 0.92)	−0.82 (−1.46 to −0.19)
FhxAD (+), APOE(+)	−0.58 (−1.30 to 0.13)	1.37 (0.60 to 2.15)	−1.54 (−2.59 to −0.50)[c]

[*] Models are adjusted for baseline age, sex, education, time, time^2, and interactions between each group with time and time^2.

Model 1 includes all study participants.

Model 2 excludes individuals diagnosed with prodromal AD or dementia.

[a] p-value=0.003 compared with reference group

[b] p-value<0.0001 compared with reference group

[c] p-value=0.007 compared with reference group