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APOE-ε4 is associated with memory decline in cognitively impaired elderly

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Article abstract—*Objective:* To investigate whether the association between APOE-ε4 and memory decline is modified by baseline cognition and age in a population-based elderly sample. *Methods:* The study sample consisted of 1,243 subjects, 62 to 85 years old, with a Mini-Mental State Examination (MMSE) score between 21 and 30 and known APOE phenotypes. Memory performance was measured with an abbreviated Auditory Verbal Learning Test (AVLT) at baseline and repeated after 3 years (n = 854). Memory decline was defined as a decrease of at least 1 SD from the mean change score on immediate recall (IR), delayed recall (DR), and retention, based on the AVLT. *Results:* Multivariate logistic regression analyses showed that APOE-ε4 is associated with memory decline in cognitively impaired subjects (MMSE score, 21 to 26) (OR for decline on IR adjusted for age, sex, education, and baseline recall score, 3.8; 95% CI, 1.4 to 10.0; adjusted OR for decline on DR, 2.9; 95% CI, 1.2 to 7.0; adjusted OR for decline on retention, 3.3; 95% CI, 1.1 to 10.1), but not in cognitively normal subjects (MMSE score, 27 to 30) (adjusted OR for decline on IR, 1.1; 95% CI, 0.6 to 2.0; adjusted OR for decline on DR, 1.0; 95% CI, 0.6 to 1.8; adjusted OR for decline on retention, 1.5; 95% CI, 0.7 to 3.0). In particular, cognitively impaired ε4 carriers older than 75 years were at high risk of memory decline (adjusted OR for decline on IR, 4.5; 95% CI, 1.4 to 13.8; adjusted OR for decline on DR, 3.6; 95% CI, 1.2 to 10.8; adjusted OR for decline on retention, 6.6; 95% CI, 1.5 to 29.7). *Conclusions:* APOE-ε4 was associated with memory decline in subjects with cognitive impairment, but not in normally functioning subjects. Contrary to AD studies, our study suggests that the risk of APOE-ε4 on memory decline does not decrease at higher ages. **Key words:** APOE—Memory decline—AD—Age—Population-based study—Elderly.

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The *APOE*-ε4 allele has been established to be a risk factor of late-onset AD.[1,2] However, studies suggest that the ε4-associated risk of incident AD decreases after age 70.[3-5] Recently, studies have focused on investigating whether *APOE*-ε4 can predict cognitive decline and progression into AD.[6-8] Decline in memory, in particular in delayed recall, has been shown to be one of the earliest indicators of dementia.[6,9] Therefore, studies that investigate the association between *APOE*-ε4 and cognitive function focus on memory decline.

There seems to be a modifying effect of baseline cognition on the association between *APOE*-ε4 and memory decline, but the studies to date present inconsistent results. A case-control study[10] reported a poorer memory performance among *APOE*-ε4 carriers with mild cognitive impairment at baseline compared with non-ε4 carriers. In subjects with baseline normal cognition, however, *APOE*-ε4 status was not associated with poor memory performance. In contrast, a longitudinal community-based study[11] could not demonstrate an association between *APOE*-ε4 and memory decline in nondemented elderly with baseline impaired cognition. Surprisingly, in subjects with normal baseline cognition, *APOE*-ε4 carriers showed a greater memory decline compared to non-ε4 carriers.

Besides baseline cognitive function, differences in age might explain the inconsistent findings. Studies among subjects younger than 60 years did not observe an association between *APOE*-ε4 and performance on delayed recall or other cognitive measures.[12,13] Most community-based studies that did find an association between the *APOE*-ε4 allele and memory performance used subjects aged 70 years and older.[2,14,15] In contrast to AD studies, these findings suggest that the risk of *APOE*-ε4 on memory decline increases with increasing age in nondemented elderly.

In the current study, we investigated whether the risk of APOE-ε4 on memory decline is modified by baseline cognition. Furthermore, we explored the role of age in the association between APOE-ε4 and memory decline. All subjects originated from a large community sample of elderly, with a wide age range.

Methods. *Sample description.* Participants for the study were obtained from the study sample of the Longitudinal Aging Study Amsterdam (LASA), a multidisciplinary study on changes in autonomy and well-being in the aging population.[16] The LASA respondents were recruited from

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the municipal registries in the regions Amsterdam, Oss, and Zwolle, resulting in 3,107 respondents aged 55 to 85 years. Both the oldest age groups and men were overrepresented, so that approximately equal numbers of men and women in each age stratum (55 to 59, 60 to 64, 65 to 69, 70 to 74, 75 to 79, and 80 to 85 years) were obtained. The sample and study design have been described in detail elsewhere.[17,18] Approval for the study was given by the local medical ethics committee and all respondents gave informed consent at the start of the study.

The study design involved blood collection and memory testing in subjects aged 62 years and older (born in 1930 or before) living in the Amsterdam and Zwolle region (n = 1,551). APOE phenotype could be determined in 1,297 subjects (83.6%). Subjects with a Mini-Mental State Examination (MMSE) score <21 were excluded because they were suspected of dementia. This resulted in a baseline sample of 1,243 subjects.

Follow-up measurement was completed for 876 subjects (70.5% of 1,243) after an average of 3.1 (SD = 0.2) years of follow-up. Loss to follow-up was caused by death (13.5%), refusal (11.1%), ineligibility due to frailty (4.4%), and loss of contact (0.5%). For 22 subjects no difference score on the memory task could be calculated, because data were missing on either the first or the second measurement. This resulted in 854 subjects with valid data on both measurements.

Measurements. Cognitive functioning. Cognitive function was measured with the MMSE at baseline.[19] Memory was measured with an abbreviated version of the Auditory Verbal Learning Test (AVLT).[20] We used three instead of five learning trials to reduce the test burden for the respondent. For each trial, the interviewer read aloud a list of 15 words, after which the respondents summed up as many words as they could remember. After an interval of approximately 20 minutes, during which a different nonverbal task was performed, the respondents were asked to recall as many words as possible (delayed recall). We noted the number of correctly recalled words (points). Words mentioned by the respondent that were not on the AVLT word list were not counted. Furthermore, words that were mentioned more than once by the respondent were only counted one time (each trial). Immediate recall (score on the third trial, range 0 to 15), delayed recall (range 0 to 15), and memory retention (delayed recall/third trial × 100%) were analyzed. At follow-up, a parallel version of the AVLT was used. The parallel versions, which are used in treatment research,[21] were validated and tested for parallelism.[22]

APOE phenotype determination. Serum samples were frozen at −80 °C until determination of APOE phenotype. APOE phenotypes were determined by isoelectric focusing of delipidated plasma samples, followed by immunoblotting.[23] Participants were classified as ε4 carriers for those with an APOE-ε4 isoform (phenotypes ε2/4, ε3/4, ε4/4) and as non-ε4 carriers for those without an APOE-ε4 isoform (phenotypes ε2/2, ε2/3, ε3/3).

Sample characteristics. At baseline, data on age and sex were derived from the municipal registries. Educational level was assessed by asking the respondent for the highest educational level completed, ranging from incomplete elementary education to university education. This was converted into years of education (range, 5 to 18). To obtain insight into the clinical characteristics of the study sample, important for distinguishing cognitive impairment from dementia, we described functional ability of the subjects. As an indicator of functional ability, the respondents were asked whether they received help with personal care.

Data analysis. The study sample was stratified into subjects with normal cognition and subjects with cognitive impairment. The baseline MMSE scores were used as an external criterium, with MMSE scores 27 to 30 indicating normal cognition and MMSE scores 21 to 26 indicating impaired cognition. These cognition strata were further divided by age (62 to 74 years and 75 to 85 years).

Between-strata differences in APOE status and sex were tested with the χ^2 test. Differences in age, years of education, MMSE, and memory test performance were studied with the Student's *t*-test for independent samples. Using the baseline data only, differences between ε4 carriers and non-ε4 carriers in memory performance were tested with the Student's *t*-test. Furthermore, multivariate linear regression analyses were performed to detect an effect of APOE-ε4 on memory performance adjusted for age (continuous variable), sex, and years of education.

The change in memory score was calculated for each individual as the difference between the baseline score and the follow-up score. Against the background of early development of AD, we were interested in clinically relevant memory decline, meaning memory decline that is substantially greater than the mean decline of the study sample. Therefore, decline in memory was defined as a decrease of at least 1 SD from the mean change score. This resulted in a decline of three or more points on immediate recall, a decline of two or more points on delayed recall, and a decline of 27% or more on retention of the AVLT. Differences in proportion of decline between ε4 carriers and non-ε4 carriers were evaluated with the χ^2 test. Multivariate logistic regression analyses were performed to investigate the association between APOE-ε4 and memory decline adjusted for age (continuous variable), sex, years of education, and baseline recall score (i.e., baseline immediate recall for decline on immediate recall, baseline delayed recall for decline on delayed recall, baseline retention score for decline on retention).

Because cut-off of the MMSE may be arbitrary, an interaction term of APOE-ε4 with the MMSE score as a continuous variable was evaluated. Also, the interaction of APOE-ε4 and age was evaluated. Furthermore, MMSE performance may be influenced by education and age. Because we wanted to explore the role of age in this study, it was not appropriate to adjust the MMSE scores for age. Therefore, MMSE scores adjusted for education were calculated, whereas age effects were preserved. This was done using a regression approach.[24] MMSE scores adjusted for education were predicted within 5-year age strata. For each subject a residual score was calculated as the observed MMSE score minus the predicted score. The adjusted score was calculated by adding the mean score of the age stratum to the residual score. These adjusted scores were categorized in the MMSE strata 21 to 26 and 27 to 30 points, and multivariate logistic regression analyses were performed. Also, we did the analyses in subjects with MMSE scores of 24 to 26 points.

Results. The distribution of the APOE phenotypes was in Hardy-Weinberg equilibrium. Loss to follow-up was associated with older age, lower education, and lower scores

Table 1 *Demographic characteristics and cognition at baseline for subjects with normal cognition (MMSE 27–30) and cognitive impairment (MMSE 21–26)*

Characteristic	MMSE 27–30, n = 866	MMSE 21–26, n = 377	*p* Value*
APOE ϵ4 +, n (%)	213 (24.6)	107 (28.4)	0.16
APOE ϵ4 −, n (%)	653 (75.4)	270 (71.6)	
Men, n (%)	440 (50.8)	193 (51.2)	0.90
Women, n (%)	426 (49.2)	184 (48.8)	
Mean (SD) age, y	72.1 (6.5)	75.6 (6.6)	<0.001
Mean (SD) education, y	9.2 (3.3)	7.7 (2.9)	<0.001
MMSE, mean (SD)	28.4 (1.0)	24.6 (1.5)	<0.001
Immediate recall, mean (SD)	7.8 (2.4)	5.9 (2.3)	<0.001
Delayed recall, mean (SD)	5.2 (2.5)	3.4 (2.2)	<0.001
Retention, mean (SD)	66.5 (27.9)	57.0 (31.4)	<0.001

* p Values indicate level of significance by χ^2 test or Student's t-test.

MMSE = Mini-Mental State Examination.

on all cognitive measures (all $p < 0.001$). More men were lost to follow-up, although differences were not significant. More importantly, loss to follow-up was not selective to APOE-ϵ4 frequency: 25.8% of ϵ4 carriers completed follow-up, compared with 25.7% of ϵ4 carriers who were lost to follow-up.

Of the 1,243 subjects in this study, at baseline 377 (30.3%) scored in the impaired range (21 to 26 points) and 866 (69.7%) scored in the normal range (27 to 30 points) of the MMSE. Table 1 shows the baseline sample characteristics for both subgroups. The groups did not differ significantly in APOE status or sex. The cognitively impaired subjects were on average older, less educated, and had lower scores on all cognitive measures compared with the cognitively normal subjects (all $p < 0.001$). Of the cognitively impaired elderly, 93.9% did not receive help with personal care, indicating that the large majority was not impaired in functional ability.

Table 2 (upper part) shows the baseline characteristics for cognitively normal and impaired subjects, separated for subjects younger and older than 75 years. The proportion of memory decline was generally highest in cognitively impaired subjects older than 75 years (table 2, lower part).

Cross-sectional analyses of the association between

Table 2 *Demographic characteristics, baseline cognition, and proportion of decline for subjects with normal cognition (MMSE 27–30) and cognitive impairment (MMSE 21–26), by age*

	MMSE 27–30			MMSE 21–26		
Characteristic	<75 y, n = 564	≥75 y, n = 302	*p* Value*	<75 y, n = 149	≥75 y, n = 228	*p* Value*
Cross-sectional						
APOE ϵ4 +, n (%)	155 (27.5)	58 (19.2)	<0.01	42 (28.2)	65 (28.5)	0.95
APOE ϵ4 −, n (%)	409 (72.5)	244 (80.8)		107 (71.8)	163 (71.5)	
Men, n (%)	273 (48.4)	167 (55.3)	0.05	70 (47.0)	123 (53.9)	0.19
Women, n (%)	291 (51.6)	135 (44.7)		79 (53.0)	105 (46.1)	
Mean (SD) age, y	68.0 (3.7)	79.5 (2.8)	<0.001	68.4 (3.5)	80.2 (2.9)	<0.001
Mean (SD) education, y	9.2 (3.1)	9.1 (3.7)	0.73	8.0 (2.9)	7.5 (3.0)	0.17
MMSE, mean (SD)	28.5 (1.0)	28.1 (1.0)	<0.001	24.9 (1.3)	24.5 (1.6)	<0.01
IR, mean (SD)	8.3 (2.4)	7.0 (2.3)	<0.001	6.9 (2.3)	5.3 (2.1)	<0.001
DR, mean (SD)	5.7 (2.5)	4.4 (2.3)	<0.001	4.2 (2.2)	2.9 (2.1)	<0.001
Ret, mean (SD)	68.7 (27.1)	62.5 (28.8)	<0.01	61.5 (29.3)	53.9 (32.4)	0.02
Longitudinal						
Decline in IR, n (%)	40 (8.8)	18 (9.9)	0.65	6 (5.9)	20 (16.9)	0.01
Decline in DR, n (%)	56 (12.3)	33 (18.2)	0.05	10 (9.9)	23 (19.5)	0.05
Decline in Ret, n (%)	33 (7.3)	25 (13.8)	0.01	12 (11.9)	14 (12.4)	0.91

* p Values indicate level of significance by χ^2 test or Student's t-test.

MMSE = Mini-Mental State Examination; IR = immediate recall; DR = delayed recall; Ret = retention.

Table 3 *Baseline memory function and proportion of decline for subjects with normal cognition (MMSE 27–30) and cognitive impairment (MMSE 21–26) in two age groups, by* APOE *status*

	MMSE 27–30		MMSE 21–26	
Characteristic	<75 y, n = 564	≥75 y, n = 302	<75 y, n = 149	≥75 y, n = 228
Cross-sectional				
IR, mean (SD)				
APOE-ϵ4 +	8.4 (2.5)	7.6 (2.4)*	6.4 (2.1)	4.9 (2.1)*
APOE-ϵ4 −	8.2 (2.3)	6.9 (2.3)	7.1 (2.3)	5.5 (2.0)
DR, mean (SD)				
APOE-ϵ4 +	5.8 (2.6)	4.7 (2.5)	3.7 (2.2)	2.5 (1.9)*
APOE-ϵ4 −	5.6 (2.5)	4.3 (2.3)	4.4 (2.2)	3.1 (2.0)
Ret, mean (SD)				
APOE-ϵ4 +	70.5 (32.0)	60.7 (31.4)	59.6 (36.1)	50.2 (36.6)
APOE-ϵ4 −	67.9 (25.0)	62.9 (28.3)	62.3 (26.2)	55.3 (30.7)
Longitudinal				
Decline in IR, n (%)				
APOE-ϵ4 +	11 (9.0)	5 (13.5)	2 (7.1)	10 (30.3)*
APOE-ϵ4 −	29 (8.7)	13 (9.0)	4 (5.5)	10 (11.8)
Decline in DR, n (%)				
APOE-ϵ4 +	18 (14.8)	6 (16.2)	3 (10.7)	10 (30.3)
APOE-ϵ4 −	38 (11.4)	27 (18.8)	7 (9.6)	13 (15.3)
Decline in ret, n (%)				
APOE-ϵ4 +	14 (11.5)*	4 (10.8)	4 (14.3)	7 (22.6)*
APOE-ϵ4 −	19 (5.7)	21 (14.6)	8 (11.0)	7 (8.5)

* Significant differences ($p \leq 0.05$) between ϵ4 carriers (ϵ4 +) and noncarriers (ϵ4 −) evaluated with Student's t-test or χ^2 test.

MMSE = Mini-Mental State Examination; IR = immediate recall; DR = delayed recall; Ret = retention.

APOE-ϵ4 and memory function did not show differences in memory function between ϵ4 carriers and non-ϵ4 carriers for both cognitively normal and cognitively impaired subjects younger than 75 years (table 3, upper part). Cognitively normal APOE-ϵ4 carriers ≥75 years scored higher on immediate recall ($p = 0.03$) than cognitively normal non-ϵ4 carriers ≥75 years; no differences were found for delayed recall performance and retention. Cognitively impaired ϵ4 carriers ≥75 years scored significantly lower on both immediate and delayed recall—not on retention—than cognitively impaired non-ϵ4 carriers ≥75 years. The differences remained significant after adjustment for age (continuous variable), sex, and education in linear regression analyses (data not shown). The proportion of decline on immediate recall and retention was significantly higher among cognitively impaired ϵ4 carriers ≥75 years as compared to non-ϵ4 carriers. Furthermore, the proportion of decline on retention was slightly but significantly higher among the youngest cognitively normal ϵ4 carriers as compared to the non-ϵ4 carriers (table 3, lower part).

Logistic regression analyses adjusted for age, sex, education, and baseline recall score showed an association between APOE-ϵ4 and memory decline only in cognitively impaired subjects (OR = 3.8, 95% CI, 1.4 to 10.0 for immediate recall; OR = 2.9, 95% CI, 1.2 to 7.0 for delayed recall; OR = 3.3, 95% CI, 1.1 to 10.1 for retention), but not in cognitively normal subjects (OR = 1.1, 95% CI, 0.6 to 2.0 for immediate recall; OR = 1.0, 95% CI, 0.6 to 1.8 for delayed recall; OR = 1.5, 95% CI, 0.7 to 3.0 for retention) (table 4). The interaction term of APOE-ϵ4 with the continuous MMSE score was significant for all memory measures. Analysis within cognition strata based on education-adjusted MMSE scores showed similar results to unadjusted MMSE strata (data not shown). Furthermore, defining cognitive impairment as MMSE scores of 24 to 26 did not change the results (data not shown).

Age did not appear to be a significant modifier of the association between APOE-ϵ4 and memory decline. Separate analyses in the two age strata showed, however, that the relative risk of decline for cognitively impaired ϵ4 carriers was particularly high in subjects older than 75 years (OR = 4.5, 95% CI, 1.4 to 13.8 for immediate recall; OR = 3.6, 95% CI, 1.2 to 10.8 for delayed recall; OR = 6.6, 95% CI, 1.5 to 29.7 for retention) (see table 4). When the cognition strata were based on education-adjusted MMSE scores, the ϵ4-related risk of memory decline in cognitively impaired elderly ≥75 years was weakened, but not lower than in subjects <75 years (<75 years: OR = 3.7, 95% CI, 0.8 to 17.2 for immediate recall; OR = 2.2, 95% CI, 0.5 to 8.8 for delayed recall; OR = 2.1, 95% CI, 0.5 to 9.9 for retention; ≥75 years: OR = 3.2, 95% CI, 1.2 to 8.3 for immediate recall; OR = 2.2, 95% CI, 0.9 to 5.6 for delayed recall; OR = 2.5, 95% CI, 0.8 to 8.1 for retention). The

Table 4 *Association between* APOE *ϵ4 and memory decline for subjects with normal cognition (MMSE 27–30) and cognitive impairment (MMSE 21–26), and by age*

Recall	MMSE 27–30, n = 635	MMSE 21–26, n = 219
Immediate	1.1 (0.6–2.0)	3.8 (1.4–10.0)
Age <75 y	1.0 (0.5–2.1)	2.9 (0.4–23.4)
Age ≥75 y	1.3 (0.4–4.0)	4.5 (1.4–13.8)
Delayed	1.0 (0.6–1.8)	2.9 (1.2–7.0)
Age <75 y	1.1 (0.6–2.2)	2.1 (0.4–10.8)
Age ≥75 y	0.9 (0.3–2.4)	3.6 (1.2–10.8)
Retention	1.5 (0.7–3.0)	3.3 (1.1–10.1)
Age <75 y	1.8 (0.8–4.4)	1.3 (0.2–8.3)
Age ≥75 y	1.0 (0.3–3.6)	6.6 (1.5–29.7)

Values expressed as OR (95% CI) adjusted for age (continuous variable), sex, education, and baseline recall score (i.e., baseline immediate recall for decline on immediate recall; baseline delayed recall for decline on delayed recall; baseline retention for decline on retention).

MMSE = Mini-Mental State Examination.

results did not change when APOE-ϵ2/4 carriers were excluded from the analyses.

Discussion. The aim of this study was to investigate whether baseline cognition modifies the association between APOE-ϵ4 and memory decline. The results show that APOE-ϵ4 is a risk factor of memory decline only in cognitively impaired and not in cognitively normal subjects. These results are in line with other studies.[9,10] In a selected sample of patients with mild cognitive impairment, a higher crossover to dementia was reported among *APOE*-ϵ4 carriers compared with non-ϵ4 carriers.[9] In another study, *APOE*-ϵ4 was associated with poorer baseline memory performance in subjects with mild cognitive impairment, but not in normal control subjects.[10]

In contrast, the longitudinal community-based Amsterdam Study of the Elderly (AMSTEL)[11] found *APOE*-ϵ4 associated with memory decline in cognitively normal but not in impaired elderly. However, based on the mean MMSE scores, the cognitively normal elderly in AMSTEL were more comparable with the cognitively impaired in our study. Moreover, the mean MMSE scores of the so-called minimal dementia subgroup in AMSTEL were lower compared with our impaired sample. Probably more subjects in early stages of AD were included in the minimal dementia sample of AMSTEL.

In our study, elderly scoring between 21 and 26 on the MMSE were considered to be cognitively impaired. This range may include a heterogeneous group of people who are normal, mildly impaired, or actually demented. However, because the majority of cases did not have an associated decline in their functional ability, any truly demented subjects were not included.[25] Furthermore, elevating the MMSE lower cut-off from 21 to 24 to exclude demented subjects with more certainty did not change the results. Also, the similar results that were found for education-adjusted cognition strata and the significant interaction of APOE-ϵ4 with the continuous MMSE score support the findings.

Our data further suggest that the ϵ4-related risk of memory decline in cognitively impaired subjects is particularly high in those older than 75 years, compared with the younger age stratum. Adjustments for education weakened the risk in those ≥75 years old, but the risk was still not lower than in those <75 years old. These results are surprising and in contrast with studies concerning the effect of age on the risk of AD associated with *APOE*-ϵ4.[4,5,26-28] Studies on AD report a lower *APOE*-ϵ4 allele frequency in older age groups,[29] suggesting selective survival by *APOE* status. In our study, the frequency of ϵ4 was not lower in cognitively impaired subjects older than 75 years, suggesting no selective attrition. This might explain the effect of ϵ4 on memory decline at higher ages in our study.

One of the strengths of this study is that we used data from a large longitudinal population-based study so that we could distinguish cognitively normal and impaired subjects from the same source population. Second, we used memory measures that are sensitive for early signs of Alzheimer-type dementia.[6,9] Moreover, these measures do not suffer from a ceiling effect, which would limit the capacity to detect decline in relatively well-functioning subjects, especially those with a high level of education. Finally, the wide age range of our study population made it possible to study the association between APOE-ϵ4 and memory decline both in subjects younger and older than 75 years.

A limitation of our study is that our stringent definition of memory decline resulted in rather small numbers of cases, in particular in the youngest cognitively impaired subgroup. We could not detect an association between APOE-ϵ4 and memory decline in this subgroup, possibly because of insufficient power. Nevertheless, in the oldest cognitively impaired subgroup we found an association between APOE-ϵ4 and memory decline.

Our study showed that the association between APOE-ϵ4 and memory decline was modified by baseline cognition. Only cognitively impaired APOE-ϵ4 carriers were at higher risk of memory decline compared with non-ϵ4 carriers, in particular those ϵ4 carriers who were older than 75 years. Contrary to AD studies, our study suggests that the effect of APOE-ϵ4 on memory decline does not decrease at higher ages. This finding raises the question whether subjects who show memory decline at older ages are at high risk for developing AD. It became clear from many studies that contributing factors other than *APOE*-ϵ4 are necessary to develop AD.[5] The important role of APOE-ϵ4 on memory decline at advanced age in this study suggests that enrichment with APOE-ϵ4 does not imply, in itself, development of AD.

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