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Memory complaints and APOE- ϵ 4 accelerate cognitive decline in cognitively normal elderly

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Article abstract—*Objective:* To investigate to what extent subjective memory complaints and APOE- ϵ 4 allele carriage predict future cognitive decline in cognitively intact elderly persons, by evaluating both their separate and combined effects. *Methods:* We selected 1,168 subjects from the population-based Longitudinal Aging Study Amsterdam who were 62 to 85 years of age and had no obvious cognitive impairment at baseline (Mini-Mental State Examination [MMSE] score, ≥ 27). Memory complaints and APOE phenotypes were assessed at baseline. MMSE, the Auditory Verbal Learning Test (memory: immediate recall and delayed recall), and the Alphabet Coding Task-15 (information processing speed) were used to study cognitive decline. Follow-up data were collected after 3 and 6 years. Data were analyzed with generalized estimating equations, adjusted for age, sex, education, and depression. *Results:* Baseline memory complaints were reported by 25.5% of the cognitively intact elderly persons. Overall, 25.3% of the subjects were carriers of at least one APOE- ϵ 4 allele. Memory complaints were associated with a greater rate of decline in all cognitive measures, except immediate recall. In addition, APOE- ϵ 4 allele carriers had a greater rate of cognitive decline shown by MMSE scores and slower information processing speeds after 6 years. The effects of both memory complaints and APOE- ϵ 4 allele carriage were additive: subjects with both factors had a two times higher cognitive decline than did subjects without both factors. *Conclusions:* Both memory complaints and APOE- ϵ 4 allele carriage predict cognitive decline at an early stage. This finding highlights the importance of subjective memory complaints, which are important even at an early stage when objective tests are still unable to detect cognitive deficits and are especially important for elderly carriers of the APOE- ϵ 4 allele because they have an additional risk.

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Elderly persons with memory complaints are often depressed.^{1,2} However, many population-based studies have reported that subjective memory complaints may predict future dementia.^{3–6} Memory complaints also predict faster cognitive decline in elderly persons with mild cognitive impairment⁷ as well as in elderly persons with normal cognition.⁸ It is important to know which elderly persons will develop mild cognitive impairment as an early stage of dementia, because intervention may soon be feasible.⁹ Because memory complaints can be easily assessed, they can identify persons who are at risk.

Small et al.¹⁰ studied individuals with mild memory complaints and found a higher proportion of memory complaints among APOE- ϵ 4 allele carriers than among non-APOE- ϵ 4 allele carriers. The APOE- ϵ 4 allele is the major known genetic risk factor for AD¹¹ and has been associated with objective cognitive decline.^{12–17} Based on the findings of the cross-sectional study by Small et al.,¹⁰ prospective studies should include both APOE- ϵ 4 allele carriage

and subjective memory complaints to determine how well these measures predict future cognitive decline.

We assessed to what extent the combination of subjective memory complaints and APOE- ϵ 4 allele carriage can predict future cognitive decline in cognitively intact subjects. Our subjects were from a large population-based cohort of older persons who were followed up for 6 years. Data were collected at study entry and after 3 and 6 years.

Methods. *Study sample.* Subjects were participants in the Longitudinal Aging Study Amsterdam, a population-based study of 3,107 subjects aged 55 to 85 years.¹⁸ The sampling and data collection procedures have been described elsewhere in detail.^{19,20} In summary, a random sample stratified by age and sex was drawn from the population registries in three geographic areas of the Netherlands. Stratification of the sample by age and sex according to expected 5-year mortality was performed to ensure sufficient sample sizes within age and sex strata for longitudinal analyses. Trained interviewers interviewed subjects at home. The local medical ethics commit-

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tee approved the study. All respondents gave informed consent at the start of the study, after the study was described completely to the subjects.

The study design involved additional medical testing for subjects 62 years of age and older ($n = 2,064$). Blood samples, from which the *APOE* phenotype could be determined, were obtained from 1,743 subjects (84.4%); the *APOE* phenotype could not be determined for 321 subjects because they did not agree to give blood. From this group, we selected subjects with normal cognition (i.e., no obvious cognitive impairment) at baseline, based on the cutoff score of the Mini-Mental State Examination (MMSE) of ≥ 27 .²¹ This selection resulted in 1,168 subjects in the baseline sample.

At the first follow-up after 3 years, 945 subjects (80.9%) took part in the study, and 223 subjects were lost to follow-up. At the second follow-up after 6 years, another 159 subjects were lost to follow-up, leaving 786 subjects (67.3%) with measurements on three occasions. Of the 382 subjects who were lost to follow-up after 6 years, 225 (19.3%) had died, 49 (4.2%) were too ill to be interviewed, 78 (6.7%) refused, 5 (0.4%) could not be contacted, and 25 (2.1%) had an unknown reason. Longitudinal analyses included data from 958 subjects that were collected at baseline and at either the first or the second follow-up.

Cognitive performance. Overall cognitive function was measured with the MMSE.²²

Memory was measured with an abbreviated version of the Auditory Verbal Learning Test (AVLT) reported by Rey.²³ We used three learning trials instead of five learning trials in AVLT to reduce the test burden for the respondent. In each trial, the interviewer read aloud a list of 15 words, after which the respondents recalled as many words as they could. We noted the number of correctly recalled words (points). Words mentioned by the respondents that were not on the AVLT word list were not counted. Furthermore, words that were mentioned more than once by the respondents were counted only once (each trial). After an interval of ≈ 20 minutes, during which a different nonverbal task was performed, the respondents were asked to recall as many words as possible (delayed recall). Immediate recall (scored during the third trial) and delayed recall were derived from this test. At the first follow-up, a parallel version of the AVLT was used. The parallel versions were validated and tested on parallelism.²⁴ At the second follow-up, the baseline version was used again.

Information processing speed was measured with an adapted version of a letter substitution task, the Alphabet Coding Task-15.²⁵ For this task, 15 combinations of two characters are shown in a row of double boxes (the substitution key). The test also includes rows of double boxes in which only the upper boxes contain characters and the lower boxes are empty. The respondent had to name the missing characters corresponding to the characters in the upper boxes (using the substitution key) as quickly and accurately as possible. The task consisted of three identical 1-minute trials. The score from each trial consisted of the number of completed characters. The mean score for the three trials was used in the analyses.

Memory complaints. Memory complaints were reported by one simple question, "Do you have problems with your memory?" Answers were coded yes or no. This one

question has been previously proven to be a sensitive and valid method to assess memory complaints and to predict objective cognitive impairment and dementia.^{7,8,26-28}

***APOE* phenotype.** Serum samples were obtained and frozen at -80°C until determination of the *APOE* phenotype. The *APOE* phenotype was determined by isoelectric focusing of serum samples stripped of lipids, followed by immunoblotting.²⁹ Subjects were classified as *APOE*- $\epsilon 4$ allele carriers if the *APOE*- $\epsilon 4$ isoform (phenotypes $\epsilon 2/4$, $\epsilon 3/4$, and $\epsilon 4/4$) was found and as non-*APOE*- $\epsilon 4$ allele carriers if the *APOE*- $\epsilon 4$ isoform (phenotypes $\epsilon 2/2$, $\epsilon 2/3$, and $\epsilon 3/3$) was not found.

Putative confounders. The analyses of memory complaints and cognitive decline were adjusted for the demographic variables age, sex, and education. Data on age and sex were derived from the population registries at baseline. Education was assessed by asking the respondent for the highest educational level completed, which was converted into the total number of years of education (range, 5 to 18 years).

Furthermore, analyses were adjusted for depression to exclude the possibility that underlying depression caused an association between complaints and cognitive decline. Depression has frequently emerged as the most prominent factor associated with memory complaints.^{5,30,31} In addition, depression is associated with cognitive decline.³²⁻³⁴ Depression was assessed with the Center for Epidemiologic Studies Depression Scale, a 20-item self-reported scale (range, 0 to 60) designed to measure depressive symptomatology in the general population. We used the generally applied cutoff score of ≥ 16 to identify clinically relevant depressive subjects.^{35,36}

Data analysis. Baseline characteristics were compared for subjects with and without memory complaints. Differences in *APOE* allele carriage, sex, and depression were evaluated with the χ^2 test. Differences in the continuous variables age and education and each cognition score were calculated by the Student's *t*-test for independent samples.

The associations between baseline memory complaints and *APOE*- $\epsilon 4$ allele carriage and cognitive decline during the 6-year follow-up were analyzed with generalized estimating equations (GEE).^{37,38} The regression models were adjusted for age, sex, education, and depression. An important feature necessary for longitudinal analyses is that GEE take into account the dependency of repeated observations within persons. This dependency is added to the analyses by assuming a certain correlation structure in the repeated observations of the outcome variable. Here, an exchangeable correlation structure was assumed, meaning that the correlation was constant between any two cognitive scores for a person.

Moreover, an advantage of GEE is that they include subjects regardless of missing values. Thus, subjects who were lost to follow-up after two measurements also were included in the analysis. This practice reduces bias that might have arisen from a differential loss to follow-up of more cognitively impaired elderly persons. Because we were interested in the rate of cognitive decline, the ascertainment of which needs two measurements, subjects with data on only one measurement were excluded from the analysis.

Because the observed data showed a linear trend for MMSE score and information processing speed, the regres-

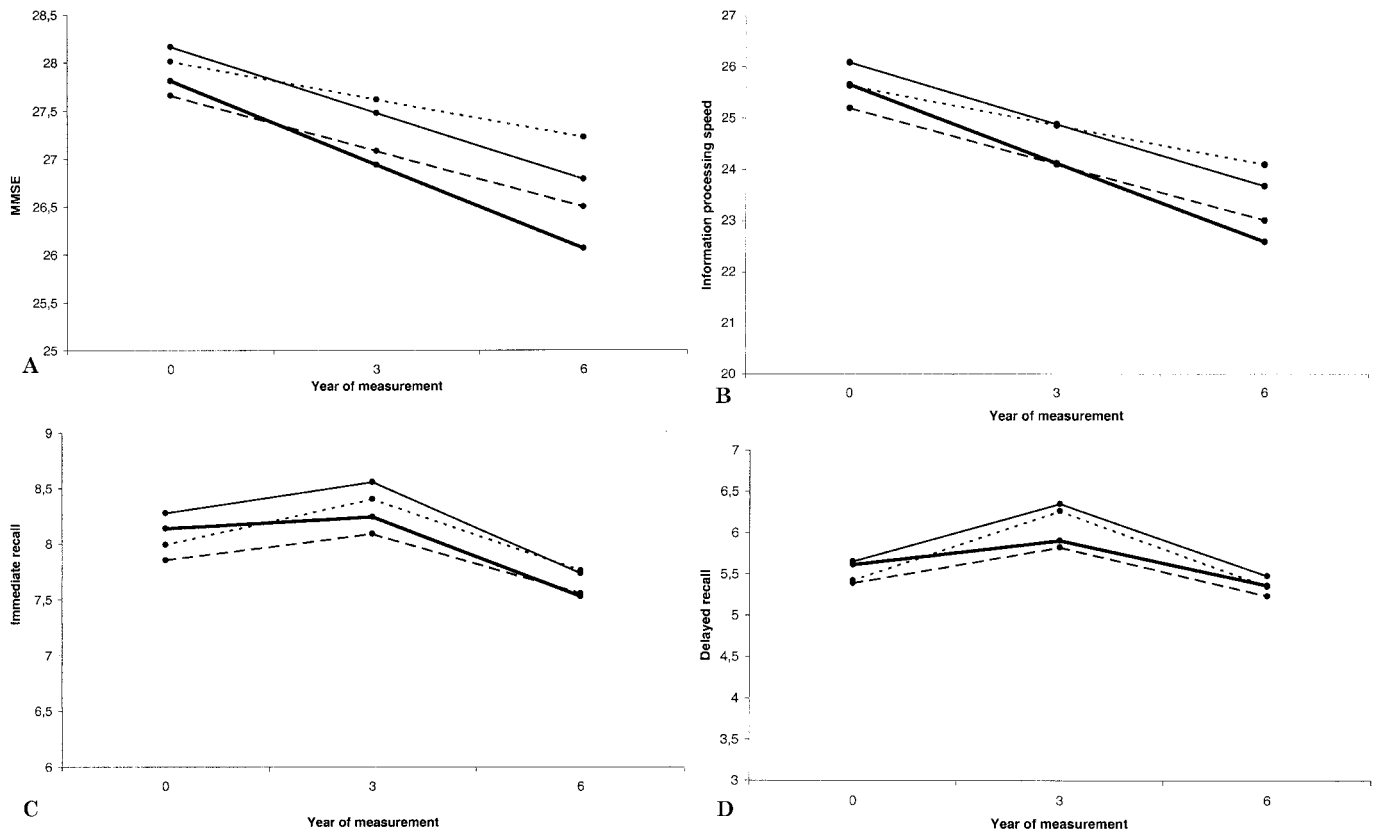


Figure. Six-year change in cognitive test scores according to memory complaints and APOE-ε4 allele carriage for elderly persons. Models of generalized estimating equations that were adjusted for age, sex, education, and depression were used to calculate data. Dotted line = subjects without memory complaints and without APOE-ε4 allele carriage ($n = 536$); solid line = subjects without memory complaints and with APOE-ε4 allele carriage ($n = 183$); dashed line = subjects with memory complaints and without APOE-ε4 allele carriage ($n = 174$); thick solid line = subjects with both memory complaints and APOE-ε4 allele carriage ($n = 65$). (A) Mini-Mental State Examination (MMSE) score. There was a significant time effect on APOE-ε4 allele carriage ($b = -0.29$; 95% CI, -0.49 to -0.09). (B) Information processing speed. There was a significant time effect on memory complaints ($b = -0.33$; 95% CI, -0.62 to -0.04) and a significant time effect on APOE-ε4 allele carriage ($b = -0.44$; 95% CI, -0.71 to -0.16). (C) Immediate recall. (D) Delayed recall. There was a significant time effect on memory complaints ($b = -1.50$; 95% CI, -2.72 to -0.29).

sion lines in GEE were modeled with a linear function with time. For both immediate recall and delayed recall, the curve of the observed data could best be modeled with a quadratic function with time. Based on the models of GEE, the adjusted cognitive scores were calculated. These scores are presented in the figure, A through D.

In addition, we determined how many study subjects met criteria for age-associated cognitive decline (AACD) at the 6-year follow-up. AACD is defined by a decline of >1 SD in any area of cognitive functioning compared with that for age-matched controls. This criterion is consistent with previously established consensus guidelines.³⁹ In a population-based study sample, AACD was shown to have a higher predictive value for dementia and to be more reliable than were criteria for mild cognitive impairment.⁴⁰ Differences between memory complaints and APOE-ε4 allele carriage were tested by the χ^2 test.

Results. Subjects who were lost to follow-up were significantly older, had lower scores on all cognition tests, and were more likely to be men and to be depressed than were subjects who were followed up (data not shown). Loss to follow-up was not associated with memory complaints

($\chi^2 = 0.88$, $df = 1$, $p = 0.35$) or APOE-ε4 allele carriage ($\chi^2 = 0.001$, $df = 1$, $p = 0.98$).

Baseline memory complaints were reported by 25.5% of the cognitively intact elderly persons (table 1). Among subjects with memory complaints, there was a slightly but not significantly higher proportion with APOE-ε4 allele carriage. A significantly higher proportion of subjects with memory complaints was depressed at baseline. Subjects with memory complaints were slightly but significantly older. The years of education and baseline scores on the cognitive tests were similar for subjects with and without memory complaints.

The cognitive decline over 6 years for cognitively normal subjects with and without memory complaints at baseline and for subjects with and without APOE-ε4 allele carriage is presented (see the figure), as calculated from the adjusted models of GEE. Subjects with memory complaints had lower cognitive scores on all three measurements than did those without memory complaints. On average, all groups had worsening of performance over the 6 years of follow-up. MMSE scores for subjects without either risk factor declined 0.8 point in 6 years. MMSE scores for subjects with only memory complaints declined 1.2 points in 6

Table 1 Baseline characteristics of 1,168 cognitively normal elderly persons (MMSE ≥ 27) with and without memory complaints in a study of the extent to which memory complaints and APOE- $\epsilon 4$ allele carriage predict cognitive decline

Characteristic	Memory complaints (n = 298)	No memory complaints (n = 870)	χ^2 (df = 1) or t (df = 1,166)	p Value
APOE- $\epsilon 4$ allele carriage, % (n)	26.8 (80)	24.8 (216)	0.48	0.49
Men, % (n)	53.7 (160)	50.3 (438)	1.00	0.32
Depression,* % (n)	18.0 (53)	8.3 (72)	21.47	<0.001
Mean age, y (SD)	72.8 (6.7)	71.8 (6.4)	-2.24	0.03
Mean education, y (SD)	9.6 (3.6)	9.1 (3.3)	-1.84	0.07
Mean MMSE score (SD)†	28.3 (1.1)	28.4 (1.0)	1.01	0.31
Mean information processing speed (SD)‡	24.4 (6.7)	25.2 (6.5)	1.71	0.09
Mean immediate recall score (SD)§	7.7 (2.6)	8.0 (2.4)	1.82	0.07
Mean delayed recall score (SD)§	5.2 (2.5)	5.4 (2.6)	1.04	0.30

* Data for five subjects were missing.

† Range, 27–30.

‡ Range, 5.0–43.0.

§ Range, 0–15.

MMSE = Mini-Mental State Examination.

years, and those for subjects with only APOE- $\epsilon 4$ allele carriage declined 1.4 points. Subjects with both risk factors had the greatest rate of decline in MMSE scores (1.7 points) in 6 years. The analysis of information processing speed produced results similar to those of the analysis of MMSE scores: subjects with both risk factors had a two times higher decline than did subjects without both factors (decline of 3.1 points versus 1.5 points, respectively). Thus, both factors are additive (i.e., subjects with memory complaints who carry the APOE- $\epsilon 4$ allele have the greatest rate of decline) (see the figure).

Scores of immediate recall and delayed recall, derived from the memory test, were increased at the 3-year follow-up and then declined to values lower than baseline scores at the 6-year follow-up (see the figure, C and D). Scores for subjects with memory complaints were lower at the 3- and 6-year follow-ups than were those for subjects without memory complaints. Immediate recall showed that APOE- $\epsilon 4$ allele carriers had higher scores at baseline than did subjects without APOE- $\epsilon 4$ allele carriage, which declined to scores for subjects without APOE- $\epsilon 4$ allele carriage at the 6-year follow-up. Delayed recall revealed that subjects with and without APOE- $\epsilon 4$ allele carriage had no obvious differences.

The test statistics of the adjusted models of GEE revealed that memory complaints were slightly but not sig-

nificantly associated with a decline in the MMSE score (b = -0.19; 95% CI, -0.40 to 0.03). Memory complaints were significantly associated with a decline in information processing speed (b = -0.33; 95% CI, -0.62 to -0.04) and delayed recall (b = -1.50; 95% CI, -2.72 to -0.29) but not with a decline in immediate recall (b = -0.60; 95% CI, -1.86 to 0.66). APOE- $\epsilon 4$ allele carriage was significantly associated with a decline in the MMSE score (b = -0.29; 95% CI, -0.49 to -0.09) and information processing speed (b = -0.44; 95% CI, -0.71 to -0.16) but not with a decline in immediate or delayed recall.

Table 2 shows the proportion of subjects with AACD in 6 years. Overall, 33.0% of the subjects met criteria for AACD at the 6-year follow-up: 47.7% of the subjects with memory complaints and APOE- $\epsilon 4$ allele carriage had AACD compared with 28.7% of the subjects without both memory complaints and APOE- $\epsilon 4$ allele carriage (p = 0.004).

Discussion. This study shows the following: 1) both subjective memory complaints and APOE- $\epsilon 4$ allele carriage independently predict future objective cognitive decline at an early stage when cognitive tests are unable to detect deficits, and 2) both factors have an additive effect on cognitive decline. These

Table 2 Proportion of 958 elderly subjects with AACD at the 6-year follow-up in a study of the extent to which memory complaints and APOE- $\epsilon 4$ allele carriage predict cognitive decline

Characteristic	Memory complaints and APOE- $\epsilon 4$ allele carriage (n = 65)	Memory complaints and no APOE- $\epsilon 4$ allele carriage (n = 174)	No memory complaints and allele carriage APOE- $\epsilon 4$ (n = 183)	No memory complaints and no APOE- $\epsilon 4$ allele carriage (n = 536)
AACD, % (n)*	47.7 (31)	38.5 (67)	35.0 (64)	28.7 (154)

* Significant difference among the four groups (χ^2 [df = 3] = 13.47, p = 0.004).

AACD = age-associated cognitive decline.

findings imply that both factors may add to the identification of a high-risk profile for elderly subjects with mild cognitive impairment, which may aid the early detection of AD. Our study showed that almost 50% of the cognitively intact *APOE-ε4* allele carriers with memory complaints had AACD within 6 years. It is likely that about 30% of these subjects will have dementia within another 3 years.⁴⁰

We selected subjects with no obvious cognitive impairment at baseline from a large longitudinal population-based study; follow-up measurements were obtained at 3 and 6 years. We assessed cognition by measures sensitive to cognitive decline. In addition, we combined these measures to study the rates of subjects who had AACD, which has been shown to be predictive for dementia in the population.⁴⁰ Furthermore, we assessed memory problems with one simple question that appeared to be a sensitive predictor of objective cognitive decline in cognitively normal elderly persons.⁸ If symptoms of dementia already exist, the caregiver's report on memory problems seems to be more reliable for diagnosing dementia than does the subject's report.^{41,42}

Most population-based longitudinal studies have reported a positive association between memory complaints and dementia^{3-5,8} and cognitive decline.^{43,44} A community study with 7 to 8 years of follow-up⁴³ explained that the previously reported negative association⁴⁵ became positive when the data were reanalyzed by a more sophisticated method. Only one study⁴⁶ found that memory complaints were not predictive of a 3-year cognitive decline, but this study was based on a cognitive screening test, the Short Portable Mental Status Questionnaire (which may not be sensitive enough to measure cognitive decline).

The cited studies on cognitive decline all included cognitively impaired elderly persons in their samples. A community-based study comparing cognitively impaired elderly persons with cognitively normal elderly persons⁷ stated that memory complaints predicted memory decline only in cognitively impaired elderly persons and not in those with normal cognition. The 1-year follow-up in that study was probably too short to detect changes in cognitively normal elderly persons (with tests that were not sensitive enough for this purpose). Our study shows that memory complaints can indeed significantly predict cognitive decline in cognitively intact elderly persons (i.e., elderly persons in whom impairment cannot be detected with objective measures). Because the rate of decline is greater among persons with memory complaints, the difference between these persons and persons without memory complaints increases every year. Consequently, the cognitive differences may not be significant after 1 year but will be after 3 and 6 years. These results are consistent with those of a community-based study;⁸ this study showed that memory complaints significantly predicted the incidence of AD at 3 years

among elderly persons with normal cognition at baseline.

In a previous study,⁴⁷ we showed that *APOE-ε4* allele carriage was associated with a decline in information processing speed rather than a decline in memory. Information processing speed may be thought of as a lower-order cognitive function, necessary for memory functioning.⁴⁸ In addition, the Alphabet Coding Task-15 also includes memory components.²⁵ The memory test clearly shows a learning effect after 3 years of follow-up. This learning effect is well established and has been previously described.^{47,49} However, scores decline during the following 3 years, and after 6 years, scores decline to values lower than those at baseline.

The only study on *APOE-ε4* allele carriage and memory complaints so far¹⁰ reported that *APOE-ε4* allele carriers are more likely to complain about their memory than are noncarriers. In contrast, memory complaints were not associated with *APOE-ε4* allele carriage in the cognitively intact subjects in our study. This finding is in accordance with expectations, because subjects do not know whether they carry the allele. Surely the *APOE-ε4* allele carriers in the former study¹⁰ had more reason to complain, because they also had lower objective cognitive scores. It is likely that the study sample was biased because of selection, which is suggested by the high proportion of *APOE-ε4* allele carriers and the high proportion of family history of AD in that study. A known family history of AD could be an alternative reason for earlier memory complaints.

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