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published in

Stroke

2000

DOI (link to publisher)

[10.1161/01.STR.31.10.2431](https://doi.org/10.1161/01.STR.31.10.2431)

document version

Publisher's PDF, also known as Version of record

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citation for published version (APA)

Dik, M. G., Deeg, D. J. H., Bouter, L. M., Corder, E. H., Kok, A., & Jonker, C. (2000). Stroke and apolipoprotein E (4 are independent risk factors for cognitive decline: a population-based study. *Stroke*, 31, 2431-6.
<https://doi.org/10.1161/01.STR.31.10.2431>

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M. G. Dik, D. J. H. Deeg, L. M. Bouter, E. H. Corder, A. Kok and C. Jonker

Stroke 2000, 31:2431-2436

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ISSN: 1524-4628

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Stroke and Apolipoprotein E ϵ 4 Are Independent Risk Factors for Cognitive Decline

A Population-Based Study

M.G. Dik, MSc; D.J.H. Deeg, PhD; L.M. Bouter, PhD; E.H. Corder, PhD;
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Background and Purpose—Stroke and apolipoprotein E ϵ 4 (ApoE ϵ 4) are individually important risk factors for cognitive decline, including Alzheimer disease. It has been suggested that ApoE ϵ 4 multiplies the risk for cognitive decline following stroke. In a population-based sample, using well-defined sensitive cognitive measures, this study investigates whether cognitive decline following stroke is worse for patients who carry the ApoE ϵ 4 allele.

Methods—Subjects were participants in the Longitudinal Aging Study Amsterdam (LASA). The sample consisted of 1224 subjects, aged 62 to 85 years, who participated in the 3-year follow-up examination and for whom ApoE and stroke data were complete. We assessed cognitive decline using the Mini-Mental State Examination, the Auditory Verbal Learning Test (memory: immediate and delayed recall), and the Coding Task (information processing speed). The effects of stroke and ApoE ϵ 4 on cognitive decline were evaluated with ANOVA and multiple logistic regression analysis, adjusted for age, sex, education, and baseline cognition.

Results—A synergistic effect modification for stroke and ApoE ϵ 4 on cognitive decline was not observed. Unexpectedly, instead, stroke patients carrying the ϵ 4 allele demonstrated a nonsignificantly lowered risk for Mini-Mental State Examination decline (OR=0.3; 95% CI 0.1 to 1.1). ApoE ϵ 4 was associated with declines in information processing speed (OR=1.5; 95% CI 1.1 to 2.1) and small declines for immediate and delayed recall.

Conclusions—Stroke and ApoE ϵ 4 may impair cognition through distinct nonsynergistic mechanisms. The slowing of information processing speed for ApoE ϵ 4 carriers was more evident than impairment in memory. (*Stroke*. 2000;31:2431-2436.)

Key Words: apolipoproteins ■ cognition ■ longitudinal studies ■ population ■ stroke

Stroke often results in cognitive impairment and decline.^{1,2} The relative risk for dementia within 4 years of ischemic stroke is 5.5, even after exclusion of patients who were demented within 3 months.³ Stroke affects many cognitive processes. General slowing in information processing and attentional deficits are prominent.⁴ The decline is sometimes progressive, leading to dementia with postmortem Alzheimer pathology.⁵

The established major genetic risk factor for cognitive decline in the elderly and for late-onset Alzheimer disease is the ϵ 4 allele for the apolipoprotein E (ApoE) gene located on chromosome 19.^{6,7} The effects of ApoE ϵ 4 seem to be most prominent on specific measures of memory function.^{8,9} Decline in memory, especially delayed recall, is an early indicator of Alzheimer disease, especially in patients with ApoE ϵ 4.^{10,11}

Taken together, both stroke and ApoE ϵ 4 are associated with cognitive decline. Furthermore, stroke and ApoE ϵ 4 may

be related to cognitive decline in a complex relationship, possibly similar to the relationship that has been proposed between subclinical cardiovascular factors, ApoE ϵ 4, and cognitive decline.¹² Slooter et al¹³ posit that the risk of ApoE ϵ 4 on cognitive decline is independent and not mediated via atherosclerosis. However, ApoE ϵ 4 seems to modulate the effects of atherosclerosis on cognitive decline. Haan et al¹² showed that ApoE ϵ 4 increased the risk of cognitive decline associated with subclinical cardiovascular disease. They did not further explore the modifying role of ApoE ϵ 4 on the association between stroke and cognitive decline. Since many subclinical cardiovascular factors are risk factors for stroke,¹⁴ such modification is plausible. Synergy between stroke and ApoE ϵ 4 in regard to cognitive decline, measured by the Mini-Mental State Examination (MMSE), has been reported by Kalmijn et al¹⁵ among 353 community-living elderly men but has not been confirmed. Recently, Zhu et al¹⁶ did not find

Received April 4, 2000; final revision received June 12, 2000; accepted July 3, 2000.

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a multiplicative effect for stroke and ApoE $\epsilon 4$ on the risk of dementia in 1301 subjects in the Kungsholmen cohort.

The purpose of this study is to examine the effect modification by ApoE $\epsilon 4$ of the association between stroke and cognitive decline in a large population-based study, with the use of specific measures sensitive to cognitive decline.

Subjects and Methods

Study Sample

Subjects were participants in the Longitudinal Aging Study Amsterdam (LASA), a population-based study among 3107 subjects aged 55 to 85 years.¹⁷ The sampling and data collection procedures have been described elsewhere in detail.^{18,19} In summary, a random sample stratified by age and sex was drawn from the population registries in 3 geographic areas of the Netherlands. Sample selection was stratified by age and sex according to expected 5-year mortality to ensure sufficient sample sizes for longitudinal analyses within age and sex strata. Subjects were interviewed at home by trained interviewers. Approval for the study was given by the local medical ethics committee, and all respondents gave informed consent at the start of the study.

For the present study, the study design involved additional medical testing for subjects aged 62 years and older ($n=2064$). Follow-up measurements were completed for 1406 subjects (68.1%) after an average of 3.1 (SD 0.2) years. Of the 658 subjects who were lost to follow-up, 320 (15.5% of 2064 subjects) had died, 8 (0.4%) could not be contacted, 107 (5.2%) were too ill to be interviewed, and 223 (10.8%) refused.

For 167 of the 1406 subjects, ApoE could not be phenotyped because no blood was available from these subjects (ie, they did not agree to give blood). In addition, for 15 subjects information on whether a stroke had occurred was missing. Therefore, our present study sample consisted of 1224 respondents who participated in the follow-up measurement after 3 years and for whom the ApoE and stroke data were complete.

Cognitive Performance

Overall cognitive function was measured with the MMSE.²⁰ Memory was measured with an abbreviated version of Rey's Auditory Verbal Learning Test (AVLT).²¹ We used 3 learning trials instead of 5 trials in Rey's 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 respondent that were not on the AVLT word list were not counted. Furthermore, words that were mentioned more than once by the respondent were counted only once (each trial). 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). Immediate recall (score on the third trial; range, 0 to 15) and delayed recall (range, 0 to 15) were derived from this test. At follow-up, a parallel version of the AVLT was used. The parallel versions, which are used in treatment research,²² were validated and tested on parallelism.²³

Information processing speed was measured with the Coding Task.²⁴ The task consisted of 3 identical trials, each lasting 1 minute, in which the respondent had to combine 2 characters according to a given example. The respondent was asked to work as quickly and accurately as possible. The score on each trial consisted of the number of completed characters. The mean score of the 3 trials (range, 4.7 to 43.0) was used in the analyses.

Apolipoprotein E

Serum samples were obtained and frozen at -80°C until determination of ApoE phenotype. The ApoE phenotype was determined by isoelectric focusing of delipidated serum samples, followed by immunoblotting.²⁵ The distribution of the ApoE phenotypes was in Hardy-Weinberg equilibrium (ApoE $\epsilon 2/2$, 0.7%; $\epsilon 2/3$, 11.1%; $\epsilon 3/3$,

61.5%; $\epsilon 2/4$, 2.7%; $\epsilon 3/4$, 21.3%; $\epsilon 4/4$, 2.7%). ApoE status was classified as $\epsilon 4$ carriers for subjects with the ApoE $\epsilon 4$ isoform (phenotypes $\epsilon 2/4$, $\epsilon 3/4$, $\epsilon 4/4$) and as non- $\epsilon 4$ carriers for subjects without the ApoE $\epsilon 4$ isoform (phenotypes $\epsilon 2/2$, $\epsilon 2/3$, $\epsilon 3/3$).

Stroke

History of stroke was obtained by diagnosis of the respondent's general practitioner (GP). Subjects who reported a stroke although their GP did not report a stroke ($n=26$) were considered free of stroke. The GP was thought to have better knowledge of the stroke diagnosis, whereas inaccurate self-reports are possibly due to labeling of symptoms such as dizziness or fainting as a cerebrovascular problem.²⁶ When information from the GP was not available ($n=211$), stroke history was based on self-report. The agreement between the patient's self-report and the GP's information was moderate ($\kappa=0.56$). The patient's self-report was not dependent on cognitive impairment.²⁶

Our study included 53 subjects who had had a stroke before the start of our study and who participated at 3-year follow-up. Because the cognitive decline after stroke is thought to be a continuous process, we believed that it was important to also include the 22 stroke patients who had had a stroke during the follow-up period. This resulted in a total of 75 stroke patients available for longitudinal analyses.

Putative Confounders

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 total number of years of education (range, 5 to 18 years).

Because depression is associated with both stroke²⁷ and cognitive decline,^{18,28} depression was considered a putative confounder. Depression was assessed with the Center for Epidemiologic Studies Depression Scale. This is a 20-item self-report scale (range, 0 to 60) designed to measure depressive symptomatology in the general population. We used the generally applied cutoff score ≥ 16 to identify clinically relevant depressive subjects.^{29,30}

Stroke severity and time interval between stroke diagnosis and cognitive testing may be related to ApoE $\epsilon 4$.³¹ In addition, it is likely that these stroke features influence the cognitive decline.^{1,4} Therefore, we investigated whether these stroke features differed for $\epsilon 4$ versus non- $\epsilon 4$ carriers. Stroke severity was assessed by asking the GP whether the patient was limited in daily living because of the consequences of the stroke. If data from the GP were not available ($n=16$), self-report data were used. Response categories were on a 3-point scale, ranging from "not at all" (1) to "severe" (3). Furthermore, additional information on date of diagnosis was collected. The time interval between stroke diagnosis and baseline cognitive testing was calculated and categorized into <1 year, 1 to 3 years, and >3 years.

Data Analysis

Differences in baseline characteristics were evaluated between stroke patients and subjects without stroke. Differences in ApoE status, stroke features, and sex were evaluated with the χ^2 test. Differences in the continuous variables age and education and each cognition score were tested with the t test for independent samples.

Cognitive change was calculated for each subject as the difference between baseline score and follow-up score. The effects of stroke and ApoE $\epsilon 4$ on cognitive change were evaluated with multiple classification analysis by ANOVA, adjusted for age, sex, education, and baseline cognition (ie, the score of the specific cognitive test for which the change score was evaluated). The effect modification was evaluated by the product term Stroke \times ApoE $\epsilon 4$ at the 0.05 level of significance. If the product term was not significant, we omitted the term from the model.

In addition, reliable cognitive change was calculated according to the Edwards-Nunnally method, which takes into account the reliability of the cognitive test and regression to the mean.³² The change scores were dichotomized into "decline" and "no decline," with

TABLE 1. Characteristics of Subjects With and Without a Stroke Diagnosis*

Characteristic	Stroke+ (n=53)	Stroke- (n=1171)
ApoE ε4, % (n)	32.1 (17)	26.5 (310)
Men, % (n)	69.8 (37)	48.3 (566)
Depression, % (n)	15.1 (8)	11.9 (139)
Age, mean (SD), y	74.6 (6.7)	72.2 (6.6)
Education, mean (SD), y	8.5 (3.4)	9.0 (3.4)
MMSE, mean (SD)†	26.5 (2.3)	27.4 (2.3)
Immediate recall, mean (SD)‡	6.8 (2.5)	7.6 (2.6)
Delayed recall, mean (SD)‡	4.1 (2.6)	5.0 (2.7)
Information processing speed, mean (SD)§	20.2 (7.9)	24.0 (7.1)
Decline in MMSE, % (n)	28.3 (15)	18.9 (220)
Decline in immediate recall, % (n)	11.8 (6)	13.6 (155)
Decline in delayed recall, % (n)	19.6 (10)	9.7 (111)
Decline in information processing speed, % (n)	18.8 (9)	19.3 (215)

Some data on cognitive measures were missing.

*Fifty-three subjects had a history of stroke at the time of baseline examination.

†Range, 13–30.

‡Range, 0–15.

§Range, 4.7–43.0.

||Significant differences ($P \leq 0.05$), evaluated with the χ^2 test or t test.

$P < 0.10$ as statistical cutoff score. The analyses were performed with multiple logistic regression models. We evaluated the effect modification by including the product term Stroke×ApoE ε4 in the model. As with ANOVA, the product term was omitted from the model if the term was not significant ($P > 0.05$). The logistic regression models were adjusted for age, sex, education, and baseline cognition score.

Results

The 53 subjects with a stroke diagnosis at the time when first examined as part of the LASA cohort were significantly older and performed lower on each cognition test than the 1171 subjects without a diagnosis (Table 1). The proportion of ApoE ε4 carriers among the stroke patients was higher than among the nonpatients, but the difference was not significant. Stroke patients with ApoE ε4 had slightly lower baseline scores on MMSE and immediate and delayed recall tests than stroke patients without ApoE ε4 (data not shown).

Table 2 shows that stroke patients with (n=17) and without (n=36) the ε4 allele for ApoE did not differ significantly on stroke severity and time interval between stroke diagnosis and cognitive testing. Since depression was not associated with stroke (Table 1) and stroke severity and time interval since stroke diagnosis were not associated with ApoE status, these were not included in the multivariate analyses as putative confounders.

For the analyses of cognitive decline, the 22 incident stroke cases (10 ε4+; 12 ε4-) were added to the 53 subjects with a stroke diagnosis at baseline. This inclusion of incident stroke cases did not influence the results because the results of only prevalent strokes were comparable to the results with included incident strokes. Furthermore, the rates of cognitive

TABLE 2. Stroke Severity and Time Interval Between Diagnosis and Baseline Cognitive Testing for ApoE ε4 and Non-ε4 Patients*

	Stroke+ ApoE ε4+ (n=17)	Stroke+ ApoE ε4- (n=36)
Limitations in daily living, % (n)†		
None	43.8 (7)	58.3 (21)
Slight	43.8 (7)	36.1 (13)
Severe	12.4 (2)	5.6 (2)
Stroke diagnosis, % (n)		
<1 y	23.5 (4)	27.8 (10)
1–3 y	35.3 (6)	25.0 (9)
>3 y	41.2 (7)	47.2 (17)

Differences ($P \leq 0.05$) were evaluated with the χ^2 test.

*Fifty-three subjects had a history of stroke at the time of baseline examination.

†Data of 1 subject were missing.

decline for prevalent and incident stroke patients were comparable (data not shown).

Change in cognition over time is described in Table 3 for the 4 groups based on stroke and ApoE status. The positive scores for the memory tests indicate improvement, consistent with a training effect on repeated testing.³³ Except for the MMSE ($P=0.01$), the interaction between stroke and ApoE ε4 was not significant ($P=0.26$ for immediate recall, $P=0.06$ for delayed recall, $P=0.82$ for information processing speed). Contrary to expectations, stroke patients without ApoE ε4 had the lowest changes in MMSE over time compared with the other groups. Consistent with expectations, stroke patients with ε4 showed greater declines in information processing speed than the other groups (−2.1 points versus −0.8 unadjusted; −2.0 versus −0.8 adjusted). However, this large difference did not reach statistical significance, possibly because of the small number of persons with both stroke and ε4.

When we considered the subjects unaffected by a stroke, the 300 carrying ApoE ε4 tended, as expected, to have more decline (or less improvement), as assessed by each cognitive measure, than the 849 who did not carry an ε4 allele. However, only the decline in information processing speed (−1.4 points versus −0.8) was statistically significant ($P=0.01$).

The odds ratios for cognitive decline over 3 years obtained from logistic regression models are shown in Table 4. Comparable to the results for continuous cognitive change (ANOVA), there was no interaction between stroke and ApoE ε4, except for the MMSE. Again contrary to expectation, stratified analyses for stroke revealed a nonsignificantly lowered risk for MMSE decline for ε4 carriers in the stroke group (OR=0.3; 95% CI 0.1 to 1.1). In the nonstroke group, the risk of MMSE decline for ε4 carriers was 1.3 (1.0 to 1.9). For decline in recall and processing speed, instead, the ε4 allele for ApoE increased the risk of decline from 20% to 50% (30% to 50% when estimated with adjustment for age and other potential confounders). This was significant for

TABLE 3. Cognitive Change (in Points) for Stroke and ApoE ϵ 4 Groups*

	Stroke+		Stroke-		P		
	ApoE ϵ 4+ (n=27)	ApoE ϵ 4- (n=48)	ApoE ϵ 4+ (n=300)	ApoE ϵ 4- (n=849)	Stroke \times ApoE ϵ 4†	Stroke	ApoE ϵ 4
Unadjusted							
MMSE‡§	-0.4	-1.6	-0.7	-0.5	0.01	0.02	0.25
Immediate recall	0.4	-0.2	0.2	0.3	NS	0.46	0.71
Delayed recall§	0.7	-0.3	0.5	0.7	NS	0.04	0.59
Information processing speed	-2.1	-1.3	-1.4	-0.8	NS	0.17	0.01
Adjusted¶							
MMSE‡	-0.3	-1.6	-0.8	-0.5	0.01	0.29	0.07
Immediate recall	0.0	0.1	0.2	0.2	NS	0.54	0.55
Delayed recall	0.1	0.2	0.5	0.6	NS	0.09	0.29
Information processing speed	-2.0	-1.4	-1.4	-0.8	NS	0.18	0.01

*The 22 patients with incident stroke were classified as Stroke+ in addition to the 53 stroke patients at baseline.

†If not significant, the interaction term was omitted from the model.

‡Significant effect modification stroke and ApoE ϵ 4 (Stroke \times ApoE ϵ 4) ($P\leq 0.05$).

§Significant effect stroke ($P\leq 0.05$).

||Significant effect ApoE ϵ 4 ($P\leq 0.05$).

¶Adjusted for age, sex, education, and baseline cognition score.

information processing speed: the odds of decline were 1.5-fold higher for ϵ 4 carriers (95% CI 1.1 to 2.1).

The complex pattern of risk for cognitive decline led us to further examine mortality for ϵ 4+ and ϵ 4- stroke patients. We examined mortality rates from baseline to 3-year follow-up and found that stroke patients with and without ϵ 4 had about the same risk of death.

Discussion

Our population-based longitudinal study supports independent effects for stroke and ApoE ϵ 4 on cognitive decline. This result differs from that reported by Kalmijn et al¹⁵ in that they found a multiplicative effect of stroke and ApoE ϵ 4 on cognitive decline, measured by the MMSE. Their finding

may be due to chance given the small size of that study (6 stroke patients carrying the ApoE ϵ 4 allele, compared with 27 stroke patients with ApoE ϵ 4 in our study). To account for differences in study design, we defined cognitive decline as a drop in the MMSE of >1 SD (>2 points) according to the definition in their study, but we found no multiplicative effect of stroke and ApoE ϵ 4 either (data not shown). Support for independent additive effects rather than a multiplicative effect of stroke and ApoE ϵ 4 was found in the population-based study on incident dementia by Zhu et al.¹⁶

It seems unlikely that the results found in our study derive from worse mortality in the stroke patients with ApoE ϵ 4 because mortality was not higher among stroke patients with ApoE ϵ 4 than in stroke patients without ApoE ϵ 4. A higher

TABLE 4. ORs (95% CI) of Cognitive Decline for Stroke and ApoE ϵ 4*

	Stroke \times ApoE ϵ 4†	Stroke	ApoE ϵ 4
Unadjusted			
MMSE‡§	0.3 (0.1-0.9)	2.5 (1.4-4.7)	1.3 (0.9-1.7)
Immediate recall	NS	0.9 (0.4-1.8)	1.2 (0.9-1.8)
Delayed recall	NS	1.8 (0.9-3.5)	1.3 (0.8-1.9)
Information processing speed	NS	1.5 (0.8-2.6)	1.5 (1.1-2.0)
Adjusted¶			
MMSE‡§	0.2 (0.1-0.9)	1.9 (1.0-3.7)	1.3 (1.0-1.9)
Immediate recall	NS	0.7 (0.4-1.6)	1.3 (0.9-1.9)
Delayed recall	NS	1.4 (0.7-2.9)	1.4 (0.9-2.1)
Information processing speed	NS	1.2 (0.7-2.1)	1.5 (1.1-2.1)

*The 22 patients with incident stroke were classified as Stroke+ in addition to the 53 stroke patients at baseline.

†If not significant, the interaction term was omitted from the model.

‡Significant effect modification stroke and ApoE ϵ 4 (Stroke \times ApoE ϵ 4) ($P\leq 0.05$).

§Significant effect stroke ($P\leq 0.05$).

||Significant effect ApoE ϵ 4 ($P\leq 0.05$).

¶Adjusted for age, sex, education, and baseline cognition score.

mortality among ApoE ϵ 4 stroke patients has been previously suggested in elderly subjects aged ≥ 75 years but has not been confirmed in younger samples.^{31,34} Another possible source of bias might have been introduced by differences in stroke features between ApoE ϵ 4 and non- ϵ 4 carriers. The severity of the stroke and the time interval between stroke diagnosis and baseline cognitive testing did not differ by ApoE ϵ 4 in our study and therefore could not explain the lack of an synergistic effect modification between stroke and ApoE ϵ 4 on cognitive decline.

Still, the finding that stroke patients without ApoE ϵ 4 showed faster decline on the MMSE than the other groups requires consideration. Most likely this is an artifact, possibly because of the skewed distribution of the MMSE and the small number of subjects in this particular group. In contrast, the rate of cognitive decline on information processing speed is highest for stroke patients carrying the ϵ 4 allele compared with the other groups.

Overall, ApoE ϵ 4 was also associated with decline in information processing speed rather than with memory decline. Although memory decline is known to be an early indicator of Alzheimer disease,^{10,11} slowing of information processing may be an even earlier indicator. This is supported by the processing-speed theory of Salthouse,³⁵ which postulates that slowing of information processing results in impairments of higher-order cognitive functions, such as memory and reasoning. Furthermore, the Coding Task was shown to also measure components of memory, in addition to information processing speed.³⁶ In a previous study⁹ we showed that ApoE ϵ 4 affected memory decline in cognitively impaired elderly but not in cognitively normal elderly. The proportion of cognitively normal elderly in the present study sample may have masked the effect of ApoE ϵ 4 on memory decline. Because the main interest of the present study was the effect of ApoE ϵ 4 in stroke patients, we did not distinguish cognitively impaired from cognitively normal subjects in this study. This would have led to numbers that were too small for analysis.

The strength of this study is that we used longitudinal data from a large population-based study. As a consequence, however, the stroke patients in this population-based study may be more heterogeneous than stroke patients in clinical studies. Moreover, more severe and complex stroke cases are prone to nonresponse and loss to follow-up because of a greater mortality of stroke patients during the study interval. The stroke cases in our study are survivors of stroke. Additional analyses showed, however, that the association between ApoE ϵ 4 and baseline cognition did not differ for nonsurvivors compared with survivors of stroke (data not shown).

A limitation of this study is that we do not have specific information on the type, size, and location of the stroke. The majority of cases will suffer from ischemic stroke.³¹ Size¹ and side⁴ of the stroke may affect cognitive decline. However, the severity of the stroke, which may be used as an indicator of stroke size, did not affect the association between ApoE ϵ 4 and stroke regarding cognitive decline in our study.

This population-based study could not confirm the suggestion that ApoE ϵ 4 modifies the effect of stroke on cognitive

decline. Recently, Haan et al¹² reported that ApoE ϵ 4 increased the effects of atherosclerotic disease on cognitive decline. Although vascular events such as stroke are commonly seen as near the end stage of atherosclerotic disease,³⁷ the mechanisms in the brain that cause cognitive decline after stroke may be different from the mechanisms that cause cognitive decline during atherosclerotic disease. ApoE ϵ 4 may affect cognitive decline in relation to atherosclerotic disease, but it may not affect cognitive decline following stroke. Our study suggests that stroke and ApoE ϵ 4 impair cognition through distinct pathogenic mechanisms.

Acknowledgments

LASA is funded by the Dutch Ministry of Health, Welfare, and Sports and the Vrije Universiteit. The study on ApoE and cognitive decline is supported by the Dutch Organization for Scientific Research (NWO). The contribution of Prof E. Corder, PhD, is supported by grant R37AG07198 from the National Institute on Aging (United States). We are grateful to the Immunochemisch Laboratorium of the Academic Hospital, Vrije Universiteit Amsterdam, directed by G.J. van Kamp, PhD, for ApoE phenotyping. We thank Prof P. Eikelenboom, MD, PhD, for his useful remarks on an earlier draft of this article.

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