Incidence of Dementia in Relation to Stroke and the Apolipoprotein E e4 Allele in the Very Old
Findings From a Population-Based Longitudinal Study

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Background and Purpose—Both stroke and the apolipoprotein E (APOE) e4 allele increase the risk of dementia. However, the interaction between stroke and APOE on dementia is still unclear. We addressed this topic by using a longitudinal design.

Methods—We followed up a community cohort of 1301 subjects aged ≥75 years, who did not have dementia at baseline. Among them, 92 subjects had a history of stroke (from 3 months to 16 years before baseline interview). After the 3-year follow-up, 224 dementia cases had been diagnosed. During the period of follow-up, 91 subjects had a first occurrence of stroke (incident stroke). The APOE genotype was known for 985 subjects. Cox proportional hazards regression models were constructed to estimate the risk for dementia in terms of relative risks (RRs) for stroke and the APOE e4 allele, with adjustment for age, sex, education, systolic blood pressure, antihypertensive medication use, and heart disease.

Results—In the entire study population, RRs for dementia related to history of stroke and incident stroke were 1.7 (95% CI, 1.1 to 2.6) and 2.4 (95% CI, 1.6 to 3.5), respectively, after adjustment for all potential confounders. Subjects with stroke that occurred within 3 years before baseline had RR of 2.4 (95% CI, 1.4 to 4.2), whereas those with stroke occurring >3 years before baseline had RR of dementia of 1.1 (95% CI, 0.6 to 2.3). Among those with APOE information, individuals with only history of stroke (that occurred within 3 years before baseline) had RR of 3.1 (95% CI, 1.4 to 6.6), individuals with only the APOE e4 allele had RR of 1.7 (95% CI, 1.1 to 2.5), and individuals with both factors had RR of 5.3 (95% CI, 2.1 to 13.4). The corresponding figures when incident stroke was examined instead of history of stroke were 2.3 (95% CI, 1.3 to 4.1), 1.7 (95% CI, 1.1 to 2.4), and 4.6 (95% CI, 2.0 to 10.6), respectively. The RR of interaction term for history of stroke and APOE e4 was 1.1 (95% CI, 0.3 to 3.8; P=0.8). The corresponding figure was 1.2 (95% CI, 0.4 to 4.4; P=0.7) for incident stroke and APOE e4. Furthermore, the RRs of dementia without any stroke and dementia with stroke in relation to APOE e4 were 1.6 (95% CI, 1.1 to 2.3) and 1.2 (95% CI, 0.6 to 2.4), respectively. In addition, the APOE e4 allele was not significantly related to the occurrence of stroke (RR=0.8; 95% CI, 0.5 to 1.5).

Conclusions—A relatively fresh stroke is a risk factor for dementia. APOE e4 increases the risk of dementia without stroke but not dementia with stroke. Our data do not support a multiplicative effect of stroke and the APOE e4 allele on the risk of dementia. However, both factors seem to have an additive effect on the risk of dementia. The APOE e4 allele does not increase the risk of stroke in this Swedish elderly population.

Key Words: apolipoproteins dementia stroke

Several studies have shown that the incidence of dementia is higher than expected in ischemic stroke patients compared with controls.1–6 The mechanisms underlying the relationship between stroke and dementia may be multiple.5,7 Stroke may be either direct or the main cause of dementia.8 In addition, stroke may act as a precipitating factor for degenerative dementia such as Alzheimer’s disease (AD).9 Furthermore, dementia and stroke may share common risk factors such as hypertension. Special attention has been paid to a genetic risk factor, the apolipoprotein E (APOE) gene,10,11 which has been suggested to carry the susceptibility to both stroke and dementia.

APOE is a plasma protein that plays an important role in the transport of cholesterol and other lipoproteins.12,13 The APOE has 3 common isoforms in plasma that are encoded by the 3 alleles (e2, e3, and e4) of a single gene on chromosome 19. The e4 allele has been found to be consistently associated with increased risk of AD, even in very old populations.14–19

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although the mechanisms are not quite understood. In contrast, the relationship between the APOE e4 allele and vascular dementia or dementia with stroke is controversial.11,17,19–28 In some studies, the APOE e4 allele has been associated with increased risk of vascular dementia,11,17,20–22 but other studies have failed to confirm this association.23–28 Finally, an ethnic variation of the APOE effect on dementia has been reported. The APOE e4 allele is not a significant risk factor for AD among blacks and Hispanics.29

The effect of APOE genotypes on the development of stroke has also been recently investigated. Compared with the e3 allele, the e4 allele is related to higher levels of serum total cholesterol and LDL cholesterol,30 and there is evidence of a role of the APOE e4 allele in atherosclerosis,31 which is a possible cause of stroke.32 However, inconsistent findings concerning the relationship between the APOE e4 genotypes and stroke have been reported. Both the APOE e4,33–34 and e235,36 alleles have been found to be related to an increased risk of ischemic stroke, whereas other studies have not found any association.37,38

There are few studies that examine the effect of interaction between APOE and stroke on the risk of dementia. In a population-based prospective study of 353 men aged 69 to 89 years, Kalmijn and coworkers39 suggested that cerebrovascular disease and the APOE e4 allele might have a synergistic effect on cognitive decline.

Few studies have directly focused on people aged ≥75 years, the age group that is more often and more severely affected by stroke and dementia. We investigated the Kungsholmen cohort aged ≥75 years to clarify the relations between stroke and the APOE e4 allele for dementia. Specifically, we tried to distinguish between stroke and APOE as independent or multiplicative risk factors for dementia.

**Subjects and Methods**

**Study Population**

The study population for this analysis is a total of 1301 dementia-free subjects at baseline who participated in the first follow-up of the Kungsholmen Project, which is a longitudinal study of aging and dementia. The details of the study design have been reported previously.39-40 In brief, the study base of the project consisted of all persons who lived in the Kungsholmen district of Stockholm and who had lived in the Stockholm area for an average of 63 years. A subject had to have been living in the Stockholm area for at least 6 years before the follow-up examination. Medical records and death certificates of these subjects were extensively reviewed. The diagnosis of dementia was confirmed using the following criteria: a history of stroke or incident stroke, and a clinical diagnosis of AD. A second group, questionable dementia, was used when there was evidence of memory impairment but dysfunction of a second cognitive ability was questionable. In a preliminary analysis, we found that both definite and questionable dementia were related to stroke and APOE e4 in a similar manner. Therefore, both categories were treated as dementia cases in the final analyses applied in the present study. Details of the clinical examination, diagnostic procedure, and primary results of age- and sex-specific incidence of dementia have been reported previously.42

**Identifying Incident Dementia**

Of the 1301 subjects, 987 (75.9%) were able to participate in the follow-up examination, which included physical, neurological, and psychiatric examinations, neuropsychological assessment, laboratory tests, and family interview. The examination was conducted between November 1990 and April 1992. There were 314 persons who died before the follow-up examination. The medical records and death certificates of these subjects were extensively reviewed. The Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) diagnostic criteria43 were used to define dementia. The cases fulfilling the criteria were defined as clinically definite dementia. A second category, questionable dementia, was diagnosed when there was evidence of memory impairment but dysfunction of a second cognitive ability was questionable. In a preliminary analysis, we found that both definite and questionable dementia were related to stroke and APOE e4 in a similar manner. Therefore, both categories were treated as dementia cases in the final analyses applied in the present study. Details of the clinical examination, diagnostic procedure, and primary results of age- and sex-specific incidence of dementia have been reported previously.42

**History of Stroke and Incident Stroke**

Information on stroke (International Classification of Diseases, Eighth Revision [ICD-8], codes 430 to 438) was derived from the Stockholm computerized inpatient register, which was started in 1969. In Sweden, >90% of patients who suffer from a stroke are admitted to a hospital.44 A previous study that examined the validity of the register data on stroke reported that 94% of hospitalized stroke cases were classified correctly.45 The cohort members in our study had lived in the Stockholm area for an average of 63 years. A subject was considered to have a history of stroke if he or she had any stroke event recorded in the register before the baseline interview. During the follow-up period, subjects with first-ever stroke of the stroke-free cohort were identified. The whole study population was divided into 3 groups: subjects with a history of stroke, with incident stroke, and with no stroke. Dementia with stroke was defined as demented cases with either a history of stroke or incident stroke.

**APOE Genotyping**

A standard polymerase chain reaction procedure was used for APOE genotyping,46 and the DNA was prepared from peripheral blood samples that were taken at baseline. The details of the procedure have been reported.46 APOE genotyping was undertaken for 75.7% (n=985) of the whole study population. We performed sensitivity analysis47 to ascertain potential bias due to the missing values of the APOE genotypes.

**Assessment of Other Covariates**

Subjects’ educational levels were based on formal schooling. Arterial blood pressure (systolic Korotkoff phase I and diastolic phase V) was measured with a mercury sphygmomanometer and with the subject in a sitting position after having rested for 5 minutes.48 Information on medication use was collected for the 2 weeks preceding the baseline interview.49 Use of both prescription and nonprescription drugs was queried, and medicine containers and prescription forms were inspected to verify this information. Anti-hypertensive drugs included all medicines potentially used for lowering blood pressure (Anatomical Therapeutic Chemical classification system50 codes C02, C03, and C07).

History and/or presence of heart disease (myocardial infarction [ICD-8 codes 410 to 412], cardiac dysrhythmia [ICD-8 code 427], and heart failure [ICD-8 code 428]) were detected from the Stockholm computerized inpatient register.

**Statistical Analysis**

Incidence rates of dementia were calculated by dividing the number of events by the number of person-years of follow-up. The follow-up time for nondemented individuals was determined from the date of the baseline interview to the date of the follow-up examination or death. For the demented individuals, half of this time was assumed
since dementia is such an insidious disease that it is difficult to determine the exact date of onset. We used Cox proportional hazards regression models to calculate the relative risk (RR) of developing dementia in relation to stroke and APOE genotype. First, only age (in years) and sex (female versus male) were included in the models; then all the potential confounders such as education (<8 versus ≥8 years), systolic pressure (2 dummy variables, <140 and >160 mm Hg, compared with 140 to 160 mm Hg), heart disease (yes versus no), antihypertensive medication use (yes versus no), age, and sex were entered. Since the results did not differ substantially, we have reported only the RRs from the models in which all the covariates were taken into account.

When the relationship between history of stroke, APOE e4 allele, and dementia was analyzed, several Cox models were constructed. Because of limited numbers, e2/e4, e3/e4, and e4/e4 were considered 1 group that was labeled e4, which was compared with the group of subjects without the e4 allele. First, history of stroke and the APOE e4 allele were included in separate models as potential risk factors for dementia. Then history of stroke and the APOE e4 allele were simultaneously included in the same models to examine the independent effect of these 2 factors on dementia. Third, 3 indicator variables representing subjects with only history of stroke, only the APOE e4 allele, and both history of stroke and the APOE e4 allele were included in the same model. Finally, to verify whether there was a synergistic effect of history of stroke and the APOE e4 allele on the risk of dementia, an interaction term for both factors was included in the model together with these 2 factors. All these models were repeated when incident stroke was studied instead of history of stroke. Persons with incident stroke were excluded when the relationship between history of stroke and dementia was studied and vice versa.

To investigate the relationship between the APOE e4 allele and dementia with and without stroke, 2 separate Cox models were constructed. Subjects with e3/e3 genotype as a reference group and subjects with any e4 and e2 (e2/e2, e2/e3) were included in the models.

Finally, sensitivity analysis for the missing values of APOE genotypes was performed by producing 2 extreme imputations. This analysis assumed that either all subjects with missing values of APOE genotypes had the e2 allele (imputation 1) or that all of them had the e4 allele (imputation 2). All of the analyses were repeated in these 2 imputations.

### Results

The mean age at baseline of the 1301 cohort members was 82.0 years (SD, 5.0); 76.1% were female. The mean baseline MMSE score was 26.6 (SD, 2.7). The mean follow-up interval of the cohort was 36.6 months, with a maximum of 63.1 months. Among the 987 who completed the clinical examination at follow-up, 199 were diagnosed as demented. Among the 314 subjects who died over the follow-up interval, 25 were diagnosed as demented. The availability of APOE genotype was 85% (840/987) in those who completed the follow-up examination and 46% (145/314) in those who died during the follow-up period.

Table 1 shows the baseline characteristics of the study population according to the occurrence of stroke.

### History of Stroke and Risk of Dementia

There were 92 subjects with a history of stroke recorded before baseline interview. These subjects had a significantly increased incidence of dementia (Table 2). Among the 92 subjects with a history of stroke, 45.7% (n=42) had had the stroke within 3 years before baseline, and 54.3% (n=50) had had the stroke >3 years before baseline. Subjects with stroke that occurred within 3 years before baseline had RR of 2.4 (95% CI, 1.4 to 4.2), whereas subjects with stroke occurring >3 years before baseline had RR of 1.1 (95% CI, 0.6 to 2.3).

### Incident Stroke and Risk of Dementia

There were 91 subjects whose first-ever stroke occurred during the follow-up period. The risk for dementia in relation to incident stroke was >2-fold (Table 2).
From the results reported above, we know that only stroke that occurred within 3 years before baseline interview was related to higher risk of dementia. Therefore, we analyzed the relationship among history of stroke, APOE e4, and dementia in 2 ways: including and excluding subjects with stroke occurrence >3 years before baseline. Stroke that occurred within 3 years before baseline and APOE e4 produced RRs of 3.0 (95% CI, 1.7 to 5.5) and 1.7 (95% CI, 1.2 to 2.4), respectively, when they were simultaneously included in the model together with all other covariables. Table 3 shows that history of stroke and APOE e4 were each significantly related to increased risk of dementia. Subjects with stroke that occurred within 3 years before baseline and APOE e4 had heavier risk of dementia than those with either of the 2 factors (Table 3, bottom). When incident stroke was studied instead of history of stroke, the adjusted RRs were 2.4 (95% CI, 1.5 to 3.9) and 1.7 (95% CI, 1.2 to 2.4), respectively, when they were simultaneously included in the model. As shown in Table 4, a pattern of the relationship among incident stroke, APOE e4, and dementia was seen that was similar to that shown in the bottom part of Table 3. We further investigated whether there was a synergistic effect between stroke and APOE e4 on the risk of dementia by including an interaction term in the Cox models. No significant multiplicative effect was seen when interaction terms were included in the models. The RRs of interaction terms for Table 3 (bottom) and Table 4 were 1.1 (95% CI, 0.3 to 3.8; P = 0.8) and 1.2 (95% CI, 0.4 to 4.4; P = 0.7), respectively.

**TABLE 2. Incidence and RR of Dementia According to Occurrence of Stroke**

<table>
<thead>
<tr>
<th></th>
<th>Without Stroke (n=1118)</th>
<th>History of Stroke (n=92)</th>
<th>Incident Stroke (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of dementia cases</td>
<td>170</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>Incidence per 1000 person-years</td>
<td>53.5</td>
<td>107.0</td>
<td>143.2</td>
</tr>
<tr>
<td>Adjusted RR (95% CI)</td>
<td>1.0 (reference)</td>
<td>1.7 (1.1–2.6)*</td>
<td>2.4 (1.6–3.5)*</td>
</tr>
</tbody>
</table>

*From 2 separate Cox models adjusted for age, sex, education, heart disease, systolic blood pressure, and antihypertensive medication use.

**APOE e4 Allele, Stroke, and Risk of Dementia**

From the results reported above, we know that only stroke that occurred within 3 years before baseline interview was related to higher risk of dementia. Therefore, we analyzed the relationship among history of stroke, APOE e4, and dementia in 2 ways: including and excluding subjects with stroke occurrence >3 years before baseline. Stroke that occurred within 3 years before baseline and APOE e4 produced RRs of 3.0 (95% CI, 1.7 to 5.5) and 1.7 (95% CI, 1.2 to 2.4), respectively, when they were simultaneously included in the model together with all other covariables. Table 3 shows that history of stroke and APOE e4 were each significantly related to increased risk of dementia. Subjects with stroke that occurred within 3 years before baseline and APOE e4 had heavier risk of dementia than those with either of the 2 factors (Table 3, bottom). When incident stroke was studied instead of history of stroke, the adjusted RRs were 2.4 (95% CI, 1.5 to 3.9) and 1.7 (95% CI, 1.2 to 2.4), respectively, when they were simultaneously included in the model. As shown in Table 4, a pattern of the relationship among incident stroke, APOE e4, and dementia was seen that was similar to that shown in the bottom part of Table 3. We further investigated whether there was a synergistic effect between stroke and APOE e4 on the risk of dementia by including an interaction term in the Cox models. No significant multiplicative effect was seen when interaction terms were included in the models. The RRs of interaction terms for Table 3 (bottom) and Table 4 were 1.1 (95% CI, 0.3 to 3.8; P = 0.8) and 1.2 (95% CI, 0.4 to 4.4; P = 0.7), respectively.

**TABLE 3. RR of Dementia According to Presence of History of Stroke and APOE e4 Allele**

<table>
<thead>
<tr>
<th>APOE e4</th>
<th>History of Stroke</th>
<th>No. of Subjects</th>
<th>No. of Dementia Cases</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke occurred at any time before baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>16</td>
<td>5</td>
<td>2.7 (1.1–6.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>251</td>
<td>44</td>
<td>1.7 (1.2–2.4)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>47</td>
<td>16</td>
<td>2.7 (1.6–4.8)</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>611</td>
<td>77</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Stroke occurred within 3 years before baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>10</td>
<td>5</td>
<td>5.3 (2.1–13.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>251</td>
<td>44</td>
<td>1.7 (1.1–2.5)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>21</td>
<td>8</td>
<td>3.1 (1.4–6.6)</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>611</td>
<td>77</td>
<td>1.0 (reference)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, education, heart disease, systolic blood pressure, and antihypertensive medication use.

**APOE e4 Allele and Risk of Dementia Without Stroke**

We further examined the relation between APOE genotype and dementia according to presence of stroke. Among the 162 dementia cases identified in those with APOE information, there were 121 patients without stroke and 41 with stroke. Table 5 shows the incidence and the RR for dementia with and without stroke in relation to the APOE genotype. APOE e4 was related to increased incidence of dementia without stroke but not dementia with stroke.

**APOE e4 Allele and Risk of Stroke**

Further analyses focused on subjects with APOE information, excluding those with stroke at baseline (n=63). Among the 60 patients whose stroke occurred during the follow-up period, 23.3% had the APOE e4 allele, which was similar to the frequency of the allele (29.1%) in those without stroke (P = 0.3). The APOE e4 allele was not significantly related to the occurrence of stroke (adjusted RR = 0.8; 95% CI, 0.5 to 1.5).

**Additional Analyses**

Very mild dementia cases among persons who screened positive (MMSE <24) still could be missed and therefore were included in the follow-up cohort. For that reason, all analyses were performed in the subpopulation of subjects with baseline MMSE ≥24 (n=1212). Subjects with only history of stroke (that occurred within 3 years before baseline), subjects with only APOE e4, and subjects with both
factors had RRs of 3.4 (95% CI, 1.3 to 8.6), 1.7 (95% CI, 1.1 to 2.6), and 3.9 (95% CI, 1.2 to 12.6), respectively. The RR of interaction term was 0.7 (95% CI, 0.1 to 3.1; \( P=0.6 \)). Subjects with only incident stroke, subjects with only APOE e4, and subjects with both factors had RRs of 2.8 (95% CI, 1.6 to 5.1), 1.7 (95% CI, 1.1 to 2.5), and 5.5 (95% CI, 2.4 to 13.0), respectively. The RR of interaction term was 1.2 (95% CI, 0.4 to 3.4; \( P=0.8 \)).

Since dementia diagnosis was based on information from 2 sources (clinical examination for those examined at follow-up and medical records or death certificates for those who died before the follow-up examination), all the analyses were repeated in the subpopulation of those who undertook the follow-up clinical examination (n=987). Subjects with only history of stroke (\( \leq 3 \) years), only APOE e4, and both factors had RRs of 2.3 (95% CI, 1.0 to 5.5), 1.6 (95% CI, 1.1 to 2.3), and 4.8 (95% CI, 1.9 to 12.1), respectively. The RR of interaction term was 1.3 (95% CI, 0.4 to 4.7; \( P=0.7 \)). Subjects with only incident stroke, only APOE e4, and both factors had RRs of 2.6 (95% CI, 1.4 to 4.8), 1.6 (95% CI, 1.1 to 2.3), and 5.3 (95% CI, 2.3 to 12.4), respectively. The RR of interaction term was 1.3 (95% CI, 0.4 to 3.8; \( P=0.6 \)).

In this study stroke was considered a single entity. To avoid a misleading result, we reanalyzed the data when subjects with hemorrhagic stroke (10% of all stroke cases) were excluded. The results did not change substantially.

Finally, sensitivity analysis of missing values of APOE genotypes was performed. When the relation among a history of stroke, APOE, and dementia was analyzed with the method reported in Table 3, the following results were obtained: (1) For imputation 1 (all subjects with missing values of APOE genotypes were assumed to have the e4 allele), the RRs for subjects with only a history of stroke, only the APOE e4 allele, and both history of stroke and the APOE e4 allele were 2.9, 1.6, and 3.4, respectively. In the analysis concerning the subjects with incident stroke, the following results were obtained. For imputation 1, the RRs in relation to only incident stroke, only APOE e4, and both factors were 2.3, 1.4, and 4.0, respectively. For imputation 2, the corresponding RRs were 2.4, 1.6, and 4.1, respectively. The interaction terms for all the sensitivity analyses were not significant. The RRs listed in Table 5 did not change substantially when the sensitivity analysis was done.

### Discussion

The main findings from our study of Swedish elderly people may be summarized in the following points: (1) A relatively fresh stroke (stroke that occurred within 3 years before baseline or during follow-up) is a risk factor for dementia. (2) The APOE e4 allele increases the risk of dementia without stroke but not dementia with stroke. APOE e4 does not increase the risk of stroke. (3) There is an additive effect between stroke and APOE e4 on the risk of dementia.

Some methodological aspects need to be addressed before these findings are discussed. There are several strengths of our study. First, this is a community-based prospective study, which is less likely to suffer from selection and survival biases. Second, the procedures for assessing dementia in this study are precise and comprehensive. All the participants were examined clinically by physicians, and those who died during follow-up were also traced through medical records and death certificates. All final diagnoses were made by specialists and based on double diagnostic procedure. Third, several factors potentially associated with dementia and stroke were taken into account in the analyses. Finally, there were very few dropouts from the dementia-free cohort at follow-up (11.8%). However, there are also some limitations that should be mentioned. The first limitation is the relatively high dropout rate of APOE genotyping. To overcome possible bias in the results due to the missing values, 2 extreme situations have been simulated. In all of these additional analyses, the results did not change substantially from the original. Second, we can study only the association of clinically overt stroke with dementia but not the role of silent brain infarction since neuroimaging data were not available in our study. There is increasing evidence that silent brain infarction is more common than clinically overt stroke.\(^{51}\) For

### TABLE 4. RR of Dementia According to Presence of Incident Stroke and APOE e4 Allele

<table>
<thead>
<tr>
<th>APOE e4</th>
<th>Incident Stroke</th>
<th>No. of Subjects</th>
<th>No. of Dementia Cases</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>14</td>
<td>6</td>
<td>4.6 (2.0–10.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>251</td>
<td>44</td>
<td>1.7 (1.1–2.4)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>46</td>
<td>14</td>
<td>2.3 (1.3–4.1)</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>611</td>
<td>77</td>
<td>1.0 (reference)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, education, heart disease, systolic blood pressure, and antihypertensive medication use.

### TABLE 5. Risk of Dementia With and Without Stroke in Relation to APOE Genotypes

<table>
<thead>
<tr>
<th>APOE Genotype</th>
<th>No. of Cases</th>
<th>Incidence Rate*</th>
<th>RR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>e2/e2, e2/e3</td>
<td>8</td>
<td>19.4</td>
<td>1.4 (0.6–3.3)</td>
</tr>
<tr>
<td>e3/e3</td>
<td>22</td>
<td>12.6</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Any e4</td>
<td>11</td>
<td>13.6</td>
<td>1.2 (0.6–2.4)</td>
</tr>
</tbody>
</table>

*Per 1000 person-years.

†Adjusted for age, sex, education, heart disease, systolic blood pressure, and antihypertensive medication use.
the same reason, we cannot specify the role of the locations of stroke on the development of dementia. The third limitation is the uncertainty of temporal relationship between stroke and dementia, especially for incident stroke and incident dementia cases. In our study, some incident stroke may have occurred after dementia onset or just at the beginning of cognitive decline, acting as a precipitating factor. At present, our data do not allow us any differentiation of a subgroup that may be classified as poststroke dementia in the incident stroke patients. Fourth, very mild cases may be missed as false-negatives at the screening test. We estimated, on the basis of our previous study, that there were 39 persons (22 men and 17 women) with false-negative results of MMSE. This misclassification was present and impossible to correct. However, very mild dementia cases may also have been present among those with MMSE < 24 but were not diagnosed as demented. Therefore, we repeated the analyses in the subpopulation of subjects with MMSE ≥ 24, and very similar results were obtained. Fifth, the incidence of dementia among subjects who died before follow-up examination was lower than that of those who survived. We may have missed some dementia cases among the deceased because of the imprecision of the diagnosis in the certificates and medical records (this also may have been due to the short time). However, similar results were obtained when all the analyses were repeated in the subpopulation of subjects who underwent the clinical examination. Finally, the definition of dementia of DSM-III-R, in which memory impairment is the main feature of dementia, may exclude patients with specific cognitive deficits rather than memory deficits, especially those with subcortical strokes, from being diagnosed with dementia. Therefore, it is possible that the number of subjects with dementia with stroke may have been underestimated in this study.

Relatively Fresh Stroke Is a Risk Factor for Dementia

Strokes that occurred within 3 years before baseline or during the follow-up doubled the risk of dementia. These RRs of dementia in relation to stroke are lower than those reported in other studies. In hospitalized patients, ischemic stroke increased the risk of dementia by 5-1 to 9-fold. A population-based study showed that the incidence of dementia in the first year was nearly 9 times greater than would have been expected in a population with the same age and sex distribution, and the risk of dementia in the cohort each year thereafter was twice the risk in the population. The reasons for the lower RR could be due to the following facts: (1) We studied dementia as a whole rather than vascular dementia or particularly stroke-related dementia. (2) Stroke patients with prevalent dementia at baseline were already excluded from the analyses. (3) A considerable proportion of subjects with a history of stroke in the analyses had stroke occurrence > 3 years before baseline. Indeed, stroke that occurred > 3 years before baseline interval did not increase the risk of dementia in this population.

APOE ε4 Increases the Risk of Dementia Without Stroke but Not Dementia With Stroke

Some studies found an increased frequency of the ε4 allele in vascular dementia patients, although others did not find the same result. In the present longitudinal study, the APOE ε4 allele did not significantly increase the risk of dementia with stroke, in disagreement with a previous case-control study. It has been shown that the APOE ε4 allele is related to early death, especially in those with good cognition. The survival variation results in low frequency of the APOE ε4 allele in those with good cognition from whom the control group is selected in case-control studies. Roos and Saunders argued that coexistence of AD may be the reason for the association between ε4 allele with vascular dementia.

APOE ε4 Allele Is Not an Important Risk Factor for Stroke in the Very Old

The association between the APOE ε4 allele and stroke supports the link between the APOE ε4 allele and vascular dementia since stroke is a risk factor for vascular dementia. We did not find any association between the APOE ε4 allele and incidence of stroke, confirming a previous report from the Kungsholmen Project and a population-based prospective study in Finland. Both APOE ε4 and ε2/3 have been reported to be related to increased risk for ischemic stroke. A recent study of 280 Austrians aged 50 to 75 years showed that APOE ε2/ε3 was related to silent microangiopathy-related cerebral damage, including white matter abnormalities and lacunar infarctions, despite the favorable effects on lipid levels. These findings underscore the complexity of the association between APOE genotypes and vascular lesions.

Relationship Between Stroke and APOE ε4 Allele on Risk of Dementia

In a population-based prospective study of 353 men aged 69 to 89, Kalmijn and coworkers suggested that cerebrovascular disease and the APOE ε4 allele might have a synergistic effect on cognitive decline. We found that there was no significant multiplicative effect between stroke and the APOE ε4 allele on the incidence of dementia. Similar results were found in different subpopulations after the missing values of the APOE genotype in the sensitivity analysis were taken into account. However, we found that stroke and the APOE ε4 allele might have an additive effect on dementia. Subjects with both stroke and APOE ε4 had a greater risk of dementia than did subjects with either of these 2 factors.

Possible Interpretations

We may speculate on the possible mechanism underlying the finding that relatively fresh stroke increases the risk of dementia. In our study, as well as other community-based studies, the majority of strokes were ischemic. Similar results were obtained when hemorrhagic strokes were excluded from the analyses. We will therefore focus the discussion on ischemic stroke.

Atherothromboembolism complicated by thrombosis or embolism is one of the most common causes of ischemic stroke. The pathophysiological process of atherothromboembolism may begin many years before the manifestation of a clinical stroke. The decline of the intellectual level of patients with overt or silent stroke varies, and only those patients with sufficient deterioration of cognitive function will meet the diagnostic criteria of dementia. Because of the adaptations of
the neural network, most patients who survive an acute stroke have at least some lessening of their neurological impairments afterward. Moreover, cognitive functions show great adaptability. This may explain the phenomenon that an old stroke with already cooled pathophysiological processes or some degree of regression did not increase the risk of dementia. Arteries have the capacity to adapt and to recover from previous lesions in experimental models of atherosclerosis regression.

Another finding in the present study is that APOE ε4 increases the risk of dementia without stroke and APOE ε4 does not increase the risk of stroke. There is evidence of individuals carrying the APOE ε4 allele with a significantly higher level of senile plaques and neurofibrillar tangles in the brain. This indicates that the APOE ε4 allele may increase the risk of degenerative dementia by acting on the amyloid cascade. However, neuropathological studies have not found any association of APOE genotype with vascular lesions in the brain. The influence of the APOE ε4 allele on cholesterol level decreases with age. It would be expected that there is a weak relationship between the APOE ε4 allele and stroke, and therefore vascular dementia, in the very old. We suggest that stroke and the APOE ε4 allele increase the risk of dementia through different pathogenic mechanisms. This view is supported by the finding that both factors had an additive rather than a synergistic effect on the development of dementia.

In summary, a relatively fresh stroke increases the risk of dementia. The APOE ε4 allele is a risk factor for dementia without stroke. There might be an additive effect of stroke and the APOE ε4 allele on dementia, although no evidence supporting a multiplicative effect was found. We suggest that, in the very old, stroke and the APOE genotype increase the risk for dementia through different pathogenic mechanisms.

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Incidence of Dementia in Relation to Stroke and the Apolipoprotein E ε4 Allele in the Very Old: Findings From a Population-Based Longitudinal Study
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