Risk Estimates of Dementia by Apolipoprotein E Genotypes From a Population-Based Incidence Study: The Rotterdam Study

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Objectives: To provide risk estimates of dementia and Alzheimer disease as a function of the apolipoprotein E (*APOE*) genotypes and to assess the proportion of dementia that is attributable to the *APOE* genotypes.

Design: Case-control study nested in a population-based cohort study with a mean (SD) follow-up of 2.1 (0.9) years.

Setting: General population in Rotterdam, the Netherlands.

Participants: A total of 134 patients with incident dementia and a random sample of 997 nondemented control subjects. No participant had dementia at baseline.

Main Outcome Measures: Odds ratios for dementia and Alzheimer disease, the fraction of dementia attributable to the *APOE* ε4 allele, and the proportion of the variance in age at the onset of dementia explained by the *APOE* genotypes.

Results: Persons with the ε4/4 genotype had a more than 10-fold higher risk of dementia (odds ratio, 11.2; 95% confidence interval, 3.6-35.2), and subjects with the ε3/4 genotype had a 1.7-fold increased risk of dementia (95% confidence interval, 1.0-2.9) as compared with persons with the ε3/3 genotype. The proportion of patients with dementia that is attributable to the ε4 allele was estimated to be 20%. The *APOE* genotypes explained up to 10% of the variance in age at the onset of dementia. The association between the ε4 allele and dementia was strongest in the youngest age category and in those with a family history of dementia.

Conclusions: The *APOE* genotype is an important determinant of the risk of dementia. At a population level, however, other factors than the *APOE* genotype may play an important role in the cause of dementia.

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ALTHOUGH THE association between the ε4 allele of the apolipoprotein E (*APOE*) gene and Alzheimer disease (AD) is well established, reported risks vary tremendously among studies.[1-7] Most of these investigations are of clinic-based patient series. In some studies, selection bias may have played a role because the ε4 frequency in memory clinic patients was found to be increased compared with patients in the general population.[8,9] Furthermore, all but 2 studies[4,5] are based on prevalent cases. Because the *APOE* genotype may be a determinant of survival in patients with dementia,[10,11] cross-sectional studies are subject to bias. In addition, it is still controversial whether the ε2 allele exerts a protective effect,[11,12] whether a family history of dementia further increases the ε4-related risk,[2,3] and whether the *APOE* genotype is a determinant of the patient's age at the onset of dementia.[1,13] Thus, reliable estimates of the risk of dementia associated with the *APOE* genotypes are cur-

rently not available, and it is not yet clear which part of all patients with dementia is attributable to the *APOE* genotypes.

The aims of this study were to provide risk estimates of dementia and AD as a function of the *APOE* genotype and to estimate the proportion of dementia and AD that can be attributed to the *APOE* genotypes. To overcome selection bias, we investigated these issues in a prospective study of a general population initially free of demetia.

RESULTS

Characteristics of the study population are shown in **Table 1**. Patients with dementia were on average older, more often female, and more often had primary education only compared with the unaffected

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SUBJECTS AND METHODS

STUDY POPULATION

The Rotterdam Study is a population-based prospective cohort study among persons aged 55 years or older[14] for which approval was given by the local medical ethics committee. Participants were recruited from 10 275 eligible residents of a suburb of Rotterdam, the Netherlands, including institutionalized persons. A total of 7983 participants (response rate, 77.7%) were examined at baseline. Of these, 7528 persons (94.3%) were evaluated for dementia, of whom 474 received diagnoses and were excluded from the present study. At follow-up, after an average (SD) of 2.1 (0.9) years, 6315 persons (79.1%) were reexamined; 768 subjects (9.6%) had died, 106 (1.3%) were unavailable, and 794 (10%) refused to participate. Follow-up of all subjects who were not examined in person was completed by evaluating medical files. Of the 7054 participants who did not have dementia at baseline, 162 were found to have dementia at follow-up.

The analyses presented here are restricted to persons from whom blood specimens were available for *APOE* typing. This was successfully determined in 134 patients with incident dementia and in a random sample of 997 nondemented control subjects.

DEMENTIA DIAGNOSIS

For the assessment of dementia, we used the same protocol at baseline and at follow-up.[15,16] Briefly, all subjects were screened on cognitive functioning. Persons with abnormal results on screening underwent further neuropsychological testing, and an informant was interviewed on the daily functioning of the participant. Persons who were suspected of having dementia were examined by a neurologist, underwent neuropsychological testing, and if possible, had a magnetic resonance imaging scan of the brain.[15,16] For subjects who could not be reexamined in person, information was obtained from general practitioners and the Regional Institute for Outpatient Mental Health Care, Rotterdam, which covers the entire study population. In the Netherlands, the Regional Institute for Outpatient Mental Health Care is consulted for social and psychiatric problems and is responsible for assessing indications for going to a dementia care facility. Examinations by the institute include (informant) interviews, neurologic and neuropsychological testing, blood biochemistry tests, and serologic tests for syphilis.

The diagnosis of dementia was made by a panel of study physicians, a neurologist, and a neuropsychologist, who reviewed all existing information and used criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*.[17] A diagnosis of AD and vascular dementia was based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,[18] and of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences.[19] Cerebrovascular disease was recognized by a history of stroke, an evident transient ischemic attack, or evidence of vascular damage on brain scans.

MEASUREMENTS

At baseline, subjects were interviewed about the attained level of education and their family history of dementia. All first-degree relatives of the participants were listed, and for each relative, the presence of dementia was evaluated with the study physician. The family history was affirmed if 1 or more first-degree relatives had dementia.

Genotyping for *APOE* was performed on coded DNA specimens without knowledge of the diagnosis. A polymerase chain reaction was performed using previously published primers.[20] The reaction mixture contained 200-ng genomic DNA as the template, 25 pmol of both primers, 0.1 U of DNA polymerase, fluorescent sequencing (AmpliTaq, Applied Biosystems, Foster City, Calif), magnesium chloride (1.5 mmol/L), Tris(hydroxymethyl)-aminomethane hydrochloride (pH 9.0) (75 mmol/L), ammonium sulfate (20 mmol/L), and 10% dimethyl sulfoxide in a total volume of 25 µL. Thirty-five cycles of 30 seconds each at 94°C, 65°C, and 70°C were performed, and the polymerase chain reaction amplification products were digested with 5 U of *Hha*I for 3 hours at 37°C. The restriction fragments were separated on precast gels (ExcelGel, Pharmacia Biotech, Uppsala, Sweden) by electrophoresis (MultiPhorII, Pharmacia Biotech) for 1½ hours at 600 V. The restriction fragments were visualized by silver staining. The results were read by 3 persons independently. In case of discrepancies, *APOE* genotyping was repeated.

STATISTICAL ANALYSIS

The relative risk of dementia or AD was estimated as an odds ratio (OR) in a multiple logistic regression model and presented with a 95% confidence interval (95% CI) using the $\epsilon3/3$ genotype as the reference. To compute the OR associated with carriership of the $\epsilon2$ or $\epsilon4$ allele, persons with $\epsilon2/2$ or $\epsilon2/3$ were grouped, as well as subjects with $\epsilon3/4$ or $\epsilon4/4$; persons carrying both the $\epsilon2$ and the $\epsilon4$ allele were excluded from these models. To adjust for confounding, age, sex, and education level were added to the above models. Education was dichotomized as primary school or less, and more than primary school. The proportion of patients with dementia that is attributable to 1 of the *APOE* genotypes was assessed with the population-attributable risk.[21]

The age at the onset of dementia was taken to be the midpoint between the baseline age and the age at follow-up. Differences in age at the onset of dementia were examined in a multiple linear regression model, and the percentage of explained variance was estimated by the squared adjusted multiple correlation coefficient.[22]

The lifetime risk of dementia was calculated for 55-year-old subjects with or without the $\epsilon4$ allele using a matched Bayesian analysis, as described earlier.[23] As patients were on average older than the controls, and the frequency of the *APOE* genotypes differed across age strata, we first matched every patient with a control subject on age (5-year interval) and sex. The a priori lifetime risk of dementia for 55-year-old persons was derived from The Rotterdam Study. Overall, this risk was estimated to be 33% for women and 16% for men, taking into account the competing risk of death.[16]

controls. Overall, a family history of dementia was not more common in patients than in controls. Patients with dementia, however, more often had 2 or more first-degree relatives with dementia than the unaffected controls (5% vs 2%; $\chi^2 = 4.1$, $P = .04$). The distribution of the *APOE* genotypes in patients and controls was in Hardy-Weinberg equilibrium.

As shown in **Table 2**, the OR for all dementia associated with ε4 homozygosity was 11.2 (95% CI, 3.6-35.2) and for AD, 6.2 (95% CI, 1.4-28.2). Persons with the ε3/4 genotype had almost a 2-fold increased risk of all dementia and AD compared with those with the ε3/3 genotype. Carriers of the ε2/3 genotype had a decreased risk of these disorders, although this did not reach statistical significance.

It was estimated that 5% (95% CI, 1%-8%) of cases of dementia could be attributed to the ε4/4 genotype, 13% (95% CI, 7%-19%) to the ε3/4 genotype, and 2% (95% CI, 0%-5%) to the ε2/4 genotype. Thus, if the ε4 allele did not have an effect on the dementia risk, the incidence would be reduced by 20%. Likewise, it was assessed that 3% (95% CI, 0%-6%) of AD cases were attributable to ε4 homozygosity, 14% (95% CI, 7%-21%) to the ε3/4 genotype, and 0% (95% CI, 0%-2%) to the ε2/4 genotype.

Among patients with dementia, ε2 carriers were on average older and ε4 carriers younger at the onset of de-

mentia than persons homozygous for ε3 (Table 2). The *APOE* genotype explained 10% of the variance in age at the onset of dementia and 4% of the variance in age at the onset of AD.

The ε4-associated OR for dementia and AD was highest in the youngest age category and decreased with aging (**Figure**). The effects of the ε2 allele were similar across age strata (data not shown). The ε4-related OR for dementia in women (2.3; 95% CI, 1.2-4.5) was comparable with the corresponding OR in men (1.9; 95% CI, 0.8-4.2). Analyses of the sex-specific OR for AD yielded similar results as well (data not shown).

A family history of dementia further increased the ε4-associated OR for dementia and AD (**Table 3**). The risk of these disorders for ε4 carriers with no family history of dementia was nonsignificantly increased (for dementia: OR, 1.7 [95% CI, 1.0-3.1]; for AD: OR, 1.3 [95% CI, 0.7-2.7]). Among persons with a family history of dementia, however, ε4 carriers had a statistically significant 4.8-fold increased risk of dementia (95% CI, 1.5-15.6) and a 4.6-fold increased risk of AD (95% CI, 1.3-16.1).

The lifetime risk of dementia for a 55-year-old carrier of at least 1 ε4 allele was estimated to be 26% for men and 46% for women. For non-ε4 carriers at a similar age, the lifetime risk was estimated to be 11% for men and 28% for women. The numbers were too small to estimate the lifetime risk of dementia associated with each *APOE* genotype separately.

COMMENT

With this prospective population-based study, we provide risk estimates for incident dementia and AD for carriers of the various *APOE* genotypes. Our study shows that the proportion of patients with dementia that is attributable to the *APOE* genotype was approximately 20% and that the *APOE* genotypes explained not more than 10% of the variance in age at the onset of dementia.

The present investigation has several advantages over most previous studies on the *APOE* genotype and dementia. Selection bias was avoided because the study was population based and had a high response rate. The diagnostic workup was comprehensive and was similar at

Table 1. Characteristics of the Study Population*

Characteristic	All Dementia (n = 134)	Alzheimer Disease (n = 97)	Control Subjects (n = 997)
Mean age at baseline (SD), y	80.8 (7.7)†	81.6 (7.0)†	68.4 (7.7)
Mean age at onset (SD), y	81.4 (7.7)	82.2 (7.0)	. . .
Men	34 (25.4)†	20 (20.6)†	398 (39.9)
Women	100 (74.6)†	77 (79.4)†	599 (60.1)
Family history of dementia	26 (20.6)	23 (25.6)	244 (24.6)
Primary education only	59 (49.2)†	46 (52.3)†	215 (21.7)

*Data on family history of dementia were missing for 8 patients with dementia and 7 controls and on educational level for 14 patients with dementia and 7 controls. Unless otherwise stated, values are number (percentage). Ellipses indicate not applicable.
†Significantly different from controls: $P < .005$.

Table 2. Adjusted Odds Ratio and Age at Onset of Dementia and Alzheimer Disease Associated With Apolipoprotein E (*APOE*) Genotypes*

Alzheimer Disease and Dementia	*APOE* Genotype					
	ε2/2	ε2/3	ε2/4	ε3/3	ε3/4	ε4/4
All dementia						
OR (95% CI)	1.5 (0.2-14.7)	0.5 (0.2-1.1)	3.6 (0.8-16.0)	1†	1.7 (1.0-2.9)‡	11.2 (3.6-35.2)§
Patients/controls, No.	1/10	10/148	4/19	70/563	42/241	7/16
Mean age at onset (SD), y	84.2 (. . .)	85.1 (6.5)	75.7 (8.7)	82.3 (7.2)	80.9 (7.7)	73.4 (8.6)§
Alzheimer disease						
OR (95% CI)	. . .	0.4 (0.1-1.0)	1.3 (0.2-8.5)	1†	1.8 (1.0-3.1)	6.2 (1.4-28.2)‡
Patients/controls, No.	0/10	6/148	2/19	55/563	31/241	3/16
Mean age at onset (SD), y	. . .	85.8 (8.5)	79.8 (7.6)	82.8 (6.9)	80.8 (7.2)	79.3 (3.7)

*Odds ratio (OR) with 95% confidence interval (CI), adjusted for age, sex, and education level. Ellipses indicate not applicable.
†Reference.
‡Significantly different from the ε3/3 group: $P < .05$.
§Significantly different from the ε3/3 group: $P < .005$.

baseline and at follow-up. For participants who could not be reexamined in person, information was obtained from general practitioners and ambulatory psychiatry services to have a complete follow-up of the cohort. We minimized survival bias by studying the relation longitudinally and by including subjects who died during follow-up. This was possible because *APOE* genotyping was performed on blood specimens collected before the onset of dementia.

A limitation of this study is the lack of autopsy confirmation. Therefore, we cannot rule out that we misclassified the dementia subtype in some instances. With clinical examination alone, however, approximately 90% of cases of AD are diagnosed correctly.[24] Furthermore, any misclassification of dementia subdiagnoses will not affect analyses on dementia in general.
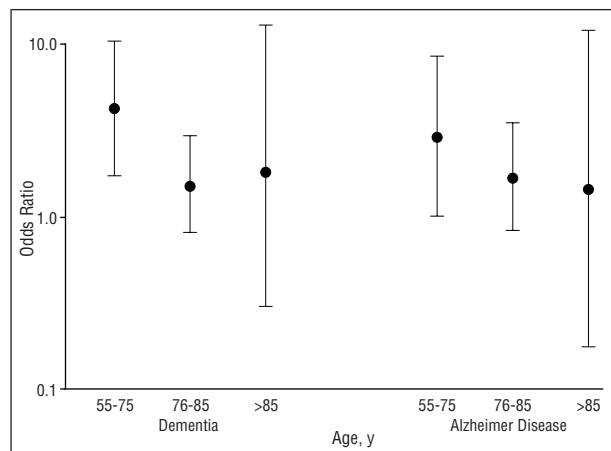
We found a higher ε4/4-associated OR for all dementia (11.2) than for AD (6.2). In addition, the *APOE* genotypes explained a higher proportion of the variance in age at the onset of dementia (10%) than of AD (4%). Although these observations are tentative given the lack

Age-specific odds ratios (95% confidence interval [vertical bars]) for dementia and Alzheimer disease associated with the ε3/4 or the ε4/4 genotype. Persons with the ε3/3 genotype were the reference group, adjusted for age (within stratum), sex, and educational level.

of neuropathological confirmation of the dementia subtype and the overlapping confidence intervals, these findings suggest that the ε4 allele is strongly associated with the non-AD dementias.[25]

We further found that carriers of ε2/3 had a nonsignificantly decreased risk of dementia and AD and were older at the onset of dementia. This is compatible with a protective effect, as has been reported previously.[12] Among patients with early-onset AD, we found an increased risk for ε2 carriers.[11] In the present investigation, the effect of the ε2 allele on early-onset AD could not be addressed because all but 3 of the patients were older than 65 years at the onset of dementia.

We confirmed that the ε4-associated risk may decrease with advancing age.[12] Although this is in contrast to findings from another population-based incidence study,[5] the latter investigation is smaller than our study. We found, further, that the ε4-related risk of dementia was similar in men and women. This is in contrast with a study on familial AD.[26] The interpretation of that study is hampered by the fact that it is based on a cross-sectional design,[26] and sex-specific differences in cardiovascular mortality related to the ε4 allele may have played a role.[27] A family history of dementia may further increase the ε4-associated risk of dementia and AD. The difference in the ε4-related risk of dementia between persons with and without a family history of dementia did not result from an asymmetric distribution of ε4 homozygotes across these strata. Also, analyses on the 6 *APOE* genotypes yielded a higher OR for dementia in those with a family history of dementia than in those without, although numbers were small (data not shown). This suggests the presence of other genetic or shared environmental factors in the cause of dementia that may interact with the effect of the ε4 allele.[2,3]

Only 2 previous studies reported lifetime risks of dementia for carriers and noncarriers of the ε4 allele specifically.[7,23] These risk estimates for ε4 carriers were lower (0.01-0.29) than ours.[7,23] The 2 studies, however, based their estimates on a meta-analysis of different case series, but the a priori risk of dementia was drawn from

Table 3. Adjusted Odds Ratio for Dementia and Alzheimer Disease Associated With Apolipoprotein E (*APOE*) Alleles and Family History of Dementia*

Alzheimer Disease and Dementia		*APOE* Allele		
		ε2+	ε3/3	ε4+
All dementia				
No family history	OR (95% CI)	0.6 (0.3-1.4)	1†	1.7 (1.0-3.1)
	Patients/controls, No.	10/126	55/437	31/173
Family history	OR (95% CI)	0.5 (0.0-5.4)	1†	4.8 (1.5-15.6)‡
	Patient controls, No.	1/31	10/121	15/83
Alzheimer disease				
No family history	OR (95% CI)	0.3 (0.1-1.1)	1†	1.3 (0.7-2.7)
	Patients/controls, No.	5/126	41/437	19/173
Family history	OR (95% CI)	0.5 (0.0-5.4)	1†	4.6 (1.3-16.1)§
	Patients/controls, No.	1/31	10/121	12/83

**Persons with the ε2/4 genotype were excluded. Data on family history of dementia were missing in 8 cases and 7 controls; OR (95% CI) denotes odds ratio with 95% confidence interval, adjusted for age, sex, and educational level.*
†*Reference.*
‡*P<.001.*
§*P<.05.*

yet another study.[7,23] We found a lifetime risk of dementia for 55-year-old ϵ4 carriers of 46% in women and 26% in men. In the absence of the ϵ4 allele, the lifetime risk was estimated to be 28% for women and 11% for men. In these calculations, the competing risk of death and the higher a priori risk in women were taken into account. In asymptomatic persons, the presence of the ϵ4 allele seems to have limited predictive value. Although there is consensus in the literature that *APOE* genotyping should not be used for presymptomatic testing,[28,29] with the expanding use of *APOE* genotyping for diagnostic purposes, a growing number of unaffected offspring will be aware of their *APOE* genotype. Therefore, reliable estimates of the lifetime risk of dementia will become important.

Although the association between the ϵ4 allele and dementia is robust, the incidence would be reduced by only 20% as the effects of ϵ4 could be blocked. In addition, the variance in age at the onset of dementia was only partly (10%) determined by the *APOE* genotypes. These findings suggest that other factors play an important role in the cause of dementia. The higher ϵ4-related risk in persons with than in subjects without a family history of dementia emphasizes the need to identify other genes or shared environmental factors.

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