

A population study of apoE genotype at the age of 85: relation to dementia, cerebrovascular disease, and mortality

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Abstract

Objectives—To study the association of apoE genotypes with dementia and cerebrovascular disorders in a population based sample of 85 year old people.

Methods—A representative sample of 85 year old people (303 non-demented, 109 demented) were given a neuropsychiatric and a medical examination and head CT. The apoE isoforms were determined. Dementia was diagnosed according to DSM-III-R.

Results—At the age of 85, carriers of the apoE $\epsilon 4$ allele had an increased odds ratio (OR) for dementia (1.9; $p < 0.01$) and its subtypes Alzheimer's disease (1.9; $p < 0.05$) and vascular dementia (2.0; $p < 0.05$). Among those categorised as having vascular dementia, the apoE $\epsilon 4$ allele was associated with mixed Alzheimer's disease-multi-infarct dementia (OR 6.5; $p < 0.05$), but not with pure multi-infarct dementia (OR 1.5; NS). Only carriers of the apoE $\epsilon 4$ allele who also had ischaemic white matter lesions on CT of the head had an increased OR for dementia (OR 6.1; $p = 0.0003$), and its main subtypes Alzheimer's disease (OR 6.8; $p = 0.002$) and vascular dementia (OR 5.6; $p = 0.0007$), whereas carriers of the apoE $\epsilon 4$ allele without white matter lesions had an OR for dementia of 1.0 (OR for Alzheimer's disease 1.8; NS and for vascular dementia 0.6; NS) and non-carriers of the apoE $\epsilon 4$ allele with white matter lesions had an OR for dementia of 2.2; NS (OR for Alzheimer's disease 2.7; NS and for vascular dementia 1.6; NS). The apoE allele variants were not related to mortality or incidence of dementia between the ages of 85 and 88. The $\epsilon 2$ allele was related to a higher prevalence of stroke or transient ischaemic attack at the age of 85 (OR 2.1; $p < 0.05$) and a higher incidence of multi-infarct dementia during the follow up (OR 2.9; $p < 0.05$).

Conclusions—Neither the apoE $\epsilon 4$ allele nor white matter lesions are sufficient risk factors by themselves for dementia at very old ages, whereas possession of both these entities increases the risk for Alzheimer's disease and vascular dementia substantially.

Keywords: dementia; apoE genotype; cerebrovascular disorder

The main risk factor for Alzheimer's disease is old age and most cases occur after the age of 80. Another prominent risk factor for Alzheimer's disease is the $\epsilon 4$ allele of apolipoprotein E (apoE), which, in numerous studies, has been associated with both sporadic and familial late onset Alzheimer's disease.¹⁻⁵ A relation between the apoE $\epsilon 4$ allele and dementia is found also in population based studies,⁶⁻¹¹ although the association is generally weaker than that found in more selected samples. It is suggested that the risk related to the $\epsilon 4$ allele decreases with increasing age.^{6 12-14} One reason may be that at old ages, several other factors may be of importance.

Vascular dementia caused by cerebrovascular disorders,¹⁵ such as multiple cerebral infarcts, lacunas, and ischaemic white matter lesions, is the other common form of dementia. An increased frequency of the apoE $\epsilon 4$ allele has been reported in middle aged persons with coronary heart disease and atherosclerosis,^{16 17} and in patients with ischaemic cerebrovascular disease.¹⁸ An increased frequency of the apoE $\epsilon 4$ allele in vascular dementia is reported in some studies,¹⁹⁻²¹ but not in all.^{8 9} Ischaemic white matter lesions refer to the histopathological picture of pronounced or diffuse demyelination accompanied by arteriosclerotic changes with lipohyalinosis of the small penetrating arteries and arterioles in the subcortical white matter.¹⁵ These lesions may be visualised by CT or MRI of the brain. ApoE is involved in growth, maintenance, and repair of myelin and neuronal membranes during development and after injury,²² and may thus be involved in white matter disease. Vascular factors may also play a part in Alzheimer's disease.¹⁴ Thus ischaemic white matter lesions are common, not only in vascular dementia, but also in late onset Alzheimer's disease.²³⁻²⁶ Recently, it was reported that there may be an interaction between atherosclerosis and the apoE $\epsilon 4$ genotype in the aetiology of both Alzheimer's disease and vascular dementia.²⁷

We examined the association of apoE genotypes with the main types of dementia—namely, Alzheimer's disease and vascular dementia—and with cerebrovascular disorders, such as white matter lesions and stroke, in a population based sample of 85 year old people as part of the Longitudinal Gerontological and Geriatric

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Population Studies in Gothenburg.²⁸⁻³⁰ The study also included a three year follow up.³¹

Methods

SUBJECTS

In 1986-7, all 85 year old people born between 1 July 1901 and 30 June 1902, registered for census purposes in Gothenburg, were invited to take part in a health survey. Both people living in the community and those in institutions were included. A systematic subsample was examined with a neuropsychiatric examination (n=494). This sample was described in detail previously,³⁰ and found to be representative of the total population for sex, marital status, psychiatric registration as an outpatient or an inpatient in Gothenburg, three year mortality, and institutionalisation.³⁰ Three hundred and forty seven were not demented, 147 had dementia. Serum samples from 412 people (83% of those who participated in the study, 303 non-demented, and 109 demented) examined at the age of 85 were obtained and kept at -70°C. Fifty two had Alzheimer's disease, 46 vascular dementia (34 multi-infarct dementia, 10 mixed Alzheimer's disease-multi-infarct dementia, two hypoperfusion dementia), and 11 other types of dementia.

A three year follow up study on those non-demented at the age of 85 was performed.³¹ One hundred and eighty eight people were examined at a neuropsychiatric examination, 73 had died, and 86 refused further examinations. Information on those who had died or refused was obtained from medical records or other sources in 132 cases.³¹ No information was available on 27 people. Sufficient information was thus obtained on 320 subjects (92.2% of the population at risk). The number of new cases of dementia was 63.³¹ We had frozen serum samples from 282 non-demented 85 year old people (88% of those with sufficient information) who were followed up to the age of 88. Of these, 59 developed dementia and 223 did not. Twenty four developed Alzheimer's disease, 28 vascular dementia (24 multi-infarct dementia, three mixed Alzheimer's disease-multi-infarct dementia, one hypoperfusion dementia), and seven other types of dementia.

Informed consent was obtained from all subjects or their relatives, and the study was approved by the ethics committee for medical research at Göteborg University.

EXAMINATIONS

The study included a medical and neuropsychiatric examination, interview of a close informant, ECG, chest radiography, an extensive battery of blood tests, and CT of the head. Medical records from psychiatric and geriatric institutions and outpatient departments in Gothenburg were examined by a psychiatrist. All neuropsychiatric examinations were performed by a psychiatrist in the subject's home or at institutions. The interview was semistructured.³⁰ Standardised information on history of stroke and transient ischaemic attacks was obtained from the subjects, close informants, and case records. Signs of stroke

were rated by the examining physician. The information had to include a history of definite acute focal neurological symptoms and signs (acute hemiparesis, acute motor aphasia).

DIAGNOSTIC PROCEDURES

Dementia was diagnosed according to the DSM-III-R criteria,³² using information from the psychiatric examination and the close informant interview.³⁰ Subjects with dementia were classified into diagnostic subgroups: Alzheimer's disease according to NINCDS-ADRDA criteria,³³ vascular dementia (multi-infarct dementia, mixed dementia, and hypoperfusion dementia), and other causes according to criteria proposed by Erkinjuntti *et al.*³⁴ Pure multi-infarct dementia was diagnosed when there were infarcts on CT or a temporal connection between the onset of dementia and a history of acute focal neurological symptoms and mixed dementia when there was a history of acute focal neurological symptoms without a temporal connection with the evolution of dementia. The presence of white matter lesions on CT was not used in the diagnosis of vascular dementia. The procedure for the aetiological diagnosis has been described in detail previously.^{30 31}

BRAIN CT

Brain CT was performed on 239 people at the age of 85, and serum samples were obtained from 189 (72 demented and 117 non-demented). All CT was performed without contrast enhancement and with 10 mm continuous slices on a Philips Tomoscan 310 and on a General Electric 8800. The scans were examined by two radiologists who were blind to the results of the other examinations. White matter lesions were defined as periventricular or subcortical areas of decreased attenuation below that expected for normal white matter. The changes were always diffusely distributed within the white matter. The presence of cortical and lacunar infarcts was also rated. The between observer reliability for these measures was satisfactory.^{23 31}

ApoE GENOTYPE

Determination of the isoforms was performed using isoelectric focusing and western blotting, with minor modifications.³⁵ Briefly, serum samples were incubated with neuraminidase to remove sialic acids. Lipoproteins were isolated by precipitation with tungstophosphoric acid and MgCl₂, and lipids were extracted using ethanol and diethyl ether. The remaining apoproteins were dissolved in tris-dithiothreitol/urea buffer, separated by isoelectric focusing, blotted on to a nitrocellulose membrane, and detected using a specific mouse monoclonal antibody against apoE (Boehringer Mannheim).

STATISTICAL METHODS

Differences in proportions were measured by odds ratios (ORs) with 95% confidence intervals (95% CIs) and tested for significance with Fisher's exact test.³⁶ Two tailed tests were used.

Table 1 ApoE alleles in 85 year old people in relation to dementia and different diagnostic categories of dementia

	Alleles (n)	Allele frequency			Subjects (n)	OR for dementia disorders in those having at least one allele of:		
		ε2	ε3	ε4		ε2 v no ε2	ε3 v no ε3	ε4 v no ε4
No dementia	606	0.112	0.670	0.218	303			
Any dementia	218	0.078	0.619	0.303*	109	0.7 (0.4 to 1.2)	0.9 (0.4 to 2.3)	1.9‡ (1.2 to 2.9)
Alzheimer's disease (AD)	104	0.067	0.625	0.308	52	0.5 (0.2 to 1.3)	1 (0.3 to 3.6)	1.9‡ (1.1 to 3.5)
Mixed dementia (MIX)	20	0.100	0.400	0.500**	10	0.9 (0.2 to 4.2)	0.1† (0.04 to 0.6)	6.2‡ (1.3 to 29.6)
Multi-infarct dementia (MID)	68	0.103	0.647	0.250	34	0.9 (0.4 to 2.2)	—	1.5 (0.8 to 3.1)
Other dementias	22	0.046	0.727	0.227	11	0.4 (0.04 to 2.8)	—	1.3 (0.4 to 4.3)
All AD (including MIX)	124	0.073	0.589	0.339**	62	0.6 (0.3 to 1.3)	0.6 (0.2 to 1.6)	2.3‡ (1.3 to 4.0)
All vascular dementia (MID+MIX+hypoperfusion)	92	0.098	0.587	0.315*	46	0.9 (0.4 to 1.9)	0.7 (0.2 to 2.1)	2.0‡ (1.1 to 3.8)

* p < 0.05; ** p < 0.01 v no dementia; † p < 0.05; ‡ p < 0.01 v those not carrying the allele.

Table 2 ApoE genotypes in 85 year old people in relation to dementia disorders

	Subjects (n)	E4/4 (n (%))	E4/3 (n (%))	E4/2 (n (%))	E3/3 (n (%))	E3/2 (n (%))	E2/2 (n (%))
No dementia	303	13 (4)	102 (34)	4 (1)	121 (40)	62 (20)	1 (0)
Dementia	109	6 (6)	53 (49)*	1 (1)	33 (30)	16 (15)	0
Alzheimer's disease (AD)	52	3 (6)	26 (50)*	0	16 (31)	7 (13)	0
Mixed AD/MID (MIX)	10	2 (20)	5 (50)	1 (10)	1 (10)	1 (10)	0
Multi-infarct dementia (MID)	34	0	17 (50)	0	10 (29)	7 (21)	0
Other dementias	11	0	5 (45)	0	5 (45)	1 (9)	0
All AD (including MIX)	62	5 (8)	31 (50)*	1 (2)	17 (27)	8 (13)	0
All vascular dementia (MID+MIX+hypoperfusion)	46	3 (7)	22 (48)	1 (2)	12 (26)	8 (17)	0

* p < 0.05 v non-demented subjects.

The incidence (*I*) of dementia was based on person-years at risk as described previously,³¹ and computed as:

$$I = \frac{\text{Subjects affected in the interval}}{\text{Sum of risk years}}$$

Confidence intervals were calculated using the individual terms of the binominal distribution.³⁷

Results

AT THE AGE OF 85

Table 1 shows the allele frequency of apoE. Those with dementia had a higher frequency of the apoE ε4 allele than those without dementia. Carriers of the apoE ε4 allele had an increased OR for dementia (1.9; p<0.01) and its subtypes Alzheimer's disease (1.9; p<0.05) and all vascular dementias (2.0; p<0.05). Among those categorised as vascular dementia, the apoE ε4 allele was associated with an increased OR for mixed Alzheimer's disease-multi-infarct dementia (6.2; p<0.05), but not with an increased OR for pure multi-infarct dementia (1.5; NS).

Table 2 shows the distribution of the apoE genotype in the population. Four per cent (n=13) of non-demented and 6% (n=6) of demented persons were homozygotic for the apoE ε4 allele. The only genotype that was significantly more common in demented persons was E4/3, which was found in 49% of the demented group and in 34% of the non-

demented group. A significant increase of the apoE 4/3 genotype was also found in persons with Alzheimer's disease.

Using those with zero ε4 (n=233) as the reference group, OR for dementia in those with one apoE ε4 allele (n=160) was 1.9 (95% CI 1.2-3.0; p=0.007) and in those with two (n=19) it was 1.7 (95% CI 0.6-4.8; NS).

Table 3 shows the type of apoE allele in relation to white matter lesions, infarcts on CT, and a history of transient ischaemic attack or stroke at the age of 85. Carriers of the apoE ε2 allele had an increased OR for having a history of stroke or transient ischaemic attack (OR 2.1; P<0.05).

We have previously reported that white matter lesions on brain CT was more common in persons with Alzheimer's disease (63.9%; p<0.01) and vascular dementia (70.2%; p<0.001) than in non-demented subjects (33.8%) in this sample.²³ In table 4, we present analyses of the interaction between white matter lesions and the apoE ε4 allele for the risk of dementia and its main subtypes Alzheimer's disease and vascular dementia using those lacking both white matter lesions and the apoE ε4 allele as the reference group (OR 1.0). Carriers of the apoE ε4 allele without white matter lesions had an OR for dementia of 1.0 (NS), non-carriers of the apoE ε4 allele with white matter lesions had an OR for dementia of 2.2 (NS), and carriers of the apoE ε4 allele with

Table 3 ApoE alleles in relation to cerebrovascular disorders in 85 year old people

	OR (95% CI) for vascular disorders in those having at least one allele of:		
	ε2 v no ε2	ε3 v no ε3	ε4 v no ε4
WMLs (n=88) v no WMLs (n=101) on CT	0.4 (0.2 to 1.0)	0.7 (0.1 to 5.2)	1.5 (0.8 to 2.7)
Infarcts (n=32) v no infarct (n=158) on CT	1.4 (0.6 to 3.6)	2.5 (0.3 to 20.3)	1.2 (0.5 to 2.5)
Strokes or TIAs (n=46) v no strokes or TIAs (n=260)	2.1* (1.1 to 4.4)	0.6 (0.2 to 2.0)	1.3 (0.7 to 2.4)

* p < 0.05 v those without the allele.

WMLs = white matter lesions; TIAs = transient ischaemic attacks.

Table 4 ORs for Alzheimer's disease, vascular dementia, and all dementias in relation to white matter lesions and possession of the apoE ε4 allele

	No dementia (n=117) n	Alzheimer's disease (n=27)			Vascular dementia (n=37)			All dementia (n=72)		
		n	OR	p Value	n	OR	p Value	n	OR	p Value
No WMLs and no apoE ε4 allele (reference group)	42	4	1.0		8	1.0		13	1.0	
No WMLs/at least one apoE ε4 allele	35	6	1.8 (0.5 to 6.9)		4	0.6 (0.2 to 2.2)		11	1.0 (0.4 to 2.5)	
WMLs/no apoE ε4 allele	23	6	2.7 (0.7 to 10.7)		7	1.6 (0.5 to 5.0)		16	2.2 (0.9 to 5.5)	
WMLs/at least one apoE ε4 allele	17	11	6.8 (1.9 to 24.3)	0.002	18	5.6 (2.0 to 15.2)	0.0007	32	6.1 (2.6 to 14.3)	0.00003

WMLs = white matter lesions.

Table 5 ApoE alleles in non-demented 85 year old people in relation to the incidence of dementia per 1000 person-years at risk between age 85 and 88

	Subjects (n)	OR for dementia disorders in those having at least one allele of:		
		ε2 v no ε2	ε3 v no ε3	ε4 v no ε4
No dementia	223			
Any dementia	59	1.2 (0.6 to 2.2)	1.7 (0.4 to 7.1)	1.2 (0.7 to 2.1)
Alzheimer's disease (AD)	24	0.3 (0.1 to 1.4)	1.4 (0.2 to 10.6)	2.1† (0.9 to 4.8)
Mixed dementia (MIX)	3	—	—	—
Multi-infarct dementia (MID)	24	2.9* (1.3 to 6.6)	1.4 (0.2 to 10.4)	0.7 (0.3 to 1.6)
Other dementias	7	0.6 (0.1 to 4.9)	—	3.8 (0.7 to 20.0)
All AD (including MIX)	27	0.3† (0.1 to 1.2)	1.6 (0.2 to 11.9)	1.6 (0.7 to 3.5)
All vascular dementia (MID+MIX+hypoperfusion)	28	2.5* (1.2 to 5.5)	1.6 (0.2 to 12.2)	0.5 (0.2 to 1.3)

* p < 0.05; † p < 0.10 v people without the allele.

— Not calculated because of small groups.

white matter lesions had an OR for dementia of 6.1 (p=0.00003). The same pattern emerged when those with Alzheimer's disease, all vascular dementias, pure multi-infarct dementia, and mixed dementia were analysed separately against the no dementia group.

Mean onset of dementia was 79.9 (SD 4.6) years in those with no apoE ε4 allele (n=45), 79.5 (SD 4.0) years in those with one (n=47), and 72.8 (SD 8.9) years (p<0.05) in those with two (n=6).

Three year follow up

Table 5 shows the apoE alleles in 85 year old people in relation to the incidence of dementia between the ages of 85 and 88 (based on number of cases/1000 risk-years). Development of dementia was not related to genotype of apoE. When development of different types of dementias was considered, carrying the apoE ε2 allele was associated with an increased risk of developing pure multi-infarct dementia (OR 2.9; p<0.05) and all vascular dementia (OR 2.5; p<0.05) and a tendency to a decreased risk of developing all Alzheimer's disease (which included also mixed dementia; OR 0.3; p<0.10). The apoE ε4 allele was associated with a tendency towards an increased risk of pure Alzheimer's disease (OR 2.1; p<0.10) and a tendency to a decreased risk for all vascular dementia (OR 0.5; p=0.17). All ORs were in the same direction when men and women were analysed separately.

The incidence of dementia between the ages of 85 and 88 in 85 year old people without an apoE ε4 allele (n=171) was 8.5/1000 person-years at risk (95%CI 6.0-11.8), for those with one (n=100) 10.3/1000 person-years at risk (95%CI 6.7-15.0) (OR 1.2, 95% CI: 0.7-2.1, NS), and for those with two (n=11) 8.1/1000 person-years at risk (95%-CI 1.0-26.2) (OR 0.9, 95% CI: 0.2-4.2; NS).

The three year mortality was 30.0% in subjects with no apoE ε4 allele (n=233), 30.6% in those with one (n=160), and 36.8% in those with two (n=19). The allele frequency in subjects who died within three years compared with survivors was for ε2, 0.111 v 0.100, for ε3, 0.639 v 0.664, and for ε4, 0.250 v 0.236. All differences were non-significant, even when men and women and demented and non-demented people were analysed separately.

Discussion

The main finding in this population study is that neither the possession of the apoE ε4 allele nor the presence of white matter lesions on CT by themselves are sufficient risk factors for dementia in 85 year old people, whereas the co-occurrence of these two entities increases the risk of both Alzheimer's disease and vascular dementia substantially, suggesting an interaction between these factors in the aetiology of dementia. White matter lesions have previously been associated both with Alzheimer's disease and vascular dementia in this sample.²³ Our present report shows that the increased risk for dementia in those with white matter lesions was significant only in those possessing the apoE ε4 allele, whereas possession of the apoE ε4 allele was only associated with an increased risk of dementia in subjects who also had white matter lesions. These findings are in line with those from another population study, which recently reported a similar interaction between generalised atherosclerosis and the apoE ε4 genotype in the aetiology of both Alzheimer's disease and vascular dementia.²⁷

The association between the apoE ε4 allele and dementia, including Alzheimer's disease, in this population based sample of 85 year old persons was weaker than previously reported from younger samples. Furthermore, the

follow up study showed that carrying one or two apoE ϵ 4 alleles did not increase the risk of developing dementia after the age of 85. These findings support previous reports of a reduced association between the apoE ϵ 4 allele and dementia or Alzheimer's disease with increasing age.^{6,9,12-14,38,39} It has been hypothesised that almost all people homozygotic for the apoE ϵ 4 allele will develop dementia by the age of 80,¹ but we found that 13 out of 19 85 year old people homozygotic for the apoE ϵ 4 allele were non-demented. Furthermore, the difference between Alzheimer's disease and controls regarding homozygosity for the apoE ϵ 4 allele was negligible (6% *v* 4%). Our findings are in line with other population studies,^{6,10,15} according to which only about one half of homozygotes are demented in very old age. In line with others,^{1,4,10,39} we found that those with two apoE ϵ 4 alleles had an earlier onset of dementia than the other groups. Onset accelerating factors (such as having two apoE ϵ 4 alleles) may be associated with an increased risk of dementia at ages before the mean onset of the disorder, but later the association will be reduced.⁴⁰ Support for this hypothesis is that carrying one apoE ϵ 4 allele (with a supposed onset intermediate between those with none and two), but not of two, was related to an increased prevalence of dementia at the age of 85, in line with analysis by Poirier *et al* of octogenarians.⁴ The apoE ϵ 4 allele may thus neither be sufficient nor necessary to produce dementia in very old age. That other genetic or environmental factors are important is also reflected by the finding that 23 out of 52 people with Alzheimer's disease lacked the apoE ϵ 4 allele.

What are the mechanisms behind our findings? It is clear that the apoE ϵ 4 allele is a risk factor for Alzheimer's disease pathology (β -amyloid plaques and neurofibrillary tangles in the brain). The association between these changes and dementia wanes with increasing age and in very old people they are common even in non-demented subjects.⁴¹ In very old age, the apoE ϵ 4 allele may only be a sufficient risk factor for Alzheimer's disease in those with white matter lesions, which then affect the clinical expression of the disease. On the other hand, white matter lesions were only related to dementia in those who possessed the apoE ϵ 4 allele. The mechanism for this may be an impaired capacity for neuronal regeneration in apoE ϵ 4 carriers.⁴²

It is often difficult to differentiate between vascular dementia and Alzheimer's disease on clinical grounds alone, and the definition of vascular dementia differs between studies.¹⁵ With the criteria used in this study, the agreement between clinical and neuropathological diagnosis of Alzheimer's disease has been reported to be 80%-90%.^{43,44} The agreement between the clinical and pathological diagnosis of multi-infarct dementia has generally been lower, between 50% and 60%.^{43,44} However, if multi-infarct dementia and mixed dementias are grouped together, the agreement increases to 80%-95%,^{34,43} and with the criteria used in this study, the diagnostic accuracy was 90%

even for multi-infarct dementia.³⁴ However, it has to be emphasised that clinicopathological correlation studies have not been performed in samples from the general population. With this in mind, some cross sectional studies report an increased frequency of the apoE ϵ 4 allele in both Alzheimer's disease and multi-infarct dementia,²⁰ in samples of patients with multi-infarct dementia,^{19,21} and in dementia with stroke including both vascular dementia and Alzheimer's disease with stroke.⁴⁵ We also found that the apoE ϵ 4 allele frequency was increased in vascular dementia at the age of 85 when a broad definition was used. When vascular dementia was categorised into those with pure multi-infarct dementia and those with mixed Alzheimer's disease-multi-infarct dementia, only the second group was associated with possession of the apoE ϵ 4 allele, which has also been reported by others.⁴⁶ However, the high OR for mixed Alzheimer's disease-multi-infarct dementia has to be taken cautiously given that only 10 patients had this diagnosis and due to the uncertainty regarding the clinicopathological correlation for this category. However, in a postmortem study from Gothenburg, an increased frequency of the apoE ϵ 4 allele was only found in Alzheimer's disease and not in multi-infarct dementia.⁴⁷

Although we did not find an association between the genotype of apoE and the incidence of all dementias, there were associations with the incidence of different types of dementia. The apoE ϵ 2 allele was associated with a higher incidence of multi-infarct dementia and a tendency towards a lower incidence of Alzheimer's disease, whereas the associations with the apoE ϵ 4 allele was in the opposite direction. Although these findings may support the hypothesis that the apoE ϵ 2 allele is protective against the development of Alzheimer's disease,⁴⁸ it may also be a consequence of current diagnostic criteria for Alzheimer's disease and multi-infarct dementia, as stroke is one of the diagnostic criteria for multi-infarct dementia and generally excludes a diagnosis of Alzheimer's disease, which may result in negative associations between risk factors for stroke and Alzheimer's disease.¹⁵ At the age of 85, patients with a history of stroke or transient ischaemic attack were more often carriers of the apoE ϵ 2 allele, in line with one previous report,⁴⁹ but by contrast with others.^{18,50} If the apoE ϵ 2 allele is associated with cerebrovascular disorder in this age group, it may spuriously lead to a negative association between this allele and Alzheimer's disease.

The allele frequency of apoE ϵ 4 in non-demented people (0.22) was higher than that previously described in most control populations (0.07-0.17),^{2-4,6,20,51} whereas that in Alzheimer's disease was similar.^{2-5,20,51} Others⁵² have reported a higher allele frequency of apoE ϵ 4 (0.20) in Sweden compared with other white populations, and a recent postmortem study from Gothenburg reported that the apoE ϵ 4 allele frequency in non-demented elderly subjects was 0.21.⁴⁷ It may be that the frequency of the apoE ϵ 4 allele is relatively high in the Swedish population.

Most studies report that the apoE $\epsilon 4$ allele frequency decreases with increasing age,^{6,9,12,14,16,52} which has been suggested to be caused by an increased mortality in those with this allele.⁵³ Although this may be true in younger populations, we did not find an increased mortality in 85 year old people carrying the apoE $\epsilon 4$ allele. Neither did Corder *et al*¹⁸ in patients affected with Alzheimer's disease, Feskens *et al*⁵⁴ in a population with a mean age of 75 years, or Corder *et al*¹⁸ in those below the age of 75. Corder *et al* reported,³⁸ however, that in those older than 85 years with normal cognitive function, the apo $\epsilon 4$ allele was related to an increased mortality.

In summary, this study shows that possession of the apoE $\epsilon 4$ allele in 85 year old people was only associated with dementia in those who also had ischaemic white matter lesions. These findings support the view that dementia in very old age involves the interaction of several pathological processes.^{41,54} The study also shows that dementia is not an inevitable consequence when subjects homozygotic for the apoE $\epsilon 4$ allele survive into extreme old age. There is a need for further research into genetic or environmental factors that modify the risk of dementia in those possessing the apoE $\epsilon 4$ allele.

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