

Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study

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Summary

Background Vascular disorders have been implicated in dementia, but whether atherosclerosis is related to the most frequent type of dementia, Alzheimer's disease, is not known. The apolipoprotein-E genotype has been associated with Alzheimer's disease, and we postulate that it plays a part, together with atherosclerosis, in the aetiology of Alzheimer's disease. We investigated the frequency of dementia and its subtypes in relation to atherosclerosis and apolipoprotein E.

Methods We did a population-based study of 284 patients with dementia, 207 of whom had Alzheimer's disease, and 1698 individuals who were not demented. Indicators of atherosclerosis included vessel wall thickness and plaques of the carotid arteries, assessed by ultrasonography, and the ratio of ankle-to-brachial systolic blood pressure as a measure of generalised atherosclerosis. Based on these indicators participants were scored from 0 (no atherosclerosis) to 3 (severe atherosclerosis) for degree of atherosclerosis. Apolipoprotein-E polymorphisms were assessed in 246 patients and in 928 controls.

Findings All indicators of atherosclerosis were associated with dementia (odds ratios ranging from 1.3 to 1.9) and its major subtypes Alzheimer's disease (odds ratios 1.3–1.8) and vascular dementia (odds ratios 1.9–3.2). The frequencies of all dementia, Alzheimer's disease, and vascular dementia increased with the degree of atherosclerosis. The odds ratio for Alzheimer's disease in those with severe atherosclerosis compared with those without atherosclerosis was 3.0 (95% CI 1.5–6.0; $p=0.001$). In participants with the apolipoprotein-E $\epsilon 4$ genotype and an atherosclerosis score of 2 or 3 the odds ratio for all dementia was 4.5 (2.0–10.1; $p<0.001$), for Alzheimer's disease was 3.9 (1.6–9.6; $p=0.002$), and for vascular dementia was 19.8 (4.1–95.0; $p<0.001$).

Interpretation These findings suggest that dementia and its two major subtypes Alzheimer's disease and vascular dementia are associated with atherosclerosis and that there is an interaction between apolipoprotein E and atherosclerosis in the aetiology of Alzheimer's disease.

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Introduction

Dementia is an important cause of disability, particularly in the elderly. The most important subtype of dementia is Alzheimer's disease, which accounts for at least half of all dementia cases.¹ The causes of dementia are largely unknown, although important progress has been made in discovering genetic factors that play a part in the aetiology of Alzheimer's disease. In particular, an association of the apolipoprotein-E $\epsilon 4$ allele with Alzheimer's disease has been reported.^{2–4} Atherosclerosis has been implicated in dementia, but except for a small group of patients diagnosed as having vascular dementia, no evidence for a role of atherosclerosis in other dementias including Alzheimer's disease, has been presented.⁵ Non-invasive techniques to assess atherosclerosis allow the study of atherosclerosis and its putative sequelae in large populations.

We report a population-based cross-sectional study of atherosclerosis, the apolipoprotein-E genotype and the prevalence of dementia and its subtypes in 284 dementia patients and 1698 individuals who were not demented.

Methods

This study was done as part of the Rotterdam Study, a single-centre prospective follow-up study in which all residents aged 55 years or over from the suburb of Ommoord in Rotterdam, Netherlands, were invited to take part. The study was approved by the Medical Ethics Committee of Erasmus University, and written informed consent was obtained from all participants. The objective of the study was to investigate determinants of chronic and disabling cardiovascular, neurodegenerative, locomotor, and ophthalmological diseases, as described in detail elsewhere.⁶ Participants were interviewed at home and then examined during two visits to a research centre. For people living in institutions the examinations were done in their institution. The first part of the Rotterdam Study, on which this report is based, was done between March, 1990, and July, 1993. 7983 (78%) of the 10 275 eligible individuals participated. Ages ranged from 55 to 106 years. Of those who participated, 7528 (94%) underwent extensive screening for dementia, and information on cardiovascular risk factors, indicators for atherosclerosis, and apolipoprotein-E genotype was obtained. The remaining 455 individuals refused to undergo cognitive examination or died before examination. Indicators for atherosclerosis for 284 patients with dementia were compared with those for 1698 control participants who were not demented.

Dementia was assessed by a three-phase approach.⁷ All participants were screened with a brief cognitive test; screen-positive participants then underwent cognitive and neurological testing; and those whose results suggested dementia underwent a detailed examination or had their diagnosis confirmed and the type of dementia established by referral to medical records.

The brief cognitive test for dementia in the first phase of assessment was a combination of the mini-mental state examination (MMSE)⁸ and the geriatric mental state examination (GMS-A organic level test).⁹ The test was administered by trained research assistants. Screen-positive individuals had a MMSE score of 25 or less, or a GMS-A score of 1 or more. In the second phase, screen-positive individuals were examined by a physician affiliated to the Rotterdam Study with the Cambridge examination for

mental disorder of the elderly (CAMDEX) diagnostic interview,¹⁰ which included an interview with a relative or other carer. Participants who scored less than 80 on the CAMDEX cognitive test or who had higher scores but were suspected of having dementia on clinical grounds were asked to participate in the third examination phase. In this diagnostic phase participants were examined by a neurologist, had a brain scan by magnetic resonance imaging, and were tested by a neuropsychologist.

Dementia was diagnosed according to the American Psychiatric Association's criteria (DSM-III-R).¹¹ The subdiagnosis of Alzheimer's disease was based on criteria of the working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).¹² For the subdiagnosis of vascular dementia the DSM-III-R definition of multi-infarct dementia was used. The type of dementia diagnosed at the onset of the disease was ascertained. Some patients with Alzheimer's disease develop symptoms of vascular dementia during the course of the disease, usually after a stroke, which may result in a sudden worsening of dementia.¹³ We classified these patients as Alzheimer's type with cerebrovascular disease.

474 cases of dementia were identified.⁷ Our analysis was restricted to 284 of those participants in whom the dementia onset was less than 3 years before they were examined as part of this study. This approach effectively restricted the analysis to participants with mild and moderate dementia, in whom the disease was unlikely to have changed the atherosclerosis status. In 228 (80.3%) of the 284 dementia patients the diagnosis was based on the CAMDEX and examination by the study neurologist; in 52 (18.3%) patients it was based on MMSE and GMS data; and for four (1.4%) individuals the diagnosis was based on medical records only. Data on apolipoprotein-E genotype were available in 246 of the patients with dementia.

A random sample of 1698 people ranging in age from 55 years to 99 years, served as controls. They were selected from the group of participants of the Rotterdam Study who were screen-negative for dementia. Data on cardiovascular risk factors and on indicators for atherosclerosis were available for all these control participants and data on apolipoprotein-E polymorphisms were available for 928 of them.

Measurements

Presence of atherosclerosis of the carotid arteries (wall thickness and plaques as measured by ultrasonography) and presence of atherosclerosis of the large vessels of the legs (assessed by the ratio of the ankle-to-brachial systolic blood pressure) were assessed as potential correlates of dementia.

Ultrasonography of both carotid arteries was done with a 7.5 MHz linear-array transducer and a duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). Intima-media thickness was measured in the common carotid arteries as described previously.¹⁴ Presence of atherosclerotic plaques, defined as a focal widening of the vessel wall relative to adjacent segments with protrusion into the lumen, was assessed in the common carotid arteries, the bifurcation of the carotid arteries, and the internal carotid arteries.¹⁵ The presence of atherosclerosis of the legs was non-invasively assessed with the use of ultrasound. The ratio of the ankle-to-brachial systolic blood pressure (ankle-brachial index) reflects the presence of atherosclerotic vessel-wall abnormalities of the arteries of the legs and is a good indicator of generalised atherosclerosis.^{16,17} Ankle systolic blood pressure was measured with the participant in a supine position at both right and left posterior tibial arteries with a doppler ultrasound transducer with a random-zero sphygmomanometer (cuff-size 38×14 cm). The average of the left and the right ankle-brachial indices was used. Peripheral arterial disease was judged to be present when left or right ankle-brachial index was less than 0.90.

Genomic DNA was used for apolipoprotein-E typing.¹⁸ The apolipoprotein-E gene was amplified by the primer and amplification conditions described by Wenham and colleagues.¹⁹ After amplification, the PCR product was digested with the restriction enzyme *HhaI* and fragments were separated by

	Mean (SD) for men		Mean (SD) for women	
	Dementia (n=82)	No dementia (n=623)	Dementia (n=202)	No dementia (n=1075)
Age (years)*	81.2 (59-97)	69.9 (55-94)	84.1 (59-98)	71.9 (55-99)
Blood pressure (mm Hg)				
Systolic	137.7 (24.5)	138.1 (20.7)	143.2 (24.6)	138.9 (22.4)
Diastolic	74.0 (16.2)	72.8 (10.9)	71.1 (14.6)	71.2 (11.6)
Total cholesterol (mmol/L)	5.8 (1.1)	6.3 (1.2)	6.3 (1.2)	6.9 (1.3)
Body-mass index (kg/m²)	24.8 (3.2)	25.9 (3.2)	25.7 (4.1)	27.0 (4.3)

*Range in parentheses.

Table 1: Characteristics of study participants

electrophoresis on a 5% agarose gel. Apolipoprotein-E alleles were visualised by staining with ethidium bromide.

Blood pressure was measured with a random-zero sphygmomanometer on the right arm of the seated participant. The average of two measurements obtained on one occasion, separated by a count of the pulse rate was used. Serum concentrations of total lipoprotein and high-density-lipoprotein (HDL) cholesterol were measured by an automated enzymatic procedure.²⁰ Body-mass index was calculated as bodyweight (kg) divided by height (m) squared.

Statistical analysis

The associations between atherosclerosis, apolipoprotein E, and dementia were analysed in four ways. First, the associations of indicators of atherosclerosis with dementia and its subtypes were estimated. To adjust for age and sex differences within the age strata, a multiple-linear regression-model was used, with age and sex added to the model. Because of the importance of age as a potential confounder, we added age as a continuous variable in years and months to the regression models, and we also added indicator variables for 5-year age bands to all regression models. The associations are presented as odds ratios with 95% CI.

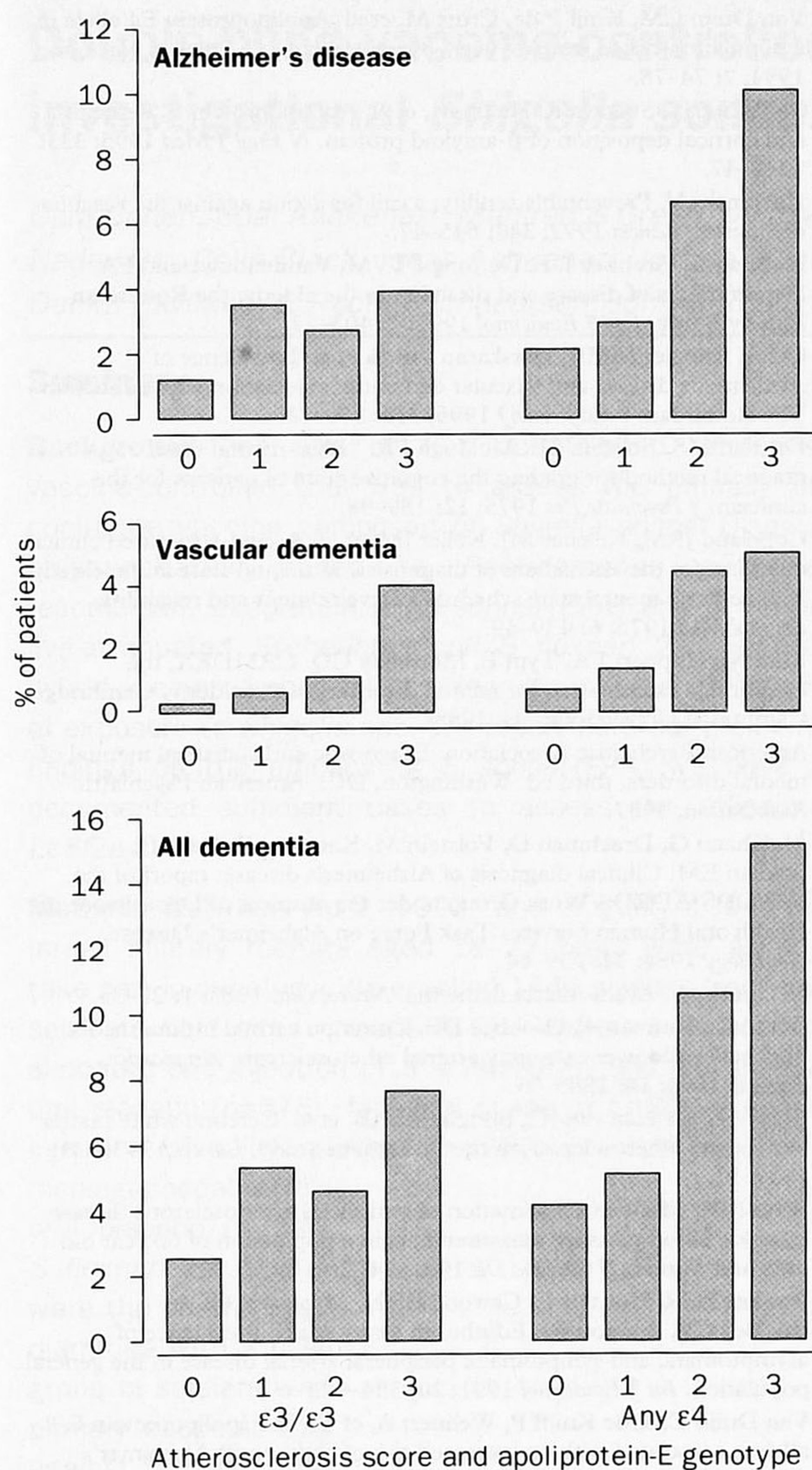
Second, a composite measure of atherosclerosis was constructed: a point was added to the atherosclerosis score if the following characteristics were present: plaques in at least one of the common carotid arteries, average wall-thickness of common carotid arteries in the highest quartile of the distribution, and evidence of peripheral arterial disease, defined as ankle-to-brachial index less than 0.90. This score of atherosclerosis was analysed in four categories corresponding to score values of 0-3. With a logistic regression model, the odds ratio of each category of atherosclerosis for dementia and its subtypes was calculated, with age and sex entered into the regression model, and with age in 5-year age bands.

Third, the association between the atherosclerosis score and dementia was assessed for subgroups of participants according to apolipoprotein-E polymorphisms; in this analysis participants homozygous for apolipoprotein E3 ($\epsilon 3/\epsilon 3$) were compared with

	Alzheimer's disease (n=207)	Vascular dementia (n=50)	Other dementia (n=27)	All dementia (n=284)
Peripheral arterial disease (95% CI)*	1.3 (0.9-1.8)	2.5 (1.3-4.8)	1.0 (0.4-2.4)	1.5 (1.1-2.0)
Plaques in common carotid arteries	1.8 (1.2-2.7)	3.2 (1.6-6.8)	1.6 (0.6-4.3)	1.9 (1.3-2.7)
Wall thickness common carotid arteries†	1.3 (1.0-1.6)	1.9 (1.3-2.8)	0.8 (0.4-1.5)	1.3 (1.1-1.6)
Atherosclerosis score				
0	1.0	1.0	1.0	1.0
1	2.2 (1.2-3.9)	1.3 (0.4-4.7)	0.1 (0.0-1.0)	1.6 (1.0-2.7)
2	2.5 (1.3-4.6)	4.8 (1.6-14.2)	0.6 (0.2-2.4)	2.3 (1.4-3.9)
3	3.0 (1.5-6.0)	9.5 (3.0-30.0)	0.7 (0.1-3.4)	3.2 (1.8-5.7)
	<0.001	<0.001	0.392	<0.001

*Adjusted for age and sex. †Odds ratio of one SD (0.20 mm) increase of wall thickness.

Table 2: Age-adjusted odds ratios of Alzheimer's disease, vascular dementia, and other dementias by indicators of atherosclerosis



Proportions of patients with Alzheimer's disease, vascular dementia, and all dementia adjusted for age and sex, by apolipoprotein-E genotype and atherosclerosis score

those with at least one apolipoprotein E4 allele ($\epsilon 4/\epsilon 2$, $\epsilon 4/\epsilon 3$, or $\epsilon 4/\epsilon 4$). The results of this analysis are presented as age-adjusted and sex-adjusted prevalence figures, both by apolipoprotein-E type and atherosclerosis score.

Fourth, in a further analysis of the interaction of atherosclerosis and apolipoprotein-E genotype, odds ratios are presented in a table with atherosclerosis of score 2 or 3 and score 0 or 1 and genotype (homozygous $\epsilon 3$, or at least one $\epsilon 4$ allele). In addition, a regression analysis was done on the full dataset with the product term for apolipoprotein genotype (in two categories as above) and atherosclerosis (also in two categories as above), as assessed with a model that also included both terms separately, adjusted for age and sex. The coefficient of the interaction term was expressed as an odds ratio with a 95% CI.

Genotype	Alzheimer's disease		Vascular dementia		All dementia	
	AS 0 or 1	AS 2 or 3	AS 0 or 1	AS 2 or 3	AS 0 or 1	AS 2 or 3
$\epsilon 3/\epsilon 3$	1.0	1.4 (0.7-3.1)	1.0	7.1 (1.5-34.3)	1.0	1.6 (0.8-3.2)
Any $\epsilon 4$	1.3 (0.6-2.7)	3.9 (1.6-9.6)	3.6 (0.8-16.2)	19.8 (4.1-95.0)	1.4 (0.7-2.7)	4.5 (2.0-10.1)

AS=atherosclerosis score.

Table 3: Age-adjusted odds ratios of Alzheimer's disease, vascular dementia, and all dementia by atherosclerosis score and apolipoprotein-genotype

No major differences in the associations between atherosclerosis and dementia were observed between men and women, and therefore the estimates are presented for men and women together.

Results

There were 82 men and 202 women with dementia. 207 (73%) demented patients were diagnosed as having Alzheimer's disease, 50 (18%) as having vascular dementia, and 27 (10%) as having other dementias. Table 1 presents some characteristics of the participants.

All indicators of atherosclerosis were significantly associated with all dementia (odds ratios ranging from 1.3 to 1.9; table 2), with Alzheimer's disease (odds ratios 1.3-1.8), and with vascular dementia (odds ratios 1.9-3.2). When patients classified as having Alzheimer's disease with cerebrovascular disease ($n=31$) were excluded from the Alzheimer's disease group, the estimates of the odds ratios were almost unchanged.

The apolipoprotein-E $\epsilon 4$ allele was associated with all dementias (odds ratio 1.8 [95% CI 1.2-2.7]), Alzheimer disease (odds ratio 1.7 [1.0-2.7]), and vascular dementia (odds ratio 2.3 [1.1-4.8]).

The odds ratios of all dementia, Alzheimer's disease, and vascular dementia increased with the score of atherosclerosis (table 2). Among patients with the apolipoprotein-E $\epsilon 4$ genotype the frequency of those with any type of dementia, with Alzheimer's disease, and with vascular dementia increased substantially with atherosclerosis score (figure).

Participants with evidence of atherosclerosis (score 2 or 3) and the apolipoprotein-E $\epsilon 4$ genotype had an increased risk for all dementia, Alzheimer's disease, and vascular dementia (table 3). The odds ratio of the interaction term of atherosclerosis and apolipoprotein genotype was 2.0 (0.7-5.9) for all dementia, and 2.4 (0.9-7.6) for Alzheimer's disease.

The observed associations of atherosclerosis and apolipoprotein-E genotype with dementia, Alzheimer's disease, and vascular dementia were almost unaltered after adjustment for blood pressure, total cholesterol, and body-mass index.

Discussion

The main findings of this study are that indicators of atherosclerosis are associated with the presence of dementia, and both of its main subtypes, Alzheimer's disease and vascular dementia, and that the association between atherosclerosis and dementia is particularly strong in those with the apolipoprotein-E $\epsilon 4$ genotype. However, limitations of the study design should be discussed.

This is a cross-sectional study, and changes in the atherosclerotic status could have occurred as a consequence of dementia. Although we believe this possibility is unlikely, we reduced it by restricting our study to patients with recent diagnoses of dementia. Another concern is the measurement of atherosclerosis. We used ultrasonographic indicators of atherosclerosis, but increased thickness of the common-carotid intima-media may not necessarily reflect atherosclerosis. It may merely reflect an adaptive response of the vessel wall to changes in the shear and tensile stress. However, increased wall thickness, measured ultrasonographically, of the common carotid artery has been associated with cardiovascular risk factors.²¹⁻²³ In addition, progression of vessel-wall thickening has been associated with risk factors for atherosclerosis.²⁴ This association supports the view that

non-invasively assessed intima-media thickness of the common carotid artery may be regarded as an indicator of atherosclerosis.

Some error could have occurred in the measurement of atherosclerosis indicators. Such error would have led to misclassification and thus to underestimation of any true association between atherosclerosis and dementia, provided that the measurement error occurred to the same extent among the dementia patients and the control participants.

A strength of our study is that it was population-based and had a high response rate and so it is unlikely that a selection bias was involved in our findings. However, how dementia and its subtypes are diagnosed is of central importance. A high sensitivity and specificity of the diagnostic procedure was ensured by the three-phase diagnosis.^{7,8,25,26} Without confirmation at necropsy, however, subtyping of dementia remains unreliable. Also, the diagnostic criteria that were used are of limited accuracy. A major concern in our study is the classification of dementia patients with cerebrovascular disease. In our main analysis, we classified primary Alzheimer's disease complicated by cerebrovascular disease as Alzheimer's disease. However, the additional analysis in which cerebrovascular patients were excluded from the Alzheimer's group yielded virtually the same results as the main analysis. Although we cannot fully exclude diagnostic misclassification even in this additional analysis, we believe that it supports the view that atherosclerosis is associated with Alzheimer's disease.

Our findings suggest that atherosclerosis is associated not only with a small subgroup of vascular, or multi-infarct dementia, but also with the major subtype of dementia, Alzheimer's disease. Our findings are in agreement with a report that suggested a role of β -amyloid peptides in vascular endothelial damage.²⁷ The large difference in the prevalence of dementia and Alzheimer's disease between those with the apolipoprotein-E ϵ 4 allele compared with those with the ϵ 3/ ϵ 3 genotype by degree of atherosclerosis suggests an interplay between apolipoprotein E and atherosclerosis in the aetiology of Alzheimer's disease. Although addition of the cardiovascular risk factors, blood pressure and serum lipids to our analysis did not change the association between indicators of atherosclerosis and dementia, these risk factors may still have a role in the aetiology of dementia.²⁸

Our data suggest an interaction between atherosclerosis and apolipoprotein E, to the effect that the increase in the prevalence of Alzheimer's disease with atherosclerosis is particularly pronounced in those with the apolipoprotein-E ϵ 4 genotype.²⁹ Unfortunately, these cross-sectional data do not allow further investigation of the interaction.

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