Risk and protective effects of the APOE gene towards Alzheimer’s disease in the Kungsholmen project: variation by age and sex

C Qiu, M Kivipelto, H Agüero-Torres, B Winblad, L Fratiglioni

Background: The risk effect of APOE ε4 allele for Alzheimer’s disease is acknowledged, whereas the protective effect of ε2 allele remains in debate. Objectives: To investigate whether inconsistent findings may be attributable to differences in age and sex composition of the study populations. Methods: A community dementia free cohort (n = 985) aged ≥75 years was followed up to detect Alzheimer’s disease cases (DSM-III-R criteria). Data were analysed using Cox models with adjustment for major potential confounders. Results: Over a median 5.6 year follow up, Alzheimer’s disease was diagnosed in 206 subjects. Compared with APOE ε3/ε3 genotype, the relative risk (RR) of Alzheimer’s disease was 1.4 (95% confidence interval (CI), 1.0 to 2.0; p = 0.03) for heterozygous ε4 allele and 3.1 (95% CI, 1.6 to 5.9) for homoczygous ε4 allele. The association between ε4 allele and Alzheimer’s disease risk was stronger in men than in women (RR related to the interaction term ε4 allele by sex, 0.4; 95% CI, 0.2 to 0.9). The ε4 allele accounted for one third of Alzheimer’s disease cases among men, but only one tenth among women. The ε2 allele was related to a reduced Alzheimer’s disease risk mainly in people aged <85 years (RR, 0.4; 95% CI, 0.2 to 0.8). The RR of Alzheimer’s disease related to the interaction term ε2 allele by age was 2.4 (95% CI, 1.0 to 6.0; p = 0.06). Conclusions: The APOE genotype specific effects on Alzheimer’s disease vary by age and sex, in which the ε4 allele has a stronger risk effect in men, and the ε2 allele confers a protective effect only in younger-old people.

The ε4 allele of the apolipoprotein E gene (APOE) has been found to be an important genetic risk factor for late onset Alzheimer’s disease in a large majority of epidemiological studies. Conversely, the relation between APOE ε2 allele (mostly the ε2/ε3 genotype and rarely the ε2/ε2 genotype) and risk of Alzheimer’s disease remains in much controversy. Although the ε2 allele was found to be a risk factor for early onset Alzheimer’s disease, the protective effect of the allele on Alzheimer’s disease in white people had been clearly indicated in a meta-analysis that covered the major studies investigating this topic until 1997. Lately, a number of population based studies have, however, shown that the ε2 allele has no protective effect on Alzheimer’s disease, or was related to a non-significantly decreased risk of the disease probably because of fewer carriers of the allele. Therefore, the suggested benefit of the ε2 allele on Alzheimer’s disease needs to be further elucidated in large scale community based studies.

The variations by age and sex in the APOE ε4 specific risk for late onset Alzheimer’s disease have been a focus of numerous epidemiological studies. The ε4 allele associated risk for Alzheimer’s disease is frequently reported to decline after around 70 years. In contrast, there has been a lot of debate about whether there is a sex difference in the ε4 allele related risk for Alzheimer’s disease. The population based prospective data from Finland showed that the association between APOE ε4 and Alzheimer’s disease was more pronounced in men than in women, which is in disagreement with some previous studies that show no sex difference or an apparent stronger ε4 allele-Alzheimer’s disease association in women than in men. By contrast, very few data are currently available concerning the age and sex variations of the ε2 specific effect on Alzheimer’s disease.

On the basis of previous population based studies, we hypothesised that APOE ε2 allele may exert a protection against Alzheimer’s disease and that the APOE genotype specific effects on the disease may vary with age and sex. The purpose of this study was to examine these hypotheses by investigating the age or sex specific association between APOE genotype and incidence of Alzheimer’s disease using the six years follow up data from the Kungsholmen project.

METHODS

Study population

The study population was derived from the Kungsholmen project, a community based cohort study of aging and dementia. Design of the project and inception of the cohort have been fully reported elsewhere. Briefly, the initial population of the project included all eligible inhabitants that were 75 years and older in October 1987 and were living in the Kungsholmen district of Stockholm, Sweden. By a two phase design, 1473 subjects were identified as being free of dementia at baseline (1987 to 1989). Of these subjects, 172 refused to undertake the first follow up contact (1991 to 1993) or had moved out of Stockholm before the contact. Information on APOE genotype was missing for 316 persons. Therefore, the population for these analyses consisted of 985 subjects who underwent at least the first follow up examination. Among the 689 subjects who were alive and remained non-demented at first follow up, 31 refused to participate in the second follow up evaluation (1994 to 1996). Medical records and death certificates were available for all the deceased subjects during the first (n = 145) and the
second (n = 123) follow up periods. All parts of the project received approval from the ethics committee of Karolinska Institutet.

**Baseline data collection**

Data on age, sex, and cognitive function (assessed with the mini-mental state examination, MMSE) were collected following standard protocols. Educational level was measured by total years of formal schooling and divided into <8 years compared with ≥8 years based on a previous study. Genomic DNA was extracted from peripheral blood samples that were taken during the baseline survey, and a standard polymerase chain reaction procedure was used for APOE genotyping. Blood pressure was measured by nurses on the right arm using a mercury sphygmomanometer. Information on history of heart disease (ICD-8 codes 410–414, 427, and 428), cerebrovascular disease (ICD-8 codes 430–438), and diabetes mellitus (ICD-8 code 250) at baseline was derived from the computerised inpatient register system that covered all hospitals in the Stockholm area since 1969. This register system recorded up to six kinds of disorders that had been identified during each period of hospitalisation. Data on medical drug use were collected for the two weeks preceding the baseline survey. Antihypertensive drugs were defined as all medicines potentially used for lowering blood pressure (that is, the Anatomical Therapeutic Chemical classification system codes C02, C03, and C07).

**Diagnosis of incident Alzheimer’s disease**

The incident cases were all people that developed Alzheimer’s disease and were detected over the two follow up periods. The follow up evaluation and diagnostic procedure have been reported elsewhere. In brief, all survivors underwent an extensive dementia examination at each follow up, including a structured interview by nurses, a comprehensive clinical examination by physicians, and neuropsychological assessments. The Diagnostic and Statistical Manual of Mental Disorders, revised third edition (DSM-III-R) criteria were used to define dementia cases with a three-step procedure—that is, two examining physicians independently made a preliminary diagnosis and a third opinion was asked in case of disagreement. The diagnosis of Alzheimer’s disease required gradual onset, progressive deterioration, and lack of any other specific causes of dementia. Alzheimer’s disease was diagnosed on a clinical basis, and neuropathological and imaging data were not available for the diagnosis. Our criteria for Alzheimer’s disease were similar to those from the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association for probable Alzheimer’s disease. For deceased subjects, two physicians made the diagnosis through reviewing the medical records and death certificates.

**Data analysis**

The statistical differences were examined with t test for continuous and χ² test for categorical variables. We used logistic regression analysis to evaluate the effect of baseline characteristics on drop outs. Incidence rate was calculated as the number of cases divided by person years at risk of follow up. Cox proportional hazards models were constructed to estimate the relative risk of Alzheimer’s disease, with corresponding 95% confidence intervals (CI). We first examined the association between APOE genotype and incidence of Alzheimer’s disease, with the e3/e3 genotype as a reference category. The modifying effects of age and sex were then evaluated by stratified analysis. Finally, we examined the statistical interaction by including the two independent variables and their cross product term in the same model. Age (in years), sex, education, systolic pressure (indicator variables with categories of <140, 140 to 159, ≥160 mm Hg, and missing values), diastolic pressure (indicator variables with categories of <70, 70 to 89, ≥90 mm Hg, and missing values), vascular disease, baseline MMSE score, and antihypertensive drug use were considered as covariates in multivariate analyses. We estimated the potential contribution of APOE e4 allele to Alzheimer’s disease by calculating the population attributable risk percentage (PAR%), that is PAR% = [p(r−1)/(1+p(r−1))]×100%, where p is the proportion of e4 allele in the population and r is the relative risk estimated from a multiple model.

**RESULTS**

Of the initial dementia free cohort (n = 1473), 488 subjects dropped out because of refusal of either the first follow up visit or the APOE genotyping. In a multiple logistic regression model, being a drop out was associated with older age (odds ratio per one year increment 1.10, 95% CI 1.07 to 1.13) and a lower baseline MMSE score (odds ratio per one point increment 0.93, 95% CI 0.89 to 0.97), but not significantly related to sex, educational level, vascular disease, or antihypertensive drug use.

The frequencies of different APOE genotypes among the 985 subjects were 0.3% (n = 3) for e2/e2, 13.2% (n = 130) for e2/e3, 1.9% (n = 19) for e2/e4, 58.0% (n = 571) for e3/e3, 24.3% (n = 239) for e3/e4, and 2.3% (n = 23) for e4/e4. Table 1 shows the baseline characteristics of the study participants by APOE genotypes. There was no significant difference in the distribution of these characteristics among APOE genotype groups.

**Relation of Alzheimer’s disease to APOE genotypes**

During the total of 4754 person years of follow up (median 5.6, range 0.1 to 8.3 years), Alzheimer’s disease was diagnosed in 206 subjects. Compared with APOE e3/e3 genotype, the e4 allele was significantly associated with an increased risk of Alzheimer’s disease in a dose-response fashion, whereas the e2 allele (that is, e2/e2 or e2/e3 genotype) was related to a reduced risk of the disease although it was not statistically significant (table 2). In this multiple Cox model, being female was associated with a relative risk of 1.7 (95% CI 1.2 to 2.5) for developing Alzheimer’s disease.

**Relation of Alzheimer’s disease to APOE genotypes by age and sex**

Overall, as shown in figure 1, the strength of association between APOE e4 allele and risk of Alzheimer’s disease did not differ considerably by age group, but the point estimate of relative risk was more than doubled in men than in women. Conversely, the e2 related relative risk for Alzheimer’s disease did not vary much by sex, whereas the e2 allele was significantly related to a reduced disease risk, especially in people under the age of 85 years. There was no protection of the e2 allele against Alzheimer’s disease in the oldest old (≥85 years). Further analysis indicated that the e2 allele specific benefit was present mainly in women aged 75 to 84 years old (n = 590, 123 Alzheimer cases; the multi-adjusted relative risk 0.4, 95% CI 0.2 to 0.7). Among men who were 75 to 84 years of age (n = 208, 26 Alzheimer cases), no benefit from carrying the e2 allele was seen (multi-adjusted relative risk 1.6, 95% CI 0.3 to 7.4). In the entire population, the multi-adjusted relative risks were 2.4 (95% CI 1.0 to 6.0, p = 0.06) for the interaction term of e2 allele by age (≥85 versus <85 years) and 0.4 (95% CI 0.2 to 0.9) for the term of e4 allele by sex. No statistical interactions of the e2 allele with sex and of the e4 allele with age were detected.
Population attributable risk estimation
In comparison with the carriers of ε3/ε3 genotype, the percentages of Alzheimer cases attributable to possession of the ε4 allele were 14.6% in the entire population, 33.3% in men, and 10.5% in women.

Additional analyses
We repeated the analysis by using non-ε4 allele as a reference group. The adjusted relative risk of Alzheimer’s disease related to any ε4 allele was 1.6 (95% CI 1.2 to 2.2), with the relative risk of 1.5 (95% CI 1.1 to 2.1) for one ε4 allele and 3.2 (95% CI 1.7 to 6.2) for two copies of the allele (p for trend <0.01). The ε4 allele related risk for Alzheimer’s disease was doubled in men (relative risk 3.1, 95% CI 1.4 to 6.5) than in women (relative risk 1.5, 95% CI 1.0 to 2.0, p = 0.02), with the relative risk of 0.4 (95% CI 0.2 to 0.9) for the interaction term of any ε4 by sex. There was no statistical interaction of ε4 allele with age. Furthermore, to assess the potential influence of APOE genotype related selective survivals, we reanalysed the data by either additionally adjusting for the vital status at the time of Alzheimer’s disease being diagnosed or excluding the deceased subjects from the study population, which yielded results similar to those from the initial analysis (data not shown).

DISCUSSION
In this comparatively homogenous population of community dwelling people aged ≥75 years, we found: (1) the ε2 allele confers a protection against Alzheimer’s disease in the younger old people (<85 years); and (2) the strength of association between APOE ε4 allele and risk of Alzheimer’s disease is stronger in men than in women. It seems unlikely that the potential confounding biases or selective survivals could explain the observed age and sex difference in the APOE genotype specific effects on the disease.

Numerous studies have reported that the APOE ε4 allele specific risk for Alzheimer’s disease increases with age until around 70 and declines thereafter.1–3 We were not able to evaluate the age variation of the ε4 allele-Alzheimer association before 75 years, but our data showed that the risk effect of the ε4 allele on Alzheimer’s disease might not vary by age after 75. This notion is in line with a previous population study,10 in which the ε4 related risk for Alzheimer’s disease appeared to have no pronounced variation with age after 75 years. A few population based studies have shown a stronger female specific impact of the ε4 allele on Alzheimer’s disease or on the development of cognitive decline.26–28 This finding has been viewed as a partial support for the higher incidence of Alzheimer’s disease in women than in men.29 By contrast, the recent population based study from north Europe indicated a stronger association between the APOE ε4 allele and Alzheimer’s disease in men than in women.29,30 In accordance with this recent study, we found an interaction between APOE ε4 and sex on the occurrence of Alzheimer’s disease, in which the ε4 allele exerted a higher risk to develop Alzheimer’s disease in men compared with women. As no sex difference in the ε4 allele frequency was seen in our population, the substantial population attributable risk of Alzheimer’s disease, which resulted from possession of the ε4 allele in men (33.3%) compared with women (10.5%), is due primarily to a stronger APOE ε4 allele-Alzheimer’s disease association in men.

Few population based prospective studies have so far assessed the gene-dose effect of the ε4 allele on the risk of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of the study participants (n = 985) by the APOE genotypes</th>
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<td>70 to 89</td>
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<tr>
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<tr>
<td>Number of subjects</td>
<td>Number of cases</td>
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<tr>
<td>ε2/ε2 or ε2/ε3</td>
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<tr>
<td>ε2/ε4 or ε3/ε4</td>
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</tr>
<tr>
<td>ε3/ε4</td>
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</table>

*MMSE, mini-mental state examination. MMSE score was from 0 (worst) to 30 (best); †at least one of heart disease, cerebrovascular disease, and diabetes mellitus was present; ‡blood pressure readings were missing for 19 subjects, including three subjects for ε2/ε2 or ε2/ε3 genotype, 14 for ε3/ε3 genotype, and two for any ε4 allele.

<table>
<thead>
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<th>Table 2</th>
<th>Crude incidence rates (per 1000 person years) and adjusted relative risks (95% CIs) of Alzheimer’s disease by APOE genotypes</th>
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<td>APOE genotype</td>
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<td>ε2/ε2 or ε2/ε3</td>
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<td>ε2/ε4 or ε3/ε4</td>
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</tr>
<tr>
<td>ε3/ε4</td>
<td>23</td>
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</table>

*The relative risks (95% CIs) were derived from different Cox proportional hazards models: model 1 included age, sex, education, and APOE genotype; model 2 included all variables in model 1 plus baseline MMSE score, systolic pressure, diastolic pressure, vascular disease, and the use of antihypertensive drugs; †p = 0.03.
Alzheimer’s disease, partly because of limited number of APOE e4 homozygous people in the general populations. In the nested case-control analysis of the Rotterdam study, the risk ratios of Alzheimer’s disease were 1.8 for the e3/e4 genotype and 6.2 for the homozygous e4 allele compared with the e3/e3 genotype, while in the Copenhagen heart study the corresponding figures were 3.3 and 10.1. Our study showed a clear dose-response relation between the number of e4 alleles and the risk of Alzheimer’s disease, but the strength of the dose association was less stronger than those previously reported. Differences in characteristics of the study population as well as in the consideration of potential confounders may largely explain these discrepancies. For instance, our study population was much older and more covariates were taken into account in our analysis. In addition, some studies have estimated the e4 allele related risk for Alzheimer’s disease by using non-e4 allele as a referent category. To compare with these studies, we also estimated the risk effect of the e4 allele versus non-e4 allele in the additional analysis, but this may generally lead to an overestimation of the risk role of the allele because of the potential protective effect of the e2 allele on the development of Alzheimer’s disease.

A meta-analysis study suggested that the e2/e3 genotype (probably the e2/e2 genotype) could exert protection against Alzheimer’s disease, but it did not vary with age. Recently, the association between e2 allele and a decreased risk of Alzheimer’s disease has been reported in a few population based studies. The non-significantly protective effect of the e2 allele seemed similar across age strata in the Rotterdam cohort aged 55 years and older. In the MRC cognitive function and ageing study, subjects possessing the e2 allele were found to have a lower risk of dementia, but the decreased risk was not significant because of small numbers. Sex specific analysis in this study did not show any difference in the allele effect between men and women. The cohort study of elderly Catholic clerics in the United States showed that APOE e2 allele could protect against episodic memory decline, a defining feature of Alzheimer’s disease. The protection of the e2 allele on Alzheimer’s disease was less evident, largely because of limited statistical power. On the other hand, two population based studies showed no evidence of any protection of the e2 allele against Alzheimer’s disease. One of the important findings in our study was that the benefit of e2 allele against Alzheimer’s disease was age dependent—that is, the apparent protection existed mainly in people aged 75 to 84 years. Although further analysis showed that the protection of e2 allele against Alzheimer’s disease was present only among women, we were not able to determine whether there was a real sex difference in the effect of e2 allele in this age group because our study cohort included too few male carriers of the allele and the confidence intervals were largely overlapping. Further clarification of the age and sex differences in the e2 allele effect on Alzheimer’s disease may be helpful to understand the previous inconsistent findings. For instance, the e2 allele specific effect for Alzheimer’s disease reported in some studies might not be specified by age and sex.

Neuropathological studies have linked the sex differences of different APOE genotypes to the densities of β-amyloid protein and neurofibrillar tangles in the brain, which are the hallmark features of Alzheimer lesions. What are the possible explanations for the age and sex variations of the APOE genotype specific effects on the disease? Firstly, in our cohort, more men were affected by vascular disease (24.7% versus 19.2%, p = 0.07), whereas more women were treated with antihypertensive drugs (46.7% versus 35.2%, p<0.01). This may partially explain the sex difference in the e4 allele-Alzheimer association because previous studies have shown that vascular disorders may advance the dementia process, while the use of antihypertensive drugs may diminish the risk effect of e4 allele on the disease. Secondly, the age and sex differences in the e4 specific risk may reflect the variant severities of Alzheimer lesions in the

Figure 1: Relation of Alzheimer’s disease (AD) to APOE genotype by age group (left) and sex (right). The relative risk (RR) and 95% confidence interval (CI) were estimated with adjustment for age (in years), education, baseline MMSE score, systolic pressure, diastolic pressure, vascular disease, antihypertensive drug use, and if applicable, for sex.
brain, as a neuropathological study indicated that the ε4 allele was related to senile plaques across all ages for men, whereas for women such a relation existed only in those under 80 years.\textsuperscript{77} Thirdly, previous studies have revealed a sex-differential effect of APOE genotype on plasma lipids metabolism and atherosclerotic disorders.\textsuperscript{78,79} In the Framingham study, for instance, after controlling for major potential confounders, possession of the ε4 allele (compared with ε3/ε3) was associated with a greater risk for cardiovascular disease only in men. As serum cholesterol and atherosclerosis may act directly or in combination with APOE ε4 to increase the risk of Alzheimer’s disease,\textsuperscript{80,81} it could contribute to the sex difference in the ε4 allele-Alzheimer association. The age and sex differential ε4 allele-Alzheimer’s disease association needs to be verified before any explanations can be offered.

A potential limitation of this study is that information on APOE genotypes was missing for nearly one third of the initial eligible dementia free subjects. However, drop out analysis suggested that this might not seriously harm the representativeness of our population, and sensitivity analysis showed no evidence for the potential influence of missing values on the estimate of APOE genotype-dementia association.\textsuperscript{82} Furthermore, the lack of neuroimaging and necropsy verified information for the diagnosis of Alzheimer’s disease may lead to misclassification, but this may merely attenuate the association between APOE genotypes and risk of the disease. Furthermore, the study population consisted of persons with a minimum age of 75 years at entry. Thus, it may not be justified in generalising these findings to younger people. Finally, the multiple hypothesis tests within a single dataset may lead to a higher rate of type I error (that is, false positive inference), which emphasises the need for further confirmation of our findings.

In summary, the APOE ε4 allele has a gene-dose effect on the risk of Alzheimer’s disease, whereas the ε2 allele confers a protection against the disease. The APOE genotype specific risks for Alzheimer’s disease vary by age and sex. These findings, if replicated, may have relevant indications for genetic counsel (for example, age and sex should be specified to estimate the APOE genotype related risk) as well as for the actiology of Alzheimer’s disease.

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REFERENCES


Serum antibodies to HSV 2 DNA. Serum VDRL and TPHA were both positive. and a negative PCR test for herpes simplex virus (HSV) 1 and microscopic examination for mycobacteria and cryptococcus, 5 IgG oligoclonal bands, a positive VDRL test, a negative intravenous penicillin G at a dosage of 4 million IU four 40 year old man suffered a 9 h dreamy state with automatons. The neurological examination revealed disinhibited behaviour, a positive Romberg sign, and absent abdominal and weak tendon reflexes. Neuropsychological examination showed a selective reduction of short term spatial memory. A brain MRI performed after 2 weeks showed a prevalently cortical lesion in the right temporal and basal frontal lobes, which was slight hypointense in T1 weighted images and hyperintense in DP and T2 weighted images (fig 1), without enhancement. Carbamazepine was introduced. About a month later a second brain MRI revealed that the lesion was reduced to a small area in the right mesiotemporal region (fig 2), hypointense in T1 weighted and hyperintense in T2 weighted images, without enhancement after intravenous gadolinium; the right temporal horn was greater than the controlateral. CSF analysis showed normal glucose content, 12 lymphocytes/mm³, slight elevated protein level (63 mg/dl, normal range: 20–40), a positive Link's index (3.5, normal <0.75), 5 IgG oligoclonal bands, a positive VDRL test, a negative microscopic examination for mycobacteria and cryptococcus, and a negative PCR test for herpes simplex virus (HSV) 1 and HSV 2 DNA. Serum VDRL and TPHA were both positive. Serum antibodies to Borrelia burgdorferi, Toxoplasma gondii, and HIV 1 and HIV 2 were negative. The patient received intravenous penicillin G at a dosage of 4 million IU four times a day for 10 days. Complex partial status epilepticus (CPSE) has been observed with neurosyphilis. The pathogenesis is thought to be the mesiotemporal localisation of luetic vasculitis. The MRI shows cortical and subcortical hyperintensity in T2 weighted images, probably due to both cytotoxic and vasogenic oedema. The images are similar to those of HSV encephalitis. The T2 hyperintense lesion in the right temporal lobe and fronto-basal region only evident on the first MRI examination and mimicking HSV encephalitis may be due to transient oedema caused by the CPSE and spontaneously resolved before penicillin treatment. The small right mesiotemporal lesion evident on the second MRI examination may have a vasculitic origin and it may be responsible for CPSE. We recommend short term repetition of brain MRI and CSF examination for differential diagnosis of mesiotemporal syndromes. References

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