# A 9-year prospective population-based study on the association between the *APOE ε4* allele and late-life depression in Sweden

## Short Title*:* The *APOE ε4* allele and late-life depression

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# Abstract

**Background**: It is well established that there is an association between the Apolipoprotein (*APOE*) ε4 allele and Alzheimer's disease (AD). It is less clear whether there is also an association with geriatric depression. Therefore, we examined the relationship between *APOE ε4* and 5-year incidence of depression in a Swedish population-based sample of older adults without dementia and excluding those who developed dementia within 4 years after the diagnosis of depression.

**Methods:** In 2000-2001, 839 women and men (aged 70-92 years, mean age 73.8 years) free from dementia and depression, underwent neuropsychiatric and neuropsychological examinations and genotyping of the *APOE* ε4 allele. Follow-ups were conducted in 2005 and 2009.The association between *APOE* ε4 allele and 5-year incidence of depression was examined, while avoiding possible confounding effects of clinical/preclinical dementia by excluding participants who had dementia at study-entry or subsequently developed dementia during the 9-year follow-up, or had a decline in Mini-Mental State Examination of 5 or more points.

**Results:** Among those without depression at study entry and without dementia or significant cognitive decline during the subsequent 9 years, *APOE ε4* was prospectively associated with more severe depressive symptoms (B = 1.56, p= 0.007), incident minor depression (OR 1.99, CI[ 1.11-3.55],p= 0.020) and any depression (OR 1.75, CI[ 1.01-3.03], p=0.048).

**Conclusions:** The presence of the *APOE ε4* allele predicted future depression in this Swedish population study, even after excluding depressed individuals who later developed dementia, suggesting that the *APOE ε4* allele could potentially identify people at high risk for clinically significant depression.

# Introduction

The *APOE ε4* allele is a risk factor for conditions that mainly affect older persons, including Alzheimer's disease (AD)(1-5), atherosclerosis(6) as well as cardiovascular and cerebrovascular disease(2, 3, 7-9). The association between *APOE ε4* and depression has been a topic of debate over the last decades. Some clinical studies show associations with geriatric depression(10-12), while others do not(13-16). Clinical studies are subject to referral bias, and many were conducted among patients from memory clinics and may thus have included persons with preclinical dementia. The need to study *APOE* ε4 and depression in unselected population-based studies has therefore been stressed(17, 18). Most population-based studies have been cross-sectional with disparate results. Some failed to show associations between *APOE ε4* and major depression(19) or depression symptom severity(20-22), but there have been exceptions(23, 24). For example, one study showed an association only in individuals above age 80 years(25).

Thus far, no longitudinal study has shown associations between *APOE ε4* and future depression(17, 26-30). Individuals who later develop dementia have not been excluded from these studies, but depression may be a prodromal symptom of dementia(31) and those who develop dementia may have a different symptomatic profile when they become depressed and thus not fulfil research criteria for depression. Hence, it is important to exclude cases of prodromal dementia in studies addressing the association between *APOE ε4* and depression. We therefore examined the relationship between *APOE ε4* and incidence of depression in a population-based sample of older Swedish adults followed over 5 years. We were able to follow the sample for a further four years to exclude new cases of dementia occurring after

the diagnosis of depression. Our hypothesis was that the *APOE ε4* allele would be related to development of depression, even after excluding depressed individuals who later developed dementia.

# Methods and Materials

### *Participants*

This analysis originates from two epidemiologic studies in Gothenburg, Sweden, the Prospective Population Study of Women (PPSW) and the Gerontological and Geriatric Population Studies (H70), both of which have been described previously(32-35). The participants were sampled from the Swedish Population Register on the basis of their birth date and were born in 1908, 1914, 1918, 1922 and 1930. Both persons living in private households and in residential care were included. In total, there were 1495 eligible individuals in 2000-2001, and 1051 agreed to participate (response rate 70.3%). Among these, 33 participants did not complete the neuropsychiatric examination, leaving 1018 participants for the present study(35). Among these, 895 (88%) consented to donate their blood for genetic analyses. The women were aged 70-92 years (4 born in 1908, 31 born in 1914, 141 born in 1918, 180 born in 1922 and 539 born in 1930). All men (n=220) were aged 70 years in 2000-2001. Of the 895 participants assessed in 2000-2001, 57 participants had dementia and one had incomplete information (5 men and 52 women) and were therefore excluded, leaving 838 individuals (mean age 73.8 years).

Follow-up examinations were conducted in 2005-2006 and 2009-2010. The follow-up examination in 2009 was used only to diagnose dementia not depression to reduce the possibility that depression in 2005 was a preclinical symptom of dementia. There were 655 participants followed-up in 2005-06 (500 women, 155 men, response rate among survivors 86.0%), and 492 in 2009-10 (response rate among survivors 78.7%). There was no relationship between having the *APOE E4* allele and attrition during the follow-up in 2005 (p=0.408) and 2009 (p=0.489).

The study was approved by the Ethics Committee for Medical Research at the University of Gothenburg, and informed consent was obtained from all participants and/ or their relatives in cases of dementia.

***Study procedures***

The clinical examination was conducted at an outpatient department or in the participant's home and included comprehensive social, functional, physical, neuropsychiatric and neuropsychological examinations, as well as a close informant interview.

***Neuropsychiatric examinations and interviews***

Semi-structured neuropsychiatric examinations were performed by trained psychiatric research nurses. These examinations included ratings of past month's psychiatric symptoms and signs according to the Comprehensive Psychopathological Rating Scale (CPRS)(36), which is valid and reliable in older populations(37), Mini-International Neuropsychiatric Interview (38) and assessment of current medications. Ratings of common symptoms and signs of dementia were also performed (e.g. assessments of memory, orientation, general knowledge, apraxia, visuospatial function, understanding proverbs, following commands, naming ability and language) and has been described in detail previously(39, 40). Cognitive function was also measured with the Mini Mental State Examination (MMSE)(41).
The psychiatric nurses who performed the examinations were supervised and trained by psychiatrists. Inter-rater reliability between psychiatrists and nurses was studied in 50 individuals who had dual ratings by either psychiatric research nurses or psychiatrists. Kappa values for the presence versus absence of symptoms and signs necessary to diagnose depression were between 0.62 and 1.00 indicating "good" (reference range kappa=0.61-0.80) or "excellent" (kappa=0.81-1.00) agreement. Inter-rater agreement for the symptoms and signs used to diagnose dementia was between good and excellent (kappa values between 0.74

and 1.00)(42). Close informant interviews were also performed. The interviews were semi-structured and comprised questions about changes in behaviour and intellectual function, psychiatric symptoms, activities of daily living, and, in cases of dementia, age of onset and disease course.

***Diagnoses***

Major and minor depression was diagnosed according to DSM-IV research criteria(43, 44), except that the use of the bereavement criterion was not applied, which makes it the same as DSM-5(45). Any depression incorporates minor and major depression. Depression symptom burden was measured with the Montgomery-Åsberg Depression Scale (MADRS)(36).

Dementia was diagnosed by geriatric psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)(46), based on symptoms rated during the neuropsychiatric examinations and information from the close informant interviews, as described previously(39).

Participants with dementia or depression at baseline were excluded from further analysis. We were not able to define depression with a first-onset in late-life.

The diagnosis of stroke was based on information from self-reports, close informants and the Swedish Hospital Discharge Register.

***Laboratory methods***

Blood samples were collected and *APOE* (gene map locus 19q13.2) genotyping was performed by minisequencing as previously described in detail(47) and was successful for 100% of the consenting participants. Genotypes were obtained for the two SNPs (rs7412 and rs429358), which are used to unambiguously define ε2, ε3, and ε4 alleles.

***Statistical analyses***

Differences in proportions were tested with Fisher's exact test. Differences in continuous variables were tested with t-test. Multivariate binary logistic and linear regressions were used to explore the association between *APOE* ε4 carriership and new depression in 2005. In all models, individuals with depression or dementia at baseline in 2000 were excluded. In a first model, new depression in 2005 or MADRS score in 2005 were dependent variables. Age, sex, *APOE* ε4, stroke until 2005 and dementia until 2005 were independent variables. In a second model, we also excluded participants who developed dementia during 2000-2009 in order to minimize possible effects of clinical or preclinical dementia. In this model, new depression in 2005 or MADRS score in 2005 were dependent variables. MMSE score, age, sex, *APOE* ε4, and stroke until 2005 were independent variables. In a final third binary logistic regression model, we excluded those participants whose MMSE score declined by 5 or more points from 2005 to 2009 and who developed dementia during 2000-2009. In this model new depression in 2005 or MADRS score in 2005 were dependent variables. Age, sex, *APOE* ε4 and stroke until 2005 were independent variables. Statistical tests were carried out using SPSS for Windows (v. 17, SPSS, Chicago, IL.). P-values <0.05 (two-tailed) were regarded as significant.

# Results

Baseline characteristics are shown in Table 1. In 2000, 32 participants were diagnosed with major depression and 94 with minor depression. No associations could be observed at baseline between the *APOE ε4* allele and minor depression (OR 1.24 CI [0.78-1.99] p= 0.36), major depression (OR 0.901 CI [0.39-2.04] p= 0.802), any depression (OR 1.16 CI [0.76-1.76] p = 0.499) or MADRS score (B = -0.46, p = 0.345) in cross-sectional analyses. No interactions by sex regarding the association between depression and *APOE ε4* could be seen (data not shown). The presence of the *APOE ε4* allele was not related to 5- or 9-year mortality (data not shown).

Model 1: In 2005-06, we examined 655 individuals. Among these, 93 were diagnosed with depression in 2000. Thus, 562 participants without depression at baseline took part in a new examination, at which 96 new cases were diagnosed with depression (14 with major depression and 82 with minor depression). Among those who had no depression or dementia in 2000, presence of the *APOE ε4* allele was associated with higher MADRS score (B=1.38; p=0.010), any depression (OR 1.65, CI [1.02-2.7]; p= 0.043) and new onset minor depression (OR 1.83 CI [1.1-3.0]; p=0.019) in 2005 (Table 2).No interactions by sex regarding the association between depression and *APOE ε4* could be seen (data not shown).

Between 2000 and 2009, 103 individuals developed dementia (50 new cases based on the 2005 examination, 53 new cases based on the 2009 examinations). In a multiple logistic regression model (including age and sex), presence of the *APOE* ε4 allele was associated with dementia development 2001-2009 (OR 1.73, CI [1.07-2.81]; p=0.026).

Model 2: In order to avoid possible effects of clinical/preclinical dementia, we re-analysed data after excluding all participants who had dementia at baseline, or developed dementia during 2000-2009. Among those who had no depression in 2000, *APOE ε4* was associated with MADRS score (B=1.57, p=0.006), any depression (OR 1.73, CI [1.0-3.0], p= 0.048), and new onset minor depression (OR 1.95, CI [1.1-3.4]; p=0.021) in 2005 in multivariate binary logistic and linear regression models. There were no significant interactions between age and the *APOE ε4* allele on the outcome of new onset depression (p= 0.311), minor depression (p= 0.573) or major depression (p=0.998).

Model 3: In this model we excluded all participants with dementia up to 2009 and those with a decline of 5 points or more in the MMSE between 2005 and 2009. Among those who had no depression in 2000, *APOE ε4* was associated with MADRS score (B 1.56, p= 0.007), any depression (OR 1.75, CI [1.01-3.03] p= 0.048), and new onset minor depression (OR 1.99, CI [1.11-3.55] p= 0.020). There were no significant interactions between age and the *APOE ε4* allele on the outcome of new onset depression (p= 0.361), minor depression (p= 0.709) or major depression (p=0.998).

# Discussion

To the best of our knowledge, this is the first longitudinal population-based study of older persons to report a relation between *APOE ε4* and development of depression. We found an association between the presence of the *APOE ε4* allele with both incident minor depression and depression symptom severity during 5-year follow-up. People who developed dementia within 9 years of study entry were excluded and the results remained when controlling for MMSE score at baseline and MMSE decline of 5 points or more between 2005 and 2009, indicating that our results were not merely due to prodromal symptoms of dementia or cognitive decline. As expected, *APOE ε4* was also associated with dementia development during follow-up.

The strength of the association between *APOE ε4* and depression is likely population-dependent, as has been shown for dementia(48-51). This may be due to both environmental and genetic differences between populations(52). Previous longitudinal population-based studies have not shown associations between *APOE ε4* and development of depression(17, 26-28, 30), but one study did show an association between *APOE ε4* and depression only in individuals with cognitive decline(29). Prior studies have been conducted in multi-ethnic American(17, 26, 27, 30), English(28) and Chinese (29) populations. This is the first longitudinal study on *APOE* ε4 and depression conducted in Scandinavia where the frequency of the *APOE* ε4 allele is relatively high(53, 54). Moreover, Sweden has one of the longest living populations in the world(55). Thus, individuals at risk for depression due to the presence of *APOE ε4* may survive to older ages.

Other possible reasons for heterogeneity and lack of associations between the *APOE ε4* allele and depression in other longitudinal studies include differences in study designs, such as the use of lay interviewers (28), not including participants living in institutions(17, 26, 27), or

having younger populations (27-30). In addition, small sample sizes sometimes resulted in low statistical power (26, 27). Other studies have not excluded individuals who later developed dementia. One study (30) aimed to solve this problem by only including individuals with very high cognitive function (i.e. 27-30 on MMSE) at baseline, and thus with a low risk to develop dementia during follow-up. This study did not find an association between *APOE ε4* and incidence of depression. However, our exclusion of individuals who later developed dementia could not entirely explain the disparate results as this did not result in dramatic changes in coefficients in our sample. It has been suggested that the association between *APOE ε4* and depression is mainly conferred to individuals above age 80 years (25), but we found no interaction with age in our study.

In our study, *APOE ε4* was related to minor depression and depressive symptoms, but not to major depression. It has to be emphasized, however, that the number with major depression at follow-up was small. Moreover, geriatric depression typically has a milder symptom burden, so the few cases with major depression is not unexpected(26, 56, 57). Previous studies suggest that incident minor depression is related more to changing life circumstances and health events(58-60) than to genetic factors. Our study is one of the first to show that a biomarker is related to minor depression while not associated with major depression. In a previous report from this study(61), WMLs and brain atrophy on CT were related to development of major depression, but not to minor depression.

The mechanism by which *APOE ε4* confers risk for geriatric depression warrants further research. One intermediating factor may be brain atrophy, which has been reported to be a risk factor for late-life depression(61). *APOE ε4* has also been related to brain atrophy, especially temporal lobe atrophy, in healthy individuals(62) (63), in patients with

257 depression(64-67) and in remitted late-onset depression patients (68). Another intermediating
258 factor may be stroke or cerebrovascular disease. *APOE ε4* is associated with stroke(69) (70,
259 71), and stroke increases the risk for depression(9) (72), including minor depression(72, 73).
260 In our study, as well as in a French study(74), the association between *APOE ε4* and
261 depression remained after adjustment for stroke, suggesting that other mechanisms are
262 involved. For example, *APOE ε4* influences neuronal priming leading to altered
263 neuroinflammatory pathways that develop during aging(75). These possible mechanisms
264 could however not explain the heterogeneity in results between samples.

265

266 Many studies report that depression increases the risk of dementia(76-78), although results are
267 inconclusive. One reason may be that depression is an intermediate step in the association
268 between *APOE ε4* and dementia, especially AD(79, 80) (29, 78, 81, 82) (14, 20, 28, 83, 84).
269 Thus, depression might be caused by early preclinical neuropathological changes triggered by
270 *APOE ε4* or may be involved in the pathogenesis of these disorders. We chose to examine
271 relationships between *APOE ε4* and depression development during a five-year follow-up, to
272 be able to exclude cases of future dementia. Our results remained even after excluding
273 dementia development up to 4 years after the diagnosis of depression and after excluding
274 participants with a steep decline in the MMSE between 2005 and 2009.

275 ***Strengths and weaknesses***

276 Among the strengths of this study are the representative population-based sample, the
277 comprehensive examinations conducted by trained psychiatric nurses blinded to allele status,
278 the long follow-up and the exclusion of participants who subsequently developed dementia or
279 experienced cognitive decline

Some limitations need to be addressed. First, the number of cases with incident major depression was small. The results on major depression must therefore be taken cautiously. Second, some of the participants may have had major or minor depressive episodes prior to baseline and others may have had such episodes between examination waves. Third, we did not have the statistical power to carry out a stratified analysis regarding heterozygous and homozygous *APO E* status. Fourth, due to the merging of two different population studies (albeit examined with identical methods during the same time), the study is unbalanced regarding gender. Therefore, the group older than 70 years at baseline only comprised women. Thus, our exploratory analyses regarding gender have to be interpreted cautiously. Fifth, attrition is always a problem in longitudinal population-based studies. However, response rates during follow-up were satisfactory. Finally, this is a population study focusing on Scandinavian participants aged 70-92 years at baseline and results cannot be generalized to clinical samples, to younger populations or to other ethnic groups.

In conclusion, our study is the first longitudinal population-based study which reports a relation between *APOE ε4* and development of depression in older people who remained free from dementia for another four years after the diagnosis of depression. Depression prevention initiatives require identification of high-risk persons(85). *APOE ε4* might be a marker for identifying older persons at high risk to develop clinically significant depression that could be employed in prevention trials.

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# Table

**Table 1** Baseline characteristics of study sample in 2000

| | Men (n=215) | Women (n=623) | p-Value[a] |
|---|---|---|---|
| Age at baseline Mean (SD)[b] | 70.6 (0.18) | 75.8 (5.44) | t=-14.0, 836 df, p<0.001 |
| Education beyond mandatory | 89 (42.6%) | 213 (35.5%) | 0.08 |
| MADRS Mean (SD) | 3.7 (0.32) | 5.7 (0.27) | t=-4.0, 794 df, p<0.001 |
| Any Depression n (%)[c] | 19 (8.8%) | 107 (17.2%) | 0.003 |
| Minor Depression n (%)[c] | 15 (7.0%) | 79 (12.7%) | 0.02 |
| Major Depression n (%)[c] | 4 (1.9%) | 28 (4.5%) | 0.10 |
| *APOE ε4* allele n (%) | 61 (28.4%) | 166 (26.6%) | 0.34 |

a. Fisher's exact tests unless otherwise specified.
b. All men in the sample were born in 1930.
c. DSM-IV/ IV research criteria.

**Table 2** Relationship between APOE ε4 allele and incident depression at 5 year follow-up in a population sample of elderly persons

| Selection criteria | No ε4 allele | Any ε4 allele | Linear and logistic regression results of ε4 allele influence on incidence of depression[d] |
|---|---|---|---|
| **Model 1**[a] | n=416 | n=146 | |
| MADRS Mean(SD) | 5.0 (5.2) | 6.4 (5.4) | B=1.38 p=0.010 |
| Any Depression n (%)[d] | 63 (15%) | 33 (23%) | OR 1.65 (1.02-2.7) p=0.04 |
| Minor Depression n (%)[d] | 52 (13%) | 30 (21%) | OR 1.83 (1.1-3.0) p=0.02 |
| Major Depression n (%)[d] | 11 (3%) | 3 (2%) | OR 0.71 (0.19-2.65) p=0.61 |
| **Model 2**[b] | n=369 | n=122 | |
| MADRS Mean(SD) | 4.8 (5.1) | 6.4 (5.6) | B=1.57 p=0.006 |
| Any Depression n (%)[d] | 50 (14%) | 25 (21%) | OR 1.73 (1.0-3.0) p=0.048 |
| Minor Depression n (%)[d] | 41 (11%) | 23 (19%) | OR 1.95 (1.1-3.4) p=0.02 |
| Major Depression n (%)[d] | 9 (2%) | 2 (2%) | OR 0.67 (0.14-3.21) p=0.62 |
| **Model 3**[c] | n= 362 | n= 118 | |
| MADRS Mean( SD) | 4.8( 5.1) | 6.4(5.6) | B=1.56 p=0.007 |
| Any Depression n(%)[d] | 47(13) | 24( 20.3) | OR 1.75( 1.01-3.0) p=0.048 |
| Minor Depression n(%)[d] | 38( 10.5) | 22( 18.6) | OR 1.99(1.1-3.5) p=0.02 |
| Major Depression n(%)[d] | 9( 2.5) | 2( 1) | OR 0.67(0.1-3.2) p=0.61 |

a.Model 1: Association of ε4 allele presence on incidence of depression from multivariate binary logistic models and MADRS score from linear regression models also including age, sex, MMSE score and cases of stroke (2005 follow up only) and dementia development up to 2005 , excluding participants with dementia or depression at baseline

b.Model 2: Association of ε4 allele presence on incidence of depression from multivariate binary logistic models and MADRS score from linear regression models also including age, sex, MMSE score and cases of stroke (2005 follow up only) excluding all participants with dementia development 2000-2009 and participants with dementia or depression at baseline.

c. Model 3: Association of ε4 allele presence on incidence of depression from multivariate binary logistic models and MADRS score from linear regression models also including age, sex, and cases of stroke (2005 follow up only) excluding all participants with a drop of 5 points in MMSE between 2005-2009 or more and participants with depression or dementia at baseline and dementia development 2000-2009.

d. DSM –IV/ IV research criteria.