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Predictive value of *APOE*- ϵ 4 allele for progression from MCI to AD-type dementia: a meta-analysis

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ABSTRACT

Background The identification of subjects with mild cognitive impairment (MCI) at high risk for Alzheimer's disease (AD) is important for prognosis and early intervention. The *APOE*- ϵ 4 allele is the strongest known genetic risk factor for AD. The authors performed a meta-analysis to establish the predictive accuracy of the *APOE*- ϵ 4 allele for progression from MCI to AD-type dementia.

Methods The authors included 35 prospective cohort studies of subjects with MCI, including 6095 subjects, of whom 1236 progressed to AD-type dementia after 2.9 years of follow-up. Pooled estimates of the OR, sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR+ and LR-) were obtained using random-effects models.

Results The OR for subjects with MCI who are carriers of *APOE*- ϵ 4 allele to progress to AD-type dementia was 2.29 (95% CI 1.88 to 2.80), the sensitivity was 0.53 (95% CI 0.46 to 0.61), the specificity was 0.67 (95% CI 0.62 to 0.71), the PPV was 0.57 (95% CI 0.48 to 0.66), the NPV was 0.75 (95% CI 0.70 to 0.80), the LR+ was 1.60 (95% CI 1.48 to 1.72), and the LR- was 0.75 (95% CI 0.67 to 0.82). Meta-regression showed that sensitivity, specificity and NPV were dependent on age, *APOE*- ϵ 4 allele background prevalence or follow-up length.

Conclusions The *APOE*- ϵ 4 allele is associated with a moderately increased risk for progression from MCI to AD-type dementia. The low sensitivity and PPV makes genotyping of limited value for predicting AD-type dementia in clinical practice. For trials aiming to prevent progression from MCI to AD-type dementia, *APOE* genotyping may be useful in selecting subjects with a higher risk for progression to AD-type dementia.

results, with ORs ranging from 0.58 to 16.7^{4 5} and with estimates for sensitivity, specificity and positive predictive value often missing.

We used a meta-analysis approach to establish the predictive value of the *APOE*- ϵ 4 allele in the progression from MCI to AD-type dementia. We also investigated study characteristics that may explain the variability of results between studies using meta-regression analysis. Study characteristics tested included age, background prevalence of the *APOE*- ϵ 4 allele in the population from which subjects were selected, Mini-Mental State Examination (MMSE) score,⁶ length of follow-up, study setting and type of MCI definition.

METHODS

Search strategy

We searched the PubMed database for publications from 1995 to 2008 on prospective cohort studies of subjects with MCI or related concepts in which the *APOE*- ϵ 4 allele was tested as predictor of progression to AD-type dementia. The search terms used were 'human' and 'amnesic,' 'amnesic syndrome,' 'memory impairment,' 'mild cognitive decline,' 'mild cognitive impairment,' 'MCI,' 'age-associated cognitive decline,' 'AACD,' 'age-associated memory impairment,' 'AAMI,' 'cognitive impairment no dementia,' 'CIND,' 'memory clinic,' 'memory disorders clinic' or 'dementia clinic.' *APOE*- ϵ 4 was not included in the search terms because this would exclude studies that did not contain the term '*APOE*- ϵ 4' in their abstracts yet provided information on *APOE* genotyping in the main text. The search resulted in 17 233 hits. Two authors reviewed the titles and abstracts, and all relevant studies were retrieved. Additional studies were identified from the reference list of retrieved publications.

Study selection

Studies were included in the analyses if they had data on *APOE* genotype, defined MCI as impairment on a cognitive test or as decline in activities of daily function with an overall Clinical Dementia Rating scale score of 0.5 or based on an equivalent measure⁷ and defined possible or probable AD at follow-up according to any of the following criteria: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),⁸ Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM IV),⁹ DSM-III-R¹⁰ or the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).¹¹

INTRODUCTION

Subjects with mild cognitive impairment (MCI) have an increased risk for Alzheimer's disease (AD), but not all subjects will eventually become demented.¹ Identifying subjects with MCI at high risk for AD is important in order to give these subjects a prognosis. Drugs with the potential to modify the disease progression are suggested to be most effective in the predementia stage of AD.

The apolipoprotein E (*APOE*) ϵ 4 allele is the strongest known genetic risk factor for AD. It is supposed to alter β -amyloid processing, a key pathological event in AD, or to modify the response to AD pathology.² Although *APOE* genotyping is not recommended for the diagnosis of AD,³ its role in predicting AD-type dementia in subjects with MCI is unclear. Previous studies yielded conflicting

Of the 17233 abstracts reviewed, we retrieved 95 full articles in English that were relevant for our study. Of the 95 studies, six were excluded because the subjects were already demented at baseline, three did not distinguish MCI from AD, eight had as an outcome AD/dementia but not conversion from MCI to AD-type dementia, six had as an outcome dementia instead of AD, one did not distinguish CIND from dementia, seven were not cohort studies, one used weighted inclusion, two had unclear *APOE* genotyping data, 15 had no *APOE* data, and 11 referred to the same cohort. In the case wherein data from the same study had been reported in multiple papers, we used the paper in which the follow-up was longest or, if that was not different, in which the sample size was largest. Thirty-five studies with AD-type dementia as outcome were finally included in the meta-analysis (figure 1).¹²

Data extraction

Three authors independently completed a data-extraction form for each study. Studies were classified according to setting in (1) clinical studies, wherein only patients presenting with cognitive impairments at a healthcare facility were included; (2) population-based studies, wherein a random sample of the general population was included; or (3) other studies, wherein subjects were recruited from both clinical and population settings, or through advertisements. MCI definitions were recorded as measured by (1) objective tests and (2) assessment of functional impairment. Definitions based on objective test performance were subdivided in studies that used amnesic MCI (aMCI) as inclusion criterion or studies that included both subjects with aMCI and non-amnesic MCI.

Data on the *APOE*- ϵ 4 allele and outcome were summarised in a 2×3 table, which specified the number of subjects who were *APOE*- ϵ 4 allele carriers and non-carriers who remained stable, progressed to AD-type dementia or progressed to other types of dementia. We did not subdivide outcome according to number of

APOE- ϵ 4 alleles, as only few studies reported data on all *APOE* genotypes.

Authors were contacted in case of incomplete data. For one study that included data from a drug trial, we included only data from placebo-treated subjects.¹³ For two trials that did not report separate data for placebo-controlled subjects, we included all subjects.^{14 15} In both trials, the drug was not associated with progression to AD-type dementia.

Assessment of methodological quality

Two authors rated each study using 17 items for subject sampling, reference diagnosis and test description selected from rating scales for methodological quality of diagnostic and prognostic studies (supplementary tables 1, 2).^{16 17} In case of discrepancies between scores, a third rater reviewed the paper, and a consensus was reached.

Statistical analysis

Random-effects models were used for the meta-analysis. Egger's regression test was conducted to test for funnel plot asymmetry. An asymmetrical funnel plot and a significant p value could indicate publication bias. The outcome measures were the pooled OR, sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR+ and LR-). The heterogeneity was assessed by a χ^2 test and is designated as Q. The amount of heterogeneity for each outcome measure was calculated using DerSimonian-Laird, with τ as an estimate for the SD of the underlying true outcomes across studies. The proportion of variation due to heterogeneity was likewise computed and expressed as I^2 .

Mixed-effects meta-regression analyses using restricted maximum likelihood (REML) estimation were conducted to examine the influence of mean age and MMSE score of the sample, the setting, definition of MCI, length of follow-up and background *APOE*- ϵ 4 allele frequency in the population in which the study was performed. Information on the background *APOE*- ϵ 4 allele prevalence in the population from which subjects were recruited was obtained from published data on the prevalence of the *APOE*- ϵ 4 allele in the general population.^{18 19} The Hardy-Weinberg equilibrium was tested using the χ^2 test in studies that reported the *APOE* alleles and frequencies. The *APOE* alleles are assumed to be in Hardy-Weinberg equilibrium if the p value obtained is greater than 0.05. The mean age and MMSE score, follow-up length and background *APOE*- ϵ 4 allele prevalence were included as continuous variables.

Analyses were performed using Stata/SE 9.2 for Mac OS X (Stata Corporation). R was used to create the figures.²⁰ In the main analyses, the outcome was dichotomised as non-demented versus AD-type dementia at follow-up because not all studies provided data on non-AD dementia at follow-up. In secondary analyses, which included all studies that provided outcome data on non-AD dementia, the outcome was dichotomised as no AD (combining subjects without dementia and subjects with non-AD type dementia) and AD-type dementia. One study presented data on subjects without dementia and subjects with non-AD type dementia as one group.¹³ We included these subjects in the non-dementia group in the main analysis. Analyses were first performed for all studies combined, and then separately for clinical, population-based and other studies.

FINDINGS

Study characteristics

We included 21 clinical, six population and eight other studies (table 1). The studies represented 7322 cases with MCI, of

Figure 1 Flow diagram of study selection (adapted from Moher *et al*¹²).

Table 1 Characteristics of studies included in the meta-analysis

Study	MCI definition	Exclusion criteria	Sample size, baseline (% FU)	Mean age (years)	Mean education (years)	MMSE score	Follow-up (years)	Converters to dementia (% AD)
Clinical studies								
1995	aMCI	DCCD	56 (100)	71.2	—	—	3	30 (100)
1996	MFI	DCCD	178 (80)	72.3	13.9	27.6	2	29 (97)*
2002	aMCI	DCCD, age <40 years	74 (85)	61.1	10.5	27.7	3.7	19 (100)
2004	MCI	DCCD, age 50–85 years	104 (87)	70.2	—	27.7	2	29 (100)
	MCI	DCCD, age <40 years, FU <6 months	75 (100)†	62.9	10.2	26.9	2.8	37 (92)
	aMCI	Depression	57 (100)	73.9	11.6	25.6	2	17 (100)
	aMCI	DCCD	37 (100)	67.1	9.6	28.0	1	8 (100)
2005	aMCI	DCCD	30 (100)	70.0	11.6	26.9	1.3	12 (100)
2006	aMCI	DCCD	137 (98)	71.0	—	27.0	5.2	78 (73)
	aMCI	DCCD	58 (100)	76.3	11.8	25.9	3	19 (100)
2007	aMCI	DCCD, MMSE <25 years	89 (100)	75.0	—	—	4.1	62 (100)*
	MCI	DCCD	64 (92)	69.6	—	25.9	1.6	33 (91)
	MCI/MFI	DCCD	139 (100)	66.8	15.2	27.5	4.2	37 (100)
	MCI	DCCD	88 (100)†	70.9	—	27.0	1.8	43 (100)
	aMCI	DCCD	105 (100)†	69.3	—	27.2	3.1	23 (87)
	MFI	DCCD, <65 years	124 (90)	74.7	10.3	25.2	1.7	42 (100)
	aMCI	—	119 (100)	70.6	7.8	26.9	1	40 (100)
	aMCI	DCCD, MMSE <24, age ≥90 years	28 (86)	70.2	9.7	26.9	1.6	10 (90)*
2008	MCI	DCCD, <50 years	40 (90)	69.3	—	27.5	2	5 (100)
	aMCI	—	21 (100)	63.6	12.7	28.2	0.7	7 (100)
	aMCI	DCCD	36 (92)	75.5	8.7	27.5	1.1	12 (92)
Population-based studies								
1999	MFI	Age <60 years	397 (50)	74.7	—	26.9	3	48 (46)
2004	MCI/MFI	Age <65 years	296 (88)	77.8	9.2	—	5	147 (48)*
2005	MCI	DCCD, age <65 years	242 (75)	78.7	17.8	27.4	5.7	82 (96)*
2006	MFI	DCCD, age <65 years	37 (100)†	86.9	13.8	27.3	7.6	23 (96)
2008	MCI	—	60 (100)	72.7	6.7	23.9	2.8	13 (77)
	MCI	Age <65 years	2882 (100)†	74.6	—	27.2‡	4	145 (77)
Other studies								
1999	aMCI	DCCD, age <60 years and >90 years	80 (96)	77.7	13.1	26.4	2.7	27 (100)
2001	MFI	DCCD, age <65 years	123 (99)	72.2	14.9	29.1	3	26 (88)*
2005	aMCI	DCCD, age <65 years	23 (100)†	82.1	16	27	3.6	11 (100)
2006	aMCI	DCCD	49 (100)†	68.5	13.4	28.4	1.3	13 (100)
	MFI	DCCD, age <60 years and >90 years	106 (68)	73.1	5.2	—	3	17 (82)*
2007	aMCI	DCCD, age <55 years and >85 years	510 (68)	70.6	11.1	26.9	4	109 (100)
	aMCI	DCCD, MMSE <24, age <55 years and >90 years	769 (70)	72.8	14.8	—	3	212 (99)*
	MCI	DCCD	79 (100)	70.4	—	24.0	4.1	33 (97)

*Study did not provide APOE data on subjects with non-AD type dementia.

†Only completed cases reported.

‡Obtained from The 3C Study Group (2003).⁵¹

AD, Alzheimer-type dementia; aMCI, amnesic mild cognitive impairment; DCCD, disorders causing cognitive decline; FU, follow-up length; MCI, mild cognitive impairment; MFI, mild functional impairment that interferes with daily living; MMSE, Mini-Mental State Examination; —, not specified/no data.

whom 56% (n=4092) were females. The majority of the subjects were from population studies (53%, n=3914), 23% (n=1668) were from clinical studies, and 24% (n=1740) were from other studies. The pooled mean baseline characteristics were as follows: age 72.1 (range 61–87) years, follow-up period 2.9 (range 1–8) years, MMSE score 27 (range 24–29) and education 11.6 (range 5–16) years.

Subjects with MCI from the population studies were older and were followed up for a longer period compared with those in the clinical and other studies (age 77.6 vs 70.1 and 73.4; follow-up length 4.7 vs 2.4 and 3.1), but these differences did not reach statistical significance ($p>0.05$).

APOE genotyping was available for 6095 subjects (table 2). Of these, 4170 were *APOE*- $\epsilon 4$ allele non-carriers, and 1925 (32%) were carriers of at least one *APOE*- $\epsilon 4$ allele. Among *APOE*- $\epsilon 4$ allele carriers, 658 (34%) progressed to AD-type dementia, 32 (1.7%) developed non-AD type dementias, and the rest were not demented. Of the non-carriers, 578 (14%) developed AD-type dementia, and 56 (1.3%) developed non-AD type dementias.

Data on zygosity were available for nine studies, representing 794 subjects with MCI, of whom 256 (32%) progressed to AD-type dementia. The *APOE* allele distribution was in Hardy–Weinberg equilibrium in the six studies ($p>0.05$; $N=762$ cases of MCI) that provided the data to allow the calculation of this equilibrium.

Meta-analysis

Visual inspection of the funnel plot for the OR did not reveal any marked asymmetry, and Egger's regression test was not significant ($p=0.94$; supplementary figure 1). This indicates that the results obtained are unlikely to be due to publication bias. A significant overall outcome was obtained for all measures of predictive accuracy (supplementary table 3). In the presence of at least one *APOE*- $\epsilon 4$ allele, the pooled OR for AD-type dementia in all studies was 2.29 (95% CI 1.88 to 2.80; figure 2), the sensitivity 0.53 (95% CI 0.46 to 0.61), the specificity 0.67 (95% CI 0.62 to 0.71), the PPV 0.43 (95% CI 0.48 to 0.66), the NPV 0.75 (95% CI 0.70 to 0.80), the LR+ 1.60 (95% CI 1.48 to 1.72) and the LR– 0.74 (95% CI 0.67 to 0.82; supplementary figure 2A to 2F, table 3). The OR (3.94, 95% CI 2.09 to 7.33), specificity (0.93, 95% CI 0.90 to 0.97) and LR+ (3.01, 95% CI 2.11 to 4.30) were higher, and the sensitivity was lower (0.21, 95% CI 0.10 to 0.33) among *APOE*- $\epsilon 4$ homozygotes (table 3). The overall effect and heterogeneity across studies (Q , I^2 and τ values) are shown in supplementary table 3.

Table 2 Number of subjects with at least one *APOE*- $\epsilon 4$ allele according to outcome and setting

		Outcome at follow-up		
		Not demented	Alzheimer-type dementia	Non-Alzheimer-type dementia
All studies				
$\epsilon 4+$	1925	1235	658	32
$\epsilon 4-$	4170	3536	578	56
Clinical studies				
$\epsilon 4+$	618	314	293	11
$\epsilon 4-$	862	615	228	19
Population-based studies				
$\epsilon 4+$	731	601	110	20
$\epsilon 4-$	2702	2436	229	37
Other studies				
$\epsilon 4+$	576	320	255	1
$\epsilon 4-$	606	485	121	0

$\epsilon 4+$, *APOE*- $\epsilon 4$ allele carriers; $\epsilon 4-$, *APOE*- $\epsilon 4$ allele non-carriers.

Figure 2 Forest plot OR. AD–, no dementia; AD+, with Alzheimer-type dementia; $\epsilon 4-$, *APOE*- $\epsilon 4$ allele non-carriers; $\epsilon 4+$, *APOE*- $\epsilon 4$ allele carriers; RE, random effects. The squares represent the weight of the particular study in the overall analysis. The horizontal line across the square shows the CI. The diamonds represent the overall effects.

There were some differences in measures of predictive accuracy between settings, but these differences were not statistically significant ($p>0.10$). Likewise, the type of MCI definition was not associated with predictive accuracy ($p>0.20$).

Assessment of methodological quality

The use of blinding procedures was the only item that could not be rated in more than 70% of the studies. Based on items that could be scored, 76% of the clinical studies and 50% of population-based and other studies had a positive score on at least 80% of the items.

Meta-regression results showed that studies with a score below 80% of the items did not differ in any outcome measure from studies that scored positive on at least 80% of the items. The results were similar when items that could not be scored were rated as a negative score.

Effect of age, background *APOE*- $\epsilon 4$ allele prevalence, MMSE score and length of follow-up on the predictive accuracy

Increasing mean study age was associated with decreased sensitivity ($p=0.001$), increased specificity ($p=0.017$) and decreased NPV ($p=0.003$) (figure 3A). Increasing background *APOE*- $\epsilon 4$ allele prevalence in the population from which subjects were selected significantly increased sensitivity ($p=0.014$) and decreased specificity ($p=0.004$, figure 3B). An increase in mean length of follow-up was associated with decreased sensitivity ($p=0.025$) and NPV ($p=0.031$, figure 3C). The mean MMSE

Table 3 Measures of predictive accuracy

Category	OR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
At least one $\epsilon 4$ allele versus no $\epsilon 4$ allele							
All studies (N=35)	2.29 (1.88 to 2.80)	0.53 (0.46 to 0.61)	0.67 (0.62 to 0.71)	0.43 (0.34 to 0.52)	0.75 (0.70 to 0.80)	1.60 (1.48 to 1.78)	0.74 (0.67 to 0.82)
Clinical studies (n=21)	2.36 (1.81 to 3.07)	0.58 (0.49 to 0.66)	0.65 (0.60 to 0.70)	0.46 (0.38 to 0.54)	0.74 (0.69 to 0.80)	1.56 (1.39 to 1.76)	0.73 (0.63 to 0.83)
Population-based studies (n=6)	1.83 (1.39 to 2.40)	0.31 (0.23 to 0.39)	0.78 (0.72 to 0.84)	0.34 (0.12 to 0.55)	0.73 (0.56 to 0.89)	1.54 (1.28 to 1.86)	0.86 (0.80 to 0.94)
Other studies (n=8)	2.64 (1.58 to 4.42)	0.60 (0.49 to 0.71)	0.64 (0.57 to 0.70)	0.42 (0.29 to 0.54)	0.81 (0.75 to 0.86)	1.61 (1.29 to 2.02)	0.63 (0.47 to 0.85)
<i>APOE</i> - $\epsilon 4$ homozygotes versus no $\epsilon 4$ allele							
All studies (N=9)	3.94 (2.09 to 7.33)	0.21 (0.10 to 0.33)	0.93 (0.90 to 0.97)	0.59 (0.50 to 0.68)	0.69 (0.60 to 0.79)	3.01 (2.11 to 4.30)	0.89 (0.79 to 0.99)

score was not associated with any outcome measure. The strength of the associations was similar when analyses were performed in clinical, population-based and other studies separately, although some associations were no longer statistically significant (data not shown).

Non-AD-type dementia

Twenty-six studies presented *APOE*- $\epsilon 4$ allele data on subjects who progressed to non-AD type dementia. Analyses with outcome AD (n=771) versus no AD (n=4049, including 3961 subjects without dementia and 88 subjects with non-AD type dementia at follow-up) yielded similar measures of predictive accuracy compared with analyses with outcome AD versus no dementia (supplementary table 4).

DISCUSSION

Meta-analysis

Our results showed that the presence of at least one *APOE*- $\epsilon 4$ allele is associated with a moderately high increased risk of progression from MCI to AD-type dementia. The estimates for sensitivity, specificity, PPV, NPV, LR+ and LR- were low to moderately high. Meta-regression showed that part of the variability between studies could be partly explained by age, background *APOE*- $\epsilon 4$ allele prevalence and length of follow-up.

APOE- $\epsilon 4$ homozygotes had a fourfold risk of progression to AD-type dementia. The specificity and LR+ were higher, and the LR- lower compared with *APOE*- $\epsilon 4$ heterozygotes. However, the sensitivity was lower, which could result in a high number of false negatives.

Figure 3 Meta-regression results. (A) Age: (i) sensitivity; (ii) specificity; (iii) negative predictive value. (B) *APOE*- $\epsilon 4$ allele background prevalence: (i) sensitivity; (ii) specificity. (C) Length of follow-up: (i) sensitivity; (ii) specificity. Shown are variables that have a statistically significant association with outcome in the meta-regression analysis. The size of the data markers indicates the weight of the study.

The OR we obtained in the presence of at least one *APOE-ε4* allele and in the presence of two *APOE-ε4* alleles was lower than the OR reported in a meta-analysis of cross-sectional studies that compared the prevalence of the *APOE-ε4* allele in subjects with AD-type dementia relative to healthy controls.^{52 53} A possible explanation for the lower OR in our meta-analysis is that not all subjects with MCI and an *APOE-ε4* allele who are destined to progress to AD-type dementia would develop AD during a mean follow-up of 3 years. This could have resulted in a higher number of false positives compared with studies that included healthy controls and subjects with AD-type dementia.

It is also worth noting that although we only included subjects from whom *APOE* data had been collected, a substantial number of subjects within these studies did not have *APOE* data available. This may have caused a bias, but this could not be ascertained.

Meta-regression

We noted a number of associations between study characteristics and predictive accuracy. With increasing age, the *APOE-ε4* allele became less sensitive and more specific for the prediction of AD. This suggests that with increasing age, the number of *APOE-ε4* allele carriers decreases, which was indeed observed in these data. This could mean that *APOE-ε4* allele carriers may either progress to AD-type dementia at a younger age or die earlier.⁵⁴ The decrease in sensitivity and negative predictive value with age suggests that with increasing age, subjects with MCI who progress to AD-type dementia are more likely to be non-carriers of the *APOE-ε4* allele, which is consistent with previous studies.⁵⁵

As would be expected, the NPV decreased with follow-up length. The decrease in sensitivity with follow-up length suggests that subjects without the *APOE-ε4* allele progress slower to AD-type dementia than subjects with the *APOE-ε4* allele.

A higher background prevalence of the *APOE-ε4* allele increased sensitivity and decreased specificity, which would be expected. Remarkably, neither the PPV nor the OR depended on the background prevalence, which suggests that the risk of progression to AD-type dementia is similar in populations with different *APOE-ε4* allele background prevalence.

A number of study characteristics were not associated with predictive accuracy. Setting was not associated with any outcome measure, although previous studies have shown that progression rates from MCI to AD-type dementia were higher in clinical settings than in the general population.⁵⁵ Still, we observed relatively large differences in sensitivity and specificity between population-based studies and clinical studies, which may not have reached statistical significance, as only six population-based studies were included in the meta-analysis.

Although MMSE score is associated with risk for AD, the mean study MMSE score did not modify the relation between the *APOE-ε4* allele and AD-type dementia. It is possible that the spread of MMSE scores in the studies was too small to detect an effect.

The relation between *APOE* genotype and risk for AD-type dementia was also not dependent on the definition of MCI used. This could be attributed to an overlap in MCI definitions. Definitions based on objective tests could include subjects with mild functional impairment and vice versa.^{56 57}

Methodological quality of studies

The scores of methodological quality were moderate. We may have underestimated these scores, as they were only based on

information provided in the paper. Information on whether clinicians were blinded to the *APOE* genotype when the follow-up diagnosis was made was often missing. This incomplete reporting was probably because the *APOE* genotype was not the main predictor in most studies. Still, we cannot exclude the possibility that the diagnostic accuracy may have been overestimated because clinicians who made the follow-up diagnosis had access to the *APOE* genotype. However, it should be noted that criteria for the diagnosis of AD refer to clinical information only, not to any biomarker. Our meta-regression analyses showed that methodological quality had no significant effect on measures of predictive accuracy.

Limitations

Our study has several limitations. First is the significant heterogeneity between studies. We modelled the heterogeneity by means of a random-effects model. With meta-regression, we found possible explanations for this heterogeneity, but other factors that contribute to the heterogeneity remain to be identified. Second, the definition of MCI varied between studies, but this effect may have been limited as discussed above. Third, meta-regression was performed with mean study scores, which may lead to an under- or overestimation of the relation between the variables tested in the meta-regression and measures of predictive accuracy.

Implications

The *APOE-ε4* allele is a moderately strong predictor of progression from MCI to AD-type dementia. The risk is twice as high for *APOE-ε4* heterozygotes and four times as high for *APOE-ε4* homozygotes compared with non-carriers. The effect of the *APOE-ε4* allele is consistent. In spite of this, the low sensitivity and PPV makes genotyping of limited value for predicting AD-type dementia in clinical practice, since half of the subjects who progressed to AD-type dementia had no *APOE-ε4* allele, while 40% of those with an *APOE-ε4* allele did not progress to AD-type dementia over a 3-year period. The background prevalence of the *APOE-ε4* allele in the population should be taken into account when interpreting the sensitivity and specificity of the *APOE-ε4* allele for the prediction of AD-type dementia. *APOE* genotyping may be of value in selecting subjects for trials that aim to prevent progression to dementia, as it helps select subjects with a higher risk for progression to AD-type dementia. For example, with an annual progression rate of 15% in subjects with MCI and 19% of subjects with MCI and at least one *APOE-ε4* allele (conversion rate based on the meta-analysis of clinical studies), the number of subjects needed in a 3-year placebo-controlled trial with 50% on active treatment designed to detect a relative decrease in conversion rate to AD-type dementia of 20% (assuming a power of 90%, a two-sided α of 5% and a drop-out rate of 30%) would be 1720 if subjects with MCI were included, and 1113 if subjects with MCI and at least one *APOE-ε4* allele were included. However, in order to select 1113 MCI *APOE-ε4* allele carriers, 2572 subjects with MCI would be needed for screening, which could be a limitation.

FUTURE PERSPECTIVES

The *APOE-ε4* allele is thus far the strongest known genetic risk factor for AD.⁵⁸ Interaction with other genes may increase the predictive accuracy. Notably, the translocase of the outer mitochondrial membrane 40 homologue (*TOMM40*) could interact with the effect of the *APOE-ε4* allele on the development of AD.^{58 59} *TOMM40* and the apoE protein are both located on

chromosome 19 and are both associated with an increased risk for AD.⁵⁹ How strong this interaction will be requires further investigation. In addition, the *APOE* genotype may interact with the predictive accuracy of other markers for AD, typically markers related to β -amyloid metabolism, such as Pittsburgh Compound-B (PIB) and β amyloid in cerebrospinal fluid (CSF).⁶⁰ Apart from selecting subjects at an increased risk for AD, *APOE* genotyping might be useful to select or stratify subjects for trials with drugs for which the mode of action of profile of side effects may be dependent on the *APOE* genotype.⁶¹

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