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APOE and *ACE* polymorphisms and dementia risk in the older population over prolonged follow-up: 10 years of incidence in the MRC CFA Study

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Abstract

Background: dementia risk conferred by *apolipoprotein-E* (*APOE*) and *angiotensin-1-converting enzyme* (*ACE*) polymorphisms have been reported for the MRC Cognitive Function and Ageing Study (CFAS) at 6-year follow-up. We concentrate on incident dementia risk over 10 years.
Methods: participants come from MRC CFAS, a multi-centre longitudinal population-based study of ageing in England and Wales. Three follow-up waves of data collection were used: 2, 6 and 10 years. Logistic regressions were undertaken to investigate associations between *APOE* (n=955) and *ACE* (n=856) alleles/genotypes and incident dementia. Two types of control groups were used: non-demented and highly functioning non-demented. Results were back-weighted.

Results: compared to *APOE* ε3, ε2 conferred protection of odds ratio (OR) = 0.3 (95% confidence interval, CI = 0.1–0.6) and ε4 risk of OR = 2.9 (95% CI = 1.7–4.9) for incident dementia. Compared to ε3/ε3, the ε3/ε4 and ε4/ε4 genotypes conferred risks of OR = 3.6 (95% CI = 1.8–7.3) and OR = 7.9 (95% CI = 1.6–39.2), respectively. The ε3/ε2 genotype protected against dementia (OR = 0.2, 95% CI = 0.1–0.7), and ε2/ε2 had a similar protective effect but with wide CIs (OR = 0.3, 95% CI = 0.1–1.7). Restricting the control group accentuated these differentials. The effects of *ACE* alleles/genotypes on incident dementia risk were small.
Conclusions: *APOE* but not *ACE* is associated with late-onset incident dementia in the population. Using longer term follow-up with proper adjustment for attrition and incident cases increases estimates of risk.

Keywords: *apolipoprotein-E, angiotensin-1-converting enzyme, population, dementia, old*

Introduction

Apolipoprotein-E (*APOE*) and *angiotensin-1-converting enzyme* (*ACE*) polymorphisms have received a great deal of attention in relation to dementia risk (e.g. [1, 2]). *APOE*, found on chromosome 19, is involved in lipid transport in the body [3]. There are three alleles—ε2, ε3, ε4—with ε3 being the most common [1]. *APOE* is associated with many neuropathological features of Alzheimer's disease (AD), the most common form of dementia, including plaque and tangle formation, β-amyloid deposition and cholinergic dysfunction (e.g. [4]). Two meta-analyses have reported that in population-based studies those with the ε4/ε4 genotype as compared to those with the ε3/ε3 are 12–13 times more likely to develop AD [1, 5]. Results are less consistent regarding individual alleles, with not all population-based studies reporting that the ε4 allele confers a risk of AD/dementia or the ε2 allele a protective effect [6–16].

ACE appears to be involved in blood pressure regulation and electrolyte balance [17]. It is found on chromosome 17 and there are two allele types, D (a deletion) and I (an insertion), relating to intron 16. Neuropathological studies have been inconsistent as to whether *ACE* is associated with neuropathological features of AD (e.g. [18, 19]). One recent meta-analysis of clinical/necropsy (i.e. non-population-based) samples reported that the D/D genotype conferred a protective effect on AD (odds ratio, OR = 0.8; 95% confidence interval, CI = 0.8–0.9), the I/D genotype a risk (OR = 1.1, 95% CI = 1.0–1.2) while the I/I had had no effect on AD—with referents being the combination of remaining genotypes [2]. Another meta-analysis on clinical/necropsy samples (i.e. not population-based) reported that the I allele conferred a 1.1 risk (95% CI = 1.0–1.2) for AD compared to the D allele; however, this association was non-significant when adjusting for Hardy–Weinberg equilibrium deviations and non-Caucasian ancestry [1]. There have been few population-based studies of *ACE* and of these they have generally reported no or small associations between the *ACE* polymorphism and AD [19–21].

As stated above, there is a great deal of evidence for *APOE* being associated with AD or dementia, and the evidence concerning *ACE* is not so consistent. Whether the effects and/or the sizes of such effects reported previously are relevant in a population context is uncertain. This is because the majority of previous research has been conducted on selected clinic/necropsy samples which do not represent the population most at risk of dementia. Accordingly, the current study aimed to assess incident late-onset dementia risk as conferred by *APOE* and *ACE* polymorphisms in a population-based sample with a long follow-up (10 years).

These analyses update previous analyses completed on the Medical Research Council Cognitive Function and Ageing Study (CFAS) sample in relation to *APOE* [22] and *ACE* [23]. This paper extends these analyses in that it includes another follow-up wave of data collection, increasing the follow-up time from 6 to 10 years which increases the number of incident dementia cases by around 60%. Results were weighted back to the original MRC CFAS sample, to fully take account of drop-out, which has recently become a standard technique. Notably, these previous papers on the MRC CFAS sample reported that the ε4 *APOE* allele conferred a small risk for all dementia [22] whilst the *ACE* polymorphism did not confer any dementia risk [23].

Methods

Sample

MRC CFAS has been fully described in Brayne *et al.* [24] and will only be briefly described here. It is a large longitudinal population-based multi-centre study on ageing and dementia in England and Wales, with participants aged ≥65 at baseline. Sampling was based on geographical areas using general practitioner registration details. The initial response rate was 82%, and there has been a drop-out rate of 13–29% between follow-up waves due to death, moving away or refusal [25, 26]. Four of the six study centres were used in these analyses: East Cambridgeshire, Gwynedd, Newcastle and Nottingham. The remaining two centres, Oxford and Liverpool, collected and analysed blood samples at different times and according to a different study protocol and are thus not included here.

In relation to the four centres included, there were 10,264 participants aged ≥65 years (stratified by equal numbers aged 65–74 and >75) at baseline ('prevalence screen')

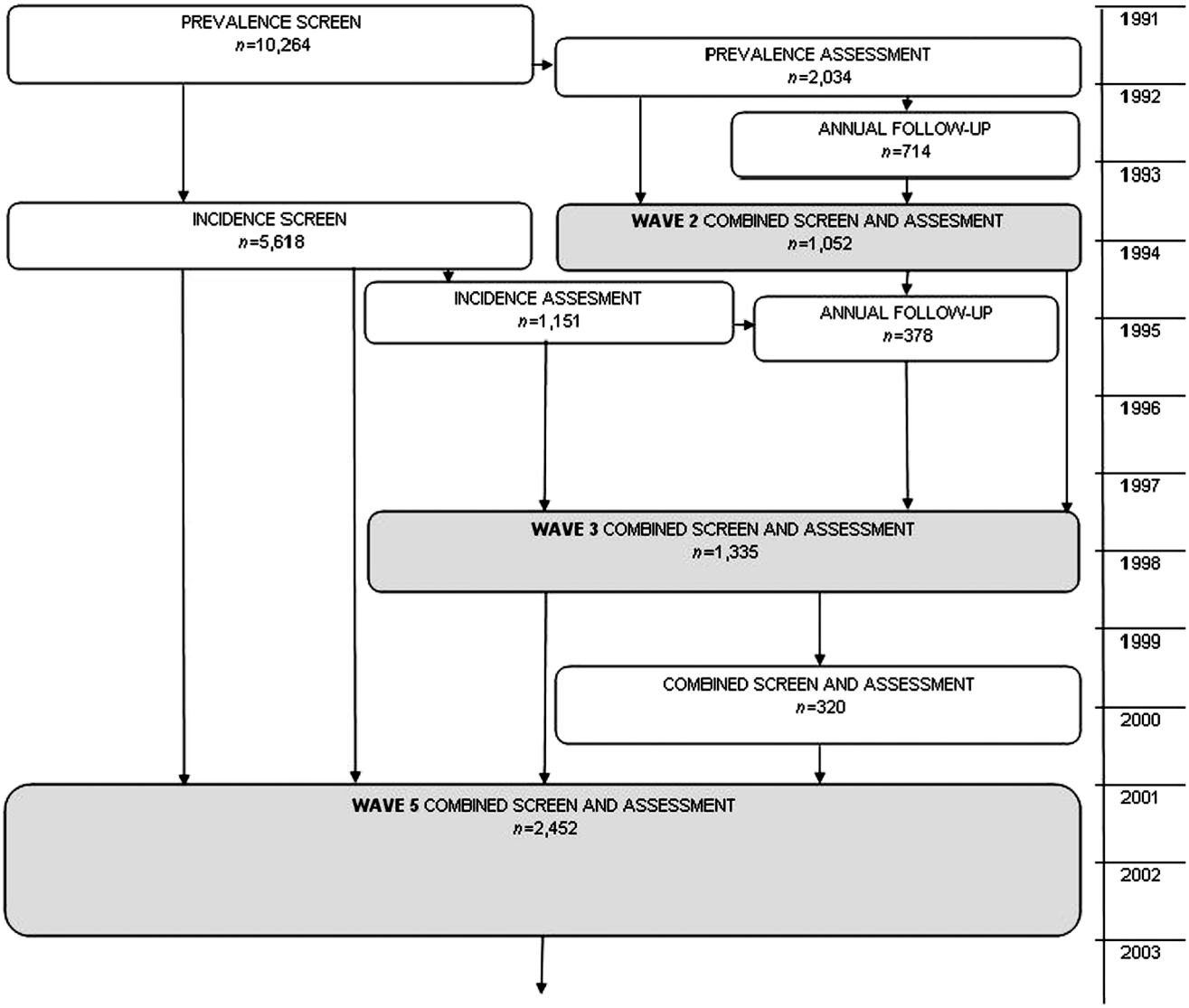

Figure 1. An illustration of the MRC CFAS study design and the number of participants seen at each screen/assessment relative to the four centres used in the current study. The grey shading indicates assessments that were used to define cases of incident dementia.

beginning in 1991. The study employed a two-phase design, with a more comprehensive assessment given to a subsample (n=2,034) at baseline ('prevalence assessment') stratified by age and cognitive function (biased toward those older and those with worse cognitive function). There have been multiple re-screens and re-assessments to detect incident dementia, of which the current study employs those at 2 (wave 2), 6 (wave 3) and 10 (wave 5) years. For this analysis, the 2-year follow-up included only those in the prevalence assessment subsample (n=1,052), the 6-year follow-up included those in the prevalence assessment subsample and another subsample of those part of the incidence screen (n=1,335), and the 10-year follow-up included all study participants still alive (n=2,452). The MRC CFAS study design is illustrated in Figure 1.

Blood or a buccal swab was collected at wave 3, 6 years into the study, with 62% (n=1,070 or n=945 excluding prevalent dementia at baseline) of participants who were included in the wave 3 interview consenting. It is these participants who consented to give genetic material that are included in these analyses. They had a mean age of 73.8 (SD=6.5) at baseline; 60% women. Ethnic background was asked in a subset of the sample, of which 99% reported being of white British background.

Measures

A computer-automated version of the Geriatric Mental State known as the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) was used to assess the presence of dementia at interview by trained interviewers from professions allied to health. Those with an AGECAT organicity rating of O3 and above (score range 0–5) were classified as demented.

The Mini-Mental State Examination (MMSE) was used to obtain further evidence of cognitive impairment (score

Table 1. Distribution of *APOE* and *ACE* genotypes and allele frequencies for cases and controls (both non-demented and HF non-demented), relative to years 2, 6 and 10 (corresponding to waves 2, 3 and 5, respectively)

	2years/wave 2						6years/wave 3						10years/wave 5					
	Incident demented		Non-demented		HF non-demented		Incident demented		Non-demented		HF non-demented		Incident demented		Non-demented		HF non-demented	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
APOE																		
Allele																		
ε2	4	10	166	9	70	9	5	3	161	9	70	9	8	7	77	10	34	9
ε3	28	70	1,471	79	639	78	114	78	1,357	79	595	77	77	71	616	79	290	80
ε4	8	20	233	12	109	13	27	18	206	12	103	13	23	21	83	11	40	11
Total	40		1,870		818		146		1,724		768		108		776		364	
Genotype																		
ε2/ε2	0	0	7	1	3	1	1	1	6	1	4	1	0	0	3	1	2	1
ε2/ε3	3	15	128	14	55	13	2	3	126	15	55	14	7	13	62	16	27	15
ε2/ε4	1	5	24	3	9	2	1	1	23	3	7	2	1	2	9	2	3	2
ε3/ε3	11	55	583	62	251	61	46	63	537	62	229	60	26	48	244	63	114	63
ε3/ε4	3	15	177	19	82	20	20	27	157	18	82	21	18	33	66	17	35	19
ε4/ε4	2	10	16	2	9	2	3	4	13	2	7	2	2	4	4	1	1	1
Total	20		935		409		73		862		384		54		388		182	
ACE																		
Allele																		
I	20	50	838	50	365	49	64	53	773	50	341	48	51	53	349	50	165	48
D	20	50	834	50	385	51	56	47	779	50	363	52	45	47	349	50	177	52
Total	40		1,672		750		120		1,552		704		96		698		342	
Genotype																		
D/D	7	35	227	27	107	29	15	25	213	27	104	30	11	23	98	28	49	29
I/D	6	30	380	45	171	46	26	43	353	45	155	44	23	48	153	44	79	46
I/I	7	35	229	27	97	26	19	32	210	27	93	26	14	29	98	28	43	25
Total	20		836		375		60		776		352		48		349		171	

Table 2. ORs and 95% CIs for associations between *APOE* allele/genotype and dementia

	Comparison using non-demented controls				Comparison using HF non-demented controls			
	Adjusted[a]		Adjusted[a] and weighted[b]		Adjusted[a]		Adjusted[a] and weighted[b]	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Allele								
ε2	0.6	0.3–0.9	0.3	0.1–0.6	0.6	0.3–1.1	0.2	0.1–0.5
ε3	1.0		1.0		1.0		1.0	
ε4	2.2	1.6–3.0	2.9	1.7–4.9	2.4	1.6–3.5	3.2	1.8–5.6
Genotype								
ε2/ε2	0.5	0.0–5.7	0.3	0.1–1.7	0.1	0.0–6.0	0.1	0.0–0.4
ε2/ε3	0.6	0.3–1.1	0.2	0.1–0.7	0.7	0.3–1.4	0.3	0.1–0.8
ε2/ε4	0.6	0.2–2.3	0.2	0.0–1.3	1.2	0.3–5.4	0.6	0.2–2.1
ε3/ε3	1.0		1.0		1.0		1.0	
ε3/ε4	2.3	1.5–3.6	3.6	1.8–7.3	2.1	1.3–3.5	3.1	1.4–6.5
ε4/ε4	5.0	1.9–13.0	7.9	1.6–39.2	9.1	3.0–27.2	18.1	4.9–67.0

[a]For age group, sex, education and social class.
[b]For study design and drop-out.

Table 3. ORs and 95% CIs for associations between *ACE* allele/genotype and dementia

	Comparison using non-demented controls				Comparison using HF non-demented controls			
	Adjusted[a]		Adjusted[a] and weighted[b]		Adjusted[a]		Adjusted[a] and weighted[b]	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Allele								
I	0.9	0.7–1.2	1.1	0.5–2.3	1.2	0.9–1.6	1.3	0.8–2.2
D	1.0		1.0		1.0		1.0	
Genotype								
I/I	0.9	0.6–1.4	0.5	0.3–1.0	0.9	0.6–1.4	0.5	0.3–1.0
I/D	1.0		1.0		1.0		1.0	
D/D	1.2	0.8–1.8	0.8	0.5–1.4	1.2	0.8–1.8	0.8	0.5–1.4

[a]For age group, sex, education, social class and *APOE* genotype.
[b]For study design and drop-out.

range from 0 to 30). The MMSE was employed to create two different control groups: 'non-demented' and 'highly functioning (HF) non-demented'. The non-demented group included participants not classified as demented (i.e. an AGECAT organicity rating of ≤O2). The HF non-demented group was not demented and also displayed no cognitive impairment, as defined as an MMSE of ≥26. By excluding those with an MMSE <26, cases with mild cognitive impairment (MCI) or low baseline cognitive ability are mostly excluded. MCI is a prodrome of dementia that has been shown to predict conversion to dementia [27] and appears to relate to *APOE* status [28]. Thus, by excluding those with MCI, those cases most likely to convert to dementia are dropped. However, those with naturally low baseline cognitive abilities are also excluded when using this MMSE cut-off, which reduces the representativeness of the sample to the population. Control groups similar to the HF non-demented group are commonly employed in genetic studies, including those using the MRC CFAS sample [22, 23]. However, the complete non-demented group most closely resembles the general population of individuals without dementia.

APOE and *ACE* genotyping was carried out in line with Wenham *et al.* [29] and Evans *et al.* [30], respectively, blind to clinical status. Ambiguous results were re-run up to three times, after which they were recorded as 'unknown'. *APOE* genotype was determined in 955 participants and *ACE* in 856 participants (excluding those with prevalent dementia at baseline).

Ethics statement

MRC CFAS has multi-centre research ethics committee's approval and ethical approval from the relevant local research ethics committees.

Analysis

Logistic regression analyses were undertaken to examine the associations between *APOE*/*ACE* polymorphisms and incident dementia (with dementia as the outcome). Prevalent dementia cases at baseline were excluded from analyses as these participants who went on to consent to DNA collection 6 years later are atypical dementia cases in terms of length of illness without death. Incident dementia was assessed at 2, 6 and 10 years (corresponding to waves 2, 3 and 5, respectively). Analyses were adjusted for wave, age group at interview (65–74, 75–84, 85–94 and 95+), education (low education ≤9 and high education >9 years) and social class. If education information was missing, it was coded as 'low education'. If social class information was missing, it was coded as 'social class missing'. *ACE* analyses were also adjusted for *APOE* genotype. Analyses were run relative to *APOE* and *ACE* genotype and allele status. The ε3 allele and ε3/ε3 genotype were employed as the reference groups in *APOE* analyses, and the D allele and I/D genotype were employed as the reference groups for *ACE*. Allelic analyses were undertaken with the assumption that the two alleles from each case were independent.

Each analysis was repeated with both control groups (non-demented and HF non-demented controls); however, analyses relating to the non-demented control group were focused on. Adjusted as well as adjusted and weighted results are presented. Back weighting was employed to provide a population estimate which takes into account the MRC CFAS sampling procedure and those who dropped out prior to the respective case finding interview. Those selected for the more comprehensive prevalence assessment were older and more likely to be cognitively impaired, though all cognitive abilities were represented. Further, those who dropped out were more likely to be cognitively impaired and older than those that did not [25]. Thus, both the sampling procedure and drop-outs influence the age of the sample. Given genetic associations with dementia, par-

ticularly with *APOE*, are stronger in the young as compared to the old [31]; not weighting back would most likely incorrectly estimate genetic associations.

Results

Table 1 displays the distribution of *APOE* and *ACE* genotypes and allele frequencies for cases and controls (both non-demented and HF non-demented) relative to 2-, 6- and 10-year follow-ups.

Table 2 displays the ORs and CIs—adjusted (for age group, sex, education and social class) as well as adjusted and weighted—for *APOE* genotype and allele status. It can be seen that the ε4 allele conferred a significant risk of dementia (OR=2.9, 95% CI=1.7–4.9) and the ε2 allele a significant protective effect (OR=0.3, 95% CI=0.1–0.6) relative to the non-demented control group (ε3 referent). Regarding *APOE* genotypes, the ε3/ε4 and ε4/ε4 genotypes conferred significant risks for dementia (OR=3.6, 95% CI=1.8–7.3 and OR=7.9, 95% CI=1.6–39.2, respectively) relative to the non-demented control group. The ε2/ε3 was associated with a decreased OR=0.3 (95% CI=0.1–0.7), with the ε2/ε2 genotype conferring a similar protective effect of OR=0.3 with a wide 95% CI (0.1–1.7), though only one individual with ε2/ε2 had dementia. Allele and genotype effects were generally more extreme for the HF non-demented control group comparisons.

Table 3 displays the ORs and 95% CIs—adjusted (for age group, sex, education and social class) as well as adjusted and weighted—for *ACE* genotype and allele status. From Table 3, it can be seen that the ACE I allele conferred a small dementia risk and the I/I and D/D genotypes a small degree of protection; however, all estimates are consistent with no effect.

Discussion

Dementia risk in the population is associated with *APOE* but not *ACE*. Effects were generally larger when employing the high functioning non-demented as compared to the total population of non-demented individuals. This is likely to be due to the exclusion of those with MCI who are at high risk of converting to dementia [27]. This finding suggests that highly selected control groups which are typically employed in genetic association studies are likely to lead to the overestimation of effect sizes, and their relevance to the population must be interpreted with caution. However, although effects were generally more extreme, 95% CIs from analyses employing either type of control group overlapped, which suggests a consistency in the direction of effects.

As expected, effects were also larger when they were weighted back to the original population sample, which accounted for the sampling procedure and drop-outs in the study, both of which influence the age of the sample. As introduced previously, *APOE* genotype affects age at dementia onset [31] and thus not weighting is likely to lead to incorrect estimates. This finding has important implications for future population-based genetic studies.

The study is not without limitations. Longitudinal follow-up studies have drop out between waves. However, the statistical method of back weighting accounted for any bias this along with attrition (due to drop-out) within the centres included may have introduced [25]. The AGECAT diagnostic algorithm was used to classify participants as demented or non-demented. Although it would have been preferential to have participants individually assessed by a clinician, this was not possible for such a large sample, and AGECAT classifications are closely related to diagnoses made by psychiatrists with the Diagnostic and Statistical Manual IIIR [32, 33]. The study also assessed dementia in general rather than specific clinical diagnoses of AD, which adds weight to the relevance of findings to the population but does not provide information regarding risk relative to specific subtypes of dementia such as AD.

Results reinforce the importance of *APOE* alleles in terms of dementia risk in the population, with previous population-based studies being somewhat inconsistent [6–10, 12], perhaps due to smaller sample sizes, the inclusion of prevalent dementia and/or short follow-up times. Regarding *APOE* genotype, the ε3/ε4 and ε4/ε4 genotypes were consistently associated with incident dementia risk—conferring four to eight times the risk (relative to the non-demented control group). This result is similar to two meta-analyses on population studies that reported the ε4/ε4 genotype was associated with 12–13 times greater AD risk [1, 5]. There was a protective effect of the ε2/ε2 genotype which is similar to a meta-analysis by Farrer *et al.* [5] who reported the AD risk conferred by ε2/ε2 to be OR=0.9 (95% CI=0.3–2.8).

It is possible that those with an *APOE* ε2 allele died before being eligible for entry into the study, given their increased mortality at younger ages [34], and thus the protective effect found could be an artefact of survival. However, the impact of these effects is concerned with those who survive into the age when dementia becomes most prevalent, in old age. APOE results from this study are more extreme than those previously reported on the MRC CFAS sample [22] most likely due to the longer follow-up time and use of back weighting.

Previous studies have reported that the *ACE* I allele confers a risk for incident dementia [1] and that the I/I and D/D genotypes protect against dementia relative to the I/D genotype [2, 19]. Our results were consistent, with small effects seen in these directions. This result is in line with small effect sizes or null results from population-based studies [19–21, 23], suggesting that the ACE effect is at best weak.

Results from the current study reiterate the importance of *APOE* in relation to incident dementia risk in the population. The current study was large and addressed many of the methodological issues in previous population-based genetic association studies: long follow-up time, exclusion of prevalent dementia at baseline and weighting back to the original population. Differences between non-demented and HF non-demented control group comparisons also highlighted how control selection affects genetic association estimates.

It should be noted that despite the large sample size and long follow-up time it would still be desirable for these to be increased in future studies. Only around 20% of cases of incident dementia in the MRC CFAS sample displayed an ε4 allele (as compared to around 12% of the non-demented regardless of control group), so it remains neither necessary nor sufficient, supporting suggestions that many other environmental and biological (including genetic) factors are involved in the clinical manifestation of dementia. From these results, it does not appear that *ACE* substantially raises the risk of incident dementia.

Key points

- *APOE* associated with incident dementia in the old.
- *ACE* does not substantially raise the risk of incident dementia.
- Control selection affects genetic association estimates.

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Conflict of interest

No conflict interest.

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