Dementia is the most common neurodegenerative condition affecting older people. It is estimated that around 550,000 people aged 65 years and over in England and Wales are suffering from dementia of mild or greater severity. Prevalence increases exponentially with age, from around 1% of 65 year olds to approximately 30% of people aged 85 years and older. Most cases (60–70%) of incident dementia are clinically diagnosed as Alzheimer’s disease, while 15–20% are accounted for by vascular dementia (VaD). However, Alzheimer-type and vascular pathology frequently occur in the same person, the neuropathological features associated with AD and VaD are present in many cognitively intact subjects, and some demented subjects do not have the neuropathological hallmarks of AD or VaD.

Alzheimer’s disease risk is unequivocally associated with polymorphisms in the apolipoprotein E (APOE) gene (chromosome 19q13.2). ApoE (OMIM *107741) is a 299 amino acid plasma glycoprotein that plays a major role in lipoprotein metabolism as a ligand for receptors of the low density acid plasma glycoprotein that plays a major role in lipoprotein metabolism as a ligand for receptors of the low density lipoprotein (LDL) receptor superfamily. Two polymorphisms in the coding region of APOE result in three major isoforms of the protein, apoE2, apoE3 (the most common isoform), and apoE4. Pooled results from association studies reported a 14-fold increased risk of AD for APOE ε4 homozygotes and a trebling of risk among APOE ε3/ε4 carriers compared with ε3/ε3 subjects.

We believe that the public are primarily concerned about their risk for dementia in general, in addition to the specific risks for AD or VaD. Similarly, from a public health perspective, it is crucial to understand how a genetic factor as important as APOE affects dementia in the general population as well as among narrowly diagnosed, selected, patient groups.

Thus, we have investigated the effect of APOE on dementia and cognitive decline risk in elderly populations across England and Wales drawn from a multicentre, population based, longitudinal study of ageing and cognitive and functional status (the MRC Cognitive Function and Ageing Study).

METHODS
Sample
The MRC Cognitive Function and Ageing Study is a multicentre, prospective study into the functional and cognitive status of the elderly in England and Wales. The centres used for the present analyses are set in two rural (Cambridgeshire and Gwynedd) and two urban (Nottingham and Newcastle) locations. A detailed description of the design of the study has been published elsewhere. Briefly, a two phase sampling design was used, where stratification for probability sampling for assessment was based on age and performance on dementia screening tests (Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) organisity items and the Mini Mental State Examination (MMSE)). A total of 2034 subjects out of 10 264 screened were sampled for assessment in this way. The assessed respondents then underwent two further follow up interviews to ascertain incident cases. Those not sampled in the first (prevalence) wave were screened during the second wave (two years later), and were selected for assessment using the same probability sampling scheme (5618 screened, 1151 assessed). Thus, 2034 + 1151 = 3185 subjects were selected for assessment over these two waves. At the third wave (approximately six years into the

Abbreviations: APOE, apolipoprotein E; AD, Alzheimer’s disease; MRC CFAS, Medical Research Council Cognitive Function and Ageing Study; VaD, vascular dementia; LDL, low density lipoprotein; MMSE, Mini Mental State Examination; AGECAT, Automated Geriatric Examination for Computer Based Taxonomy; OR, odds ratio
study), a combined screen and assessment was completed on 1730 of this cohort who were still alive, accessible, and who had consented to remain in the study. Of this number, 1070 consented to give a blood sample or buccal swab for genetic studies.

Assessment
Respondents were assessed by trained interviewers from professions allied to medicine. The assessment interview provides information processed by the computer algorithm AGECAT, which generates a diagnosis of dementia (as well as affective and anxiety disorders) on the basis of criteria compatible with those of the International Classification of Diseases, 9th revision (ICD-9) and the Diagnostic and Statistical Manual (DSM-III-R). Dementia is diagnosed if a person has an AGECAT organicity rating of O3 or above, which is highly correlated with clinical assessment of dementia status.

Cases comprised all blood/saliva contributing participants who had been assigned an AGECAT organicity level of O3 or higher at any point during the three assessment waves and an MMSE score of 21 or less at the third assessment wave. The control group comprised subjects with AGECAT organicity level below O3 and an MMSE score of 26 or greater at the third assessment wave. The sectional association between APOE and dementia risk, conducted with third wave data only, to examine the cross

<table>
<thead>
<tr>
<th>Allele</th>
<th>Controls</th>
<th>Cases</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
<th>Rubinsztein and Easton†</th>
<th>Farrer et al‡‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Population based</td>
<td>Clinic/necropsy</td>
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<tr>
<td>c3</td>
<td>722</td>
<td>246</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<td>c2</td>
<td>85</td>
<td>26</td>
<td>0.9 (0.6 to 1.4)</td>
<td>0.7 (0.4 to 1.2)</td>
<td>0.7 (0.6 to 0.8)</td>
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<tr>
<td>c4</td>
<td>125</td>
<td>52</td>
<td>1.2 (0.9 to 1.7)</td>
<td>1.5 (1.1 to 2.2)</td>
<td>3.4 (3.0 to 3.6)</td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c3/c3</td>
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<td>97</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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</tr>
<tr>
<td>c2/c2</td>
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<td>3</td>
<td>2.1 (0.5 to 9.7)</td>
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<td>0.9 (0.4 to 2.0)</td>
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<td>c2/c3</td>
<td>67</td>
<td>15</td>
<td>0.6 (0.3 to 1.2)</td>
<td>0.5 (0.2 to 1.2)</td>
<td>0.6 (0.5 to 0.7)</td>
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<tr>
<td>c2/c4</td>
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<td>5</td>
<td>1.0 (0.4 to 2.6)</td>
<td>1.7 (0.4 to 6.6)</td>
<td>1.9 (1.3 to 2.8)</td>
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</tr>
<tr>
<td>c3/c4</td>
<td>101</td>
<td>37</td>
<td>1.0 (0.7 to 1.6)</td>
<td>1.1 (0.6 to 1.9)</td>
<td>3.4 (3.0 to 3.9)</td>
<td></td>
</tr>
<tr>
<td>c4/c4</td>
<td>7</td>
<td>5</td>
<td>2.0 (0.6 to 6.6)</td>
<td>3.8 (1.0 to 14.0)</td>
<td>13.3 (9.9 to 17.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and years of full time education.
†Pooled estimate OR (95% CI) for Alzheimer’s disease. APOE (the reference group), e2/e2, e2/e3, e2/e4, e3/e4, and e4/e4.
‡‡Pooled estimate OR (95% CI) for Alzheimer’s disease, adjusted for age and study.

RESULTS
Table 1 shows the distribution of APOE genotype and allele frequencies for cases and controls, as well as crude and adjusted (for age, sex, and years in full time education) odds ratios. The APOE e4 allele confers moderately increased risk for dementia (OR=1.5, 95% CI=1.1 to 2.2) in the MRC CFAS sample. However, this odds ratio estimate is lower than the pooled OR estimate for Alzheimer’s disease drawn from clinic and necropsy based studies (OR=3.8, 95% CI=1.0 to 14.0). (While the crude OR for APOE e4/e4 appears to be lower than the adjusted OR, the 95% CI overlap. The difference in these ORs is largely attributable to the effects of age.) APOE e3/e4 subjects, however, were not at

Table 1 Allele and genotype frequencies at the APOE locus among demented and non-demented CFAS subjects, overall

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Population based</th>
<th>Clinic/necropsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>e3/e3</td>
<td>10.5, p&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>e3/e4</td>
<td>3.8, p=0.01</td>
<td></td>
</tr>
<tr>
<td>e4/e4</td>
<td>13.3, p&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

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increased risk (OR=1.1, 95% CI=0.6 to 1.9). Our dementia odds ratio estimates and 95% CI for e3/e4 were also lower and did not overlap those from other clinic/necropsy based or population based studies. Subjects possessing the e2 allele had a lower risk of dementia, although, because of small numbers, the odds ratio was not significant. Sex specific analyses (table 2) did not show any differences in allele and gene effects between men and women.

The back transformed mean MMSE scores at wave 3 by APOE genotypes were:
e3/e3=25.4, e2/e2=24.4, e2/e3=25.9, e2/e4=25.8, and e3/e4=25.2. MMSE scores at the third wave were not significantly different between APOE genotypes (F score (5 df) =0.2, p=0.9).

We were interested in the effects of APOE genotypes on the rate of cognitive decline, as measured by the MMSE difference between the initial and third assessment waves, in our entire sample. In one set of analyses, we compared the distribution of MMSE difference across APOE genotypes in the sample separated into four subgroups based on subjects’ MMSE scores at the prevalence wave (namely, 0-17, 18-21, 22-25, and 26-30). We adopted this strategy, since a given difference in MMSE scores over time would have a different meaning depending on the starting MMSE score. Fig 1A-D shows the distribution of the differences in MMSE scores between assessment waves 3 and 1 across APOE genotypes, according to baseline MMSE level.

In another analysis, we looked at the distribution of MMSE difference across the different APOE genotypes among subjects scoring between 22 and 25 and between 26 and 30 on the MMSE at wave 3. This strategy was used to see whether APOE genotypes affected the rate of cognitive decline in subjects who were ostensibly non-demented throughout the

### Table 2

<table>
<thead>
<tr>
<th>Allele</th>
<th>Male</th>
<th>Controls</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
<th>Female</th>
<th>Controls</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>e3</td>
<td>69</td>
<td>360</td>
<td>1.0 (0.4 to 2.2)</td>
<td>0.7 (0.3 to 2.0)</td>
<td>177</td>
<td>362</td>
<td>1.0 (0.5 to 1.5)</td>
<td>0.6 (0.3 to 1.4)</td>
</tr>
<tr>
<td>e2</td>
<td>7</td>
<td>38</td>
<td>1.3 (0.7 to 2.5)</td>
<td>1.3 (0.6 to 2.8)</td>
<td>19</td>
<td>47</td>
<td>0.8 (0.3 to 2.0)</td>
<td>0.6 (0.2 to 1.4)</td>
</tr>
<tr>
<td>e4</td>
<td>14</td>
<td>56</td>
<td>1.1 (0.7 to 1.7)</td>
<td>1.6 (0.9 to 2.7)</td>
<td>38</td>
<td>69</td>
<td>0.7 (0.4 to 1.3)</td>
<td>1.0 (0.5 to 1.8)</td>
</tr>
</tbody>
</table>

*Adjusted for age and years of full time education.

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**Table 2**

Allele and genotype frequencies at the APOE locus among demented and non-demented CFAS subjects, sex specific

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**Figure 1**

Distribution of MMSE difference (wave 3-wave 1) by APOE genotype, stratified by baseline MMSE score. (A) Baseline MMSE 17 or less (numbers included: e3/e3=23, e3/e4=4, e2/e3=3, e2/e2=1), Kruskal-Wallis statistic (\(\chi^2\), 3 df) = 1.9, p=0.6. (B) Baseline MMSE 17-21 (numbers included: e3/e3=55, e3/e4=14, e2/e3=13, e2/e4=5, e4/e4=2, e2/e2=1), Kruskal-Wallis statistic (\(\chi^2\), 5 df) = 7.4, p=0.2. (C) Baseline MMSE 22-25 (numbers included: e3/e3=213, e3/e4=70, e2/e3=47, e2/e4=7, e4/e4=10, e2/e2=2), Kruskal-Wallis statistic (\(\chi^2\), 5 df) = 4.6, p=0.5. (D) Baseline MMSE 26 and above (numbers included: e3/e3=315, e3/e4=99, e2/e3=68, e2/e4=13, e4/e4=6, e2/e2=5), Kruskal-Wallis statistic (\(\chi^2\), 5 df) = 3.0, p=0.7.
particular importance, the APOE ɛ3/ɛ4 genotype (the most common AD risk genotype) was not significantly associated with increased dementia risk (OR=1.1, 95% CI=0.6 to 1.9), although ɛ4 homozygotes are just under four times as likely to be demented as ɛ3 homozygotes (the reference group).

The MRC CFAS study uses AGECAT to diagnose dementia. It is a robust algorithm, with a high overall index of agreement (k=0.78) with psychiatrists’ diagnoses in both the community and geriatric hospital settings (and excellent agreement regarding diagnosis of organic disorders, k=0.82).14 15 It is possible that the impact of APOE ɛ4 is greatest for AD pathology and may have less importance for the other processes that contribute to dementia in the general population. It is interesting to note that the APOE ɛ4 odds ratios we observed were similar to those reported for all dementias in the population based Rotterdam study (OR 1.8, 95% CI 1.2 to 2.7).16

The apparent discrepancies between our data and those of published meta-analyses may be because most demented subjects in the general population are in their eighth and ninth decades of life. Farrer et al17 reported that AD relative risks for APOE ɛ3/ɛ4 and ɛ4/ɛ4 decline with increasing age (and these are for clinic/necropsy based studies). For people 80 years old, the odds ratios (compared to APOE ɛ3/ɛ3) are 2.0 for ɛ3/ɛ4 and 6.0 for ɛ4/ɛ4. Among 85 year olds, the ORs are under 2.0 for ɛ3/ɛ4 and around 4.0 for ɛ4/ɛ4.

The incidence of Alzheimer's disease increases exponentially with age and more than half of all cases of AD occur among people older than 75 years.18 19 In the UK population, 5.8% of demented subjects are aged between 65 and 69 years, 8.7% between 70 and 74, 19% between 75 and 79, 24% between 80 and 84, and 43% 85 years and over.20 The demented cases in the CFAS sample had a median age of 85 years (25th centile=80 years, 75th centile=89 years), and thus are fairly representative of cases of dementia in the general population.

Our results show that APOE genotypes are not associated with either cross sectionally determined cognitive function or cognitive decline as measured by the MMSE difference between baseline and last assessment wave. This finding is in agreement with a number of studies reporting no association between APOE genotype/allele and rate of cognitive decline or incidence of cognitive impairment among both AD patients and the non-demented elderly.21-24 Although it appears that as many studies report increased rates of functional and cognitive decline among people with the APOE ɛ4 allele,25-27 Plasman and Breitner28 have commented on the possible reasons why studies failed to detect any differences in rate of decline among AD patients and the elderly in general. They point to non-linearity and individual variability in rates of pathogenesis, as well as the difficulties of controlling for all other determinants of neural reserve when examining trajectories of cognitive decline by APOE genotype. Furthermore, they point to the limitations of psychometric instruments used: neuropsychological performance is measured as a correlate of cognitive change, and tests tend to be less sensitive to change in subjects who have either mild or severe symptoms, and their scores do not vary in strict proportion to the underlying progression of the disease process. MMSE, for instance, as well as having documented ceiling and floor effects, provide ordinal and not ratio data, so that a three point decline from 19 to 16 is not necessarily equivalent to a decline from 27 to 24. However, we stratified our sample by both initial and final MMSE scores and still no effects emerged for APOE.

In conclusion, while APOE is unequivocally associated with Alzheimer's disease and is likely to play a key role in AD pathogenesis, our data suggest that its real influence on dementia risk in the general population may be smaller than that estimated for AD.

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Apolipoprotein E4, a weak predictor of dementia

and their relatives for their participation in this long running project, and the MRC CFAS Internal Cambridge Advisory Group and Dr David Clayton for comments. AV is grateful to the Cambridge Overseas Trust and the European Dana Alliance for the Brain for funding. DCR is a Wellcome Trust Senior Research Fellow in Clinical Science.

References


