Dementia is the most common neurodegenerative condition affecting older people. It is estimated that around 550,000 subjects aged 65 years and over in England and Wales suffer 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 have clinical diagnoses of 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 people, and some dementia 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. However, APOE accounts for around half of the genetic risk for AD. Recent data suggest that the angiotensin-I converting enzyme or ACE gene (chromosome 17q23) may also be involved in genetic susceptibility to AD. ACE (OMIM *106180) is a dipeptidyl carboxypeptidase that plays an important role in blood pressure regulation and electrolyte balance by hydrolysing angiotensin-I into angiotensin-II, a potent vasopressor and aldosterone stimulating peptide, and inactivating bradykinin, a potent vasodilator. An insertion (I)/deletion (D) polymorphism situated in intron 16 of the gene accounts for 50% of the interperson variability of plasma ACE concentration, and its links with myocardial infarction and other ischaemic heart disease and longevity have been studied extensively. There are few published studies on the association between the ACE I/D polymorphism and AD risk: Kehoe et al reported increased risk for AD among I allele carriers; however, this result was not uniformly replicated in subsequent studies. Results from our pooled analysis suggest a slightly increased risk (odds ratio 1.2, 95% confidence interval 1.1 to 1.3) for AD among I allele carriers.

We believe that the public are primarily concerned about their risk for dementia in general, in addition to the specific risks of AD or VaD. Similarly, from a public health perspective, it is crucial to understand how the ACE D/I polymorphism impacts on dementia in the general population as well as among narrowly diagnosed, selected, patient groups.

Thus, we have investigated the effects of ACE on dementia risk, cognitive function, and rates of cognitive decline (as measured by serial Mini Mental State Examination scores) 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).
centile=79.5; female=225: median age at wave 3=76, 25th centile=72, 75th centile=81).  

APOE genotyping was performed as described by Wenham et al and ACE genotypes were determined using the method described by Evans et al. All genotyping was carried out by the first author (AY), and genotype assignments double checked for accuracy by the corresponding author (DCR). Samples with ambiguous genotypes were rerun. Three genotyping attempts were performed for each sample, after which the APOE/ACE status of unsuccessfully typed samples were recorded as unknown/failed. APOE genotype was successfully determined in 1030 subjects and ACE genotype in 922. There are 913 subjects whose APOE and ACE genotypes are both known.

The association between ACE and dementia risk was examined by unconditional logistic regression. The analyses were conducted using third wave data only, to examine the cross sectional association between ACE and dementia risk, adjusting for age, sex, education, and APOE e4 carrier status. Separate analyses for men and women, controlling for age and years in full time education were also carried out. The categorical variable ACE was classified by genotype: DD (reference group), DI, and II. Additionally, an odds ratio was calculated for allele I relative to D. This analysis assumes that the maternal and paternal alleles act multiplicatively on risk, so that, for example, the odds ratio associated with DI relative to DD is the product of the odds ratios of D and I (that is, the same as the odds ratio of I). Under this model the two alleles

| Table 1 Allele and genotype frequencies at the ACE locus among demented and non-demented CFAS subjects — overall |
|--------------------------|--------------------------|--------------------------|--------------------------|
| Allele | Cases (%) | Controls (%) | Crude OR (95% CI) | Adjusted* OR (95% CI) | Narain et al† |
| D | 103 (43.6) | 428 (49.4) | 1.0 | 1.0 | 1.0 |
| I | 133 (56.4) | 438 (50.6) | 1.3 (0.9 to 1.7) | 1.4 (1.0 to 2.0) | 1.2 (1.1 to 1.3) |
| Genotype | | | | | |
| DD | 28 (23.7) | 116 (26.8) | 1.0 | 1.0 | 1.0 |
| DI | 47 (39.8) | 196 (45.3) | 1.0 (0.6 to 1.7) | 1.2 (0.6 to 2.2) | 1.3 (1.1 to 1.5) |
| II | 43 (36.4) | 121 (27.9) | 1.5 (0.9 to 2.5) | 1.9 (1.0 to 3.7) | 1.4 (1.1 to 1.6) |

*Adjusted for age, sex, years in full time education, and APOE e4 carrier status (for genotype).
†Pooled estimate OR (95% CI) for Alzheimer’s disease.

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| Figure 1 Distribution of MMSE difference (wave 3-wave 1) by ACE genotype, stratified by baseline MMSE score. (A) Baseline MMSE 17 or less: DD=5, DI=15, II=10. Kruskall-Wallis statistic (χ², 2 df=1.8, p=0.4). (B) Baseline MMSE 17-21: DD=24, DI=28, II=27. Kruskall-Wallis test (χ², 2 df=1.1, p=0.6). (C) Baseline MMSE 22-25: DD=82, DI=141, II=83. Kruskall-Wallis test (χ², 2 df=1.6, p=0.4). (D) Baseline MMSE 26 and above: DD=118, DI=207, II=129. Kruskall-Wallis test (χ², 2 df=0.2, p=0.9). |
The back transformed mean MMSE scores (see Methods) at wave 3 by ACE genotypes are: DD = 25.5, DI = 25.6, II = 25.6. MMSE scores at the third wave were not significantly different between ACE genotypes (F score (2 df) = 0.1, p = 0.9).

We were interested in the effects of ACE genotypes on the rate of cognitive decline, as measured by the difference in MMSE scores between the initial and third assessment waves, in our entire sample. In one set of analyses, we compared the distribution of MMSE differences across ACE genotypes in the sample separated into four subgroups based on people’s MMSE scores at the prevalence wave (namely, 0 to 17, 18 to 21, 22 to 25, and 26 to 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. In another analysis, we looked at the distribution of MMSE differences across the different ACE 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 ACE genotypes affected the rate of decline in people who were ostensibly non-demented throughout the study. In other words, we wanted to test if ACE effects the rate of cognitive decline before the onset of dementia.

Fig 1 shows the distribution of the difference in MMSE score between assessment waves 1 and 3 across ACE genotypes, according to baseline MMSE level. Fig 2 shows the MMSE difference across ACE genotypes among non-demented subjects at wave 3 who scored between 22 and 25 and 26 and over on the MMSE. There are no discernible differences across ACE genotypes when the sample was analysed using either of the strategies described above. Furthermore, ACE genotypes did not have any effect on change in MMSE score when the entire sample was analysed without any stratification (data not shown).

DISCUSSION

The aim of this study was to investigate the impact of ACE on dementia in the general population. This is in contrast with most published studies (both clinic/necropsy based and population based), which have looked into the impact of ACE on AD risk specifically, and have tended to use younger samples which may not reflect the population in which dementia occurs most frequently. While ACE does not appear to have a major effect on dementia/AD risk in the general population, it warrants further investigation. Larger samples are required before one can exclude small effects that may be operating at this locus for dementia/AD; in order to achieve 80% power to detect an odds ratio of 1.2, given 50% prevalence of the risk allele among
non-cases, we would need just under 400 cases and controls. Robust confirmation of an AD risk gene is valuable, even if the effect is small, as it would contribute to our understanding of AD pathology and furthermore may suggest potential therapeutic strategies.

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