Premorbid cognitive testing predicts the onset of dementia and Alzheimer’s disease better than and independently of APOE genotype

J Cervilla, M Prince, S Joels, S Lovestone, A Mann

Objective: To determine whether a cognitive test package can predict the onset of dementia up to 11 years later, and the extent to which this prediction is independent of that provided by APOE genotype.

Methods: Prospective cohort study based on 54 general practices in the UK; 657 survivors of the 1088 participants in the MRC treatment trial of hypertension in older adults were followed for up to 11 years; 370 participants (57% of survivors) were traced, screened for dementia, and genotyped for APOE in 1994. Baseline assessments included trail making test A, paired associated learning test, Raven’s progressive matrices, and national adult reading test. At follow up, both mini-mental state examination and CAMCOG were used. Outcome measures were DSM-III-R dementia and NINCDS-ADRDA possible and probable Alzheimer’s disease.

Results: All the cognitive tests completed in 1983 predicted onset of dementia and Alzheimer’s disease up to 11 years later, as did APOE genotype. Cognitive test performance was not associated with APOE genotype. Addition of cognitive tests increased the area under the ROC curve for the prediction of Alzheimer’s disease provided by age, family history, and APOE genotype (0.81 v 0.69, p = 0.048); addition of APOE genotype did not increase the area under the ROC curve for the prediction provided by age, family history, and cognitive tests (0.81 v 0.77, p = 0.28).

Conclusions: Simple tests of cognitive ability provide useful predictive information up to a decade before the onset of dementia. The predictive information provided is independent of, but not enhanced by, the addition of APOE genotype.
trial compared mortality and morbidity among 4396 subjects randomised to receive a β blocker, a thiazide diuretic, or placebo. Inclusion criteria were age 65 to 75 years and systolic blood pressure 160 to 209 mm Hg. Those with serious intercurrent illnesses, including dementia, were excluded. Participants were recruited in 226 United Kingdom MRC general practice research framework practices. Invitations for screening had been sent to all registered patients within the eligible age range. In 1991 we reviewed a subsample of 1545 participants from 71 of the 226 practices in an attempt to ascertain all cases of dementia and Alzheimer’s disease incident since the beginning of the MRC trial. In 1994 we updated this procedure by aiming to screen all surviving participants from the practices included in the earlier case-control study. In the event, 54 practices were still attached to the MRC GP framework and were willing to take part in the follow up.

As previously reported, of the initial cohort of 1088 subjects recruited in these 54 practices, 431 had died; of the 657 survivors, 158 (24%) declined to participate in the follow up survey, and 112 (17%) had moved away from their research practice; thus 387 subjects participated and blood samples were obtained from 370, constituting 56% of eligible survivors and 34% of the entire cohort. Figure 2 shows a summary of the sampling process. Those successfully followed up in 1994 differed systematically from those who had refused to participate, who tended to have lower premorbid intelligence and poorer performance on cognitive tests of non-verbal (fluid) intelligence, sensitive to age related cognitive decline.

### Dementia diagnosis in 1994

We used a standard three stage dementia diagnosis procedure. The MRC research nurse first administered the mini-mental state examination (MMSE) to all consenting participants. All those who scored less than 27/30, and all those educated beyond the age of 16 who scored less than 25/30, and all who had refused to participate, who tended to have lower premorbid intelligence and poorer performance on cognitive tests at entry to the trial than did other groups. The mean (SD) age of the achieved sample was 80.1 (2.9) years (range 74.2 to 85.6) at the mid-point of the re-survey.

### APOE genotype

APOE genotype was determined from blood samples obtained from consenting survivors during the course of the 1994 follow up. The frequencies of the APOE genotypes in the whole sample were as follows: 2/2, three (0.8%); 2/3, 40 (10.8%); 3/3, 221 (59.7%); 2/4, seven (1.9%); 3/4, 97 (26.2%); and 4/4, two (0.5%). Therefore 28.6% had one or more e4 alleles, 59.6% were e3/3, and 11.6% were e2/2 or 2/3. The APOE genotype was strongly associated with both dementia and Alzheimer’s disease diagnoses in 1994. The prevalence of all dementia rose from 4.7% among those with a 2/2 or 2/3 genotype to 9.0% for those with 3/3 and 17.0% for those with any e4 allele ($\chi^2 = 6.3, p = 0.012$). For NINCDS/ADRDA probable and possible Alzheimer’s disease, the association was even stronger, with a prevalence of 2.4% among those with a 2/2 or 2/3 genotype, rising to 4.7% for those with 3/3 and 12.9% for those with any e4 allele ($\chi^2 = 7.6, p = 0.006$).

### The predictive test variables

**Assessment of cognitive function at entry to the MRC trial**

The following assessments were used:

- **The paired associate learning test (PALT).** This tests the capacity to recall the second half of a pair of words cued by the first half of the couplet, thus addresses episodic memory.
- **The trail making test (TMT), part A.** This tests attention, concentration, and psychomotor function. Subjects are timed while they join consecutive numbers, arranged at random.
- **The new adult reading test (NART).** This is a stable measure of premorbid (crystallised) intelligence.
- **Raven’s progressive matrices (RPM) parts A and B.** These are tests of non-verbal (fluid) intelligence, sensitive to age related cognitive decline.

All tests were administered by MRC general practice research framework research nurses who had been specifically trained for the purpose. The PALT and the TMT were administered repeatedly through the MRC trial; the mean of the entry and one month assessments was used in this analysis. The NART and RPM were measured at entry to the trial only.

### Family history of dementia

Family history of dementia was assessed from a questionnaire administered both to the subject and to a reliable informant in the 1994 follow up study. Vital status, current ages or ages at death, and dementia histories were systematically ascertained for all first degree relatives. A family history of dementia loading was derived taking into account both the numbers of relatives affected and the family person-years at risk for the disease.

### Analysis

To assess the likely independence of the prediction of dementia onset by the cognitive tests from that provided by APOE genotype, we first assessed the association between APOE and each of the four cognitive tests using one way ANOVA, with $\chi^2$ as a measure of the effect size for the association. We used identical analyses to assess the associations between APOE genotype and both age and family history of dementia loading.
We then compared mean entry (1983) cognitive test scores for those who were and were not found to have dementia or Alzheimer’s disease at the 1994 follow up. Given the long follow up period, we explored heterogeneity of prediction by time of onset by stratifying 1994 dementia cases into two groups according to onset before or after the first 1991 follow up. Identical analyses were carried out for the family history of dementia loading and for age. To facilitate comparison of discrimination between tests, all mean differences were standardised, expressed as a proportion of the standard deviation of the relevant variable. Predicted standardised mean differences between dementia cases and non-cases are also presented after adjusting for APOE genotype, and after adjusting for years of education.

We next predicted probabilities of Alzheimer’s disease and dementia caseness for each participant from the following logistic regression models:

- Age and family history of dementia loading
- Age and family history of dementia loading and APOE genotype
- Age and family history of dementia loading and cognitive tests
- Age and family history of dementia loading and cognitive tests and APOE genotype

For the purposes of these analyses the distribution of each cognitive test, and of age and family history loading, was divided into thirds, and APOE genotype into 2/2 or 2/3, 3/3, and 4/4. The sample was divided into tenths according to subjects’ predicted probability of caseness, and the sensitivity and specificity for the diagnosis calculated at each decile cut off point. Sensitivity was then plotted against 1 – specificity (false positive rate) to produce a receiver operating characteristic (ROC) curve. Using non-parametric procedures, the area under each curve was calculated, with 95% confidence intervals, as an overall measure of the discriminability of the test package. The discriminability of pairs of test packages was compared statistically using z tests. For both dementia and Alzheimer’s disease we compared test packages 2 v 1, 3 v 1, and 3 v 4. All ROC analyses were carried out using ROC Analyzer software.

RESULTS
Association between APOE genotype and cognitive test performance in 1983
None of the cognitive tests completed in 1983 before any of the participants had gone on to develop dementia was associated to any degree with APOE genotype (table 1). There was also no association in subgroups consisting of those who did and did not go on to develop dementia. There was a non-significant trend for an association between APOE genotype and both age and family history of dementia loading in the direction 2/2 or 2/3 (oldest, and lowest family history loading), 3/3 (intermediate), and 4/4 (youngest, and highest loading).

Associations between cognitive test performance in 1983 and dementia onset by 1994
Each of the cognitive tests completed at entry to the MRC trial in 1983 predicted onset of dementia and Alzheimer’s disease by 1994, with poorer test performance among those who went on to develop dementia (table 2). Patterns of prediction were similar for the 41 dementia cases and the subset of 24 Alzheimer’s disease cases. Likewise, patterns of prediction were similar for the seven cases of dementia with onset between 1983 and the 1991 follow up, and the 34 with onset between 1991 and 1994 (results not shown). The TMT-A gave the most marked discrimination, with around 0.6 SD difference between baseline times for test completion. Next came the two tests of general intelligence, the NART (crystallised intelligence) and RPM (fluid intelligence), each with around 0.5 SD difference, and the PALT with 0.25 SD difference. The difference on the PALT was not statistically significant at the 5% level. Given that PALT scores, unlike the other cognitive tests, were heavily negatively skewed, with 35% of subjects scoring the maximum of 18 at baseline and one month assessments, we also tested using the non-parametric Mann–Whitney procedure for associations with dementia onset (p = 0.26) and Alzheimer’s disease onset (p = 0.70).

The standardised mean differences on the four cognitive tests between those experiencing and those not experiencing a later onset of dementia were little altered after adjusting for APOE genotype (table 2). The findings for the adjusted mean


**Table 1** Associations between APOE genotype and cognitive test scores (1983), age, and family history of dementia

<table>
<thead>
<tr>
<th>APOE 2/2 or 2/3 (n = 43)</th>
<th>APOE 3/3 (n = 221)</th>
<th>APOE 4/* (n = 106)</th>
<th>$\chi^2$</th>
<th>F value (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT-A</td>
<td>50.1 (1.4)</td>
<td>51.6 (20.5)</td>
<td>50.5 (19.4)</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>PALT</td>
<td>17.0 (1.1)</td>
<td>17.0 (1.3)</td>
<td>17.1 (1.1)</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>RPM</td>
<td>16.5 (3.3)</td>
<td>16.1 (3.9)</td>
<td>16.1 (4.0)</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>NART</td>
<td>31.6 (11.0)</td>
<td>31.3 (10.8)</td>
<td>31.8 (10.7)</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Age</td>
<td>70.7 (2.8)</td>
<td>70.2 (2.9)</td>
<td>69.8 (2.6)</td>
<td>1.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Family history of dementia loading</td>
<td>0.80 (0.13)</td>
<td>0.82 (0.13)</td>
<td>0.85 (0.12)</td>
<td>1.0</td>
<td>1.9</td>
</tr>
</tbody>
</table>

NART, new adult reading test; PALT, paired associate learning test; RPM, Raven’s progressive matrices; TMT-A, trail making test A.

**DISCUSSION**

While several studies have reported the ability of tests of cognitive function administered well before the onset of dementia to predict the onset of dementia in the short term, few have studied this phenomenon over a period of 10 years. The large majority of our dementia cases experienced an onset of the condition seven years or more after the tests were administered. This is also the first community based study to look at the combined effect of cognitive tests and APOE genotype in predicting dementia.

Cognitive tests completed in 1983, when all subjects were free of dementia, predicted robustly which among those who survived went on to develop dementia by 1994. We used APOE as a potential predictive factor not only for Alzheimer’s disease but for dementia too, given that in 1994 there was uncertainty about the specificity of the association between APOE and Alzheimer’s disease. In our previous report, we found that APOE associated increasingly strongly to dementia, possible Alzheimer’s disease, and probable Alzheimer’s disease, respectively. APOE genotype was also a strong predictor of dementia onset, and this prediction was independent of that provided by cognitive tests, and vice versa. All predictive models showed greater discriminability for the specific outcome of Alzheimer’s disease compared with all dementia. Despite the mutual independence of these predictive factors, the areas under the ROC curves—summarising the overall prediction provided by the tests (that is, the greater the area under the curve the better is the test)—were increased to a statistically significant degree when cognitive tests were added to a test package consisting of age and family history of dementia alone, but not when the same test package was extended by the inclusion of APOE genotype. Likewise the area under the ROC curve for age, family history of dementia, and APOE genotype was significantly increased by the addition of cognitive tests, but the ROC curve for age, family history of dementia, and cognitive tests was not significantly increased by the addition of APOE genotype. Thus APOE genotype, although an independent predictor, in practice added little if anything to the discriminability of a test package based upon simple tests of cognitive function administered well before the onset of dementia.

This was a relatively small sample, and an unusual one given the age and high blood pressure levels of all participants, so our results may not reflect the findings expected in a non-hypertensive population. The fact that our differences between Alzheimer’s disease cases and non-cases were similar (results not shown). After adjusting for years of education, mean differences on the RPM and NART were somewhat attenuated and no longer statistically significant at the 5% level; TMT-A was little affected.

The odds ratios for the independent associations of the test variables with dementia outcome for three of the four predictive models are given in table 3. These three models form a hierarchy, and tests of statistical significance were done for each block. Family history and age were minimally predictive. The four cognitive tests made the largest contribution, with TMT-A predominating and PALT showing a very weak non-significant trend for higher risk with better test performance. APOE genotype still predicted dementia onset ($\chi^2 = 6.8, 2$ df; $p = 0.03$) after adjusting for age, family history of dementia, and cognitive test scores in 1983. Results for prediction of Alzheimer’s disease onset were similar and are not shown in detail: age and family history were again little associated ($\chi^2 = 3.3, 4$ df; $p = 0.51$); cognitive tests were strongly associated ($\chi^2 = 19.7, 8$ df; $p = 0.01$) although again the PALT made little independent contribution; and APOE genotype predicted Alzheimer’s disease onset ($\chi^2 = 9.7, 2$ df; $p = 0.008$) somewhat more robustly than it had predicted dementia onset. The ROC curves for each of the four predictive models are given for dementia (fig 3) and Alzheimer’s disease (fig 4).

**Table 2** Standardised mean differences on cognitive tests

<table>
<thead>
<tr>
<th></th>
<th>All dementia (n = 41)</th>
<th>AD (n = 24)</th>
<th>No dementia (n = 346)</th>
<th>AD v no dementia*</th>
<th>Dementia v no dementia adjusted for APOE genotype*</th>
<th>Dementia v no dementia adjusted for years of education*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT-A</td>
<td>61.8 (19.1)</td>
<td>60.9 (15.4)</td>
<td>49.8 (19.2)</td>
<td>0.58 (0.17 to 0.99)</td>
<td>0.62 (0.30 to 0.94)</td>
<td>0.61 (0.27 to 0.93)</td>
</tr>
<tr>
<td>PALT</td>
<td>16.7 (1.5)</td>
<td>16.7 (1.7)</td>
<td>17.0 (1.2)</td>
<td>0.26 (0.16 to 0.67)</td>
<td>0.24 (0.09 to 0.56)</td>
<td>0.27 (0.06 to 0.60)</td>
</tr>
<tr>
<td>RPM</td>
<td>14.8 (3.9)</td>
<td>14.6 (3.8)</td>
<td>16.3 (3.8)</td>
<td>0.43 (0.02 to 0.85)</td>
<td>0.39 (0.07 to 0.71)</td>
<td>0.41 (0.08 to 0.74)</td>
</tr>
<tr>
<td>NART</td>
<td>27.6 (11.9)</td>
<td>26.3 (12.2)</td>
<td>31.9 (10.6)</td>
<td>0.52 (0.10 to 0.95)</td>
<td>0.40 (0.08 to 0.73)</td>
<td>0.40 (0.07 to 0.73)</td>
</tr>
<tr>
<td>Age</td>
<td>70.3 (2.9)</td>
<td>70.2 (3.0)</td>
<td>70.1 (2.8)</td>
<td>0.01 (−0.40 to 0.42)</td>
<td>0.08 (−0.27 to 0.42)</td>
<td>0.20 (−0.14 to 0.54)</td>
</tr>
<tr>
<td>FH of dementia</td>
<td>0.86 (0.12)</td>
<td>0.85 (0.14)</td>
<td>0.82 (0.13)</td>
<td>0.23 (−0.23 to 0.62)</td>
<td>0.27 (−0.06 to 0.60)</td>
<td>0.10 (−0.24 to 0.43)</td>
</tr>
</tbody>
</table>

Values are mean (SD), or *mean (95% confidence interval).
AD, Alzheimer’s disease; FH, family history; NART, new adult reading test; PALT, paired associate learning test; RPM, Raven’s progressive matrices; TMT-A, trail making test A.
sample comprised subjects with mild hypertension may also explain the unexpected finding of an absence of an association between our episodic memory test (the PALT) and cases of dementia, although our finding replicates a previous study that also indicated such lack of association.39 Furthermore, the strength of the association that we observed between APOE genotype and both dementia and Alzheimer’s disease was consistent with that reported by many other previous studies; hence it is unlikely that our conclusions are undermined either by sampling error or by an unusually weak level of association in aged hypertensive subjects. Bias was also unlikely, given that the assessment of cognitive function was carried out blind to APOE status, and vice versa, and both assessments were carried out blind to dementia outcome. Additionally, we cannot rule out the possibility that our screening process may have resulted in false negatives—that is, people with dementia who were not detected by the screening procedure and who might have interfered with our final results. However, we did interview thoroughly all possible cases using a high MMSE cut off point of 25 (27 if highly educated) in order to minimise false negatives as a result of our screening.

Why do tests of cognitive ability predict dementia onset over 11 years, and why is this prediction independent of APOE genotype? It is tempting to conclude that subtle premorbid impairment of cognitive ability represents a decline from a previous level of functioning, and is an early marker of the pathological process of Alzheimer’s disease that begins well in advance of the clinical onset.1 However, if cognitive decline is an integral component of the dementia syndrome, how can APOE genotype be a direct risk factor for Alzheimer’s disease and yet not be associated with incipient cognitive decline? Our findings in this respect concur with other evidence—many studies have failed to find an association between APOE and global cognitive decline.30–32 Positive reports for such an association do exist but they have been found to be weak33,34 or circumscribed to specific areas of cognitive decline, mostly semantic memory.35 The model that we have posited, which supposes a continuum between cognitive decline and dementia, cannot be made to fit these observations. An alternative and perhaps more parsimonious explanation is that premorbid tests of cognitive ability are stable markers of early intellectual development—a process that, at least in infants, seems not to be influenced by APOE.31 32

Intellectual development may be related to risk for dementia by one of two processes. First, well developed brains with a richly complex cortical synaptic architecture may be intrinsically less likely to sustain Alzheimer’s disease pathology and the precipitous decline in cognitive ability that accompanies it.36 This theory is supported by the findings from the nuns’ study, in which idea density ascertained from biographies written at the age of 18 was negatively associated not only with late life cognitive impairment in vivo, but also with the density of neurofibrillary tangles at necropsy.37 Second, in the course of the pathological process of Alzheimer’s disease, cognitive or neuronal reserve may delay the onset of clinically relevant cognitive and functional impairment, a theory advanced to explain the consistent observation of a lower risk of dementia among intelligent and well educated people.34 This “reserve hypothesis” predicts more advanced Alzheimer’s disease pathology among the

<table>
<thead>
<tr>
<th>Test/Genotype</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
<td>&lt;0.78</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Loading</td>
<td>0.79 to 0.89, 1.40 (0.57 to 3.46)</td>
<td>1.43 (0.56 to 3.68)</td>
<td>1.34 (0.51 to 3.49)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.0 to 68.9, 1.60 (0.68 to 3.75)</td>
<td>1.60 (0.68 to 3.75)</td>
<td>1.71 (0.72 to 4.04)</td>
</tr>
<tr>
<td>TMT-A</td>
<td>&lt;40 s, 3.00 (1.00 to 10.8)</td>
<td>3.00 (1.00 to 10.8)</td>
<td>3.49 (1.05 to 11.6)</td>
</tr>
<tr>
<td>NART</td>
<td>27, 0.74 (0.31 to 1.78)</td>
<td>0.74 (0.31 to 1.78)</td>
<td>0.69 (0.28 to 1.70)</td>
</tr>
<tr>
<td>APOE</td>
<td>2/2 or 2/3, 1.24 (0.47 to 3.24)</td>
<td>1.24 (0.47 to 3.24)</td>
<td>1.24 (0.47 to 3.24)</td>
</tr>
</tbody>
</table>

†With 95% confidence intervals.
FH, family history; NART, new adult reading test; PALT, paired associate learning test; RPM, Raven’s progressive matrices; TMT-A, trail making test A.
better educated for any given clinical stage of dementia, and is lent support by the finding of increased mortality in better educated persons with dementia, after adjusting for clinical dementia staging.\textsuperscript{39} APOE genotype might then exert its effect through a different pathway, for example modifying the cumulative impact of a variety of brain insults sustained across the life course.\textsuperscript{40}

Our research suggests that predictive tests for Alzheimer’s disease and other dementias may be an achievable objective, even with existing technologies. Ascertainment of APOE genotype seems to confer no advantage over lower technology cognitive test packages, and earlier cautions against the indiscriminate use of genotyping as a diagnostic or predictive procedure are well founded.\textsuperscript{41} 42 Computed tomography or magnetic resonance imaging, particularly if applied sequentially,\textsuperscript{43}–\textsuperscript{45} may add usefully to the discriminability of a cognitive test package, but this possibility has not been formally explored. There is as yet no clinical application for a predictive test package with the level of discriminability reported here (50–60% sensitivity with a 10% false positive rate), but this conclusion would change in the event of the introduction of a treatment with the ability to modify the disease course. Epidemiological studies have suggested that both non-steroidal anti-inflammatory drugs\textsuperscript{46} 47 and hormone replacement therapy\textsuperscript{48} 49 might substantially protect against Alzheimer’s disease. New compounds designed to interfere with the amyloid cascade process are also in an advanced stage of development.\textsuperscript{50} Further research to refine predictive test packages is therefore an urgent priority.

**ACKNOWLEDGEMENTS**

The United Kingdom Medical Research Council supported this study. We thank the MRC Working Party and the MRC Epidemiology and Medical Care Unit (Director Professor T Meade) for allowing us to continue to investigate trial participants, and the MRC General Practice Research Framework general practitioners and research nurses (coordinator Mrs W Browne) for collecting much of the data. APOE genotyping was undertaken at the Institute of Psychiatry by Dr John Powell and Mr Carsten Russ.

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Competing interests: none declared

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**Figure 3** Receiver operating curve (ROC) analysis: the prediction of dementia onset. Areas under the ROC curves (AUC) for each model predicting dementia and tests for the significance of the differences between them.

<table>
<thead>
<tr>
<th>Predictive model</th>
<th>AUC (95% CI)</th>
<th>Significance test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FH + age</td>
<td>0.60 [0.50 to 0.70]</td>
<td></td>
</tr>
<tr>
<td>2. FH + age + APOE genotype</td>
<td>0.65 [0.59 to 0.74]</td>
<td>2 v 1: p = 0.26</td>
</tr>
<tr>
<td>3. FH + age + cognitive tests</td>
<td>0.74 [0.67 to 0.81]</td>
<td>3 v 1: p = 0.015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 v 2: p = 0.069</td>
</tr>
<tr>
<td>4. FH + age + cognitive tests + APOE genotype</td>
<td>0.77 [0.69 to 0.85]</td>
<td>4 v 3: p = 0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 v 2: p = 0.026</td>
</tr>
</tbody>
</table>

**Figure 4** Receiver operating curve (ROC) analysis: the prediction of Alzheimer’s disease onset. Areas under the ROC curves for each model predicting Alzheimer’s disease and tests for the significance of the differences between them.

<table>
<thead>
<tr>
<th>Predictive model</th>
<th>AUC (95% CI)</th>
<th>Significance test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FH + age</td>
<td>0.61 [0.49 to 0.73]</td>
<td></td>
</tr>
<tr>
<td>2. FH + age + APOE genotype</td>
<td>0.69 [0.59 to 0.79]</td>
<td>2 v 1: p = 0.16</td>
</tr>
<tr>
<td>3. FH + age + cognitive tests</td>
<td>0.77 [0.69 to 0.85]</td>
<td>3 v 1: p = 0.016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 v 2: p = 0.16</td>
</tr>
<tr>
<td>4. FH + age + cognitive tests + APOE genotype</td>
<td>0.81 [0.72 to 0.90]</td>
<td>4 v 3: p = 0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 v 2: p = 0.048</td>
</tr>
</tbody>
</table>
REFERENCES

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