APOE and mild cognitive impairment: the Framingham Heart Study

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Abstract

Background: the risk apolipoprotein E-4 (APOE4) poses for mild cognitive impairment (MCI) may vary based on the neuropsychological definition of MCI.

Setting: a community-based cohort study.

Methods: using two psychometric neuropsychological impairment definitions, we examined APOE4 and prevalent MCI among older adults or pre-MCI among middle-aged adults. Neuropsychological, clinical and genetic data were collected on 2,239 Framingham Offspring Cohort participants free from clinical stroke or dementia (62 ± 9 years; 54% women). Prevalent amnestic MCI was defined from neuropsychological performances ≥1.5 SD below the mean based on (i) age and education or (ii) age and Wide Range Achievement Test-3 Reading (WRAT-3 Reading) performance adjustment.

Results: in the entire sample, multivariable-adjusted logistic regressions found that APOE4 was associated with amnestic MCI when using the age and WRAT Reading definition (odds ratio [OR] = 1.7, \( P = 0.002 \)) but not the age and education definition (OR = 1.0, \( P = 0.90 \)). Results were modified by age, such that APOE4 was associated with amnestic MCI in participants ≥65 years using both the age and WRAT Reading definition (OR = 2.4, \( P < 0.001 \)) and the age and education definition (OR = 1.7, \( P = 0.04 \)).

Conclusion: APOE4 risk for prevalent amnestic MCI varies depending on the definition of objective neuropsychological impairment for MCI. Our findings support existing literature emphasising the need to refine MCI neuropsychological profiling methods.

Keywords: Alzheimer’s disease, APOE, genetic risk, mild cognitive impairment, older people, risk factors

Introduction

Recently updated MCI diagnostic criteria support the idea that preclinical Alzheimer’s disease (AD) spans decades [1], emphasising the need for earlier detection, perhaps even in midlife. As early detection becomes increasingly important, the methods by which we define neuropsychological impairment for mild cognitive impairment (MCI) are drawing more empirical interest. A traditional approach to defining neuropsychological impairment is to apply normative data to raw objective neuropsychological performance using an impairment threshold (e.g. 1.0–1.5 SD [1]). Normative data are generally from convenience or epidemiological samples and broken down by age, education or demographic variables. Such normative variables may bias impairment definitions, especially for individuals whose characteristics fall outside the range. For example, education is an easily quantified benchmark but may be confounded by sex, race, income and geography [2].

An emerging framework for MCI detection is an intra-individual or personalised benchmark to define neuropsychological impairment that offers more precision in identifying meaningful cognitive changes. While MCI defined using a personalised benchmark has been related to clinical AD [3], it is unclear whether such personalised definitions are associated with AD genetic susceptibility. Apolipoprotein E-4 (APOE4) is the primary genetic susceptibility risk factor for AD. While APOE4 confers greater risk for MCI [4], it is not yet known whether such susceptibility is evident during earlier decades when neuropsychological changes may be at pre-MCI stages and whether APOE4 confers a greater risk of early AD symptoms in midlife or late life. Increasing knowledge about the
risk APOE4 poses for MCI and pre-MCI is important in light of a growing emphasis on understanding the AD pathological cascade over the entire lifespan [5], especially given limited research examining genetic risk among adults who met pathological criteria for AD post-mortem but were not clinically symptomatic in vivo [6].

The current study assesses relations between APOE4 and prevalent MCI among adults aged 65 and older and pre-MCI among adults aged 45–64. We hypothesised that APOE4 would relate to amnestic MCI, because APOE4 acts as a chaperone for beta-amyloid processing [7]. Second, considering the MCI definition requires neuropsychological impairment representing a decline from premorbid function, it is essential that the benchmark for defining premorbid functioning is as precise as possible. Thus, we tested whether applying a personalised criterion for performance standardisation (using age and Wide Range Achievement Test: Third Edition (WRAT-3) Reading Subtest [8]) compared with a traditional approach (using age- and education-adjusted normative data) would attenuate the APOE4 and MCI association. The WRAT-3 Reading Subtest assesses reading for words with irregular sound-to-spelling correspondence and was included as the personalised criterion, because it is purportedly a proxy measure for education quality [9] or cognitive reserve [10]. That is, literacy likely represents inherent skills [11] or intellectual capacity [12], and acquiring reading abilities over the developmental lifespan may augment the brain organisation [13] or synaptic density [11]. Thus, reading skills may offer a more personalised and precise criterion for assessing decline from premorbid neuropsychological functioning. Finally, we examined whether associations between APOE4 and MCI vary by age group, hypothesising that APOE4 confers a risk for MCI among older adults (at greatest risk because of their advancing age) compared with middle-aged adults who may more appropriately meet definition for pre-MCI.

Materials and methods

Participants

The Framingham Offspring Study design has been described elsewhere [14]. The current sample was derived from 2,523 participants who consented to an ancillary neuropsychological and brain MRI study between April 1999 and August 2005. Participants were excluded from the present study if they were <45 years of age (n = 63) and had a confounding neurological condition (e.g. dementia, stroke; n = 95), no APOE [15] information (n = 51) or missing co-variate data (n = 75). The study was approved by the Institutional Review Board. Participants provided written informed consent.

Prevalent MCI outcome

Prevalent amnestic MCI was defined a priori as a sum composite of Logical Memory Delayed Recall and Visual Reproduction Delayed Recall. The two psychometric methods to define neuropsychological impairment within the amnestic MCI subtype (age and education versus age and WRAT-3 Reading) were applied separately. First, using the baseline sample free of stroke, dementia and other neurological illnesses (n = 2,506), Logical Memory Delayed Recall and Visual Reproduction Delayed Recall were separately regressed onto age and education (defined categorically in Table 1). Residuals were standardised to z-scores, and impairment was defined as a z-score equal to or less than −1.5 (i.e. age and education definition). The second method used the same baseline sample free of stroke, dementia and other neurological illnesses (n = 2,506), but each neuropsychological measure was regressed onto age and WRAT-3 Reading performance [8]. Residuals were then standardised to z-scores, and impairment was defined as a z-score equal to or less than −1.5 (i.e. age and WRAT-3 Reading definition).

There are methodological advantages associated with this neuropsychological impairment definition for MCI. First, psychometric thresholds of impairment eliminate the selection bias that comes from clinical studies [16]. Utilisation of a single referent sample rather than multiple samples permits comparisons between standardised performances across tests and MCI definitions. Finally, the Offspring Cohort provides highly representative normative data for FHS community-based cohort members, which is important given we previously reported cohort effects on neuropsychological performances [17].

Statistical analysis

Logistic regression models related APOE4 status (positive defined as e2/e4, e3/e4, e4/e4 versus negative defined as e2/e2, e2/e3, e3/e3 [18]) to the presence of amnestic MCI, adjusting for age and sex. Models were run for age- and sex-adjusted analyses.

Table 1. Participant characteristics

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Total</th>
<th>Age- and education-defined MCI</th>
<th>Age- and WRAT-3 Reading-defined MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, n</td>
<td>2,239</td>
<td>172</td>
<td>158</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>54</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Age, years</td>
<td>62 ± 9</td>
<td>64 ± 9</td>
<td>64 ± 9</td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;8th grade but not high school graduate, %</td>
<td>3</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>High school graduation/no college, %</td>
<td>32</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>Some college/no college degree, %</td>
<td>27</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>College degree, %</td>
<td>19</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Post college, %</td>
<td>19</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>126 ± 19</td>
<td>128 ± 18</td>
<td>128 ± 19</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>12</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension treatment, %</td>
<td>31</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Prevalent CVD, %</td>
<td>11</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>APOE4, %</td>
<td>22</td>
<td>23</td>
<td>32</td>
</tr>
</tbody>
</table>

Clinical characteristics denoted as percentages or mean ± SD; CVD does not include clinical stroke or transient ischaemic attack.
education-defined MCI and again for age- and WRAT-3 Reading-defined MCI. In secondary analyses, models were repeated adjusting for vascular co-variates associated with increased risk of neuropsychological impairment defined at the 7th examination cycle, including the mean of two systolic blood pressure measurements obtained by a Framingham Heart Study (FHS) physician, current cigarette smoking (i.e. yes/no within the year prior to examination 7), diabetes mellitus (i.e. previous or current fasting blood glucose ≥126 mg/dl or previous or current use of oral hypoglycaemic or insulin ascertained by self-report), anti-hypertensive medication (i.e. ascertained by self-report) and prevalent cardiovascular disease (CVD) defined as coronary heart disease, heart failure and intermittent claudication (i.e. obtained via medical histories and physical examinations conducted at the FHS, as well as hospitalisation and personal physician records). A panel of three experienced investigators adjudicated CVD events [19]. Secondary models used interaction terms to assess effect modification by sex and age (<65 versus ≥65 years). Significance was set at $P<0.05$ for all models and $P<0.10$ for analyses assessing effect modification. Data were analysed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Participant characteristics**

The mean sample age was 62 (45–89 years) and 54% were women. Age- and education-defined MCI was present in 8% of the sample while age- and WRAT Reading-defined MCI was present in 7% of the sample. See Table 1.

**APOE4 and prevalent MCI**

APOE4 was not associated with age- and education-defined MCI. However, APOE4 was associated with age- and education-defined MCI in participants aged ≥65 (odds ratio [OR] = 1.68; $P = 0.039$). Findings were similar in secondary models adjusting for vascular health factors. See Table 2.

APOE4 was associated with age- and WRAT Reading-defined MCI (OR = 1.74; $P = 0.002$). There was an interaction in which the association between APOE4 and age-and WRAT Reading-defined MCI was stronger among women (OR = 2.54; $P < 0.001$) and participants aged ≥65 (OR = 2.35; $P < 0.001$). Findings were similar in secondary models adjusting for vascular health factors. See Table 2.

**Conclusions**

Among community-dwelling adults aged 45–86, APOE4 was associated with prevalent amnestic MCI based on an age and WRAT Reading psychometric definition, which was predominantly driven by participants aged 65 and older. In this subset of older adults (aged ≥65), APOE4 was also related to the age and education definition of amnestic MCI, though the effect size was smaller. The observed relations between APOE4 and amnestic MCI are likely attributable to the clinical manifestation of issues in amyloid metabolism [20] and beta-amyloid clearance [21], mechanisms underlying pathological AD.

Implementation of a more personalised benchmark for defining neuropsychological impairment is an emerging framework in the early detection of MCI [3, 22, 23]. While this framework remains in early development, there may be important implications for its clinical utility in detecting AD in both mid- and late life. A personalised benchmark may function as a better definition of neuropsychological impairment over traditional psychometric definitions, particularly when traditional methods are less accurate at profiling impairment at extreme ends of the normative data range [2]. Such benchmarks may also be useful if future studies show them to be equivalent or superior to expensive and invasive AD biomarker methods currently under validation. This possibility is especially promising in light of recent research suggesting psychometric MCI defined using a personalised benchmark has strong associations with incident dementia [3]. Third, a personalised benchmark establishes an estimate of lifelong cognition as the referent for defining change, which is

**Table 2. Odds ratios for APOE4 and prevalent MCI**

<table>
<thead>
<tr>
<th></th>
<th>Age- and education-defined MCI</th>
<th>Age- and WRAT Reading-defined MCI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Primary analysis$^a$</td>
<td>Secondary analysis$^b$</td>
</tr>
<tr>
<td></td>
<td>OR [95% CI]</td>
<td>$P$ value</td>
</tr>
<tr>
<td>All ages, $n = 2,239$</td>
<td>1.02 [0.71–1.49]</td>
<td>0.901</td>
</tr>
<tr>
<td>Ages 45–64, $n = 1,367$</td>
<td>0.59 [0.32–1.08]</td>
<td>0.085</td>
</tr>
<tr>
<td>Ages ≥65, $n = 872$</td>
<td>1.68 [1.03–2.75]</td>
<td>0.039</td>
</tr>
</tbody>
</table>

**Bold values indicate statistically significant observations at alpha=0.05.**

$^a$Adjusted for age and sex.

$^b$Adjusted for age, sex, systolic blood pressure, current smoking, diabetes mellitus, anti-hypertensive medications and prevalent CVD.

$^c$Interaction with sex, $P = 0.028$; interaction with age ≥65 years, $P = 0.008$.

$^d$Interaction with sex, $P = 0.029$; interaction with age ≥65 years, $P = 0.107$.

$^e$Mean ± SD of 56 ± 5 years.

$^f$Interaction with sex, $P = 0.027$.

$^g$Interaction with sex, $P = 0.030$.

$^h$Mean ± SD of 72 ± 4 years.
especially valuable when detailed clinical information is lacking. More research is needed to understand how personalised benchmark definitions of MCI relate to neuropsychological trajectory and neuropathological underpinnings.

Age and sex appear to be effect modifiers for the association between APOE4 and MCI. For instance, findings are strongest in adults aged 65 and older. The lack of association between APOE4 and pre-MCI among our middle age cohort supports prior meta-analytical work reporting that APOE4 has limited association with early-life cognition [24]. However, some prior work suggests cerebrospinal fluid biomarkers of AD are associated with APOE4 in middle age [25]. Findings were also stronger in women, perhaps because the WRAT Reading test is a better proxy of premorbid functioning in women due to socio-cultural factors impacting educational attainment more so than for men.

An important aspect of our study is that findings are adjusted for vascular co-variates known to confer risk for AD. APOE4 is an effect modifier in associations between vascular health and mid- [26] and late life markers of AD pathophysiology [27] and incident AD [28]. The mechanism underlying such effect modification is purportedly because APOE4 is associated with beta-amyloid metabolism, aggregation and clearance [20, 21] and simultaneously underlies maladaptive responses to other forms of brain injury, such as ischaemia [29].

MCI prevalence in our sample ranged from 7% (age and WRAT Reading defined) to 8% (age and education defined). These rates are lower than reports of community-based prevalence rates, some of which are as high as 16% [30]. One explanation for the difference may be that we applied a statistical (psychometric) definition of impairment for MCI based on a normal distribution of each measure individually. By taking a portion of the distribution for each subtype (i.e. performances at least 1.5 SD below the mean), results yield similar impairment prevalence across the two definitions.

Strengths of the current study include the large community-based cohort free of clinical dementia and stroke, comprehensive ascertainment of potential confounding variables, stringent quality control procedures for neuropsychological assessment and single laboratory processing for APOE. Reliance on a psychometric definition of impairment is a strength, as it eliminates the selection bias from clinical referral studies and provides an unbiased cut-off normed to the sample of origin. However, the present findings have several caveats. First, multiple comparisons were made. Had we applied a strict (Bonferroni) correction factor, the significance threshold would have been 0.004 (i.e. 0.05/12 comparisons). Using this more stringent threshold, four of six significant observations would have sustained the correction, all of which support our a priori hypotheses that (i) APOE4 strongly correlates with amnestic MCI, (i) a more personalised criterion for defining neuropsychological impairment attenuates associations between APOE4 and MCI and (iii) these associations are strongest in adults aged 65 and older. Nevertheless, we cannot rule out the possibility of a false-positive finding. Second, the demographic composition of the Framingham Offspring Study is White and of European descent, so the generalisability to other races and ethnicities is unknown. A psychotic definition of MCI may not have yielded cases entirely concordant with a clinically defined MCI diagnostic method. Finally, our analysis is cross-sectional.

**Key points**

- Using two psychometric definitions for neuropsychological impairment, we related APOE4 to prevalent MCI among older adults and pre-MCI among middle-aged adults.
- APOE4 was associated with prevalent amnestic MCI based on an age- and WRAT Reading-adjusted psychometric definition, which was predominantly driven by participants aged ≥65.
- Among the older adults (aged ≥65), APOE4 was related to the age- and education-adjusted definition of amnestic MCI, though the effect size was smaller.
- Our findings support existing literature emphasising the need to refine MCI neuropsychological profiling methods.

**Conflicts of interest**

None declared.

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