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Age and APOE genotype influence the predictive accuracy of CSF biomarkers in subjects with MCI


IN PREPARATION
ABSTRACT

Background
We assessed the effect of age on predictive accuracy of CSF Aβ1-42 and t-tau and the influence of APOE genotype on this age effect.

Methods
We selected MCI subjects from the DESCRIPA cohort and Amsterdam Dementia Cohort. We assessed predictive accuracy of CSF Aβ1-42 and t-tau for progression to AD-type dementia in younger (≤ 70 years) and older (> 70 years) subjects. In addition we examined APOE-ε4 positive and negative subjects separately.

Results
We included 98 younger and 96 older MCI subjects. During a mean follow up of 2.3 years 31% of the younger and 46% of the older subjects progressed to AD-type dementia. In older subjects overall predictive accuracy was lower for CSF Aβ1-42 and tended to be lower for CSF t-tau. Positive predictive value of the markers was not affected by age, but negative predictive accuracy decreased with age. We found an increase of abnormal biomarkers with age in cognitively stable subjects for CSF Aβ1-42 in APOE-ε4 negative subjects and for CSF t-tau in APOE-ε4 positive subjects.

Conclusion
The risk for dementia with abnormal CSF biomarkers was similar for younger and older subjects, but the risk of dementia in subjects with normal scores increased with age. APOE genotype modifies the effect of age differently for CSF Aβ1-42 and t-tau.
INTRODUCTION

Alzheimer’s disease (AD) is the most common cause of dementia, with a prevalence strongly increasing with age.1,2 Biomarkers in cerebrospinal fluid (CSF) predict progression to AD-type dementia in subjects with mild cognitive impairment (MCI)3-6 and have been incorporated in research criteria for the diagnosis of AD in subjects with MCI.7,8 These new research criteria are a major step forward for early diagnosis of AD, but need further validation. One major concern is whether the criteria perform similarly in young and old subjects. Previous studies showed that in subjects with MCI, the overall predictive value of biomarkers for AD decreases with age,9-11 although one of these studies also showed that the conversion rates in biomarker positive subjects (positive predictive value (PPV)) and biomarker negative subjects (negative predictive value (NPV) were only slightly affected by age.10 In addition, it needs to be investigated whether the effect of age on predictive accuracy is influenced by the apolipoprotein E (APOE) genotype, since the APOE-ε4 allele is known to affect both age of AD onset and CSF biomarker concentrations.12-21

The aim of the present study was to assess the effect of age and APOE genotype on the predictive accuracy of CSF Aβ1-42 and t-tau for AD-type dementia in subjects with MCI. We first assessed the association between age and biomarker levels for subjects with and without AD-type dementia at follow up in the total sample and for APOE-ε4 negative and positive subjects separately. Subsequently, we tested predictive accuracy for AD-type dementia of CSF Aβ1-42 and CSF t-tau in younger and older MCI subjects and in APOE-ε4 negative and positive subjects separately.

METHODS

Subjects

We selected subjects from the DESCRIPA cohort and Amsterdam Dementia Cohort. DESCRIPA is a European multicenter study performed in a memory clinic setting.22 The VU University Medical Center (VUmc) was one of the DESCRIPA partners and contributed an additional sample of subjects from the Amsterdam Dementia Cohort that were seen outside the DESCRIPA inclusion period. Inclusion criteria were a clinical diagnosis of MCI, availability of cerebrospinal fluid (CSF) and at least one follow up diagnosis. Subjects with obvious causes for MCI other than AD, such as alcohol abuse or severe depression, were excluded. In total we included 108 subjects from the DESCRIPA cohort and an additional 86 subjects from the Amsterdam Dementia Cohort. The medical ethics committee at each center approved the study. All patients provided written informed consent.

Clinical assessment

Diagnosis of MCI was made according to the criteria of Petersen,23 based on scores on psychometric tests as described in more detail previously.22,24 Follow-up assessment was performed annually up to 5 years. For subjects from the Amsterdam Dementia Cohort, follow up was part of regular patient care. Diagnosis of AD-type dementia was made according to the DSM-IV25 and NINCDS-ADRDA criteria.2 In addition, patients with AD-type dementia fulfilled the core clinical criteria of the NIA-AA.26 Time to dementia was defined as the time between baseline visit and the date AD-type dementia was diagnosed.
CSF analyses

CSF was collected by lumbar puncture, centrifuged, and stored in polypropylene tubes at -80°C (DESCRIPA) and -20°C (Amsterdam Dementia Cohort) respectively. One sample was thawed twice but analyses without this sample revealed similar results. CSF β-amyloid1-42 (Aβ1-42) and total tau (t-tau) were measured with Innotest sandwich ELISAs (Innogenetics, Ghent, Belgium) in Gothenburg for the DESCRIPA cohort and in Amsterdam for the Amsterdam Dementia Cohort. The Aβ1-42 and t-tau ELISA methods have been described in detail elsewhere.27,28 We corrected for interlaboratory ELISA differences by means of 33 samples that were analysed at both labs and adjusted Amsterdam Dementia Cohort values to those of DESCRIPA using the equating formula: Gothenborg = (SD Gothenborg/SD Amsterdam)* Amsterdam + average Gothenborg −(SD Gothenborg /SD Amsterdam)*average Amsterdam.29

APOE genotyping

DNA was isolated from 10 ml EDTA blood for apolipoprotein E (APOE) genotyping, using the light cycler APOE mutation detection kit (Roche Diagnostics GmbH, Mannheim, Germany). APOE genotype was determined in 168 subjects (86%). Subjects were classified as APOE-ε4 positive when having one or two APOE-ε4 alleles.

Statistical analyses

Analyses were performed with SPSS 18.0 (Chicago IL, USA) and statistical software package R version 2.15.2.30 For group comparisons of younger (< 70 years at baseline) and older (> 70 years) subjects and subjects with and without AD-type dementia at follow up we used chi-squared tests for categorical variables and Student’s t-tests for continuous variables. For the subanalyses comparing more than two groups we used analyses of variances (ANOVA) with post-hoc multiple comparisons with Bonferroni adjustment. For the analyses with continuous variables, data of the CSF markers were log transformed in order to obtain an approximately normal distribution. We performed linear regression analyses with the (log transformed) continuous values of the biomarkers as dependent variable to assess whether there was an interaction between follow up diagnosis and age in the whole sample and for APOE-ε4 negative and positive subjects separately. In addition we performed receiver operating characteristic (ROC) curves for the continuous values of the CSF biomarkers. We compared the area under the curve (AUC) of different subgroups based on age and APOE genotype using method of DeLong in R.31 For analyses with dichotomized values we used clinically validated cut-off points for CSF Aβ1-42 (<550 pg/ml) and t-tau (>375 pg/ml),32 unless otherwise indicated. We calculated age-optimized cut points for the CSF biomarkers based on the maximum Youden score (sensitivity + specificity – 1). We used Cox proportional hazards model to calculate hazard ratio’s (HR) for progression to AD-type dementia using dichotomized values of the biomarkers. We performed all analyses for younger and older subjects. In addition we performed subanalyses for APOE-ε4 positive and negative subjects in both age groups.
RESULTS

Baseline characteristics

We included 194 subjects, who were classified depending on their age at baseline as either younger (< 70 years, N=98) or older (> 70 years, N=96). Baseline characteristics are shown in Table 1. Older subjects had lower levels of CSF Aβ1-42, more frequently abnormal CSF t-tau and tended to have lower MMSE score at baseline than younger subjects. Forty-eight percent of the younger and 51% of the older subjects had at least one APOE-ε4 allele. During a mean follow up of 2.3 years 74 subjects (38%) progressed to AD-type dementia. Older subjects more frequently progressed to AD-type dementia than younger subjects (46% and 31% respectively, p=0.03). Three younger (3%) and three older (3%) subjects progressed to other types of dementia. They were included in the analyses in the group of subjects who did not progress to AD-type dementia, excluding those subjects from the analyses did not change the results.

Effect of age and APOE genotype on CSF biomarker levels

CSF Aβ1-42

The level of CSF Aβ1-42 decreased with age in the total sample of subjects (unstandardized β =-0.02, standard error (SE)=0.004, p=0.001). The age-related decrease of CSF Aβ1-42 was

Table 1. Baseline characteristics of subjects included in the analyses

<table>
<thead>
<tr>
<th></th>
<th>≤ 70 years</th>
<th>&gt; 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>Age</td>
<td>63.0±4.5</td>
<td>75.8±3.9†</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>39 (40)</td>
<td>41 (43)</td>
</tr>
<tr>
<td>Education, years</td>
<td>10.7±3.0</td>
<td>10.8±3.6</td>
</tr>
<tr>
<td>MMSE score</td>
<td>27.0±2.4</td>
<td>26.3±2.9</td>
</tr>
<tr>
<td>Follow up, years</td>
<td>2.4±1.2</td>
<td>2.2±1.1</td>
</tr>
<tr>
<td>Progression to AD-type dementia</td>
<td>30 (31)</td>
<td>44 (46)†</td>
</tr>
<tr>
<td>Progression to other dementia</td>
<td>3 (3)§</td>
<td>3 (3)‡</td>
</tr>
<tr>
<td>APOE available (%)</td>
<td>84 (86)</td>
<td>84 (88)</td>
</tr>
<tr>
<td>APOE-ε4 positive, n (%)</td>
<td>40 (48)</td>
<td>43 (51)</td>
</tr>
<tr>
<td>Aβ1-42, pg/ml</td>
<td>660±315</td>
<td>505±197†</td>
</tr>
<tr>
<td>Aβ1-42, abnormal*, n (%)</td>
<td>46 (47)</td>
<td>57 (59)</td>
</tr>
<tr>
<td>T-tau, pg/ml</td>
<td>463±361</td>
<td>503±263</td>
</tr>
<tr>
<td>T-tau, abnormal*, n (%)</td>
<td>45 (46)</td>
<td>68 (71)‡</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation unless otherwise indicated

*abnormal values were defined as <550 pg/ml for CSF Aβ1-42 and >375 pg/ml for CSF t-tau
†one frontal temporal lobe dementia, one vascular dementia, one unknown etiology. 
‡two frontal temporal lobe dementia, one Lewy body dementia
§p<0.05 compared to younger subjects

Abbreviations: MMSE = Mini-Mental State Examination, AD = Alzheimer’s disease, APOE = apolipoprotein E, CSF = cerebrospinal fluid, Aβ1-42 = beta amyloid1-42, t-tau = total tau

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only present in subjects who did not progress to AD-type dementia (MCI-no AD) (β -0.02 (SE 0.006), p<0.001). In subjects who progressed to AD-type dementia (MCI-AD) CSF Aβ1-42 tended to increase with age (β 0.01 (SE 0.005), p=0.08, Figure 1A). When analyses were performed in APOE subgroups, CSF Aβ1-42 decreased with age in APOE-ε4 negative MCI-no AD subjects (β -0.03 (SE 0.009), p=0.007), while it did not change in APOE-ε4 negative MCI-AD subjects (β 0.01 (SE 0.01), p=0.22). In the APOE-ε4 positive subjects CSF Aβ1-42 did not change in the MCI-no AD subjects (β -0.01 (SE 0.008), p=0.13) or in the MCI-AD subjects (β -0.002 (SE 0.008), p=0.82, Figure 1A).

**CSF t-tau**

The level of CSF t-tau increased with age in the total sample of subjects (unstandardized β 0.01, standard error (SE) 0.006, p=0.02). The age-related increase of CSF t-tau was only present in subjects with MCI-no AD (β 0.02 (SE 0.007) p=0.02). In MCI-AD subjects CSF t-tau tended to decrease with age (β -0.01 (SE 0.009), p=0.14, Figure 1B). In the APOE-ε4 negative subjects CSF t-tau did not change with age in the MCI-no AD subjects (β 0.003 (SE 0.009) p=0.76) or the MCI-AD subjects (β 0.01 (SE 0.02), p=0.53). In the APOE-ε4 positive subjects CSF t-tau increased in the MCI-no AD subjects (β 0.03 (SE 0.01) p=0.01), while CSF t-tau did not change with age in the MCI-AD subjects (β -0.02 (SE 0.01), p=0.11, Figure 1B).

**Effect of age on predictive accuracy of CSF biomarkers**

**CSF Aβ1-42**

**All subjects**

The AUC of CSF Aβ1-42 for progression to AD-type dementia was higher in younger subjects (0.81 (95% confidence interval 0.72-0.89)) than in older subjects (0.55 (0.44-0.67), p-value difference <0.001, Table 2). Using the predefined cut-point of 550 pg/ml the HR for progression to AD-type dementia was 8.7 (3.0-25.1) in younger subjects and 1.8 (0.9-3.4) in older subjects (p-value difference=0.007). The lower overall predictive accuracy in older subjects was caused by both a lower sensitivity and specificity. The positive predictive value was similar for both age groups, but

| Table 2. Predictive accuracy of CSF Aβ1-42 and t-tau with respect to age and APOE genotype |
|---------------------------------------------|----------------|----------------|
| Age                                         | CSF Aβ1-42     | CSF t-tau      |
| All subjects                                |                |                |
| ≤ 70 years                                   | 0.81 (0.72-0.89) | 0.83 (0.73-0.92) |
| > 70 years                                   | 0.55 (0.44-0.67) | 0.74 (0.64-0.84) |
| APOE-ε4 negative                            |                |                |
| ≤ 70 years                                   | 0.85 (0.73-0.96) | 0.60 (0.32-0.87) |
| > 70 years                                   | 0.50 (0.32-0.68) | 0.72 (0.55-0.89) |
| APOE-ε4 positive                            |                |                |
| ≤ 70 years                                   | 0.69 (0.52-0.85) | 0.87 (0.75-0.98) |
| > 70 years                                   | 0.60 (0.43-0.77) | 0.74 (0.59-0.89) |

Data are shown as area under the curve (95% confidence interval)

p<0.005 compared to younger subjects

Abbreviations: CSF = cerebrospinal fluid, Aβ1-42 = beta amyloid1-42, t-tau = total tau, APOE = apolipoprotein E
the negative predictive value was lower for older subjects. Age-optimized cut-points were similar to the predefined cut-point and did not change overall predictive accuracy (Supplementary Table 1).

**APOE subgroups**

In APOE-ε4 negative subjects the AUC of CSF Aβ1-42 was 0.85 (0.73-0.96) in younger subjects and 0.50 (0.32-0.68) in older subjects (p-value difference=0.003). As in the total sample, in the APOE-ε4 negative subjects sensitivity, specificity and negative predictive value of CSF Aβ1-42 were lower for older than for younger subjects (Table 3).

In APOE-ε4 positive subjects predictive accuracy was not affected by age, with an AUC of 0.69 (0.52-0.85) for younger and an AUC of 0.60 (0.43-0.77) for older subjects (p-value difference=0.5, Table 2, Figure 2). Specificity of CSF Aβ1-42 was lower in older than in younger subjects (Table 3).
Table 3. Predictive accuracy of CSF A\(\beta\)1-42 and CSF t-tau for AD-type dementia

<table>
<thead>
<tr>
<th>Age</th>
<th>Subjects in group a/b/c/d*</th>
<th>CSF A(\beta)1-42</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td></td>
<td>≤ 70 years 26/4/20/48</td>
<td>0.87</td>
<td>0.71</td>
<td>0.57</td>
<td>0.92</td>
<td>8.7 (3.0-25.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70 years 30/14/27/25</td>
<td>0.68</td>
<td>0.48</td>
<td>0.53</td>
<td>0.64</td>
<td>1.8 (0.9-3.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤ 70 years 25/5/20/48</td>
<td>0.83</td>
<td>0.71</td>
<td>0.56</td>
<td>0.91</td>
<td>6.3 (2.4-16.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70 years 37/7/31/21</td>
<td>0.84</td>
<td>0.40</td>
<td>0.54</td>
<td>0.75</td>
<td>2.9 (1.3-6.5)</td>
</tr>
<tr>
<td>APOE-(\epsilon)4 negative'</td>
<td></td>
<td>≤ 70 years 6/1/9/28</td>
<td>0.86</td>
<td>0.76</td>
<td>0.40</td>
<td>0.97</td>
<td>14.9 (1.8-124.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70 years 9/9/10/13</td>
<td>0.50</td>
<td>0.57</td>
<td>0.47</td>
<td>0.59</td>
<td>1.5 (0.6-4.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤ 70 years 4/3/10/27</td>
<td>0.57</td>
<td>0.73</td>
<td>0.29</td>
<td>0.90</td>
<td>2.2 (0.5-10.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70 years 13/5/10/13</td>
<td>0.72</td>
<td>0.57</td>
<td>0.57</td>
<td>0.72</td>
<td>2.8 (1.0-8.1)</td>
</tr>
<tr>
<td>APOE-(\epsilon)4 positive'</td>
<td></td>
<td>≤ 70 years 17/2/10/11</td>
<td>0.89</td>
<td>0.52</td>
<td>0.63</td>
<td>0.85</td>
<td>4.8 (1.1-21.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70 years 17/3/14/9</td>
<td>0.85</td>
<td>0.39</td>
<td>0.55</td>
<td>0.75</td>
<td>2.2 (0.6-7.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤ 70 years 18/1/10/11</td>
<td>0.95</td>
<td>0.52</td>
<td>0.64</td>
<td>0.92</td>
<td>10.8 (1.4-81.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 70 years 19/1/18/5</td>
<td>0.95</td>
<td>0.22</td>
<td>0.51</td>
<td>0.83</td>
<td>4.2 (0.5-32.6)</td>
</tr>
</tbody>
</table>

Abbreviations: AD = Alzheimer’s disease, CSF = cerebrospinal fluid, A\(\beta\)1-42 = beta amyloid1-42, t-tau = total tau, PPV = positive predictive value, NPV = negative predictive value, HR = hazard ratio
* Group a: subjects with abnormal biomarker values who progressed to AD-type dementia, group b: subjects with normal biomarker values who progressed to AD-type dementia, group c: subjects with abnormal biomarker values who did not progress to AD-type dementia, group d: subjects with normal biomarker values who did not progress to AD-type dementia
’ APOE genotype was available of 84 younger (86%) and 84 older (88%) subjects

CSF t-tau

All subjects

The AUC of CSF t-tau was 0.83 (95% confidence interval 0.73-0.92) for younger subjects and 0.74 (0.64-0.84) for older subjects (p-value difference=0.2, Table 2). Using the predefined cut point of 375 pg/ml\(^{32}\) HR was 6.3 (2.4-16.4) for younger subjects and 2.9 (1.3-6.5) for older subjects (p-value difference=0.18). Specificity and negative predictive value were lower in older subjects but sensitivity and positive predictive value were similar in both age groups. Calculating age-optimized cut-points resulted in a higher cut-point for older subjects (511 pg/ml) and a slightly lower cut-point for younger subjects (361 pg/ml). The use of these cut-points improved specificity at the cost of a lower sensitivity in older subjects, but did not result in a substantial increase in HR for older subjects (3.8 (1.9-7.2), Supplementary Table 1).

APOE subgroups

In APOE-\(\epsilon\)4 negative subjects AUC was 0.60 (0.32-0.87) in younger subjects and 0.72 (0.55-0.89) in older subjects (p-value difference=0.5). The overall predictive accuracy of CSF t-tau did
not change with age, but in older subjects sensitivity and positive predictive value were higher and specificity and negative predictive value were lower (Table 3).
In APOE-ε4 positive subjects AUC was 0.87 (0.75-0.98) for younger subjects and 0.74 (0.59-0.89) for older subjects (p-value difference=0.2, Table 2, Figure 2). In older subjects specificity and positive predictive value were lower than in younger subjects (Table 3).

**DISCUSSION**
Overall predictive accuracy of CSF Aβ1-42 for AD-type dementia decreased with age and overall predictive accuracy of CSF t-tau tended to decrease with age. The positive predictive value of both markers remained stable, but the negative predictive value was lower in older subjects. The effect of age on predictive accuracy for CSF Aβ1-42 and t-tau depended on APOE genotype.

**CSF Aβ1-42**
In the total group we found a decrease in overall predictive accuracy of CSF Aβ1-42 with age, due to a decrease in both sensitivity and specificity. This is in line with previous findings. A new
finding is that this age effect occurred only in the APOE-ε4 negative subjects. The lower predictive accuracy in older subjects was caused by more abnormal levels of CSF Aβ1-42 in older compared to younger APOE-ε4 negative MCI-no AD subjects is consistent with the previously described increasing prevalence of amyloid pathology with age in cognitively healthy subjects.\textsuperscript{15,17,33,34} In addition, older APOE-ε4 negative MCI-AD subjects had less abnormal levels of CSF Aβ1-42 than to younger APOE-ε4 negative MCI-AD subjects. Apparently, in older APOE-ε4 negative subjects AD-type dementia can present at relatively high levels of CSF Aβ1-42. In the APOE-ε4 positive subjects CSF Aβ1-42 did not change much with age in MCI no-AD or MCI-AD subjects. Levels of CSF Aβ1-42 in younger APOE-ε4 positive MCI-no AD subjects were already close to those in MCI-AD subjects. This might indicate that in APOE-ε4 carriers CSF Aβ1-42 decreases and reaches a plateau at young age, consistent with the early age of onset in APOE-ε4 carriers.\textsuperscript{12,14}

CSF t-tau

Overall predictive accuracy of CSF t-tau tended to decrease with age, in line with previous findings.\textsuperscript{9,11} This decrease was due to a decrease in specificity, although the difference did not reach statistical significance. The effect of age on biomarker concentrations and overall predictive accuracy was largest in APOE-ε4 carriers and was due to an increase of CSF t-tau with age in APOE-ε4 positive MCI-no AD subjects. A possible explanation might be that the toxic effect of APOE-ε4 genotype adds up over the years causing increasing neuronal damage with age, consistent with the suggestion that neuronal injury is a relatively late event in the amyloid cascade.\textsuperscript{35} This was further supported by the finding that in the APOE-ε4 negative subjects, CSF t-tau did not change much with age. In APOE-ε4 negative MCI no-AD subjects CSF t-tau remained in the normal range across the age range.

Effect on positive and negative predictive value

From a clinical perspective, information on the risk of AD in subjects with abnormal scores (PPV) and normal biomarker scores (NPV) is crucial. Despite the change in overall predictive accuracy with age, the PPV in the total group did not change much with age, indicating that the prognosis of an abnormal CSF Aβ1-42 and t-tau concentration is similar for younger and older subjects. The NPV however, decreased with age and therefore the difference in dementia risk in subjects with a normal and abnormal biomarker score decreased. These results are in line with a previous study.\textsuperscript{10} A new finding is that the decrease in NPV was most notably for CSF Aβ1-42 in elderly APOE4 non-carriers, as in those subjects the risk for dementia was almost similar for subjects with abnormal and normal CSF Aβ1-42.

Limitations

This study has several limitations. The mean follow up duration was two years. From a clinical perspective this is a reasonable follow up duration, as patients might want to know whether they will progress to AD-type dementia at short notice, but from a pathophysiological perspective a longer follow up duration would be preferable. This limited follow up time most likely also contributes to the relatively low positive predictive values we found. As abnormal CSF biomarkers precede cognitive decline, during a longer follow up time more subjects, especially those with...
abnormal CSF biomarkers, might progress to AD-type dementia. We classified subjects as either younger or older at baseline, using 70 years as a cut-point. It could well be that the age differences we found would be even larger when including more subjects in the oldest-old range analyses. Unfortunately, with only 10% of the subjects being 80 years or older we lacked the power to do so. Furthermore, in our subanalyses in APOE-ε4 positive and negative subjects separately sample sizes were relatively small, limiting power. Subsequently, the results of the subanalyses should be interpreted with caution and need to be confirmed in larger groups. As this multicenter study was performed in memory clinics, results may be applicable to other memory clinics, but cannot be generalized to other settings as the general population.

**Implications**

CSF Aβ1-42 and CSF tau are less useful to predict progression to AD-type dementia in older than in younger subjects. While the risk for dementia with abnormal scores was similar for younger and older subjects, the risk for dementia in subjects with normal scores increased with age. The finding that APOE genotype modifies the age effect on predictive accuracy differently for CSF Aβ1-42 and t-tau is in line with order of events suggested in the amyloid cascade hypothesis.\(^{36-38}\) We found no reason to use age-adjusted cut-points for CSF Aβ1-42 and t-tau, as using age optimized cut-points did not increase overall predictive accuracy.

**REFERENCES**


Supplementary table 1. Predictive accuracy of CSF Aβ1-42 and CSF t-tau for AD-type dementia using age specific cut-points

<table>
<thead>
<tr>
<th>Cut-point*</th>
<th>Age</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF Aβ1-42</td>
<td>551 pg/ml</td>
<td>All</td>
<td>0.77</td>
<td>0.61</td>
<td>0.55</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>533 pg/ml</td>
<td>≤ 70 years</td>
<td>0.87</td>
<td>0.72</td>
<td>0.58</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>551 pg/ml</td>
<td>&gt; 70 years</td>
<td>0.70</td>
<td>0.48</td>
<td>0.53</td>
<td>0.66</td>
</tr>
<tr>
<td>CSF t-tau</td>
<td>538 pg/ml</td>
<td>All</td>
<td>0.65</td>
<td>0.86</td>
<td>0.74</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>361 pg/ml</td>
<td>≤ 70 years</td>
<td>0.87</td>
<td>0.71</td>
<td>0.57</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>511 pg/ml</td>
<td>&gt; 70 years</td>
<td>0.68</td>
<td>0.77</td>
<td>0.71</td>
<td>0.74</td>
</tr>
</tbody>
</table>

*Age specific cut-points based on maximal Youden index (sensitivity + specificity – 1)

Abbreviations: AD = Alzheimer’s disease, CSF = cerebrospinal fluid, Aβ1-42 = beta amyloid1-42, t-tau = total tau, PPV = positive predictive value, NPV = negative predictive value, HR = hazard ratio