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# Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease

OPEN ▲

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## ABSTRACT

**Objective:** To compare the diagnostic accuracy of CSF biomarkers and amyloid PET for diagnosing early-stage Alzheimer disease (AD).

**Methods:** From the prospective, longitudinal BioFINDER study, we included 122 healthy elderly and 34 patients with mild cognitive impairment who developed AD dementia within 3 years (MCI-AD).  $\beta$ -Amyloid ( $A\beta$ ) deposition in 9 brain regions was examined with [ $^{18}$ F]-flutemetamol PET. CSF was analyzed with INNOTEST and EUROIMMUN ELISAs. The results were replicated in 146 controls and 64 patients with MCI-AD from the Alzheimer's Disease Neuroimaging Initiative study.

**Results:** The best CSF measures for identifying MCI-AD were  $A\beta_{42}$ /total tau (t-tau) and  $A\beta_{42}$ /hyperphosphorylated tau (p-tau) (area under the curve [AUC] 0.93–0.94). The best PET measures performed similarly (AUC 0.92–0.93; anterior cingulate, posterior cingulate/precuneus, and global neocortical uptake). CSF  $A\beta_{42}$ /t-tau and  $A\beta_{42}$ /p-tau performed better than CSF  $A\beta_{42}$  and  $A\beta_{42}/40$  (AUC difference 0.03–0.12,  $p < 0.05$ ). Using nonoptimized cutoffs, CSF  $A\beta_{42}$ /t-tau had the highest accuracy of all CSF/PET biomarkers (sensitivity 97%, specificity 83%). The combination of CSF and PET was not better than using either biomarker separately.

**Conclusions:** Amyloid PET and CSF biomarkers can identify early AD with high accuracy. There were no differences between the best CSF and PET measures and no improvement when combining them. Regional PET measures were not better than assessing the global  $A\beta$  deposition. The results were replicated in an independent cohort using another CSF assay and PET tracer. The choice between CSF and amyloid PET biomarkers for identifying early AD can be based on availability, costs, and doctor/patient preferences since both have equally high diagnostic accuracy.

**Classification of evidence:** This study provides Class III evidence that amyloid PET and CSF biomarkers identify early-stage AD equally accurately. *Neurology*® 2015;85:1240–1249

## GLOSSARY

**A $\beta$**  =  $\beta$ -amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **AUC** = area under the receiver operating characteristic curve; **CI** = confidence interval; **MCI-AD** = mild cognitive impairment later developing into AD; **MCS** = mild cognitive symptoms; **MSD** = Meso Scale Discovery; **OR** = odds ratio; **p-tau** = hyperphosphorylated tau; **ROC** = receiver operating characteristic; **SUVr** = standardized uptake value ratio; **t-tau** = total tau; **VOI** = volume of interest; **YI** = Youden index.

Biomarkers of cerebral  $\beta$ -amyloid ( $A\beta$ ) are used in the criteria for the early stages of Alzheimer disease (AD),<sup>1,2</sup> and are increasingly used in clinical trials.<sup>3–5</sup> This stresses the need for reliable and available biomarkers of brain  $A\beta$  pathology. Two  $A\beta$  modalities have been established—CSF  $A\beta_{42}$  and amyloid PET—which both correlate highly with brain biopsy findings.<sup>6,7</sup> A potential advantage of amyloid PET over CSF  $A\beta_{42}$  as an early diagnostic marker is the possibility to detect regional  $A\beta$  depositions that might occur before the global neocortical signal becomes pathologic. On the other hand, CSF analysis has the advantages that it may easily incorporate assessments

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Part of the data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([adni.loni.usc.edu](http://adni.loni.usc.edu)). As such, the investigators within the ADNI contributed to the design and implementation of ADNI or provided data but did not participate in analysis or writing of this report.

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such as tau (a measure of neuronal degeneration<sup>8</sup>) and hyperphosphorylated tau (p-tau; a potential marker of tau pathology).<sup>9</sup>

Several studies have examined the agreement between amyloid PET and CSF A $\beta$ 42,<sup>10–22</sup> but head-to-head studies comparing their diagnostic accuracy for incipient AD are scarce. Very few studies have used clinically relevant, consecutively recruited patients. To our knowledge, no previous study has compared the accuracy of regional amyloid PET and different CSF assays or ratios of CSF biomarkers such as A $\beta$ 42/40, A $\beta$ 42/total tau (t-tau), and A $\beta$ 42/p-tau when identifying cases with incipient AD. We therefore performed a detailed head-to-head comparison of regional and global amyloid PET and CSF analysis with 2 different assays in a clinical cohort of consecutive patients with mild cognitive impairment who later developed AD dementia (MCI-AD). We also examined the diagnostic benefit of combining CSF and PET measures.

**METHODS** This study conducts a head-to-head comparison of the diagnostic accuracy of amyloid PET and CSF biomarkers for identifying early-stage AD. It provides Class III evidence that amyloid PET and CSF biomarkers identify early-stage AD equally accurately.

**Subjects.** The present study population was part of the prospective and longitudinal Swedish BioFINDER study, which, among other cohorts, consecutively enrolls patients without dementia with mild cognitive symptoms (MCS) from 3 participating memory clinics in Sweden. More information about the design and populations is available at [biofinder.se](http://biofinder.se) and in the online supplement (e-Methods on the *Neurology*<sup>®</sup> Web site at [Neurology.org](http://Neurology.org)). We included patients with MCS who had progressed to AD dementia during the follow-up period (hereafter referred to as MCI-AD). This resulted in a sample of 34 patients with MCI-AD. The mean follow-up time was 2.0 years (range 0.8–3.4). A consensus group (Katarina Nägga, P.J., S.P.) determined the follow-up diagnosis probable AD<sup>23</sup> in September 2014. The group was blinded to all biomarker data. At baseline in the MCS cohort, 3 patients (9%) had subjective cognitive decline and 31 (91%) had MCI (48% amnesic single-domain, 39% amnesic multidomain, and 12% nonamnesic). A total of 122 cognitively healthy elderly from the BioFINDER study were included as controls.<sup>24</sup>

**Standard protocol approvals, registrations, and patient consents.** The Ethics Committee in Lund, Sweden, approved the study. All patients gave their written informed consent.

**Amyloid PET scanning and analysis.** Cerebral A $\beta$  deposition was visualized with the PET tracer <sup>18</sup>F-flutemetamol (approved by the Food and Drug Administration and the European Medical Agency).<sup>25</sup> PET/CT scanning of the brain was conducted at 2 sites using the same type of scanner (Gemini, Philips Healthcare, Best, the Netherlands). Baseline sum images from 90–110 minutes postinjection were analyzed using the software NeuroMarQ (GE Healthcare, Cleveland, OH). A volume of interest (VOI)

template was applied for the following 9 bilateral regions: prefrontal, parietal, lateral temporal, medial temporal, sensorimotor, occipital, anterior cingulate, posterior cingulate/precuneus, and a global neocortical composite region.<sup>26</sup> The standardized uptake value ratio (SUVR) was defined as the uptake in a VOI normalized for the cerebellar cortex uptake.

**CSF analysis.** The procedure and analysis of the CSF followed the Alzheimer's Association Flow Chart for CSF biomarkers.<sup>8</sup> Baseline lumbar CSF samples were collected at the 3 centers and analyzed at one center on one occasion using single batch analysis according to a standardized protocol.<sup>8,20</sup> CSF t-tau, A $\beta$ 40, and A $\beta$ 42 were analyzed by EUROIMMUN (®) ELISAs (EUROIMMUN AG, Lübeck, Germany). CSF A $\beta$ 42 and tau phosphorylated at Thr181 (p-tau) were analyzed with INNOTEST (™) ELISAs (Fujirebio Europe, Ghent, Belgium). The following 8 variables were derived from the CSF analyses: A $\beta$ 42<sup>IT</sup>, A $\beta$ 42<sup>EI</sup>, A $\beta$ 42<sup>IT</sup>/A $\beta$ 40<sup>EI</sup>, A $\beta$ 42<sup>IT</sup>/t-tau<sup>EI</sup>, A $\beta$ 42<sup>IT</sup>/p-tau<sup>IT</sup>, A $\beta$ 42<sup>EI</sup>/A $\beta$ 40<sup>EI</sup>, A $\beta$ 42<sup>EI</sup>/p-tau<sup>IT</sup>, A $\beta$ 42<sup>EI</sup>/t-tau<sup>EI</sup>.

**Hippocampus volume and cognition.** All patients were examined using a single 3T MRI scanner (Trio, Siemens, Munich, Germany). Hippocampal volume was analyzed with FreeSurfer version 5.1. The smallest hippocampal volume (left or right) was used. Global cognition was assessed with the Mini-Mental State Examination. Memory was assessed with the 10-word delayed recall test from the Alzheimer's Disease Assessment Scale—cognitive subscale.<sup>27</sup>

**Alzheimer's Disease Neuroimaging Initiative cohort.** To validate the results from BioFINDER in an independent cohort, we used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI; [adni.loni.usc.edu](http://adni.loni.usc.edu)). The sample consisted of 64 patients with MCI-AD and 146 controls who had undergone CSF sampling and A $\beta$  PET at baseline of ADNI-2 (table 1 and reference 19). In sum, the PET tracer <sup>18</sup>F-florbetapir was used to quantify A $\beta$  in different brain regions (and globally), normalized for the cerebellar uptake. CSF A $\beta$ 42, t-tau, and p-tau were measured using xMAP Luminex (Luminex Corp., Austin, TX) with the INNOBIA AlzBio3 kit (Innogenetics, Ghent, Belgium).<sup>28</sup> A consensus group blinded to the biomarker data determined the follow-up diagnoses.

**Statistical analysis.** Group differences were calculated with the Mann-Whitney *U* test (table 1). The area under the receiver operating characteristic (ROC) curve (AUC) was used to examine the diagnostic accuracy of the continuous CSF and PET variables (table 2). The 95% confidence interval (CI) and significance for differences between the AUCs were calculated using bootstrap techniques.<sup>29</sup> The AUCs of the combined CSF and PET variables were derived from logistic regressions. Nonoptimized and unbiased cutoffs were established using mixture modeling.<sup>30</sup> A Youden index (YI; sensitivity + specificity – 1) was used for an easier comparison of sensitivities and specificities. Odds ratios (OR) were calculated with multivariate logistic regression analysis (table 3). The statistical analyses were performed with MedCalc version 14 (MedCalc Software, MariaKerke, Belgium); SPSS, version 22.0 (SPSS Inc., Chicago, IL); MATLAB release 2014, Statistics Toolbox (MathWorks, Natick, MA); and *R* version 3.0.2.

**RESULTS** Baseline characteristics are shown in table 1. There were no significant differences in age, *APOE4*, or sex between the ADNI and BioFINDER cohorts, but education differed between control and MCI-AD populations (higher in ADNI, *p* < 0.001,

**Table 1** Baseline characteristics of MCI-AD patients and cognitively healthy elderly from the BioFINDER study and the ADNI study

|   | BioFINDER MCI-AD<br>(n = 34) | BioFINDER controls<br>(n = 122) | p Value BioFINDER<br>MCI-AD vs controls | ADNI MCI-AD<br>(n = 64) | ADNI controls<br>(n = 146) | p Value ADNI<br>MCI-AD vs controls |
|---|------------------------------|---------------------------------|---|-------------------------|----------------------------|------------------------------------|
| <b>Demographics</b>                     |                              |                                 |   |                         |                            |                                    |
| Age, y (range)                          | 72.7 (63-80)                 | 73.5 (65-85)                    | 0.29                                    | 72.1 (48-85)            | 73.2 (56-89)               | 0.79                               |
| Female, %                               | 54                           | 64                              | 0.60                                    | 45                      | 52                         | 0.42                               |
| Education, y                            | 11.9 ± 3.8                   | 11.3 ± 3.3                      | 0.67                                    | 16.0 ± 2.8              | 16.6 ± 2.5                 | 0.13                               |
| APOE ε4, ≥1 allele, %                   | 61                           | 24                              | <0.001                                  | 73                      | 27                         | <0.001                             |
| MMSE, points                            | 26.7 ± 1.5                   | 29.0 ± 0.9                      | <0.001                                  | 27.0 ± 1.8              | 29.1 ± 1.2                 | <0.001                             |
| 10-word delayed recall, errors          | 7.2 ± 2.3                    | 2.0 ± 2.0                       | <0.001                                  |                         |                            |                                    |
| Hippocampus volume, cm <sup>3</sup>     | 3.1 ± 0.5                    | 3.6 ± 0.4                       | <0.001                                  |                         |                            |                                    |
| <b>PET regions</b>                      |                              |                                 |   |                         |                            |                                    |
| Global/composite                        | 2.11 ± 0.47                  | 1.29 ± 0.28                     | <0.001                                  |                         |                            |                                    |
| Prefrontal                              | 2.11 ± 0.49                  | 1.24 ± 0.31                     | <0.001                                  |                         |                            |                                    |
| Anterior cingulate                      | 2.36 ± 0.52                  | 1.41 ± 0.34                     | <0.001                                  |                         |                            |                                    |
| Posterior cingulate/precuneus           | 2.26 ± 0.48                  | 1.39 ± 0.33                     | <0.001                                  |                         |                            |                                    |
| Parietal                                | 1.98 ± 0.44                  | 1.23 ± 0.26                     | <0.001                                  |                         |                            |                                    |
| Lateral temporal                        | 2.14 ± 0.50                  | 1.39 ± 0.25                     | <0.001                                  |                         |                            |                                    |
| Medial temporal                         | 1.58 ± 0.29                  | 1.36 ± 0.16                     | <0.001                                  |                         |                            |                                    |
| Occipital                               | 1.83 ± 0.40                  | 1.37 ± 0.19                     | <0.001                                  |                         |                            |                                    |
| Sensorimotor                            | 1.81 ± 0.42                  | 1.31 ± 0.18                     | <0.001                                  |                         |                            |                                    |
| <b>CSF analyses</b>                     |                              |                                 |   |                         |                            |                                    |
| Aβ42 <sup>EI</sup>                      | 333 ± 114                    | 538 ± 186                       | <0.001                                  |                         |                            |                                    |
| Aβ42 <sup>IT</sup>                      | 380 ± 102                    | 659 ± 184                       | <0.001                                  |                         |                            |                                    |
| Aβ40 <sup>EI</sup>                      | 4,881 ± 1,877                | 4,516 ± 1,522                   | 0.47                                    |                         |                            |                                    |
| t-tau <sup>EI</sup>                     | 581 ± 213                    | 318 ± 113                       | <0.001                                  |                         |                            |                                    |
| p-tau <sup>IT</sup>                     | 92.4 ± 33.9                  | 53.5 ± 18.0                     | <0.001                                  |                         |                            |                                    |
| Aβ42 <sup>EI</sup> /Aβ40 <sup>EI</sup>  | 0.072 ± 0.024                | 0.12 ± 0.038                    | <0.001                                  |                         |                            |                                    |
| Aβ42 <sup>IT</sup> /Aβ40 <sup>EI</sup>  | 0.086 ± 0.034                | 0.16 ± 0.052                    | <0.001                                  |                         |                            |                                    |
| Aβ42 <sup>EI</sup> /t-tau <sup>EI</sup> | 0.63 ± 0.27                  | 1.87 ± 0.76                     | <0.001                                  |                         |                            |                                    |
| Aβ42 <sup>EI</sup> /p-tau <sup>IT</sup> | 3.96 ± 1.73                  | 11.0 ± 4.42                     | <0.001                                  |                         |                            |                                    |
| Aβ42 <sup>IT</sup> /t-tau <sup>EI</sup> | 0.73 ± 0.33                  | 2.31 ± 0.89                     | <0.001                                  |                         |                            |                                    |
| Aβ42 <sup>IT</sup> /p-tau <sup>IT</sup> | 4.59 ± 2.0                   | 13.7 ± 5.39                     | <0.001                                  |                         |                            |                                    |

Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; EI = EUROIMMUN assay; IT = INNOTEST assay; MCI-AD = patients with mild cognitive impairment who developed Alzheimer disease within 3 years; MMSE = Mini-Mental State Examination; p-tau = hyperphosphorylated tau; t-tau = total tau. Biomarker data of the replication population (ADNI study) can be found in table e-1. As for comparisons between demographics in the BioFINDER and ADNI cohorts, only education differed significantly ( $p < 0.001$ ). Values are mean ± SD, unless otherwise specified. CSF measures are given in pg/mL and PET score in mean standardized uptake value ratio.

table 1). Biomarker data could not be directly compared between the studies because of different CSF assays and PET tracers (table 1 and table e-1).

**CSF biomarkers for classification of MCI-AD and controls.** The CSF biomarkers had diagnostic accuracies for MCI-AD ranging from AUC 0.82 (CSF Aβ42<sup>EI</sup>) to AUC 0.93–0.94 (CSF Aβ42/t-tau and Aβ42/p-tau ratios independent of assay; table 2). CSF Aβ42<sup>IT</sup>/t-tau<sup>EI</sup> and Aβ42<sup>IT</sup>/p-tau<sup>IT</sup> had significantly better accuracies than CSF Aβ42<sup>IT</sup>

(AUC difference: 0.04–0.05,  $p = 0.02$ ) and Aβ42<sup>EI</sup>/Aβ40<sup>EI</sup> (AUC difference: 0.08,  $p < 0.001$ ). CSF Aβ42<sup>EI</sup> had significantly lower AUC compared to most other biomarkers, but this could be partly overcome by the ratio of Aβ42<sup>EI</sup>/Aβ40<sup>EI</sup>. The diagnostic accuracy of CSF Aβ42<sup>IT</sup>, on the other hand, was not improved when used as a ratio with Aβ40<sup>EI</sup> (table 2).

**Regional and composite PET biomarkers for classification of MCI-AD vs controls.** The AUCs of the amyloid PET biomarkers ranged from 0.75 to

**Table 2** Classification of MCI-AD and healthy controls in BioFINDER based on ROC analyses in BioFINDER

| Variable (in order of AUC value)            | AUC (95% CI)     | AUC significantly better than  |
|---|------------------|--|
| CSF Aβ42 <sup>IT</sup> /p-tau <sup>IT</sup> | 0.94 (0.89–0.97) | PET medial temporal, PET occipital, CSF Aβ42 <sup>EI</sup> /Aβ40 <sup>EI</sup> , Aβ42 <sup>EI</sup> , Aβ42 <sup>IT</sup> |
| CSF Aβ42 <sup>EI</sup> /t-tau <sup>EI</sup> | 0.93 (0.88–0.97) | PET medial temporal, CSF Aβ42 <sup>EI</sup> /Aβ40 <sup>EI</sup> , Aβ42 <sup>EI</sup>                                     |
| CSF Aβ42 <sup>IT</sup> /t-tau <sup>EI</sup> | 0.93 (0.88–0.97) | PET medial temporal, PET occipital, CSF Aβ42 <sup>EI</sup> /Aβ40 <sup>EI</sup> , Aβ42 <sup>EI</sup> , Aβ42 <sup>IT</sup> |
| CSF Aβ42 <sup>EI</sup> /p-tau <sup>IT</sup> | 0.93 (0.88–0.96) | PET medial temporal, CSF Aβ42 <sup>EI</sup> /Aβ40 <sup>EI</sup> , Aβ42 <sup>EI</sup>                                     |
| PET posterior cingulate/precuneus           | 0.93 (0.87–0.96) | PET medial temporal, PET occipital, PET sensorimotor, CSF Aβ42 <sup>EI</sup>   |
| PET anterior cingulate                      | 0.92 (0.87–0.96) | PET medial temporal, PET occipital, CSF Aβ42 <sup>EI</sup>   |
| PET composite                               | 0.92 (0.86–0.95) | PET medial temporal, PET occipital   |
| PET prefrontal                              | 0.91 (0.86–0.95) | PET medial temporal, CSF Aβ42 <sup>EI</sup>  |
| PET parietal                                | 0.91 (0.85–0.95) | PET medial temporal, PET occipital, PET sensorimotor   |
| CSF Aβ42 <sup>IT</sup>                      | 0.90 (0.84–0.94) | PET medial temporal, CSF Aβ42 <sup>EI</sup>  |
| PET lateral temporal                        | 0.90 (0.84–0.94) | PET medial temporal, PET occipital   |
| CSF Aβ42 <sup>IT</sup> /Aβ40 <sup>EI</sup>  | 0.88 (0.80–0.94) | PET medial temporal  |
| CSF Aβ42 <sup>EI</sup> /Aβ40 <sup>EI</sup>  | 0.86 (0.80–0.91) | PET medial temporal  |
| PET sensorimotor                            | 0.85 (0.79–0.90) | PET medial temporal  |
| PET occipital                               | 0.84 (0.77–0.89) | PET medial temporal  |
| CSF Aβ42 <sup>EI</sup>                      | 0.82 (0.74–0.89) |  |
| PET medial temporal                         | 0.75 (0.68–0.82) |  |

Abbreviations: AUC = area under the curve; CI = confidence interval; EI = EUROIMMUN assay; IT = INNOTEST assay; MCI-AD = patients with mild cognitive impairment who developed Alzheimer disease within 3 years; p-tau = hyperphosphorylated tau; ROC = receiving operating characteristic; t-tau = total tau.

AUC was calculated with ROC analysis. The 95% CI and significance for differences between the AUCs were calculated using bootstrap techniques with 5,000 bootstrap replicas.

0.92 (table 2). The AUCs of the composite PET SUVR and best regional PET SUVRs (anterior cingulate and posterior cingulate/precuneus) were equally good ( $p = 0.35–0.46$ ). The prefrontal and parietal regional SUVRs had similar AUCs ( $p = 0.49–0.99$ ). The medial temporal SUVR performed significantly worse than all other PET measures (AUC difference 0.09–0.17,  $p = 0.0001–0.02$ ).

**Comparison of CSF and PET biomarkers for classification of MCI-AD vs controls.** The best CSF biomarkers (CSF Aβ42<sup>IT</sup>/t-tau<sup>EI</sup> and Aβ42<sup>IT</sup>/p-tau<sup>IT</sup> ratios) had similar AUCs (0.93–0.94) as the best PET measures (AUC 0.92–0.93;  $p = 0.34–0.60$ ). CSF Aβ42<sup>IT</sup> also performed similar to the best PET measures (table 2). CSF Aβ42<sup>EI</sup>/Aβ40<sup>EI</sup> had a numerically poorer AUC compared to all PET variables except for the sensorimotor, occipital, and medial temporal regions, but the differences were not significant ( $p = 0.09–0.40$ ).

**Combination of CSF and PET biomarkers.** To examine the potential benefit of combining PET and CSF analysis, we tested models with CSF Aβ42<sup>IT</sup>/p-tau<sup>IT</sup> and the composite PET SUVR entered separately and together as predictors of diagnosis in logistic regression analyses. When used together, the AUC was 0.96 (95% CI 0.92–0.97) and both variables were independent significant predictors ( $p < 0.01$ ). This was numerically higher than for models using the individual modalities, but the differences were not significant (AUC difference 0.021–0.047,  $p = 0.07–0.08$ ). A combined model of the composite PET SUVR and CSF p-tau<sup>IT</sup> had equal AUC value as CSF Aβ42<sup>IT</sup>/p-tau<sup>IT</sup> (both were 0.94, 95% CI 0.89–0.97).

**Classification of incipient AD and controls at specific cutoffs.** All Aβ variables had a bimodal distribution suitable for establishing nonoptimized, unbiased cutoffs with mixture modeling except for CSF Aβ42<sup>EI</sup>, which was excluded from this analysis. When using these cutoffs in the ROC analysis, CSF Aβ42<sup>IT</sup>/t-tau<sup>EI</sup> and CSF Aβ42<sup>IT</sup>/p-tau<sup>IT</sup> had the best sensitivities and specificities of all CSF and PET measures (table 3). The 2 best PET measures were the prefrontal and the posterior cingulate/precuneus regions. Scatterplots show that the differences in specificities between CSF and PET are mostly caused by controls with normal PET and abnormal CSF values (figures e-1 and e-2). In logistic regressions, CSF Aβ42<sup>IT</sup>/t-tau<sup>EI</sup> and CSF Aβ42<sup>IT</sup>/p-tau<sup>IT</sup> had the highest OR, when adjusting for age, sex, memory function, APOE ε4, and hippocampal volume (table 3).

The diagnostic accuracy of biomarkers used in the clinic should preferably not be very sensitive to smaller changes in cutoff values, if they are to be generalizable between different centers and settings. In figure 1, A and B, continuous sensitivities and specificities of 4 CSF and PET measures are shown as a function of the cutoff point. The CSF and PET measures were not dependent on an optimized cutoff but provide high accuracies from cutoff values spanning at least 1 SD in the current sample. The exception was CSF Aβ42<sup>EI</sup>/40<sup>EI</sup>, which had a slightly narrower interval with near optimal YI.

**Comparison with the ADNI data.** Accuracies for CSF and PET biomarkers were also analyzed in the independent ADNI cohort (table 4). All CSF and PET variables had similar AUCs ranging from 0.86 to 0.87 and no significant differences were found ( $p = 0.17–0.93$ ). As in BioFINDER, CSF Aβ42<sup>IT</sup>/t-tau and Aβ42<sup>IT</sup>/p-tau had higher AUCs than CSF Aβ42 alone (both 0.87 vs 0.85), but in ADNI the differences were not significant ( $p = 0.60–0.65$ ). In ADNI, the AUCs of t-tau (0.81, 95% CI 0.74–0.88) and p-tau (0.82, 95% CI 0.75–0.88) were lower than in

**Table 3** ROC analysis in BioFINDER of MCI-AD and healthy controls based on unbiased cutoffs

| Variable (in order of Youden index)                        | Unbiased cutoff <sup>a</sup> | Youden index (95% CI) <sup>b,c</sup> | Sensitivity (%) <sup>b</sup> | Specificity (%) <sup>b</sup> | Adjusted OR (95% CI) <sup>d</sup> |
|--|------------------------------|--------------------------------------|------------------------------|------------------------------|-----------------------------------|
| CSF A $\beta$ 42 <sup>IT</sup> /t-tau <sup>EI</sup>        | 1.25                         | 0.80 (0.68–0.87)                     | 97                           | 83                           | 62 (4.9–796)                      |
| CSF A $\beta$ 42 <sup>IT</sup> /p-tau <sup>IT</sup>        | 7.24                         | 0.79 (0.66–0.87)                     | 94                           | 85                           | 34 (4.4–263)                      |
| CSF A $\beta$ 42 <sup>EI</sup> /p-tau <sup>IT</sup>        | 5.67                         | 0.74 (0.56–0.84)                     | 88                           | 86                           | 20 (3.3–126)                      |
| PET prefrontal   | 1.48                         | 0.74 (0.56–0.84)                     | 88                           | 86                           | 29 (3.6–239)                      |
| CSF A $\beta$ 42 <sup>EI</sup> /t-tau <sup>EI</sup>        | 0.96                         | 0.73 (0.59–0.83)                     | 91                           | 82                           | 44 (4.3–447)                      |
| PET posterior cingulate/precuneus                          | 1.62                         | 0.73 (0.56–0.83)                     | 88                           | 84                           | 24 (3.3–182)                      |
| PET anterior cingulate                                     | 1.62                         | 0.72 (0.56–0.81)                     | 91                           | 80                           | 22 (2.9–170)                      |
| PET composite  | 1.51                         | 0.72 (0.55–0.83)                     | 85                           | 87                           | 29 (3.6–239)                      |
| PET lateral temporal                                       | 1.58                         | 0.71 (0.54–0.83)                     | 85                           | 86                           | 30 (3.6–250)                      |
| PET parietal   | 1.43                         | 0.70 (0.53–0.81)                     | 85                           | 84                           | 25 (3.2–190)                      |
| PET sensorimotor   | 1.53                         | 0.69 (0.51–0.81)                     | 79                           | 89                           | 30 (3.8–231)                      |
| CSF A $\beta$ 42 <sup>EI</sup> /A $\beta$ 40 <sup>EI</sup> | 0.092                        | 0.67 (0.50–0.78)                     | 88                           | 79                           | 14 (2.5–82)                       |
| CSF A $\beta$ 42 <sup>IT</sup>                             | 500                          | 0.60 (0.42–0.72)                     | 85                           | 75                           | 6.1 (1.2–30)                      |
| CSF A $\beta$ 42 <sup>IT</sup> /A $\beta$ 40 <sup>EI</sup> | 0.10                         | 0.59 (0.39–0.73)                     | 76                           | 83                           | 8.2 (1.7–40)                      |
| PET occipital  | 1.68                         | 0.49 (0.30–0.66)                     | 56                           | 93                           | 27 (2.8–263)                      |
| PET medial temporal  | 1.69                         | 0.20 (0.07–0.38)                     | 23                           | 97                           | Nonsignificant                    |

Abbreviations: CI = confidence interval; EI = EUROIMMUN assay; IT = INNOTEST assay; MCI-AD = patients with mild cognitive impairment who developed Alzheimer disease within 3 years; OR = odds ratio; p-tau = hyperphosphorylated tau; ROC = receiving operating characteristic; t-tau = total tau.

Area under the curve was calculated with ROC analysis. The 95% CI and significance for differences between the AUCs were calculated using bootstrap techniques with 5,000 bootstrap replicas. PET values are shown in standardized uptake value ratio and CSF levels in pg/mL (except for the CSF ratios).

<sup>a</sup>Established with mixture modeling analysis (described in Methods).

<sup>b</sup>Based on the ROC analysis (not derived from the logistic regression analysis).

<sup>c</sup>Youden index (sensitivity + specificity – 1) is provided for an easier comparison of the combined value of the sensitivity and specificity, e.g., the diagnostic accuracy of CSF and PET measures as dichotomized variables. The value is based on the unbiased cutoffs.

<sup>d</sup>A logistic regression analysis was performed with the diagnosis (MCI-AD or control) as the dependent variable and the dichotomized CSF/PET variable as a covariate to yield an OR. Age, sex, APOE  $\epsilon$ 4 allele, memory function, and hippocampal volume were adjusted for in the model.

BioFINDER (t-tau 0.88, 95% CI 0.82–0.93 and p-tau 0.87, 95% CI 0.80–0.91; data not shown in the tables). However, no significant differences could be tested since the results were derived from 2 different cohorts.

When combining CSF A $\beta$ 42/p-tau and composite PET SUVR in ADNI, the AUC was 0.87 (95% CI 0.82–0.93). This did not differ significantly from using the variables separately (AUC difference: 0.00–0.01;  $p = 0.40$ –0.53).

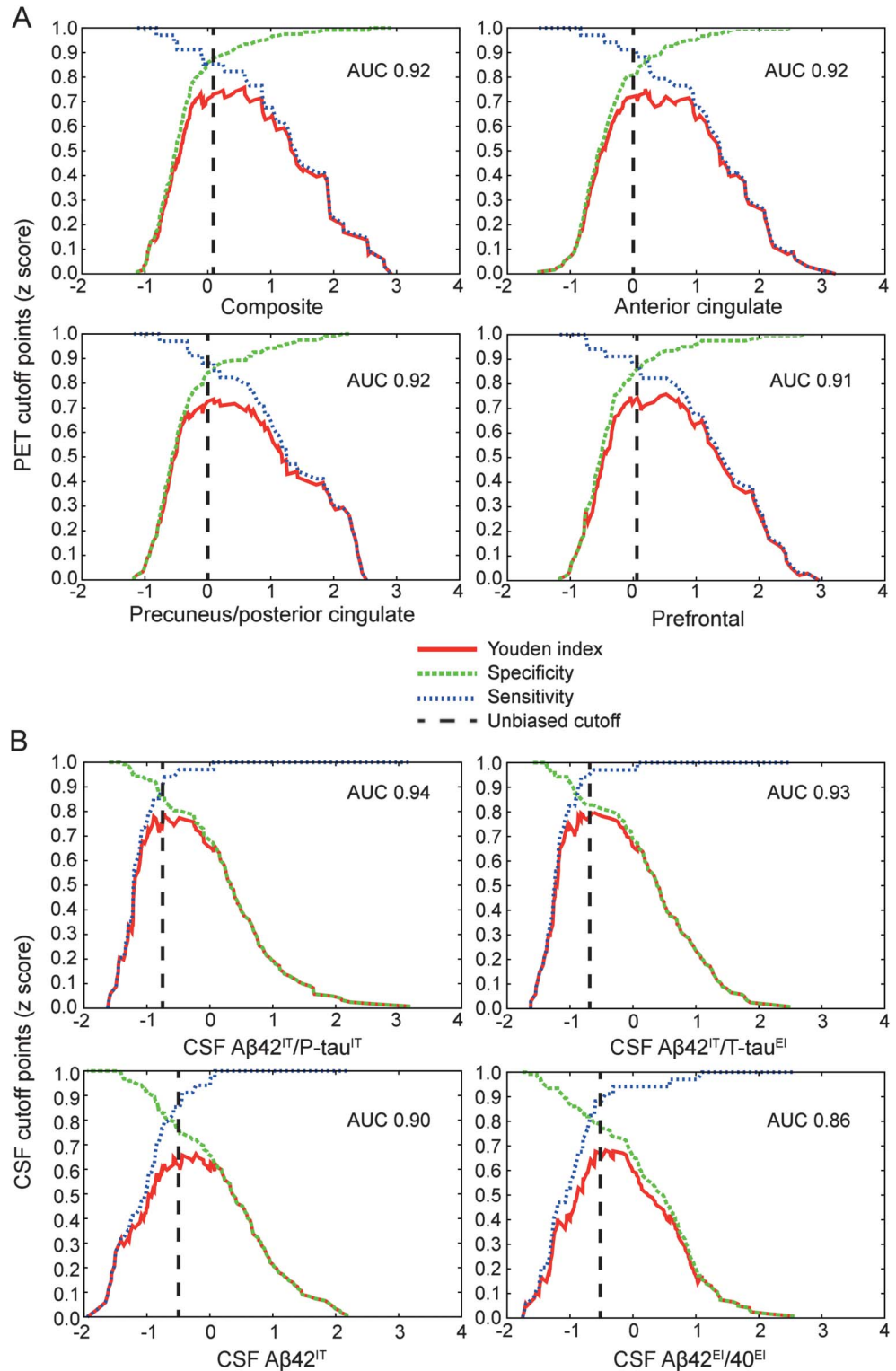
**DISCUSSION** The main finding of this study was that the diagnostic accuracy of CSF and A $\beta$  PET biomarkers to identify MCI-AD was similar when using <sup>18</sup>F-flutemetamol amyloid PET and several different CSF biomarkers. Specifically, the best CSF measures (CSF A $\beta$ 42/t-tau and A $\beta$ 42/p-tau ratios) had similar diagnostic accuracies as the best PET measures (composite and cingulate SUVRs; table 2). We also found that no regional PET biomarker was better than the neocortical composite PET SUVR (table 2). For CSF biomarkers, the CSF A $\beta$ 42/t-tau or A $\beta$ 42/p-tau ratios had significantly higher diagnostic accuracy compared to using CSF A $\beta$  biomarkers alone. When using unbiased cutoffs,

CSF A $\beta$ 42/t-tau had the highest sensitivity and specificity of all CSF and PET biomarkers (table 3). Finally, the combination of the best CSF and PET biomarkers did not provide any added diagnostic value compared to using either modality separately. The overall results were replicated in an independent cohort (ADNI).

Although we found that CSF A $\beta$ 42<sup>IT</sup> and A $\beta$ 42<sup>EI</sup>/A $\beta$ 40<sup>EI</sup> performed similarly to the best SUVRs of <sup>18</sup>F-flutemetamol PET in terms of AUCs (table 2), these CSF biomarkers generally had lower specificities than the PET biomarkers when using unbiased cutoffs (table 3). The addition of t-tau or p-tau to A $\beta$ 42 (as ratios) significantly increased the diagnostic accuracy of CSF biomarkers (table 2). This supports the common usage of CSF A $\beta$ 42 in combination with t-tau or p-tau in clinical practice, and is in agreement with previous studies.<sup>31–34</sup>

The diagnostic accuracy of CSF A $\beta$ 42 was lower for EUROIMMUN compared with INNOTEST (table 2 and figure e-3). This was partly overcome by using the A $\beta$ 42/40 ratio, which did not improve the accuracy of A $\beta$ 42 INNOTEST (table 2). This finding has not been shown previously and needs to be replicated in future studies, since the causes are

**Figure 1** Sensitivities, specificities, and Youden indices of all possible cutoff points



(A, B) The cutoffs have been transformed to z scores (SD) for easier comparison between variables. Near optimal Youden indices are found for a relatively wide range of cutoffs ( $>1$  SD) for all variables except for CSF Aβ42/Aβ40<sup>EI</sup>, which have a slightly narrower span. The different cutoffs within this near optimal range thus only change the relationship between the sensitivity and specificity, but not the overall classification accuracy. This wide range of near optimal cutoffs suggests that the cutoffs are likely to produce high diagnostic accuracies in other populations. AUC = area under the receiver operating characteristic curve.

unknown. Few studies have compared different ELISAs for CSF Aβ42 to identify MCI-AD. Hertz et al.<sup>33</sup> found that CSF Aβ42 analyzed with xMAP

AlzBio3 had higher diagnostic accuracy compared with the Meso Scale Discovery (MSD) assay, but this was overcome by using the Aβ42/Aβ40 MSD ratio.

**Table 4** Classification of MCI-AD and healthy controls based on ROC analyses in ADNI

| Variable (in order of AUC value) | AUC (95% CI)     | Unbiased cutoff <sup>a</sup> | Youden index (95% CI) <sup>b,c</sup> | Sensitivity (%) <sup>b</sup> | Specificity (%) <sup>b</sup> |
|----------------------------------|------------------|------------------------------|--------------------------------------|------------------------------|------------------------------|
| PET frontal                      | 0.87 (0.82-0.91) | 1.13                         | 0.63 (0.51-0.73)                     | 89                           | 74                           |
| CSF A $\beta$ 42/t-tau           | 0.87 (0.80-0.92) | 1.71                         | 0.65 (0.53-0.76)                     | 80                           | 86                           |
| CSF A $\beta$ 42/p-tau           | 0.87 (0.80-0.92) | 3.83                         | 0.65 (0.52-0.75)                     | 84                           | 81                           |
| PET composite                    | 0.86 (0.81-0.91) | 1.13                         | 0.66 (0.54-0.75)                     | 91                           | 75                           |
| PET parietal                     | 0.86 (0.81-0.91) | 1.11                         | 0.59 (0.47-0.69)                     | 91                           | 68                           |
| PET temporal                     | 0.86 (0.80-0.92) | 1.08                         | 0.66 (0.54-0.76)                     | 89                           | 77                           |
| PET cingulate                    | 0.86 (0.80-0.91) | 1.20                         | 0.56 (0.44-0.66)                     | 89                           | 66                           |
| CSF A $\beta$ 42                 | 0.85 (0.79-0.90) | 173                          | 0.60 (0.50-0.70)                     | 94                           | 66                           |

Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; AUC = area under the receiver operating characteristic curve; CI = confidence interval; MCI-AD = patients with mild cognitive impairment who developed Alzheimer disease within 3 years; p-tau = hyperphosphorylated tau; ROC = receiving operating characteristic; t-tau = total tau.

No significant differences between the AUCs were found ( $p = 0.17-0.93$ ).

<sup>a</sup>Established with mixture modeling analysis (described in Methods).

<sup>b</sup>Derived from the ROC analysis.

<sup>c</sup>Youden index (sensitivity + specificity - 1) is provided for an easier comparison of the combined value of the sensitivity and specificity, e.g., the diagnostic accuracy of CSF and PET measures as dichotomized variables. The value is based on the unbiased cutoffs.

Similar to the present study, they showed that A $\beta$ 42/t-tau was superior to A $\beta$ 42 and A $\beta$ 42/A $\beta$ 40.

A possible advantage of A $\beta$  PET over CSF A $\beta$ 42 as an early marker for amyloid pathology is that A $\beta$  PET may be able to identify early region-specific pathology. However, this was not supported by our study, since the global A $\beta$  uptake performed similar compared to the best regional SUVRs (tables 2 and 4). Only one previous study has examined this and found similar results.<sup>19</sup> The similar AUCs for the best PET regions support the notion that the A $\beta$  deposition is uniformly distributed in the neocortical association areas already at the MCI stage of AD.<sup>35</sup>

We used classification cutoffs established with mixture modeling, which is a robust way of determining unbiased thresholds and used in several studies.<sup>20,36,37</sup> Even so, the cutoffs (table 3) should not be considered generalizable, but study-specific for comparative purposes. However, figure 1 shows that although a cutoff is not optimized for the current population, it can still provide good diagnostic accuracy because of the broad range of high YI. The stability of cutoffs between populations is also supported by a previous cross-validation study on CSF A $\beta$ 42 and amyloid PET cutoffs.<sup>20</sup> However, even though the classification accuracy stays the same, a change in cutoff will of course result in a higher sensitivity/lower specificity or lower sensitivity/higher specificity, and this must be taken into consideration depending on the clinical aim of the examination.

The overall results were similar between the BioFINDER and ADNI cohorts. In ADNI, the same comparable results between regional and composite SUVRs, as well as equal diagnostic accuracies of CSF and PET measures, were seen (table 4). This

similarity between studies is especially interesting considering the use of different PET tracers and different CSF assays. In both cohorts, numerically higher AUCs were seen for the CSF A $\beta$ 42/t-tau or p-tau ratios compared with just A $\beta$ 42, but in ADNI the increase was not significant (tables 2 and 4). This could be attributed to the poorer AUCs of t-tau and p-tau in ADNI (0.81 and 0.82; AlzBio3) compared with BioFINDER (0.88 and 0.87; EUROIMMUN and INNOTEST). A similar difference between INNOTEST and AlzBio3 regarding A $\beta$ 42/tau ratios was also found in a previous study.<sup>38</sup> It was notable that the AUCs of all brain regions were similar in ADNI (AUC range 0.01; table 4), in contrast to BioFINDER (AUC range 0.17; table 2). The reason for this could be that in ADNI the regions were coarser and not able to detect differences between, e.g., the medial and lateral temporal lobe.

The diagnostic accuracy of A $\beta$  PET and CSF biomarkers to detect incipient AD has only been compared head-to-head in one previous study, which partly used the same ADNI data used for replication in the present study.<sup>19</sup> In that study, the accuracy between stable MCI (2- to 3-year follow-up without progression) and MCI-AD was compared. In the present study, we instead compared healthy elderly and patients with MCI-AD, which resulted in higher AUCs (on average about 0.05 in the ADNI study; compare reference 19 and table 4). The rationale behind comparing controls and MCI-AD is that >5-10 years of follow-up is required before one can say that a patient with MCI is truly stable.<sup>36</sup> Among patients with stable MCI with a short follow-up time, there are several cases with early-stage AD. These patients with stable MCI will in most cases be correctly identified as MCI-AD by the biomarkers, but result in



false low specificity (and a false low AUC) due to the incorrect clinical diagnosis/short follow-up. We therefore compared patients with MCI-AD and controls, given the relatively short follow-up data in the ADNI and BioFINDER populations, for a more robust comparison of A $\beta$  biomarkers.

The novelties of the present study compared with the previous study<sup>19</sup> include a comparison between MCI-AD and controls, a more detailed analysis of regional A $\beta$  PET data, analyses of ratios of CSF A $\beta$ 42/A $\beta$ 40, A $\beta$ 42/t-tau, and A $\beta$ 42/p-tau, a comparison of 2 different ELISAs for CSF A $\beta$ 42, and evaluation of the combination of PET and CSF biomarkers.

The similar results we found for CSF biomarkers and amyloid PET suggest that other factors than their diagnostic accuracy may be considered when deciding which biomarker to use. CSF analysis has the advantages that it may easily incorporate other biomarkers to improve the differential diagnosis (e.g., leukocytes, albumin ratio, neurofilament,  $\alpha$ -synuclein), requires less advanced instruments than PET, and is in some countries more available in clinical practice. Amyloid PET, on the other hand, is less invasive and has a higher reliability in longitudinal examinations and between centers. With appropriate standardized procedures,<sup>20,39,40</sup> CSF analysis and amyloid PET perform equally well and either method can be used in the clinical workup of AD for increased diagnostic accuracy.

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data, accepts responsibility for conduct of research and final approval, statistical analysis. Oskar Hansson: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, contribution of vital reagents/tools/patients, acquisition of data, study supervision, obtaining funding.

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## DISCLOSURE

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