Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-142952
IOS Press

Concordance and Diagnostic Accuracy of [^{11}C]PIB PET and Cerebrospinal Fluid Biomarkers in a Sample of Patients with Mild Cognitive Impairment and Alzheimer's Disease

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Accepted 12 January 2015

Abstract.

Background: Alzheimer's disease (AD) pathology can be quantified *in vivo* using cerebrospinal fluid (CSF) levels of amyloid-$\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$), total-tau (t-tau), and phosphorylated tau (p-tau_{181p}), as well as with positron emission tomography (PET) using [^{11}C]Pittsburgh compound-B ([^{11}C]PIB). Studies assessing concordance between these measures, however, have provided conflicting results. Moreover, it has been proposed that [^{11}C]PIB PET may be of great clinical utility in terms of identifying patients with mild cognitive impairment (MCI) who will progress to the dementia phase of AD.

Objective: To determine concordance and classification accuracy of CSF biomarkers and [^{11}C]PIB PET in a cohort of patients with MCI and AD.

Methods: 68 patients (MCI, $n=33$; AD, $n=35$) underwent [^{11}C]PIB PET and CSF sampling. Cutoffs of >1.41 ([^{11}C]PIB), <450 pg/mL—and a more lenient cutoff of 550 pg/mL—($A\beta_{1\text{-}42}$), <6.5 ($A\beta_{1\text{-}42}$/p-tau_{181p}), and 1.14 ($A\beta_{1\text{-}42}$/t-tau), were used to determine concordance. Logistic regression was used to determine classification accuracy with respect to stable MCI (sMCI) versus MCI who progressed to AD (pMCI).

Results: Concordance between [^{11}C]PIB and $A\beta_{1\text{-}42}$ was highest for sMCI (67%), followed by AD (60%) and pMCI (33%). Agreement was increased across groups using $A\beta_{1\text{-}42}$ <550 pg/mL, or $A\beta_{1\text{-}42}$ to tau ratios. Logistic regression showed that classification accuracy of [^{11}C]PIB, between sMCI and pMCI, was superior to $A\beta_{1\text{-}42}$ (73% versus 58%), $A\beta_{1\text{-}42}$/t-tau (63%), and $A\beta_{1\text{-}42}$/p-tau_{181p} (65%).

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ISSN 1387-2877/15/$35.00

Conclusion: In the present study, [^{11}C]PIB proved a better predictor of progression to AD in patients with MCI, relative to CSF measures of $A\beta_{1\text{-}42}$ or $A\beta_{1\text{-}42}$/tau. Discordance between PET and CSF markers for $A\beta_{1\text{-}42}$ suggests they cannot be used interchangeably, as is currently the case.

Keywords: [^{11}C]PIB, Alzheimer's disease, amyloid, cerebrospinal fluid, mild cognitive impairment, positron emission tomography, tau

INTRODUCTION

While at present incurable, intensive efforts to develop disease-modifying drugs to counteract the progression of Alzheimer's disease (AD) are ongoing. Given the increasing consensus that such drugs must be administered early on in the disease course if they are to prove effective, the further development and validation of diagnostic tools capable of accurately identifying AD pathophysiology at an early stage has become an important area of research. In addition to aiding in the selection of patients appropriate for inclusion in clinical trials of disease modifying drugs, effective diagnostic tools will also be required in routine clinical practice to identify patients with mild cognitive impairment (MCI) due to AD so as to provide treatment should these drugs be approved for widespread use.

On the basis of the current hypothetical model of dynamic biomarkers for AD [1], the aggregation and deposition of the 42 amino acid variant of amyloid-β ($A\beta_{1\text{-}42}$) is thought to set in motion various neurodegenerative processes that result in cognitive impairment, and, ultimately, dementia. Indeed, biomarker studies in sporadic AD have shown that decreased cerebrospinal fluid (CSF) levels of $A\beta_{1\text{-}42}$ is a very early change [2, 3], with studies in familial AD suggesting that these reductions precede expected symptom onset by 25 years [4]. In addition to low $A\beta_{1\text{-}42}$, increased CSF levels of total tau (t-tau) and tau phosphorylated at threonine 181 (p-tau_{181p}) are typically seen in AD [5–7]. In this respect, a previous study reported that ratios of CSF $A\beta_{1\text{-}42}$ to t-tau ($A\beta_{1\text{-}42}$/t-tau) and p-tau_{181p} ($A\beta_{1\text{-}42}$/p-tau_{181p}) outperformed any single analyte in discriminating patients with and without cortical amyloid deposition [8], suggesting that a combinatorial approach is best when evaluating CSF biomarkers.

In addition to CSF measurements, cerebral amyloid deposition can be determined using positron emission tomography (PET) and amyloid-binding radiotracers, such as [^{11}C]-labelled Pittsburgh compound B ([^{11}C]PIB). The most widely studied PET amyloid ligand to date, [^{11}C]PIB uptake has been shown to be significantly increased in familial AD mutation carriers 15 years prior to expected symptom onset [4], and strongly associated with region-matched, quantitative analyses of Aβ in postmortem AD tissue [9, 10]. In MCI, [^{11}C]PIB uptake follows a bimodal distribution, with patients showing uptake values that overlap with those seen in cognitively normal controls (i.e., below the threshold required for [^{11}C]PIB positivity) or that correspond to those seen in AD [11].

Previous studies using both continuous and dichotomous correlations have shown the information obtained using [^{11}C]PIB PET and CSF $A\beta_{1\text{-}42}$ to be in strong agreement [12–14], pointing to convergent validity of both types of biomarkers [15, 16]. A recent study, however, suggests that [^{11}C]PIB may be more sensitive than the concentration of CSF $A\beta_{1\text{-}42}$ with respect to the detection of cerebral amyloidosis in MCI [17]. In line with this report, a study addressing the diagnostic performance of CSF $A\beta_{1\text{-}42}$ and PET [^{18}F]florbetapir—a radiofluorinated amyloid tracer exhibiting high agreement with [^{11}C]PIB [18]—showed that while the diagnostic accuracy of both measures were similar, PET had greater specificity owing to discordance between measures [19]. Importantly, PET and CSF amyloid biomarkers are considered clinically equivalent on the basis of the recently revised diagnostic criteria for MCI and dementia due to AD [20, 21].

Using a memory clinic sample of patients with MCI and AD, the present study investigated 1) concordance between CSF $A\beta_{1\text{-}42}$ (both alone, and combined with tau) and [^{11}C]PIB PET; and 2) classification accuracy of [^{11}C]PIB PET and CSF $A\beta_{1\text{-}42}$ (both alone, and combined with tau) with respect to stable MCI (sMCI) versus MCI who progressed to AD dementia (pMCI). It was hypothesized that [^{11}C]PIB PET and CSF measures of $A\beta_{1\text{-}42}$, $A\beta_{1\text{-}42}$/t-tau, and $A\beta_{1\text{-}42}$ /p-tau_{181p} would exhibit high concordance, and that PET would prove superior to CSF measures in the case of discerning sMCI from pMCI.

METHODS

Patients

Thirty-three MCI and 35 AD patients were recruited from the Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. All patients underwent a comprehensive routine assessment procedure, including a physical examination, evaluation of neurological and psychiatric status, blood (including apolipoprotein E (APOE) genotyping), serum and urine analysis, structural imaging, CSF sampling, and neuropsychological assessment. MCI patients met the Petersen criteria [22, 23], with the diagnosis of probable AD based on the National Institute of Neurological and Communication Disorders, Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [24]. In all cases, diagnosis was issued via a consensus based committee approach, which included neurologists, clinical neuropsychologists, and specialist nurses.

MCI patients underwent regular clinical follow-ups, with 12 progressing to AD dementia (pMCI). Classification of MCI patients into sMCI and pMCI took into account findings from CSF, but not [11C]PIB-PET. 8 out of 31 MCI received treatment with acetylcholinesterase (AChE) inhibitors. In the AD group, 30 received treatment with AChE inhibitors—including 14 with phenserine—with 5 subjects receiving no pharmacological treatment. All patients and their caregivers provided written informed consent to participate in the investigation, which was conducted according to the declaration of Helsinki and subsequent revisions. Ethical approval was obtained from the regional human ethics committee of Stockholm and the Faculty of Medicine and Radiation, Hazard Ethics Committee of Uppsala University Hospital, Sweden.

Neuropsychological assessment

A routine clinical neuropsychological assessment was performed on all participants. Global cognition was assessed using the Mini-Mental State Examination (MMSE) and a composite measure including the Information and Similarities subscales of the Wechsler Adult Intelligence Scale (language), Block design and Rey Osterrieth copy (visuospatial), Digit Span and Corsi Span (working memory), the Digit Symbol and Trail Making Tests A and B (attention/executive domains). In addition, episodic memory was assessed using the Rey Auditory Verbal Learning Test learning and retention, as well as the Rey Osterrieth retention. Patients' raw neuropsychological test scores were transformed into z-scores with respect to a reference group of healthy elderly controls from Karolinska University Hospital, Huddinge, Sweden [25]. Applying a cutoff of -1.5 SD to this composite episodic memory score, 12 out of 21 MCI patients were considered as amnestic MCI.

PET imaging

PET investigations were performed at Uppsala PET Centre on ECAT EXACT HR+scanners (Siemens/CTI) or a Discovery ST PET/CT scanner (GE). The orbito-meatal line was used to center the head of the participants. PET data was acquired in 3D mode yielding a 155-157 mm field of view. The [11C]PIB-PET data acquisitions consisted of 24 frames (4×30, 9×60, 3×180, and 8×300 s), acquired over 60 min. A late 40–60 min [11C]PIB summation image was created and used for subsequent image analysis. The mean injected dose was 295 ± 69.5 MBq.

All emission data were reconstructed with filtered back projection (FBP) using a 4 mm Hanning filter, resulting in a transaxial spatial resolution of 5 mm in the FOV. The matrix included 128×128 pixels, with a zoom factor of 2.5. All reconstructed frames were re-aligned to correct for between frame patient motion.

PET data analysis

Individual 40–60 min integral [11C]PIB images were nonlinearly spatially normalized to a population-based [11C]PIB template (see Nordberg et al. [26] for a detailed description of the [11C]PIB template) using the normalize function in SPM5 (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, UCL, London, UK). Spatially normalized images were then resampled using a 23-region grey matter atlas, created in parallel to the [11C]PIB template [26]. Subsequently, standardized uptake value ratio (SUV_R) images were calculated by normalizing the activity within frontal, temporal, parietal, occipital, parahippocampal, anterior, and posterior cingulate regions to mean cerebellar grey matter (vermis excluded) activity. Using the upper 95% confidence limit of 1.41 from a previously characterized population of normally distributed healthy controls [26], patients were subdivided into [11C]PIB 'positive' ([11C]PIB+), and [11C]PIB 'negative' ([11C]PIB-).

CSF measurements

CSF samples were obtained via lumbar puncture (LP) from 67 patients (all MCI and 34 of 35 AD). LP was performed under non-fasting conditions, between 8 and 11 a.m., with a total of 10 mL of CSF collected. After discarding the first 0.5 mL, samples were centrifuged at 1500 × g (3000– 4000 rpm) for 10 min at +4°C. Samples were then stored at –80°C in 1 ml portions pending biochemical analysis, without being thawed or refrozen. Levels of $A\beta_{1\text{-}42}$, t-tau, and p-tau_{181p} were determined using commercially available sandwich ELISAs (Innogenetics, Ghent, Belgium) [27–29]. For the MCI group, levels of $A\beta_{1\text{-}42}$ and t-tau were obtained for all subjects, with p-tau_{181p} available for 26 of 33 subjects. For the AD group, tau levels (total and phosphorylated) were unavailable for 2 and 10 subjects, respectively. Cutoff values of <450 pg/mL ($A\beta_{1\text{-}42}$), >400 pg/mL (t-tau), and >80 pg/mL (p-tau_{181p}) were adopted based on receiver operating characteristic analyses previously conducted by the department of Clinical Chemistry, Karolinska University Hospital Huddinge [30, 31]. In addition, we applied a more lenient cutoff of <550 pg/mL for $A\beta_{1\text{-}42}$ since preliminary findings from the Biomarkers for Alzheimer's and Parkinson's disease (BIOMARKAPD) initiative [32] suggest this to be an optimal cutoff (unpublished data). Cutoffs of 1,14 for $A\beta_{1\text{-}42}$/t-tau and 6.5 for $A\beta_{1\text{-}42}$/p-tau_{181p} were taken from the literature [17, 33].

Statistics

Statistical analyses were conducted using SPSS version 20.0 (IBM Corp, Armonk, NY), with a $p \leq 0.05$ used to indicate statistical significance. Patient characteristics were compared using analysis of variance (ANOVA), Kruskal-Wallis ANOVA, and χ^2. *Post-hoc t*-tests and were performed where appropriate.

Concordance between [11C]PIB PET and CSF $A\beta_{1\text{-}42}$ was defined as the proportion of subjects positive or negative for both (i.e., [11C]PIB+ and CSF $A\beta_{1\text{-}42}$ <450 pg/mL or [11C]PIB- and CSF $A\beta_{1\text{-}42}$ >450 pg/mL). Concordance between [11C]PIB and CSF t-tau and p-tau_{181p} was determined in the same fashion, using the cutoffs outlined above. Discordance between [11C]PIB PET and CSF biomarkers was defined as the proportion of cases exhibiting only one abnormal biomarker, with the other being above its respective cutoff. Logistic regression among MCI was used to assess the classification accuracy of [11C]PIB PET and CSF biomarkers, with progression to dementia due to AD as the dependent variable.

RESULTS

Patient characteristics according to diagnostic group are shown in Tables 1 and 2. Groups did not differ with respect to age, education, gender, or frequency of the APOE $\varepsilon 4$ allele. As expected, AD patients had lower MMSE relative to sMCI and pMCI ($p < 0.001$), with pMCI patients showing lower scores relative to sMCI ($p < 0.05$). Using the composite neuropsychological score for global cognition, performance of pMCI patients was below that of sMCI ($p < 0.05$)—as was the case with AD ($p < 0.001$)—with no differences found between pMCI and AD. Using the composite score for episodic memory, performance of pMCI patients was worse than that of sMCI patients ($p < 0.01$), with AD patients performing worse than both sMCI ($p < 0.001$) and pMCI patients (0.01). Regarding use of AChE inhibitors, prescription rates were higher in the AD group (relative to sMCI, $p < 0.001$, pMCI $p < 0.01$). No group differences were found for the period of time between PET and CSF assessments. With respect to the classification of sMCI versus pMCI, clinical follow-up times were longer in sMCI ($p < 0.001$).

Global [11C]PIB PET SUV_R was higher in AD, relative to both sMCI ($p < 0.001$) and pMCI ($p < 0.05$), with levels in pMCI greater than sMCI ($p < 0.01$). In addition, regional analyses showed significant differences in [11C]PIB between sMCI and pMCI in the temporal lobe ($p = 0.05$), the anterior cingulate ($p < 0.001$), the posterior cingulate ($p < 0.001$), the frontal cortex ($p < 0.01$), the parietal cortex ($p < 0.01$), as well as the parahippocampus and insula ($p < 0.01$) Relative to AD, [11C]PIB retention in pMCI differed only in the frontal cortex ($p < 0.05$; see Supplementary Table 1). CSF levels of $A\beta_{1\text{-}42}$ were lower in AD and pMCI,

Table 1
Subject demographics

	sMCI	pMCI	AD
n	21	12	35
Age, years	63.52 ± 8.23	62.33 ± 6.96	67.12 ± 8.82
Education, years	13.10 ± 3.24	13.58 ± 3.40	11.79 ± 3.79
Gender, f	10 (48%)	9 (75%)	21 (60%)

Data are presented as mean ± standard deviation, or as n (%). sMCI, stable mild cognitive impairment (i.e., those who had not progressed to dementia at clinical follow-up); pMCI, progressive mild cognitive impairment (i.e., those who had developed to dementia of the Alzheimer's type at clinical follow-up); AD, dementia due to Alzheimer's disease; f, female. Differences between groups were assessed using ANOVA (age, education) and χ^2 (gender).

Table 2
Neuropsychological, clinical, and imaging data according to diagnostic group

	sMCI	pMCI	AD
n	21	12	35
MMSE	28.43 ± 1.32	27.08 ± 1.62 ^{a*}	23.51 ± 3.72 ^{a,b***}
Global cognition	−0.43 (1.26)	−1.22 (1.84)^{a***}	−1.72 (2.89)^{a,b,***}
Episodic memory	−0.59 (1.07)	−1.46 (0.66) ^{a***}	−2.01 (2.50) ^{a,b,***}
Amnestic subtype	8 (38%)	4 (33%)	–
APOE ε4 frequency	12 (57%)	10 (83%)	28 (80%)
AChE inhibitors	4 (19%)	4 (33%)	30 (86%) ^{a***,b**}
Global [^{11}C]PIB PET SUV_R	1.38 ± 0.3	1.68 ± 0.16 ^{a**}	1.82 ± 0.24 ^{a***,b*}
CSF $A\beta_{1\text{-}42}$	656.20 ± 275.59	490.92 ± 100.37 ^{a*}	439.83 ± 157.02 ^{a**}
CSF t-tau	383.67 ± 196.78	459.67 ± 157.14	563.06 ± 251.03 ^{†,a**}
CSF p-tau	65.26 ± 25.26 ‡	68.72 ± 18.54 †	88.31 ± 32.88 ^{¶,a*}
CSF $A\beta_{1\text{-}42}$/t-tau	2.26 ± 1.49	1.17 ± 0.39 ^{a**}	0.92 ± 0.54 ^{†,a**}
CSF $A\beta_{1\text{-}42}$/p-tau_{181p}	12.52 ± 8.07	7.49 ± 2.09 ^{a*}	5.90 ± 2.87 ^{a**}
Time PET to CSF, months	12.49 ± 21.44	5.22 ± 2.99	9.01 ± 9.30
Time PET to FU, months	44.46 ± 22.61^{b***}	11.92 ± 12.77	–
Time CSF to FU, months	49.85 ± 27.70 ^{b***}	15.95 ± 11.81	–
% positive [^{11}C]PIB PET	6 (29%)	12 (100%) ^{a***}	35 (100%) ^{a***}
% positive $A\beta_{1\text{-}42}$	5 (24%)	4 (33%) ^{a*}	21 (60%) ^{a*}
% positive CSF t-tau	7 (33%)	8 (67%) ^{a*}	23 (68%) ^{†,a*}
% positive CSF p-tau_{181p}	4 (27%) ‡	3 (27%) †	14 (54%) ^{¶,a*}
% positive $A\beta_{1\text{-}42}$/t-tau	6 (29%)	6 (50%) ^{a**}	24 (67%) ^{†,a**}
% positive $A\beta_{1\text{-}42}$/p-tau_{181p}	3 (20%) ‡	5 (45%) ^{†,a*}	19 (73%) ^{¶,a**}

Data are presented as mean ± standard deviation, or as n (%). sMCI, stable mild cognitive impairment (i.e., those who had not progressed to dementia at clinical follow-up); pMCI, progressive mild cognitive impairment (i.e., those who had developed to dementia of the Alzheimer's type at clinical follow-up); AD, dementia due to Alzheimer's disease; MMSE, Mini-Mental State Examination; Global cognition, composite of the Information and Similarities subscales of the Wechsler Adult Intelligence Scale (language), Block design and Rey Osterrieth copy (visuospatial), Digit Span and Corsi Span (working memory), the Digit Symbol and Trail Making Tests A and B (attention/executive domains); Episodic memory, composite of the Rey Auditory Verbal Learning Test learning and retention, and the Rey Osterrieth retention. Amnestic subtype, amnestic MCI; - Does not apply; AChE inhibitors, acetylcholinesterase inhibitors; Global [^{11}C]PIB PET SUV_R, cutoff >1.41; CSF $A\beta_{1\text{-}42}$, cutoff <450 pg/mL; CSF t-tau, cutoff >400 pg/mL; CSF p-tau, cutoff >80 pg/mL; CSF $A\beta_{1\text{-}42}$/t-tau, cutoff <1.14; CSF $A\beta_{1\text{-}42}$/p-tau, cutoff <6.5; Time PET to FU, time between [^{11}C]PIB PET and clinical follow-up, in months; Time CSF to FU, time between CSF sampling and clinical follow-up, in months. This period can also be considered representative of the total follow-up time since CSF sampling preceded baseline diagnosis by a short, but variable, time interval; – Since the focus of clinical follow-ups in the present study was to determine whether patients with MCI had progressed to dementia due to AD, follow-up times for AD are not reported. Differences between groups were assessed using ANOVA (MMSE, Global cognition, Episodic memory, Global [^{11}C]PIB PET SUV_R, CSF $A\beta_{1\text{-}42}$, t-tau, p-tau, $A\beta_{1\text{-}42}$/t-tau, $A\beta_{1\text{-}42}$/p-tau, Time PET to CSF, Time PET to FU, Time CSF to FU, months) and χ^2 (Amnestic subtype, APOE ε4 frequency, % positive [^{11}C]PIB PET, CSF $A\beta_{1\text{-}42}$, t-tau, p-tau, $A\beta_{1\text{-}42}$/t-tau, $A\beta_{1\text{-}42}$/p-tau). ^{a}relative to sMCI, ^{b}relative to pMCI, ^{c}relative to AD. $^{*}p<0.05$ $^{**}p<0.01$ $^{***}p<0.001$.

relative to sMCI ($p<0.001$ and 0.05, respectively). Relative to sMCI, CSF levels of total and phosphorylated tau were higher in AD ($p<0.01$ and 0.05, respectively). Using the ratio of $A\beta_{1\text{-}42}$ to t-tau, pMCI and AD patients showed lower ratio values compared to sMCI ($p<0.01$), with the same pattern observed for $A\beta_{1\text{-}42}$/p-tau_{181p} ($p<0.05$ and 0.01, respectively). Compared to sMCI, [^{11}C]PIB PET was more often found to be abnormal in pMCI and AD ($p<0.001$), as was the case for CSF $A\beta_{1\text{-}42}$ ($p<0.05$), t-tau ($p<0.05$), $A\beta_{1\text{-}42}$ /t-tau ($p<0.01$), and CSF $A\beta_{1\text{-}42}$ /p-tau_{181p} ($p<0.01$). Stable and pMCI did not differ in levels of p-tau_{181p}. Relative to sMCI, levels of p-tau_{181p} were greater in AD ($p=0.05$).

Across groups, concordance between [^{11}C]PIB PET and CSF $A\beta_{1\text{-}42}$ was 57% (see Table 3, Fig. 1). Using a higher, more lenient cutoff of <550 pg/mL for CSF $A\beta_{1\text{-}42}$—or a combination of $A\beta_{1\text{-}42}$ and tau (both total and phosphorylated)—concordance reached 79%, 69%, and 70%, respectively. Within groups, concordance between [^{11}C]PIB PET and CSF $A\beta_{1\text{-}42}$ was highest for sMCI (67%), followed by AD (60%), and pMCI (33%). Though the use of this more lenient cutoff did not increase concordance within the sMCI group, agreement increased to 83% and 86% in pMCI and AD, respectively. Using $A\beta_{1\text{-}42}$/t-tau and $A\beta_{1\text{-}42}$/p-tau_{181p}, concordance was highest for sMCI (81% and 80%), followed by AD (71% and 77%), and

Table 3
Concordance between [11C]PIB PET SUV_R and CSF biomarkers

[11C]PIB PET SUV_R	All	sMCI	pMCI	AD
CSF $A\beta_{1-42}$ <450	57%	67%	33%	60%
CSF $A\beta_{1-42}$ <550	79%	67%	83%	86%
CSF t-tau	70% †	76%	67%	68% †
CSF p-tau_{181p}	58% §	87% ‡	27%†	54% ¶
CSF $A\beta_{1-42}$/t-tau	69% †	81%	50%	71% †
CSF $A\beta_{1-42}$/p-tau_{181p}	70% §	80% ‡	45%†	77% ¶

All, all groups. sMCI, stable mild cognitive impairment (i.e. those who had not progressed to dementia at clinical follow-up); pMCI, progressive mild cognitive impairment (i.e. those who had developed to dementia of the Alzheimer's type at clinical follow-up). AD, dementia due to Alzheimer's disease. [11C]PIB PET SUV_R, based on a global cutoff of >1.41. CSF $A\beta_{1-42}$ <450, CSF cut-off of <450 pg/mL. CSF $A\beta_{1-42}$ <550, CSF cut-off of <550 pg/mL. CSF t-tau, CSF cut-off of >400 pg/mL. CSF p-tau_{181p}, CSF cut-off based on >80 pg/mL. CSF $A\beta_{1-42}$/t-tau, CSF cut-off based on <1.14. CSF $A\beta_{1-42}$/p-tau_{181p}, CSF cut-off based on <6.5. † data for 1 subject missing. ‡ data for 6 subjects missing. ¶ data for 9 subject missing. § data for 16 subjects missing.

pMCI (50% and 45%). In terms of discordance, PET was more often positive than CSF $A\beta_{1-42}$, using both 450 pg/mL and 550 pg/mL cutoffs (see Figs. 2 and 3).

Logistic regression among MCI subjects showed that the classification accuracy of [11C]PIB-PET was

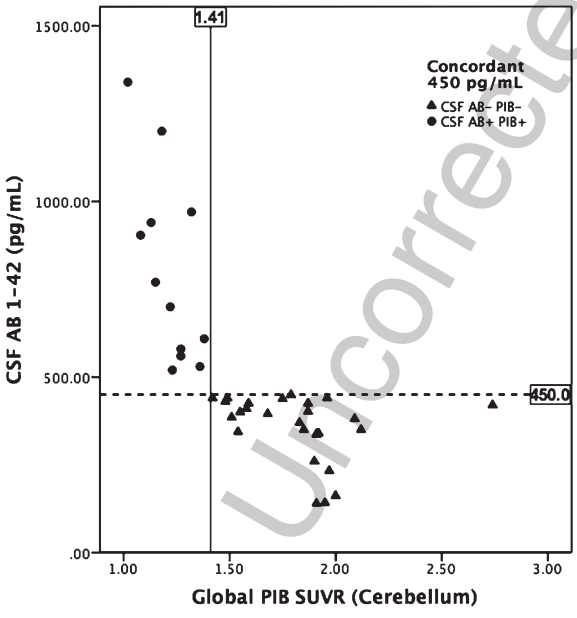

Fig. 1. Concordance between [11]PIB PET and CSF $A\beta_{1-42}$, using a CSF cutoff of 450 pg/mL. Scatterplot showing concordance between concordance between [11]PIB PET and CSF $A\beta_{1-42}$ (cut-off <450 pg/mL). Triangles indicate [11]PIB PET-, CSF $A\beta_{1-42}$- subjects; circles indicate [11]PIB PET+, CSF $A\beta_{1-42}$+ subjects. Horizontal solid line indicates cut-off for abnormal [11]PIB PET (SUVR >1.41); horizontal dashed line indicates cut-off for abnormal CSF $A\beta_{1-42}$ (<450 pg/mL).

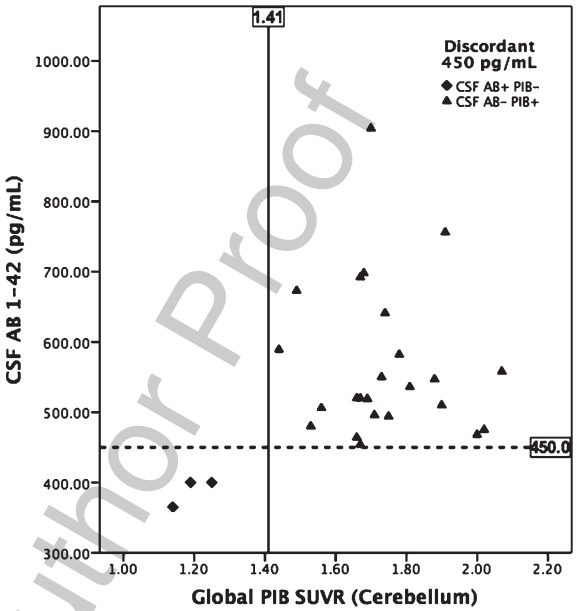

Fig. 2. Concordance between [11]PIB PET and CSF $A\beta_{1-42}$, using a CSF cutoff of 450 pg/mL. Scatterplot showing discordance between [11]PIB PET and CSF $A\beta_{1-42}$ (cut-off <450 pg/mL). Diamonds indicate [11]PIB PET-, CSF $A\beta_{1-42}$+ subjects; triangles indicate [11]PIB PET+, CSF $A\beta_{1-42}$- subjects. Horizontal solid line indicates cut-off for abnormal [11]PIB PET (SUVR >1.41); horizontal dashed line indicates cut-off for abnormal CSF $A\beta_{1-42}$ (<450 pg/mL).

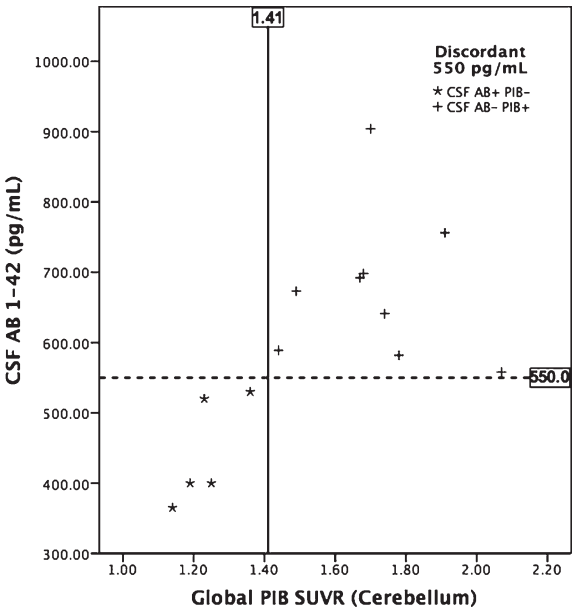

Fig. 3. Concordance between [11]PIB PET and CSF $A\beta_{1-42}$, using a CSF cutoff of 550 pg/mL. Scatterplot showing discordance between [11]PIB PET and CSF $A\beta_{1-42}$ (cut-off <550 pg/mL). Stars indicate [11]PIB PET-, CSF $A\beta_{1-42}$+ subjects; crosses indicate [11]PIB PET+, CSF $A\beta_{1-42}$- subjects. Horizontal solid line indicates cut-off for abnormal [11]PIB PET (SUVR >1.41); horizontal dashed line indicates cut-off for abnormal CSF $A\beta_{1-42}$ (<550 pg/mL).

Table 4
Logistic regression derived classification accuracies for [11C]PIB PET and CSF biomarkers, both alone and with use of demographic and clinical covariates

[11C]PIB PET SUV_R	Accuracy (alone)	p	Accuracy (covariates)	Model[a]	p[b]
Global	73%	**	79%	**	NS
Frontal	73%	*	82%	*	**
Anterior cingulate	73%	**	82%	***	*
Posterior cingulate	79%	**	82%	**	*
Insula	67%	**	79%	**	NS
Parietal	67%	**	70%	**	NS
Temporal	58%	*	82%	*	NS
Caudate nucleus	64%	*	85%	**	*
Putamen	64%	**	88%	**	*
Nucleus accumbens	70%	**	85%	**	*
Hippocampus	64%	NS	79%	*	NS
Parahippocampal	75%	*	72%	*	NS
CSF					
$A\beta_{1\text{-}42}$	58%	NS	82%	**	NS
t-tau	58%	*	82%	*	NS
p-tau_{181p}	54%	NS	70%	NS	NS
$A\beta_{1\text{-}42}$/t-tau	63%	NS	83%	**	NS
$A\beta_{1\text{-}42}$/p-tau_{181p}	64%	NS	77%	*	NS

NS. not significant. sMCI, stable mild cognitive impairment (i.e., those who had not progressed to dementia at clinical follow-up); pMCI, progressive mild cognitive impairment (i.e., those who had developed to dementia of the Alzheimer's type at clinical follow-up); AD, dementia due to Alzheimer's disease. [a]significance level of the model. [b]significance level of the variable within the model. Covariates: age, gender, education, MMSE, and APOE $\varepsilon 4$ genotype. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

superior to $A\beta_{1\text{-}42}$ (73% versus 58%), t-tau (58%), p-tau_{181p} (54%), $A\beta_{1\text{-}42}$/t-tau (63%), and $A\beta_{1\text{-}42}$/p-tau_{181p} (65%) (see Table 4). Using regional [11C]PIB uptake, classification accuracy was highest using the posterior cingulate (79%) and parahippocampal gyrus (75%), with additional regions proving similar to or inferior to global [11C]PIB. Inclusion of age, gender, education, MMSE, and APOE $\varepsilon 4$ genotype as covariates generally increased classification accuracy of PET (using both global and regional values) and CSF. While the regression models were considered statistically significant when taken together—save for p-tau_{181p}—only [11C]PIB values within the frontal cortex, the cingulate gyrus, the caudate, and the nucleus accumbens within the models themselves cross the threshold for significance ($p<0.05$).

Characteristics of patients showing discordance between amyloid biomarkers are presented in Table 5. Though raising the cutoff to 550 pg/mL within the group discordant at 450 pg/mL increased agreement, 21% (14 out of 68) of subjects remained discordant. Among discordant subjects, 80% had a positive [11C]PIB scan and normal CSF $A\beta_{1\text{-}42}$. Concordant and disconcordant subjects differed only with respect to age (concordant 450 pg/mL > discordant 450 pg/mL, $p<0.05$) and global cognition (concordant 450 pg/mL > discordant 550 pg/mL, $p<0.01$). As a whole, discordant subjects were within one standard deviation (SD) of the 450 pg/mL cut-off (mean ± SD: 563.54 ± 129.54). While the predominant diagnosis in the group discordant at 450 pg/mL was AD, in those discordant at 550 pg/mL it was sMCI.

DISCUSSION

The present study showed that global and regional [11C]PIB PET proved superior to CSF $A\beta_{1\text{-}42}$—both alone, and combined with tau—in terms of differentiating cases of stable MCI from those who progressed to dementia due to AD. Though the classification accuracies of [11C]PIB and CSF measures were comparable following the addition of clinical and demographic covariates, only frontal, cingulate gyrus, caudate nucleus, and putaminal [11C]PIB values retained statistical significance. In this respect, previous work has shown that MCI who progressed to AD had higher [11C]PIB retention in these regions, when compared with MCI who did not progress [34]. We reproduced this finding in the present study, with pMCI subjects showing higher [11C]PIB values within these regions, relative to sMCI subjects. This finding suggests that regional analysis—including, in particular, striatal components—may prove superior to the use of a global [11C]PIB with respect to predicting progression toward AD dementia in patients with MCI.

As expected, the proportion of subjects showing abnormal [11C]PIB and CSF $A\beta_{1\text{-}42}$ was greater in pMCI and AD. Using 450 pg/mL as a cutoff, agreement between CSF $A\beta_{1\text{-}42}$ and [11C]PIB PET was inferior to that using $A\beta_{1\text{-}42}$ to tau ratio values across all groups, with the reverse being true in pMCI and AD when using the more lenient cutoff of 550 pg/mL. In sMCI, agreement between $A\beta_{1\text{-}42}$ and [11C]PIB PET was unchanged by cutoff levels, with agreement between [11C]PIB and $A\beta_{1\text{-}42}$/tau ratios higher relative to pMCI and AD. These concordance findings reflect the fact that nearly half of the sMCI subjects were amyloid negative, with the syndrome likely the result of non-AD pathology. Comparisons between concordant and discordant subjects proved unremarkable, with only subjects concordant and discordant at 450 pg/mL differing in age.

Our findings using the more lenient $A\beta_{1\text{-}42}$ cutoff are in line with previous studies showing high concordance between CSF $A\beta_{1\text{-}42}$ and [11C]PIB PET [13, 15, 31, 35–37]. Moreover, our results lend support to

Table 5
Characteristics of patients showing discordance between [^{11}C]PIB PET and CSF A$\beta_{1\text{-}42}$

	Concordant 450 pg/mL	Discordant 450pg/mL	Discordant 550 pg/mL
Total	39 (57%)	27 (40%)	14 (21%)
sMCI	14 (36%)	7 (26%)	7 (50%)
pMCI	4 (10%)	8 (30%)	2 (14%)
Amnestic subtype	8 (44%)	6 (40%)	3 (33%)
AD	21 (54%)	12 (44%)	5 (36%)
Age, years	$66.82 \pm 8.90^{a*}$	62.59 ± 7.57	65.00 ± 7.16
Education	12.10 ± 3.78	13.14 ± 3.17	12.71 ± 3.14
Gender, f	20 (51%)	18 (67%)	6 (60%)
MMSE	25.58 ± 3.50	25.34 ± 3.83	26.21 ± 3.95
Global cognition	1.15 ± 2.71	-0.94 ± 2.10	-0.64 ± 1.72 [b**]
Episodic memory	-1.09 ± 1.70	-1.23 ± 1.49	-1.06 ± 1.49
APOE ε4 frequency	27 (69%)	21 (78%)	11 (79%)
AChE inhibitors	22 (54%)	17 (63%)	8 (57%)
Global [^{11}C]PIB PET SUV_R	1.64 ± 0.37	1.68 ± 0.23	1.55 ± 0.29
CSF A$\beta_{1\text{-}42}$	494.10 ± 265.56	548.03 ± 117.89	593.42 ± 149.35
CSF t-tau	463.82 ± 237.76	525.93 ± 241.70	488.07 ± 277.15
CSF p-tau$_{181p}$	69.72 ± 25.62[§]	84.23 ± 27.18 [‡]	76.78 ± 33.67 [†]
CSF A$\beta_{1\text{-}42}$/t-tau	1.45 ± 1.25	1.31 ± 0.87	1.67 ± 1.17
CSF A$\beta_{1\text{-}42}$/p-tau$_{181p}$	8.89 ± 7.01[§]	7.38 ± 2.73 [‡]	10.10 ± 4.31 [†]
Time PET to CSF, months	10.36 ± 15.16	8.63 ± 12.19	15.17 ± 24.14

Data are presented as mean ± standard deviation, mean ± standard deviation (z-scores), or as n (%). sMCI, stable mild cognitive impairment (i.e. those who had not progressed to dementia at clinical follow-up); pMCI, progressive mild cognitive impairment (i.e., those who had developed to dementia of the Alzheimer's type at clinical follow-up); AD, dementia due to Alzheimer's disease; f, female; MMSE, mini-mental state examination; Global cognition, composite of the Information and Similarities subscales of the Wechsler Adult Intelligence Scale (language), Block design and Rey Osterrieth copy (visuospatial), Digit Span and Corsi Span (working memory), the Digit Symbol and Trail Making Tests A and B (attention/executive domains); Episodic memory, composite of the Rey Auditory Verbal Learning Test learning and retention, and the Rey Osterrieth retention. APOE ε4, apolipoprotein ε4 allele; AChE inhibitors, acetylcholinesterase inhibitor. Global [^{11}C]PIB PET SUV_R, cutoff >1.41; CSF A$\beta_{1\text{-}42}$, cutoff <450 pg/mL; CSF t-tau, cutoff >400 pg/mL; CSF p-tau, cutoff >80 pg/mL; CSF A$\beta_{1\text{-}42}$/t-tau, cutoff <1.14; CSF A$\beta_{1\text{-}42}$/p-tau, cutoff <6.5. Differences between groups were assessed using ANOVA (MMSE, Global cognition, Episodic memory, Global [^{11}C]PIB PET SUV_R, CSF A$\beta_{1\text{-}42}$, t-tau, p-tau, A$\beta_{1\text{-}42}$/t-tau, A$\beta_{1\text{-}42}$/p-tau, Time PET to CSF, months) and χ^2 (Amnestic subtype, APOE ε4 frequency, % positive [^{11}C]PIB PET, CSF A$\beta_{1\text{-}42}$, t-tau, p-tau, A$\beta_{1\text{-}42}$/t-tau, A$\beta_{1\text{-}42}$/p-tau). [†] data for 5 subjects missing. [‡] data for 6 subjects missing. data for 10 subjects missing. [a]relative to subjects discordant at 450 pg/mL. [b]relative to subjects concordant at 450 pg/mL. $^{*}p < 0.05$ $^{**}p < 0.01$.

previous work showing that A$\beta_{1\text{-}42}$/tau ratios are superior to these CSF markers individually with respect to predicting progression to AD dementia in patients with MCI [37]. While the majority of subjects discordant for A$\beta_{1\text{-}42}$ were within one SD of the threshold for abnormality, the fact that discordant cases were primarily [^{11}C]PIB+ conflicts with the current hypothetical model of AD biomarkers [1], in which concentrations of A$\beta_{1\text{-}42}$ are thought to cross the threshold for abnormality prior to positive findings using amyloid PET.

Given the sizeable body of evidence showing decreased levels of CSF A$\beta_{1\text{-}42}$ in MCI and AD [5–8, 14, 38–41], our finding of high levels of A$\beta_{1\text{-}42}$ (i.e., those discordant at 550 pg/mL) in [^{11}C]PIB+ subjects may represent a methodological artifact tied to preanalytical or assay-related factors. Specifically, increased concentrations of CSF A$\beta_{1\text{-}42}$ have been shown to relate to the time interval between CSF collection and centrifugation, as well as to dilution and buffer factors [39]. The effects of differing calibrator peptides and antibodies within immunoassay kits—as well as batch-to-batch variation—[42] likewise cannot be ruled out since the CSF samples utilized in this study were collected over a relatively long period of time. Indeed, this explanatory stance seems reasonable since similar factors were purported to be at play in the only study to date reporting increased levels of CSF A$\beta_{1\text{-}42}$ in MCI and AD [43]. Finally, insufficient quality and quantity of sleep have been shown to augment CSF levels of A$\beta_{1\text{-}42}$ [44], an important consideration given the high prevalence of sleep disorders in AD [45]. As such, sleep insufficiency may have contributed to the discordance between [^{11}C]PIB and CSF A$\beta_{1\text{-}42}$, though this was not assessed.

Though [11C]PIB possesses high affinity for fibrillary Aβ found in cored plaques and cerebral amyloid angiopathy, it binds only weakly to amorphous Aβ plaques [46, 47]. As such, [11C]PIB may prove unable to detect variants of AD characterized by the predominance of diffuse (nonfibrillar) plaques [48]. In support of this hypothesis, low levels of CSF $A\beta_{1\text{-}42}$ have been reported in a case of sporadic AD with negative [11C]PIB PET and an abundance of diffuse, but not neuritic (fibrillary), plaques at postmortem, two years following the CSF and [11C]PIB assessments [48]. The low CSF $A\beta_{1\text{-}42}$ in the absence of [11C]PIB positivity observed in a subset of MCI patients in the present study may therefore reflect the aggregation of Aβ in diffuse ([11C]PIB-negative) plaques, or the accumulation of oligomeric forms prior to substantial fibrillary ([11C]PIB-positive) Aβ deposition [49]. Though recent work suggests that [11C]PIB uptake increases over time in some patients with MCI [50], PET studies were conducted after CSF assessment in the present study, suggesting that [11C]PIB-negativity in this subgroup is not simply a reflection of lower disease burden. Finally, though four out of five of the [11C]PIB-/CSF $A\beta_{1\text{-}42+}$ subjects were classified as nonamnestic—a subtype typically thought to represent the prodromal phase of non-AD dementias—longitudinal studies highlight a significant rate of progression to AD dementia within this population [51–54]. Further clinical follow-up of these patients will be required to address these possibilities.

Certain methodological aspects, however, limit interpretation of the present findings. In addition to a relatively small sample size, we were unable to obtain measurements for $\text{p-tau}_{181\text{p}}$ in a number of subjects as this measurement was not routinely done in older CSF samples, with repeat analysis of the original samples an impossibility. Another limitation of this study was the use of literature-derived cutoffs for Aβ to tau ratios, given the large between center variability reported for CSF measurements [42]. The temporal dissociation between CSF and PET assessments stands as another potential limitation, as ideally the two procedures would have been separated by as short an interval as possible. Several studies have shown, however, that changes in CSF levels of $A\beta_{1\text{-}42}$, t-tau, and $\text{p-tau}_{181\text{p}}$ are minimal or absent during both the progression from MCI to AD dementia [28], and during the course of dementia due to AD [54–56]. Taken together, these results suggest that pathologic CSF levels are most likely reached during the preclinical, asymptomatic phase of the disease [28, 55–57]. Even assuming increased levels of fibrillary ([11C]PIB-positive) amyloid in our MCI subjects [50]—in line with the recent findings mentioned above—between CSF and PET assessments, the fact that CSF sampling was conducted before PET suggests that the discordance observed between CSF $A\beta_{1\text{-}42}$ and [11C]PIB PET is unlikely to be due the delay between the two assessments.

Despite these caveats, our results suggest that relative to CSF measures of $A\beta_{1\text{-}42}$ or $A\beta_{1\text{-}42}$/tau, [11C]PIB PET may prove a better predictor of progression to AD in patients with MCI. Moreover, our findings suggest that evaluation of [11C]PIB-binding in AD signature regions may provide additional diagnostic information relative to global cortical to cerebellar binding. Finally, though the use of a more lenient cut-off greatly increased agreement between CSF $A\beta_{1\text{-}42}$ and [11C]PIB PET, continued discordance in a subset of MCI patients suggests that these two biomarkers cannot be used interchangeably, as is currently the case.

ACKNOWLEDGMENTS

This study was financially supported by, the Swedish Research Council (project 05817), Swedish Brain Power, the regional agreement on medical training and clinical research (ALF) between Stockholm County Council, The Strategic Research Program in Neuroscience at Karolinska Institutet, Knut and Alice Wallenberg Foundation, the foundation for Old Servants, Gun and Bertil Stohnes Foundation, KI foundations, The Swedish Brain Foundation, the Alzheimer Foundation in Sweden, EU FW6 network of excellence program DiMI (http://www.dimi.eu) and within the design of the EU FW7 large scale integrating project INMiND (http://www.uni-muenster.de/INMiND), the JPND Project BIOMARKAPD. The authors are grateful to Dr. Jian Fransén for the processing of the [11C]PIB imaging data.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/14-2952r1).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-142952.

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