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Derivation and utility of an Aβ-PET pathology accumulation index to estimate Aβ load

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Abstract

Objective: To evaluate a novel Aβ-PET based quantitative measure (Aβ accumulation index [Aβ-index]), including the assessment of its ability to discriminate between subjects based on Aβ-status using visual-read, CSF Aβ42/Aβ40 and *post-mortem* neuritic-plaque burden as standards of truth.

Methods: 1121 subjects (with and without cognitive impairment) scanned with Aβ-PET: Swedish BioFINDER, n=392, [18F]flutemetamol; ADNI, n=692, [18F]florbetapir; a phase-3 end-of-life study, n=100, [18F]flutemetamol). The relationships between Aβ-index and standardized uptake values ratios (SUVR) from Aβ-PET were assessed. The diagnostic performance of Aβ-index and SUVR were compared when using visual reads, CSF Aβ42/Aβ40 and Aβ-histopathology as reference standards.

Results: Strong associations were observed between Aβ-index and SUVR (R^2, BioFINDER, 0.951; ADNI, 0.943, end-of-life, 0.916). Both measures performed equally well in differentiating Aβ-positive from Aβ-negative subjects, with AUCs of 0.979-0.991 to detect abnormal visual reads, AUCs of 0.961-0.966 to detect abnormal CSF Aβ42/40 and AUCs of 0.820-0.823 to detect abnormal Aβ-histopathology. Both measures also showed a similar distribution across *post-mortem* based Aβ-phases (based on anti-Aβ 4G8 antibodies). By comparison to models using visual-read alone, the addition of the Aβ-index resulted in a significant increase in AUC and a decrease in Akaike information criterion to detect abnormal Aβ-histopathology.

Conclusions: The proposed Aβ-index showed a tight association to SUVR and carries an advantage over the latter in that it does not require the definition of regions of interest nor the use of MRI. Aβ-index may thus prove simpler to implement in clinical settings and may also facilitate the comparison of findings using different Aβ-PET tracers.

Classification of evidence

This study provides Class III evidence that the Aβ accumulation index accurately differentiates Aβ-positive from Aβ-negative subjects when compared to Aβ-PET visual reads, CSF Aβ42/Aβ40 and Aβ-histopathology.

Introduction

Aβ-PET tracers such as [^{18}F]flutemetamol are currently approved for visual assessment only (whereby images are rated as negative/positive (normal/abnormal) by a trained rater).[1, 2] Evidence suggests, however, that quantifying the amount of tracer retention in the brain may improve agreement between raters [3] and aid in the monitoring of treatment effects in anti-Aβ trials.[4] The most commonly used quantitative measure for Aβ-PET is the standardized uptake value ratio (SUVR), where tracer concentration in cortical (target) regions is divided by that within a reference region assumed to be free of Aβ-pathology. Though high resolution structural magnetic resonance imaging (MRI) is ideally used to delineate these regions-of-interest (ROIs), this technique is not always available in clinical settings and is frequently contraindicated among elderly patient.[5]

In the absence of MRI, PET-only approaches can be used.[6] Here, a PET image is first transformed from a standardized coordinate space (spatial normalization); ROIs are then defined using a probabilistic atlas. Using such an approach, we recently described a novel measure of brain Aβ-burden (Aβ-index).[7] As it does not require the definition of ROIs, it is simpler to implement that SUVR. Herein, we aimed to 1) compare Aβ-index and SUVR in three independent cohorts; 2) to assess their ability to differentiate Aβ-positive and Aβ-negative subjects using visual read, CSF Aβ42/Aβ40 or *post-mortem* neuritic plaque burden as standards-of-truth.; and 3) to assess whether a combination of visual read and Aβ-index

was superior to visual read alone to predict Aβ-positivity using CSF Aβ42/Aβ40 and *post-mortem* neuritic plaque burden as standards-of-truth. We hypothesized that across these aims, Aβ-index would show non-inferiority to SUVR.

Methods

Participants

Our population consisted of 1121 subjects with Aβ-PET, from three separate cohorts: 392 from the Swedish BioFINDER study (clinical trial no. NCT01208675), scanned with [18F]flutemetamol (251 cognitively unimpaired (CU), including 129 elderly controls and 122 with subjective cognitive decline, and 141 CI subjects with mild cognitive impairment [MCI]), 629 from ADNI (clinical trial no. NCT00106899) (246 CU controls and 383 CI subjects [MCI]), scanned with [18F]florbetapir, and 100 subjects from a phase 3 end-of-life study (clinical trial no. NCT01165554 and NCT02090855) who were scanned with [18F]flutemetamol *ante-mortem* and autopsied after death.[8-10] Inclusion for CU and CI individuals from BioFINDER and ADNI have been described elsewhere[11, 12] and are described in the Supplement (Appendices e-1 and e-2, doi:10.5061/dryad.2547d7wnf). In the end-of-life study, subjects were ≥ 55 years of age, terminally ill with a life expectancy < 3 years and with general health sufficient to allow for completion of study procedures. Dementia, defined according to the DSM-IV criteria, was noted as present or absent, as reported in case notes. The relationship between Aβ-index and SUVR was also examined in patients with AD dementia, using CSF Aβ42/Aβ40 as the standard of truth for Aβ status (BioFINDER, n=25 with [18F]flutemetamol PET available and n=25 from ADNI using [18F]florbetapir).

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all patients (or guardians of patients)

participating in the study (consent for research). Ethical approval for BioFINDER was given

by the Regional Ethical Committee of Lund University. Approval for PET imaging was

obtained from the Swedish Medical Products Agency and the local Radiation Safety

Committee at Skåne University Hospital. For the ADNI and end-of-life cohorts, study

protocols were approved by local ethical committees.

Image Acquisition and Processing

For BioFINDER, [18F]flutemetamol studies were performed using a Philips Gemini TF

PET/CT scanner (Philips Medical Systems, Amsterdam, Netherlands) over the interval 90- to

110-min post-injection; data was acquired in list-mode and binned into frames using an

iterative Vue Point HD algorithm (six subsets, 18 iterations with 3mm filter and no time-of-

flight correction). All participants underwent 3T MRI scans (Siemens MAGNETOM Prisma),

acquiring isometric 1 mm³ T1-weighted magnetization-prepared rapid gradient echo

(MPRAGE) images. For ADNI, [18F]florbetapir image data acquired 50- to 70-min post-

injection[13] and T1-weighted MRI scans using a sagittal volumetric MPRAGE sequence

acquired at 3T were used.[14] For the phase 3 end-of-life study, [18F]flutemetamol PET images

were acquired on PET/CT cameras over the interval 90- to 110-min post-injection. As both

ADNI and the phase 3 end-of-life study were multicentric in nature, images were smoothed to

achieve a uniform imaging resolution.

Aβ-PET images were spatially normalized using two approaches: an MRI driven

approach included in SPM12, and a PET driven principal component approach.[7] For the end-

of-life cohort, normalization of [18F]flutemetamol images was only performed using the

principal component approach as MRI was not available. The purpose of this dual approach

was to ensure that SUVRs from the principal component approach were highly correlated with those derived using the MRI driven gold standard approach. The complete details of the principal component approach can be found in the original publication.[7] Briefly, tracer specific principal component images are first calculated by singular value decomposition of Aβ-PET SUVR images. Two principal components were chosen as these captured ~95% of the variance in the dataset. The first principal component represents the average of all the images the dataset, the second, the different between Aβ-positive and Aβ-negative images (i.e. specific binding). A synthetic template ($I_{Synthetic}$) can then be modelled as a linear combination of the first and second principal component images (I_{PC1} and I_{PC2}, respectively). As part of this operation, I_{PC2} is multiplied by a weighting factor (Aβ-index; i.e. $I_{Synthetic} = I_{PC1} + A\beta\text{-}index \ ^{*} \ I_{PC2}$) representing a global measure of brain Aβ pathology. Here, a positive Aβ-index yields a template with a more Aβ-positive appearance and a negative value yields a template with a more Aβ-negative appearance. Using an algorithm that incorporates both the Aβ-index and the parameters required for the spatial transformation, the synthetic template can then be used to normalize Aβ-PET images.

In the present study, pre-existing synthetic templates derived from phase 2 studies were used for [18F]flutemetamol[15] and [18F]florbetapir.[16, 17] Following spatial normalization of [18F]flutemetamol and [18F]florbetapir scans, two sets of SUVRs were calculated (one for each normalization method) for BioFINDER and ADNI subjects using a composite cortical region of interest (ROI)—encompassing brain regions typically showing high Aβ load in AD, including frontal, temporal and parietal cortices, precuneus, anterior striatum, and insular cortex—and the pons and cerebellum as reference tissues[18] for [18F]flutemetamol and [18F]florbetapir, respectively. As described above, SUVR values for [18F]flutemetamol scans from the end-of-life cohort were based on the principal component based normalization alone.

The term "principal component" herein refers to the principal component driven normalization approach (and, for instance, SUVR values derived from images normalized using this approach) and not the Aβ-index per se (which is generated when using the principal component driven approach for spatial normalization).

CSF Biomarkers

Lumbar puncture and CSF handling followed structured protocols in the BioFINDER and ADNI studies.[11] In BioFINDER, the fully automated Elecsys assays (Roche Diagnostics) were used, as described elsewhere, [19, 20] with samples analyzed at the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden. In ADNI, CSF Aβ42/Aβ40 was determined using Aβ42 and Aβ40 measurements derived from a liquid chromatography with tandem mass spectrometric detection (UPLC-MS-MS) method,[21] with samples analyzed in the Biomarker Research Laboratory, University of Pennsylvania, USA.

Post-Mortem Aβ-Pathology Assessment

Post-mortem based estimates of Aβ plaque pathology were based on autopsy brain tissue previously collected in support of the GE067-007/GE-067-026 phase 3 clinical trials for [^{18}F]flutemetamol PET.[22] As described elsewhere,[10] after formalin fixation, brains were coronally sliced and macroscopically screened. The Bielschowsky silver method was then applied to paraffin-embedded tissue from eight neocortical regions, as defined by the Consortium to Establish a Registry for Alzheimer's disease (CERAD).[23] In each region, neuritic plaque densities were recorded as 0 (no plaques), 1 (sparse; 1–5 plaques), 2 (moderate; 6–19 plaques), or 3 (frequent; >20 plaques), per 100x field of view.[23, 24] A modified CERAD based assessment approach was then applied whereby the arithmetic mean of neuritic plaque density was calculated across the eight investigated regions (30 measures

per region), giving a continuous variable. The Aβ-phases according to Thal et al.[9] describing

the hierarchical spreading of Aβ plaque pathology in the brain were determined after

screening the Aβ-stained sections (anti-Aβ 4G8 antibodies) for plaque distribution.

Definition of Aβ Status

Aβ status (positive/negative), as a standard of truth, was defined using three approaches: in

ADNI and BioFINDER, using consensus read of Aβ-PET uptake images and CSF

Aβ42/Aβ40; and in the end-of-life trial, using the *post-mortem* based Bielschowsky

histopathology score. For CSF Aβ42/Aβ40, cut-offs of 0.059 (BioFINDER)[25] and 0.137

(ADNI) were used, based on Gaussian mixture modelling applied to the BioFINDER and

ADNI cohorts. For Bielschowsky silver stain, each assessed brain region was scored from 0

to 3 (calculated as the arithmetic mean of 30 measures); a score above 1.5, previously shown

to represent the threshold between the categories of sparse and moderate neuritic plaques,[10] in

any of the eight investigated regions was considered abnormal, with the brain classified as

Aβ-positive.

Statistical Analyses

Between group characteristics were compared using Kruskall-Wallis' or Fisher's exact tests.

The relationship between Aβ-index and SUVR from [18F]flutemetamol and [18F]florbetapir

was examined using linear regression and coefficient of determination (R^2). Receiver

operating characteristic (ROC) analyses were performed to generate area-under-the-curve

(AUC) values for both Aβ-index and SUVR. Differences in AUC values for these measures

were evaluated using bootstrap (n=1000) procedures. In order to assess the added clinical

value of the Aβ-index, AUC and Akaike information criterion (AIC) values from binary

logistic regression models (using CSF Aβ42/Aβ40 (BioFINDER and ADNI) and

Bielschowsky histopathology (end-of-life cohort) as the outcome variables

[positive/negative]) and visual read (model 1) or visual read in combination with Aβ-index

(continuous, model 2) were compared. For comparison, a third model combining visual read

and SUVR was included. All analyses were performed in R (v.3.5.3; https://www.R-

project.org/), with significance set at *P*<0.05, two-sided.

Primary research question

How do Aβ-index and SUVR from Aβ PET compare in their ability to differentiate subjects

based on their Aβ-status. This study provides Class III evidence that the Aβ accumulation

index accurately differentiates Aβ-positive from Aβ-negative subjects when compared to Aβ-

PET visual reads, CSF Aβ42/Aβ40 and Aβ-histopathology.

Data Availability

Anonymized study data for the primary analyses presented in this report are available on

request from any qualified investigator for purposes of replicating the results.

Results

Cohort characteristics are summarized in tables 1 (BioFINDER and ADNI) and 2 (end-of-life

study). Among the 85 cases in the end-of-life cohort with an antemortem diagnosis of

dementia, 28 (33%) had a post-mortem neuropathological diagnosis of pure AD, 33 (39%) a

diagnosis of AD plus at least one other pathology (e.g. cerebral amyloid angiopathy or TDP-

43) and 24 (28%) a non-AD pathology such as Lewy body or vascular dementia. Figure 1

provides an overview of the steps required to generate the Aβ-index. Principal component

images for [18]flutemetamol and [18F]florbetapir are provided in figure e-1

(doi:10.5061/dryad.2547d7wnf). Comparison of SUVR values using principal component and

MRI (SPM12) driven normalization approaches showed good agreement (figure e-2;

doi:10.5061/dryad.2547d7wnf), with R^2 values of 0.997 for [18F]flutemetamol and 0.995 for [18F]florbetapir (*P*<0.001). Characteristics of AD dementia subjects are summarized in table e-1 (doi:10.5061/dryad.2547d7wnf).

Strong associations were observed between Aβ-index and principal component derived SUVR values in both cohorts (BioFINDER, R^2 = 0.951 [95% confidence interval, 0.933-0.961]; ADNI, R^2 = 0.943 [95% confidence interval, 0.927-0.952]; *P*<0.001) (figure 2). Comparison of ROC derived AUC values from Aβ-index and SUVR showed that both measures performed equally well in differentiating Aβ-positive from Aβ-negative subjects, using both visual read (AUCs = 0.979 [95% confidence interval, 0.972-0.989] to 0.991 [95% confidence interval, 0.972-0.989]) and CSF Aβ42/Aβ40 (AUCs = 0.961 [95% confidence interval, 0.939-0.983] to 0.971 [95% confidence interval, 0.949-0.981]) as standards of truth (figure 3), with no significant difference found between AUC values. Similar findings were obtained when looking at AD dementia cases (figure e-3; doi:10.5061/dryad.2547d7wnf).

In the [18F]flutemetamol end-of-life cohort we found that both Aβ-index and SUVR could predict i) abnormal Bielschowsky silver stain scores (AUCs = 0.820 [95% confidence interval, 0.716-0.923] to 0.823 [95% confidence interval, 0.725-0.921]) and ii) visual read outcomes (AUCs = 0.938 [95% confidence interval, 0.889-0.984] to 0.949 [95% confidence interval, 0.911-0.988]) (figure 4), with no significant difference found between AUC values. Using the Aβ phases (Thal et al.[26]) as neuropathological readout, a similar distribution was seen for [18F]flutemetamol Aβ-index and SUVR across Aβ phases (figure 4). Comparison of SUVR and Aβ-index measures between Aβ phases (i.e. phase 1 vs 2, 2 vs 3, 3 vs 4 and 4 vs 5) showed significant differences for both measures between phases for the contrasts phase 3 vs 4 (SUVR and Aβ-index, *P*<0.001) and phase 4 vs 5 (SUVR and Aβ-index, *P*<0.01).

Finally, we studied whether a combination of Aβ-index and visual read was superior to visual read alone. By comparison to the binary logistic regression model using only visual read as a predictor, the addition of the Aβ-index resulted in a significant increase in AUC (Aβ-status as outcome) using CSF Aβ42/Aβ40 (BioFINDER: 0.868 [95% confidence interval 0.843 to 0.894] vs 0.962 95% confidence interval 0.932-0.987], $P<0.001$; ADNI: 0.881 [95% confidence interval 0.856-0.906] vs 0.943 [95% confidence interval 0.923-0.962], $P<0.001$) and Bielschowsky histopathology (0.910 [95% confidence interval 0.883 to 0.937] vs 0.961 [95% confidence interval 0.936-0.986), $P<0.05$). Moreover, addition of the Aβ-index resulted in an improved model fit (AIC) (using CSF Aβ42/Aβ40 BioFINDER: 253.94 vs 167.78; ADNI: 400.59 vs 328.89; using Bielschowsky histopathology in the end-of-life cohort, 60.24 vs 53.86).[27] Similar findings were observed when using SUVR for both AUC (AUC: CSF Aβ42/Aβ40, BioFINDER 0.868 [95% confidence interval 0.843-0.894] vs 0.942 [95% confidence interval 0.914-0.968], $P<0.001$; ADNI: 0.881 [95% confidence interval 0.859-0.905] vs 0.954 [95% confidence interval 0.925-0.983], $P<0.001$; Bielschowsky, end-of-life cohort, 0.910 [95% confidence interval 0.889-0.933] vs 0.942 [95% confidence interval 0.917-0.969], $P<0.05$ and AIC (CSF Aβ42/Aβ40, BioFINDER: 253.94 vs 161.08; ADNI: 400.59 vs 306.31; and in the end-of-life cohort using Bielschowsky histopathology: 60.24 vs 56.94).

Discussion

The objective of the present study was to assess the relationship between Aβ-index and Aβ-PET SUVR, including a comparison of the ability of both measures to differentiate between subjects on the basis of their Aβ status, using several standards of truth (visual read, CSF Aβ42/Aβ40 and *post-mortem* Aβ histopathology). First, using both [18F]flutemetamol and [18F]florbetapir, we showed that the principal component based approach to normalization

was precise and accurate, with SUVRs from this approach correlating highly with those derived from the MRI based method in SPM. Using this PET driven approach, we then showed a close correspondence between the Aβ-index and SUVR, with both measures performing equally well in identifying Aβ-positive cases and showing a similar pattern of increase across *post-mortem* Aβ-phases. Finally, we showed that the addition of the Aβ-index improved prediction of Aβ-status relative to the use of visual read alone.

Given recent evidence showing that Aβ-PET imaging led to changes in the clinical management of CI individuals,[28] the importance of accurate and reproducible Aβ image interpretation is clear. Though the visual assessment of Aβ scans as positive or negative has been shown to be an adequately sensitive method with respect to *post-mortem* estimates of plaque burden, studies have shown significant variability across readers.[29, 30] Findings from several studies indicate that use of quantitation could prove a helpful adjunct to visual interpretation,[31-34] similar to other areas of nuclear medicine involving PET imaging.[35, 36] Quantitation of Aβ-PET images using SUVR derived from commercial software packages, for instance, has been shown to improve the accuracy of visual reads in clinically relevant cases.[37] This was also the case in the present study, where the addition of the Aβ-index improved prediction of histopathology based Aβ-status. The addition of an objective measure, like Aβ-index or SUVR, will probably be even more important in clinical practice, where many readers are not as experienced as those evaluating clinical PET images in academic research studies or clinical trials. The the Aβ-index—along with a cut-off indicating whether or not the scan is positive—could easily be incorporated into currently available commercial software.[38] Quantitation has also been shown to result in more consistent detection of early Aβ plaque pathology in CU older adults.[39] This finding in particular is of importance given that CU older individuals who are accumulating Aβ in the Aβ negative range—where visual

read alone is likely to prove insensitive—may prove a key target population for anti-Aβ clinical trials.[40]

A fundamental step prerequisite to quantitation in PET is the spatial transformation of data into a common space (i.e. spatial normalization). SUVR values derived using the proposed principal component method were tightly correlated to those based on the dual-scan (MRI, PET) MRI driven approach used in SPM, indicating that accurate spatial normalization was achieved. Further, this method removes the need for a separate MRI scan; this is a highly desirable quality given that MR imaging is not always available as part of routine clinical workup and can be complicated by high rates of nonparticipation due to difficulty lying still during the examination, claustrophobia, contraindications such as pacemaker, metallic implants and other reasons.[5] In addition, removing the need for MRI would decrease the burden placed on patients and caregivers, and a short computer tomography scan is often adequate to exclude secondary causes of cognitive impairment such as subdural hematoma and tumours and can be done in conjunction with the PET scan. In terms of clinical translation, additional studies are required to address whether the improvements in inter-reader agreement seen when adding SUVR to visual read of Aβ-PET images [3, 37] are also observed when using Aβ-index.

In both BioFINDER and ADNI, a range of Aβ-index values were observed for a given SUVR level. Despite identical SUVR levels, interpreted as indicating no difference in overall brain Aβ load, differences in the topography of Aβ pathology can be seen between subjects. These intersubject differences may explain the variability seen in Aβ-index for a given SUVR value. Though Aβ-index as a global metric of Aβ pathology may be of greatest interest from a clinical standpoint, further work addressing whether Aβ-index can in fact also provide information about Aβ pathology within different brain regions may be of interest, particularly with respect to the validation of PET based Aβ staging schemes[26, 41] and with an eye to testing

this approach with tau PET. The finding that Aβ-index values were only significantly different when comparing between advanced Aβ phases (3 vs 4 and 4 vs 5)—as for SUVR—however, is in line with earlier work showing that [^{18}F]flutemetamol PET primarily detects Aβ pathology in cases with advanced plaque pathology (i.e. Aβ phase $\geq$ 4).[42]

Two previous studies have used adaptive[43] and principal component derived templates[44] with Aβ-PET. In the study by Lundqvist et al.[43] using [^{18}F]flutemetamol PET, intercept and slope images were generated using linear regression; the slope image in combination with a weight is then used to generate a template. While the slope image is similar to our second principal component image, the principal component derived template appeared to provide greater accuracy.[7] In the study by Fripp et al.[44] an adaptive template was generated using [^{11}C]PIB and spline based transformations for the normalization step; due to the use of splines, however, the computational time of their approach exceeds six hours, in contrast to an average processing time of ~20 seconds per subject using our method. Furthermore, a novel measure termed Aβ load (Aβ$_L$) was recently presented.[24] A metric of global Aβ burden, Aβ$_L$ is calculated as a linear combination of two canonical images (nonspecific binding and a carrying capacity image representing the maximum possible concentration of Aβ).[45] Though these images and Aβ$_L$ are conceptually similar, respectively, to our principal component images and Aβ-index, in contrast to the method by Gunn et al. our method does not require the use of MRI and is several orders of magnitude faster from a per subject computational standpoint.

Due to variability in the acquisition windows used for scanning, analysis methods and ROI selection, quantitatively expressed Aβ-PET outcome data cannot currently be directly compared. In an attempt to address this, a method was proposed whereby Aβ-PET values are standardized to a 100-point scale using a linear scaling procedure.e The units of this scale are termed "Centiloids", with 0 representing the average uptake in Aβ-negative subjects and 100,

the average in patients with mild-to-moderate AD.[18] While the Aβ-index could be converted

to Centiloids via the prescribed steps, the fact that it is independent of ROI definition suggests

that it could be directly comparable between Aβ-PET tracers, without the need for conversion

to the Centiloid scale. This would require, however, that a universal adaptive template be

established by applying a principal component-based analysis to a data set comprising

existing commercial Aβ-PET tracers. Future work is required to explore this possibility.

Strengths of the present study include the use of two different Aβ-PET tracers across

three independent cohorts, a large sample size and the use of multiple standards of truth for

defining Aβ-status. Certain limitations apply as well, however. First, cases of AD dementia or

non-AD neurodegenerative disorders were not included. The close association of Aβ-index to

SUVR across a range of values, however, indicates that the relationship between these metrics

is governed by brain Aβ levels and is therefore independent of clinical diagnosis. As such,

omitting these diagnostic groups is unlikely to have affected our results. Second, the patients

in the Swedish BioFINDER study have been recruited in a consecutive fashion at three

different memory clinics, with approximately 90% of these referred by primary care

physicians. In the ADNI study, the patients were recruited from many different clinics, and

thereby represent a more selected sample. Still, the results obtained for the Aβ-PET pathology

accumulation index in both these studies are very similar. In light of findings showing that

clinic-based cohorts—such as ADNI and, to a lesser extent, BioFINDER—might have a

lower prevalence of infarcts and mixed pathologies, [46] further studies are required to validate

the use of Aβ-index in community-based cohorts. Third, we did not examine the effect of

atrophy on Aβ and SUVR. As neurodegenerative disorders such as AD are accompanied by

progressive cortical atrophy, susceptibility to partial volume effects increases which, in the

case of Aβ-PET, can diminish estimates of tracer retention.[54] While partial volume effects

were likely present to some degree in the BioFINDER and ADNI cohorts, the strong

correlation between Aβ-index and SUVR across subjects suggests that these metrics were not

differentially affected. We cannot exclude, however, that the strength of the association

between Aβ-index and SUVR may be affected by atrophy in individual cases. Though fully

quantitative measures (i.e. binding potential [BP_{ND}]) or distribution volume ratio [DVR])

would have been preferable over the use of SUVR—due the sensitivity of SUVR to cerebral

blood flow induced changes in tracer kinetics[47]—BP_{ND} and DVR require the use of dynamic

data, which was not available. Lastly, in addition to the lack of *antemortem* diagnosis (beyond

the presence or absence of dementia), there was considerable variation in the PET to *post-

mortem* delay (scan-to-death time interval) in the end-of-life cohort; though this may have

resulted in changes in Aβ burden not captured by the initial [^{18}F]flutemetamol studies, our

findings with the Aβ phases and prior work showing that the PET-to-death time interval did

not affect the diagnostic performance of [^{18}F]flutemetamol,[48] argues against this being the

case.

Conclusions

Though the proposed Aβ-index showed a tight association to SUVR values and similar

discriminative and predictive performance, it carries an advantage over SUVR in that it does

not require the definition of target and reference regions. The Aβ-index may therefore prove

simpler to implement in clinical settings. Further work is needed to address whether the Aβ-

index could be implemented as a common measure across different Aβ tracers and analytical

approaches, without the need for standardization to the Centiloid scale. An Aβ-index driven

approach would require the availability a of hybrid template derived from all three

commercially available Aβ tracers. This template is under development and will be the focus

of future work.

Figure legends

Figure 1. Flow diagram providing an overview of the MRI-free normalization method

Shown are the steps required to generate the adaptive template and to spatially normalize the input Aβ-PET image. In the upper right corner, the role of the Aβ-index is illustrated: the first principal component image is combined with a weighted version of the second component image, yielding a template image optimal for the input image.
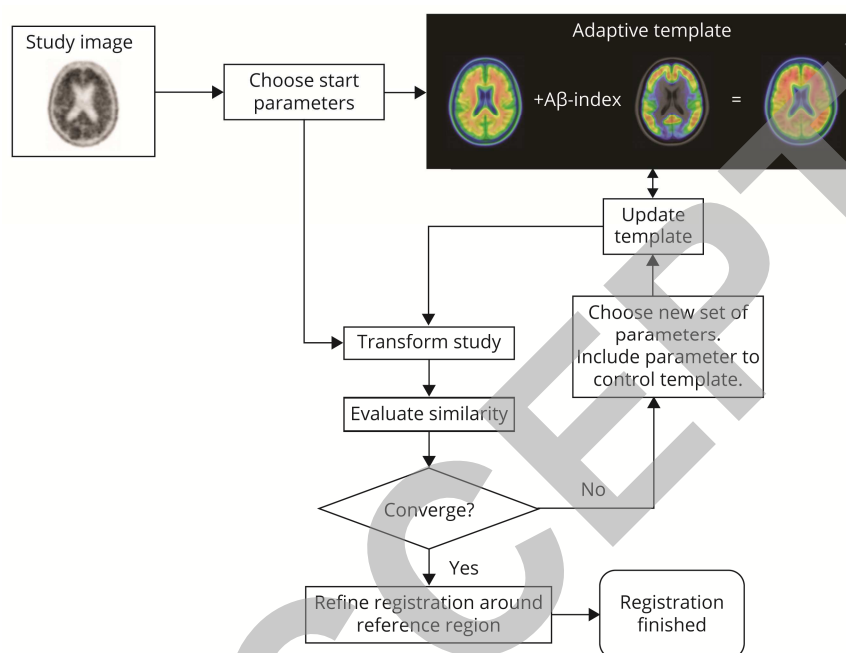
Figure 2. Scatterplots showing the relationship between Aβ-index and SUVR

The association between Aβ-index and SUVR is shown for [18F]flutemetamol (BioFINDER cohort; A and C) and [18F]florbetapir (ADNI cohort; B, D) PET, with Aβ status defined using visual read (A, B) and CSF Aβ42/Aβ40 (C, D) as standards of truth for Aβ status.
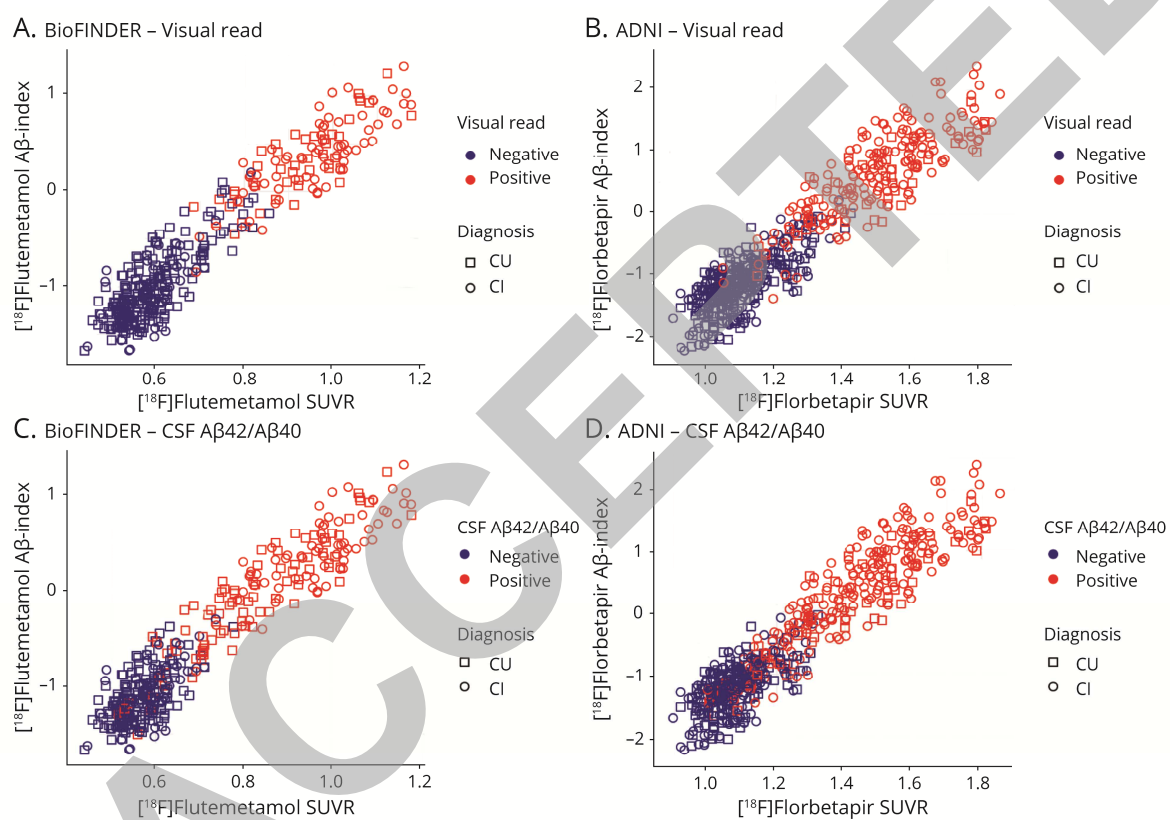
Figure 3. Receiver operating characteristic plots using Aβ-index and SUVR

Receiver operating characteristic plots for [^{18}F]flutemetamol (BioFINDER cohort; A, C) and [^{18}F]florbetapir (ADNI cohort; B, D) for distinguishing Aβ-negative and Aβ-positive subjects using visual read (A, B) and CSF Aβ42/Aβ40 (C, D) as standards of truth for Aβ status.
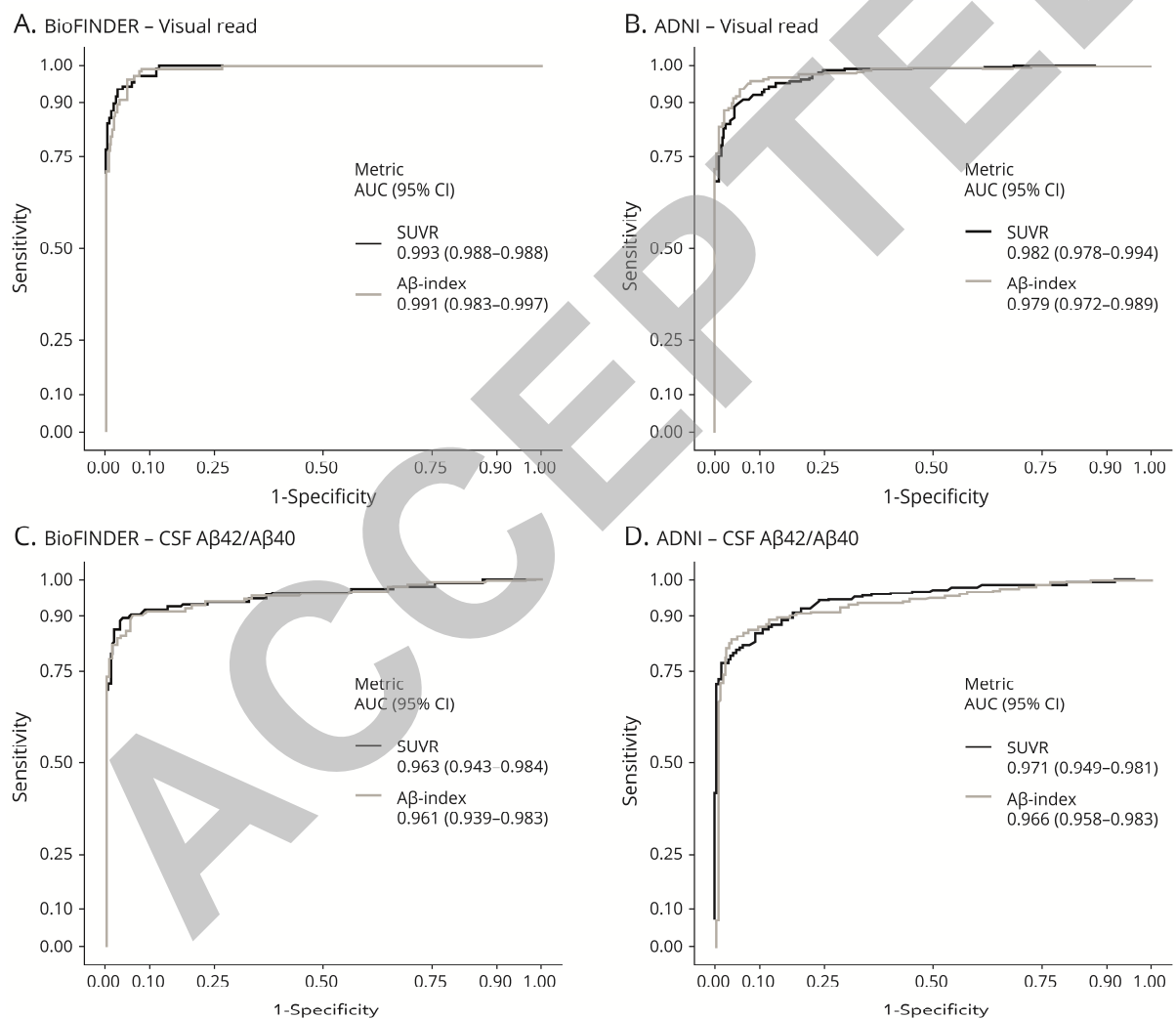
Figure 4. Findings from the [^{18}F]flutemetamol phase 3 end-of-life cohort

Receiver operating characteristic plots for distinguishing Aβ-negative and Aβ-positive

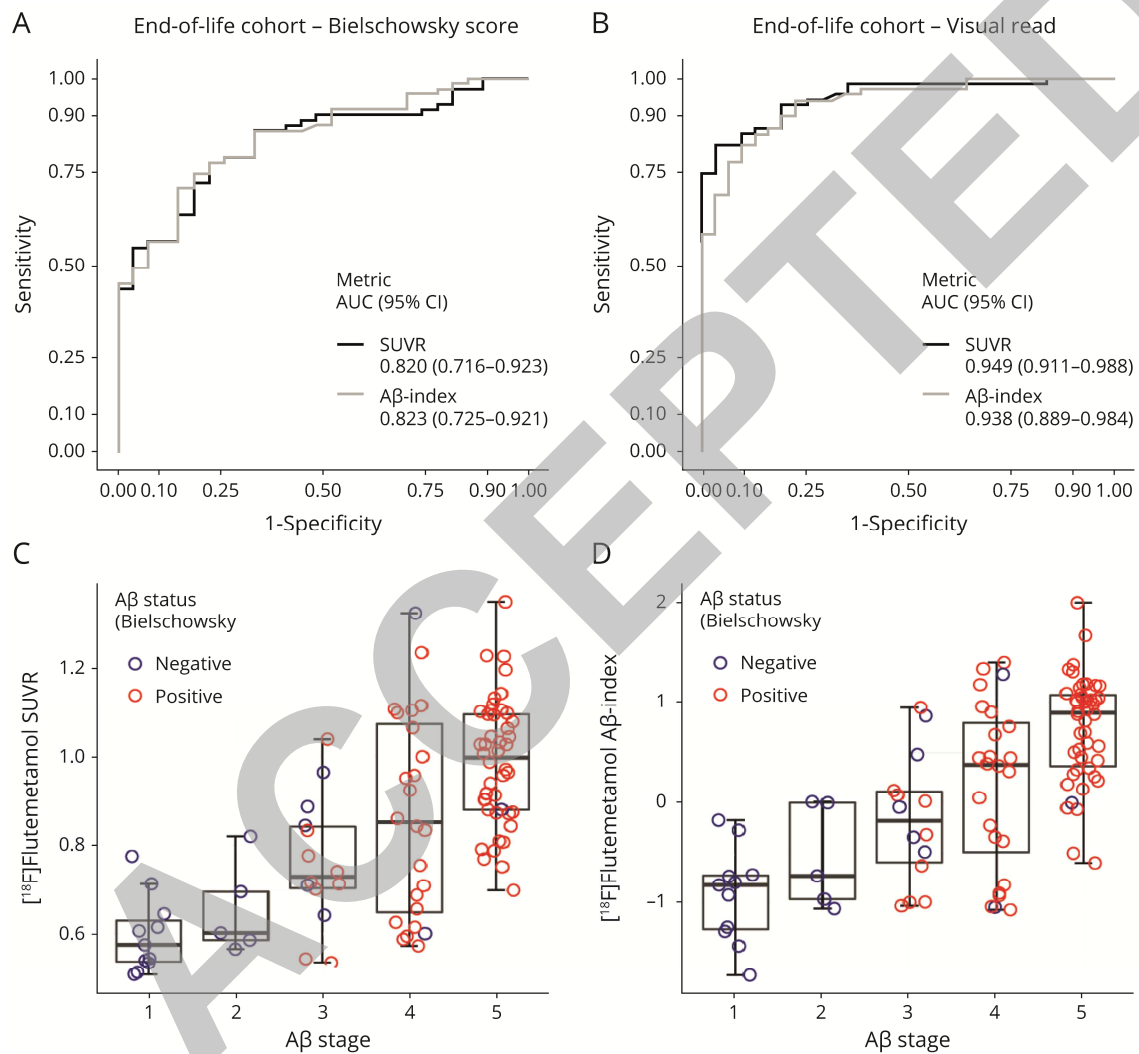subjects using the Bielschowsky silver stain score and visual read are shown in A and B,

respectively.

Table 1. BioFINDER and ADNI cohort characteristics

	BioFINDER		ADNI	
Characteristic	CU	CI	CU	CI
N	251	141	246	383
Age, y, mean (SD) [range]	71.92 (5.15) [59, 85]	70. 91 (5.58) [60, 80]	72.16 (5.79) [56, 89]	71.05 (7.53) [55, 89]
Sex, Male/Female (% Male)	109/142 (43%)	88/53 (62%)	121/125 (49%)	208/175 (54%)
Education, years	12.17 (3.39)	11.14 (3.29)	16.82 (2.49)	16.3 (2.59)
MMSE score	28.79 (1.23)	27.26 (1.71)	29.05 (1.18)	28.11 (1.73)
APOE ε4 + n %	91 (36%)	66 (47%)	51 (28%)	221 (58%)
CSF Aβ42/Aβ40 + n %	71 (28%)	88 (62%)	71 (29%)	211 (55%)
Aβ PET, visual read + n %	48 (19%)	79 (56%)	51 (21%)	185 (48%)
Aβ PET, SUVR	0.65 (0.15)	0.81 (0.21)	1.17 (0.19)	1.28 (0.24)
Aβ PET, Aβ-index	-0.79 (0.63)	-0.21 (0.78)	-0.82 (0.84)	-0.23 (0.95)

Table 2. End-of-life cohort characteristics

Characteristic	Dementia	No-dementia	All subjects
N	85	15	100
Age, y, mean (SD) [range]	82.71 (7.91) [60, 96]	78.40 (11.09) [60, 93]	82.10 (8.54) [60, 96]
Sex, Male/Female (% Male)	32/53 (38%)	5/10 (33%)	42/58 (58%)
Dementia, n %	85 (100%)	0 (0%)	85 (85%)
Bielschowsky silver stain	2.00 (0.79)	1.31 (1.13)	1.90 (0.88)
Thal Aβ phase, n, 1/2/3/4/5	6/4/10/21/44	5/1/4/2/3	11/5/14/24/46
Braak tau stage, n, I-II/III-IV/V-VI	14/17/50	4/8/1	18/25/51
CERAD, N/S/M/F	4/18/26/37	5/1/6/2	9/20/32/39
Aβ PET, visual read + n %	67 (79%)	5/10 (33%)	72 (72%)

Aβ PET, SUVR	0.88 (0.20)	0.79 (0.22)	0.87 (0.21)
Aβ PET, Aβ-index	0.31 (0.81)	-0.19 (0.89)	0.23 (0.84)
Scan-to-death, days	234.95 (215.48)	234.13 (189.26)	234.83 (210.86)

Abbreviations: N/S/M/F=None/Sparse/Moderate/Frequent

Appendix 1: Authors

Name	Location	Contribution
Antoine Leuzy, PhD	Lund University, Malmö, Sweden	Design and conceptualized study; analyzed the data; performed the statistical analyses. Drafted the manuscript for intellectual content
Johan Lilja, PhD	Lund University, Malmö, Sweden	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Christopher J. Buckley, PhD	GE Healthcare Life Sciences, Amersham, UK	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Rik Ossenkoppele, PhD	Lund University, Malmö, Sweden; VU University Medical Center, Amsterdam, The Netherlands	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Sebastian Palmqvist, MD, PhD	Lund University, Malmö, Sweden; Skåne University Hospital, Lund, Sweden	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Mark Battle, MSc	GE Healthcare Life Sciences, Amersham, UK	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Gill Farrar, PhD	GE Healthcare Life Sciences, Amersham, UK	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Dietmar R. Thal, MD	Leuven Brain Institute, Leuven, Belgium; UZ-Leuven, Leuven, Belgium	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Shorena Janelidze, PhD	Lund University, Malmö, Sweden	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content

Erik Stomrud, MD, PhD	Lund University, Malmö, Sweden; Skåne University Hospital, Lund, Sweden	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Olof Strandberg, PhD	Lund University, Malmö, Sweden	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
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