Abnormal amyloid load in mild cognitive impairment: The effect of reducing the PiB-PET threshold

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Running title: The effect of 11C-PiB PET threshold changes

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Abstract

Background and purpose: In vivo detection of β-amyloid (Aβ) plaques in Alzheimer’s disease (AD) is now possible with $^{11}$C-PiB positron emission tomography (PET). Conventionally, a cortical:cerebellar PiB uptake ratio threshold of 1.4-1.5 has been used to categorise at-risk subjects as ‘amyloid-positive’ and ‘amyloid-negative’. It has been suggested that this threshold is too conservative and may miss early amyloid pathology. We investigated the relationship between conventional and lower baseline $^{11}$C-PiB PET thresholds for raised amyloid load and the subsequent clinical and radiological progression of mild cognitive impairment (MCI) cases longitudinally.

Methods: We serially determined the cortical amyloid load with $^{11}$C-PiB PET of 44 MCI subjects over two years and compared findings with those for 12 healthy controls (HC) and 5 AD cases.

Results: Twenty-four subjects were classified as normal Aβ load at baseline with mean cortical PiB standard uptake value ratios (SUVR) between 1.2-1.5. Their cognitive status remained stable over time. Three of these cases increased their amyloid load above a threshold of 1.5 over two years. Twenty-seven ‘raised Aβ’ MCI cases with baseline cortical SUVRs above 1.5, showed deteriorating cognition. 50% of these cases converted clinically to AD during the follow-up period.

Conclusion: Use of a PiB SUVR threshold of >1.5 to categorise subjects as having raised amyloid missed 14.3% of MCI cases who likely had Thal stage 1 or 2 pathology and showed a progressive Aβ load increase over two years. Lowering the threshold for abnormally raised Aβ to 1.3 abolished all false negatives but resulted in 75% of HCs being falsely diagnosed as raised amyloid subjects.
Introduction

Alzheimer’s disease (AD) is the most common form of dementia and is characterised clinically by progressive impairment of cognitive function and altered behaviour in fully conscious subjects. AD is characterised histopathologically by the presence of cerebral extracellular fibrillary β-amyloid protein (Aβ) deposits (plaques) and tau neurofibrillary tangles (NFT). Identifying subjects with Aβ deposition as early as possible is important to better understand the time course of AD pathologies and for the development of early therapeutic interventions.

Positron emission tomography (PET) imaging of Aβ fibrils has now become possible in vivo using markers such as carbon-11 labelled Pittsburgh compound-B ([11C-PiB]), a neutral thioflavin T analogue which crosses the blood-brain barrier and binds to Aβ plaques in post-mortem AD brain slices. Correct classification of individuals as raised and normal Aβ load with amyloid PET is clinically important as it can help support or reject a clinical diagnosis of AD. PET can also detect aggregated Aβ pathology in cases at higher risk of dementia such as subjects with mild cognitive impairment (MCI) or who carry susceptibility genes. However, different PET signal thresholds for defining amyloid-positivity have been used across centres depending on the camera used and analytical approach for modelling tracer uptake.

The pathological distribution of senile amyloid plaques has been described and rated according to Thal staging based on histochemical methods in 5 phases, symptomatic AD cases usually have a phase 3-5 extent of amyloid deposition. Conventionally, cortical:cerebellar PiB standard uptake ratios (SUVRs) above 1.4-1.5 measured 40-60 or 60-90 minutes after intravenous tracer administration have been taken as a threshold for defining raised Aβ load in subjects. However, it has been suggested by Villeneuve and co-workers that using such a high PiB SUVR threshold may categorise early
Thal phase 1 and 2 amyloid cases as normal and that lower, more conservative thresholds are needed in order to detect early AD pathology. Thal and colleagues concluded that conventional amyloid PET analyses detect only phase 3 – phase 5 stages of Aβ pathology as having raised amyloid load in preclinical, prodromal, and established AD cases.\textsuperscript{14}

The aim of our longitudinal PET study was to investigate how a cohort of MCI cases categorised as either high amyloid load or normal using both conventional and lowered baseline PiB SUVR thresholds subsequently progressed both clinically and with regard to changes in amyloid load over the following two years. In view of the possibility of missing early Thal phase 1 and 2 cases, the longitudinal findings for MCI subjects with baseline cortical PiB SUVR values lying between 1.2-1.5 were particularly monitored.

**Methods**

**Study subjects**

Forty four MCI subjects and 12 healthy controls (HC) were enrolled into our longitudinal study, recruited from Dementia/Memory clinics in Denmark and by advertisement. MCI subjects with a history of worsening memory complaints corroborated by an informant were recruited for the study, as reported previously.\textsuperscript{5} Subject age ranged between 50-85 years. Enrolled subjects had a modified Hachinski Ischemic Scale score $\leq 4$, and a Geriatric Depression Scale (version with 15 questions) score $\leq 6$. None had a neurological or psychiatric disorder, were taking drugs associated with cognitive impairment or had any contraindication for magnetic resonance imaging (MRI). The HCs had no complaints of memory decline.
Five AD subjects were recruited from Dementia clinics and were diagnosed according to the ICD-10 Alzheimer’s disease criteria\(^1\); they fulfilled the same inclusion and exclusion criteria as MCI subjects.

All subjects underwent \(^{11}\text{C-PiB}\) PET and were assessed with a standard neuropsychological test battery along with general cognition (Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating (CDR) scores).

The study was approved by the Central Denmark Region Committees on Health Research Ethics in accordance to the Declaration of Helsinki. All subjects provided written informed consent prior to participating.

**Image processing**

MRI and PET were acquired as previously described.\(^5\) High-resolution 3D T1-weighted magnetic resonance imaging (MRI) was performed on a 3T MRI scanner (*Skyra Magnetom, Siemens, Erlangen, Germany*) and used for structural coregistration of PET and to define cerebral grey matter masks. \(^{11}\text{C-PiB}\) PET scans were acquired with a High Resolution Research Tomograph (*ECAT HRRT; CTI/Siemens, Knoxville, TN*) using a previously published scan protocol.\(^5\) A target dose of 400 MBq \(^{11}\text{C-PiB}\) was intravenously injected over 10 seconds, followed by a 10 ml saline flush. PET emission data were acquired for 50 minutes in list mode 40-90 minutes post injection.

MINC software ([http://en.wikibooks.org/wiki/MINC](http://en.wikibooks.org/wiki/MINC))\(^{16}\) was used to segment MRI volumes into images of cerebral grey (GM) and white (WM) matter and cerebrospinal fluid (CSF).\(^{17}\) GM masks were convolved with a probabilistic atlas\(^{18}\) to define regions of interest (ROIs) on each individual’s GM template. The spatially normalized PiB images were summed from 60-
90 minutes and voxel signals were divided by the mean signal from the cerebellar GM to generate PiB SUVR images. To minimize spill-in/spill-out contamination, images were not smoothed prior to sampling activity from the composite cortical volume of interest. The composite cortical PiB SUVR was computed as a volume-weighted average of frontal, lateral, posterior temporal, precuneus, parietal and posterior cingulate cortical ROIs.

**Statistical analysis:**

Data were statistically interrogated using STATA version 14.2 (StataCorp LP, Texas, USA). Group differences in non-imaging variables were assessed using t-tests, Pearson’s $\chi^2$ tests for categorical variables, and Wilcoxon rank-sum tests for skewed ordinal variables. P-values $<$ 0.05 were considered statistically significant.

**Determining amyloid status:**

The initial threshold used in this report to assign MCI cases to raised and normal amyloid load categories was a composite cortical:cerebellar PiB SUVR of 1.5 as the baseline ratio distribution was bimodal with a clear separation between raised MCI and control ranges at this ratio. Following this initial analysis, the effects of lowering the SUVR threshold to 1.3 to categorise groups as raised and normal amyloid was examined. Assignment of individuals to a raised or normal amyloid load group was then compared with their clinical and PiB PET outcomes after longitudinal follow-up for two years.
Results

Demographics and cognitive ratings are presented in Table 1. Forty-four MCIs and 12 HCs had baseline PiB PET and 24 of these subjects (16 MCIs and 8 HC; mean baseline age 66 years; range 50-79 years), had baseline composite cortical PiB SUVRs ranging between 1.2-1.5. Of these, 15 MCIs and 6 HCs completed their 2-year follow-up. Twenty-seven MCI cases had a raised baseline composite cortical SUVR above 1.5 and 23 of these returned for their 2-year follow-up PiB PET and neuropsychological assessment (figure 1).

When we surveyed the low PiB-uptake cases with baseline composite cortical SUVRs below 1.5, one subject was excluded from the analysis. Although initially diagnosed as MCI, this subject developed clinical progressive supranuclear palsy (PSP) during follow-up, which is usually due to a tauopathy rather than Alzheimer’s pathology.

Over two years 39 MCIs in total returned for their 2-year follow-up (24.5 ± 1.8 months). An overall 0.15 ± 0.26 increase in mean PiB SUVR was seen across all 39 MCIs over two years (P=0.0008), detailed regional cortical SUVR values are presented in table 2. A non-significant mean increase (0.072 ± 0.14, P=0.15) was observed over two years for the HC group, in line with previous findings. Individual changes and grouping of all subjects are presented in figure 1.

Normal PiB group (SUVRs 1.2-1.5):

Individual changes in composite cortical PiB SUVR for the normal PiB cohort (MCIs and HCs) are shown in figure 2A. Interrogating the combined composite cortical PiB SUVRs for these 21 normal PiB SUVR subjects with a paired t-test showed no significant mean change over two years (P=0.08).
However, three subjects (3 MCIs) individually changed their PET status over two years from a normal composite cortical PiB SUVR below 1.5 to one raised above 1.5 (Fig. 2A). At baseline, these three subjects all fell in the SUVR range of 1.3-1.5 and, of these three, one MCI showed an increase in SUVR of more than 20% over two years. This subject also showed deteriorating cognitive rating over two years (MMSE 26 to 24, MoCA 20 to 19, CDR-SOB 3 to 4.5) and was an APOE4 carrier. The other two MCI cases also showed SUV increases greater than the reported 7% test-retest variability (9 and 11%),\textsuperscript{21,22} although their cognitive scores stayed stable.

1.4-1.5 SUVR subgroup (figure 2B):

Four subjects had baseline PiB SUVRs lying between 1.4-1.5 (2 MCIs and 2 HC) - the two MCIs have been described above. Changes in the two HC SUVRs over two years were within the range of test-retest variability.

1.3-1.4 SUVR subgroup (figure 2C):

Nine subjects (8 MCIs and 1 HC), Fig. 2C, fell in a PiB SUVR range of 1.3-1.4. The majority of their SUVRs stayed stable and changes seen were in the range of test-retest variability. Three MCIs had SUVRs that increased by 8 % or more but only 1 MCI, reached a threshold of 1.5 - all were cognitively stable.

Below 1.3 SUVR subgroup (figure 2D):

Eight subjects fell in this subgroup and two - both HCs - showed an 8-9% increase in SUVR over two years (Fig. 2D). All the PiB-SUVRs remained below 1.4, and the cognitive status of the group remained stable.
The mean cognitive ratings (MMSE, CDR-SOB, MoCA) remained stable for the normal cohort (MCIs and HC) with PiB SUVRs 1.2-1.5 over the 25.8 ± 3.1 months follow-up assessments (P=0.07 for MoCA) (Figure 3). The three subjects whose PiB SUVRs rose above a 1.5 threshold over two years are marked with unfilled triangles in figures 2 and 3. Two of these three had stable cognitive ratings. The third subject showed a significantly lower cognitive score along with their significant increase in amyloid load. A fourth subject in the 1.2-1.5 PiB SUVR group also showed a significant cognitive decline but their amyloid load remained stable. Their worsening cognition, therefore, may reflect the presence of a pathology other than AD.

High PiB Group (PiB SUVR >1.5):

Twenty-seven of our 44 MCIs had a baseline composite cortical SUVRs raised above 1.5 and 23 (85%) of these returned for follow-up PiB PET and neuropsychological assessment after 24.3 ± 1.2 months (Table 1). Four of our 12 HC with normal cognitive scores had PiB SUVR values raised above 1.5 at baseline and these increased over time suggestive of the presence of preclinical AD. This finding is in line with previous reports. Twenty-seven MCI cases with raised SUVRs above 1.5 deteriorated significantly in their mean cognitive ratings (MMSE, MoCA and CDR SOB) over two years and the mean PiB SUVR value for this group increased significantly (mean 0.211 ± 0.323 SUVR (8.4 %); P=0.0048) - Table 1. The ApoE status was available for all but two of our subjects. Seventeen (63%) raised PiB subjects were carriers of the ApoE4 allele compared with only 4 (25 %) of the normal PiB group.
Figure 1 shows raised PiB group SUVR values over time in comparison with the normal PiB SUVR HC and AD cases. There was a clear SUVR separation of the raised and normal PiB MCI subgroups when using an SUVR threshold of 1.5 for abnormality at baseline. In our AD comparator group, none of the subjects had an SUVR below 2.0.

Converters:

Over two years, 13 (56%) of the 23 MCI subjects who returned for follow-up from the raised PiB group converted to clinical AD diagnosed according to ICD-10 criteria. The changes in PiB SUVRs for the converters are seen in Fig. 1. All but one of the AD converters, had a baseline PiB SUVR above 2.0 and nine (69%) were ApoE4 carriers.

There was a difference in the prevalence of raised and normal PiB SUVR subjects recruited from dementia clinics and advertisements. Seventy-four percent of the raised PiB group subjects were recruited from Dementia clinics and only 26 % by advertisement whereas only 35 % of the normal PiB group were recruited from Dementia clinics and 65 % came via advertisement. Sixty-nine percent of MCIs that converted to AD were recruited from a Dementia clinic.

Discussion

A composite cortical SUVR value of 1.5 completely separated the normal range of MCI PiB SUVRs from the range of Alzheimer PiB SUVRs. The MCI subjects fell into two clear groups with raised and normal PiB SUVR using a 1.5 threshold for abnormality. However, because of the risk that some of the MCI cases with normal PiB SUVRs 1.2-1.5 may have had
occult Thal stage 1 or 2 amyloid we investigated the effect of lowering the threshold for abnormally raised amyloid from 1.5 to 1.3 and followed these subjects for two years. We reasoned that MCI cases with possible early amyloid deposition corresponding to Thal stages 1 and 2 in our normal PiB uptake subjects would show increasing PiB SUVRs, possibly rising above our threshold of 1.5, over a two-year time period.

We examined the changes in amyloid load and cognitive ratings over two years for 15 MCI subjects who had cortical PiB SUVRs between 1.2 and 1.5 and found that 10 of the 15 MCIs in this group showed no significant change in their amyloid load (≤8 % increase)\(^1\) or cognitive status. This suggests that early prodromal AD in these ten cases was not being missed using a 1.5 SUVR threshold. However, three normal PiB uptake MCIs, who fell in the SUVR range of 1.3-1.5, had PiB SUVRs that increased to above 1.5 over two years. Here we may have missed early AD pathology by using an SUVR threshold of 1.5 – one of these three MCIs had a baseline composite PiB SUVR on the borderline of 1.5. All the HCs with normal PiB SUVRs remained stable. Overall, the use of a PiB SUVR threshold of 1.5 led to 85.7 % - (18 of 21) of the low PiB subjects being assigned a ‘correct’ amyloid normal diagnosis based on a two-year follow-up findings.\(^1\) All the 27 MCI cases who were categorised as amyloid positive with PiB SUVRs above 1.5 continued to show raised amyloid status and retained their diagnosis of prodromal Alzheimer’s disease.

Three other cases with normal amyloid levels (2 MCIs and 1 HC) increased their cortical SUVRs over two years to a greater extent than could be explained by test-retest variability (>8 %),\(^1\)\(^2\) though none reached a PiB SUVR threshold of 1.5 (fig. 2A). It is possible that with a longer follow-up these cases would have reached our 1.5 threshold and have been recategorized as raised PiB SUVR and that they represent baseline Thal 1 or 2 phases.\(^1\)
Against this conclusion, however, was the finding that their cognitive status did not deteriorate.

*Raising the threshold to above 1.5 – say 1.6-1.8 – does not improve specificity by reducing false positives, but sensitivity decreases as the risk of missing raised amyloid cases increases, in addition to categorising one clinical AD subject as normal (figure 1).*

Dropping the PiB threshold from 1.5 to 1.4 eliminated two of the three potential false negatives, but led to a further two HCs being scored as having raised amyloid. This would lead to a total of 6 out of our 12 HCs (50 %) becoming categorized as having raised PiB, a higher prevalence than reported by other series.\(^{20,23–25}\)

Dropping the PiB SUVR threshold further to 1.3 eliminated all the potential false negatives in our low PiB SUVR group, but 9 out of the 12 of the HCs (75%) now became scored as having raised amyloid. *Seven (58 %) of the normal PiB SUVR MCIs also became incorrectly assigned as having raised amyloid based on follow-up clinical outcome. What is clear, however, is that baseline assignment of MCI cases to raised or normal amyloid categories becomes questionable if their PiB SUVR values lie close to a threshold value of 1.5 and both imaging and clinical follow-up is required in these borderline cases.\(^{6,27}\)* This conclusion of course applies to findings using an HRRT PET camera. The optimal threshold for dividing raised and normal PiB SUVRs is likely to be lower - say 1.4 – for centres using a lower resolution PET-CT.

In this study we focussed on older MCI subjects. A PiB SUVR threshold of 1.5 to delineate raised amyloid deposition may be too high when dealing with younger subjects. We also used a time window of 60-90 minutes rather than 40-60 minutes as used in some centres. A 60-90 minute window will lead to a higher threshold for separating raised and normal PiB SUVRs as the SUVR curves for PiB are still rising at 40 minutes.\(^{28}\) Additionally, PiB uptake by AD
cases is more prolonged than in HCs and plateaus later for subjects with significant PiB uptake. The choice of time window thus is dependent on several parameters including the scanner type, the injected dose and the population of interest. The raised PiB MCI group showed a significant deterioration in their mean cognitive scores over two years. Conversion to AD over time did not correlate with levels of amyloid load as reflected by cortical SUVRs. The majority (two thirds) of subjects in the raised PiB group were carriers of the ApoE4 allele as were 70% of the converters to AD, whereas only 25% of the normal PiB MCI subjects were ApoE4 carriers. One of our subjects clinically converted to AD with a PiB SUVR of 1.6 at baseline, which is low compared with all our other converters and showed no SUVR change at follow-up. This case was a carrier of the ApoE4 gene. Conversion of MCI to AD is based on clinical criteria, such as loss of independence and progressing cognitive deficits. Conversion is, therefore, an individual judgement and this could have led to a questionable AD classification here. Alternatively, the subject may have had other pathology such as a tauopathy. The raised PiB SUVR group showed a mean increase in PiB SUVR over time. Some of these individuals showed decreases in PiB SUVR but these were all within the range of test-retest variability (<7 %) with one exception where a decrease of 12 % was seen. The cerebellar reference region activity for this subject remained stable over time.

A limitation of our study is the absence of partial volume corrections for atrophy effects on PIB-SUVRs. Atrophy may have acted to lower PiB SUVRs by a few percent. No correlation was seen between the changes in PiB SUVR and changes in composite cortical ROI volume. Our use of a high resolution scanner will also have helped to minimise effects of atrophy over time.
Our longitudinal PiB PET study on MCI cases suggests that, while the use of a current cortical SUVR threshold of 1.5 to define raised amyloid may lead to occasional false negatives, over 80% of cases are correctly assigned to raised or normal amyloid categories. A lowering of the threshold eliminated false negatives but resulted in a high percentage of false positive cases and reduced the specificity of identifying true negatives. Where cases have PiB SUVRs close to the cut off level of 1.4-1.5 then follow-up is required to make a confident assignment to an amyloid positive or negative status. Overall setting an SUVR threshold is a trade-off between eliminating false negatives generated and generating false positives by lowering the threshold in our series.
References


Table 1: Participant characterisation

<table>
<thead>
<tr>
<th></th>
<th>MCI – normal PiB</th>
<th></th>
<th>MCI – raised PiB</th>
<th></th>
<th>Healthy control</th>
<th></th>
<th>MCI (total)</th>
<th></th>
<th>AD</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline (n=17)</td>
<td>Follow up (n=16)</td>
<td>Baseline (n=27)</td>
<td>Follow up (n=23)</td>
<td>Baseline (n=12)</td>
<td>Follow up (n=10)</td>
<td>Baseline (n=44)</td>
<td>Follow up (n=39)</td>
<td>Baseline (n=5)</td>
</tr>
<tr>
<td>Age, years</td>
<td>66.2 ± 8.3</td>
<td>68.3 ± 8.5</td>
<td>73.3 ± 6.1</td>
<td>75.1 ± 5.9</td>
<td>68.8 ± 5.2</td>
<td>72.5 ± 4.4</td>
<td>70.6 ± 7.8</td>
<td>72.3 ± 7.8</td>
<td>96.8 ± 9.9</td>
</tr>
<tr>
<td>Males/females</td>
<td>9/8</td>
<td>9/7</td>
<td>9/18</td>
<td>7/16</td>
<td>7/12</td>
<td>5/10</td>
<td>26/18</td>
<td>23/16</td>
<td>3/2</td>
</tr>
<tr>
<td>Education, years</td>
<td>11.9 ± 3.5</td>
<td>12.5 ± 3.0</td>
<td>13.3 ± 2.5</td>
<td>12.3 ± 2.5</td>
<td>12.3 ± 3.2</td>
<td>11.1 ± 2.7</td>
<td>11.1 ± 2.7</td>
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<td></td>
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<tr>
<td>MMSE</td>
<td>27.8 ± 1.8</td>
<td>26.5 ± 2.5</td>
<td>24.3 ± 3.8</td>
<td>28.2 ± 1.3</td>
<td>28.2 ± 1.3</td>
<td>0.21</td>
<td>27.2 ± 1.8</td>
<td>25.2 ± 3.4</td>
<td>0.0002*</td>
</tr>
<tr>
<td>CDR sum-of-boxes</td>
<td>1.0 [0.5; 2.5]</td>
<td>1.25 [0.0; 7.0]</td>
<td>5.5 [0.0;10.0]</td>
<td>&lt;0.0001*</td>
<td>0.0 [0.0; 0.0]</td>
<td>0.0 [0.0; 0.0]</td>
<td>0.5</td>
<td>1.5 [0.0; 4.0]</td>
<td>&lt;0.0001*</td>
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<tr>
<td>MoCA</td>
<td>25.7 ± 2.8</td>
<td>24.8 ± 3.7</td>
<td>23.6 ± 3.8</td>
<td>21.4 ± 4.8</td>
<td>26.5 ± 1.6</td>
<td>25.3 ± 2.8</td>
<td>0.33</td>
<td>24.4 ± 3.2</td>
<td>18.2 ± 5.7</td>
</tr>
<tr>
<td>PiB dose, MBq</td>
<td>410 ± 24.5</td>
<td>418 ± 14.5</td>
<td>367 ± 78</td>
<td>390 ± 56</td>
<td>422 ± 27.5</td>
<td>401 ± 30.3</td>
<td>0.09</td>
<td>384 ± 66</td>
<td>416 ± 18</td>
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<tr>
<td>PiB SUVR</td>
<td>1.325 ± 0.07</td>
<td>1.4 ± 0.15</td>
<td>2.53 ± 0.53</td>
<td>2.71 ± 0.51</td>
<td>1.49 ± 0.32</td>
<td>1.60 ± 0.44</td>
<td>0.15</td>
<td>2.06 ± 0.73</td>
<td>3.14 ± 0.88</td>
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<tr>
<td>Apoe E4, n (%)</td>
<td>4 (24 %)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 (25 %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17 (62 %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16 (69 %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (27 %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (22 %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21 (50 %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20 (51 %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (30 %)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Follow up (month)</td>
<td>24.8 ± 2.5</td>
<td></td>
<td>24.3 ± 1.2</td>
<td></td>
<td>26.1 ± 3.8</td>
<td></td>
<td>24.5 ± 1.8</td>
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Table 1: Participant characterisation. Normal and raised PiB defined as below and above 1.5 SUVR, respectively. Normally distributed data are presented in mean ± SD. Not normally distributed data are presented in median and [range]. n = number; MMSE = minimental state examination; CDR = clinical dementia rating; MoCA = Montreal Cognitive Assessment. P-values of paired tests between baseline and follow up. * significant P values, <sup>a</sup>2 missing values, <sup>b</sup>1 missing value, <sup>c</sup>6 missing values.
Table 2: Regional SUVR values

<table>
<thead>
<tr>
<th></th>
<th>Normal PiB group</th>
<th></th>
<th>High PiB group</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>N</td>
<td>21</td>
<td>21</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>1.35 ± 0.069</td>
<td>1.42 ± 0.17</td>
<td>2.53 ± 0.58</td>
<td>2.74 ± 0.52*</td>
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<td>Temporal cortex</td>
<td>1.17 ± 0.087</td>
<td>1.20 ± 0.10</td>
<td>1.96 ± 0.39</td>
<td>2.13 ± 0.42*</td>
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<tr>
<td>Parietal cortex</td>
<td>1.41 ± 0.096</td>
<td>1.46 ± 0.16</td>
<td>2.51 ± 0.50</td>
<td>2.72 ± 0.48*</td>
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<tr>
<td>Anterior cingulate</td>
<td>1.41 ± 0.21</td>
<td>1.50 ± 0.11</td>
<td>2.70 ± 0.63</td>
<td>2.94 ± 0.60*</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>1.46 ± 0.12</td>
<td>1.47 ± 0.19</td>
<td>2.78 ± 0.63</td>
<td>3.03 ± 0.60*</td>
</tr>
<tr>
<td>Precuneus</td>
<td>1.35 ± 0.089</td>
<td>1.42 ± 0.16</td>
<td>2.89 ± 0.69</td>
<td>3.14 ± 0.67*</td>
</tr>
<tr>
<td>Composite</td>
<td>1.33 ± 0.081</td>
<td>1.37 ± 0.14</td>
<td>2.50 ± 0.54</td>
<td>2.71 ± 0.51*</td>
</tr>
</tbody>
</table>

Table 2: Regional and composite PiB SUVR values in normal and high PiB group. N= number. The baseline to follow up time is 2 years. Data presented in mean±SD. *Statistically significant difference from baseline by two-sample t-test (p<0.05).
Figure 1: Scatterplots showing individual baseline and follow-up PiB SUVR values in the HC, MCI, and AD groups. The time-range between baseline and follow is 2 years. Blue lines and dots indicate normal-PiB cases. Red lines and dots indicate raised PiB cases. Purple dashed line in the MCI group indicates one progressive supranuclear palsy subject. Black lines in the MCI group indicate the converters to AD.
Figure 2: Changes in MCI and HC subjects in the normal PiB-group. The time-range between baseline and follow is 2 years. Full lines represent MCI subjects and dashed lines represent HC. A: The 3 subjects crossing the 1.5 threshold are marked with unfilled triangles. B: Changes in 4 subjects with baseline PiB SUVR values between 1.4-1.5. C: Changes in 8 subjects with PiB SUVR values between 1.3-1.4. D: Changes in 9 subjects with PiB SUVR values below 1.3.
Figure 3: Cognitive scores of MCI and HC subjects in the raised PiB- (circles) and normal PiB-group (triangles). Unfilled circles indicate the AD-converters amongst the raised PiB-group. Unfilled triangles indicate the three subjects who crosses the 1.5 threshold. Time-range between baseline and follow-up is 2 years. MoCA = Montreal Cognitive Assessment; CDR-SOB = clinical dementia rating – sum of boxes; MMSE = minimental state examination.