Title: Serum levels and mutual correlations of amyloid β in patients with depression.

Running title: Serum Aβ oligomer in MDD

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ABSTRACT

**Aim:** Epidemiological studies have demonstrated that depression is a risk factor for Alzheimer’s disease (AD). Although the biological mechanism underlying the link between depression and AD is unclear, altered amyloid β (Aβ) metabolism in patients with depression has been suggested as a potential mechanism. Results from previous studies of Aβ metabolism in patients with depression have been inconsistent, and Aβ polymerization, which is a crucial process in AD pathology, has not previously been assessed.

**Methods:** Serum levels of Aβ40, Aβ42, and Aβ oligomers were evaluated in 104 inpatients with major depressive disorder (MDD) and 132 healthy control individuals.

**Results:** Lower serum Aβ42 levels were observed in patients with MDD, but there was no difference in serum Aβ oligomer levels between the MDD group and the healthy control group, even in elderly subjects. Interestingly, serum Aβ oligomer levels in patients with MDD were dependent on serum Aβ42 levels, regardless of age, and this relationship was not observed in the control group.

**Conclusions:** These results suggest that Aβ42 is more prone to aggregation and polymerization in patients with depression than in healthy subjects, suggesting a possible mechanism underlying the transition from depression to AD.
Keywords: amyloid β, depression, major depressive disorder, oligomer, serum,
1. INTRODUCTION

Although epidemiological studies have demonstrated that depression may increase the risk for developing Alzheimer's disease (AD), whether depression is a risk factor for or a prodromal symptom of AD is still a matter of debate \(^1\) \(^2\). Some studies have shown that elderly patients with late-onset depression are at higher risk of developing dementia, suggesting that depression is a precursor to dementia including AD \(^3\). In support of this hypothesis, a recent study of over 10,000 participants demonstrated that the presence of depressive symptoms in the early study phase did not increase the risk for dementia, whereas their presence in later phases did carry a higher risk for dementia. In contrast, some studies (including a meta-analysis) have shown that early-onset depression increases the risk of AD \(^4\), and a systematic review suggested that depression, and especially early-onset depression, may be a risk factor for AD \(^1\). Finally, a recent systematic review including 51 studies showed that both early- or late-onset depression increase the risk of developing AD \(^2\).

AD is characterized by senile plaques and neurofibrillary tangles in the brain, and amyloid β protein (Aβ) is a major component of senile plaques. Aβ monomers are generated by proteolytic cleavage of the amyloid precursor protein by β- and γ-secretase. Aβ aggregates and polymerizes to oligomers, which eventually become
insoluble and are deposited as extracellular amyloid plaques. Aβ has two main isoforms: 
Aβ40 and Aβ42. Aβ42 is more easily polymerized and deposited in earlier stages of AD 
than Aβ40. Soluble Aβ oligomers are neurotoxic, and can be responsible for synapse 
failure. Aβ can be detected in the brain, cerebrospinal fluid (CSF), plasma and serum. 
Aβ42 levels in CSF are reported to decrease in MCI and in the preclinical phase of AD.
It has been suggested that these changes occur as a result of selective Aβ42 deposition 
in the brain. This reduction in CSF Aβ42 levels has been used to diagnose AD. 
Although plasma Aβ levels have been reported to exhibit a decrease that is correlated 
with brain Aβ levels in a mouse model of AD, results from studies of Aβ levels in the 
plasma of patients with AD have been contradictory. However, a recent study that 
measured plasma Aβ levels by immunoprecipitation coupled with mass spectrometry 
demonstrated that plasma Aβ levels (e.g., the Aβ40/Aβ42 ratio) correlated with CSF 
Aβ42 levels and amyloid deposition via Aβ positron-emission tomography (PET) 
imaging, suggesting that plasma Aβ levels may predict the burden of Aβ in the brain. 
Cohort studies of healthy older individuals have shown that a higher baseline plasma 
Aβ40/Aβ42 ratio may increase the risk of developing AD.

Previous studies of CSF and plasma/serum Aβ levels in patients with depression
have reported inconsistent results. Increased plasma Aβ42 levels and a decreased Aβ40/42 ratio have been reported in elderly patients with depression. However, decreased plasma Aβ42 levels and an increased Aβ40/Aβ42 ratio have also been reported in elderly patients with depression. A recent meta-analysis showed that the plasma Aβ40/Aβ42 ratio is higher in elderly individuals with depression than in their healthy counterparts. These studies exploring peripheral Aβ levels in patients with depression involved only elderly subjects. Thus, we investigated serum Aβ levels in a wider age range of patients, including younger subjects (< 40 years old), and found that the serum Aβ40/Aβ42 ratio was significantly higher in patients with depression than in healthy controls, even in younger patients. Moreover, we demonstrated that there is a significant negative correlation between the Aβ40/Aβ42 ratio and age at onset of depression in elderly patients, suggesting that patients with an earlier onset of depression may have a more serious alteration in Aβ metabolism. Based on the results from these studies, we hypothesized that Aβ metabolism may be affected by depression, and that this biological mechanism could explain the link between depression and AD. However, previous studies (including ours) have not assessed Aβ polymerization, which is a crucial process in AD pathology.

To better understand the contribution of Aβ, and especially Aβ polymerization, to...
the relationship between depression and AD, in this study we evaluated serum levels of Aβ40, Aβ42, and Aβ oligomers and analyzed the relationships among them in patients with depression and in healthy controls. This study was performed as part of the Juntendo University Mood Disorder Project (JUMP).

2. METHODS

2.1. Participants

A total of 130 inpatients with depression were recruited from Juntendo Koshigaya Hospital, Saitama, Japan, between June 2010 and November 2016. All patients met DSM-IV or DSM-V criteria for major depressive disorder (MDD). Patients were excluded if they had a history of other psychiatric disorders, severe or acute medical illnesses, neurologic disorders, or use of drugs that may cause psychosis or depression (n = 0). Patients showing clinical evidence of dementia or with Mini–Mental State Examination (MMSE) scores < 24 were also excluded (n = 26). After all ineligible patients were excluded, 104 inpatients with MDD (32 men, 72 women; mean age = 57.5 years; age range, 20–85 years) were enrolled in the study. Depressive symptoms were
assessed by the Hamilton Rating Scale for Depression (HAM-D). All patients were taking antidepressants at the time of the study.

A total of 132 healthy participants (65 men, 67 women; mean age = 49.3 years; age range, 16–80 years) were recruited as a control group. None of these participants had any history of depression, dementia, or other neuropsychiatric disease, or had an MMSE score < 24. Thus, all healthy participants were enrolled in this study as controls.

The study protocols were approved by the Medical Ethics Committee of Juntendo University, and were performed in accordance with the regulations outlined by the university. All participants provided written informed consent prior to participation.

2.2. Serum Aβ40, Aβ42, and Aβ oligomer measurements

Fasting blood samples were drawn into serum separator tubes and were centrifuged immediately. Serum samples were stored at −80 °C until use. Serum Aβ40 and Aβ42 levels were measured using a sandwich Aβ enzyme-linked immunosorbent assay kit (WAKO, Osaka, Japan), as described previously. The Aβ(1-40) kit uses the BAN50 monoclonal antibody, which specifically detects the N-terminal portion of human Aβ(1-16), and the BA27 monoclonal antibody, which detects the C-terminal portion of Aβ(1-40). The Aβ(1-42) kit uses BAN50 and the BC05 monoclonal antibody,
which detects the C-terminal portion of Aβ(1-42). The sensitivity was 0.019 pmol/L (dynamic range: 1.0–100 pmol/L) for Aβ40 and 0.06 pmol/L (dynamic range: 0.1–20 pmol/L) for Aβ42. The intra-assay coefficients of variation (CVs) were 4.8% at a mean of 14.2 pmol/L, 4.25% at a mean of 36.0 pmol/L, and 3.6% at a mean of 75.5 pmol/L for Aβ40, and 0.8% at a mean of 3.2 pmol/L, 0.8% at a mean of 7.4 pmol/L, and 1.0% at a mean of 16.4 pmol/L for Aβ42. The inter-assay CVs were 3.2% at a mean of 14.8 pmol/L, 1.1% at a mean of 33.6 pmol/L, and 2.5% at a mean of 75.7 pmol/L for Aβ40, and 8.3% at a mean of 3.2 pmol/L, 11.3% at a mean of 7.1 pmol/L, and 5.8% at a mean of 16.4 pmol/L for Aβ42.

Serum Aβ oligomer levels were measured using a Human Amyloid β Oligomers (82E1-specific) Assay Kit (IBL, Gunma, Japan) according to the manufacturer’s instructions. This ELISA kit detects human Aβ molecules that bind to an anti-human Aβ N-terminal antibody (82E1) via two or more epitopes (including Aβ oligomers and Aβ bound to other proteins). The sensitivity was 4.41 pmol/L. The intra-assay CVs were 5.0 % at a measurement value of 314.24 pmol/L, 2.9 % at a measurement value of 88.32 pmol/L, and 5.4 % at a measurement value of 33.66 pmol/L (n = 24). The inter-assay CVs were 3.1 % at a measurement value of 310.02 pmol/L, 5.2 % at a measurement value of 76.92 pmol/L, and 10.0 % at a measurement value of 27.39 pmol/L (n = 5).
2.3. Apolipoprotein E phenotype determination

Apolipoprotein E (ApoE) phenotypes for all samples were determined by isoelectric focusing carried out at SRL, Tokyo, Japan.

2.4. Data analysis

The age, education, and MMSE scores of participants in the MMD and control groups were compared using the two-tailed unpaired Student’s t test. The χ² test was used to compare the sex and ApoE4 variables. Serum levels of Aβ40, Aβ42, and Aβ oligomers were compared using the Mann–Whitney U test because of the skewed distribution. The relationship between serum Aβ40 or Aβ42 and Aβ oligomers were analyzed using Spearman’s rank Correlation Coefficient test. To control confounding factors, multiple regression analyses were conducted using Aβ oligomer levels as the dependent variable and age, sex, Aβ40, and Aβ42 as independent variables. The Aβ40, Aβ42, and Aβ oligomer values were log-transformed for the multiple regression analysis because of their skewed distribution. A significance level of P < 0.05 was used. Statistical procedures were performed using the Japanese version of SPSS v.21 software (SPSS Japan Inc., Tokyo, Japan).
3. Results

3.1. Sociodemographic and clinical characteristics

A detailed description of the demographic and clinical features of the study participants is shown in Table 1. The participants in the MDD group were significantly older (p < 0.001) and had a significantly lower level of education (p = 0.007) than those in the control group. There was no significant difference in MMSE scores and ApoE4 frequencies between the two groups. There were significantly more women in the control group than in the MDD group (p = 0.005).

3.2. Comparisons of serum levels of Aβ40, Aβ42 and Aβ oligomer between MDD and controls

Serum Aβ40 levels were significantly higher (p = 0.001) and serum Aβ42 levels (p < 0.001) and Aβ oligomer levels (p = 0.001) were significantly lower in patients with MDD compared with the control group (Table 1). However, these results may have been influenced by confounding factors, especially the age difference. Thus, we conducted a multiple regression analysis using the level of each form of Aβ as a
dependent variable, and age, sex, education, and group (MDD or control) as
independent variables (Table 2). The results showed that Aβ40 (p < 0.001) and Aβ42 (p
= 0.004) levels differed significantly based on the group, but that Aβ oligomer levels
were not affected by the group, after controlling age, sex, and education. This indicates
that Aβ40 and Aβ42 levels were different in the MDD group compared with the control
group, but that there was no difference in serum Aβ oligomer levels between the MDD
and control groups. When the data from the elderly subjects (> 60 years old) only were
analyzed, there was still no significant difference in Aβ oligomer levels between the two
groups (β = 0.010, p = 0.957).

3.3. Correlations between total Aβ and Aβ oligomer in MDD and controls

Serum Aβ oligomer levels showed a significantly positive correlation with serum
Aβ42 levels (R= 0.246, P < 0.001) in all subjects. In the MDD group, serum Aβ
oligomer levels showed a significantly positive correlation with Aβ42 levels (R= 0.216,
P = 0.035), however, that correlation was not shown in the control group (Table 3).

Multiple regression analysis showed that neither Aβ40 levels nor Aβ42 levels were
correlated with Aβ oligomer levels in the control group, after controlling for age and
sex. In the MDD group, Aβ40 levels were not correlated with Aβ oligomer levels, while
Aβ42 levels were positively correlated with Aβ oligomer levels ($\beta = 0.475, p = 0.022$) (Table 4).

4. DISCUSSION

The present study evaluated serum levels of Aβ40, Aβ42, and Aβ oligomers in patients with MDD and healthy individuals. We previously reported that patients with MDD had significantly lower serum Aβ42 levels $^{17,18}$ and a tendency toward higher serum Aβ40 levels compared with healthy subjects. The present study showed that participants in the MDD group had higher Aβ40 and lower Aβ42 serum levels compared with the control group, which is partly consistent with these previous results and a recent meta-analysis $^{13}$. In addition, the present study demonstrated that there was no significant difference in serum Aβ oligomers levels between patients with MDD and healthy controls, even in elderly subjects. To the best of our knowledge, this is the first study that has investigated peripheral Aβ oligomer levels in patients with depression.

Although there have been no studies of peripheral Aβ oligomer levels in patients with depression, peripheral Aβ oligomer levels have been assessed in patients with AD. Based on epidemiological data suggesting a link between depression and AD, we hypothesized that serum Aβ oligomer levels in patients with MDD would show similar trends to plasma or serum Aβ oligomer levels in patients with AD. Several previous
studies have reported higher Aβ oligomer levels in the CSF of patients with AD compared with controls, and a negative correlation between the CSF Aβ oligomer levels and MMSE scores has also been reported. In contrast, other studies have reported that there is no difference in CSF Aβ oligomer levels between patients with AD compared with control subjects. In addition, a longitudinal study demonstrated that the CSF Aβ oligomer levels decrease on an annual basis, and that this decrease is associated with cognitive decline. It has been suggested that the reason for these contradictory results is methodological differences between the studies. Studies using flow cytometry and ELISA have reported higher plasma Aβ oligomer levels in patients with AD compared with non-demented control subjects. The present study did not detect any difference in serum Aβ oligomer levels in patients with MDD compared with healthy controls, even among elderly subjects. A longitudinal study of AD and mild cognitive impairment (MCI) showed that baseline CSF levels of Aβ oligomers did not predict future conversion from MCI to AD; however, an annual decrease in Aβ oligomer levels was associated with progressive cognitive decline. This suggests that peripheral Aβ oligomer levels may not show any change until cognitive dysfunction is evident, even if this cognitive decline is a precursor to AD.
However, there was a significant positive correlation between serum Aβ42 (polymerizable isoform) and Aβ oligomers in the MDD group, but not in the control group, after controlling age and sex. That is, serum Aβ oligomer levels were dependent on serum Aβ42 levels in patients with MDD, regardless of age. This may suggest that Aβ42 is more likely to aggregate and polymerize in patients with MDD than in healthy subjects, although the reason for this and the underlying mechanism are unclear.

Hyperactivity of the hypothalamus-pituitary-adrenal axis and the resulting increase in glucocorticoid secretion are well-described in patients with depression. In addition, an association between plasma cortisol (glucocorticoid) levels and brain Aβ burden, as measured by Pittsburgh Compound B-positron emission tomography (PiB-PET), has been reported in patients with AD. Thus, it is possible that increased cortisol levels in patients with MDD may play a role in promoting Aβ42 polymerization.

The present study has several limitations. First, the ELISA kit used to measure the Aβ oligomers in this study did not contain heterophilic antibody (HA) inhibitors. Previous research has suggested that this type of ELISA method is vulnerable to HA interference, suggesting that the detected signals may have contained artifacts due to HA interference. Moreover, more than half of Aβ proteins are bound with albumin or high-density lipoprotein particles in the plasma/serum, and the ELISA method cannot
discriminate genuine toxic oligomers from non-pathological Aβ complexes. Based on these factors, it is possible that the current results regarding Aβ oligomers did not indicate pure “pathological” Aβ oligomers. However, previous studies measuring plasma oligomers using different methods (flow cytometry and ELISA) and comparing AD patients with healthy subjects have shown similar results. On the basis of these previous results, we believe that the present oligomer data indicate the relative differences between depression and healthy individuals, despite the possible presence of artifacts. Second, although most previous studies measured plasma Aβ, serum Aβ was measured in the present study. Previous studies have suggested that aggregated platelets release Aβ, as well as ADP and clusterin, which promote Aβ aggregation. Moreover, a previous study comparing plasma and serum Aβ levels reported approximately 2-fold increases in Aβ levels in serum samples, compared with plasma samples. The relationship between clusterin and Aβ aggregation may have a particular impact on Aβ oligomer levels. Based on these previous reports, the results of the present study may have been influenced by the use of serum samples. However, a previous study comparing serum and plasma Aβ levels between AD patients and healthy controls reported similar results. This previous report suggests that the results of the present study may indicate relative differences between depression and healthy individuals.
better understand the kinetics of Aβ levels in patients with depression, the CSF should be monitored in future studies. Third, all of the patients with MDD who participated in the study were on medication, primarily antidepressants. A few studies have shown that antidepressants do not influence blood Aβ levels $^{14} 15 17 16$, and one study reported that treatment with antidepressants may reduce the brain levels of Aβ, as measured by PiB-PET $^{34}$. Moreover, multiple regression analysis using daily antidepressant doses as an independent variable showed that antidepressant use did not influence Aβ oligomer levels in our cohort ($\beta = 0.239, p = 0.110$). Therefore, antidepressant use is unlikely to be a major confounding factor influencing the results. However, the influence of medication on Aβ polymerization is unknown. Thus, further studies should investigate drug-naïve patients to avoid any potential influence of antidepressant use. Finally, while we propose the relationship between glucocorticoid and Aβ levels as a possible mechanism explaining the results from this study, we did not evaluate cortisol levels. Finally, this was a cross-sectional study. A prospective follow-up study should be performed to confirm the transition from depression to AD.

In conclusion, this is the first report of peripheral Aβ oligomer levels in patients with depression. Lower serum Aβ42 levels were observed in patients with depression, but there was no difference in serum Aβ oligomer levels compared with the healthy
control group, even in elderly subjects. Interestingly, serum Aβ oligomer levels were
dependent on serum Aβ42 levels in patients with depression, regardless of age, but this
relationship was not observed in healthy subjects. These results suggest that Aβ42 is
more likely to aggregate and polymerize in patients with depression than in healthy
subjects, which could promote the transition from depression to AD. Our findings
suggest that depression may be a risk factor, not a prodrome, for AD.
ACKNOWLEDGEMENTS

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DISCLOSURE STATEMENT

The authors have no disclosures or relevant conflicts of interest.
REFERENCES


[19] Eto M, Watanabe K, Ishii K. A rapid flat gel isoelectric focusing method for the


2010; 21: 1295-301.


Table 1. Demographic and Comparison Data of MDD and Comparisons

<table>
<thead>
<tr>
<th></th>
<th>MDD (n = 104)</th>
<th>Controls (n = 132)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td><strong>Mean (SD)</strong></td>
<td><strong>P Value</strong></td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>57.5 (14.0)</td>
<td>49.3 (16.8)</td>
<td>&lt; 0.001(^a)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>32/72</td>
<td>65/67</td>
<td>0.005(^b)</td>
</tr>
<tr>
<td>Education (Years)</td>
<td>13.1 (2.5)</td>
<td>14.2 (3.0)</td>
<td>0.007(^a)</td>
</tr>
<tr>
<td>Ham-D score</td>
<td>23.9 (8.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age at Onset</td>
<td>50.3 (15.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of Depressive Episodes</td>
<td>3.0 (5.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total Duration of Medication (M)</td>
<td>53.1 (75.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total Dose of Antidepressant (mg) (^d)</td>
<td>172.0 (83.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.8 (2.7)</td>
<td>27.1 (2.5)</td>
<td>0.50(^a)</td>
</tr>
<tr>
<td>ApoE4 N/total (%)</td>
<td>20/104 (19.2)</td>
<td>26/132 (19.7)</td>
<td>0.57(^b)</td>
</tr>
<tr>
<td>Aβ40 (pmol/L)</td>
<td>27.6 (15.0)</td>
<td>20.7 (10.9)</td>
<td>0.001(^c)</td>
</tr>
<tr>
<td>Aβ42 (pmol/L)</td>
<td>3.8 (5.3)</td>
<td>5.1 (4.2)</td>
<td>&lt; 0.001(^c)</td>
</tr>
<tr>
<td>Aβ Oligomer (pmol/L)</td>
<td>28.1 (50.8)</td>
<td>51.6 (81.3)</td>
<td>0.001(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Student's *t*-Test, \(^b\) χ² Test, \(^c\) Mann-Whitney *U* Test, \(^d\) Antidepressants were converted into imipramine doses.

MDD: Major Depressive Disorder, Ham-D: Hamilton rating scale of depression, MMSE: Mini-Mental State Examination, ApoE4: apolipoprotein ε4 carrier, Aβ: amyloid β protein
Table 2. Result of Multiple Regression Analysis of Aβs

<table>
<thead>
<tr>
<th></th>
<th>Log\textsubscript{10} Aβ40\textsuperscript{a}</th>
<th>Log\textsubscript{10} Aβ42\textsuperscript{a}</th>
<th>Log\textsubscript{10} Aβ Oligomer\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β Estimate (SE)</td>
<td>P Value</td>
<td>β Estimate (SE)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.168 (0.002)</td>
<td>0.036</td>
<td>-0.371 (0.001)</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.111 (0.044)</td>
<td>0.109</td>
<td>-0.060 (0.038)</td>
</tr>
<tr>
<td>Education</td>
<td>0.073 (0.009)</td>
<td>0.346</td>
<td>0.048 (0.008)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>0.303 (0.045)</td>
<td>&lt; 0.001</td>
<td>-0.194 (0.040)</td>
</tr>
</tbody>
</table>

Aβ: amyloid β protein
\textsuperscript{a} Aβ values were transformed to log10 (Aβ) because of the skewed distributions.
Table 3: Correlations between Aβ Oligomer and age, education, Aβ40 or Aβ42 levels

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>MDD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P Value</td>
<td>R</td>
</tr>
<tr>
<td>Age</td>
<td>-0.137</td>
<td>0.036</td>
<td>-0.233</td>
</tr>
<tr>
<td>Education</td>
<td>0.060</td>
<td>0.380</td>
<td>0.073</td>
</tr>
<tr>
<td>Aβ40</td>
<td>0.009</td>
<td>0.899</td>
<td>-0.038</td>
</tr>
<tr>
<td>Aβ42</td>
<td>0.246</td>
<td>&lt;0.001</td>
<td>0.216</td>
</tr>
</tbody>
</table>

Spearman's rank Correlation Coefficient correlation coefficients.
Table 4. Result of Multiple Regression Analysis of Aβ Oligomer

<table>
<thead>
<tr>
<th></th>
<th>MDD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β Estimate (SE)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age</td>
<td>-0.020 (0.004)</td>
<td>0.888</td>
</tr>
<tr>
<td>Sex</td>
<td>0.000 (0.134)</td>
<td>0.991</td>
</tr>
<tr>
<td>Log₁₀ Aβ₄₀ᵃ</td>
<td>-0.145 (0.228)</td>
<td>0.658</td>
</tr>
<tr>
<td>Log₁₀ Aβ₄₂ᵃ</td>
<td>0.475 (0.193)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Aβ: amyloid β protein

ᵃ Aβ values were transformed to log₁₀ (Aβ) because of the skewed distributions.