

Glucocorticoid may influence amyloid β metabolism in patients with depression

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ABSTRACT

Epidemiological studies have demonstrated that depression may be a risk factor for Alzheimer's disease (AD); however, the biological mechanisms of the transition from depression to AD are still not clear. Changes of amyloid β protein ($A\beta$) metabolism and increased glucocorticoid (GC) levels have been found in both depression and AD. Moreover, several studies in animal models have demonstrated that GC administration changes $A\beta$ metabolism. To reveal whether GC affects amyloid metabolism in patients with depression, we evaluated serum levels of $A\beta_{40}$, $A\beta_{42}$ and cortisol at admission in 187 inpatients with major depressive disorder (MDD) and 224 healthy comparisons. Additionally, 27 patients with MDD were re-evaluated serum for $A\beta$ s 1 year later. The results of multiple regression analyses revealed that serum cortisol and $A\beta$ levels are not correlated at the time of admission. However, serum cortisol levels at admission correlated with serum $A\beta_{42}$ levels and $A\beta_{40}/A\beta_{42}$ ratio 1 year later. These findings suggest that increased cortisol in patients with MDD may influence the metabolism of $A\beta$ over prolonged periods of time.

Keywords:

depression, Alzheimer's disease, amyloid, glucocorticoid, cortisol, serum

1. Introduction

Epidemiological studies have demonstrated that depression may be a risk factor for Alzheimer's disease (AD) (Barnes et al., 2012; Byers et al., 2011; da Silva et al., 2013; Devanand et al., 1996; Diniz et al., 2013; Irie et al., 2008; Ownby et al., 2006; Wilson et al., 2002). This association has been shown even in cases where depression occurs long before the onset of AD (Green et al., 2003; Ownby et al., 2006). Recent studies have supported the idea that early-onset depression also increases the risk of developing AD (Byers et al., 2011; da Silva et al., 2013; Geerlings et al., 2008). Moreover, the number of depressive episodes (Dotson et al., 2010; Kessing et al., 2004) and severity of depressive symptoms (Saczynski et al., 2010; Wilson et al., 2002) may increase the risk of dementia including AD. Whether depression is a prodromal symptom of AD or risk factor that contributes to its onset is still debated, although previous reports suggest the latter.

Although the biological mechanism underlying the transition from depression to AD is still not clear, alterations of amyloid β protein ($A\beta$) metabolism in depression may be the possible background (Baba et al., 2012; Byers et al., 2011; Kita et al., 2009; Namekawa et al., 2013).

$A\beta$ is the major component of senile plaques in AD and is a 40- or 42-amino acid peptide cleaved from the amyloid precursor protein (APP) by β - and γ -secretase.

Cerebrospinal fluid (CSF) levels of A β 42 are reduced in patients with AD (Andreasen et al., 1999; Schroder et al., 1997), but increase at the early stage of the disease (Jensen et al., 1999). These variations may be associated with the selective deposition of A β 42 in the brain. However, studies of plasma A β levels in subjects with AD have been contradictory (Ertekin-Taner et al., 2008; Fukumoto et al., 2003; Lopez et al., 2008; Sobow et al., 2005). The reason for this discrepancy remains unclear, although blood or CSF A β levels could alter according to AD stage (Kawarabayashi et al., 2001). Although the results have not been consistent, several epidemiological studies have indicated that changes in peripheral levels of A β , especially higher A β 40/A β 42 ratios, represent a risk for future onset of AD (Graff-Radford et al., 2007; Lambert et al., 2009; Mayeux et al., 2003; Mayeux et al., 1999; Schupf et al., 2008; van Oijen et al., 2006).

Peripheral A β levels in elderly patients with depression have been found to be inconsistent (Pomara et al., 2006; Sun et al., 2007; Sun et al., 2008). We previously reported that serum A β 40/A β 42 ratios were significantly higher in patients with major depressive disorder (MDD) than in healthy comparisons, and this difference is seen in both elderly and younger subjects (Baba et al., 2012; Kita et al., 2009). We suggest that A β metabolism may be affected in depression, and this may indicate why even

early-onset depression is a risk factor for developing AD. However, the mechanism of the association between depression and A β is still unclear.

Hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis, which is well described in MDD (Marques et al., 2009; Pariante et al., 2008), is also observed in AD and results in increased glucocorticoid (GC, cortisol in primates) levels in blood and CSF (Caraci et al., 2010; Chi et al., 2014; Crochemore et al., 2005; Davis et al., 1986; Krishnan et al., 2008; Martignoni et al., 1990; Popp et al., 2009; Popp et al., 2015; Rasmuson et al., 2001; Rasmuson et al., 2002).

Stressful stimuli induce hyperactivity of the HPA-axis and result in an increase of GC secretion from the adrenal cortex. Normally, the GC increase is transient due to a negative-feedback system (Sapolsky et al., 1986). In patients with depression and AD, impairment of the negative-feedback system has been suggested to occur. Excessively increased GC may damage neural cells in the hippocampus, inducing hippocampal volume loss and memory impairment (Butters et al., 2008; Byers et al., 2011; Sierksma et al., 2010).

Interestingly, some studies have demonstrated that GC administration increases A β and tau pathology in a mouse model of AD (Green et al., 2006), and that chronic GC administration decreases plasma A β 42 levels in a macaque (Kulstad et al., 2005).

Combining these previous results, we hypothesized that increased levels of GC may lead to pathological changes in amyloid metabolism in patients with depression. We evaluated serum A β 40, A β 42, and cortisol levels in patients with MDD and healthy comparisons, and analyzed the correlations between A β and cortisol levels. Additionally, patients were followed and their A β re-evaluated 1-year later to reveal any long-term influence of cortisol on A β . This study is a part of the Juntendo University Mood Disorder Project (JUMP).

2. Methods

2.1. Patient population

Two hundred and one depressive inpatients (77 male, 124 female; mean age, 52.2 years; range, 27–84 years) were recruited from Juntendo Koshigaya Hospital, Saitama, Japan, between January 2005 and October 2016. All patients met the Diagnostic and Statistical Manual for Mental Disorders, 4th and 5th editions, criteria for MDD. We are using semi-quantitative routine procedures modified from SCID-IV for clinical diagnosis. Patients were excluded if they had histories of other psychiatric disorders including delusions, severe or acute medical illnesses, use of drugs that may cause depression, or neurological disorders including dementia and Mini-Mental State

Examination (MMSE) (Folstein et al., 1975) scores of less than 24 after remission.

Finally, 187 cognitively intact patients with MDD (73 male, 114 female; mean age, 54.7 years; range, 26–84 years) were enrolled. Depressive symptoms were assessed using the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). Age at onset, number of depressive episodes, and total duration of illness were confirmed via medical records. All patients were on antidepressant medication at the time of the study, and the doses were converted to equivalent doses of imipramine (Inagaki et al., 2006). Patients were followed-up and A β s re-assessed 1 year later to reveal the long-term effect of cortisol on A β .

Another 231 participants were recruited from the general population as healthy comparisons. The same exclusion criteria used for patients applied, but with the addition of having a history of depression. Resulting, 224 participants were enrolled as healthy comparisons (47 male, 177 female; mean age 48.9 years; range, 18–75 years).

The study protocol was approved by the Medical Ethics Committee of Juntendo University, performed in accordance with the regulations outlined by Juntendo University, and conformed to the provisions of the Declaration of Helsinki (1995). All participants provided written informed consent prior to participation.

2.2. Experimental procedure

Blood samples were collected at 7:00 am on the day following admission (before breakfast and any drug administration) and were centrifuged immediately. Serum samples were stored at -80°C until use. Serum levels of A β 40 and A β 42 were measured as described in a previous report (Baba et al., 2012), using sandwich A β enzyme-linked immunosorbent assay kits (WAKO, Osaka, Japan). The A β (1-40) kit uses the BAN50 monoclonal antibody, which specifically detects the N-terminal portion of human A β (1-16) and the BA27 monoclonal antibody, which detects the C-terminal portion of A β (1-40). The A β (1-42) kit uses BAN50 and BC05 monoclonal antibodies, which detect the C-terminal portion of A β (1-42). The sensitivities, intra-assay coefficients of variation, and inter-assay CVs can be found in a previous report (Baba et al., 2012).

Cortisol levels were measured by competitive immunoassay using the ADVIA Centaur Cortisol assay (Siemens Healthcare Diagnostic Inc., Tokyo, Japan). This assay measures serum cortisol concentrations up to 75 $\mu\text{g/dL}$ (2069 nmol/L) with a minimum detectable concentration (analytical sensitivity) of 0.20 $\mu\text{g/dL}$ (5.5 nmol/L). The intra-assay CVs were <15%.

Apolipoprotein E (ApoE) phenotypes for all samples were determined by isoelectric focusing carried out at SRL, Tokyo, Japan (Eto et al., 1985).

2.3. Statistical analysis

Age, education, MMSE scores, and serum cortisol levels were compared between MDD and healthy comparisons using two-tailed unpaired Student's t-tests. The χ^2 test was used to compare sex. Serum A β 40 and A β 42 levels, and the A β 40/A β 42 ratio were compared using the Mann-Whitney U test, with median values used for variables with skewed distributions (Baba et al., 2012; Graff-Radford et al., 2007; Sun et al., 2008). Multiple regression analysis was conducted only in the MDD group, using A β 40 and A β 42 levels, and the A β 40/A β 42 ratio as dependent variables. As the number of depressive episodes and severity of depressive symptoms have been reported to influence the risk of developing dementia, age, sex, the number of depressive episodes, HAM-D scores at admission and cortisol levels were used as independent variables. A β 40 and A β 42 levels, and A β 40/A β 42 ratios were \log_{10} transformed for multiple regression analysis due to the skewed distribution of these variables. The χ^2 test was used to compare the variables sex and frequency of ApoE4 phenotype.

As a longitudinal study, multiple regression analyses were conducted using A β 40 and A β 42 levels, and A β 40/A β 42 ratios at 1 year as dependent variables, and age, sex, number of depressive episodes, HAM-D score at admission, and cortisol level at

admission as independent variables.

A significance level of $p < 0.05$ was used. Statistical procedures were performed using the Japanese version of SPSS v21.0 (SPSS Japan, Tokyo, Japan).

3. Results

The detailed demographic and clinical features of participants, serum A β 40 and A β 42 levels, A β 40/A β 42 ratios, and cortisol levels at admission are shown in Table 1. No significant differences in education, MMSE scores or ApoE4 frequencies were identified between MDD patients and healthy comparisons. Comparisons were significantly younger than MDD patients ($p < 0.001$), and there were significantly more female comparisons than female with MDD ($p < 0.001$).

There were no differences in serum A β 40 levels between patients with MDD and comparisons. However, serum A β 42 levels were significantly lower ($p < 0.001$), and A β 40/A β 42 ratios significantly higher ($p < 0.001$), in patients with MDD compared with comparisons. Cortisol levels were significantly higher ($p = 0.003$) in patients with MDD compared with comparisons.

Multiple regression analysis showed that A β 40 levels at admission were not correlated with any variables. A β 42 levels at admission did correlate with the number of depressive episodes ($\beta = 0.25$, $p = 0.012$) and tended to relate to cortisol level ($\beta =$

-0.17, $p = 0.074$). A β 40/A β 42 ratios at admission did correlate with the number of depressive episodes ($\beta = -0.24$, $p = 0.015$) but not cortisol levels ($\beta = 0.31$, $p = 0.181$) (Table 3). Similar results were found in non-ApoE4 carriers (data not shown). When a multiple regression analysis was conducted including ApoE4 as a dependent variable, ApoE4 did not influence on A β 2 results ($\beta = 0.076$, $p = 0.124$), suggesting that the relationship between A β and cortisol were independent of ApoE4. To exclude the possible influence of preclinical dementia, the analysis was performed using only patients under 65 years ($n = 129$), giving similar results (data not shown).

Of the patients with MDD, 27 were followed for 1 year and their A β s re-assessed (most patients transited to another hospital or clinic from our university hospital, and several patients disagreed with re-examination). All the follow-up patients were in remission (HAM-D < 7) at the time of re-assessment. For comparison of A β s at admission and 1 year after, for the data at admission, the data of only 27 patients who re-assessed 1 year after were used. The comparison data of A β s in these 27 patients of MDD group at admission and 1 year after are indicated in Table 2. A β 40/A β 42 ratios 1 year later were significantly lower compared with those at admission ($p = 0.001$). A β s of these 27 patients were compared with those of healthy comparisons, using the Mann-Whitney U test. In these small number of patients, serum levels of A β 40 at

admission did not differ with comparisons ($p = 0.444$), and the A β 40 levels 1 year later were significantly lower than those in comparison ($p = 0.033$). Lower levels of serum A β 42 ($p = 0.001$) and higher A β 40/A β 42 ratios ($p = 0.025$) at admission were not significantly different 1 year later, compare to healthy comparisons (A β 42; $p = 0.067$, A β 40/A β 42 ratios; $p = 0.061$). We conducted multiple regression analysis using the 1-year A β results as dependent variables, and the same independent variables as previously, including cortisol level at admission. A β 40 levels 1 year later were not significantly correlated with any variable. A β 42 levels 1 year later significantly and negatively correlated with HAM-D scores ($\beta = -0.62$, $p = 0.015$) and cortisol levels ($\beta = -0.43$, $p = 0.046$) at admission. A β 40/A β 42 ratios at 1 year were also significantly and positively correlated with HAM-D scores ($\beta = 0.64$, $p = 0.011$) and cortisol levels ($\beta = -0.62$, $p = 0.005$) at admission. A higher cortisol levels at admission were correlated with lower A β 42 levels and higher A β 40/A β 42 ratios 1 year later. And the higher HAM-D score at admission was also correlated with lower A β 42 and higher A β 40/A β 42 ratios 1 year later.

Moreover, a multiple regression analysis using 1-year MMSE score as a dependent variable was conducted. The result showed that serum cortisol levels at admission did not affect to MMSE score 1 year later ($\beta = 0.10$, $p = 0.639$).

4. Discussion

In this study, serum A β 42 levels were significantly lower, and A β 40/A β 42 ratios significantly higher, in patients with MDD compared with comparisons, consistent with our previous reports (Baba et al., 2012; Namekawa et al., 2013). At the time of admission, serum cortisol did not correlate with serum A β levels, disagreeing with our hypothesis. However, serum cortisol levels at admission did correlate with serum A β 42 levels and A β 40/A β 42 ratios 1 year later.

Pomara et al. (Pomara et al., 2003) first raised the possibility of A β abnormalities in depression, and reported higher plasma A β 42 levels in elderly patients with MDD. Moon et al. (Moon et al., 2011) also found higher A β 42 plasma levels in elderly patients with depressive symptoms. In contrast, Qiu et al. and Sun et al. reported lower plasma A β 42 levels and higher A β 40/A β 42 ratios in a large sample of elderly depressive individuals (Qiu et al., 2007; Sun et al., 2009; Sun et al., 2007; Sun et al., 2008). However, these previous studies investigated elderly subjects, so it is possible that the subjects include patients in the early or preclinical stages of dementia. Our previous study demonstrated lower A β 42 levels and higher A β 40/A β 42 ratios in 193 patients with MDD (age range, 27–84 years) compared with 413 healthy controls, and found

similar findings even in younger subjects (Baba et al., 2012). The present study also examined patients with a wide age range (26–84 years), and these results are consistent with our previous reports.

The current results show higher serum cortisol levels in patients with MDD than comparisons. Most studies have shown that patients with MDD have increased cortisol secretion (Marques et al., 2009; Pariante et al., 2008), consistent with our results. Hyperactivity of the HPA axis is a common finding in patients with MDD (Marques et al., 2009; Pariante et al., 2008), and dysregulation has also been observed in patients with AD (Rothman et al., 2010). Increased cortisol levels have been reported in the CSF (Davis et al., 1986; Popp et al., 2009; Popp et al., 2015), plasma (Csernansky et al., 2006; Davis et al., 1986; Martignoni et al., 1990; Umegaki et al., 2000; Zverova et al., 2013), and serum (Laske et al., 2009; Rasmuson et al., 2002) in patients with AD. Increased plasma cortisol levels have been associated with more rapid increases in the symptoms of dementia and more rapid decreases in cognitive performance (Csernansky et al., 2006). Moreover, it has been reported that serum cortisol levels are significantly inversely correlated with CSF levels of total-tau, and phosphorylated-tau, and have a trend towards a positive correlation with CSF A β 42 levels (Laske et al., 2009).

Green et al.(Green et al., 2006) administered GC at levels relating to physiological stress into an AD mouse model. Their results revealed increased steady-state levels of amyloid precursor protein and β -secretase in GC-treated AD mouse, resulting in increased $A\beta$ levels and $A\beta$ deposition in the brain. They also found accelerated development of tau pathology as a result of GC administration. From these results, the authors suggested that GC may play an important role in the development and progression of AD. In the present study, serum $A\beta_{42}$ levels and the $A\beta_{40}/A\beta_{42}$ ratios at admission were correlated with number of depressive episodes. It may speculate that there be a process of facilitation of the HPA axis occurring with increasing numbers of depressive episodes.

In this study, however, serum cortisol levels at admission were not related to simultaneous serum $A\beta$ levels. However, serum cortisol levels at admission did correlate with serum $A\beta_{42}$ levels and $A\beta_{40}/A\beta_{42}$ ratios 1 year later. Kulstad et al. (Kulstad et al., 2005) chronically (12 months) administered high-dose GC (cortisol) and placebo to macaques. GC-treated macaques showed increased $A\beta_{42}$ levels and decreased $A\beta_{40}$ levels in the inferior frontal cortex, as well as decreased plasma $A\beta_{42}$ levels. Moreover, the changes in plasma $A\beta_{42}$ levels negatively correlated with CSF cortisol levels. The authors suggested that the plasma $A\beta_{42}$ level decreases were

provoked by increased GC, and that these changes may have a cumulative physiological impact when they persist over prolonged periods of time. Combining these previous reports and our results, we speculate that cortisol elevation in patients with MDD may affect the metabolism of A β , and that this change may gradually progress over a long time. Higher HAM-D score and higher cortisol levels at admission correlated with lower A β 42 and higher A β 40/A β 42 ratios 1 year later. From these results, we speculate that more hyper and more long-term exposure from cortisol may be related to larger alternation of amyloid metabolism.

Additionally, the current results demonstrated tendencies of decreased serum A β 40 levels and increased A β 42 levels during 1-year follow up periods. These results were consistent with results of previous study evaluated CSF A β s in patients with late-life depression (Pomara et al., 2016). The previous study also demonstrated that decreased CSF A β 40 levels and increased A β 42 levels during 3-year follow up periods, similarly with our results. Moreover, the study reported that the change of A β 42 levels were associated with severity of depression and those of A β 40 levels were associated only with age. The authors suggest that A β 42 may have state-dependency and A β 40 may be associated with age. We also suggest for the results of our present study that

serum A β 42 levels and A β 40/A β 42 ratios may recover toward healthy level from acute phase of depression to remission depending with the state.

On the other hand, a longitudinal study investigated associations between plasma A β s and depression demonstrated that plasma A β 42/A β 40 ratios were associated with developing depression in ApoE4 carriers, independent with dementia (Metti et al., 2013). The authors suggest that plasma A β may be a biomarker for some type of depression. Recent animal studies demonstrated that A β treated rats showed depression-related behavioral and biochemical changes (Colaianna et al., 2010), and these A β -induced changes recovered by treatment with antidepressants (Schiavone et al., 2017). From these previous reports, it is possible that A β may influence occurring depressive symptoms. Combining these previous and our present results, it may also speculate that AD and some type of depression may have a common underlying pathway.

The present study has several limitations. First, all of the patients with MDD were receiving antidepressant medication, and it is a possible that serum cortisol and A β levels might have been influenced by this medication. However, it has been reported that plasma A β 42 levels do not change with antidepressant treatment (Baba et al., 2012;

Namekawa et al., 2013; Pomara et al., 2006; Sun et al., 2007), and a multiple regression analysis of the present results also showed no correlation between total antidepressant dose and A β indices or cortisol levels (data not shown). Therefore, antidepressant treatment is unlikely to be a major factor influencing the present results. Second, Blood samples in this study were collected at 7:00 am. Plasma cortisol levels show the diurnal variation, with the mean peak occurring around 8:00 am and the mean nadir occurring in the midnight. And the mean difference between depressed patients and healthy subjects seems to be small at the circadian peak (Wong et al., 2000). This might explain the lack of correlation between cortisol and serum A β levels at admission. Lack of consideration in circadian changes of serum cortisol levels is a limitation of this study. Third, the number of follow-up patients was only 27. The small number of patients is a limitation, and further studies with larger numbers of patients are needed. ~~Third~~ Fourth, some studies have demonstrated a relationship between blood and CSF A β levels (Kawarabayashi et al., 2001; Mehta et al., 2001), while several other studies have failed to show this relationship (Giedraitis et al., 2007; Le Bastard et al., 2009). The lack of CSF data is another limitation of the present study. However, because of a less invasive, serum sample may be better than CSF for taking samples with multiple time points.

In conclusion, this is the first report investigating the relationship between

peripheral glucocorticoid and A β levels in patients with depression. Our results have shown lower A β 42 serum levels, and higher A β 40/A β 42 ratios and serum cortisol levels in patients with MDD than in controls. Although cortisol was not strongly correlated with simultaneous serum A β levels, it was related to serum A β levels 1 year later. These findings suggest that increased cortisol levels in patients with MDD may influence the metabolism of A β over prolonged periods of time.

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Conflicts of interest

No Disclosures to Report

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Table 1. Demographic and Comparison Data of MDD and Control Groups

	MDD (n = 187)	Comparison (n = 224)	<i>P Value</i>
	at Admission Mean (SD)	Mean (SD)	
Age (Years)	54.7(14.7)	48.9(14.3)	< 0.001 ^a
Sex (M/F)	73/114	47/177	< 0.001 ^b
Education (Years)	13.1(2.6)	13.2(3.3)	0.901 ^a
Ham-D score	21.0(10.2)	-	
Age at Onset	48.7(14.8)	-	
Number of Depressive Episodes	2.1(1.5)	-	
Total Duration of Medication (M)	50.6(85.3)	-	
Total Dose of Antidepressant (mg) ^d	129.1(93.8)	-	
MMSE	27.4(2.0)	27.8(1.8)	0.105 ^a
ApoE4 N/total (%)	22.2	21.2	0.446 ^b
Cortisol (µg/dL)	16.0 (6.7)	14.3 (4.8)	0.003 ^a
	median (Q1-Q3)	median (Q1-Q3)	<i>P Value</i>
Aβ40 (pmol/L)	21.5 (13.8 - 28.3)	22.0 (14.7 - 29.6)	0.379 ^c
Aβ42 (pmol/L)	1.3 (0.9 - 3.0)	2.4 (1.6 - 4.0)	< 0.001 ^c
Aβ40/Aβ42 ratio	12.6 (7.6 - 21.3)	8.5 (5.8 - 11.4)	< 0.001 ^c

^a Student's *t*-Test (df=149), ^bχ²Test (df=1), ^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, Q: quartile

Table 2. Comparison Data in MDD Group at Admission and 1 Year after (n=27)

	at Admission	1 Year after	<i>P Value</i>
	median (Q1-Q3)	median (Q1-Q3)	
A β 40 (pmol/L)	19.3 (14.8 - 27.7)	15.5 (7.3 - 33.2)	0.374
A β 42 (pmol/L)	1.2 (0.8 - 3.0)	1.7 (1.5 - 3.0)	0.149
A β 40/A β 42 ratio	12.3 (5.1 - 24.8)	7.0 (3.4 - 9.1)	0.001

Wilcoxon signed-rank test

MDD: Major Depressive Disorder, A β : amyloid β protein, Q: quartile

Table 3. Result of Multiple Regression Analysis of A β and Cortisol

	at Admission						1 Year After					
	Log ₁₀ A β 40 ^a		Log ₁₀ A β 42 ^a		Log ₁₀ A β 40/42 ratio ^a		Log ₁₀ A β 40 ^a		Log ₁₀ A β 42 ^a		Log ₁₀ A β 40/42 ratio ^a	
	β Estimate	<i>P</i> Value	β Estimate	<i>P</i> Value	β Estimate	<i>P</i> Value	β Estimate	<i>P</i> Value	β Estimate	<i>P</i> Value	β Estimate	<i>P</i> Value
Age	-0.710	0.525	-0.118	0.267	0.088	0.414	0.400	0.114	0.349	0.149	-0.169	0.463
Sex	0.007	0.948	-0.113	0.267	0.127	0.219	-0.323	0.119	-0.241	0.221	0.050	0.790
Ham-D score	0.046	0.664	0.106	0.299	-0.088	0.390	-0.472	0.064	-0.619	0.015	0.637	0.011
Number of Depressive Episodes	0.044	0.661	0.245	0.012	-0.240	0.015	0.313	0.130	0.236	0.230	-0.054	0.775
Cortisol	-0.101	0.332	-0.174	0.074	0.131	0.181	-0.200	0.346	-0.428	0.046	0.621	0.005

Multiple regression analyses; Log₁₀ A β s as the dependent variable.

HAM-D: Hamilton rating scale of depression, A β ; amyloid β protein

^a A β values were transformed to log₁₀ (A β s) because of the skewed distributions.