

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

メタデータ	言語: English 出版者: 公開日: 2019-03-20 キーワード: 作成者: 安田, 誠太 メールアドレス: 所属:
URL	https://jair.repo.nii.ac.jp/records/2002238

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

Running title: Serum A β oligomer in MDD

Seita Yasuda ^{1,*}, Hajime Baba ^{1,2,*}, Hitoshi Maeshima ^{1,2}, Takahisa Shimano ², Megumi

Inoue ², Tomoya Ichikawa ¹, Hiroko Shukuzawa ^{1,2}, Toshihito Suzuki ^{1,2}, Heii Arai ¹

1. Department of Psychiatry & Behavioral Science, Juntendo university Graduate School of Medicine, Tokyo, Japan
2. Juntendo University Mood Disorder Project (JUMP), Department of Psychiatry, Juntendo Koshigaya Hospital, Saitama, Japan

* Contributed equally to this work.

Correspondence

H Baba, MD, PhD, Juntendo University Mood Disorder Project (JUMP), Department of Psychiatry, Juntendo Koshigaya Hospital, Fukuroyama 560, Koshigaya, Saitama 343-0032, Japan.

Email: hbaba@juntendo.ac.jp

Tel: +81-48-975-0321

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 ($A\beta$) metabolism in patients with depression has been suggested as a potential mechanism. Results from previous studies of $A\beta$ metabolism in patients with depression have been inconsistent, and $A\beta$ polymerization, which is a crucial process in AD pathology, has not previously been assessed.

Methods: Serum levels of $A\beta_{40}$, $A\beta_{42}$, and $A\beta$ oligomers were evaluated in 104 inpatients with major depressive disorder (MDD) and 132 healthy control individuals.

Results: Lower serum $A\beta_{42}$ levels were observed in patients with MDD, but there was no difference in serum $A\beta$ oligomer levels between the MDD group and the healthy control group, even in elderly subjects. Interestingly, serum $A\beta$ oligomer levels in patients with MDD were dependent on serum $A\beta_{42}$ levels, regardless of age, and this relationship was not observed in the control group.

Conclusions: These results suggest that $A\beta_{42}$ 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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Keywords: amyloid β , depression, major depressive disorder, oligomer, serum,

For Peer Review

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 ($A\beta$) is a major component of senile plaques. $A\beta$ monomers are generated by proteolytic cleavage of the amyloid precursor protein by β - and γ -secretase. $A\beta$ aggregates and polymerizes to oligomers, which eventually become

1
2
3
4
5
6 insoluble and are deposited as extracellular amyloid plaques. A β has two main isoforms:
7
8
9 A β 40 and A β 42. A β 42 is more easily polymerized and deposited in earlier stages of AD
10
11
12 than A β 40. Soluble A β oligomers are neurotoxic, and can be responsible for synapse
13
14
15 failure ⁵.

16
17
18 A β can be detected in the brain, cerebrospinal fluid (CSF), **plasma** and **serum**.
19
20
21 **A β 42 levels in CSF are reported to decrease in MCI and in the preclinical phase of AD**
22
23
24 ⁶. It has been suggested that these changes occur as a result of selective A β 42 deposition
25
26
27 in the brain. This reduction in CSF A β 42 levels has been used to diagnose AD ⁷.
28
29
30 Although plasma A β levels have been reported **to exhibit a decrease that is correlated**
31
32
33 with brain A β levels in a mouse model of AD ⁸, results from studies of A β levels in the
34
35
36 **plasma** of patients with AD have been contradictory ⁹. However, a recent study that
37
38
39 measured plasma A β levels by immunoprecipitation coupled with mass spectrometry
40
41
42 demonstrated that plasma A β levels (e.g., the A β 40/A β 42 ratio) correlated with CSF
43
44
45 A β 42 levels and amyloid deposition via A β positron-emission tomography (PET)
46
47
48 imaging, suggesting that plasma A β levels may predict the burden of A β in the brain ¹⁰.
49
50
51 Cohort studies of healthy older individuals have shown that a higher baseline plasma
52
53
54 A β 40/A β 42 ratio may increase the risk of developing AD ^{11 12} .

55
56
57 Previous studies of CSF and **plasma/serum** A β levels in patients with depression
58
59
60

1
2
3
4
5
6 have reported inconsistent results ¹³. Increased plasma A β 42 levels and a decreased
7
8 A β 40/42 ratio have been reported in elderly patients with depression ¹⁴. However,
9
10 decreased plasma A β 42 levels and an increased A β 40/A β 42 ratio have also been
11
12 reported in elderly patients with depression ^{15 16 17}. A recent meta-analysis showed that
13
14 the plasma A β 40/A β 42 ratio is higher in elderly individuals with depression than in
15
16 their healthy counterparts ¹³. These studies exploring peripheral A β levels in patients
17
18 with depression involved only elderly subjects. Thus, we investigated serum A β levels
19
20 in a wider age range of patients, including younger subjects (< 40 years old), and found
21
22 that the serum A β 40/A β 42 ratio was significantly higher in patients with depression
23
24 than in healthy controls, even in younger patients ¹⁷. Moreover, we demonstrated that
25
26 there is a significant negative correlation between the A β 40/A β 42 ratio and age at onset
27
28 of depression in elderly patients, suggesting that patients with an earlier onset of
29
30 depression may have a more serious alteration in A β metabolism ¹⁶. Based on the
31
32 results from these studies, we hypothesized that A β metabolism may be affected by
33
34 depression, and that this biological mechanism could explain the link between
35
36 depression and AD. However, previous studies (including ours) have not assessed A β
37
38 polymerization, which is a crucial process in AD pathology.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

56
57 To better understand the contribution of A β , and especially A β polymerization, to
58
59
60

1
2
3
4
5
6 the relationship between depression and AD, in this study we evaluated serum levels of
7
8
9 A β 40, A β 42, and A β oligomers and analyzed the relationships among them in patients
10
11
12 with depression and in healthy controls. This study was performed as part of the
13
14
15 Juntendo University Mood Disorder Project (JUMP).
16
17
18
19
20
21
22
23
24

25 **2. METHODS**

26 **2.1. Participants**

27
28
29
30 A total of 130 inpatients with depression were recruited from Juntendo Koshigaya
31
32
33 Hospital, Saitama, Japan, between June 2010 and November 2016. All patients met
34
35
36 DSM-IV or DSM-V criteria for major depressive disorder (MDD). Patients were
37
38
39 excluded if they had a history of other psychiatric disorders, severe or acute medical
40
41
42 illnesses, neurologic disorders, or use of drugs that may cause psychosis or depression
43
44
45 (n = 0). Patients showing clinical evidence of dementia or with Mini-Mental State
46
47
48 Examination (MMSE) scores < 24 were also excluded (n = 26). After all ineligible
49
50
51 patients were excluded, 104 inpatients with MDD (32 men, 72 women; mean age = 57.5
52
53
54 years; age range, 20–85 years) were enrolled in the study. Depressive symptoms were
55
56
57
58
59
60

1
2
3
4
5
6 assessed by the Hamilton Rating Scale for Depression (HAM-D) . All patients were
7
8
9 taking antidepressants at the time of the study.
10

11
12 A total of 132 healthy participants (65 men, 67 women; mean age = 49.3 years; age
13
14 range, 16–80 years) were recruited as a control group. None of these participants had
15
16 any history of depression, dementia, or other neuropsychiatric disease, or had an MMSE
17
18 score < 24. Thus, all healthy participants were enrolled in this study as controls.
19
20
21
22

23
24 The study protocols were approved by the Medical Ethics Committee of Juntendo
25
26 University, and were performed in accordance with the regulations outlined by the
27
28 university. All participants provided written informed consent prior to participation.
29
30
31
32

33 34 35 36 **2.2. Serum A β 40, A β 42, and A β oligomer measurements**

37
38
39 Fasting blood samples were drawn into serum separator tubes and were centrifuged
40
41 immediately. Serum samples were stored at -80°C until use. Serum A β 40 and A β 42
42
43 levels were measured using a sandwich A β enzyme-linked immunosorbent assay kit
44
45 (WAKO, Osaka, Japan), as described previously ^{16 17 18}. The A β (1-40) kit uses the
46
47 BAN50 monoclonal antibody, which specifically detects the N-terminal portion of
48
49 human A β (1-16), and the BA27 monoclonal antibody, which detects the C-terminal
50
51 portion of A β (1-40). The A β (1-42) kit uses BAN50 and the BC05 monoclonal antibody,
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6 which detects the C-terminal portion of A β (1-42). The sensitivity was 0.019 pmol/L
7
8
9 (dynamic range: 1.0–100 pmol/L) for A β 40 and 0.06 pmol/L (dynamic range: 0.1–20
10
11
12 pmol/L) for A β 42. The intra-assay coefficients of variation (CVs) were 4.8% at a mean
13
14
15 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
16
17
18 for A β 40, and 0.8% at a mean of 3.2 pmol/L, 0.8% at a mean of 7.4 pmol/L, and 1.0%
19
20
21 at a mean of 16.4 pmol/L for A β 42. The inter-assay CVs were 3.2% at a mean of 14.8
22
23
24 pmol/L, 1.1% at a mean of 33.6 pmol/L, and 2.5% at a mean of 75.7 pmol/L for A β 40,
25
26
27 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
28
29
30 of 16.4 pmol/L for A β 42.
31
32

33 Serum A β oligomer levels were measured using a Human Amyloid β Oligomers
34
35 (82E1-specific) Assay Kit (IBL, Gunma, Japan) according to the manufacturer's
36
37 instructions. This ELISA kit detects human A β molecules that bind to an anti-human A β
38
39 N-terminal antibody (82E1) via two or more epitopes (including A β oligomers and A β
40
41 bound to other proteins). The sensitivity was 4.41 pmol/L. The intra-assay CVs were
42
43
44 5.0 % at a measurement value of 314.24 pmol/L, 2.9 % at a measurement value of 88.32
45
46
47 pmol/L, and 5.4 % at a measurement value of 33.66 pmol/L (n = 24). The inter-assay
48
49
50 CVs were 3.1 % at a measurement value of 310.02 pmol/L, 5.2 % at a measurement
51
52
53 value of 76.92 pmol/L, and 10.0 % at a measurement value of 27.39 pmol/L (n = 5).
54
55
56
57
58
59
60

2.3. Apolipoprotein E phenotype determination

Apolipoprotein E (ApoE) phenotypes for all samples were determined by isoelectric focusing carried out at SRL, Tokyo, Japan ¹⁹.

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 χ^2 test was used to compare the sex and ApoE4 variables. Serum levels of A β 40, A β 42, and A β oligomers were compared using the Mann–Whitney U test because of the skewed distribution ¹⁷. The relationship between serum A β 40 or A β 42 and A β oligomers were analyzed using Spearman's rank Correlation Coefficient test. To control confounding factors, multiple regression analyses were conducted using A β oligomer levels as the dependent variable and age, sex, A β 40, and A β 42 as independent variables. The A β 40, A β 42, and A β oligomer values were log-transformed for the multiple regression analysis because of their skewed distribution ¹⁷. 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 A β 40, A β 42 and A β oligomer between MDD and controls

Serum A β 40 levels were significantly higher ($p = 0.001$) and serum A β 42 levels ($p < 0.001$) and A β 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 A β as a

1
2
3
4
5
6 dependent variable, and age, sex, education, and group (MDD or control) as
7
8
9 independent variables (Table 2). The results showed that A β 40 ($p < 0.001$) and A β 42 (p
10
11
12 = 0.004) levels differed significantly based on the group, but that A β oligomer levels
13
14
15 were not affected by the group, after controlling age, sex, and education. This indicates
16
17
18 that A β 40 and A β 42 levels were different in the MDD group compared with the control
19
20
21 group, but that there was no difference in serum A β oligomer levels between the MDD
22
23
24 and control groups. When the data from the elderly subjects (> 60 years old) only were
25
26
27 analyzed, there was still no significant difference in A β oligomer levels between the two
28
29
30 groups ($\beta = 0.010$, $p = 0.957$).
31
32
33
34
35

3.3. Correlations between total A β and A β oligomer in MDD and controls

36
37
38
39 Serum A β oligomer levels showed a significantly positive correlation with serum
40
41
42 A β 42 levels ($R = 0.246$, $P < 0.001$) in all subjects. In the MDD group, serum A β
43
44
45 oligomer levels showed a significantly positive correlation with A β 42 levels ($R = 0.216$,
46
47
48 $P = 0.035$), however, that correlation was not shown in the control group (Table 3).
49
50

51
52 Multiple regression analysis showed that neither A β 40 levels nor A β 42 levels were
53
54
55 correlated with A β oligomer levels in the control group, after controlling for age and
56
57
58 sex. In the MDD group, A β 40 levels were not correlated with A β oligomer levels, while
59
60

1
2
3
4
5
6 A β 42 levels were positively correlated with A β oligomer levels ($\beta = 0.475$, $p = 0.022$)
7
8
9 (Table 4).
10

11 12 **4. DISCUSSION** 13

14
15 The present study evaluated serum levels of A β 40, A β 42, and A β oligomers in
16
17 patients with MDD and healthy individuals. We previously reported that patients with
18
19 MDD had significantly lower serum A β 42 levels^{17 18} and a tendency toward higher
20
21 serum A β 40 levels compared with healthy subjects. The present study showed that
22
23 participants in the MDD group had higher A β 40 and lower A β 42 serum levels
24
25 compared with the control group, which is partly consistent with these previous results
26
27 and a recent meta-analysis¹³. In addition, the present study demonstrated that there was
28
29 no significant difference in serum A β oligomers levels between patients with MDD and
30
31 healthy controls, even in elderly subjects. To the best of our knowledge, this is the first
32
33 study that has investigated peripheral A β oligomer levels in patients with depression.
34
35
36
37
38
39
40
41
42
43
44

45 Although there have been no studies of peripheral A β oligomer levels in patients
46
47 with depression, peripheral A β oligomer levels have been assessed in patients with AD.
48
49 Based on epidemiological data suggesting a link between depression and AD, we
50
51 hypothesized that **serum** A β oligomer levels in patients with MDD would show similar
52
53 trends to **plasma or serum** A β oligomer levels in patients with AD. Several previous
54
55
56
57
58
59
60

1
2
3
4
5
6 studies have reported higher A β oligomer levels in the CSF of patients with AD
7
8
9 compared with controls ^{20 21} , and a negative correlation between the CSF A β oligomer
10
11
12 levels and MMSE scores has also been reported ²¹. In contrast, other studies have
13
14
15 reported that there is no difference in CSF A β oligomer levels between patients with
16
17
18 AD compared with control subjects ^{22 23}. In addition, a longitudinal study demonstrated
19
20
21 that the CSF A β oligomer levels decrease on an annual basis, and that this decrease is
22
23
24 associated with cognitive decline ²². It has been suggested that the reason for these
25
26
27 contradictory results is methodological differences between the studies ²⁴. Studies using
28
29
30 flow cytometry ²⁵ and ELISA ^{26 27} have reported higher plasma A β oligomer levels in
31
32
33 patients with AD compared with non-demented control subjects. The present study did
34
35
36 not detect any difference in serum A β oligomer levels in patients with MDD compared
37
38
39 with healthy controls, even among elderly subjects. A longitudinal study of AD and
40
41
42 mild cognitive impairment (MCI) showed that baseline CSF levels of A β oligomers did
43
44
45 not predict future conversion from MCI to AD; however, an annual decrease in A β
46
47
48 oligomer levels was associated with progressive cognitive decline ²². This suggests that
49
50
51 peripheral A β oligomer levels may not show any change until cognitive dysfunction is
52
53
54 evident, even if this cognitive decline is a precursor to AD.
55
56
57
58
59
60

1
2
3
4
5
6
7 However, there was a significant positive correlation between serum A β 42
8
9 (polymerizable isoform) and A β oligomers in the MDD group, but not in the control
10
11 group, after controlling age and sex. That is, serum A β oligomer levels were dependent
12
13 on serum A β 42 levels in patients with MDD, regardless of age. This may suggest that
14
15 A β 42 is more likely to aggregate and polymerize in patients with MDD than in healthy
16
17 subjects, although the reason for this and the underlying mechanism are unclear.
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Hyperactivity of the hypothalamus-pituitary-adrenal axis and the resulting increase in glucocorticoid secretion are well-described in patients with depression ²⁸. In addition, an association between plasma cortisol (glucocorticoid) levels and brain A β burden, as measured by Pittsburgh Compound B-positron emission tomography (PiB-PET), has been reported in patients with AD ²⁹. Thus, it is possible that increased cortisol levels in patients with MDD may play a role in promoting A β 42 polymerization.

The present study has several limitations. First, the ELISA kit used to measure the A β 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 ³⁰. Moreover, more than half of A β proteins are bound with albumin or high-density lipoprotein particles in the plasma/serum, and the ELISA method cannot

1
2
3
4
5
6 discriminate genuine toxic oligomers from non-pathological A β complexes. Based on
7
8
9 these factors, it is possible that the current results regarding A β oligomers did not
10
11
12 indicate pure “pathological” A β oligomers. However, previous studies measuring
13
14
15 plasma oligomers using different methods (flow cytometry and ELISA) and comparing
16
17
18 AD patients with healthy subjects have shown similar results. On the basis of these
19
20
21 previous results, we believe that the present oligomer data indicate the relative
22
23
24 differences between depression and healthy individuals, despite the possible presence of
25
26
27 artifacts. Second, although most previous studies measured plasma A β , serum A β was
28
29
30 measured in the present study. Previous studies have suggested that aggregated platelets
31
32
33 release A β , as well as ADP and clusterin, which promote A β aggregation³¹. Moreover,
34
35
36 a previous study comparing plasma and serum A β levels reported approximately 2-fold
37
38
39 increases in A β levels in serum samples, compared with plasma samples³². The
40
41
42 relationship between clusterin and A β aggregation may have a particular impact on A β
43
44
45 oligomer levels³³. Based on these previous reports, the results of the present study may
46
47
48 have been influenced by the use of serum samples. However, a previous study
49
50
51 comparing serum and plasma A β levels between AD patients and healthy controls
52
53
54 reported similar results³². This previous report suggests that the results of the present
55
56
57 study may indicate relative differences between depression and healthy individuals. To
58
59
60

1
2
3
4
5
6 better understand the kinetics of A β levels in patients with depression, the CSF should
7
8
9 be monitored in future studies. Third, all of the patients with MDD who participated in
10
11
12 the study were on medication, primarily antidepressants. A few studies have shown that
13
14
15 antidepressants do not influence blood A β levels^{14 15 17 16}, and one study reported that
16
17
18 treatment with antidepressants may reduce the brain levels of A β , as measured by
19
20
21 PiB-PET³⁴. Moreover, multiple regression analysis using daily antidepressant doses as
22
23
24 an independent variable showed that antidepressant use did not influence A β oligomer
25
26
27 levels in our cohort ($\beta = 0.239$, $p = 0.110$). Therefore, antidepressant use is unlikely to
28
29
30 be a major confounding factor influencing the results. However, the influence of
31
32
33 medication on A β polymerization is unknown. Thus, further studies should investigate
34
35
36 drug-naïve patients to avoid any potential influence of antidepressant use. Finally, while
37
38
39 we propose the relationship between glucocorticoid and A β levels as a possible
40
41
42 mechanism explaining the results from this study, we did not evaluate cortisol levels.
43
44
45 Finally, this was a cross-sectional study. A prospective follow-up study should be
46
47
48 performed to confirm the transition from depression to AD.
49
50

51
52 In conclusion, this is the first report of peripheral A β oligomer levels in patients
53
54 with depression. Lower serum A β 42 levels were observed in patients with depression,
55
56
57 but there was no difference in serum A β oligomer levels compared with the healthy
58
59
60

1
2
3
4
5
6 control group, even in elderly subjects. Interestingly, serum A β oligomer levels were
7
8
9 dependent on serum A β 42 levels in patients with depression, regardless of age, but this
10
11
12 relationship was not observed in healthy subjects. These results suggest that A β 42 is
13
14
15 more likely to aggregate and polymerize in patients with depression than in healthy
16
17
18 subjects, which could promote the transition from depression to AD. Our findings
19
20
21 suggest that depression may be a risk factor, not a prodrome, for AD.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7 **ACKNOWLEDGEMENTS**
8

9 This research was supported by AMED (grant no. JP18dk0307060) and the Research
10
11
12 Support Foundation of the Juntendo Institute of Mental Health.
13
14
15

16
17
18 **DISCLOSURE STATEMENT**
19

20
21 The authors have no disclosures or relevant conflicts of interest.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

- [1] Byers AL, Yaffe K. Depression and risk of developing dementia. *Nature reviews Neurology* 2011; **7**: 323-31.
- [2] da Silva J, Goncalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: systematic review. *The British journal of psychiatry : the journal of mental science* 2013; **202**: 177-86.
- [3] Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *The British journal of psychiatry : the journal of mental science* 2013; **202**: 329-35.
- [4] Geerlings MI, den Heijer T, Koudstaal PJ, Hofman A, Breteler MM. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. *Neurology* 2008; **70**: 1258-64.
- [5] Ferreira ST, Klein WL. The Abeta oligomer hypothesis for synapse failure and memory loss in Alzheimer's disease. *Neurobiology of learning and memory* 2011; **96**: 529-43.
- [6] Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *The New England journal of medicine* 2012;

1
2
3
4
5
6 **367**: 795-804.
7

8
9 [7] Schroder J, Pantel J, Ida N, et al. Cerebral changes and cerebrospinal fluid
10 beta-amyloid in Alzheimer's disease: a study with quantitative magnetic resonance
11
12
13
14
15 imaging. *Molecular psychiatry* 1997; **2**: 505-7.
16

17
18 [8] Kawarabayashi T, Younkin LH, Saido TC, Shoji M, Ashe KH, Younkin SG.
19
20 Age-dependent changes in brain, CSF, and plasma amyloid (beta) protein in the
21
22
23
24 Tg2576 transgenic mouse model of Alzheimer's disease. *The Journal of neuroscience* :
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
the official journal of the Society for Neuroscience 2001; **21**: 372-81.

[9] Lopez OL, Kuller LH, Mehta PD, et al. Plasma amyloid levels and the risk of AD
in normal subjects in the Cardiovascular Health Study. *Neurology* 2008; **70**: 1664-71.

[10] Nakamura A, Kaneko N, Villemagne VL, et al. High performance plasma
amyloid-beta biomarkers for Alzheimer's disease. *Nature* 2018; **554**: 249-54.

[11] van Oijen M, Hofman A, Soares HD, Koudstaal PJ, Breteler MM. Plasma
Abeta(1-40) and Abeta(1-42) and the risk of dementia: a prospective case-cohort
study. *Lancet neurology* 2006; **5**: 655-60.

[12] Graff-Radford NR, Crook JE, Lucas J, et al. Association of low plasma
Abeta42/Abeta40 ratios with increased imminent risk for mild cognitive impairment
and Alzheimer disease. *Archives of neurology* 2007; **64**: 354-62.

1
2
3
4
5
6 [13] Nascimento KK, Silva KP, Malloy-Diniz LF, Butters MA, Diniz BS. Plasma and
7 cerebrospinal fluid amyloid-beta levels in late-life depression: A systematic review and
8 meta-analysis. *Journal of psychiatric research* 2015; **69**: 35-41.
9
10
11

12
13
14
15 [14] Pomara N, Doraiswamy PM, Willoughby LM, et al. Elevation in plasma
16 Abeta42 in geriatric depression: a pilot study. *Neurochemical research* 2006; **31**:
17 341-9.
18
19
20
21
22

23
24 [15] Sun X, Mwamburi DM, Bungay K, et al. Depression, antidepressants, and
25 plasma amyloid beta (Beta) peptides in those elderly who do not have cardiovascular
26 disease. *Biological psychiatry* 2007; **62**: 1413-7.
27
28
29
30
31
32

33 [16] Namekawa Y, Baba H, Maeshima H, et al. Heterogeneity of elderly
34 depression: increased risk of Alzheimer's disease and Abeta protein metabolism.
35 *Progress in neuro-psychopharmacology & biological psychiatry* 2013; **43**: 203-8.
36
37
38
39
40
41

42 [17] Baba H, Nakano Y, Maeshima H, et al. Metabolism of amyloid-beta protein
43 may be affected in depression. *The Journal of clinical psychiatry* 2012; **73**: 115-20.
44
45
46
47

48 [18] Inoue M, Baba H, Yamamoto K, et al. Serum Levels of Albumin-beta-Amyloid
49 Complex in Patients with Depression. *The American journal of geriatric psychiatry* :
50 *official journal of the American Association for Geriatric Psychiatry* 2016; **24**: 764-72.
51
52
53
54
55

56 [19] Eto M, Watanabe K, Ishii K. A rapid flat gel isoelectric focusing method for the
57
58
59
60

determination of apolipoprotein E phenotypes and its application. *Clinica chimica acta; international journal of clinical chemistry* 1985; **149**: 21-8.

[20] Herskovits AZ, Locascio JJ, Peskind ER, Li G, Hyman BT. A Luminex assay detects amyloid beta oligomers in Alzheimer's disease cerebrospinal fluid. *PloS one* 2013; **8**: e67898.

[21] Savage MJ, Kalinina J, Wolfe A, et al. A sensitive abeta oligomer assay discriminates Alzheimer's and aged control cerebrospinal fluid. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2014; **34**: 2884-97.

[22] Jongbloed W, Bruggink KA, Kester MI, et al. Amyloid-beta oligomers relate to cognitive decline in Alzheimer's disease. *Journal of Alzheimer's disease : JAD* 2015; **45**: 35-43.

[23] Yang T, O'Malley TT, Kanmert D, et al. A highly sensitive novel immunoassay specifically detects low levels of soluble Abeta oligomers in human cerebrospinal fluid. *Alzheimer's research & therapy* 2015; **7**: 14.

[24] Schuster J, Funke SA. Methods for the Specific Detection and Quantitation of Amyloid-beta Oligomers in Cerebrospinal Fluid. *Journal of Alzheimer's disease : JAD* 2016; **53**: 53-67.

[25] Santos AN, Simm A, Holthoff V, Boehm G. A method for the detection of

1
2
3
4
5
6 amyloid-beta1-40, amyloid-beta1-42 and amyloid-beta oligomers in blood using
7
8
9 magnetic beads in combination with Flow cytometry and its application in the
10
11
12 diagnostics of Alzheimer's disease. *Journal of Alzheimer's disease : JAD* 2008; **14**:
13
14
15 127-31.

16
17
18 [26] Xia W, Yang T, Shankar G, et al. A specific enzyme-linked immunosorbent
19
20
21 assay for measuring beta-amyloid protein oligomers in human plasma and brain tissue
22
23
24 of patients with Alzheimer disease. *Archives of neurology* 2009; **66**: 190-9.

25
26
27 [27] Zhou L, Chan KH, Chu LW, et al. Plasma amyloid-beta oligomers level is a
28
29
30 biomarker for Alzheimer's disease diagnosis. *Biochemical and biophysical research*
31
32
33 *communications* 2012; **423**: 697-702.

34
35
36 [28] Marques AH, Silverman MN, Sternberg EM. Glucocorticoid dysregulations and
37
38
39 their clinical correlates. From receptors to therapeutics. *Annals of the New York*
40
41
42 *Academy of Sciences* 2009; **1179**: 1-18.

43
44
45 [29] Toledo JB, Toledo E, Weiner MW, et al. Cardiovascular risk factors, cortisol,
46
47
48 and amyloid-beta deposition in Alzheimer's Disease Neuroimaging Initiative.
49
50
51 *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2012; **8**: 483-9.

52
53
54 [30] Sehlin D, Sollvander S, Paulie S, et al. Interference from heterophilic
55
56
57 antibodies in amyloid-beta oligomer ELISAs. *Journal of Alzheimer's disease : JAD*
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2010; **21**: 1295-301.

[31] Donner L, Gremer L, Ziehm T, et al. Relevance of N-terminal residues for amyloid-beta binding to platelet integrin alphaIIb beta3, integrin outside-in signaling and amyloid-beta fibril formation. *Cell Signal* 2018; **50**: 121-30.

[32] Abdullah L, Paris D, Luis C, et al. The influence of diagnosis, intra- and inter-person variability on serum and plasma Abeta levels. *Neuroscience letters* 2007; **428**: 53-8.

[33] Nuutinen T, Suuronen T, Kauppinen A, Salminen A. Clusterin: a forgotten player in Alzheimer's disease. *Brain Res Rev* 2009; **61**: 89-104.

[34] Caraci F, Copani A, Nicoletti F, Drago F. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. *European journal of pharmacology* 2010; **626**: 64-71.

Table 1. Demographic and Comparison Data of MDD and Comparisons

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

^a Student's *t*-Test, ^b χ^2 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 ϵ 4 carrier, A β : amyloid β protein

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For Peer Review

Table 2. Result of Multiple Regression Analysis of A β s

	Log ₁₀ A β 40 ^a		Log ₁₀ A β 42 ^a		Log ₁₀ A β Oligomer ^a	
	β Estimate (SE)	<i>P</i> Value	β Estimate (SE)	<i>P</i> Value	β Estimate (SE)	<i>P</i> Value
Age	- 0.168 (0.002)	0.036	-0.371 (0.001)	< 0.001	-0.211 (0.003)	0.053
Sex	-0.111 (0.044)	0.109	-0.060 (0.038)	0.346	-0.137 (0.084)	0.163
Education	0.073 (0.009)	0.346	0.048 (0.008)	0.502	-0.001 (0.015)	0.989
Diagnosis	0.303 (0.045)	< 0.001	-0.194 (0.040)	0.004	-0.051 (0.089)	0.598

A β : amyloid β protein

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

Table.3 Correlations between A β Oligomer and age, education, A β 40 or A β 42 levels

	A β Oligomer levels					
	All subjects		MDD		Controls	
	R	<i>P Value</i>	R	<i>P Value</i>	R	<i>P Value</i>
Age	-0.137	0.036	-0.233	0.018	-0.024	0.786
Education	0.060	0.380	0.073	0.491	-0.012	0.895
A β 40	0.009	0.899	-0.038	0.704	0.146	0.114
A β 42	0.246	<0.001	0.216	0.035	0.170	0.065

Spearman's rank Correlation Coefficient correlation coefficients.

Table 4. Result of Multiple Regression Analysis of A β Oligomer

	Log ₁₀ A β Oligomer ^a			
	MDD		Controls	
	β Estimate (SE)	<i>P</i> Value	β Estimate (SE)	<i>P</i> Value
Age	- 0.020 (0.004)	0.888	- 0.158 (0.004)	0.328
Sex	0.000 (0.134)	0.991	- 0.145 (0.117)	0.247
Log ₁₀ A β 40 ^a	- 0.145 (0.228)	0.658	0.055 (0.163)	0.665
Log ₁₀ A β 42 ^a	0.475 (0.193)	0.022	0.177 (0.247)	0.268

A β : amyloid β protein

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