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Amyloid-Associated Depression:

A Prodromal Depression of Alzheimer Disease?

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Abstract

Context—A high ratio of plasma amyloid-β peptide 40 ($A\beta_{40}$) to$A\beta_{42}$, determined by both high $A\beta_{40}$ and low $A\beta_{42}$ levels, increases the risk of Alzheimer disease. In a previous study, we reported that depression is also associated with low plasma $A\beta_{42}$ levels in the elderly population.

Objective—To characterize plasma $A\beta_{40}$:$A\beta_{42}$ ratio and cognitive function in elderly individuals with and without depression.

Design—Cross-sectional study.

Setting—Homecare agencies.

Participants—A total of 995 homebound elderly individuals of whom 348 were defined as depressed by a Center for Epidemiological Studies Depression score of 16 or greater.

Main Outcome Measures—Cognitive domains of memory, language, executive, and visuospatial functions according to levels of plasma $A\beta_{40}$ and $A\beta_{42}$ peptides.

Results—Subjects with depression had lower plasma $A\beta_{42}$ levels (median, 14.1 vs 19.2 pg/mL; $P = .006$) and a higher plasma $A\beta_{40}$:$A\beta_{42}$ ratio (median, 8.9 vs 6.4; $P < .001$) than did those without depression in the absence of cardiovascular disease and antidepressant use. The interaction between depression and plasma $A\beta_{40}$:$A\beta_{42}$ ratio was associated with lower memory score ($\beta = -1.9$, SE = 0.7, $P = .006$) after adjusting for potentially confounders. Relative to those without depression, “amyloid-associated depression,” defined by presence of depression and a high plasma $A\beta_{40}$:$A\beta_{42}$ ratio, was associated with greater impairment in memory, visuospatial ability, and executive function; in contrast, nonamyloid depression was not associated with memory impairment but with other cognitive disabilities.

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Conclusion—Amyloid-associated depression may define a subtype of depression representing a prodromal manifestation of Alzheimer disease.

Two Large Population studies, the Rotterdam and the Mayo Clinic cohorts, have shown that a low concentration of amyloid-β peptide 42 ($A\beta_{42}$) combined with a high concentration of $A\beta_{40}$ in plasma increases the risk of developing Alzheimer disease (AD).[1,2] Depression also increases the risk or is an early symptom of AD in the elderly population.[3] We recently reported that depressed elderly individuals without cardiovascular disease (CVD) have a lower concentration of $A\beta_{42}$, leading to a high $A\beta_{40}$:$A\beta_{42}$ ratio, in plasma compared with both depressed elderly individuals with CVD and those without depression in a homebound elderly population. [4] This result led us to hypothesize that depression characterized by a high $A\beta_{40}$: $A\beta_{42}$ ratio may represent a distinct depression subtype, which we have termed *amyloid-associated depression*.

Although plasma Aβ peptides cannot be used to diagnose AD,[5] plasma $A\beta_{42}$ levels decline significantly at a preclinical or early stage of AD,[6] suggesting a biomarker for a prodrome of the disease. In amyloid precursor protein (APP) transgenic mice, plasma $A\beta_{42}$ level declines significantly before the pathological changes of AD are formed in the brain.[7,8] Elevated plasma $A\beta_{40}$ level is correlated with cerebral microvascular pathological features, which are linked with both late-life depression and AD.[9,10] Therefore, it is possible that the combination of high $A\beta_{40}$ and low $A\beta_{42}$ levels in plasma may be used as a biomarker of pathological change in the brain at a preclinical stage of AD.

Studies have demonstrated that there is an increased risk of the development of AD in some, but not all, individuals with late-life depression, suggesting a prodromal state of AD.[11,12] We hypothesized that a high plasma $A\beta_{40}$:$A\beta_{42}$ ratio plus clinical symptoms of depression may represent a prodromal depression of AD and may lead to a more imminent cognitive deterioration than in those who have a high plasma $A\beta_{40}$: $A\beta_{42}$ ratio without depression. If our assumption is correct, at the cross-sectional level, patients with amyloid-associated depression should present with a pattern of cognitive impairment consistent with prodromal AD, ie, prominent memory dysfunction, compared with those with nonamyloid depression or those without depression. To test this hypothesis, we investigated the relationships among plasma Aβ peptide levels, depression, and cognitive function in a homebound elderly population.

METHODS

STUDY POPULATION AND RECRUITMENT

We studied a group of 995 subjects, all of whom had been tested for depression status and plasma Aβ peptide levels in the Nutrition, Aging, and Memory in the Elderly study, an ongoing, population-based study supported by the National Institute on Aging. Subjects included homebound elderly clients who were enrolled in 1 of 4 home care agencies in the Boston area between 2003 and 2006. Anyone receiving home care services was registered with 1 of these agencies if he or she lived in the city of Boston, had an annual income less than $18 890, and needed home care service. All of the homebound elderly subjects 60 years or older from each of the 4 agencies were invited to participate in the study.

Eligibility for enrollment required that the participants speak English, be physically able to participate in the study home visits, and have sufficient vision and hearing to read and hear the content of the neuropsychological tests. Of all 1803 eligible subjects, 1190 individuals (66.0%) enrolled and gave informed consent to participate in the study. The population was screened for significant cognitive impairment by means of the Mini-Mental State Examination (MMSE)[13] and for estimated verbal IQ by means of the North American Adult

Reading Test.14 Those with MMSE scores of 10 or less or verbal IQ less than 75 were not eligible to continue in the study, and eligible subjects were subsequently examined. Each subject engaged in 3 home visits conducted by a research assistant, who drew a fasting blood sample and collected data on depression and medical conditions. 15 Among them, 995 subjects had both blood samples available for plasma Aβ measurements and data on depression.

PLASMA $A\beta_{40}$ AND $A\beta_{42}$ MEASUREMENTS

The blood samples were centrifuged immediately after the blood was drawn. The sandwich Aβ enzyme-linked immunosorbent assay was used. Plates were coated with 2G3 (anti-$A\beta_{40}$) and 21F12 (anti-$A\beta_{42}$) antibodies overnight at 4°C. Samples were then loaded and incubated overnight at 4°C followed by incubation with a biotinylated monoclonal anti–*N*-terminus Aβ antibody (3D6B) for 2 hours. Finally, streptavidin-conjugated alkaline phosphatase (Promega Corp, Madison, Wisconsin) was added and incubated, and the signal was amplified by adding alkaline phosphatase fluorescent substrate (Promega Corp), which was then measured. The lowest detection for both Aβ peptides was 1.6 pg/mL in the standard curves, with percentage coefficient of variation between 1.1 and 7.2, and these were used as the cutoff points for comparison and regression if levels were below the cutoff point of detection (6 samples). The samples with higher levels than the standard curve were repeated with dilutions for measurement. The intracorrelations with 2 other laboratories that have published the results of their Aβ measurements[16,17] showed $r = 0.63$ and 0.84 for $A\beta_{40}$ and $r = 0.90$ and 0.96 for $A\beta_{42}$.

DEFINITION OF DEPRESSION

Depressive symptoms were assessed by means of the Center for Epidemiological Studies Depression Scale (CES-D)[18]; a CES-D score of 16 or greater was used as the cutoff point for clinical depression.19 In 106 subjects in our study, this CES-D cutoff point had a sensitivity of 0.90 and a specificity of 0.83 for the *DSM-IV* diagnosis of major depression by a board-certified psychiatrist.

Subjects with a CES-D score of 16 or greater and a plasma $A\beta_{40}$:$A\beta_{42}$ ratiogreater than the median (7.1) were defined as having amyloid-associated depression (n = 177). Those with a CES-D score of 16 or greater and a plasma $A\beta_{40}$:$A\beta_{42}$ ratio less than or equal to the median were defined as having nonamyloid depression (n = 171). The other subgroup included those without depression (CES-D score <16; n = 647).

MEASUREMENTS

Cognition—Research assistants, trained by a board-certified neuropsychologist, administered the following cognitive tests.

1. Digit Symbol: Nine different shapes were coded with the numbers 1 to 9. The subject was given 2 minutes to draw the appropriate shapes in the allotted space according to the code. The total number of correct shapes was recorded. This test was used to evaluate nonverbal general cognition.
2. Wechsler Adult Intelligence Scale III Block Design: The subject was asked to replicate pictures of colored designs by using a set of blocks. Total raw score based on the number of correct designs completed in the given amount of time was recorded to assess both visuospatial and executive functions.
3. Trails B: The subject was asked to perform alternations between numbers and letters while the time of the task was recorded. The cap time was 301 seconds. This test was used to measure executive function.

4. Verbal Fluency (Controlled Oral Word Association Test): The subject was given 1 minute to say as many words as possible that began with a certain letter, 3 separate times. The total number of correct responses to the 3 different letters was recorded. This test was used to measure language ability that is also related to executive function.

5. Wechsler Memory Scale III Logical Memory (LM): Two stories (A and B) were read aloud to the subject; the subject was then asked to repeat as many details from the story as possible after each reading for immediate recall. After 30 minutes, the subject was asked to repeat details from both stories, which were recorded as Delayed Recall. These tests measured a different aspect of memory from word list learning, which is described in the next paragraph.

6. Wechsler Memory Scale III Word List Learning: The subject was read a list of 12 words, 4 separate times. The subject was asked to recall the list after each time it was read. The recall total score was calculated for immediate recall. After 30 minutes, the subject was asked to recall the same list of words again, which was recorded as the Delayed Recall score. These tests were used to measure verbal learning and memory.

Other Measurements—Subjects were classified as having CVD according to whether they had been previously informed by a physician that they had congestive heart failure, coronary heart disease, angina pectoris, or a heart attack. Diabetes mellitus was defined as the use of antidiabetic medication or fasting glucose level greater than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) (available on 96% of the samples). Stroke history was recorded. Current hypertension was defined as the average of systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg at 2 determinations or was considered present if the subject was taking antihypertensive medications.

A 244–base pair segment of the *APOE* gene (OMIM 107741), which included the 2 polymorphic sites, was amplified by polymerase chain reaction with a robotic thermal cycler (ABI 877; Applied Biosystems, Foster City, California). The polymerase chain reaction products were digested with 5 U of *Hha*I, and the fragments were separated by electrophoresis on 8% polyacrylamide nondenaturing gel. The specific allelic fragments were E2, E3, and E4. *APOE4* was defined by E4/4, E3/4, or E2/4.[20] Renal function, which is associated with plasma Aβ,[21] was assessed through measurements of serum creatinine.

STATISTICAL ANALYSIS

Statistical analysis was performed with SAS (version 9.1; SAS Institute Inc, Cary, North Carolina). Mean with standard deviation and *t* test or analysis of variance were used for the variables with a normal distribution, and median (quartile 1–quartile 3 [Q1–Q3]) and Wilcoxon ranksumtest or Kruskal-Wallis test were used for the variables with a skewed distribution. The χ^2 test was used to compare proportions for binary end points. Subjects' data were also divided into plasma Aβ quartiles and stratified by depression. Linear regression was used to examine associations between different cognitive domains as an outcome and the interaction between depression and plasma $A\beta_{40}$:$A\beta_{42}$ ratio or amyloid-associated depression or nonamyloid depression while adjusting for potential confounders including age, race, sex, school, creatinine level, *APOE4*, vascular diseases, and antidepressant medication use. All $A\beta_{40}$, $A\beta_{42}$, and $A\beta_{40}$:$A\beta_{42}$ ratio values were transformed to $\log_{10}$ (logAβ). These analyses were also stratified by the cognitive scores (MMSE score ≤23 and >23; LM Delayed Recall score ≤14.6and >14.6) to observe the relationships in subjects with and without significant cognitive impairment. The correlations

between log$A\beta_{42}$ and the different cognitive scores were analyzed by Spearman correlation in each quartile of plasma $A\beta_{40}$ stratified by depression status. Because Bonferroni correction was applied for regression analyses, the 2-sided significance level of $P<.0167$ was used.

RESULTS

STUDY POPULATION

Nine hundred ninety-five subjects with depression status and plasma Aβ measurements from the Nutrition, Aging, and Memory in the Elderly study were included in this analysis. The average age of this sample was 75.3 (SD, 8.4) years, and 757 subjects (76.1%) were female. The sample was multiethnic, with 607 (61.0%) white, 375 (37.7%) African American, and 13 (1.3%) other ethnicities. Of 989 subjects who provided information on education, 641 (64.8%) had completed high school.

DEPRESSION AND PLASMA Aβ PEPTIDES

Depression, defined as a CES-D score of 16 or greater, was observed in 348 of the subjects (35.0%). Subjects with depression were younger (mean [SD] age, 73.8 [8.5] vs 76.0 [8.3]; $P < .001$) and tended to have less education than those without depression, whereas there were no differences in sex and ethnicities between the groups (Table 1). Medically, the depression subgroup had similar *APOE4* frequencies, lipid profile, and rates of hypertension, stroke, and diabetes mellitus. Those with depression had higher rates of CVD (51.5% vs 38.6%; $P < .001$) and were more likely to be taking antidepressants (40.1% vs 21.8%; $P < .001$) than were those without depression. In addition, subjects with depression tended to have a slightly higher level of creatinine than did those without depression.

Distributions of plasma Aβ peptides were skewed, showing the following levels: $A\beta_{40}$: median, 132.7 pg/mL; minimum, 1.6 pg/mL; maximum, 1324.9 pg/mL; $A\beta_{42}$: median, 18.7 pg/mL; minimum, 1.6 pg/mL; maximum, 780.8 pg/mL; and $A\beta_{40}$:$A\beta_{42}$ ratio: median, 7.1; minimum, 0.04; maximum, 86.0. Subjects with depression had a lower concentration of plasma $A\beta_{42}$ (median, 17.1 vs 19.4 pg/mL; $P = .02$) than did those without depression, but there were no differences in plasma $A\beta_{40}$ level and $A\beta_{40}$:$A\beta_{42}$ ratio between those with and without depression (Table 1). When the subjects with CVD and antidepressant use were removed, those with depression had significantly higher plasma $A\beta_{40}$:$A\beta_{42}$ ratios (median, 8.9 vs 6.4; $P < .001$), lower concentrations of plasma $A\beta_{42}$ (median, 14.1 vs 19.2 pg/mL; $P = .006$), and a tendency toward higher concentrations of plasma $A\beta_{40}$ (median, 138.7 vs 125.9 pg/mL; $P = .06$) than did those without depression. This result was consistent with our previously published study.[4,22]

ASSOCIATION OF COMBINATION OF HIGH PLASMA $A\beta_{40}$:$A\beta_{42}$ RATIO AND DEPRESSION WITH COGNITIVE IMPAIRMENT

In this study sample, subjects with depression showed significantly lower scores in every cognitive domain than did those without depression (data not shown). With multivariate linear regression analysis after adjusting for potential confounders including age, education, the *APOE4* allele, and medical conditions, the interaction between depression and a high plasma $A\beta_{40}$:$A\beta_{42}$ ratio was found to be associated with cognitive impairment (Table 2), especially with memory (LM Delayed Recall:$\beta = -1.9$, SE = 0.7, $P = .006$) and tended to be associated with language (Verbal Fluency: $\beta = -1.8$, SE = 0.9, $P = .05$) and executive function (Trails B: $\beta = 9.0$, SE = 5.7, $P = .12$). Because plasma Aβ is associated with the preclinical stage of AD[1,2] but the association disappears once the disease occurs,[5] we expected that these relationships should be different between those with and without significant cognitive impairment if these associations truly represent a prodromal stage of

AD. As shown in Table 2, the interaction between depression and plasma $A\beta_{40}$:$A\beta_{42}$ ratio remained associated with cognitive impairment among those with an MMSE score greater than 23 or with an LM Delayed Recall score greater than 14.6 (the norm −1.5 SDs), cutoffs used to exclude cases with severe cognitive impairment including potential cases with dementia in the study sample[23]; however, the relationships disappeared among those with an MMSE score of 23 or less or with an LM Delayed Recall score of 14.6 or less. Adding cholesterol and high-density lipoprotein cholesterol levels into the regression models did not influence the relationships (data not shown).

These relationships were further visualized by dividing subjects into 4 quartiles by plasma $A\beta_{40}$:$A\beta_{42}$ ratio (Figure). Among subjects who had current depression, LM Delayed Recall scores decreased with every increase of plasma $A\beta_{40}$:$A\beta_{42}$ quartile, with a *P* value of .03 (Figure, A), and this relationship became more significant (mean [SE]: Q1, 18.6 [1.4]; Q2, 18.6 [1.3]; Q3, 14.3 [1.4]; Q4, 13.7 [1.0]; $P = .007$) when the subjects who were using antidepressants were removed (Figure, B). Word Learning List Delayed Recall, which assessed not only memory but also verbal learning, and the other cognitive scores tended to decrease with the increase in each $A\beta_{40}$:$A\beta_{42}$ quartile but did not reach statistical significance among subjects with depression (Figure, C–E). In contrast, at the cross-sectional level, mean cognitive scores were similar across all quartiles of $A\beta_{40}$:$A\beta_{42}$ in those without depression (Figure).

ASSOCIATION OF DECREASED PLASMA $A\beta_{42}$ IN DEPRESSION WITH COGNITIVE IMPAIRMENT ONLY AMONG THOSE WITH THE HIGHEST CONCENTRATION OF PLASMA $A\beta_{40}$

To investigate the interplaying role of both peptides, the relationship between plasma $A\beta_{42}$ and cognition was further analyzed within each $A\beta_{40}$ quartile. Among the depressed subjects in the highest plasma $A\beta_{40}$ quartile (Table 3), plasma $A\beta_{42}$ concentration was positively correlated with LM Delayed Recall scores ($r = 0.29$, $P = .005$) and tended to correlate with MMSE scores ($r = 0.22$, $P = .04$) and inversely with Trails B scores ($r = -0.23$, $P = .03$), but was not correlated with verbal fluency. In contrast, all of these correlations between plasma $A\beta_{42}$ and cognitive functions were not observed among nondepressed subjects, even though they also had the highest quartile of plasma $A\beta_{40}$ (Table 3). There was no correlation between plasma $A\beta_{42}$ levels and cognitive function among those in the lower quartiles of plasma $A\beta_{40}$ regardless of depression status (data not shown).

COGNITIVE CHARACTERIZATION OF AMYLOID-ASSOCIATED DEPRESSION

While subjects in the fourth quartile had an $A\beta_{40}$:$A\beta_{42}$ ratio with a median equal to 14.2, which is near the levels (> 12 to 16) shown to increase the risk of AD in the 2 cohorts,[1,2] both the fourth and third quartiles showed significantly lower LM Delayed Recall scores than the first or second quartile of $A\beta_{40}$:$A\beta_{42}$ among subjects with depression (Figure). We therefore used the $A\beta_{40}$:$A\beta_{42}$ median of the whole sample to define amyloid-associated depression as the following: (1) no depression: CES-D score less than 16; (2) amyloid-associated depression: CES-D score of 16 or greater and $A\beta_{40}$:$A\beta_{42}$ greater than the median; and (3) nonamyloid depression: CES-D score of 16 or greater and $A\beta_{40}$:$A\beta_{42}$ ratio less than or equal to the median.

While no differences were found in any of the other variables between the 2 depression subgroups, subjects with amyloid-associated depression were older (mean [SD] age, 74.9 [8.5] vs 72.7 [8.3] years; $P = .01$), had a slightly higher level of creatinine (mean [SD], 1.3 [1.2] vs 1.1 [1.0] mg/dL; $P = .01$) (to convert creatinine to micromoles per liter, multiply by 88.4), and were less likely to take antidepressants (32.4% vs 46.2%; $P = .009$) than were those with nonamyloid depression (Table 4).

Although there was no difference in CES-D scores between the 2 subgroups, those with amyloid-associated depression had poorer memory scores in the LM Delayed Recall (mean [SD], 15.9 [9.6] vs 18.9 [9.2]; $P = .004$) and tended to have lower Word Learning List Delayed Recall scores (mean [SD], 3.0 [2.7] vs 3.6 [2.6]; $P = .03$), lower language ability (Verbal Fluency mean [SD], 23.9 [10.9] vs 26.5 [11.7]; $P = .03$), and lower executive function (Trails B test mean [SD], 236.0 [77.8] vs 214.1 [84.3]; $P = .01$) than did those with nonamyloid depression (Table 4). In contrast, scores evaluating general cognition measured by either the MMSE or Digit Symbol and scores on visuospatial function measured by Block Design were similar between those with amyloid-associated depression and those with nonamyloid depression.

To further test the existence of the foregoing depression subtypes, multivariate linear regression analysis was applied to investigate the relationship between each cognitive domain and amyloid-associated depression vs nonamyloid depression relative to those without depression, after adjusting for potential confounders. Among the subjects with amyloid-associated depression and those without depression combined, amyloid-associated depression was associated with poor memory (LM Delayed Recall: β estimate = −1.9, SE = 0.4; $P < .001$), visuospatial dysfunction (Block Design: β estimate = −1.4, SE = 0.4; $P < .001$) (Table 5), and executive dysfunction (Trails B: β estimate = 16.0, SE = 3.3; $P < .001$) after adjusting for the confounders including antidepressant use and others. Although subjects with nonamyloid depression had a significantly higher level of plasma $A\beta_{42}$ (median, 30.7 vs 19.2 pg/mL; $P < .001$), but not $A\beta_{40}$, than those without depression, nonamyloid depression was not associated with memory performance (LM Delayed Recall: β estimate = −0.9, SE = 0.8; $P = .30$) but was related to visuospatial (Block Design: β estimate = −3.0, SE = 0.8; $P < .001$) (Table 5) and executive (Trails B: β estimate = 21.2, SE = 6.8; $P = .002$) dysfunction after adjusting for these confounders. Adding covariables of lipids and statins did not affect these relationships (data not shown).

COMMENT

The relationships between plasmaAβ level, cognitive function, and depression remain complex. The present study suggests that there may be at least 2 depression subtypes from the cognitive perspective: (1) amyloid-associated depression, which is associated with poor memory and other cognitive dysfunction (Table 2 and Figure), and (2) nonamyloid depression, which is associated with only visuospatial and executive dysfunction (Tables 4 and 5). Because a high plasma $A\beta_{40}$:$A\beta_{42}$ ratio increases the risk of AD prospectively,[1,2] we hypothesize that amyloid-associated depression is more likely to be a prodromal stage of AD than is a high $A\beta_{40}$:$A\beta_{42}$ ratio without depression. Antidepressants, specifically selective serotonin reuptake inhibitors, have been shown to be associated with lower plasma $A\beta_{40}$ levels.[22] Consistently, this study showed that fewer subjects with amyloid-associated depression took antidepressants than did those with nonamyloid depression (Table 4).

There is growing evidence in the literature that depression may be either a risk factor for AD[3,24–27] or an early symptom of AD.[12,28–32] A neuropathology study has shown that history of depression is associated with increased amyloid plaques and neurofibrillary tangles, which are the neuropathological hallmarks of AD.[33] The pattern of cognitive impairment, prominently poor memory, in amyloid-associated depression (Table 4 and 5) was consistent with mild cognitive impairment (MCI),[23] which is presumed to be a prodromal stage of AD.27,34 Although MCI is associated with depression, depression is also found to increase the risk of developing MCI.32,[35,36]

The severity of depressive symptoms was correlated with lower concentration of plasma $A\beta_{42}$, a determining factor of $A\beta_{40}$:$A\beta_{42}$ ratio, only when CVD cases were excluded from

the study sample.4 Most likely there are different subtypes of depression in the elderly population, including (1) early-onset depression, (2) poststroke depression, 37 (3) vascular depression related to CVD and other vascular risk factors that lead to executive dysfunction, 38 (4) preclinical depression of AD, and (5) comorbid depression in AD. Because these depression subtypes have different underlying pathological characteristics and prognoses, not all should be related to plasma Aβ levels, or they may be related to plasma Aβ levels differently. In contrast to amyloid-associated depression, non-amyloid depression was not found to be associated with memory (Table 5) even though these subjects had higher levels of plasma $A\beta_{42}$ than did those without depression. Although the rates of CVD (92 of 171 [53.8%] vs 82 of 177 [46.3%]; $P = .32$) and stroke (31 of 171 [18.1%] vs 35 of 177 [19.8%]; $P = .89$) were similar between subjects with nonamyloid depression and those with amyloid-associated depression, cerebral microvascular pathological data in these cases is unknown. Regardless, nonamyloid depression was strongly associated with a cognitive pattern of vascular depression and visuospatial and executive dysfunction (Table 5). This and other factors may explain the seemingly conflicting result in another study in which depressed patients had a higher, not lower, level of plasma $A\beta_{42}$ than the controls.[39,40] In fact, our own study has also shown that vascular depression related to CVD is not associated with lower plasma $A\beta_{42}$ levels.[4]

It is intriguing to find that the combination of 2 peptides in plasma, a high level of $A\beta_{40}$ and a low level of $A\beta_{42}$, was associated with poor memory, whereas each peptide alone was not found to have this relationship in the regression analysis (Table 3). The peptides $A\beta_{42}$, a major component of AD pathological findings in the brain,[41] and $A\beta_{40}$, a component of cerebral amyloid angiopathy, [42] are produced by the processing of APP. Although plasma Aβs reflect dynamic levels governed by both peripheral[21,43–46] and central[47] nervous system origins, these 2 peptides in plasma have been linked to pathological conditions in the brain. First, high plasma $A\beta_{40}$ level is associated with cerebral microvascular pathological changes, white matter hyperintensities, and lacunar infarct.[9,10] Both white matter hyperintensities and lacunar infarcts are linked to cognitive impairment,[48,49] dementia incidence,[50] and depression[49] in the elderly population. Second, studies using APP transgenic mice have demonstrated that plasma $A\beta_{42}$ level declines significantly before $A\beta_{42}$ is deposited in the brain to form the AD changes.[7,8] Therefore, a high $A\beta_{40}$:$A\beta_{42}$ ratio in plasma may be a biomarker to indicate cerebral microvascular pathological changes, which are associated with high plasma $A\beta_{40}$ level, coexisting with the AD pathological features, which may be linked to plasma $A\beta_{42}$ decline at the preclinical stage. These 2 pathological conditions in the brain additively or synergistically result in more severe cognitive dysfunction than either condition alone.[51,52]

Plasma Aβ level correlates with cerebrospinal fluid Aβ concentration in APP transgenic mice when they are young and pathological changes of AD have not yet formed. However, this correlation disappears as the animals age and Aβ is deposited in the brain.[47] Similarly in humans, although plasma Aβ level cannot be used for the diagnosis of AD,[5,18,53,54] it is still possible that plasma Aβ level can be used as a screening tool for the risk of AD. In this study, the relationship between poor memory and a high plasma $A\beta_{40}$:$A\beta_{42}$ ratio in depression was observed among subjects with normal cognition or MCI, but the relationship disappeared among those with severe cognitive impairment (Table 2). Two large population studies, mainly containing patients with late-onset AD, have shown that a high plasma $A\beta_{40}$:$A\beta_{42}$ ratio, determined by both low $A\beta_{42}$ and high $A\beta_{40}$ levels, increases the risk of AD prospectively.[1,2] Although another population study reports that high plasma $A\beta_{42}$ level is associated with the risk of AD,[55] plasma $A\beta_{42}$ level declines in these subjects before the onset of the disease, leading to low levels of plasma $A\beta_{42}$ at the prodromal stage. Unlike late-onset AD, both early-onset AD[56] and Down syndrome[57–59] present with high plasma $A\beta_{42}$ level at the preclinical stage. Another study shows that patients with MCI have higher

levels of plasma $A\beta_{42}$ than do controls but only in women.[60] It is not yet known whether plasma Aβ status is different at the preclinical stage of AD with and without depression. Because only a subset of the patients with late-onset AD present with depression at the start of the disease, our data suggest that the combination of depressive symptoms and plasma Aβ level may more specifically inform the prodromal stage of AD than does either one status alone.

Although our study found that amyloid-associated depression presented with poor memory, and others hypothesized that elevated plasma $A\beta_{42}$ level in depression may contribute to AD,[61] without a longitudinal study we cannot yet conclude that amyloid-associated depression vs nonamyloid depression is a precursor of AD. We have used different analytical methods and applied Bonferroni correction to prevent against type I error, but the cross-sectional design is still the major limitation of our study. Other limitations include the following: (1) depression was based on the CES-D score rather than the *DSM-IV* criteria, and we had no information about the onset and the course; (2) some variables, such as CVD and stroke, were self-reported; (3) the complexity of plasma Aβ62‚63 requires brain investigation to validate amyloid-associated depression as a unique depression subtype; (4) although our assays in measurements of $A\beta_{40}$ vs $A\beta_{42}$ in plasma had high sensitivity and specificity, the field lacks standard assays for interlaboratory comparisons; and (5) the correlation coefficients shown in Table 3 were significant, but probably not large enough to be applied in clinical practice. Nevertheless, our discoveries have found the relationship between depression severity and low plasma $A\beta_{42}$ level[4] and further have linked a high plasma $A\beta_{40}$:$A\beta_{42}$ ratio in depression with poor memory, especially among those with normal or mildly impaired cognition. Our findings warrant prospective studies to examine whether amyloid-associated depression is related to pathological changes in the brain and predict the onset of cognitive decline and AD in this and other populations.

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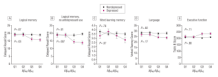

Figure.
Quartiles (Q1–Q4) of the ratio of plasma amyloid-β peptide 40 to amyloid-β peptide 42 ($A\beta_{40}$:$A\beta_{42}$) and cognitive function among those with and without depression. Different cognitive domains are shown in each $A\beta_{40}$:$A\beta_{42}$ quartile among those with and without depression. Values are shown as mean[SE]. *P* values are for comparisons among the 4 quartiles in those with and without depression.

Table 1

Demographic, Medical, and Plasma Aβ Data Among Subgroups With and Without Depression

Covariables	Depression (n=348)	No Depression (n=647)	*P* Value
Age, mean (SD), y	73.8 (8.5)	76.0 (8.3)	<.001
Sex, No. F/total (%)	267/348 (76.7)	490/647 (75.7)	.73
Education, No. high school and above/total (%)	209/347 (60.2)	432/642 (67.3)	.07
Race, No. African American/total (%)	129/348 (37.1)	246/647 (38.0)	.26
No. with *APOE4*/total (%)	73/346 (21.1)	163/636 (25.6)	.12
Total cholesterol, mean (SD), mg/dL	184.5 (44.3)	186.9 (42.7)	.33
HDL cholesterol, mean (SD), mg/dL	50.1 (14.6)	51.4 (14.8)	.24
Hypertension, No./total (%)	300/341 (88.0)	536/624 (85.9)	.56
Stroke, No./total (%)	64/337 (19.0)	129/634 (20.3)	.61
Diabetes, No./total (%)	136/329 (41.3)	214/622 (34.4)	.04
CVD, No./total (%)	174/338 (51.5)	240/622 (38.6)	<.001
Creatinine, mean (SD), mg/dL	1.2 (1.1)	1.1 (0.9)	.06
Antidepressant use, No./total (%)	137/342 (40.1)	138/632 (21.8)	<.001
Plasma Aβ peptides			
Overall			
$A\beta_{40}$:$A\beta_{42}$ ratio, median (Q1–Q3)	7.2 (4.5–11.4)	7.0 (4.0–10.4)	.16
$A\beta_{40}$, pg/mL, median (Q1–Q3)	131.3 (92.2–175.7)	133.0 (96.6–172.7)	.51
$A\beta_{42}$, pg/mL, median (Q1–Q3)	17.1 (11.7–28.0)	19.4 (12.8–29.5)	.02
Among those without CVD	(n=164)	(n=382)	
$A\beta_{40}$:$A\beta_{42}$ ratio, median (Q1–Q3)	7.3 (5.3–11.4)	6.7 (3.9–9.6)	.05
$A\beta_{40}$, pg/mL, median (Q1–Q3)	129.8 (89.9–172.2)	126.6 (92.6–167.6)	.91
$A\beta_{42}$, pg/mL, median (Q1–Q3)	15.7 (11.3–23.4)	19.2 (12.7–30.4)	.003
Among those without CVD who did not use antidepressants	(n=85)	(n=303)	
$A\beta_{40}$:$A\beta_{42}$ ratio, median (Q1–Q3)	8.9 (5.9–12.6)	6.4 (3.4–10.3)	<.001
$A\beta_{40}$, pg/mL, median (Q1–Q3)	138.7 (98.5–184.7)	125.9 (94.2–172.7)	.06
$A\beta_{42}$, pg/mL, median (Q1–Q3)	14.1 (10.1–22.8)	19.2 (13.1–33.3)	.006

Abbreviations: Aβ, amyloid-β; $A\beta_{40}$, amyloid-β peptide 40; $A\beta_{42}$, amyloid-β peptide 42; CVD, cardiovascular disease; HDL, high-density lipoprotein; Q, quartile. SI conversion factors: To convert total cholesterol and HDL cholesterol to millimoles per liter, multiply by 0.0259; creatinine to micromoles per liter, multiply by 88.4.

Table 2

Linear Multivariate-Adjusted Correlates of Each Cognitive Domain as an Outcome[a]

	LM Delayed Recall (n=885)		Verbal Fluency (n=888)		Trails B (n=873)	
	β Estimate (SE)	*P* Value	β Estimate (SE)	*P* Value	β Estimate (SE)	*P* Value
Age, y	−0.3 (0.04)	<.001	−0.2 (0.1)	.001	3.3 (0.3)	<.001
School, y	0.9 (0.1)	<.001	1.1 (0.1)	<.001	−7.9 (0.8)	<.001
APOE4	−1.1 (0.7)	.11	1.2 (0.9)	.19	4.2 (5.8)	.47
Depression	1.1 (1.4)	.43	0.2 (1.9)	.94	8.1 (12.2)	.50
Antidepressant use	1.0 (0.7)	.13	1.0 (0.9)	.28	11.2 (5.7)	.05
Log$A\beta_{40}$:$A\beta_{42}$	0.2 (0.4)	.62	0.5 (0.5)	.32	−2.1 (3.3)	.53
Depression × log$A\beta_{40}$:$A\beta_{42}$	−1.9 (0.7)	.006	−1.8 (0.9)	.05	9.0 (5.7)	.12
Depression × log$A\beta_{40}$:$A\beta_{42}$ by subgroup						
MMSE score > 23 (n=652)[b]	−1.3 (0.4)	<.001	−1.6 (0.5)	<.001	+11.4 (3.1)	<.001
MMSE score ≤ 23 (n=233)[b]	−0.03 (0.5)	.95	−1.0 (0.6)	.10	+3.4 (3.1)	.24
LM Delayed Recall score > 14.6 (n=575)[b]	−0.7 (0.3)	.02	−1.6 (0.6)	.003	+11.9 (3.6)	.001
LM Delayed Recall score ≤ 14.6 (n=310)[b]	−0.4 (0.3)	.15	−0.9 (0.6)	.13	+7.1 (3.5)	.04

Abbreviations: $A\beta_{40}$, amyloid-β peptide 40; $A\beta_{42}$, amyloid-β peptide 42; LM, Logical Memory; MMSE, Mini-Mental State Examination.

[a] Additional variables adjusting for sex, race, creatinine level, diabetes mellitus, stroke, and cardiovascular disease are also included. Depression × log$A\beta_{40}$:$A\beta_{42}$ is the interaction between depression (defined as Center for Epidemiological Studies Depression Scale score ≥ 16) and $\log_{10}$ of plasma $A\beta_{40}$:$A\beta_{42}$ ratio. The same regression models were applied to subgroups according to cognitive scores after adjusting for age, school, *APOE4*, depression, antidepressant use, and log$A\beta_{40}$:$A\beta_{42}$ in addition to sex, race, creatinine level, diabetes mellitus, stroke, and cardiovascular disease, and only the data on depression × log$A\beta_{40}$:$A\beta_{42}$ are shown. Because Bonferroni correction was applied, $P<.0167$ is considered significant.

[b] Includes all of the above adjusting variables.

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Table 3

Univariate Correlation Between Plasma $A\beta_{42}$ and Cognitive Function in Those in the Highest Quartile of Plasma $A\beta_{40}$ and Comparisons Between Those With and Without Depression[a]

	LogAβ_{42} in Patients in Highest Aβ_{40} Quartile	
	Depression (n=91)	**No Depression (n=159)**
MMSE score		
r	0.22	0.046
P value	.04	.046
LM Delayed Recall		
r	0.29	0.10
P value	.005	.24
Verbal Fluency		
r	0.06	0.04
P value	.59	.58
Trails B		
r	−0.23	−0.02
P value	.03	.76

Abbreviations: $A\beta_{40}$, amyloid-β peptide 40; $A\beta_{42}$, amyloid-β peptide 42; LM, Logical Memory; MMSE, Mini-Mental State Examination.

[a]Because Bonferroni correction was applied, $P < .0167$ is considered significant.

Table 4

Comparison of Cognitive Domains Between Subjects With Amyloid-Associated Depression and Those With Nonamyloid Depression

	Amyloid-Associated Depression (n=177)	Nonamyloid Depression (n=171)	*df*	*t* Value	*P* Value[a]
Age, mean (SD), y	74.9 (8.5)	72.7 (8.3)	346	−2.46	.01
Antidepressant use, No./total (%)	56/173 (32.4)	78/169 (46.2)	1	6.82	.009
CES-D score, mean (SD)	24.4 (7.3)	24.9 (8.3)	346	0.63	.67
APOE4, No./total (%)	39/175 (22.3)	34/171 (19.9)	1	0.30	.58
General cognition					
MMSE score, mean (SD)	24.2 (3.9)	24.9 (3.4)	346	1.82	.15
Digit Symbol, mean (SD)	31.0 (13.6)	32.6 (14.1)	334	1.04	.32
Visuospatial function					
Block Design, mean (SD)	18.6 (8.6)	18.8 (8.8)	324	0.65	.59
Executive function					
Trails B, mean (SD)	236.0 (77.8)	214.1 (84.3)	334	−2.48	.01
Language					
Verbal Fluency, mean (SD)	23.9 (10.9)	26.5 (11.7)	342	2.15	.03
Memory					
LM Delayed Recall, mean (SD)	15.9 (9.6)	18.9 (9.2)	340	2.99	.004
WLL Delayed Recall, mean (SD)	3.0 (2.7)	3.6 (2.6)	342	1.94	.03

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; LM, Logical Memory; MMSE, Mini-Mental State Examination; WLL, Word List Learning.

[a] By *t* test for means and χ^2 test for numbers and percentages.

Table 5

Multivariate-Adjusted Correlates of Each Cognitive Domain as an Outcome in Subjects Without Depression Combined With Those With Either Amyloid-Associated Depression or Nonamyloid Depression[a]

	Subjects With Amyloid-Associated Depression + Without Depression				Subjects With Nonamyloid Depression + Without Depression			
	LM Delayed Recall (n=735)		Block Design (n=710)		LM Delayed Recall (n=730)		Block Design (n=704)	
	β Estimate (SE)	*P* Value	β Estimate (SE)	*P* Value	β Estimate (SE)	*P* Value	β Estimate (SE)	*P* Value
Age, y	−0.3 (0.04)	<.001	−0.2 (0.04)	<.001	−0.3 (0.04)	<.001	−0.2 (0.04)	<.001
School, y	0.9 (0.1)	<.001	0.8 (0.1)	<.001	0.9 (0.1)	<.001	0.9 (0.1)	<.001
APOE4	−1.5 (0.7)	.04	−2.0 (0.7)	.005	−1.1 (0.8)	.16	−1.1 (0.7)	.14
Antidepressant use	1.3 (0.8)	.09	0.1 (0.7)	.87	0.4 (0.8)	.65	0.5 (0.7)	.46
Amyloid-associated depression	−1.9 (0.4)	<.001	−1.4 (0.4)	<.001				
Nonamyloid depression					−0.9 (0.8)	.30	.30	<.001

Abbreviation: LM, Logical Memory.

[a]All of the listed variables were included in the regression model after adjusting for sex, race, creatinine level, diabetes mellitus, stroke, and cardiovascular disease. Because Bonferroni correction was applied, *P*<.0167 is considered significant.