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Depression and Plasma Amyloid β Peptides in the Elderly with and without the Apolipoprotein E4 Allele

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Abstract

Depression associated with low plasma Amyloid- β peptide 42 (A β 42) leading to a high ratio of A β 40/A β 42, a biomarker of Alzheimer's disease (AD), may represent a unique depression subtype. The relationship between low plasma A β 42 in depression and the major risk factor of AD, Apolipoprotein E4 (ApoE4), is unknown. With the goal of clarifying this relationship, we analyzed 1060 homebound elders with ApoE characterization and depression status in a cross-sectional study. Plasma A β 40 and A β 42 were measured, and cognition were evaluated. In the absence of the ApoE4 allele, depressed subjects had lower plasma A β 42 [median (Q1, Q3): 17.1 (11.6, 27.8) vs. 20.2 (12.9, 32.9) pg/ml, $P = 0.006$], a higher A β 40/A β 42 ratio [median (Q1, Q3): 7.1 (4.6, 11.3) vs. 6.9 (3.4, 9.7), $P = 0.03$], and lower cognitive function (mean $\pm$ SD of Mini-Mental State Examination: 24.5 ± 3.1 vs. 25.5 ± 3.3 , $P < 0.0001$) than those without depression. In contrast, these relationships were not observed in the presence of ApoE4. Instead, regardless the depression status ApoE4 carriers had lower plasma A β 42 and a higher A β 40/A β 42 ratio than non-ApoE4 carriers. Using multivariate logistic regression, it was found that depression was not associated with ApoE4 allele, but with the interaction between plasma A β 42 and ApoE4 (OR = 3.94, 95% CI = 1.50, 10.33, $P = 0.005$), denoting low plasma A β 42 in the absence of ApoE4. Both ApoE4 carriers and non-ApoE4 carriers with depression had lower A β 42 and a higher A β 40/A β 42 ratio in plasma compared to non-ApoE4 carriers without depression in the homebound elderly. Since a combination of low plasma A β 42 and high plasma A β 40 has been shown to increase the risk of AD in two large cohort studies, amyloid-associated depression shown in this study may suggest a risk factor of AD in the absence of ApoE4.

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1. Introduction

Depression is a clinical syndrome with multiple pathologies and etiologies, and prodromal depression of Alzheimer's disease (AD) is one subtype of depression in the elderly¹⁻³. Clinically, it is often seen that some depressed, elderly patients are diagnosed and treated for depression, and then longitudinally these patients develop cognitive decline and AD. Therefore, finding specific biomarkers to differentiate prodromal depression of AD from other depression subtypes is critical, especially when therapies targeting at the early stage of AD are currently under development.

Our recent study has shown that depressed elders without cardiovascular disease (CVD) have a lower concentration of plasma A β 42, a biomarker of AD, compared to depressed elders with CVD and those without depression in a homebound population⁴. In addition, we found that depression with a high plasma A β 40/A β 42 ratio, determined by both low A β 42 and high A β 40, is associated with poor memory in the same population⁵. Because two large cohort studies have shown that a high A β 40/A β 42 ratio in plasma increases the risk of developing AD^{6, 7}, it is hypothesized that depression characterized by low A β 42 and a high A β 40/A β 42 ratio in plasma may represent prodromal depression of AD that is distinct from vascular depression⁸. We have termed it "amyloid-associated depression".

The Apolipoprotein E4 (ApoE4) allele is the major genetic risk factor of late-onset AD⁹. Some studies have shown that late life depression is not associated with ApoE4^{10, 11}. However, among the elderly aged 80 and older who have a much higher AD prevalence than those with a younger age, a relationship between ApoE4 and depression is observed, suggesting the existence of a prodromal depression of AD^{12, 13}. ApoE4 is associated with higher amyloid plaque burden composed mainly by A β 42 in AD brains than those carrying ApoE2 and E3¹⁴, probably through reduced clearance or accelerated aggregation of the peptide. Although the meaning of the relationship between depression and low concentration of A β 42 in plasma is unclear, plasma A β 42 declines significantly in the preclinical stage of AD¹⁵⁻¹⁸. These studies suggest that reduced plasma A β 42 either plays a role in AD pathogenesis or is a biomarker predicting the onset of AD. Since both ApoE4 and depression could be a prodromal stage of AD, we hypothesize that they may share some AD biomarkers, such as A β in plasma. To investigate this possibility, we explored the relationship between plasma A β 42 and depression in those with and without the ApoE4 allele in a homebound elderly population.

2. Materials and methods

2.1 Study Population and Recruitment

We studied a group of 1060 subjects, all of whom had been characterized for ApoE and depression status from an ongoing, population-based study, the Nutrition, Aging and Memory in the Elderly (NAME) study. Subjects included homebound elderly clients who were enrolled in one of four homecare agencies in the Boston area between 2003 and 2006. Elders aged 60 and older were invited to participate in the study. Anyone receiving homecare services was registered with one of these agencies if he/she lives in the city of Boston, had an annual income < \$18,890 and needed homecare service. All homebound elders aged 60 and older at each of the four agencies were invited to participate in the study. Eligibility for enrollment required that the participants spoke English, were physically able to participate in the study home visits, and had sufficient vision and hearing to read and hear the content of the neuropsychological tests. Those with Mini-Mental State Examination (MMSE) ≤ 10 or verbal IQ < 75 were not eligible to continue in the study. Of all eligible subjects, 66% enrolled in the study, and gave informed consent. Each subject participated in

three home visits conducted by a research assistant, who drew fasting blood and collected data on depression and medical conditions ¹⁹.

2.2 Measurements

ApoE genotyping—A 244 bp fragment of the apoE gene including the two polymorphic sites was amplified by PCR using a robotic Thermal Cycler (ABI 877, Perkin-Elmer/Applied Biosystems), using oligonucleotide primers F4 (5'-ACAGAATTCGCCCCGGCCTGGTACAC-3') and F6 (5'-TAAGCTTGGCACGGCTGTCCAAGGA-3'). The PCR products were digested with 5 units of Hha I and the fragments separated by electrophoresis on 8% polyacrylamide non-denaturing gel. The specific allelic fragments were: E2; E3; and E4. ApoE4 was defined by E4/4, E3/4 or E2/4 ²⁰.

Plasma A β 40 and A β 42—The blood samples were centrifuged immediately after the blood draw. The sandwich A β ELISA was used. Plates were coated with 2G3 (anti-A β 40) and 21F12 (anti-A β 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 A β antibody (3D6B) for 2 hrs. Finally, streptavidin-conjugated alkaline phosphatase (Promega, USA) was added and incubated, and the signal was amplified by adding alkaline phosphatase fluorescent substrate (Promega, USA), which was then measured. The lowest detection for both A β peptides was 1.6 pg/ml in the standard curves with %CV between 1.1 to 7.2. However, we used 3.1 pg/ml for both A β 1-40 (2 sample) and 1-42 (10 samples) as a low cut-point. A β samples were treated as the cut-points for comparison and regression if their levels were below the cut-point of detection. The samples with higher levels than the standard curve were repeated with dilutions for measurement. The intra-correlations with two other laboratories, which have published the results of the A β measurement ^{21, 22}, showed R = 0.63 and 0.84 for A β 40 and R = 0.90 and 0.96 for A β 42.

Depression: Depressive symptoms were assessed by using the Center for Epidemiological Studies Depression scale (CES-D) ²³; a CES-D score of ≥ 16 was used as the cut-off point for clinical depression ²⁴. This CES-D cut-off 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 in our study. Vascular depression was defined by a CES-D score ≥ 16 and the presence of CVD.

Cognition: Research assistants, trained by a board certified neuropsychologist, administered the cognitive tests. The subjects were screened for severe cognitive impairment using the Mini Mental State Examination (MMSE) ²⁵. Those with MMSE < 24 were defined for cognitive impairment and MMSE ≥ 24 for intact cognition. WMS-III Logical Memory: Two stories (A and B) were read aloud to the subject; the subject was then asked to repeat each story to assess immediate recall. After 30 minutes, the subject was asked to repeat both stories, which served as a measure of delayed recall.

CVD and other measurements—Subjects were classified as having CVD according to whether they had been previously informed by a doctor that they had congestive heart failure, coronary heart disease, angina pectoris or a heart attack. Stroke history was recorded. Body mass index (BMI) was measured and calculated as body mass (in kg) over the squared height (in m²). Current hypertension was defined by the average of systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg at two determinations. Renal function, which is associated with plasma A β ²⁶, was assessed by measurements of serum creatinine.

2.3 Statistical Analysis

Statistical analysis was performed using SAS (version 9.1). Normally distributed variables such as age were presented as mean $\pm$ SD and compared using T-test. Variables with skewed distributions (plasma A β 40 and A β 42) were presented as median (25th, 75th percentiles) and compared using Wilcoxon rank sum test ⁴. The Chi-Square test was used to compare proportions for binary endpoints. Both A β 40 (Log A β 40) and A β 42 (Log A β 42) were transformed to log₁₀ for multivariate regression due to skewed distributions. Logistic regression was used to examine associations between depression (CES-D score $\geq$ 16 vs. not) or intact cognition (MMSE score $>$ 24 vs. not) and Log A β 40 or LogA β 42 while adjusting for CVD, ApoE4 and other confounders of age, race, gender, school and creatinine. The interactions between LogA β 42 and ApoE4 or between LogA β 42 and depression were applied to the logistic models. For all analyses, the two-sided significant level of 0.05 was used.

3. Results

3.1 Comparisons between ApoE4 carriers and non-ApoE4 carriers

One thousand and sixty subjects from the ongoing NAME study characterized for ApoE were used in this analysis. The average age (mean $\pm$ SD) of this population was 75.3 $\pm$ 8.4 years old, and 76% were female. It was multi-ethnic with 61% Caucasian, 35% African American and 4% other ethnicities. Sixty two percent of subjects had at least high school education. Depression, defined as a CES-D score $\geq$ 16, was observed in 34% (365/1060) of the subjects. ApoE allele frequencies were ApoE2/2 = 15/1060 (1%); ApoE2/3 = 141/1060 (13%); ApoE2/4 = (32/1060 (3%); ApoE3/3 = 649/1060 (61%); ApoE3/4 = 204/1060 (19%) and ApoE4/4 = 19/1060 (2%). Overall, there were 255 subjects (24%) carrying at least one ApoE4 allele.

Table 1 shows that other than ethnicity there were no differences in demographics in those with and without ApoE4 allele. There were a higher proportion of African American subjects in those carrying the ApoE4 allele than those without ApoE4 (49% vs. 33%, $P < 0.0001$). The rates of cardiovascular disease (CVD) and other vascular diseases of diabetes, stroke and current hypertension were similar in those with and without ApoE4. Compared to non-ApoE4 carriers, ApoE4 carriers were found to have a comparable rate of depression (Table 1) or average CES-D score (Mean $\pm$ SD: 13.3 $\pm$ 10.2 vs. 12.7 $\pm$ 10.2, $P = 0.42$). The proportions of those with cognitive impairment, as defined by MMSE score $<$ 24, were similar in those with and without the ApoE4 allele.

ApoE4 carriers had a lower concentration of plasma A β 42 (median: 17.4 vs. 19.2, $P = 0.02$) and a higher A β 40/A β 42 ratio (median: 7.9 vs. 6.9, $P = 0.002$) than non-ApoE4 carriers (Table 2). In contrast, no differences in plasma A β 40 (median: 137.3 vs. 130.6, $P = 0.34$) and creatinine (mean $\pm$ SD: 1.3 $\pm$ 1.5 vs. 1.1 $\pm$ 0.8, $P = 0.54$) were found in those with and without ApoE4.

3.2 Depression and plasma A β peptides stratified by the ApoE4 status

Since depression is associated with low plasma A β 42 ⁴, in this study we examined the effects of the ApoE4 allele on depression and plasma A β peptides. Subjects were further divided into depression and no depression subgroups in both ApoE4 carriers and non-ApoE4 carriers (Table 3). In the absence of the ApoE4 allele, depressed subjects had significantly lower plasma A β 42 [median (Q1, Q3): 17.1 (11.6, 27.8) vs. 20.2 (12.9, 32.9) pg/ml, $P = 0.006$] (Figure 1) and a higher A β 40/A β 42 ratio [median (Q1, Q3): 7.1 (4.6, 11.3) vs. 6.9 (3.4, 9.7), $P = 0.03$] than those without depression. When subjects with CVD were excluded from this subset of non-ApoE4 carriers, the differences in plasma A β 42 concentration

(median: 15.7 vs. 20.7, $P < 0.0001$) and A β 40/A β 42 ratio (median: 7.4 vs. 6.3, $P = 0.002$) in those with and without depression became more significant. In contrast, in the presence of ApoE4, no difference in plasma A β 42 was found in those with and without depression (Figure 1). Nevertheless, it was noted that ApoE4 carriers regardless of depression status and non-ApoE4 carriers with depression had lower plasma A β 42 compared to non-ApoE4 carriers without depression (Figure 1 and Figure 3). No difference in plasma A β 40 was found between the subgroups with and without depression regardless of ApoE status (data not shown).

Additionally, in the absence of ApoE4, depressed subjects had significantly lower scores on MMSE (mean $\pm$ SD: 24.5 ± 3.1 vs. 25.5 ± 3.3 , $P < 0.0001$), and a greater number had cognitive impairment defined by a MMSE score lower than 24 (39% vs. 22%, $P < 0.0001$) (Figure 2) compared to those without depression. Furthermore, in the absence of ApoE4, depressed subjects had lower scores on logical memory (mean $\pm$ SD: 17.3 ± 9.7 vs. 19.4 ± 9.6 , $P = 0.002$) than those without depression. In contrast, in the presence of ApoE4 no difference in MMSE (mean $\pm$ SD: 25.0 ± 3.8 vs. 25.0 ± 3.8 , $P = 0.88$) was found in those with and without depression in this population (Figure 1B).

3.3 Analysis with multivariate regression

To further explore the relationship between depression and plasma A β 42 in the presence and absence of ApoE4, multivariate logistic regression was performed (Table 4). Since it is well documented that late life depression is highly related to vascular diseases, such as CVD, the analytic models were built based on demographic variables in addition to vascular diseases to characterize any potential confounders, which might be expected. Low plasma A β 42 (OR = 0.63, 95% CI = 0.42, 0.94, $P = 0.02$) and CVD (OR = 1.79, 95% CI = 1.35, 2.37, $P < 0.0001$) were independently associated with depression after adjusting for confounders of age, race, gender, diabetes, creatinine and A β 40. There was no relationship between the ApoE4 allele and depression (Table 4: Model I). Since the relationship between depression and plasma A β 42 was strengthened after stratification with ApoE4 (Figure 1A), we, therefore, analyzed the interaction between plasma A β 42 and ApoE4. This interaction, denoting low plasma A β 42 in the absence of ApoE4, was found to be positively associated with depression with OR = 3.94, 95% CI = 1.50, 10.33, $P = 0.005$ (Table 4: Model II), and the relationship was further strengthened after adjusting for MMSE with OR = 4.65, 95% CI = 1.73, 12.5, $P = 0.002$ (Table 4: Model III).

The proportions of depressed African American subjects compared to the non-depressed subgroups were different in the presence (41% vs. 53%, $P = 0.01$) and absence (36% vs. 31%, $P = 0.07$) of ApoE4 (Table 3). Ethnicity, however, was not associated with depression (Table 4). While in the absence of ApoE4 more depressed subjects had diabetes compared to those without depression, no difference was found in rates of diabetes between these subgroups in the presence of ApoE4 (Table 3). Again, diabetes status was not found to be associated with depression in this study sample (Table 4). The rates of stroke between those with and without depression were similar in the presence or absence of ApoE4, and stroke was not found to be associated with depression using multivariate regression analysis (data not shown).

4. Discussion

ApoE4 is the major risk factor of AD⁹, and is associated with low level of A β 42 in cerebral spinal fluid (CSF) even among the elderly with normal cognition²⁷. Late life depression has also been shown to occur prior to AD¹⁻³. Using a homebound elderly population, the subset of depressed non-ApoE4 carriers was found to have low plasma A β 42 and a high A β 40/A β 42 ratio, as would be expected had they been ApoE4 carriers (Tables 2 and 4, Figure 1

and Figure 3). And these depressed subjects had cognitive impairment, including poor memory (Figure 2 and Figure 3). As a high plasma A β 40/A β 42 ratio has been found to increase the risk of AD in two longitudinal studies^{6, 7}, we hypothesize that amyloid-associated depression, characterized by low plasma A β 42 and high A β 40/A β 42 ratio, might represent another preclinical stage or a risk of AD in addition to ApoE4.

We recently reported 4 that there are at least two separate depression subtypes in this homebound elderly population: 1) vascular depression 8, which is linked with CVD and not necessarily associated with low plasma A β 42²⁸, and 2) amyloid-associated depression, which is associated with low plasma A β 42²⁸. In this study, we found that depression in the absence of ApoE4 was associated with low plasma A β 42 and high A β 40/A β 42 ratio (Figure 1). In the presence of the ApoE4 gene, however, low plasma A β 42 and high A β 40/A β 42 ratio were found regardless of depression status (Table 2 and Figure 1). Plasma A β 42 levels decline significantly prior to the onset of AD and in its early stages¹⁵, leading to a high plasma A β 40/A β 42 ratio which significantly increases the risk of AD longitudinally^{6, 7}. Depression may also precede AD²⁹⁻³³. Therefore, while ApoE4 might lead to AD regardless of depression status, amyloid-associated depression accompanied by a decline in plasma A β 42 may herald AD even in the absence of the ApoE4 allele.

Studies have shown that plasma A β peptides cannot be used to diagnose AD 34, 35. Our findings in this study were consistent with these previous studies in that we did not find a relationship between cognition and plasma A β 42 alone in the homebound elderly (data not shown). We found, however, that cognitive impairment was associated with the co-occurrence of low plasma A β 42 and depression in the absence of ApoE4 (Figure 2), even after adjusting for confounders (data not shown). This result suggests that, despite its lack of usefulness in diagnosing the disease in its later stage, low plasma A β 42 might represent a prognostic biomarker indicating a pre-clinical stage or an early stage of AD^{6, 7}, especially in those who have depression. Low A β 42 in CSF, a consensus diagnostic test for AD 36, correlates with plasma A β 42 at the pre-clinical stage of AD, but this relationship disappears in the later stage of the disease 37.

Multiple etiologies of AD involving multiple pathways can result in the brain AD pathologies: A β plaques and neurofibrillary tangles. ApoE4 is one major AD risk factor, and its role in AD pathogenesis is probably mediated through increased aggregation of A β or impaired clearance of A β in the brain (reviewed by Holtzman DM, 2004) 38. It is not yet clear how late life depression influences the degenerative process of AD. A history of depression correlates with an increase in both amyloid plaques and neurofibrillary tangles in AD 39. On the other hand, approximately 80% of the depressed elderly do not develop AD after a 4-year follow-up 3. This suggests that there are different subtypes of depression in the elderly including 1) early-onset depression; 2) post-stroke depression 40; 3) vascular depression related to CVD and other vascular risk factors that lead to executive dysfunction 8; 4) pre-clinical depression of AD and 5) comorbid depression in AD. In our study, after adjusting for MMSE the relationship between depression and plasma A β 42 in the absence of ApoE4 was strengthened (Table 4: Model III), suggesting that different depression subtypes have different cognitive patterns and prognoses. Since these depression subtypes may have different underlying pathologies, not all would be expected to be related to plasma A β , or plasma A β might bear upon the subtypes in different ways. The finding that depression associated with a high plasma A β 40/A β 42 ratio present with significant poorer memory compared to those with a low plasma A β 40/A β 42 ratio argues that amyloid-associated depression is probably a preclinical stage of AD⁵.

Our study did not find a difference in depression rates between those with and without ApoE4 (Table 1). This result was consistent with previously published studies that showed

that the ApoE4 allele does not increase the risk of late life depression^{10, 11}. Other studies showed that in subjects aged 80 and older, a relationship between ApoE4 and depression is observed^{12, 13}, probably suggesting a prodromal depression of AD. It is noted that the average age of our study sample was 75. Longitudinal studies have shown that ApoE4 increases the risk of cognitive decline in the elderly⁴¹⁻⁴³. In our study, those non-ApoE4 carriers with depression had lower cognitive function compared to those who did not have depression (Figure 2). At cross-sectional level, those ApoE4 carriers tended to have more cognitive impairment than those non-ApoE4 carriers without depression, but did not reach the statistical significance.

Although our study and others^{6,7} have shown that low plasma A β 42 levels have a potential to be used as a prognostic biomarker of AD, another population study reports that high plasma A β 42 is associated with the risk of AD, but plasma A β 42 declines before the onset of the disease⁴⁴, which could lead to low levels of plasma A β 42 at the prodromal stage. Unlike late-onset AD, both early-onset AD⁴⁵ and Down syndrome⁴⁶ present with high plasma A β 42 levels at the pre-clinical stage. One study shows that MCI patients have higher levels of plasma A β 42 than the controls only in women⁴⁷. It is not yet known whether plasma A β status is different at the pre-clinical stage of AD with and without depression. Importantly, despite that our assays in measurements of A β 40 vs. A β 42 in plasma had high sensitivity and specificity, the field lacks standard assays for inter-laboratory comparisons. Therefore, the complexity of plasma A β 48⁴⁹ requires brain investigation and a longitudinal follow-up to validate amyloid-associated depression as a unique depression subtype. Other limitations of this study include: 1) the cross-sectional design prevents the study from exploring the possibility that depressed elderly with ApoE4 have shorter life spans and would therefore be less likely to be included in this study; 2) depression was based on the CES-D score rather than DSM-IV criteria, and we have no information about its onset and the course; 3) we are unable to determine whether amyloid-associated depression is a precursor of AD without longitudinal data of the study. Nevertheless, our findings link amyloid-associated depression characterized by low plasma A β 42 and a high A β 40/42 ratio to cognitive impairment specifically in non-ApoE4 carriers. Prospective studies and brain investigations are needed to determine whether amyloid-associated depression is an independent risk factor for AD.

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Plasma Abeta42, depression and ApoE4

Figure 1a,b. Depression and A β peptides among those with and without the ApoE4 allele

The subgroups with (a) and without (b) depression were compared in the content of ApoE4 status. Plasma A β 42 levels were compared between different subgroups. Median (Q1, Q3) and Wilcoxon rank sum test were used. P values for the statistical significance between the two subgroups are shown.

Cognition, depression and ApoE4

Figure 2. Depression and cognitive status among those with and without the ApoE4 allele
 The subgroups with and without depression were compared in the content of ApoE4 status.
 (A) Plasma A β 42 levels were compared between different subgroups. Median and Wilcoxon rank sum test were used. (B) Proportions of subjects in different subgroups with Mini-mental State Exam (MMSE) score < 24 were compared by Chi-square test. P values for the statistical significance between the two subgroups are shown.

Figure 3.

Table 1

Demographic and medical status of non-ApoE4 and ApoE4 carriers in the homebound elderly population

<u>Demographic Data</u>	ApoE4 - N = 805	ApoE4 + N = 255	P values
Age, year, mean $\pm$ SD (n = 1058)	75.3 $\pm$ 8.5	74.7 $\pm$ 8.3	0.32
High School Graduate and above, n/total (%)	499/805 (62%)	152/242 (63%)	0.65
BMI, kg/m², mean $\pm$ SD (n = 987)	31.8 $\pm$ 8.9	31.3 $\pm$ 8.4	0.59
African Americans, n/total (%)	265/805 (33%)	126/255 (49%)	< 0.0001
Female, n/total (%)	607/805 (75%)	197/255 (77%)	0.61
<u>Medical Conditions</u>			
Cardiovascular disease, n/total (%)	337/779 (42%)	142/243 (43%)	0.64
Stroke, n/total (%)	162/786 (21%)	45/247 (18%)	0.47
Diabetes, n/total (%)	278/773 (36%)	89/245 (36%)	0.94
<u>Psychiatric Conditions</u>			
Depression, n/total (%)	285/805 (35%)	80/255 (31%)	0.24
MMSE Score < 24, n/total (%)	228/805 (28%)	69/255 (27%)	0.75

Mean $\pm$ SD or n/total (%) are presented. P values for statistical significance are shown.

Table 2Plasma A β peptides and creatinine of non-ApoE4 and ApoE4 carriers in the homebound elderly population

	ApoE4 - N = 805	ApoE4 + N = 255	P values
A β 42, pg/ml, median (Q1, Q3)	19.2 (12.4, 34.5)	17.4 (11.6, 25.7)	0.02
A β 40, pg/ml, median (Q1, Q3)	130.6 (93.9, 171.2)	137.3 (93.4, 186.1)	0.34
A β 40/A β 42 Ratio, median (Q1, Q3)	6.9 (4.1, 10.4)	7.9 (4.9, 12.0)	0.002
Creatinine, mg/DL, mean $\pm$ SD	1.1 $\pm$ 0.8	1.3 $\pm$ 1.5	0.54

Median, Q1 and Q3 or Mean $\pm$ SD are presented. P values for statistical significance are shown.

Table 3
Demographic and medical status of those with and without depression in the content of ApoE4 status

Demographic Data	ApoE4 -			ApoE4 +		
	Depression N = 285	No Depression N = 520	P values	Depression N = 80	No Depression N = 175	P values
Age, year, mean $\pm$ SD (n = 1058)	73.7 $\pm$ 8.5	76.1 $\pm$ 8.4	0.0004	72.7 $\pm$ 8.0	75.5 $\pm$ 8.3	0.01
High School Graduate and above, n/total (%)	167/285 (59%)	332/517 (64%)	0.04	43/79 (54%)	113/173 (65%)	0.008
African Americans, n/total (%)	103/285 (36%)	162/520 (31%)	0.07	33/80 (41%)	93/175 (53%)	0.01
Female, n/total (%)	219/285 (77%)	388/520 (75%)	0.50	58/80 (73%)	139/175 (73%)	0.26
<u>Medical Conditions</u>						
Cardiovascular disease, n/total (%)	140/276 (51%)	197/503 (39%)	0.002	42/78 (54%)	59/165 (36%)	0.008
Stroke, n/total (%)	52/274 (19%)	210/512 (21%)	0.46	16/79 (20%)	29/168 (17%)	0.60
Diabetes, n/total (%)	112/267 (42%)	166/506 (33%)	0.01	28/76 (36%)	61/169 (36%)	1.00

Mean $\pm$ SD or n/total (%) are presented. P values for statistical significance are shown.

Table 4

Effects of ApoE4 allele, plasma A β peptides, and the interaction between plasma A β 42 and ApoE4 status on depression

	Model I Depression (N = 919)		Model II Depression (N = 919)		Model III Depression (N = 914)	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Age, year	0.96 (0.94, 0.98)	0.03	0.96 (0.94, 0.98)	0.007	0.95 (0.93, 0.97)	<0.0001
Female	1.14 (0.82, 1.59)	0.43	1.16 (0.83, 1.62)	0.37	1.21 (0.86, 1.69)	0.27
Caucasian	1.04 (0.77, 1.40)	0.79	1.02 (0.76, 1.38)	0.88	1.29 (0.93, 1.77)	0.12
Creatinine	1.11 (0.96, 1.28)	0.17	1.09 (0.96, 1.26)	0.24	1.10 (0.95, 1.27)	0.22
Diabetes	1.06 (0.79, 1.44)	0.69	1.05 (0.78, 1.43)	0.75	0.94 (0.69, 1.28)	0.69
Cardiovascular disease	1.79 (1.35, 2.37)	<0.0001	1.78 (1.34, 2.37)	<0.0001	1.80 (1.34, 2.42)	<0.0001
Log A β 40	1.26 (0.71, 2.25)	0.44	1.24 (0.69, 2.24)	0.47	1.19 (0.66, 2.16)	0.56
Log A β 42	0.63 (0.42, 0.94)	0.02	0.48 (0.31, 0.76)	0.002	0.48 (0.30, 0.77)	0.002
ApoE4	0.77 (0.55, 1.08)	0.14	0.14 (0.04, 0.49)	0.003	0.11 (0.03, 0.42)	0.001
LogA β 42*ApoE4	-	-	3.94 (1.50, 10.33)	0.005	4.65 (1.73, 12.50)	0.002
MMSE Score	-	-	-	-	0.90 (0.86, 0.94)	<0.0001

Multivariate logistic regression analyses were performed. CES-D = Center for Epidemiological Studies Depression scale, and CES-D score ≥ 16 was used to define current depression and served the outcome of the analysis; Log A β 40 = logarithms of A β 40; Log A β 42 = logarithms of A β 42; LogA β 42*ApoE4 = interaction between logarithms of A β 42 and ApoE4; MMSE = Mini Mental State Exam P values for statistical significance are shown.