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The Demographic and Medical Correlates of Plasma Aβ40 and Aβ42

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Abstract

Plasma amyloid beta-42 (Aβ42) and Aβ42/Aβ40 are increasingly recognized as biomarkers for dementia, with low levels indicating increased risk. Little is known about the demographic and medical correlates of plasma Aβ40 or Aβ42. In 997 community-dwelling, non-demented older adults from the Health, Aging and Body Composition Study, we determined the cross-sectional association between a wide range of demographic and medical variables with Aβ40 and Aβ42. In multivariate stepwise linear regression models, Aβ40 was significantly associated with race (β=−14.70, F=22.01, p<0.0001), age (β=1.34, F=6.39, p=0.01), creatinine (β=52.91, F=151.77, p<0.0001), and serum brain-derived neurotrophic factor (BDNF) (β=−0.0004, F=7.34, p=0.007); Aβ42 was significantly associated with race (β=−3.72, F=30.83, p<0.0001), sex (β=1.39, F=4.32, p=0.04), education (β=1.50, F=4.78, p=0.03), Apolipoprotein E (APOE) e4 allele status (β=−2.82, F=16.57, p<0.0001), and creatinine (β=9.32, F=120.09, p<0.0001). These correlates should be considered as potential confounders in future studies investigating plasma Aβ as a biomarker of dementia. Understanding fully how these correlates mediate or modify the association between plasma Aβ and dementia will be a fundamental step in determining the biological pathways through which plasma Aβ40 and Aβ42 are associated with dementia, and in determining their full potential as biomarkers.

Keywords

Plasma amyloid beta; dementia; cognitive decline; biomarker; epidemiology

Introduction

Recent studies have indicated that plasma amyloid beta-40 (Aβ40), Aβ42 and the ratio (Aβ42/Aβ40) may be promising biological markers for cognitive impairment or dementia in older adults. For example, decreased plasma Aβ42 was shown to be associated with increased risk for developing Alzheimer's disease (AD) and increased cognitive decline over

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Conflicts of Interest
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time.[1–4] Similarly, a prospective longitudinal study found that low plasma Aβ40 was associated with incident AD in older men.[5] Low Aβ42/Aβ40 has also been associated with increased cognitive decline over time among non-demented elders, and with increased risk for AD.[1, 6] These two proteins are of interest because they accumulate in the brain, forming the plaques found in AD patients. Furthermore, these proteins have been well established as biomarkers for AD when measured from cerebrospinal fluid (CSF) samples. For example, CSF Aβ42 declines in patients with incident dementia, and has been documented as one of the most sensitive biomarkers for detecting prevalent AD.[7, 8] Similarly, some studies have shown that low CSF Aβ40 is associated with mild cognitive impairment (MCI) or the early stages of dementia.[9] The possibility of identifying Aβ as a useful biomarker from plasma is clinically important because a simple blood draw is much less invasive and less expensive than the lumbar puncture required to obtain CSF.

In spite of this ongoing research, little is known about the general demographic and medical correlates of plasma Aβ40 and Aβ42, and how correlates may impact the relationship between plasma Aβ and cognitive decline. This information is important so these proteins can be fully understood as biomarkers, and so future studies investigating the potential use of plasma Aβ40 and Aβ42 as biomarkers for cognitive decline can measure and account for all potential confounders. Furthermore, understanding what factors are related to plasma Aβ40 and Aβ42 may shed some light on the mechanisms underlying an association between plasma Aβ and cognitive function. Importantly, one previous study has investigated correlates of plasma Aβ, but the study population consisted of only 205 cognitively normal controls, while the remaining sample was comprised of patients with MCI (n=348) or AD (n=162).[10] As previous studies have shown that plasma Aβ levels change at different stages of disease progression[11, 12], more studies are needed to investigate correlates of these markers in community-dwelling, non-demented older adults. Thus, the objective of this study is to describe the demographic and medical correlates of plasma Aβ40 and Aβ42 in a population of community-dwelling, non-demented, black and white older adults, age 70–79 at baseline.

Methods

Study Population

Community-dwelling white and black older adults were enrolled in the ongoing Health Aging and Body Composition (Health ABC) study. This prospective cohort study began in 1997, and adults ranged in age from 70 to 79 years at enrollment, and lived in Memphis, TN or Pittsburgh, PA. Participants were recruited from a random sample of Medicare eligible adults living within the designated zip codes, and were eligible if they reported no difficulties performing activities of daily living, walking a quarter mile, or climbing 10 steps without resting. They also had to be free of life-threatening cancers, and plan to remain within the study area for at least three years.[13] Plasma Aβ42 and Aβ40 were measured in a random sample of 1000 sex and race stratified participants. Of those, 3 had incomplete plasma amyloid data due to insufficient amounts of stored blood or measurement error; thus our analytic cohort was comprised of 997 participants. All participants included in this analytic cohort were free of cognitive impairment at baseline; consistent with previous literature, cognitive impairment was defined as a Modified Mini-Mental Status Exam (3MS) score <80.[14] Compared to Health ABC participants who did not have plasma Aβ measured, those in the subgroup were more likely to be black, female, and to have lower mean education, but did not differ on other characteristics. This study was approved by the institutional review boards of the University of Pittsburgh and the University of Tennessee, Memphis, and that of the Coordinating Center, the University of California, San Francisco. All participants signed a written informed consent.

Beta Amyloid

Stored plasma obtained at the first Health ABC follow-up visit was used to measure Aβ40 and Aβ42. Plasma was stored at −70° C at Fisher BioServices, Inc. Laboratories and shipped directly to the analytical laboratory. Plasma Aβ was measured at the laboratory of Dr. Steven Younkin at the Mayo Clinic using Innogenetics INNO-BIA assays. The detection limit for this assay is 12 pg/ml for Aβ40 and 5 pg/ml for Aβ42. Mean inter-assay coefficient of variation was 9.9% for Aβ40 and 9.3% for Aβ42 and mean intra-assay coefficient of variation was 3.5% for Aβ40 and 2.3% for Aβ42. Consistent with previous literature, tertile cutoffs were used to categorize Aβ42 and Aβ42/Aβ40 into “low” “medium” and “high” groups.

Potential Correlates

At baseline, demographic data including self-reported participant age, race, sex and education were recorded. Literacy was measured at baseline with the Rapid Estimate of Adult Literacy in Medicine (REALM).[15] REALM scores were categorized as 8th grade and ≤8th grade, as it has been reported that this cutoff differentiates those who are functionally illiterate versus literate in a healthcare setting.[16, 17] Cognitive function at baseline was measured with the Modified Mini-Mental Status Exam (3MS). The 3MS is an assessment of global cognitive function with components for orientation, concentration, language, praxis, and immediate and delayed memory.[18] Social support scores were based on the average frequency of visits per week with friends, neighbors, and relatives. Scores were dichotomized into two groups: < the median or ≥ the median. Self-reported information on smoking history was recorded and dichotomized into never versus ever having smoked.

Prevalent disease algorithms based on both self-report and physician diagnoses, recorded medications and laboratory data were used to create comorbidity variables indicating presence of diabetes mellitus, hypertension, stroke or transient ischemic attack (TIA), and myocardial infarction (MI). The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms with a score ≥16 consistent with possible depression.[19] Body mass index (BMI) (kg/m^2) was calculated from direct height and weight measurements at baseline. Physical activity level was determined using a standardized questionnaire designed specifically for the Health ABC study, which has been previously described.[20] Total physical activity including household chores, paid work, volunteer work, care giving, stair climbing, non-exercise walking, walking for exercise and other moderate and vigorous exercise activities, were measured in kilocalories per week (kcal/wk).[20]

Apolipoprotein E (APOE) e4 allele status was determined using standard Single Nucleotide Polymorphism (SNP) genotyping techniques and dichotomized into having one or more APOE e4 allele versus no allele.[21] Brain-derived neurotrophic factor (BDNF) was measured from frozen serum collected at the first follow-up visit. Assays were performed by R&D Systems’ Analytical Testing Service, using their own commercial kit employing an enzyme-linked immunosorbent assay method. The detection limit for this assay is 1250 pg/mL. The mean inter-assay coefficient of variation is 9.0%, and the mean coefficient of variation within assay is 5.0%.

At baseline, low-density lipoprotein cholesterol (LDL) (mg/dl), high-density lipoprotein cholesterol (HDL) (mg/dl), total cholesterol (mg/dl) and triglycerides (mg/dl) were measured from fasting blood serum. Measures of high sensitivity C-reactive protein (CRP), tumor necrosis factor-α (TNFα), interleukin-6 (IL-6) and creatinine were obtained from frozen serum or plasma collected at baseline after an overnight fast. Samples were frozen at −70°C and were shipped to the Core Laboratory at the University of Vermont.[22, 23] Serum CRP was measured in duplicate by enzyme-linked immunosorbent assay on the basis of

purified protein and polyclonal anti-CRP antibodies, and assays were standardized according to the World Health Organization First International Reference Standard with a sensitivity of 0.08 μg/ml.[22] Plasma IL-6 and TNFα were measured in duplicate by ELISA kits from the R&D Systems (Minneapolis, MN).[24] The detectable limit for IL-6 was 0.10 pg/ml, and for TNFα was 0.18 pg/ml.[24] Creatinine was measured with the colorimetric technique on a Johnson & Johnson VITROS 950 Chemistry Analyzer (Johnson & Johnson, New Brunswick, N.J., USA) using the enzymatic method.[23]

Statistical Analyses

To describe the distribution of plasma Aβ40 and Aβ42, a variety of descriptive statistics were calculated including assessment of the mean, median, range and standard deviation. The relationship between Aβ40 and Aβ42 was examined using Spearman's correlation coefficient. Fisher's exact, Pearson's chi-square, and t-tests were used, as appropriate, to determine the association between plasma Aβ40 and Aβ42 tertile and baseline participant characteristics. Finally, stepwise multivariate linear regression models were examined for both Aβ40 and Aβ42 to determine which characteristics independently predicted plasma level. Variables that were associated in bivariate analyses ($p<0.10$) with Aβ40 or Aβ42, respectively, were considered for these models. We used a forward stepwise selection process with variables significant at the $p=0.15$ entry and exit criteria to determine the final multivariate models. The relative strength of the associations was expressed as an absolute difference in units of change chosen to approximate 1 SD in the distribution for each continuous variable or null category for dichotomous variables, similar to previous studies investigating correlates of markers in older adults.[25, 26] The formula used to calculate the absolute difference in rate of change in plasma Aβ per unit change (SD) of the independent variable was $\beta^* =$ unstandardized β x unit change in independent variable. The corresponding 95% confidence intervals (CIs) were calculated using the following formula: $\beta \pm (1.96 \times SE) \times$ unit change. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

Among the 997 community-dwelling older adults, the mean (standard deviation) of Aβ40 and Aβ42 were 191.6 pg/ml (50.3) and 33.9 (9.6), respectively. The median of Aβ40 was 192.5 pg/ml, and of Aβ42 was 32.8 pg/ml. The Spearman correlation coefficient was 0.51 ($p<0.0001$) for both markers as continuous variables, and 0.42 ($p<0.0001$) for both markers with tertile cutoffs.

Those with low plasma Aβ40 were significantly younger (73.6±3.0 years for low tertile vs. 74.5±2.9 for high tertile, p-value = 0.0001), more likely to have less than a high school education (N(%), 223 (67.2%) vs. 197 (59.5%), p-value = 0.03) to be black (201 (60.4%) vs. 147 (44.1%), p-value <0.0001), to have lower serum creatinine (mg/dl, 1.0±0.2 vs. 1.2±0.5, p-value <0.0001), to have higher HDL cholesterol (mg/dl, 56.6±17.7 vs. 52.9±16.5, p-value=0.02), to have higher BDNF (pg/ml, 23361.6±10648.3 vs. 20944.4±10022.9, p-0.006), and to have lower TNFα (pg/ml, 3.3±2.1 vs. 3.7±1.7, p=0.0007) (Table 1). There were no differences of Aβ40 by sex, literacy, baseline 3MS scores, social support, physical activity, history of stroke/TIA, diabetes history, myocardial infarction, BMI, depressive symptoms, APOE e4 allele status, C-reactive protein, IL-6, total cholesterol, LDL cholesterol, triglycerides, or smoking history.

Those with low plasma Aβ42 were more likely to be female (196 (59.8%) vs. 183 (55.5), p-value = 0.05), to have less than a high school education (231 (70.6%) vs. 193 (58.8%), p-value = 0.006), to be black (214 (65.2%) vs. 151 (45.8%), p-value <0.0001), to have a history of diabetes (94 (29.8%) vs. 68 (21.3%), p-value = 0.04) to have at least 1 APOE e4

allele (118 (38.3%) vs. 73 (23.1%), p-value=0.0002), to have lower creatinine (mg/dl, 1.0±0.2 1.1±0.6, p-value<0.0001), to have greater social support (179 (54.6%) vs. 154 (46.7%), p-value=0.05), and to have higher HDL cholesterol (mg/dl, 57.3±17.9 vs. 53.5±16.9, p=0.007) (Table 2). There were no differences by Aβ42 and age, literacy, baseline 3MS scores, physical activity, history of stroke/TIA, myocardial infarction, BMI, depressive symptoms, C-reactive protein, TNFα, IL-6, BDNF, total cholesterol, LDL cholesterol, triglycerides, or smoking history.

In a stepwise multivariate linear regression model, Aβ40 was significantly associated with age (β=1.34, F=6.39, p=0.01), race (β = −14.70, F=22.01, p<0.0001), creatinine (β = 52.91, F=151.77, p<0.0001), and BDNF (β=−0.0004, F=7.34, p=0.007) (Table 3). Similarly, Aβ42 was significantly associated with race (β=−3.72, F=30.83, p<0.0001), sex (β=1.39, F=4.32, p=0.04), education (β=1.50, F=4.78, p=0.03), APOE e4 allele status (β=−2.82, F=16.57, p<0.0001), and creatinine (β=9.32, F=120.09, p<0.0001) (Table 3).

The strength of the associations expressed as an absolute difference in units of change (1 SD for continuous variables or null category for dichotomous variables) are shown in Table 4. Age, race, creatinine, and BDNF were all significant correlates of Aβ40; race, sex, education, APOE e4, and creatinine were all significant correlates of Aβ42, although sex and education were borderline (Table 4).

Discussion

Our results indicated that plasma Aβ40 and Aβ42 are fairly normally distributed among older adults without dementia. Furthermore, our results suggested that in a community-dwelling sample of white and black older adults, plasma Aβ40 significantly differed by age, race, education, serum creatinine, serum BDNF, HDL cholesterol and the inflammatory marker TNFα. Similarly, plasma Aβ42 was significantly associated with race, sex, education, social support, a history of diabetes, HDL cholesterol, serum creatinine and APOE e4 allele status.

Our results are supported by prior indirect associations between demographic and medical risk factors and AD. For example, we found black race was associated with significantly lower levels of plasma Aβ40 and Aβ42, and being female was significantly associated with a lower level of Aβ42. As it has been shown that African Americans and females have an increased risk of AD, and other studies have shown low Aβ42 is associated with increased risk of dementia, these results seem consistent.[4, 27]

Our results showing an association between diabetes and plasma Aβ42 are in support of earlier studies suggesting that consistently increased insulin levels in the brain may lead to increased Aβ42 deposition and plaque formation, and subsequent decreases in peripheral plasma Aβ42.[28, 29] Our results differ from another longitudinal study that recently found higher total cholesterol and higher LDL cholesterol predicted low plasma Aβ42.[30] Furthermore, this previous study found no association between HDL cholesterol and Aβ42 at baseline or over time, as we did with plasma Aβ40 and Aβ42.[30] Similarly, we found no association between Aβ40 or Aβ42 with LDL, total cholesterol, triglycerides, or history of myocardial infarction or stroke – both of which have high cholesterol as a common risk factor. Finally, the association we found between both plasma Aβ40 and Aβ42 and serum creatinine – a measure of renal function – is supported by another study which found that in older patients with chronic renal failure, dialysis significantly lowered plasma Aβ42 level; these results indicate a close relationship may exist between renal function and plasma Aβ42.[31]

It is widely known that APOE e4 allele is associated with increased risk for AD, and in this study we found older adults with at least one APOE e4 allele were more likely to have low Aβ42; APOE has also been shown to modify the association between Aβ42 and Aβ42/Aβ40 and cognitive decline.[6, 32] An interesting finding was the association between higher serum BDNF and low plasma Aβ40. BDNF is thought to have neuroprotective effects and to promote brain plasticity.[33] BDNF has also been shown to regulate the Amyloid Precursor Protein (APP) which is thought to reduce the production of amyloid peptides (i.e. Aβ40).[33] Thus, it is possible that higher levels of serum BDNF may, at least in part, regulate plasma Aβ40, resulting in the lower plasma Aβ40 level. There was no relationship found between plasma Aβ42 and serum BDNF. The inflammatory marker TNFα has been shown to be associated with increased risk of cognitive decline over time.[34] While we found an association between low TNFα and low plasma Aβ40, which is contrary to what we expected, we believe this could be due to the less specific association between Aβ40 and AD or cognitive decline (versus the relationship between Aβ42 and cognitive function).[34]

Importantly, our results are also supported in part by the previous study investigating correlates and predictors of plasma Aβ in a population of cognitive normal, MCI and AD patients.[10] Both studies reported relatively normal distributions of both plasma Aβ40 and Aβ42, indicating no need to log-transform plasma Aβ40 or Aβ42 when analyzing as continuous variables, although it was reported that the ratio needed log-transformation.[10] Furthermore, both studies found significant associations between higher Aβ40 and Aβ42 and poorer kidney function in t-tests, and found that creatinine significantly predicted both markers.[10] Other similarities were significant associations between age and Aβ42, APOE and Aβ42 and cholesterol and Aβ40.[10] This study did not support our findings in that it found no association between education or race with either plasma marker; in models the most significant predictors of Aβ40 and Aβ42 were creatinine, total proteins and cholesterol, while our results showed different significant predictors of Aβ42 and Aβ40.[10] Interestingly in the other study, age, education nor APOE e4 significantly predicted either marker as we found, and these are known strong risk factors for AD.[10] Finally, the prior study found a much stronger correlation between plasma Aβ40 and Aβ42 ($r=0.83$ vs. $r=0.51$).[10] We believe differences are most likely attributable to different populations, as our study was made up of community-dwelling older adults who were all dementia free, compared to a population of primarily MCI and AD patients with only a small proportion of cognitively normal controls.[10] Given these characteristics, the contrasting results could reflect that disease progression largely affects plasma Aβ measurements and correlates. Ultimately, more studies are needed to better understand the fluctuations of plasma Aβ40 and Aβ42 in older adults who age without cognitive decline, with MCI and with AD to better understand these relationships.

If plasma Aβ40 and Aβ42 indeed are useful biomarkers of cognitive decline and dementia, then it is important to fully understand how these biomarkers are influenced by demographic and medical conditions for several reasons. First of all, at a very basic level, it will be important so that future studies can measure and adjust for all potential confounders when investigating the association of plasma Aβ to ensure the most accurate results are presented. Understanding demographic and medical correlates will also be crucial in considering what factors may regulate plasma Aβ. This will be critical for gaining a better understanding of the mechanisms underlying cognitive decline and dementia. It will also help in identifying possible targets for interventions in reducing risk of or preventing dementia.

This study had several strengths, including the large sample size providing ample analytical power for this study. Measurement of numerous potential confounders allowed us to investigate a large number of demographic and medical characteristics in one sample. Finally, Innogenetics INNO-BIA assays were used for our measurements of Aβ42 and

Aβ40, and this method may provide more accurate measurements of Aβ42 and Aβ40 due to its high sensitivity, low variability, and high reproducibility.[35] There are also several weakness that should be taken into consideration when interpreting these results. These adults were all well functioning and community-dwelling at baseline, so results may not be generalizable to all older adults – for example, nursing home populations. Another potential weakness is that we did not have CSF measurements of Aβ and thus, we could not correlate plasma Aβ to measurements of CSF Aβ. As CSF Aβ has been such a well-established biomarker for dementia, it would have been useful.

This study identified the demographic and medical correlates of plasma Aβ40 and Aβ42. The correlates identified in this paper should be considered in future studies as potential confounders of the association between plasma Aβ and cognitive decline or dementia. Understanding fully how these correlates mediate or modify the association between plasma Aβ and dementia will be a fundamental step in determining the biological pathways through which plasma Aβ contributes to dementia and cognitive decline. Future studies should continue to investigate exactly how these demographic and medical correlates may influence the relationship between plasma Aβ40 and Aβ42, as it may help us target interventions for preventing and reducing the risk of AD and dementia.

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Table 1

Demographic and medical correlates of plasma Aβ40 among 997 older adults

Baseline Characteristics N (%) or Mean (SD)	Tertile 1 n=333	Tertile 2 n=331	Tertile 3 N=333	p-value
Age, years	73.6 (3.0)	74.0 (2.8)	74.5 (2.9)	.0001
Black Race	201 (60.4)	190 (57.4)	147 (44.1)	<.0001
Female Sex	184 (55.3)	187 (56.5)	179 (53.8)	.78
Education (≥HS)	223 (67.2)	226 (68.5)	197 (59.5)	.03
Literacy (REALM, ≥8th grade)	94 (29.9)	85 (27.8)	87 (27.8)	.79
3MS	91.0 (5.4)	91.2 (5.5)	91.1 (5.2)	0.90
Social Support *	171 (51.4)	165 (49.9)	152 (45.7)	0.26
Body Mass Index	27.7 (5.2)	28.0 (4.8)	27.5 (4.8)	.35
Physical Activity (kcal per week)	1055.5 (2373.2)	1133.3 (2455.5)	982.4 (1465.0)	0.66
Depressive Symptoms (CES-D≤16)	13 (3.9)	22 (6.7)	11 (3.3)	.09
Stroke/TIA History	25 (7.5)	33 (10.1)	37 (11.3)	.25
Diabetes History	74 (23.2)	83 (25.6)	83 (25.9)	.69
Myocardial Infarction History	25 (7.6)	38 (11.6)	42 (12.8)	.07
Cholesterol (mg/dl)	202.7 (37.6)	208.4 (41.1)	202.2 (39.3)	0.08
Triglycerides (mg/dl)	126.8 (80.6)	131.1 (100.5)	138.5 (68.0)	0.19
HDL (mg/dl)	56.6 (17.7)	55.1 (16.7)	52.9 (16.5)	0.02
LDL (mg/dl)	121.4 (34.5)	127.2 (35.5)	121.6 (35.4)	0.06
APOE e4 allele (≤1 e4 allele)	96 (30.9)	101 (32.2)	93 (29.5)	.77
BDNF (pg/ml)	23361.6 (10648.3)	21206.2 (11064.9)	20944.4 (10022.9)	0.006
Creatinine (mg/dl)	1.0 (0.2)	1.0 (0.3)	1.2 (0.5)	<.0001
C-reactive Protein (μg/mL)	3.0 (3.9)	2.9 (4.0)	3.4 (7.3)	.42
Tumor Necrosis Factor (pg/ml)	3.3 (2.1)	3.2 (1.3)	3.7 (1.7)	0.0007
IL-6 (pg/ml)	2.3 (1.9)	2.2 (1.7)	2.4 (1.8)	0.28
Smoker (Ever vs. Never)	183 (55.0)	180 (54.4)	180 (54.4)	.99

* N (%) below the median; variable defined as a combination of friends, neighbors and relatives who visit per week.

Aβ40 indicates amyloid beta-40; SD standard deviation; HS high school; REALM Rapid Estimate of Adult Literacy in Medicine; 3MS Modified Mini-Mental Status Exam; CES-D Center for Epidemiologic Studies Depression Scale; TIA transient ischemic attack; HDL high-density lipoprotein cholesterol; LDL low-density lipoprotein cholesterol; APOE Apolipoprotein E; BDNF brain-derived neurotrophic factor; IL-6 interleukin-6.

Table 2

Demographic and medical correlates of plasma Aβ42 among 997 older adults

Baseline Characteristics N (%) or Mean (SD)	Tertile 1 n=328	Tertile 2 n=339	Tertile 3 n=330	p-value
Age, years	74.0 (3.0)	73.8 (2.9)	74.2 (2.9)	.17
Black Race	214 (65.2)	173 (51.0)	151 (45.8)	<.0001
Female Sex	196 (59.8)	171 (50.4)	183 (55.5)	.05
Education (≤HS)	231 (70.6)	222 (65.7)	193 (58.8)	.006
Literacy (REALM, ≤8th grade)	95 (30.8)	97 (30.9)	74 (23.8)	.08
3MS Score	90.7 (5.5)	91.1 (5.3)	91.4 (5.3)	0.30
Social Support *	179 (54.6)	155 (45.7)	154 (46.7)	0.05
Body Mass Index	27.6 (5.2)	27.5 (4.3)	28.1 (5.3)	.26
Physical Activity (kcal per week)	929.8 (1971.7)	1042.1 (1733.5)	1198.4 (2669.9)	0.27
Depressive Symptoms (CES-D ≥16)	13 (4.0)	12 (3.5)	21 (6.7)	.17
Stroke/TIA History	28 (8.6)	31 (9.3)	36 (11.0)	.56
Diabetes History	94 (29.8)	78 (23.7)	68 (21.3)	.04
Myocardial Infarction History	39 (8.9)	34 (10.2)	42 (12.9)	.24
Cholesterol (mg/dl)	203.2 (38.0)	205.4 (39.2)	204.6 (41.2)	0.76
Triglycerides (mg/dl)	128.5 (80.9)	127.4 (65.6)	140.8 (101.9)	0.08
HDL (mg/dl)	57.3 (17.9)	53.9 (15.9)	53.5 (16.9)	0.007
LDL (mg/dl)	120.8 (34.7)	125.8 (35.4)	123.5 (35.4)	0.20
APOE e4 allele (≥1 e4 allele)	118 (38.3)	99 (31.3)	73 (23.1)	.0002
BDNF (pg/ml)	22798.0 (10910.9)	21328.8 (10138.0)	21408.9 (10810.7)	0.14
Creatinine (mg/dl)	1.0 (0.2)	1.0 (0.2)	1.1 (0.6)	<.0001
C-reactive Protein (μg/mL)	3.2 (6.4)	2.7 (3.4)	3.4 (5.8)	.16
Tumor Necrosis Factor (pg/ml)	3.3 (2.1)	3.3 (1.4)	3.6 (1.7)	0.07
IL-6 (pg/ml)	2.2 (1.5)	2.4 (2.0)	2.4 (1.9)	0.58
Smoker (Ever vs. Never)	192 (58.5)	184 (54.3)	167 (50.9)	.15

* N (%) below the median; variable defined as a combination of friends, neighbors and relatives who visit per week.

Aβ42 indicates amyloid beta-42; SD standard deviation; HS high school; REALM Rapid Estimate of Adult Literacy in Medicine; 3MS Modified Mini-Mental Status Exam; CES-D Center for Epidemiologic Studies Depression Scale; TIA transient ischemic attack; HDL high-density lipoprotein cholesterol; LDL low-density lipoprotein cholesterol; APOE Apolipoprotein E; BDNF brain-derived neurotrophic factor; IL-6 interleukin-6.

Table 3

Stepwise multivariate linear regression associations with plasma Aβ40 and Aβ42

Variable	Parameter (β)	Standard Error	F-value	p-value
		Aβ40		
Age	1.34	0.53	6.39	0.01
Black race	−14.70	3.13	22.01	<0.0001
Creatinine	52.91	4.29	151.77	<0.0001
Serum BDNF	−0.0004	0.0001	7.34	0.007
		Aβ42		
Black race	−3.72	0.67	30.83	<0.0001
Femal sex	1.39	0.67	4.32	0.04
Education	1.50	0.69	4.78	0.03
APOE e4	−2.82	0.69	16.57	<0.0001
Creatinine	9.32	0.85	120.09	<0.0001

Aβ40 indicates amyloid beta-40; Aβ42 amyloid beta-42; BDNF brain-derived neurotrophic factor; APOE Apolipoprotein E.

Table 4

Multivariate correlates of the rate of change in plasma Aβ40 and Aβ42.

		Rate of change in plasma Aβ (95% CI) per unit	
Variable	**Unit**	**Aβ40**	**Aβ42**
Age	2.91	3.90 (0.88, 6.92)	NA
Race	1	−14.70 (−20.83, −8.57)	−3.72 (−5.03, −2.41)
Sex	1	NA	1.39 (0.08, 2.70)
Education	1	NA	1.50 (0.15, 2.85)
Creatinine	0.85 mg/dl	19.58 (16.47, 22.69)	−2.82 (−4.17, −1.47)
APOE e4	1	NA	3.45 (2.83, 4.07)
BDNF	10631.18 pg/ml	−4.25 (−6.33, −2.17)	NA

Aβ40 indicates amyloid beta-40; Aβ42 amyloid beta-42; CI confidence interval; NA not applicable; APOE Apolipoprotein E; BDNF brain-derived neurotrophic factor.