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Ten-year change in plasma amyloid β levels and late-life cognitive decline

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Abstract

Background—Plasma levels of the amyloid β-peptides (Aβ) are potential biomarkers of early cognitive impairment and decline, and of Alzheimer disease (AD) risk.

Objective—To relate mid-life plasma Aβ measures, and ten-year change in plasma Aβ since mid-life, to later-life cognitive decline.

Design, setting, participants—Plasma Aβ-40 and Aβ-42 levels were measured in 481 Nurses' Health Study participants in late mid-life (mean age=63.6 years) and again 10 years later (mean age=74.6 years). Cognitive testing also began 10 years after the initial blood draw. Participants completed three repeated telephone-based assessments (average span=4.1 years). Multivariable linear mixed effects models were used to estimate relations of mid-life plasma Aβ-40:Aβ-42 ratios and Aβ-42 levels to later-life cognitive decline, and to relate ten-year change in Aβ-40:Aβ-42 and Aβ-42 to cognitive decline.

Main Outcome Measures—The primary outcomes were: the Telephone Interview for Cognitive Status (TICS); a global score averaging all tests (TICS, immediate and delayed verbal recall, category fluency, and attention); and a verbal memory score averaging four tests of verbal recall.

Results—Higher mid-life plasma Aβ-40:Aβ-42 ratio was associated with worse later-life decline on the global score (p-trend=0.04). Furthermore, an increase in Aβ-40:Aβ-42 since mid-life predicted greater decline on the global score (p-trend=0.03) and the TICS (p-trend=0.02). There was no

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association between mid-life plasma Aβ-42 levels alone – or change in Aβ-42 since mid-life – and cognitive decline.

Conclusions—In this large community-dwelling sample, higher plasma Aβ-40:Aβ-42 ratios in late mid-life, and increases in Aβ-40:Aβ-42 ten years later, were significantly associated with greater decline in global cognition at late-life.

Keywords

Alzheimer disease; amyloid; mid-life; plasma assay; biomarker; cognitive function

INTRODUCTION

Alzheimer disease (AD) is generally diagnosed at old ages; however, pathology begins many years earlier. Thus, identifying easily-measurable biomarkers at mid-life that can predict dementia is a priority for AD prevention.[1] Moreover, because subtle cognitive decline is associated with higher risk of subsequent AD,[2] biomarkers of decline in "young-old" persons may be particularly valuable. Plasma levels of circulating amyloid β-peptides (Aβ) ending at amino acid 40 (Aβ-40) or 42 (Aβ-42) have increasingly been explored as such biomarkers.

Specifically, it has been suggested that decreases in plasma Aβ may reflect decline of soluble Aβ in the periphery as it accumulates in insoluble brain plaques in Alzheimer's patients.[3] Data on plasma Aβ have been mixed, however, with respect to predicting dementia.[3-9] Several studies have reported associations between absolute plasma Aβ-40 or Aβ-42 levels and dementia, but directions of associations have varied. Interestingly, results have been more consistent when considering the ratio between plasma Aβ-40 and Aβ-42 at older ages.[5,7,8,10] For example, Graff-Radford and colleagues[7] observed that healthy elders with Aβ-42:Aβ-40 ratios in the lower quartiles had a higher relative risk of developing mild cognitive impairment (MCI) and AD (p=0.04) (i.e., *higher* Aβ40:Aβ42 ratio associates with higher risk). The first large investigation[5] of change in plasma Aβ ratios demonstrated that decreases (assessed over 4.5 years) in the Aβ42:Aβ40 ratio (i.e., *increases* in Aβ40:Aβ42 ratio) at older ages predicted greater rates of incident AD.

However, there have been few large-scale, prospective studies relating plasma Aβ to the outcome of cognitive decline. Furthermore, prior work focused on participants who were elderly. Consequently, there is limited knowledge on whether plasma Aβ levels reflect existing pathology or can actually predict decline in younger persons. Furthermore, change in plasma Aβ from mid-life to later-life may be of interest in identifying trajectories of cognitive decline. Thus, we measured plasma Aβ-40 and Aβ-42 – at late mid-life and 10 years later – in 500 women from a population-based sample. We related mid-life levels of plasma Aβ-40:Aβ-42 ratio and Aβ-42, as well as *change* in Aβ-40:Aβ-42 ratio and Aβ-42 levels over the subsequent 10 years, to cognitive decline.

METHODS

The Nurses' Health Study and Cognitive Sub-Study

The Nurses' Health Study (NHS) included 121,700 female, U.S. registered nurses, aged 30 to 55 years when the study began in 1976. Since then, participants have completed biennial mailed questionnaires updating health and lifestyle information. Between 1989 and 1990, blood samples were provided by 32,826 women, and 18,672 of these provided blood again from 1999 −2001. Characteristics of those who gave blood twice were similar to the entire blood cohort: e.g., mean alcohol intake was 5.3 g/day and prevalence of past smoking was 40% in both

groups; mean body mass index (BMI) was 25.2 kg/m^2 among women who gave blood twice and 25.4 kg/m^2 among the entire blood cohort.

In addition, from 1995−2001, all NHS participants aged 70+ years and without diagnosed stroke were invited to participate in a telephone-based study of cognition, and 19,395 women (93.3% of those eligible) completed an initial assessment. Two additional assessments were performed approximately 2 years apart. Follow-up exceeds 90% for the cognitive study.

Specimen collection and detailed protocol for Aβ assays

Venous whole blood samples were obtained in heparin tubes, shipped on ice to a central facility, processed (centrifuged and aliquotted as plasma, buffy coat, and red blood cells), and then stored at −130° C. The vast majority of samples arrived within 26 hours of being drawn; precautions were taken to prevent thawing of specimens during storage.

Using stored blood samples, we assayed plasma Aβ-40 and Aβ-42 by sandwich ELISA. Nunc MaxiSorp 384-well plates were coated with capture antibodies (2G3 for Aβ-40 and 21F12 for Aβ-42) in PBS and incubated for 4 hours at room temperature (RT), then blocked overnight at 4° C. Plates were washed 3 times with PBS-T, and samples were loaded into the wells and incubated with detector antibody (biotinylated 266 to the mid-region of Aβ) for 2 hours at RT. Samples were then re-incubated in solution of this detector antibody for 2 hours at RT. Finally, samples were incubated with streptavidin AP (Promega, Madison, WI, USA) in PBS for 1 hour at RT and washed 3 times with TBS. The signal was amplified with AttoPhos (Promega, Madison, WI, USA) and measured with a Victor2 fluorescent plate reader (PerkinElmer, Boston, MA, USA).

Since we measured Aβ collected at two timepoints and were concerned that plate-to-plate variation might interfere with assessing within-subject changes in Aβ over time, the samples were paired on a single plate and measured simultaneously. All sample pairs, including blinded quality control (QC) pairs, were distributed randomly across plates.

Reliability of plasma Aβ assays

We assessed the plasma Aβ assays both prior to and during this study. A total of 7 plates were used for the ELISAs. Blinded duplicate QC pairs were included on each plate. Overall coefficients of variation (CVs) for the 100 QC samples were high: 45.0% for Aβ-40 and 34.7% for Aβ-42. However, median within-pair CVs (across 50 QC pairs) were low: 7.1% for Aβ-40 and 7.6% for Aβ-42; thus, we had excellent ability to consider within-person changes in Aβ. In addition, high between-plate variability appeared to explain the high overall CVs. For example, after separating between- and within-plate variability, average within-plate CV was 10.2%. High between-plate variability but low within-plate variability has been reported previously in plasma Aβ ELISAs and has led to the recommendation of comparing samples loaded on the same plate.[11]

In earlier work, we established the stability of Aβ-40 and Aβ-42 levels in specimens with varying processing times.[12] Although processing delays for NHS blood samples are typically no longer than 24 hours, we demonstrated intraclass correlations of >0.95 for Aβ-40 and Aβ-42 values after processing delays of up to 48 hours.[12] Furthermore, we addressed the reliability of Aβ measures in long-archived plasma samples. The median (range) CVs for replicates of 12 plasma samples that had been in frozen storage (−130° C) for an average of 17 years were 9.7% (0.2−16.1%) for Aβ-40 and 14.8% (9.9−17.3%) for Aβ-42. Thus, we established that NHS blood collection and storage conditions were adequate for yielding valid results.

Assessment of cognitive function

Testing included the Telephone Interview for Cognitive Status[13] (TICS), a test of general cognition similar to the Mini-Mental State Examination[14]; immediate and delayed recall trials of the East Boston Memory Test[15] (EBMT); category fluency (naming as many different animals as possible during one minute); delayed recall of the TICS 10-word list; and digit span backward (repeating backward increasingly long series of digits). Reliability and validity of this method have been established.[16] Test-retest ($r=0.7$, $p<0.001$) reliability was high. In 61 highly educated women, the global score from the telephone battery correlated strongly ($r=0.81$) with a global score from 21 in-person neuropsychological tests. Finally, in a small clinical validation study, poor performance on our telephone battery was significantly associated with an 8-fold risk of dementia diagnosis.

General cognition and verbal memory were the primary outcomes; verbal memory, in particular, is a strong predictor of eventual AD.[17] To assess general cognition, we considered the TICS, as well as a global score, calculated by averaging the z-scores of all 6 tests. The verbal memory score was calculated by averaging z-scores of the immediate and delayed recalls of the EBMT and the TICS 10-word list.[18,19] Global and verbal memory scores were only calculated for those who completed all component tests.

Determination of the population for analysis

To maximize efficiency, we obtained the current study sample (n=500) by first over-sampling participants from the top and bottom 20% of the distributions of cognitive decline in our population, and then selecting random participants from the remainder of the distribution. This sampling strategy ensured adequate power to detect differences in cognitive change across plasma Aβ groups without measuring Aβ in the entire cohort. Finally, we excluded 19 women from analyses, as their Aβ-40 or Aβ-42 levels were below the limit of detection. Thus, the final sample included 481 women. Health and lifestyle characteristics were similar between this sample (mean alcohol intake=5.3 g/day; mean activity=17.2 METS/week; mean BMI=25.0 kg/m^2) and all cognitive participants who returned blood samples (mean alcohol intake=5.3 g/day; mean activity=17.4 METS/week; mean BMI=25.2 kg/m^2).

This study was approved by the Institutional Review Board of Brigham and Women's Hospital, Boston, MA.

Statistical analyses

Because of the plate-to-plate variation discussed above, we created batch-specific z-scores of mid-life plasma Aβ-40:Aβ-42 ratios and Aβ-42 levels. Thus, the unit of analysis was a batch-specific 1-SD (standard deviation) difference. For analyses of change in Aβ measures since mid-life, we calculated the percent change in each. Mid-life and later-life samples for each nurse were always assayed on the same plate, and within-pair CVs were low (as above); thus, batch correction was unnecessary in analyses using percent change. We calculated relations of percent change in Aβ-40:Aβ-42 ratio and Aβ-42 to cognitive decline using a 1-SD increment for each. In order to address possible non-linear relations (e.g., threshold effects), we also performed categorical analyses utilizing quartiles of percent change in Aβ measures.

We used linear mixed effects models[20] to examine relations of mid-life Aβ-40:Aβ-42 ratio and Aβ-42 levels, as well as change in Aβ-40:Aβ-42 ratio and Aβ-42, to cognitive decline across three repeated assessments. The model included the following fixed effects: time since initial cognitive assessment (years), age, education (associate/bachelor/master or doctoral), Aβ-40:Aβ-42 ratio or Aβ-42, interaction terms of time-by-age and time-by-Aβ-40:Aβ-42 ratio (or by-Aβ-42), as well as the following potential confounders: BMI (kg/m^2), history of hypertension (yes/no), history of dyslipidemia (yes/no), history of heart disease (yes/no: any

history of myocardial infarction, chronic angina, angiography confirmed coronary disease, coronary angioplasty or coronary artery bypass grafting), cigarette smoking (current/past/never), postmenopausal hormone use (current/past/never), physical activity (metabolic equivalents/week), and alcohol use (g/day), all of which were determined as of blood draw, as well as history of depression (yes/no: determined either by meeting the validated cutoff on the Medical Outcomes Short-Form 36 Mental Health index[21] or regular antidepressant use), which was ascertained as of cognitive assessment. Added to these fixed effects were two person-specific random effects: baseline cognitive level (random intercept) and rate of change (random slope).

Since many participants completed initial cognitive testing just prior to their second blood draw, in a secondary analysis, we evaluated cognitive change between the second and third assessments (i.e., change after the second blood draw). This guaranteed a strict prospective analysis – although, the majority of participants (60%) provided their second blood sample no later than 12 months after initial cognitive assessment and 85% provided the sample within 18 months. We used linear regression to estimate mean differences in cognitive change (mean interval between 2nd and 3rd assessments=2.4 years) associated with intra-individual changes in plasma Aβ-40:Aβ-42 ratio and Aβ-42. However, results were identical to analyses that included all assessments; thus, we only present the data for all three assessments.

We conducted a key secondary analysis to address concerns that relations of Aβ measures to vascular factors and/or subclinical vascular disease could explain associations between Aβ and cognitive decline. Rather than considering confounders as of the first blood draw, we considered history of vascular factors at any time as of initial cognitive testing. The models included many vascular factors: smoking, BMI, physical activity, hypertension, dyslipidemia, diabetes, and heart disease. Furthermore, we adjusted for history of transient ischemic attack (TIA) during follow-up, and removed from analysis participants who developed stroke during the course of cognitive testing or underwent carotid endarterectomy (CEA) at any point (n=12). Although the influence of impaired renal function on plasma Aβ is also of concern[4], there were no women in this sample with any history of renal disease.

Finally, although addressing later-life predictors was not the primary goal of this project, we examined later-life plasma *Aβ* measures in relation to cognitive outcomes in separate analyses.

All statistical analyses were conducted using SAS© version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Table 1 shows participant characteristics at mid-life, by quartiles of Aβ-40:Aβ-42 ratio. Overall, characteristics were similar across the quartiles. However, there was a trend of increased prevalence of depression with increasing Aβ-40:Aβ-42 ratio. Women with the lowest Aβ-40:Aβ-42 ratios tended to have lower prevalence of heart disease and current smoking, and there was some suggestion of higher physical activity in this group. Women in the lowest quartile also appeared to have a higher prevalence of current postmenopausal hormone use.

Distributions of plasma Aβ measures at mid-life and later-life are summarized in Table 2. Overall, the range of late-life Aβ-42 values appeared marginally lower than mid-life values; late-life Aβ-40:Aβ-42 ratios appeared higher than mid-life ratios.

Age-and-education-adjusted models showed significantly faster rates of decline in global score associated with higher mid-life Aβ-40:Aβ-42 ratio, with borderline findings for the TICS (Table 3). Estimates from multivariable-adjusted models were identical. For example, each 1-SD increment in mid-life Aβ-40:Aβ-42 ratio was associated with a −0.02 unit/year decrease

in global score. To help interpret this estimate, we compared it to the effect of age. In our population, each additional year of age was associated with an increased rate of decline of −0.01 unit/year in global score; thus, each 1-SD increment in mid-life Aβ-40:Aβ-42 ratio was cognitively equivalent to 2 years of aging. In analyses of Aβ-42 alone, there were no associations between mid-life plasma Aβ-42 levels and any outcome (Table 3).

In analyses of temporal change in plasma Aβ, we observed significantly faster multivariable-adjusted rates of decline on both the TICS and global score in participants with higher percent increases in Aβ-40:Aβ-42 ratio (Table 4). For example, each 1-SD increment of percent change in Aβ-40:Aβ-42 ratio was associated with a −0.08 point/year greater decline on the TICS – cognitively equivalent to 2 years of aging. The association between change in Aβ-40:Aβ-42 ratio since mid-life and cognitive decline on the TICS was slightly stronger than that observed with the mid-life Aβ-40:Aβ-42 ratio alone. Each 1-SD increment of percent change in Aβ-40:Aβ-42 ratio was associated with a −0.02 unit/year greater decline on the global score – cognitively equivalent to 2 years of age and identical to the effect observed for mid-life Aβ-40:Aβ-42 ratio. In categorical analyses, there was no evidence of threshold effects on the TICS or global score of higher percent change in Aβ-40:Aβ-42 ratio, as there were linear trends across the quartiles for both. For example, the multivariable-adjusted mean differences in decline on the TICS were −0.15, −0.16 and −0.21 points/year, respectively, in the second, third and fourth quartiles of percent increase in Aβ-40:Aβ-42 ratio; the effect of being in the highest quartile compared to being in the lowest quartile was cognitively equivalent to nearly 5 years of age (data not shown in table). Finally, there were no associations between temporal change in plasma Aβ-42 alone and any outcome (Table 4).

All findings were unchanged after addressing confounding by vascular factors as of initial cognitive testing and excluding those who developed stroke or underwent CEA. For example, each 1-SD increment of mid-life Aβ-40:Aβ-42 ratio was associated with a −0.02 unit/year greater decline on the global score (p-trend=0.02), and each 1-SD increment of percent change in Aβ-40:Aβ-42 ratio was associated with a −0.08 point/year greater decline on the TICS (p-trend=0.02) (data not shown in tables).

In separate analyses, we found that late-life Aβ-40:Aβ-42 ratio predicted subsequent decline in general cognition: e.g., each 1-SD increment of percent change in late-life Aβ-40:Aβ-42 ratio was associated with a −0.02 unit/year (p=0.02) greater decline on the global score (data not shown in tables).

Although not the focus of the current analyses, we also examined relations of mid-life plasma Aβ-40 levels alone, as well as temporal change in Aβ-40, to later-life cognitive decline. There were no associations between plasma Aβ-40 itself and any outcomes (data not shown).

DISCUSSION

Mid-life plasma Aβ-40:Aβ-42 ratio, but not plasma Aβ-42 level alone, was associated with significantly worse late-life decline in global cognition, after adjustment for multiple potential confounders. Similarly, a greater temporal increase in Aβ-40:Aβ-42 ratio – but not Aβ-42 itself – from mid-life to later-life also predicted a significantly faster rate of cognitive decline.

When comparing estimates associated with the mid-life plasma Aβ-40:Aβ-42 ratio vs. the change in plasma Aβ-40:Aβ-42 ratio since mid-life, temporal change since mid-life appeared to be a slightly stronger predictor of decline on one of the cognitive measures. Furthermore, the association between accelerated cognitive decline and the observed temporal increases in plasma Aβ-40:Aβ-42 ratio is compelling biologically, as it is compatible with a plausible mechanism. Specifically, decreases in CSF and plasma Aβ are expected over time as soluble Aβ peptide gradually accrues into insoluble Aβ plaques in the brain – a probable early event

in AD pathogenesis.[22] Indeed, CSF Aβ42 is observed to decline during development of amnestic MCI and AD. To the extent that peripheral decline in Aβ-42 may be greater than that of Aβ-40,[23] a temporal change in the Aβ-40:Aβ-42 ratio may provide a stronger indication of this pathology than Aβ-42 itself or a single measure of the Aβ-40:Aβ-42 ratio.

To our knowledge, no prior studies involving large cohorts have addressed the predictive ability of both mid-life plasma Aβ and change in plasma Aβ since mid-life, with regard to decline on repeated cognitive measures. Thus, our findings contribute uniquely to the literature. Nevertheless, results from recent investigations involving older subjects appear consistent with our findings on the Aβ-40:Aβ-42 ratio, indicating that this may be the most valuable predictor in terms of plasma Aβ. Graff-Radford et al.[7] observed an association (p=0.02) between lower late-life Aβ-42:Aβ-40 ratio (i.e., *higher* Aβ-40:Aβ-42 ratio) and subsequent decline on the Mattis Dementia Rating Scale[24] among 379 persons (median age=77 years at blood draw) administered cognitive testing approximately 5 years apart. Similarly, Sun et al.[10] reported a cross-sectional association between higher late-life Aβ-40:Aβ-42 ratio and poorer cognition among depressed elders (mean age=73.8 years). Most[5,7,8] but not all[4] studies of dementia that have addressed ratios between plasma Aβ-40 and Aβ-42 have identified significant associations. Overall, it appears that longitudinal studies measuring the Aβ-40:Aβ-42 ratio may hold the most promise for using plasma Aβ to identify persons at risk for late-life cognitive dysfunction.

In addition to measuring change in Aβ over 10 years, the present study has several strengths. First, measuring mid-life Aβ values likely yields less confounding due to age (and the accompanying variability in levels with aging[3,9]) or other related health variables (e.g., vascular disease). In addition, we adjusted for a variety of potential confounders, including depression, heart disease, hypertension and dyslipidemia. While we did not collect data on some vascular measures (e.g., white matter lesions), it is reassuring that we found no change in estimates after controlling for lifetime history of a wide array of cardio- and cerebrovascular factors. This was especially important, as vascular disease may affect plasma Aβ levels,[4,25] and cardiovascular disease may have an independent path to cognitive decline.[26] Finally, the use of repeated cognitive measures allowed evaluation of differences in paths of change.

Limitations should also be considered. First, overall CVs for plasma Aβ-40 and Aβ-42 were high, due to plate-to-plate variation. Measurement variation could result in underestimation of relations between plasma Aβ and cognition. However, within-plate measurement error was low, and analyses corrected for the between-plate variation. Moreover, there was excellent within-pair reliability; thus, analyses of intra-individual change in Aβ would be less affected by measurement variability. Finally, generalizability is a concern in our population of largely Caucasian, female health professionals. Although biological mechanisms among these women are likely similar to those in the general population, research addressing diversity is needed: e.g., studies may examine differing impacts of mid-life plasma Aβ on age-of-onset of cognitive decline among ethnic minorities.

In conclusion, this prospective study provides preliminary evidence that higher plasma Aβ-40:Aβ-42 ratios at mid-life and later-life, as well as increases in the Aβ-40:Aβ-42 ratio between mid-life and later-life, may predict cognitive decline. These associations require confirmation in other large-scale, longitudinal studies. Interestingly, mid-life Aβ-40:Aβ-42 alone predicted later-life cognitive decline, suggesting that this ratio may prove valuable for early identification of those at high risk of cognitive impairments. Nonetheless, more work is needed to address whether changes in plasma Aβ-40:Aβ-42 ratio since mid-life are ultimately more sensitive predictors than Aβ-40:Aβ-42 ratio at a single timepoint. The benefits of such work are clear. Plasma biomarkers could aid in targeting prevention within large populations, by identifying high risk individuals years before clinical symptoms are evident.

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Table 1

Characteristics of the Sample (n=481), by Quartiles of Mid-life Plasma Amyloid β 40:42 Ratio*

CHARACTERISTIC	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Median (IQR)† amyloid β 40:42 ratio	3.3 (2.1 − 4.7)	6.6 (5.2 − 8.0)	11.3 (8.8 − 13.9)	24.6 (18.2 − 37.5)
Mean age at blood draw (SD)† (years)	63.2 (2.2)	63.9 (2.4)	63.2 (2.4)	64.0 (2.4)
Mean (SD)† body mass index (kg/m^2)	25.1 (3.7)	24.7 (4.0)	23.5 (3.9)	24.9 (4.0)
Master's degree or higher education	6.3	6.9	6.7	9.5
History of hypertension	28.6	27.1	34.5	36.2
History of dyslipidemia	22.3	30.5	35.3	31.0
History of heart disease	2.7	9.3	5.9	8.6
Smoking: Current	4.5	10.2	12.6	9.5
Past	41.1	31.4	45.4	40.5
Hormones: Current use	35.7	31.4	33.6	21.6
Past use	17.9	26.3	23.6	32.8
History of depression	1.8	7.6	6.7	11.2
Mean (SD)† exercise level (METS/week)	19.0 (20.3)	17.1 (21.4)	14.1 (16.2)	15.4 (17.8)
Mean (SD)† alcohol intake (grams/day)	5.2 (8.3)	7.1 (10.6)	3.9 (6.8)	4.0 (8.1)

*Figures are expressed as percentages, unless otherwise stated. Depression status is as of initial cognitive testing.

†IQR = interquartile range. SD = standard deviation.

Table 2

Plasma Amyloid-beta Measures at Mid-Life and Late-life

	Mid-life	Late-life
Mean age at blood draw (SD)* (years)	63.6 (2.4)	74.6 (2.4)
Median (IQR)* amyloid-beta 40 (pM)	81 (43 − 178)	79 (42 − 182)
Median (IQR)* amyloid-beta 42 (pM)	9 (3 − 26)	9 (3 − 23)
Median (IQR)* amyloid-beta 40:42 ratio	8.3 (5.0 − 14.6)	8.7 (4.9 − 17.0)

*SD = standard deviation. IQR = interquartile range.

Table 3

Mean Differences (95% CI) in Cognitive Decline, per Standard Deviation of Amyloid β Measures at Mid-life*

COGNITIVE TEST	TICS	GLOBAL SCORE	VERBAL SCORE
Amyloid β 40:42 Ratio			
Age/education-adjusted	−0.07 (−0.14, −0.00)	−0.02 (−0.04, −0.00)	−0.02 (−0.04, 0.00)
p-trend	0.05	0.02	0.08
Multivariable-adjusted	−0.07 (−0.14, 0.00)	−0.02 (−0.04, −0.00)	−0.02 (−0.04, 0.01)
p-trend	0.07	0.04	0.16
Amyloid β 42			
Age/education-adjusted	−0.01 (−0.08, 0.07)	0.00 (−0.02, 0.02)	−0.00 (−0.03, 0.02)
p-trend	0.88	0.96	0.79
Multivariable-adjusted	−0.00 (−0.08, 0.07)	0.00 (−0.02, 0.02)	−0.00 (−0.03, 0.02)
p-trend	0.89	0.99	0.77

* Models adjusted for age at baseline interview and education; cigarette smoking, postmenopausal hormone use, hypertension, elevated cholesterol, body mass index, alcohol intake and physical activity level as of blood draw; and depression status as of start of cognitive testing. Mean (range) testing interval was 4.1 (3.1 − 5.5) years.

Table 4

Mean Differences (95% CI) in Cognitive Decline*, by Percent Change over Ten Years in Plasma Amyloid β Measures

COGNITIVE TEST	TICS	GLOBAL SCORE	VERBAL SCORE
Amyloid β 40:42 Ratio			
Age/education-adjusted	−0.08 (−0.15, −0.01)	−0.02 (−0.04, −0.00)	−0.02 (−0.04, 0.01)
p-trend†	0.02	0.03	0.16
Multivariable-adjusted‡	−0.08 (−0.15, −0.01)	−0.02 (−0.04, −0.00)	−0.02 (−0.04, 0.01)
p-trend†	0.02	0.03	0.18
Amyloid β 42			
Age/education-adjusted	0.03 (−0.03, 0.10)	0.01 (−0.01, 0.02)	−0.00 (−0.03, 0.02)
p-trend†	0.32	0.56	0.67
Multivariable-adjusted‡	0.04 (−0.03, 0.11)	0.01 (−0.01, 0.02)	−0.01 (−0.03, 0.02)
p-trend†	0.31	0.57	0.65

*Mean (range) cognitive testing interval was 4.1 (3.1 − 5.5) years.

†Linear trend for each SD *increase* in percent change of Aβ−40:Aβ−42 ratio or Aβ−42. Mean (range) interval between first and second plasma collection was 11.1 (9.2 − 12.2) years.

‡Models adjusted for age at baseline interview and education; cigarette smoking, postmenopausal hormone use, hypertension, elevated cholesterol, body mass index, alcohol intake and physical activity level as of blood draw; and depression status as of start of cognitive testing.