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Plasma Amyloid β predicts cognitive decline

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Abstract

Context—Amyloid β (Aβ) is a key pathophysiological feature of Alzheimer's disease (AD). Baseline and change values of plasma Aβ have been associated with AD risk.

Objective—To determine if plasma Aβ levels: 1) can be linked to specific cognitive changes which constitute conversion to AD; and 2) correspond to cognitive change independent of dementia.

Setting—Northern Manhattan community.

Design—Longitudinal study including three visits over ~4.5 years (2000–2006).

Participants—880 individuals, from a population based and ethnically diverse sample, who had two plasma Aβ measurements and were dementia-free at the time of the first Aβ sample; 481 remained cognitively healthy, 329 were cognitively or functionally impaired at any point, and 70 converted to AD.

Main Outcome Measures—General Estimating Equations tested the association between plasma Aβ (baseline and change values) and cognitive change (composite score, and memory, language, and visuospatial indices).

Results—High baseline plasma Aβ42 (p=.01)and Aβ40 (p=.01), and decreasing/relatively stable Aβ42 (p=.01) were associated with faster decline in multiple cognitive domains. In those who remained cognitively healthy, high baseline plasma Aβ42 (p=.01) and decreasing/relatively stable plasma Aβ42 (p=.01) was associated with faster cognitive decline, primarily in memory.

Conclusions—The association between plasma Aβ and multiple aspects of cognition more clearly specifies the previously documented downward trajectory of plasma Aβ with AD onset. The predominant association with memory seen only in healthy elders also suggests that plasma Aβ is linked with even earlier neurologic changes that may or may not culminate in dementia.

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INTRODUCTION

The amyloid cascade hypothesis suggests that aberrant metabolism of the amyloid precursor glycoprotein (APP), and subsequent accumulation of soluble oligomers Aβ40 and Aβ42, is the primary trigger for the development of AD.[1, 2] TheTg2576 mouse model of AD has shown that plasma Aβ levels decrease as brain Aβ levels increase[3], generating interest in the suitability of plasma Aβ level as a risk biomarker for AD. Indeed, we have reported that elevated plasma Aβ42 at baseline[4] and decreasing levels over time[5, 6] predicts conversion to AD, and other studies support these findings.[15, 16] The current study sought to specify existing work by investigating the extent to which plasma Aβ levels: 1)can be linked to specific cognitive changes which constitute conversion to AD; and 2) may be relevant for cognition independent of dementia.

METHODS

Participants

Participants were drawn from the Washington Heights and Inwood Columbia Aging Project (WHICAP), a prospective, population-based study of aging and dementia in Medicare recipients, 65 years and older, residing in northern Manhattan (Washington Heights, Hamilton Heights, Inwood) that has been described in detail in earlier work.[7, 8] The population from which participants were drawn is comprised of individuals from several countries of origin and represents three broadly defined ethnic categories (i.e., Caribbean Hispanic, African American, and non-Hispanic White). Potential participants were excluded at the time of recruitment if they did not speak English or Spanish. Ethnic group was classified by participant's self-report using the format of the 1990 US Census. Participants were asked if they considered themselves white, black or other, and then asked if they were Hispanic. Each participant underwent an in-person interview of general health and functional ability at study entry followed by a standardized assessment, including medical history, physical and neurological examination and neuropsychological testing. Participants were recruited in two waves (1992–1994 and 1999–2002)and assessed at approximately 18-month intervals. Evaluations were conducted in either English or Spanish, based on the preference of the participant.

Consensus diagnoses of "dementia" or "no dementia" were based on physician-administered physical and neurological examinations in conjunction with the neuropsychological battery[9] according to criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) and determined by neurologists and neuropsychologists at a consensus conference. Evidence of social or occupational impairment, and deficits in memory and an additional cognitive domain were required for a diagnosis of dementia. Diagnosis of probable or possible AD was made based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association [10]. The study was approved by the Columbia University institutional review board, and written informed consent was obtained from all subjects.

Participants were included in the current study if they were non-demented at the first Aβ measurement, and had a second Aβ measurement taken ~4.5 years later. The primary sample consisted of: 1) 481 individuals who were cognitively healthy at all study visits; 2) 329 classified as cognitively or functionally at any study visit; and 3) 70 who converted to AD by the second follow-up (~4.5 years later).

Plasma Aβ42 and Aβ40

10 ml venous blood sample (K_3EDTA lavender-top tube) were used to assess plasma Aβ levels. Plasma levels were measured blind to cognitive status using a combination of

monoclonal antibody 6E10 (specific to an epitope present on 1–16 amino acid residues of Aβ), and rabbit antisera (R165 vs. Aβ42 and R162 vs. Aβ40) in a double antibody sandwich ELISA as described previously. [5, 11] This method measures the free or soluble form of Aβ, not the oligomeric or bound forms. The detection limit for these assays is 9 picograms per milliliter (pg/ml). Aβ peptide levels from each blood draw were measured in duplicate, using separate aliquots so that none of the samples were re-frozen and re-thawed for the repeat assay. The correlation between the repeat Aβ40 and Aβ42 measurements was substantial ($p < .001$) for both peptides at baseline(Aβ40: $r = .97$; Aβ42: $r = .94$) and at the second follow-up (Aβ40: $r = .94$; Aβ42: $r = .91$). The means of the two measurements were used in statistical analyses. Aβ levels were not considered for diagnosis.

Apolipoprotein E(APOE) Genotype

Genotypes were obtained by amplification of genomic DNA with polymerase chain reaction subjected to *Cfo*I restriction analysis using APOE primers and conditions similar to those described by Hixson and Vernier [12] and modified by Maestre and colleagues. [13] Participants were classified according to the presence of at least one ε4 allele.

Statistical Analyses

Multivariate general linear models and partial correlations adjusting for age, were used to examine the relationship between baseline cognition and continuous values of plasma Aβ. Generalized estimating equations (GEE)[14] were then used to determine if: 1)baseline Aβ predicted rate of cognitive change; or 2) change in Aβ over time was associated with rate of cognitive change. GEE takes into account the multiple visits per subject and the fact that characteristics of an individual over time are likely correlated. Repeated measures for each subject are treated as a cluster. A significant interaction term (time × Aβ predictor) in the model indicates that rate of cognitive decline varies with the Aβ predictor, with negative terms reflecting faster decline than that in the reference group and positive terms indicating slower decline. Primary analyses were conducted in the entire sample (n = 880) and separately in elders who were cognitively healthy at all visits(n = 481). The group of individuals with cognitive or functional impairment at any point in the study (n = 329) was not a primary focus of the current study because the factors underlying impairment in this group are heterogeneous. However, supplementary analyses were conducted to determine whether the primary findings applied to this sample, as well as to the small sample of incident AD (n=70). To examine the potential influence of cognitive reserve on associations between plasma Aβ and dementia status, a supplementary one-way ANOVA was conducted in participants with high risk Aβ profiles to examine differences in education between those who did and did not convert to AD.

GEE Predictors—Baseline Aβ42 and Aβ40 peptide levels, and change in these values over time, were the four predictors tested. Ordinal groupings were used to avoid non-linear threshold effects, and to facilitate examination of large differences in Aβ levels on cognitive function. Quartiles were used to achieve as finely graded groupings as possible without sacrificing statistical power. However, to ensure that results were not simply dependent on the manner in which the data was grouped, we repeated the primary analysis of global cognitive change as a function of Aβ tertile at baseline. Change values were characterized using a median split(increasing= reference group). Ordinal values were determined based on the distribution of Aβ in the specific sample included in each model. Supplementary analyses examined the Aβ42:40 ratio as a predictor.

GEE Covariates—Age, sex, ethnic group, body mass index (BMI), *APOE*-ε4 status, and recruitment wave were included as covariates. Because Aβ42 and Aβ40 are highly correlated, each was included as a covariate of the other to determine if independent

relationships with cognition were present. Finally, models examining Aβ change were adjusted for baseline Aβ quartile.

GEE Outcome Measures—The GEE model assessed rate of change in the primary outcome which was a composite cognitive z-score representing performance in: 1*) Memory*: total recall, delayed recall, and recognition from the Selective Reminding Test; 2) *Language*: 15-item Boston Naming Test; the eight high probability items from the Repetition subtest of the Boston Diagnostic Aphasia Examination (BDAE); the first six items of the BDAE Comprehension subtest; WAIS-R Similarities subtest raw score; average score for phonemic fluency(C, F, L); and average score for category fluency (Animals, Food, Clothing); and 3) *Visuospatial Abilities*: five selected items from the Rosen drawing test; the matching and recognition components of the Benton Visual Retention Test; and total score from the Identities and Oddities subtest of the Dementia Rating Scale. Cognitive data were acquired when Aβ was first collected, at a follow-up visit ~2 years later, and at a third visit ~4.5 years later when Aβ was again measured. Overall scores for each cognitive domain were created by transforming raw scores into z-scores (using the mean and standard deviation of the entire WHICAP sample at baseline). Individual z-scores were averaged to create a score for each cognitive domain. The three domain z-scores were averaged to create a composite cognitive z-score.

RESULTS

Missing Data Analyses

880 of 2412 non-demented participants seen in 1999 had Aβ samples from baseline and second follow-up. See Table 1 for demographic characteristics and mean Aβ values. Overall, these subjects were younger (76.04 versus 77.99; $p < .01$) and had higher composite cognitive scores (0.32 versus 0.19; $p < .01$) than subjects without complete Aβ data but education, sex, ethnic group, and *APOE*ε4 status were comparable. Of the 880 with available Aβ samples, individuals with incident AD were significantly older ($F = 67.20$, $p < .01$) and had fewer years of formal education ($F = 102.34$, $p < .01$) than the healthy elders in the sample.

Plasma Aβ and Cognition at Baseline

After adjusting for age, sex, and ethnic group, multivariate general linear models in the entire sample revealed no difference in any of the baseline cognitive scores(composite, memory, language, or visuospatial) by baseline Aβ42($F = 1.24$, $p = .27$) or Aβ40 ($F = 1.08$, $p = .37$)quartiles. Partial correlations adjusting for age revealed no association between composite cognitive score and continuous Aβ values at baseline [Aβ42 ($r = -.02$, $p = .56$); Aβ40 ($r = .01$, $p = .78$)].

GEE: Rate of Global Cognitive Change by Baseline Aβ

Table 2 details the predictive value of baseline Aβ for cognitive change in the entire sample and healthy elders only. Aβ quartiles were comparable for both samples. In the entire sample, individuals in the top three Aβ42 quartiles declined faster than those in the lowest quartile. Results were largely comparable in the healthy elders. Individuals in the top three Aβ40 quartiles also declined faster than those in the lowest quartile. In the healthy elders, only the highest quartile declined faster than those in the lowest. The Aβ42:40 ratio was not a significant predictor. Beta values and significance levels were essentially identical when the data was examined by tertile, such that individuals in the highest two tertiles of both baseline Aβ40 and Aβ42 declined more quickly than those in the reference group. It should be noted that the significance was marginal in healthy elders who had the highest levels of Aβ42, and this was true when grouping by quartile or tertile.

GEE: Rate of Global Cognitive Change by Aβ Change

In the entire sample and healthy elders only, those with relatively stable or decreasing Aβ42 had faster cognitive decline than those with increasing Aβ42 (Entire Sample: β = −.02; p = .01; Healthy Elders: β = −.01; p = .02). Removing baseline Aβ42 values from these models did not change the results. Change in Aβ40 was not associated with cognitive change in either sample. In individuals with high risk Aβ42 profiles (highest baseline quartile and decreasing or relatively stable over time), incident AD cases had less education than those who remained dementia free over follow-up (age and ethnicity adjusted means 7.99 versus 11.74; F = 49.34, p < .01).

GEE: Cognitive Change in Specific Domains by Aβ

Tables 3 and 4 outline the results regarding specific cognitive domains. In the entire sample, baseline Aβ42 predicted cognitive change in all three domains, with individuals in the highest Aβ42 quartile consistently declining faster than those in the lowest. Cognitive change in the second and third Aβ42 quartiles was less consistently different from that of the lowest quartile. Baseline Aβ40 quartile predicted: 1) change in memory with individuals in the second and third quartiles declining faster than those in the lowest; and 2) change in language with individuals in the highest quartile declining faster than those in the lowest. Finally, change in Aβ42 predicted change in memory and visuospatial scores, with relatively stable or decreasing Aβ42 predicting faster decline.

In healthy elders, baseline Aβ42 quartile predicted change primarily in memory, with higher Aβ42 at baseline generally predicting faster decline. Baseline Aβ40 was generally unrelated to cognitive change although individuals in the 2nd quartile had faster memory decline than those in the lowest. Change in Aβ42 was not associated with change in any domain, although there was a trend toward faster memory decline in individuals with relatively stable or decreasing Aβ42, and the magnitude of the effect was identical to that in the entire sample. Finally, change in Aβ40 over time was not related to cognitive change in the entire sample or healthy elders.

Supplementary Analyses

We ran additional exploratory analyses examining the association between plasma Aβ and global cognition in: 1) the group of 329 individuals with cognitive or functional change but no dementia, and 2) the 70 cases of incident AD. Indeed, the beta coefficients were in the same direction and largely comparable in the 329 individuals as in the entire sample, and even stronger in the AD sample (e.g., −.04 to −.09). This was true for both baseline and change analyses. While the results were not statistically significant in these two additional groups, this likely reflected a lack of power in these smaller samples.

COMMENT

Recent work by our group found that higher baseline values of plasma Aβ42 and the Aβ42:40 ratio, and decreases in these values over time, predicted AD onset after approximately 4.5 years.[6] The increased risk of AD conferred by high plasma Aβ42 has also been documented in two cross-sectional studies reporting high plasma Aβ42 in amnestic MCI. [15, 16] While several studies have produced seemingly discrepant results,[17–20] differences in the timing of the plasma sample and disease stage of the participants are important factors to consider. For example, an increased risk of AD in those with low Aβ42:40 ratios two years prior to conversion may be consistent with a high ratio 4.5 years prior to conversion, preceding a decline in Aβ42. [21] The current study sought to specify earlier work by investigating the association between plasma Aβ and cognition. Overall, high initial levels of plasma Aβ40 and Aβ42, and stable or decreasing Aβ42 at follow-up,

were associated with faster global cognitive decline regardless of dementia status at follow-up. However, the cognitive domains associated with plasma Aβ were not independent of final dementia status, the potential relevance of which is discussed below.

Aβ and Cognitive Change in the Context of Incident AD

The relatively rapid cognitive decline seen as a function of high baseline plasma Aβ and stable or decreasing Aβ42 in the entire sample is not surprising given that a similar plasma Aβ profile predicted conversion to AD in this same sample[6], and cognitive decline in more than one domain is a prerequisite for incident AD. However, current results provide greater specificity to the association between plasma Aβ and AD diagnosis, implicate a direct and linear association with multiple aspects of cognitive change, and lend support to the potential utility of plasma Aβ as an indicator of disease progression. Moreover, separate examination of healthy elders offered the opportunity to further clarify the relationship between plasma Aβ and cognition by assessing individuals at the earliest stages of age-related cognitive change, and removing individuals who by definition have some aspect of cognitive decline (incident AD) or who may be close to the point of converting to AD. It should be noted, however, that the relationship between plasma Aβ and cognition in the entire sample was not necessitated by inclusion of individuals with incident AD; although it is necessary for this group to demonstrate some aspect of cognitive decline, such decline may occur in any cognitive domain, and need only cross the diagnostic cut point (i.e., rate of change or amount of change is not considered in diagnosis).

Aβ and Cognitive Change in Healthy Elders

The relationship between plasma Aβ levels and global cognitive change was largely the same once we restricted our analyses to individuals who remained cognitively healthy over the course of follow-up. Prior to this, one small study (n = 34) examining plasma Aβ and global cognition produced similar findings. [22] However, examination of specific cognitive domains in the current study revealed that global cognitive change in the healthy elders was driven primarily by memory, rather than language or visuospatial abilities. This seemingly selective association with memory has several interpretations. First, it may suggest that healthy elders with a high risk Aβ profile are in the early stages of AD but have not yet demonstrated sufficient change in non-memory domains to meet criteria for dementia. This would be consistent with the fact that episodic memory loss is generally the earliest clinical sign of AD. It is possible that despite memory change and high risk Aβ profiles, these elders remained dementia-free over the course of the study and may remain so over the long-term, due to biological factors such as the ability to clear Aβ42 or psychosocial factors such as cognitive reserve. The potential influence of cognitive reserve was supported by our findings that amongst individuals with high-risk Aβ42 profiles, those who remained dementia-free had four more years of education on average than those who converted to AD.

Another interpretation of the association between plasma Aβ42 and memory in healthy elders is that amyloid changes are an important factor in cognitive aging, independent of underlying AD. Stated differently, the observable change in both plasma Aβ and memory in this group could be a fundamentally different process than that involved in AD, or might fall short of a critical threshold beyond which the full pathological presentation and clinical dementia syndrome of AD would unfold. A recent editorial on the relevance of brain amyloid burden raises such a possibility, noting that amyloid accumulation might also be a marker for non-AD pathology related to a variety of brain insults earlier in life.(1) It is thus important for future work to determine more definitively the specificity of Aβ profiles for predicting dementia, versus their significance for cognitive aging more generally. Comprehensive understanding of plasma Aβ across the cognitive spectrum and its relation to

dementia will require collection of plasma Aβ over multiple times points beginning in early to mid life, as well as validation against Aβ imaging and autopsy.

Limitations of this study include only two plasma Aβ measurements, and two follow-up assessments preventing examination of later conversion to dementia in cognitively healthy elders. However, strengths of this study include a large and ethnically diverse sample, examination of Aβ change, comprehensive cognitive evaluation across three time points, and inclusion of both incident dementia cases and dementia free individuals. Moreover, direct examination of cognition rather than diagnosis provides insight into the factors which may constitute conversion to AD. Continued measurement of plasma Aβ in these individuals, and examination of its course in relation to cerebral amyloid accumulation, cognitive change, and potential mediating factors such as cortical atrophy[24, 25] is ongoing.

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Table 1

Baseline and Change Characteristics for Cognition and Aβ

	Healthy Elders (n = 481) Mean (SD)	Incident AD (n = 70) Mean (SD)	Entire Sample (n = 880) Mean (SD)
Age	74.52 (5.37)	80.84 (6.98)	76.07 (6.07)
Education	12.42 (4.15)	6.72 (4.73)	10.58 (4.73)
Female	67%	67%	68%
Hispanic	25%	60%	37%
Caucasian	43%	10%	31%
AA	31%	29%	31%
APOE-ε4	26%	29%	26%
Cognitive z-Score	.64 (.36)	−.37 (.44)	.33 (.52)
Cognitive Change	−.07 (.27)	−.58 (.42)	−.16 (.35)
Baseline Aβ40	63.11 (43.97)	73.41 (50.69)	62.67 (44.00)
Aβ40 Change	$^{+}$48.60 (50.74)	$^{+}$50.87 (52.25)	$^{+}$51.91 (52.17)
Baseline Aβ42	30.62(18.02)	37.59 (18.16)	31.19 (19.50)
Aβ42 Change	$^{+}$13.22 (20.57)	$^{+}$8.77 (22.72)	$^{+}$13.29 (21.09)
Aβ42:40 Ratio	.63 (.48)	.70 (.76)	.64 (.50)

Note. SD = Standard Deviation; AA = African American; APOE-ε4 = Presence of at least one e4 allele; Cognitive z-score reflects average performance on memory, language, and visuospatial indices at baseline; Cognitive change was measured by subtracting performance at the time of the second sample from the first sample; Aβ values are presented in picograms per milliliter (pg/ml).

Table 2

GEE Models of Composite Cognitive Decline as a function of Aβ

Ordinal Predictors	Continuous Aβ values in Entire Sample	Results in Entire Sample (n = 876)		Continuous Aβ values in Cognitively Healthy Elders	Results in Cognitively Healthy Elders (n = 478)	
Baseline Aβ42		**Beta**	***p***		**Beta**	***p***
Aβ42 (Quartile 1)	9.00 – 15.10	REF	REF	9.00 – 15.73	REF	REF
Aβ42 (Quartile 2)	15.11 – 28.90	−.02	**<.01**	15.74 – 28.90	−.02	**.01**
Aβ42 (Quartile 3)	28.91 – 41.20	−.02	**<.01**	28.91 – 39.83	−.02	**<.01**
Aβ42 (Quartile 4)	41.21 – 198.75	−.03	**<.01**	39.84 – 136.20	−.01	.07
Aβ42 Change		**Beta**	***p***		**Beta**	***p***
Aβ42 (Dec/Stable)	$^{-}44.00$ — $^{+}11.50$	−.02	**<.01**	$^{-}41.35$ — $^{+}11.90$	−.01	**.02**
Aβ42 (Increasing)	$^{+}11.51$ – $^{+}82.85$	REF	REF	$^{+}11.91$ – $^{+}70.70$	REF	REF
Baseline Aβ40		**Beta**	***p***		**Beta**	***p***
Aβ40 (Quartile 1)	9.00 – 28.05	REF	REF	9.00 – 28.83	REF	REF
Aβ40 (Quartile 2)	28.06 – 55.75	−.02	**.01**	28.84 – 57.80	−.01	.08
Aβ40 (Quartile 3)	55.76 – 91.20	−.02	**.01**	57.81 – 91.00	−.01	.17
Aβ40 (Quartile 4)	91.21 – 455.90	−.02	**.01**	91.01 – 455.90	−.02	**.02**
Aβ40 Change		**Beta**	***p***		**Beta**	***p***
Aβ40 (Dec/Stable)	$^{-}103.85$ — $^{+}52.85$	−.01	.18	-103.85 — $^{+}49.60$	<−.01	.49
Aβ40 (Increasing)	$^{+}52.86$ – $^{+}259.60$	REF	REF	$^{+}49.61$ – $^{+}232.55$	REF	REF

Note. Dec/Stable = Decreasing/Stable; REF = Reference group. Four subjects were excluded from analyses due to GEE requirements that each subject have non-missing data for all variables in the model at ≥ 1 time point. Beta values pertain to the interaction term in the GEE model (predictor * time) and reflect rate of cognitive decline in comparison to that in the reference group with negative betas indicating faster decline and positive betas indicating slower decline.

Table 3

GEE Models of Specific Cognitive Decline in Entire Sample as a function of Aβ

Predictor	**Memory**		**Language**		**Visuospatial**	
Baseline Aβ42	**Beta**	***p***	**Beta**	***p***	**Beta**	***p***
Aβ42 (Q2)	−.03	**.01**	−.02	.06	−.02	.09
Aβ42 (Q3)	−.02	.11	−.02	**.01**	−.03	**<.01**
Aβ42 (Q4)	−.03	**.02**	−.03	**<.01**	−.02	**.03**
Aβ42 Change	**Beta**	***p***	**Beta**	***p***	**Beta**	***p***
Aβ42 (Dec/Stable)	−.02	**.03**	−.01	.20	−.02	**.03**
Baseline Aβ40	**Beta**	***p***	**Beta**	***p***	**Beta**	***p***
Aβ40(Q2)	−.04	**<.01**	−.01	.29	−.02	.09
Aβ40(Q3)	−.04	**.01**	−.02	.08	−.02	.10
Aβ40(Q4)	−.02	.20	−.03	**.00**	−.01	.17
Aβ40 Change	Beta	*p*	Beta	*p*	Beta	*p*
Aβ40(Dec/Stable)	−.01	.06	<.01	.65	−.01	.28

Note. Q = Quartile. Dec/Stable= Decreasing/Stable. The reference group for models examining baseline values is the lowest quartile. The reference group for models examining change as a predictor is increasing values. Beta values pertain to the interaction term in the GEE model (predictor * time) and reflect rate of cognitive decline in comparison to that in the reference group with negative betas indicating faster decline and positive betas indicating slower decline.

Table 4

GEE Models of Specific Cognitive Decline in Healthy Elders as a function of Aβ

Predictor	**Memory**		**Language**		**Visuospatial**	
Baseline Aβ42	**Beta**	***p***	**Beta**	***P***	**Beta**	***p***
Aβ42 (Q2)	−.03	**.02**	−.02	.07	−.02	.09
Aβ42 (Q3)	−.03	**.02**	−.02	.14	−.02	**.03**
Aβ42 (Q4)	−.01	.37	−.01	.14	−.02	.09
Aβ42 Change	**Beta**	***p***	**Beta**	***p***	**Beta**	***p***
Aβ42 (Dec/Stable)	−.02	.06	−.01	.17	−.01	.18
Baseline Aβ40	**Beta**	***p***	**Beta**	***p***	**Beta**	***p***
Aβ40(Q2)	−.03	**.02**	< −.01	.62	−.01	.24
Aβ40(Q3)	−.02	.09	< −.01	.91	−.01	.21
Aβ40(Q4)	−.02	.10	−.02	.12	−.02	.08
Aβ40 Change	Beta	*p*	Beta	*p*	Beta	*p*
Aβ40(Dec/Stable)	−.01	.26	.01	.33	−.01	.53

Note. Q = Quartile. Dec/Stable= Decreasing/Stable. The reference group for models examining baseline values is the lowest quartile. The reference group for models examining change as a predictor is increasing values. Beta values pertain to the interaction term in the GEE model (predictor * time) and reflect rate of cognitive decline in comparison to that in the reference group with negative betas indicating faster decline and positive betas indicating slower decline.