

Association of Plasma β -Amyloid Level and Cognitive Reserve With Subsequent Cognitive Decline

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AN ESTIMATED 36 MILLION people currently have dementia, with the prevalence expected to double every 20 years.¹ Thus, biomarkers to identify elderly persons at risk of developing dementia could be useful for early prevention, if and when such interventions are available, and treatment. Plasma β -amyloid measurement has emerged as a promising biomarker, with lower β -amyloid 42 and 42/40 levels shown to be associated with increased risk of developing Alzheimer disease (AD).²⁻⁴ However, both cross-sectional and prospective studies have reported conflicting results⁵⁻⁷ that may be due to variations in participant diversity, follow-up time, and choice of laboratory assays.^{2,3,5,6} In addition, few studies have investigated the association of plasma β -amyloid level and rate of cognitive decline as opposed to dementia.

See also pp 275 and 304.

Context Lower plasma β -amyloid 42 and 42/40 levels have been associated with incident dementia, but results are conflicting and few have investigated cognitive decline among elders without dementia.

Objective To determine if plasma β -amyloid is associated with cognitive decline and if this association is modified by measures of cognitive reserve.

Design, Setting, and Participants We studied 997 black and white community-dwelling older adults from Memphis, Tennessee, and Pittsburgh, Pennsylvania, who were enrolled in the Health ABC Study, a prospective observational study begun in 1997-1998 with 10-year follow-up in 2006-2007. Participant mean age was 74.0 (SD, 3.0) years; 55.2% (n=550) were female; and 54.0% (n=538) were black.

Main Outcome Measures Association of near-baseline plasma β -amyloid levels (42 and 42/40 measured in 2010) and repeatedly measured Modified Mini-Mental State Examination (3MS) results.

Results Low β -amyloid 42/40 level was associated with greater 9-year 3MS cognitive decline (lowest β -amyloid tertile: mean change in 3MS score, -6.59 [95% confidence interval [CI], -5.21 to -7.67] points; middle tertile: -6.16 [95% CI, -4.92 to -7.32] points; and highest tertile: -3.60 [95% CI, -2.27 to -4.73] points; $P < .001$). Results were similar after multivariate adjustment for age, race, education, diabetes, smoking, and apolipoprotein E [APOE] e4 status and after excluding the 72 participants with incident dementia. Measures of cognitive reserve modified this association whereby among those with high reserve (at least a high school diploma, higher than sixth-grade literacy, or no APOE e4 allele), β -amyloid 42/40 was less associated with multivariate adjusted 9-year decline. For example, among participants with less than a high school diploma, the 3MS score decline was -8.94 (95% CI, -6.94 to -10.94) for the lowest tertile compared with -4.45 (95% CI, -2.31 to -6.59) for the highest tertile, but for those with at least a high school diploma, 3MS score decline was -4.60 (95% CI, -3.07 to -6.13) for the lowest tertile and -2.88 (95% CI, -1.41 to -4.35) for the highest tertile ($P = .004$ for interaction). Interactions were also observed for literacy ($P = .005$) and for APOE e4 allele ($P = .02$).

Conclusion Lower plasma β -amyloid 42/40 is associated with greater cognitive decline among elderly persons without dementia over 9 years, and this association is stronger among those with low measures of cognitive reserve.

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Thus, one objective of our study was to prospectively investigate the association between plasma β -amyloid 42 and 42/40 levels and cognitive decline over 9 years in a large cohort of biracial, community-dwelling older adults without dementia.

Although evidence suggests that β -amyloid accumulation in the brain is one of the key aspects of AD clinicopathology,⁸⁻¹⁰ there is tremendous variation in β -amyloid deposition, as measured by autopsy or neuroimaging, and manifestation of clinical symptoms.¹¹⁻¹³ One explanation for this difference, the cognitive reserve hypothesis, proposes that some older adults with AD pathology experience fewer clinical symptoms because of a variety of compensatory factors, such as higher occupational or educational achievement, greater efficiency or flexibility of neural networks, and larger brain size.^{14,15} Indeed, several studies have demonstrated that among people with higher education, amyloid burden as measured by neuroimaging was less associated with cognitive function compared with those with less education.^{12,13} Therefore, another goal of our study was to determine whether measures of cognitive reserve modified the effect of plasma β -amyloid level on cognitive decline.

METHODS

Study Population

Participants were enrolled in the ongoing Health, Aging and Body Composition (Health ABC) study, a prospective cohort of 3075 community-dwelling white and black older adults. The study enrollment period was 1997-1998, and at baseline the adults ranged in age from 70 to 79 years and lived in Memphis, Tennessee, or Pittsburgh, Pennsylvania. 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 planning to

remain within the study area for at least 3 years.¹⁶

Of the 22 999 elderly persons identified, 8695 were unavailable for eligibility screening; 897 were institutionalized or dead or had moved; 7250 declined to participate; and 3082 were ineligible. The remaining 3075 were enrolled in Health ABC. Our analytical cohort was composed of a subgroup of 997 participants with repeated cognitive testing who had β -amyloid 42 and β -amyloid 40 measurement (a random sample of sex- and race-stratified participants with baseline and ≥ 1 other cognitive measure over time). Compared with the Health ABC participants who did not have β -amyloid measured, those in the subgroup were more likely to be female and black and to have lower mean education but did not differ in other basic 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 provided written informed consent.

Measurements

β -Amyloid. β -Amyloid 40 and β -amyloid 42 levels were measured from stored plasma obtained at the first Health ABC follow-up visit (median time from baseline of 53.4 weeks [25th-75th percentile, 51.0-58.1 weeks]). Plasma was stored at -70°C and shipped directly to the analytical laboratory. Plasma β -amyloid was measured in 2010 by the laboratory of S. G. Y. at the Mayo Clinic, Jacksonville, Florida, using Innogenetics (Ghent, Belgium) INNO-BIA assays. The detection limit for this assay is 12 pg/mL for β -amyloid 40 and 5 pg/mL for β -amyloid 42. The mean interassay coefficient of variation was 9.9% for β -amyloid 40 and 9.3% for β -amyloid 42, and the mean within-assay coefficient of variation was 3.5% for β -amyloid 40 and 2.3% for β -amyloid 42.

Cognitive Function and Dementia Incidence. Cognitive function was mea-

sured with the Modified Mini-Mental State Examination (3MS). The 3MS, an assessment of global cognitive function, is a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory with a maximum or best score of 100.¹⁷ The 3MS was administered to participants during the baseline visit (year 1) and repeated at the year 3 ($n=932$), 5 ($n=854$), 8 ($n=642$), and 10 ($n=568$) follow-up visits ending in 2006-2007. Incident dementia was recorded during follow-up and ascertained from use of dementia medications at each visit (cholinesterase inhibitors and memantine) and from review of hospitalization records.

Cognitive Reserve. Several studies have used measures of education and intelligence as markers or proxies of cognitive reserve.^{12,13,18} Based on this, we used years of education and literacy, 2 common measures of reserve. Self-reported years of education were coded as less than a high school diploma and at least a high school diploma. Literacy was measured with the Rapid Estimate of Adult Literacy in Medicine (REALM).^{19,20} The REALM instrument has been validated in adult populations, and scores are highly correlated with other tests of literacy.²¹ REALM scores were categorized as at least sixth grade (REALM score ≤ 44) and higher than sixth grade (REALM score ≥ 45), as suggested by the scale developers, who reported that this cut-off differentiates those who are functionally illiterate vs literate in a health care setting.²² As a measure of genetic vulnerability or reserve, we also assessed apolipoprotein E (APOE) $\epsilon 4$ allele status using standard SNP techniques and dichotomized into having 1 or more APOE $\epsilon 4$ allele vs having no APOE $\epsilon 4$ allele (rs429358 and rs7412).

Covariates. At baseline, participants reported their age, race, and sex. 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 (based on fasting blood glucose level, current medications, or self-report), hypertension (based on clinic measure, current medications, or self-report), stroke or transient ischemic attack (based on self-report), and myocardial infarction (based on self-report). Body mass index was calculated from direct height and weight measurements at baseline. Participants self-reported current smoking, alcohol use, and physical activity (evaluated by a modified Paffenbarger Scale to calculate total kilocalories expended per week).²³ The Center for Epidemiologic Studies Depression Scale was used to assess depressive symptoms, with a score of 16 or higher consistent with possible depression.²⁴ High-sensitivity C-reactive protein and serum creatinine were also measured from baseline blood samples.

Statistical Analyses

We determined a priori to categorize β-amyloid 40, 42, and 42/40 levels into lowest, middle, and highest tertiles. We then determined the association between baseline participant characteristics and β-amyloid 42/40 tertile using Pearson χ^2 and analysis of variance tests. The analysis of variance model used was a fixed-effects model of the means of each variable across the 3 tiers of β-amyloid level. To determine the association between β-amyloid 42, 40, and 42/40 tertiles and longitudinal repeated measures of 3MS, unadjusted mixed-effects models were used.

We then created multivariate models controlling for the dependent nature of observations of the same individual through time as well as adjusting for characteristics that significantly differed across tertile at baseline ($P < .05$) (TABLE 1) or that have been previously shown to be associated with cognitive function (age, race, education, diabetes, and APOE ε4 status). Literacy and education were tightly correlated, so only education was included in the adjusted model. Because plasma β-amyloid 42 and β-amyloid 40 levels may be sensitive to serum creatinine level,²⁵ we also adjusted mod-

Table 1. Baseline Characteristics by β-Amyloid 42/40 Tertile Among 997 Elderly Adults^a

Characteristics	Lowest Tertile (<0.16) (n = 330)	Middle Tertile (0.16-0.19) (n = 338)	Highest Tertile (>0.19) (n = 329)	P Value ^b
Age, mean (SD), y	74.1 (3.0)	74.0 (2.7)	73.8 (3.0)	.34
Black	201 (60.9)	172 (50.9)	165 (50.1)	.008
Female	188 (57.0)	182 (53.8)	180 (54.7)	.70
At least a high school diploma	193 (58.5)	225 (66.6)	211 (64.1)	.06
Stroke	33 (10.0)	34 (10.0)	28 (8.5)	.73
Diabetes	95 (28.8)	76 (22.5)	69 (21.0)	.04
Myocardial infarction	38 (11.5)	32 (9.5)	35 (10.6)	.73
Hypertension	228 (69.1)	223 (66.0)	207 (62.9)	.25
Body mass index, mean (SD) ^c	27.6 (4.6)	27.7 (5.0)	27.9 (5.2)	.79
Exercise, mean (SD), kcal/wk	973.0 (1724.2)	1041.6 (1907.1)	1156.7 (2685.9)	.53
Current smoker	42 (12.7)	24 (7.2)	31 (9.5)	.05
Heavy drinker	24 (7.3)	16 (4.7)	26 (7.9)	.22
Depression score ≥16	12 (3.6)	18 (5.3)	16 (4.9)	.56
Apolipoprotein E ε4 allele	120 (36.4)	98 (29.0)	72 (21.9)	<.001
C-reactive protein, mean (SD), μg/mL ^d	3.1 (5.4)	2.9 (3.8)	3.2 (4.6)	.57
Higher than sixth-grade literacy	270 (81.8)	295 (87.3)	280 (85.1)	.03
Memphis, Tennessee, site	157 (47.6)	174 (51.5)	156 (47.4)	.49
Baseline modified Mini-Mental State Examination score, mean (SD)	90.7 (5.4)	91.4 (5.4)	91.1 (5.4)	.26
β-Amyloid 42 level, mean (SD), pg/mL	27.9 (7.0)	35.1 (6.4)	38.6 (11.5)	<.001
β-Amyloid 40 level, mean (SD), pg/mL	209.1 (44.6)	199.6 (36.4)	165.7 (57.2)	<.001
β-Amyloid 42/40 ratio, mean (SD)	0.13 (0.02)	0.18 (0.01)	0.25 (0.09)	<.001

^aData are expressed as No. (%) of participants unless otherwise indicated.

^bP value by unadjusted analysis of variance for continuous variables and χ^2 test for categorical variables.

^cBody mass index is calculated as weight in kilograms divided by height in meters squared.

^dC-reactive protein median, 1.6 (range, 0.3-85.2) μg/mL.

els for serum creatinine, but this did not significantly change any results, so our final model did not include this variable. Finally, we conducted a series of preplanned, adjusted mixed-effects models to determine whether the β-amyloid associations with cognitive decline were modified by measures of cognitive reserve (education, literacy, or APOE ε4 status) and tested for an interaction. We also repeated all analyses excluding participants with incident dementia and evaluating β-amyloid as a continuous predictor. All analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina), and were 2-tailed with the statistical significance level set at $P < .05$.

RESULTS

At baseline, mean age was 74.0 (SD, 3.0) years, 550 (55.2%) were female, and 538 (54.0%) were black. The mean β-amyloid 42 level of the 997

participants was 33.9 (SD, 9.6) pg/mL, β-amyloid 40 was 191.6 (SD, 50.6) pg/mL, and β-amyloid 42/40 was 0.19 (SD, 0.17). Participants in the lowest β-amyloid 42/40 tertile were more likely to be black ($P = .008$), to have diabetes ($P = .04$), to have lower literacy ($P = .03$), to smoke currently ($P = .05$), and to have an APOE ε4 allele ($P < .001$) (Table 1). Those in the lowest tertile tended to be less educated ($P = .06$) but did not differ in other baseline characteristics.

In unadjusted, mixed-effects, repeated-measures models, β-amyloid 42/40 was not associated with baseline 3MS score (TABLE 2). However, low β-amyloid 42/40 level was associated with greater cognitive decline over 9 years (change in 3MS score: lowest tertile, -6.59 [95% confidence interval {CI}, -5.21 to -7.67] points, middle tertile, -6.16 [95% CI, -4.92 to -7.32], and highest tertile, -3.60 [95% CI, -2.27 to -4.73]; $P < .001$) (Table 2). After ad-

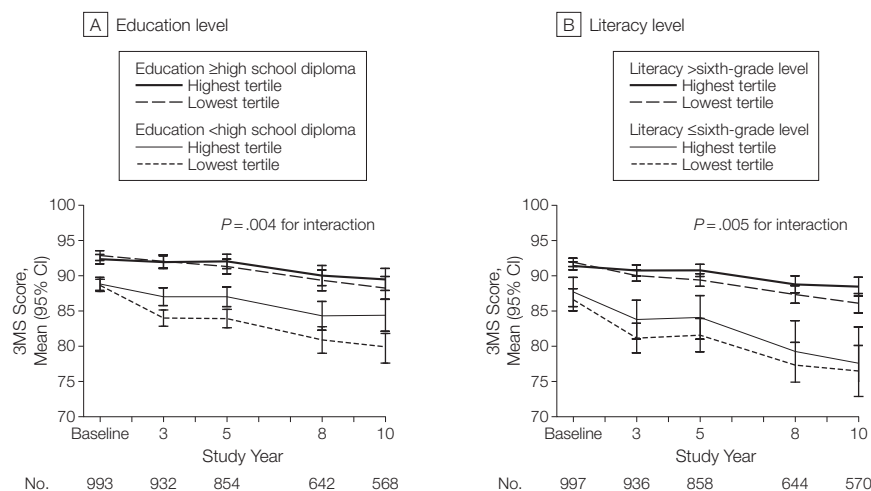
Table 2. Mean 3MS Scores by Plasma β-Amyloid 42 and β-Amyloid 42/40 Tertiles

	Lowest Tertile (n = 328)	Middle Tertile (n = 339)	Highest Tertile (n = 330)	P Value ^a
β-amyloid 42				
Baseline 3MS score, mean (95% CI)	90.75 (90.21 to 91.43)	91.11 (90.57 to 91.75)	91.40 (90.85 to 92.03)	.30
9-Year 3MS change, mean (95% CI)	-6.96 (-5.26 to -8.03)	-5.14 (-3.94 to -6.34)	-4.30 (-3.03 to -5.47)	.007
β-amyloid 42/40				
Baseline 3MS score, mean (95% CI)	90.74 (90.19 to 91.37)	91.44 (90.88 to 92.06)	91.09 (90.57 to 91.79)	.26
9-Year 3MS change, mean (95% CI)	-6.59 (-5.21 to -7.67)	-6.16 (-4.92 to -7.32)	-3.60 (-2.27 to -4.73)	<.001

Abbreviations: CI, confidence interval; 3MS, modified Mini-Mental State Examination.

^aUnadjusted mixed-effects models of the association between plasma β-amyloid 42 and β-amyloid 42/40 tertiles and baseline and change in 3MS score.

Figure. Multivariate Mixed-Effects Model for Adjusted Mean 3MS Score by Years of Follow-up, Education/Literacy Level, and β-Amyloid 42/40 High/Low Tertiles



3MS indicates Modified Mini-Mental State Examination. Error bars indicate 95% confidence intervals (CIs). A, For education level, models are adjusted for age, race, diabetes, smoking, and apolipoprotein E (APOE) e4 status; the interaction term is between education level and β-amyloid 42/40 tertile. B, For literacy level, models are adjusted for age, race, diabetes, smoking, and APOE e4 status; the interaction term is between literacy level and β-amyloid 42/40 tertile.

justment for age, race, education, diabetes, smoking and APOE e4 status, the results remained statistically significant (change in 3MS score: lowest tertile, -6.38 [95% CI, -5.15 to -7.61]; middle tertile, -6.09 [95% CI, -4.89 to -7.29]; and highest tertile, -3.44 [95% CI, -2.21 to -4.67]; $P = .02$). There was also a significant association between plasma β-amyloid 42 and cognitive decline (change in 3MS score: lowest tertile, -6.96 [95% CI, -5.53 to -8.03]; middle tertile, -5.14 [95% CI, -3.94 to -6.34]; and highest tertile, -4.30 [95% CI, -3.03 to -5.47]; $P = .007$), and multivariate adjustment for age, race, education, diabetes, smoking, and APOE e4 status did not appreciably change these

results (change in 3MS score: lowest tertile, -6.70 [95% CI, -5.45 to -7.95]; middle tertile, -5.03 [95% CI, -3.81 to -6.25]; and highest tertile, -4.29 [95% CI, -3.06 to -5.52]). There was no association between plasma β-amyloid 40 and baseline cognitive function or decline. When β-amyloid 42/40 was analyzed as a continuous predictor, the β coefficient for 9-year cognitive decline in multivariate-adjusted models was 0.68 per 1 SD of β-amyloid 42/40 ($P = .03$).

In multivariate-adjusted models, cognitive reserve measures modified the association between β-amyloid 42/40 level and cognitive decline. Older adults with low reserve (as measured by less

than a high school diploma or sixth-grade or lower literacy) had an even greater association with β-amyloid 42/40 level, whereas those with high reserve had less association ($P < .05$ for interaction for both measures on 3MS decline) (FIGURE). For example, among participants with less than a high school diploma, the 9-year decline on the 3MS was -8.94 (95% CI, -6.94 to -10.94) for the lowest β-amyloid 42/40 tertile compared with -4.45 (95% CI, -2.31 to -6.59) for the highest tertile, but among those with at least a high school diploma, the 9-year decline for the lowest tertile was -4.60 (95% CI, -3.07 to -6.13) and for the highest tertile was -2.88 (95% CI, -1.41 to -4.35) ($P = .004$ for interaction).

APOE e4 status also modified the association between β-amyloid 42/40 level and cognitive decline, such that older adults with an e4 allele had an even greater association with β-amyloid 42/40 level. Among participants with an e4 allele, the 9-year decline on the 3MS was -7.75 (95% CI, -5.75 to -9.75) for the lowest tertile compared with -5.00 (95% CI, -2.37 to -7.62) for the highest tertile, but among those with no e4 allele, decline was -5.50 (95% CI, -3.95 to -7.05) for the lowest and -3.03 (95% CI, -1.64 to -4.42) for the highest tertile ($P = .02$ for interaction).

Over the course of the follow-up, 72 participants had incident dementia, and we repeated the analyses after excluding these individuals. The association between plasma β-amyloid 42/40 tertile and 9-year cognitive decline remained statistically significant (change in 3MS score: lowest tertile, -5.49 [95%

CI, -4.29 to -6.69]; middle tertile, -5.26 [95% CI, -4.10 to -6.42]; and highest tertile, -3.16 [95% CI, -1.98 to -4.34]; $P = .002$). The interaction among education, plasma β -amyloid 42/40, and cognitive decline remained statistically or borderline significant ($P = .03$) whereas the interaction with literacy was no longer significant ($P = .08$). The interaction among *APOE* $\epsilon 4$, β -amyloid 42/40, and cognitive decline also was nonsignificant ($P = .43$).

COMMENT

Our results suggest that older adults without dementia and with lower β -amyloid 42/40 levels have an increased rate of cognitive decline over 9 years compared with those with higher levels and that this relationship is modified by measures of cognitive reserve. Specifically, our results indicate that the association between β -amyloid plasma level is greater among those with less education, lower literacy, and an *APOE* $\epsilon 4$ allele. These results are important, as the prevalence of cognitive impairment is increasing exponentially and prevention will be crucial.¹ To identify those at risk of dementia, biomarkers like plasma β -amyloid level that are relatively easy to obtain and minimally invasive could be useful. In addition, our finding of an interaction of cognitive reserve with the association of plasma β -amyloid level and cognitive decline could have public health importance because it may suggest pathways for modifying β -amyloid effects on cognition.

Our results are supported by those from several prospective studies that reported an association between the β -amyloid 42/40 ratio and dementia.^{2,26,27} Notably, one of these studies also used the Innogenetics INNO-BIA assay, which is one of the newest methods of quantifying plasma β -amyloid.^{26,28} However, our results differ from several other studies that found the opposite or no association between plasma β -amyloid 42 or the ratio and dementia.^{6,7,29} Difficulty in interpreting and comparing these results stems from heterogeneous study de-

signs and differences in follow-up time and methods of quantifying β -amyloid. It is also possible that studies that did not find an association between plasma β -amyloid and cognitive decline or dementia included participants with high cognitive reserve.

The accumulation of β -amyloid 42 in the cortex is one of the hallmarks of AD pathology.⁸⁻¹⁰ This has been documented not only in autopsy studies but also with in vivo imaging of β -amyloid.^{10,30,31} However, some studies have indicated that clinically "normal" elderly persons have β -amyloid deposition as well, suggesting a disconnect between clinical and pathological findings at times. For example, some individuals with extensive β -amyloid deposition as measured by autopsy or neuroimaging demonstrate little to no clinical symptoms of AD.¹¹⁻¹³ This has led to a hypothesis of cognitive reserve.^{13,15}

Cognitive reserve is a broad concept used to explain why some individuals have a measureable pathological burden of β -amyloid but do not experience clinical symptoms of cognitive decline.¹⁵ The concept is often explained by a wide variety of compensatory factors, including more synapses, more flexible neural networks, larger brain size, and beneficial life factors such as higher achieved education and occupational achievement.^{14,15} Although these characteristics are difficult to quantify, studies have used education and literacy as measures of cognitive reserve.^{12,13,18}

Our results extend the hypothesis that cognitive reserve modifies the association between β -amyloid and cognitive impairment.^{12,13,18} We found that participants with high cognitive reserve (high education, high literacy, and no *APOE* $\epsilon 4$ allele) experienced less cognitive decline than those with low reserve, and, most importantly, those with high cognitive reserve had less or no association with β -amyloid level and rate of decline. Our findings are supported by reports that the association between cognitive performance and amyloid burden on imaging or pa-

thology was modified by reserve, as measured by education and intelligence.^{13,18} A recent study reported that both baseline and decreasing levels of plasma β -amyloid 42 are associated with cognitive decline in older adults.³² However, no prior study has demonstrated this pattern of an interaction with cognitive reserve and plasma or cerebrospinal fluid (CSF) β -amyloid level on rate of cognitive decline.

This study has several strengths, including the prospective design, a relatively large sample size, and that cognitive function was measured repeatedly throughout the study. We were able to adjust for numerous potential confounders, including those that have previously been shown to be related to cognitive function. We used Innogenetics INNO-BIA assays to measure β -amyloid 42 and 40, which may provide more accurate measurements of β -amyloid 42 and β -amyloid 40 because of its high sensitivity, low variability, and high reproducibility.²⁸ Finally, we were able to assess cognitive reserve in terms of education, literacy, and *APOE* $\epsilon 4$ allele.

There are also several weaknesses that should be taken into consideration when interpreting these results. Because we did not have CSF measurements of β -amyloid, we could not correlate plasma β -amyloid to measurements of CSF β -amyloid. We also did not have measures on all cognitive domains, so future studies should investigate if similar results are found when different measures of cognitive function are used. In addition, while we used variables that often are used to assess cognitive reserve, we did not use others such as occupation or intellectual activity. Finally, the relative differences in cognitive decline in our cohort are moderate; however, a decline of 5 points on the 3MS has been used to define clinically significant cognitive impairment,³³ and the observed difference between the highest and lowest β -amyloid tertiles in our study is approximately 3 points. This difference may be clinically significant and was sufficient to demonstrate the in-

teraction of cognitive reserve with β-amyloid and cognitive decline.

Our results suggest that the plasma β-amyloid 42/40 ratio appears to be a biomarker of cognitive decline. Furthermore, we found that the association between this measure and rate of decline is modified by cognitive reserve. This suggests possible pathways such as cognitive activity or ongoing education for mitigating or preventing β-amyloid effects on cognition. Future studies should further explore the use of plasma β-amyloid as a biomarker, assess the mechanisms by which cognitive reserve modifies this association, and determine whether increasing cognitive reserve through interventions can reduce the risk of AD.

Author Contributions: Dr Yaffe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Yaffe, Satterfield, Simonsick, S. G. Younkin, L. H. Younkin, Ding, Harris.

Analysis and interpretation of data: Yaffe, Weston, Graff-Radford, Simonsick, L. H. Younkin, Kuller, Ayonayon, Ding.

Drafting of the manuscript: Yaffe, Weston, Ding.

Critical revision of the manuscript for important intellectual content: Weston, Graff-Radford, Satterfield, Simonsick, S. G. Younkin, L. H. Younkin, Kuller, Ayonayon, Ding, Harris.

Statistical analysis: Weston.

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Study supervision: S. G. Younkin, L. H. Younkin.

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