

ONLINE FIRST

Plasma β -Amyloid and Cognitive Decline

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Objectives: To determine if plasma β -amyloid ($A\beta$) levels (1) can be linked to specific cognitive changes that constitute conversion to Alzheimer disease (AD) and (2) correspond to cognitive change independent of dementia.

Design: Longitudinal study including 3 visits during approximately 4½ years (2000-2006).

Setting: Northern Manhattan community.

Participants: Eight hundred eighty individuals from a population-based and ethnically diverse sample who had 2 plasma $A\beta$ measurements and were dementia free at the time of the first $A\beta$ sample; 481 remained cognitively healthy, 329 were cognitively or functionally impaired but not demented at any point, and 70 developed AD.

Main Outcome Measures: General estimating equations tested the association between plasma $A\beta$ (baseline and change in values) and cognitive change (com-

posite score and memory, language, and visuospatial indices).

Results: High baseline plasma $A\beta_{42}$ ($P=.01$) and $A\beta_{40}$ ($P=.01$) and decreasing/relatively stable $A\beta_{42}$ ($P=.01$) values were associated with faster decline in multiple cognitive domains. In those who remained cognitively healthy, high baseline plasma $A\beta_{42}$ ($P=.01$) and decreasing/relatively stable plasma $A\beta_{42}$ ($P=.01$) were associated with faster cognitive decline, primarily in memory.

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

Arch Neurol. Published online August 9, 2010.
doi:10.1001/archneurol.2010.189

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THE AMYLOID CASCADE hypothesis suggests that aberrant metabolism of the amyloid precursor glycoprotein, and subsequent accumulation of soluble oligomers β -amyloid 40 ($A\beta_{40}$) and 42 ($A\beta_{42}$), is the primary trigger for the development of Alzheimer disease (AD).^{1,2} The Tg2576 mouse model of AD has shown that plasma $A\beta$ levels decrease as brain $A\beta$ levels increase,³ generating interest in the suitability of plasma $A\beta$ level as a risk biomarker for AD. Indeed, we have reported that elevated plasma $A\beta_{42}$ at baseline⁴ and decreasing levels over time^{5,6} predict conversion to AD, and other studies support these findings.^{7,8} The current study sought to specify existing work by investigating the extent to which plasma $A\beta$ levels (1) can be linked to specific cognitive changes that 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, a prospective, population-based study of aging and dementia in Medicare recipients aged 65 years and older residing in northern Manhattan (Washington Heights, Hamilton Heights, and Inwood) that has been described in detail in earlier work.^{9,10} The population from which participants were drawn is composed of individuals from several countries of origin and represents 3 broadly defined ethnic categories (ie, Caribbean Hispanic, African American, and white). Potential participants were excluded at the time of recruitment if they did not speak English or Spanish. Ethnic group was classified by participants' 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 2 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 battery¹¹ according to criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised) 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 Disease and Related Disorders Association.¹² 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 nondemented at the first A β measurement and had a second A β measurement taken approximately 4½ 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 impaired but not demented at any study visit; and (3) 70 who developed AD by the second follow-up (approximately 4½ years later).

PLASMA A β 42 AND A β 40

Ten-milliliter venous blood samples (tri-potassium EDTA) were used to assess plasma A β 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 A β) and rabbit antisera (R165 vs A β 42 and R162 vs A β 40) in a double antibody sandwich enzyme-linked immunosorbent assay as described previously.^{5,13} This method measures the free or soluble form of A β , not the oligomeric or bound forms. The detection limit for these assays is 9 pg/mL. The A β peptide levels from each blood draw were measured in duplicate, using separate aliquots so that none of the samples were refrozen and rethawed for the repeat assay. The correlation between the repeat A β 40 and A β 42 measurements was substantial ($P < .001$) for both peptides at baseline (A β 40, $r = 0.97$; A β 42, $r = 0.94$) and at the second follow-up (A β 40, $r = 0.94$; A β 42, $r = 0.91$). The means of the 2 measurements were used in statistical analyses. β -Amyloid levels were not considered for diagnosis.

APOE GENOTYPE

Genotypes were obtained by amplification of genomic DNA with polymerase chain reaction subjected to *CfoI* restriction analysis using *APOE* primers and conditions similar to those described by Hixson et al¹⁴ and modified by Maestre and colleagues.¹⁵ Participants were classified according to the presence of at least 1 $\epsilon 4$ allele.

STATISTICAL ANALYSIS

Multivariate general linear models and partial correlations adjusting for age were used to examine the relationship between baseline cognition and continuous values of plasma A β . Generalized estimating equations (GEEs)¹⁶ were then used to determine if (1) baseline A β predicted rate of cognitive change or (2) change in A β over time was associated with rate of cognitive change. The GEE takes into account the multiple visits per sub-

ject 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 \times A β predictor) in the model indicates that rate of cognitive decline varies with the A β 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 elderly individuals 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 A β and dementia status, a supplementary 1-way analysis of variance was conducted in participants with high-risk A β profiles to examine differences in education between those who did and did not develop AD.

GEE PREDICTORS

Baseline A β 42 and A β 40 peptide levels and change in these values over time were the 4 predictors tested. Ordinal groupings were used to avoid nonlinear threshold effects and to facilitate examination of large differences in A β 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 were grouped, we repeated the primary analysis of global cognitive change as a function of A β tertile at baseline. Change in A β values was characterized using a median split (increasing value was the reference group). Ordinal values were determined based on the distribution of A β in the specific sample included in each model. Supplementary analyses examined the A β 42:A β 40 ratio as a predictor.

GEE COVARIATES

Age, sex, ethnic group, body mass index, *APOE* $\epsilon 4$ status, and recruitment wave were included as covariates. Because A β 42 and A β 40 are highly correlated, each was included as a covariate of the other to determine if independent relationships with cognition were present. Finally, models examining A β change were adjusted for baseline A β 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 8 high probability items from the repetition subtest of the Boston Diagnostic Aphasia Examination; the first 6 items of the Boston Diagnostic Aphasia Examination comprehension subtest; Wechsler Adult Intelligence Scale-Revised similarities subtest raw score; average score for phonemic fluency (C, F, and L); and average score for category fluency (animals, food, and clothing); and (3) visuospatial abilities: 5 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 A β was first collected, at a follow-up visit approximately 2 years later, and at a second follow-up visit approximately 4½ years later when A β was again measured. Overall scores for each

Table 1. Study Participant Characteristics, A β Values, and Cognition

Characteristic	Mean (SD)		
	Healthy Elderly Subjects (n=481)	Subjects With Incident AD (n=70)	Entire Sample (N=880)
Age, y	74.52 (5.37)	80.84 (6.98)	76.07 (6.07)
Education, y	12.42 (4.15)	6.72 (4.73)	10.58 (4.73)
Female sex, %	67	67	68
Race, %			
Hispanic	25	60	37
White	43	10	31
African American	31	29	31
≥ 1 APOE $\epsilon 4$, %	26	29	26
Cognitive z score ^a	0.64 (0.36)	-0.37 (0.44)	0.33 (0.52)
Change in cognitive score ^a	-0.07 (0.27)	-0.58 (0.42)	-0.16 (0.35)
A $\beta 40$, pg/mL			
Baseline	63.11 (43.97)	73.41 (50.69)	62.67 (44.00)
Change	48.60 (50.74)	50.87 (52.25)	51.91 (52.17)
A $\beta 42$, pg/mL			
Baseline	30.62 (18.02)	37.59 (18.16)	31.19 (19.50)
Change	13.22 (20.57)	8.77 (22.72)	13.29 (21.09)
A $\beta 42$:A $\beta 40$ ratio	0.63 (0.48)	0.70 (0.76)	0.64 (0.50)

Abbreviations: A β , β -amyloid; AD, Alzheimer disease.

^aCognitive 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.

cognitive domain were created by transforming raw scores into z scores (using the mean and SD of the entire Washington Heights and Inwood Columbia Aging Project sample at baseline). Individual z scores were averaged to create a score for each cognitive domain. The 3 domain z scores were averaged to create a composite cognitive z score.

RESULTS

MISSING DATA ANALYSIS

Eight hundred eighty of 2412 nondemented participants seen in 1999 had A β samples from baseline and the second follow-up. **Table 1** presents demographic characteristics and mean A β values. Overall, these subjects were younger (76.04 vs 77.99 years, $P < .001$) and had higher composite cognitive scores (0.32 vs 0.19, $P < .001$) than subjects without complete A β data, but education, sex, ethnic group, and APOE $\epsilon 4$ status were comparable. Of the 880 with available A β samples, individuals with incident AD were significantly older ($F = 67.20$, $P < .001$) and had fewer years of formal education ($F = 102.34$, $P < .001$) than the healthy elderly individuals in the sample.

PLASMA A β 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 A $\beta 42$ ($F = 1.24$, $P = .27$) or A $\beta 40$ ($F = 1.08$, $P = .37$) quartiles. Partial correlations adjusting for age revealed no as-

sociation between composite cognitive score and continuous A β values at baseline (A $\beta 42$, $r = -0.02$, $P = .56$; A $\beta 40$, $r = 0.01$, $P = .78$).

GENERAL ESTIMATING EQUATIONS

Rate of Global Cognitive Change by Baseline A β

Table 2 details the predictive value of baseline A β for cognitive change in the entire sample and healthy elderly individuals only. β -Amyloid quartiles were comparable for both samples. In the entire sample, individuals in the top 3 A $\beta 42$ quartiles declined faster than those in the lowest quartile. Results were largely comparable in the healthy elderly subjects. Individuals in the top 3 A $\beta 40$ quartiles also declined faster than those in the lowest quartile. In the healthy elderly individuals, only the highest quartile declined faster than those in the lowest. The A $\beta 42$:A $\beta 40$ ratio was not a significant predictor. β Values and significance levels were essentially identical when the data were examined by tertile, such that individuals in the highest 2 tertiles of both baseline A $\beta 40$ and A $\beta 42$ declined more quickly than those in the reference group. It should be noted that the significance was marginal in healthy elderly subjects who had the highest levels of A $\beta 42$ and this was true when grouping by quartile or tertile.

Rate of Global Cognitive Change by A β Change

In the entire sample and healthy elderly individuals only, those with relatively stable or decreasing A $\beta 42$ values had faster cognitive decline than those with increasing A $\beta 42$ values (entire sample, $\beta = -0.02$, $P = .01$; healthy elderly individuals, $\beta = -0.01$, $P = .02$). Removing baseline A $\beta 42$ values from these models did not change the results. Change in A $\beta 40$ was not associated with cognitive change in either sample. In individuals with high-risk A $\beta 42$ 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 vs 11.74 years of education; $F = 49.34$, $P < .001$).

Cognitive Change in Specific Domains by A β

Table 3 outlines the results regarding specific cognitive domains. In the entire sample, baseline A $\beta 42$ predicted cognitive change in all 3 domains, with individuals in the highest A $\beta 42$ quartile consistently declining faster than those in the lowest. Cognitive change in the second and third A $\beta 42$ quartiles was less consistently different from that of the lowest quartile. Baseline A $\beta 40$ 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 A $\beta 42$ predicted change in memory and visuospatial scores, with relatively stable or decreasing A $\beta 42$ predicting faster decline.

In healthy elderly individuals, baseline A $\beta 42$ quartile predicted change primarily in memory, with higher A $\beta 42$ at baseline generally predicting faster decline. Base-

Table 2. GEE Models of Composite Cognitive Decline as a Function of A β ^a

Ordinal Predictor	Entire Sample (N=876)			Cognitively Healthy Elderly Individuals (n=478)		
	Continuous A β Value, pg/mL	β	P Value	Continuous A β Value, pg/mL	β	P Value
Baseline A β 42						
Quartile 1	9.00 to 15.10	Reference	Reference	9.00 to 15.73	Reference	Reference
Quartile 2	15.11 to 28.90	-.02	.003	15.74 to 28.90	-.02	.01
Quartile 3	28.91 to 41.20	-.02	.001	28.91 to 39.83	-.02	<.01
Quartile 4	41.21 to 198.75	-.03	.001	39.84 to 136.20	-.01	.07
Change in A β 42						
Decreasing/stable	-44.00 to 11.50	-.02	.006	-41.35 to 11.90	-.01	.02
Increasing	11.51 to 82.85	Reference	Reference	11.91 to 70.70	Reference	Reference
Baseline A β 40						
Quartile 1	9.00 to 28.05	Reference	Reference	9.00 to 28.83	Reference	Reference
Quartile 2	28.06 to 55.75	-.02	.01	28.84 to 57.80	-.01	.08
Quartile 3	55.76 to 91.20	-.02	.01	57.81 to 91.00	-.01	.17
Quartile 4	91.21 to 455.90	-.02	.01	91.01 to 455.90	-.02	.02
Change in A β 40						
Decreasing/stable	-103.85 to 52.85	-.01	.18	-103.85 to 49.60	<-.01	.49
Increasing	52.86 to 259.60	Reference	Reference	49.61 to 232.55	Reference	Reference

Abbreviations: A β , β -amyloid; GEE, general estimating equation.

^aFour subjects were excluded from analyses owing to GEE requirements that each subject have nonmissing data for all variables in the model at 1 or more points. β Values pertain to the interaction term in the GEE model (predictor \times time) and reflect rate of cognitive decline compared with that in the reference group, with negative β indicating faster decline and positive β indicating slower decline.

Table 3. GEE Models of Specific Cognitive Decline as a Function of A β ^a

Predictor	Memory		Language		Visuospatial	
	β	P Value	β	P Value	β	P Value
Entire Sample						
Baseline A β 42						
Quartile 2	-.03	.01	-.02	.06	-.02	.09
Quartile 3	-.02	.11	-.02	.01	-.03	.005
Quartile 4	-.03	.02	-.03	.004	-.02	.03
Decreasing/stable change in A β 42	-.02	.03	-.01	.20	-.02	.03
Baseline A β 40						
Quartile 2	-.04	.005	-.01	.29	-.02	.09
Quartile 3	-.04	.01	-.02	.08	-.02	.10
Quartile 4	-.02	.20	-.03	.00	-.01	.17
Decreasing/stable change in A β 40	-.01	.06	<.01	.65	-.01	.28
Healthy Elderly Individuals						
Baseline A β 42						
Quartile 2	-.03	.02	-.02	.07	-.02	.09
Quartile 3	-.03	.02	-.02	.14	-.02	.03
Quartile 4	-.01	.37	-.01	.14	-.02	.09
Decreasing/stable change in A β 42	-.02	.06	-.01	.17	-.01	.18
Baseline A β 40						
Quartile 2	-.03	.02	<-.01	.62	-.01	.24
Quartile 3	-.02	.09	<-.01	.91	-.01	.21
Quartile 4	-.02	.10	-.02	.12	-.02	.08
Decreasing/stable change in A β 40	-.01	.26	.01	.33	-.01	.53

Abbreviations: A β , β -amyloid; GEE, general estimating equation.

^aThe reference group for models examining baseline values is the lowest quartile. The reference group for models examining change as a predictor is increasing values. β Values pertain to the interaction term in the GEE model (predictor \times time) and reflect rate of cognitive decline compared with that in the reference group, with negative β indicating faster decline and positive β indicating slower decline.

line A β 40 was generally unrelated to cognitive change, though individuals in the second quartile had faster memory decline than those in the lowest. Change in A β 42 was not associated with change in any domain, though there was a trend toward faster memory decline in indi-

viduals with relatively stable or decreasing A β 42, and the magnitude of the effect was identical to that in the entire sample. Finally, change in A β 40 over time was not related to cognitive change in the entire sample or healthy elderly individuals.

SUPPLEMENTARY STATISTICAL ANALYSIS

We ran additional exploratory analyses examining the association between plasma A β 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 β 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 (eg, -0.04 to -0.09). This was true for both baseline and change analyses. While the results were not statistically significant in these 2 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 A β 42 and the A β 42:A β 40 ratio and decreases in these values over time predicted AD onset after approximately 4½ years.⁶ The increased risk of AD conferred by high plasma A β 42 level has also been documented in 2 cross-sectional studies reporting high plasma A β 42 in amnesic mild cognitive impairment.^{7,8} 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 A β 42:A β 40 ratios 2 years prior to conversion may be consistent with a high ratio 4½ years prior to conversion, preceding a decline in A β 42 level.²¹ The current study sought to specify earlier work by investigating the association between plasma A β and cognition. Overall, high initial levels of plasma A β 40 and A β 42 and stable or decreasing A β 42 at follow-up were associated with faster global cognitive decline regardless of dementia status at follow-up. However, the cognitive domains associated with plasma A β were not independent of final dementia status, the potential relevance of which we will discuss.

A β AND COGNITIVE CHANGE IN THE CONTEXT OF INCIDENT AD

The relatively rapid cognitive decline seen as a function of high baseline plasma A β and stable or decreasing A β 42 in the entire sample is not surprising given that a similar plasma A β profile predicted conversion to AD in this same sample⁶ and cognitive decline in more than 1 domain is a prerequisite for incident AD. However, current results provide greater specificity to the association between plasma A β and AD diagnosis, implicate a direct and linear association with multiple aspects of cognitive change, and lend support to the potential utility of plasma A β as an indicator of disease progression. Moreover, separate examination of healthy elderly people offered the opportunity to further clarify the relationship between plasma A β 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 developing AD. It should be noted, however, that the relationship between plasma A β 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 cutoff (ie, rate of change or amount of change is not considered in diagnosis).

A β AND COGNITIVE CHANGE IN HEALTHY ELDERLY PEOPLE

The relationship between plasma A β 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, 1 small study ($n=34$) examining plasma A β level and global cognition produced similar findings.²² However, examination of specific cognitive domains in the current study revealed that global cognitive change in healthy elderly individuals 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 elderly people with a high-risk A β profile are in the early stages of AD but have not yet demonstrated sufficient change in nonmemory 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 A β profiles, these elderly individuals remained dementia free over the course of the study and may remain so over the long-term owing to biological factors such as the ability to clear A β 42 or psychosocial factors such as cognitive reserve. The potential influence of cognitive reserve was supported by our findings that among individuals with high-risk A β 42 profiles, those who remained dementia free had 4 more years of education on average than those who developed AD.

Another interpretation of the association between plasma A β 42 and memory in healthy elderly people is that amyloid changes are an important factor in cognitive aging, independent of underlying AD. Stated differently, the observable change in both plasma A β 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 editorial²³ 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. It is thus important for future work to determine more definitively the specificity of A β profiles for predicting dementia vs their significance for cognitive aging more generally. Comprehensive understanding of plasma A β across the cognitive spectrum and its relation to dementia will require collection of plasma A β at multiple times beginning in early to mid life as well as validation against A β imaging and autopsy.

Limitations of this study include only 2 plasma A β measurements and 2 follow-up assessments, preventing examination of later conversion to dementia in cognitively healthy elderly people. However, strengths of this study include its large and ethnically diverse sample, examination of change in A β level, comprehensive cogni-

tive evaluation across 3 periods, and inclusion of both incident dementia cases and dementia-free individuals. Moreover, direct examination of cognition rather than diagnosis provides insight into the factors that may constitute conversion to AD. Continued measurement of plasma A β 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.

Accepted for Publication: June 2, 2010.

Published Online: August 9, 2010. doi:10.1001/archneurol.2010.189

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Financial Disclosure: None reported.

Funding/Support: This work was supported by grants PO1-AG07232 and P50-AG08702 from the National Institutes of Health. Dr Cosentino 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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