Higher serum glucose levels are associated with cerebral hypometabolism in Alzheimer regions

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ABSTRACT

Objective: To investigate whether higher fasting serum glucose levels in cognitively normal, nondiabetic adults were associated with lower regional cerebral metabolic rate for glucose (rCMRgl) in brain regions preferentially affected by Alzheimer disease (AD).

Methods: This is a cross-sectional study of 124 cognitively normal persons aged 64 ± 6 years with a first-degree family history of AD, including 61 *APOE* ϵ 4 noncarriers and 63 carriers. An automated brain mapping algorithm characterized and compared correlations between higher fasting serum glucose levels and lower [18 F]-fluorodeoxyglucose-PET rCMRgl measurements.

Results: As predicted, higher fasting serum glucose levels were significantly correlated with lower rCMRgl and were confined to the vicinity of brain regions preferentially affected by AD. A similar pattern of regional correlations occurred in the *APOE* ϵ 4 noncarriers and carriers.

Conclusions: Higher fasting serum glucose levels in cognitively normal, nondiabetic adults may be associated with AD pathophysiology. Findings suggest that the risk imparted by higher serum glucose levels may be independent of *APOE* ϵ 4 status. This study raises additional questions about the role of the metabolic process in the predisposition to AD and supports the possibility of targeting these processes in presymptomatic AD trials. *Neurology*® 2013;80:1557-1564

GLOSSARY

AD = Alzheimer disease; **FDG** = [18 F]-fluorodeoxyglucose; **rCMRgl** = regional cerebral metabolic rate for glucose; **SPM** = statistical parametric mapping; **SVC** = small volume correction.

Diabetes and related metabolic disorders have been associated with an increased risk of the development of Alzheimer disease (AD).^{1,2} Elevated fasting serum glucose, an indicator of metabolic dysfunction, has been linked to decreased memory functioning in cognitively normal older adults³ and may be a risk factor for cognitive impairment⁴ or predisposition to AD.⁵ Therefore, AD prevention research may benefit from the study of elevated fasting serum glucose and the factors that regulate glucose control in cognitively normal individuals without diabetes.

[18 F]-Fluorodeoxyglucose (FDG)-PET has demonstrated reduced regional cerebral metabolic rate for glucose (rCMRgl) in specific brain regions of patients with AD.^{6,7} Cognitively healthy, older individuals with 1 or 2 copies of the *APOE* ϵ 4 allele have exhibited reductions in these same AD-affected areas, which may indicate a predisposition to AD.^{8,9} As in similar studies designed to assess the genetic, nongenetic, and perhaps interacting factors contributing to AD development,^{10,11} we propose the use of FDG-PET as a measure of presymptomatic risk¹² in the evaluation of the association between fasting serum glucose levels and rCMRgl in nondiabetic, healthy adults before the onset of AD.

In the present study, we utilized FDG-PET to test the hypothesis that higher fasting serum glucose levels in cognitively normal adults without diabetes are associated with lower rCMRgl in brain regions previously demonstrated to be affected in AD.⁶ We also characterized these associations in *APOE* ϵ 4 noncarriers and carriers, and tested for a predicted interaction between elevated fasting serum glucose and *APOE* ϵ 4 status in AD-affected brain regions.

Supplemental data at
www.neurology.org

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METHODS Participants. Participant data for this cross-sectional study originate from an ongoing longitudinal study.⁹ To protect against acquiring a biased sample, data selection was based on the availability of a recent FDG-PET performed on a specific model scanner as highlighted below. Recruitment material for the original study included newspaper, magazine, and direct mail ads, newspaper articles, and community presentations. Eligible study participants were cognitively healthy, aged 47 to 68 years, with a family history of probable AD in a first-degree relative. Participation entailed *APOE*ε4 testing, a medical examination, clinical ratings, neuropsychological tests, volumetric MRI, and FDG-PET, with longitudinal assessment occurring once every 2 years.⁹ Neuropsychological tests included the Auditory Verbal Learning Tests, Complex Figure Test, Boston Naming Test, Wechsler Adult Intelligence Scale–Revised, Controlled Oral Word Association Test, and the Wechsler Memory Scale–Revised. Participants understood that they would not be informed of their *APOE*ε4 genotype.

Participants denied memory or other cognitive impairment, had a minimum score of 28 on the Mini-Mental State Examination, and had normal neurologic examinations. Based on a structured psychiatric interview, study participants did not satisfy criteria for a current psychiatric disorder and had a score of less than 10 on the Hamilton Depression Rating Scale. Exclusion criteria included a history of diabetes (or documented use of a glucose-lowering medication), stroke, or other neurologic conditions. Hachinski ischemic scores were calculated for all participants.

Acquisition of fasting serum glucose levels occurred throughout the entire PET procedure to permit the quantification of cerebral glucose utilization. The LifeScan SureStep Flexx handheld glucometer acquired and analyzed 5 venous blood samples over the course of the 60-minute scan (at 7, 12, 20, 25, and 45 minutes post-FDG injection). For the purpose of the present study, each participant's fasting serum glucose level is defined as the level assessed at the 7-minute time mark.

The present cross-sectional study compares the most recent clinical ratings, neuropsychological test scores, FDG-PET measurements, and fasting serum glucose levels for 124 cognitively normal participants with a mean age of 64.0 years (SD = 6.1 years). The sample included 23 *APOE*ε4 homozygotes, 40 heterozygotes, and 61 noncarriers. Fasting serum glucose levels ranged from 76 to 126 mg/dL with an average fasting serum glucose value of 96.9 (SD = 9.9). For the purpose of this research protocol, fasting status was defined as a minimum of 4 hours, which is consistent with guidelines provided by the Society of Nuclear Medicine for FDG-PET brain imaging.¹³

Brain imaging. Each participant's most recent scan was used for the present study. Volumetric T1-weighted MRI and PET were performed as previously described and highlighted herein.⁹ All PET scans were performed on the same HR+ scanner (Siemens, Knoxville, TN) in the 3-dimensional mode. The procedure included a transmission scan, an IV injection of 5 to 8 mCi of FDG, and a 60-minute dynamic sequence of emission scans. Study personnel instructed participants to lie quietly with their eyes closed in the darkened scanner room. The reconstructed images consist of 63 horizontal slices with a center-to-center slice separation of 2.46 mm, an axial field of view of 15.5 cm, an in-plane resolution of 4.2 to 5.1 mm full width at half maximum, and an axial resolution of 4.6 to 6.0 mm full width at half maximum. PET images (counts relative to the whole-brain uptake) acquired during the last 30 minutes were used for the voxel-based analyses. Statistical parametric mapping (SPM)5 (Wellcome Department of Cognitive Neurology, London, UK) linearly and nonlinearly deformed the image of each subject into the coordinate space of a standard brain atlas,¹⁴ normalized the data

for variation in absolute whole-brain measurements using proportionate scaling, and smoothed images using a 3-dimensional Gaussian filter with 12 mm full width at half maximum.

General linear model–based, voxel-wise analyses examined whether a) higher levels of fasting serum glucose levels were associated with lower rCMRgl in the entire sample; b) higher levels of fasting serum glucose levels were associated with lower rCMRgl in each of the *APOE*ε4 noncarrier and carrier groups; and c) there was an interaction between fasting serum glucose levels and *APOE*ε4 status on rCMRgl in AD-affected areas. As in previous analyses,^{10,11} interaction analyses were performed by using the regression line slopes of the associations between the predictor variable and rCMRgl in each of the genetic groups. In areas in which elevated fasting serum glucose was associated with lower rCMRgl, generalized linear model–based *t* tests were used to determine whether the rCMRgl/fasting serum glucose regression line slope was significantly greater in carriers relative to noncarriers. The statistical maps were superimposed onto a map of rCMRgl reductions previously generated for probable AD patients⁶ and a spatially standardized, volume-rendered MRI in SPM.

Voxel-based analyses of this type, which involve a large number of comparisons, are subject to type I error rate inflation. Previous research has indicated that an uncorrected *p* < 0.005 enables a reduction in type I errors without missing results that may have empirical importance.¹⁵ The present study has retained this threshold for all imaging-related analyses. To correct for multiple comparisons, the small volume correction (SVC) procedure in SPM was utilized, as indicated, to adjust significance levels for the number of resolution elements in a priori areas of interest including the precuneus, posterior cingulate, parietal, temporal, prefrontal, and occipital brain regions. The SVC procedure utilized a *p* < 0.05 threshold.

Standard protocol approvals and patient consents. This study received approval from the Human Subjects Committees at Banner Good Samaritan Medical Center and Mayo Clinic. All participants for this study provided written informed consent.

RESULTS A description of the participants can be found in table 1. There were no statistically significant differences between *APOE*ε4 subgroups in age, sex, education, clinical ratings, neuropsychological test scores, or fasting serum glucose levels. A nonsignificant trend was observed for the Auditory Verbal Learning Test long-term memory score, in which the *APOE*ε4 homozygous group scored lower. This was not unexpected, given that the literature suggests this particular test to be sensitive to *APOE*ε4 effects.¹⁶ Hachinski scores ranged from 0 to 1 with 23.4% of the sample receiving a score of 1. Every score of 1 was attributed to a history of hypertension. Although high cerebrovascular risk was not expected in this sample of cognitively healthy adults, a history of hypertension could potentially be correlated with this study's predictor variable. Therefore, a point biserial correlation was run (*p* < 0.05, 1-tailed) treating the Hachinski measure in this study as a dichotomous variable (1 or 0). Results indicate there was no correlation between Hachinski score and fasting serum glucose (*r*_{pb} = −0.06, *p* = 0.24).

Higher fasting serum glucose levels were significantly correlated with lower rCMRgl in right temporal

Table 1 Participant characteristics, clinical ratings, neuropsychological test scores, and fasting serum glucose measurements^a

	APOEε4			
	Carriers			p Value
	Homozygotes (n = 23)	Heterozygotes (n = 40)	Noncarriers (n = 61)	
Age, y	63.1 (6.3)	64.3 (6.0)	64.2 (6.2)	0.72
Sex (%F)	16 (69.6)	25 (62.5)	39 (63.9)	0.85
Education, y	15.7 (2.1)	16.3 (2.2)	15.9 (2.1)	0.44
Fasting serum glucose, mg/dL	96.7 (10.0)	98.1 (10.9)	96.1 (9.2)	0.61
History of hypertension ^b	7 (30.4)	10 (25.0)	12 (19.7)	0.57
MMSE	29.5 (1.0)	29.6 (1.0)	29.6 (.9)	0.95
HAM-D	2.5 (2.2)	1.6 (2.1)	2.1 (2.5)	0.35
AVLT				
Total learning	48.0 (12.7)	51.3 (10.5)	48.3 (8.3)	0.28
Short-term memory	8.8 (3.7)	10.3 (3.4)	9.2 (2.7)	0.14
Long-term memory	8.0 (4.4)	10.1 (3.4)	9.1 (3.1)	0.07
Complex Figure Test				
Copy	34.4 (2.0)	33.7 (3.5)	34.4 (2.0)	0.41
Recall	18.1 (7.8)	21.3 (6.6)	20.1 (7.2)	0.22
Boston Naming Test	56.6 (3.7)	56.8 (3.7)	56.6 (4.1)	0.97
WAIS-R				
Information	12.1 (1.8)	13.0 (2.0)	13.0 (3.7)	0.38
Digit span	12.3 (3.0)	11.6 (3.1)	11.4 (2.8)	0.46
Block design	12.4 (3.1)	13.2 (2.6)	12.4 (2.5)	0.23
Arithmetic	11.5 (3.2)	12.7 (2.7)	12.2 (2.7)	0.25
Similarities	13.1 (1.5)	13.2 (2.2)	12.8 (2.2)	0.59
COWAT	51.7 (10.4)	49.0 (11.7)	47.3 (9.6)	0.22
WMS-R Orientation	13.9 (0.3)	13.9 (0.3)	13.9 (0.6)	0.97

Abbreviations: AVLT = Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test; HAM-D = Hamilton Depression Rating Scale; MMSE = Mini-Mental State Examination; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS-R = Wechsler Memory Scale-Revised.

^aUnless otherwise indicated, values are mean (SD). p Values were calculated with analysis of variance or χ^2 test, uncorrected for multiple comparisons ($p < 0.05$).

^bReported as number (percentage) of participants with a history of hypertension.

areas and bilaterally in precuneus/posterior cingulate, parietal, prefrontal, and occipital brain regions that have previously been implicated⁶ in AD (figure e-1 on the *Neurology*[®] Web site at www.neurology.org). Statistical correction for multiple comparisons in AD-related search regions revealed similar findings in all regions except right temporal and left occipital areas (figure 1). Post hoc analyses were performed on the data to control for the effects of age, sex, and education on rCMRgl outcomes. Findings were replicated in all areas except the right temporal and left occipital areas, with the remaining areas surviving SVC. Table 2 lists the brain atlas coordinates and magnitude of the most significant correlations in AD-related locations. As figure 2 illustrates, the

right parietal area demonstrated the greatest association between higher fasting serum glucose levels and reduced rCMRgl.

A series of post hoc analyses were performed to further examine whether study results were specific to AD-related regions. Additional SVC analyses were performed in 2 non-AD-related areas that demonstrated a significant association between higher fasting serum glucose and lower rCMRgl ($p < 0.005$, uncorrected for multiple comparisons). Findings in the primary visual and sensorimotor cortices, regions typically spared by AD pathology, did not survive SVC.

In APOE ϵ 4 noncarriers, higher fasting serum glucose was associated with reduced rCMRgl predominantly in AD-related left prefrontal and right

Figure 1 Association between higher fasting serum glucose levels and reduced rCMRgl in AD-related brain regions

Statistical maps generated from this study were projected onto the lateral and medial surfaces of the left and right cerebral hemispheres and feature brain regions in which elevated serum glucose levels are associated with reduced rCMRgl. Initial findings ($p < 0.005$) in AD-related search regions (see figure e-1) were corrected for multiple comparisons and yield a similar pattern of results ($p < 0.05$). AD = Alzheimer disease; rCMRgl = regional cerebral metabolic rate for glucose.

temporal areas, and bilaterally in precuneus and parietal areas (figure e-2A), with a similar pattern of results surviving correction for multiple comparisons, particularly in bilateral parietal and precuneus areas (figure 3A). In carriers of the *APOEε4* allele, higher fasting serum glucose was correlated with reduced rCMRgl predominantly in AD-related bilateral prefrontal and parietal areas (figure e-2B). Correction for multiple comparisons yielded similar findings (figure 3B). Associations between elevated fasting serum glucose and rCMRgl were significantly greater for carriers than noncarriers in left parietotemporal areas, but these findings did not survive correction for multiple comparisons.

To clarify this relationship in each *APOEε4* carrier subgroup, post hoc analyses at the original uncorrected type I error threshold of $p = 0.005$ were performed in *APOEε4* homozygotes and heterozygotes. Higher levels of fasting serum glucose were associated with reduced rCMRgl in left prefrontal and left parietal AD-related regions in the homozygote group, and right temporal and bilateral parietal AD-related regions in the heterozygote group.

Therefore, in summary, higher levels of fasting serum glucose were associated with reduced rCMRgl in AD-related areas, and in each of the *APOEε4* genetic subgroups. With the exception of 1 nonsignificant

trend observed in the left parietotemporal region, these associations were not significantly greater in carriers than in noncarriers. Exploratory analyses revealed that significant findings in areas of the brain that are typically spared in AD did not survive correction for multiple comparisons.

DISCUSSION This study of cognitively normal older adults demonstrated an association between higher fasting serum glucose levels and lower rCMRgl in precuneus/posterior cingulate, parietal, prefrontal, and occipital brain regions previously determined to be preferentially affected by AD.⁶ Our preliminary observations are specific to adults with no reported history of diabetes, thereby extending previous FDG-PET findings in diabetic and prediabetic participants.¹⁷ Furthermore, these associations were present in both noncarriers and carriers of the *APOEε4* allele, and did not appear to be significantly greater in carriers than noncarriers. Based on these results, we propose that the risk imposed by elevated fasting serum glucose levels on the development of AD may be present before the onset of diagnosed problems with glycemic control, and that it may be independent of the genetic risk associated with possession of the *APOEε4* allele.

In our prior FDG-PET studies of cognitively normal older adults, we had identified other cardiometabolic risk factors for the development of AD, including total serum cholesterol and hypertension.^{10,11} Higher levels of both were found to be significantly correlated with lower rCMRgl in AD-affected brain regions including parietal,¹¹ precuneus, parietotemporal, and prefrontal areas.¹⁰ However, higher levels of cholesterol and hypertension were additionally associated with lower rCMRgl in frontal areas previously determined to be affected by normal aging,¹⁸ which led us to posit that the AD risk imposed by certain cardiometabolic risk factors may be due, in part, to acceleration of brain changes associated with normal aging.¹⁰ Unlike these previous results, the pattern of reduced rCMRgl associated with elevated fasting serum glucose levels in this study was confined to the vicinity of AD-affected brain regions. Thus, although we have previously proposed that higher total cholesterol in later life may accelerate some of the brain changes associated with normal aging and conspire with other AD risk factors,¹⁰ we now suggest that higher fasting serum glucose levels may more directly affect brain processes implicated in the predisposition to AD.

The current study provides additional evidence that higher fasting serum glucose in the absence of diabetes may be related to brain changes related to dementia risk. It supports results from a recent longitudinal MRI study of cognitively healthy, nondiabetic adults that demonstrated that higher levels of baseline fasting serum glucose were associated with measures

Table 2 Location and magnitude of the most significant correlations between fasting serum glucose levels and rCMRgl^a

	Atlas coordinates (mm) ^b						
AD-related brain region	X	Y	Z	Brodmann area	Correlation coefficient	p Value ^c	Volume ^d
Precuneus/posterior cingulate							
Left	−14	−83	48	7	−0.35	2.2 × 10 ^{−5}	246
Right	20	−83	48	7	−0.27	9.5 × 10 ^{−4}	36
Parietal							
Left	−46	−64	47	40	−0.37	7.5 × 10 ^{−6}	482
Right	48	−57	54	40	−0.41	4.7 × 10 ^{−7}	176 ^e
Temporal							
Right	73	−33	−2	21	−0.25	2.0 × 10 ^{−3*}	N/A
Prefrontal							
Left	−42	14	44	8	−0.31	1.4 × 10 ^{−4}	33
Right	51	10	40	8	−0.29	5.0 × 10 ^{−4}	5
Occipital							
Left	−42	−89	4	19	−0.26	1.2 × 10 ^{−3*}	N/A
Right	32	−90	27	19	−0.36	2.5 × 10 ^{−5}	88

Abbreviations: AD = Alzheimer disease; N/A = not applicable; rCMRgl = regional cerebral metabolic rate for glucose.

^aThe data were extracted from voxels associated with the most significant correlations in regions previously found to be associated with abnormally low rCMRgl in patients with AD.⁶

^bThe coordinates were obtained from Talairach and Tournoux.¹⁴ X is the distance to the right (+) or left (−) of the midline, Y is the distance anterior (+) or posterior (−) to the anterior commissure, and Z is the distance superior (+) or inferior (−) to a horizontal plane through the anterior and posterior commissures.

^cThe reported significance levels are 1-tailed and uncorrected for multiple comparisons ($p < 0.005$). Unless indicated with an asterisk, these correlations remained significant ($p < 0.05$) after correcting for multiple comparisons.

^dNumber of voxels that survived SVC. “N/A” appears in regions where findings did not survive small volume correction. Voxel size = $2.0 \times 2.0 \times 2.0$ mm.

^eData from this location are plotted in figure 2.

*These correlations did not remain significant after correcting for multiple comparisons ($p < 0.05$) in the AD-related search regions, nor did they remain significant after post hoc analyses designed to control for the effects of age, education, and sex ($p < 0.005$).

of amygdalar and hippocampal atrophy.¹⁹ Other imaging studies have investigated insulin resistance as a risk factor for AD. An FDG-PET study comprised of older adults with confirmed prediabetes or diabetes demonstrated findings similar to those of the present study, in that reduced rCMRgl was evident in AD-related frontal, parietotemporal, and cingulate brain regions in individuals with higher levels of insulin resistance.¹⁷ Other structural MRI studies of AD risk have also demonstrated that higher levels of insulin resistance have been associated with increased total cerebral brain atrophy²⁰ and lower right and total hippocampal volume.²¹ Furthermore, select studies also considered the genetic contribution to imaging outcomes. Findings were similar to those of the current study, in that results were not solely attributable to possession of the *APOEε4* allele.^{17,19,21} This similarity further supports our assertion that factors associated with glucose control may impart an independent contribution to AD risk.

We have previously proposed utilizing FDG-PET measurements of rCMRgl as a presymptomatic quantitative endophenotype of AD,⁹ a biological measure

more closely related to disease predisposition than the clinical syndrome itself.²² Although this study supports the use of FDG-PET measurements as a quantitative endophenotype in the evaluation of cardiometabolic risk for AD, it may also support their application in the tracking of presymptomatic treatments,¹² although current efforts targeting glucose control have predominantly studied patient samples. Most recently, the use of intranasal insulin has demonstrated improvements in delayed recall in patients with mild cognitive impairment and AD, maintenance of daily living in patients with AD, preservation of general cognitive abilities in patients with mild cognitive impairment, and relatively less pronounced reductions in FDG-PET rCMRgl in relevant brain regions in treatment groups relative to placebo.²³

Limitations of the present study are primarily a consequence of the fact that the parent study was not prospectively designed to assess glucose control in study participants. For example, although fasting status in the present study (a minimum of 4 hours) was appropriate per standard FDG-PET imaging procedures,¹³ more

Figure 2 Scatterplot of the highest significant correlation between higher fasting serum glucose levels and reduced rCMRgl

This correlation occurred in an Alzheimer disease-related right parietal cortex voxel ($r = -0.41$, $p = 0.00014$) and survived correction for multiple comparisons ($p < 0.05$). rCMRgl = regional cerebral metabolic rate for glucose.

stringent methodologies to assess glycemic status in PET AD research^{17,19} are recommended. Within the context of recent FDG-PET studies that investigated the link

between insulin resistance and risk for AD,^{17,23} we acknowledge that the current study did not clarify the extent to which reductions in rCMRgl were related to higher glucose levels, higher insulin levels, or both. We note that although elevated serum glucose levels may affect long-standing and progressive rCMRgl declines, they may also have an acute and potentially reversible effect on regional rCMRgl, or on the competition between labeled FDG and unlabeled glucose. For instance, the induction of hyperglycemia in younger adults has yielded reduced rCMRgl in AD-related brain regions.²⁴ Although the explanation for this relationship warrants further clarification, exploratory findings from our post hoc analyses of areas that are spared in AD suggest that there may be specific metabolic processes that are occurring in these AD-relevant brain regions.

Furthermore, much of the evidence regarding cardiometabolic risk for AD arises from studies of insulin resistance^{2,25} or metabolic syndrome,²⁶ thus it is important to acknowledge that elevated fasting serum glucose may only partially contribute to the risk that is associated with glucoregulatory dysfunction. However, findings from the current study remain encouraging because they provide converging evidence regarding the role glucose control has in the development of AD. Lastly, because of the parent study's inclusion criteria, findings are generalizable solely to samples that report a first-degree family history of AD.

This study provides additional evidence for the relationship between higher fasting serum glucose levels and the predisposition to AD. It suggests that, in cognitively normal older adults without a history of

Figure 3 Association between higher fasting serum glucose and reduced rCMRgl by APOE ϵ 4 carrier group in AD-related brain regions

Statistical maps generated from this study were projected onto the lateral and medial surfaces of the left and right cerebral hemispheres and feature brain regions in which elevated serum glucose levels are associated with reduced rCMRgl in non-carriers (A) and carriers (B) of the APOE ϵ 4 allele. Initial findings ($p < 0.005$) in AD-related search regions (see figure e-2) were corrected for multiple comparisons and yield a similar pattern of results ($p < 0.05$). AD = Alzheimer disease; rCMRgl = regional cerebral metabolic rate for glucose.

diabetes, higher serum glucose levels may convey a risk for AD that may be unrelated to *APOE*ε4 gene dose or the acceleration of normal aging processes seen in other FDG-PET studies of cardiometabolic risk.^{10,11} Results encourage ongoing studies that consider metabolic dysfunction as a target for AD prevention trials, such as the use of intranasal insulin.²³ Lastly, this study continues to support the use of PET as a quantitative presymptomatic endophenotype, complementing more traditional retrospective case-control and time-consuming prospective cohort studies in the assessment of AD risk factors and the design of effective preventive interventions.¹²

AUTHOR CONTRIBUTIONS

Christine M. Burns, MA, was responsible for study concept and design, statistical analysis and interpretation of the data, and drafting the manuscript for content. Kwei Chen, PhD, was responsible for statistical analysis and interpretation of the data and revising the manuscript for content. Alfred W. Kaszniak, PhD, was responsible for study design and concept, interpretation of the data, and revising the manuscript for content. Wendy Lee, MS, was responsible for statistical analysis of data. Gene E. Alexander, PhD, was responsible for study design and concept, interpretation of the data, and revising the manuscript for content. Daniel Bandy, MS, was responsible for study design and acquisition of data. Adam S. Fleisher, MD, was responsible for revising the manuscript for content and study supervision. Richard J. Caselli, MD, was responsible for revising the manuscript for content and study supervision. Eric M. Reiman, MD, was responsible for study design, interpretation of the data, revising the manuscript for content, study supervision, and obtaining funding.

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He is a site investigator for GE, Avid, Lilly, Merck, Roche, Targacept, Janssen, Pfizer, Wyeth, and Genentech, and serves as a consultant and medical director to the Alzheimer's Disease Cooperative Study. R.J. Caselli receives research support from the NIH/NIA and the Arizona Alzheimer's Research Consortium. E.M. Reiman reports serving as a scientific advisor to Sygnis, AstraZeneca, Bayer, Eisai, Elan, Eli Lilly, GlaxoSmithKline, Intellect, Link Medicine, Novartis, Siemens, and Takeda. He has had research contracts with AstraZeneca and Avid/Eli Lilly; a patent pending for a biomarker strategy to evaluate preclinical AD treatments (through Banner Health); and research grants from NIH (NIA), Anonymous Foundation, Nomis Foundation, Banner Alzheimer's Foundation, and the State of Arizona. Go to Neurology.org for full disclosures.

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