Higher brain *BDNF* gene expression is associated with slower cognitive decline in older adults

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ABSTRACT

Objectives: We tested whether brain-derived neurotrophic factor (*BDNF*) gene expression levels are associated with cognitive decline in older adults.

Methods: Five hundred thirty-five older participants underwent annual cognitive assessments and brain autopsy at death. *BDNF* gene expression was measured in the dorsolateral prefrontal cortex. Linear mixed models were used to examine whether *BDNF* expression was associated with cognitive decline adjusting for age, sex, and education. An interaction term was added to determine whether this association varied with clinical diagnosis proximate to death (no cognitive impairment, mild cognitive impairment, or dementia). Finally, we examined the extent to which the association of Alzheimer disease (AD) pathology with cognitive decline varied by *BDNF* expression.

Results: Higher brain *BDNF* expression was associated with slower cognitive decline ($p < 0.001$); cognitive decline was about 50% slower with the 90th percentile *BDNF* expression vs 10th. This association was strongest in individuals with dementia. The level of *BDNF* expression was lower in individuals with pathologic AD ($p = 0.006$), but was not associated with macroscopic infarcts, Lewy body disease, or hippocampal sclerosis. *BDNF* expression remained associated with cognitive decline in a model adjusting for age, sex, education, and neuropathologies ($p < 0.001$). Furthermore, the effect of AD pathology on cognitive decline varied by *BDNF* expression such that the effect was strongest for high levels of AD pathology ($p = 0.015$); thus, in individuals with high AD pathology (90th percentile), cognitive decline was about 40% slower with the 90th percentile *BDNF* expression vs 10th.

Conclusions: Higher brain *BDNF* expression is associated with slower cognitive decline and may also reduce the deleterious effects of AD pathology on cognitive decline. *Neurology*® 2016;86:735–741

GLOSSARY

AD = Alzheimer disease; **BDNF** = brain-derived neurotrophic factor; **DLPFC** = dorsal lateral prefrontal cortex; **FPKM** = fragments per kilobase per million; **LBD** = Lewy body disease; **MCI** = mild cognitive impairment; **NCI** = no cognitive impairment.

Developing treatments for cognitive decline is a major public health priority in our aging population. While considerable progress has been made in elucidating the complex relationship between age-related neuropathology and resilience factors that affect the rate of cognitive decline, there are no treatments that slow or prevent cognitive decline in older adults. Converging preclinical and human studies suggest that brain-derived neurotrophic factor (*BDNF*) may influence late-life cognitive impairment.^{1,2} Moreover, *BDNF* may mitigate the deleterious effects of Alzheimer disease (AD) pathology in the brains of older adults and have a role in the pathogenesis of AD.³ Moreover, these reports led to studies that found that low serum or plasma *BDNF* levels may predict more rapid cognitive decline and may be lower in AD.^{1,4} However, we are not aware of studies that have examined the association of brain *BDNF* gene expression with the rate of cognitive decline.

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Supplemental data
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We used data from more than 500 older persons participating in 2 community-based cohort studies that include autopsy at death, to the test the hypothesis that brain *BDNF* gene expression is associated with the rate of cognitive decline during life.^{5,6} The rate of cognitive decline over an average of 6 years was derived from a structured annual cognitive assessment, brain *BDNF* gene expression was obtained from the dorsal lateral prefrontal cortex (DLPFC), and neuropathology indices were obtained from structured brain autopsy. First, we tested whether *BDNF* gene expression levels were associated with the rate of cognitive decline and whether this association varied by clinical diagnosis proximate to death. Then we examined whether this association was attenuated when we adjusted for the presence of common age-related neuropathologies. Finally, we determined whether the relation of AD pathology with the rate of cognitive decline varied by *BDNF* expression.

METHODS Participants. Data came from 2 longitudinal clinical autopsy studies, the Religious Orders Study and the Rush Memory and Aging Project.^{5,6} Next-generation RNA-seq data were generated in 2012 and 541 datasets passed quality control and 6 cases with incomplete neuropathology measures were excluded.

Cognitive function and clinical diagnoses. Each year, trained technicians administered 19 cognitive tests; 17 tests were used to generate a composite measure of global cognition as previously described (appendix e-1 on the *Neurology*[®] Web site at Neurology.org).^{5,6} Age in years was computed from self-report date of birth and date of death. Sex and education were recorded at the baseline interview. After death of a patient, a neurologist who was blinded to autopsy data reviewed all available cognitive and clinical data to assign a clinical diagnosis. Dementia and its causes were determined using the guidelines of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association.⁷ Individuals with cognitive impairment who did not meet dementia criteria were diagnosed with mild cognitive impairment (MCI).⁸ Individuals without dementia or MCI were classified as having no cognitive impairment (NCI).⁹

Postmortem brain indices. Brain removal, tissue sectioning and preservation, and a uniform examination with quantification of postmortem indices followed a standard protocol.^{5,6} Postmortem measures included the presence of pathologic AD based on National Institute on Aging criteria, a continuous measure summarizing the burden of AD pathology, as well as amyloid load and tangles. In addition, the presence of chronic macroscopic infarcts, Lewy body disease (LBD) pathology, and hippocampal sclerosis were recorded. These measures are described more fully in appendix e-1.

Table 1 Clinical characteristics proximate to death and postmortem indices of study cases (n = 535)

Measure	
Clinical	
Age baseline, y, mean (SD)	81.4 (7.1)
Age at death, y, mean (SD)	88.5 (6.6)
Follow-up, y, mean (SD)	6.3 (3.9)
Male sex, n (%)	196 (36.6)
Education, y, mean (SD)	16.5 (3.5)
MMSE score (0–30), mean (SD)	21.4 (8.9)
No cognitive impairment, n (%)	170 (31.8)
Mild cognitive impairment, n (%)	138 (25.8)
Dementia, n (%)	227 (42.4)
Val66Met (rs6265) 1 copy, n (%)	154 (30.6)
Val66Met (rs6265) 2 copies, n (%)	17 (3.4)
Postmortem	
Postmortem interval, h, mean (SD)	7.2 (4.8)
NIA-Reagan AD, n (%)	318 (59.4)
Global AD pathology, mean (SD) ^a	0.72 (0.39)
Macroscopic infarcts, n (%)	187 (35.0)
Lewy bodies, n (%)	99 (18.5)
Hippocampal sclerosis, n (%)	41 (7.7)
<i>BDNF</i> expression, mean (SD) ^b	−0.61 (1.17)

Abbreviations: AD = Alzheimer disease; *BDNF* = brain-derived neurotrophic factor; MMSE = Mini-Mental State Examination; NIA = National Institute on Aging.

^aThe measure was square root-transformed.

^bThe measure was log₂-transformed.

Brain *BDNF* gene expression. RNA was extracted from postmortem tissue from the gray matter of DLPFC using Qiagen's miRNeasy Mini Kit (cat. no. 217004, Valencia, CA) and the RNase-Free DNase Set (cat. no. 79254). RNA was quantified using Nanodrop following a quality checking using RNA integrity scores as previously described.¹⁰ RNA-seq library was prepared on the Broad Institute's Genomics Platform and the sequencing was performed on the Illumina HiSeq with coverage of at least 75 M 101-bp paired-end reads. The fragments per kilobase per million (FPKM) for each gene were quantified using RSEM software with Bowtie alignment. The FPKM were quantile-normalized with batch effects removed using combat.^{11–13} These normalized values estimate the expression level for each gene where higher values correspond to higher levels of expression. *BDNF* expression values were right-skewed and a base-2 logarithm transformation was applied before the analysis.

***BDNF* Val66Met polymorphism.** DNA was extracted and genotyped as previously reported.¹⁴ Briefly, standard quality control measures, implemented in PLINK, were applied at both sample and polymorphism levels. Population outliers were identified and removed using EIGENSTRAT. Genotype imputation was performed using BEAGLE with the 1000 Genomes Project (2011 Phase 1b data freeze) as the reference panel. We focused our analysis on the Val66Met polymorphism (rs6265), which has been linked

in some studies to incident AD and cognitive decline.¹⁵ Dosage values of the polymorphism were extracted from the genome-wide imputed data. The dosage, coded with respect to the T allele (allele frequency 0.19) in our data, ranges from 0 to 2.

Statistical analysis. The *t* tests were used to examine the difference of brain *BDNF* expression by presence of common neuropathologic conditions. Linear mixed models with both random intercept and random slope were used to examine the association of brain *BDNF* expression with annual rate of change in cognitive function. In these models, the repeated cognitive measures collected multiple years before death were the longitudinal outcome, and *BDNF* expression was the primary predictor. The slope, estimated by a term for time in years before death, measures the average annual rate of change in cognition. The interaction between time and *BDNF* expression estimates the association of the *BDNF* expression with rate of change in cognition. A significant and positive coefficient for the interaction suggests that a higher level of *BDNF* expression is associated with slower cognitive decline. The random intercept captures person-specific variations from the mean level of cognition proximate to death, and the random slope captures person-specific variations from the mean rate of cognitive decline. The random effects follow a bivariate normal distribution with an unstructured 2×2 covariance matrix, and the residual error follows a univariate normal distribution. The model was adjusted for age, sex, and education. Next, we augmented the prior model with a 3-way interaction term to examine whether *BDNF* expression modified the association of clinical diagnosis with cognitive decline.

Pearson correlations assessed the unadjusted association of *BDNF* expression with continuous measures of global AD pathology. Multivariable linear regression models were performed with *BDNF* expression as the outcome and neuropathologic indices as the predictors, adjusted for age, sex, and education. Next, we added terms to adjust for 4 neuropathologies to the linear mixed model described above. Then, we augmented the prior model with a 3-way interaction term to examine whether *BDNF* expression modified the association of AD pathology with cognitive decline. All of the analyses were conducted using SAS/STAT software, version 9.3 (SAS Institute Inc., Cary, NC)¹⁶ and statistical packages in R version 3.1.2 (www.r-project.org). We applied a nominal threshold of $p < 0.05$ for statistical significance.

Standard protocol approvals, registrations, and patient consents. The study was approved by the institutional review board of Rush University Medical Center. Written informed consent and an anatomical gift act for brain donation at the time of death was obtained from all study participants.

RESULTS There were 535 cases included in these analyses, and their clinical characteristics and autopsy findings are summarized in table 1.

***BDNF* brain expression and cognitive decline.** *BDNF* expression was detected in all postmortem brains. During up to 16 years of follow-up (mean 6.3 years, SD = 3.9 years), on average, cognition declined by about 0.10 U/y. Using a linear mixed-effect model, we examined the association of the level of *BDNF* expression with the rate of change in cognition. In a model adjusted for demographics, a higher level of *BDNF* expression was associated with a slower rate of cognitive decline (table 2). Figure 1

Table 2 *BDNF* gene expression association with level and annual rate of decline in cognition

	Global cognition	Episodic memory	Semantic memory	Working memory	Visual spatial skills	Perceptual speed
Cognitive change/y	−0.082 (0.008), <0.001	−0.083 (0.009), <0.001	−0.067 (0.010), <0.001	−0.054 (0.008), <0.001	−0.123 (0.010), <0.001	−0.060 (0.009), <0.001
<i>BDNF</i> expression	0.233 (0.041), <0.001	0.245 (0.050), <0.001	0.229 (0.049), <0.001	0.181 (0.036), <0.001	0.226 (0.044), <0.001	0.129 (0.037), <0.001
Cognitive change/y × <i>BDNF</i> expression	0.022 (0.004), <0.001	0.020 (0.005), <0.001	0.025 (0.005), <0.001	0.020 (0.004), <0.001	0.017 (0.005), <0.001	0.018 (0.005), <0.001

Abbreviation: *BDNF* = brain-derived neurotrophic factor.

Data represent β (SE), *p* value. Each column is estimated from a mixed-effect model examining the association of brain *BDNF* expression with the level of global cognition or 1 of 5 cognitive abilities at the last visit before death and with the annual rate of change in cognition (cognitive change/y × *BDNF* expression). Estimate (SE), *p* value: The β estimate in each model compares the annual rates of cognitive decline between 2 average participants with *BDNF* expression levels that differed by approximately 1 SD. Each model also included 6 additional terms (not shown) controlling for age, sex, education, and their interaction with cognitive change/y.

Figure 1 Brain *BDNF* expression level and the rate of cognitive decline

To display this association, 3 hypothetical average participants with their estimated rate of cognitive decline based on the complete model with all the cases analyzed in this study are illustrated. Model derived trajectories of cognitive decline for 3 participants with low (red, 10th percentile), average (black, 50th percentile) and high (blue, 90th percentile) brain *BDNF* expression levels in the dorsal lateral prefrontal cortex. *BDNF* = brain-derived neurotrophic factor.

illustrates the differences in trajectories of cognitive decline between persons with low (10th percentile), median (50th percentile), and high (90th percentile) level of the *BDNF* gene expression. Thus, the rate of

cognitive decline was reduced by about half (48.3%) in persons with the 90th percentile of *BDNF* expression vs 10th percentile.

The rate of cognitive decline varies with clinical diagnosis and is most rapid in dementia.¹⁷ Next, we added a 3-way interaction term that showed that *BDNF* expression modified the association of clinical diagnosis and the rate of cognitive decline (rate of cognitive decline $\times$ *BDNF* expression $\times$ clinical diagnosis [estimate = 0.013, SE = 0.004, p = 0.002]).

Figure e-1 illustrates that the cognitive slowing associated with higher *BDNF* expression was most striking for dementia (blue dotted line vs red dotted line). Consistent with this figure, stratified analyses showed that the effect of higher *BDNF* expression was strongest in individuals with dementia (estimate = 0.013, SE = 0.004, p = 0.003), weakly significant in MCI (estimate = 0.008, SE = 0.004, p = 0.045), and not significant in NCI (estimate = 0.0004, SE = 0.003, p = 0.907).

Global cognition comprises measures of 5 related but relatively dissociable cognitive systems. In further analyses, brain *BDNF* expression levels were associated with the rate of decline of all 5 cognitive abilities (table 2).

***BDNF* brain expression and brain pathology.** In a linear regression model adjusted for age, sex, and education, *BDNF* expression was associated with pathologic AD (estimate = -0.295 , SE = 0.10, p = 0.006) but not with macroscopic infarcts, LBD, or hippocampal sclerosis (table e-1). Next, we replaced binary pathologic AD with a continuous measure of global AD, which was also significantly inversely correlated with *BDNF* expression (estimate = -0.531 , SE = 0.131, p < 0.001) such that brains with more AD pathology had a lower expression level (table e-1).

In further analyses, we replaced AD pathology with amyloid load or tangles. We found that amyloid load and tangles measured in 8 different cortical regions were all inversely associated with *BDNF* expression levels measured in the DLPFC (table e-2).

***BDNF* expression, brain pathology, and cognitive decline.** We augmented the model described above in table 2 by including terms for 4 pathologic indices and their interaction with cognitive decline. *BDNF* expression remained associated with cognitive decline after adjusting for the presence of neuropathology. AD, LBD, and hippocampal sclerosis pathologies were also associated with a faster rate of cognitive decline, but not macroscopic infarcts (table 3). In this model, demographics accounted for 3.3% of the variance of cognitive decline, common neuropathologies accounted for 26.8%, and *BDNF* accounted for an additional 2.1%. Similar results were obtained when we included a term for amyloid load or tangles instead

Table 3 Association of brain *BDNF* gene expression level, brain pathology, and cognitive decline

	β (SE), p
Cognitive change/y	0.012 (0.012), 0.292
Macroscopic infarcts	-0.202 (0.091), 0.026
Lewy body pathology	-0.372 (0.109), <0.001
Hippocampal sclerosis	-0.586 (0.163), <0.001
AD pathology	-1.292 (0.112), <0.001
<i>BDNF</i> expression	0.157 (0.037), <0.001
Cognitive change/y $\times$ macroinfarcts	-0.017 (0.010), 0.091
Cognitive change/y $\times$ Lewy body pathology	-0.046 (0.012), <0.001
Cognitive change/y $\times$ hippocampal sclerosis	-0.043 (0.017), 0.011
Cognitive change/y $\times$ AD pathology	-0.120 (0.012), <0.001
Cognitive change/y $\times$ <i>BDNF</i> expression	0.015 (0.004), <0.001

Abbreviations: AD = Alzheimer disease; *BDNF* = brain-derived neurotrophic factor. Estimated from a mixed-effect model examining the association of brain *BDNF* expression with the level of cognition at the last visit before death and with the annual rate of change in cognition (cognitive change/y $\times$ *BDNF* expression). The model also includes terms for 4 neuropathologies and their interaction with the annual rate of change in cognition. The model also included 6 terms (not shown) controlling for age, sex, education, and their interaction with cognitive change/y: estimate (SE), p value.

Figure 2 Brain *BDNF* expression level modifies the association of AD pathology and the rate of cognitive decline

To display this association, 3 pairs of hypothetical average participants with their estimated rate of cognitive decline based on the complete model with a 3-way interaction term with all the cases analyzed in this study are illustrated. Model derived trajectories of cognitive decline for participants with low (red, 10th percentile) and high (blue, 90th percentile) brain *BDNF* gene expression levels with 3 levels of AD pathology: low (10%, solid), median (50%, dashed), and high (90%, dotted). At all levels of AD pathology, the rate of cognitive decline is slower in individuals with high levels of *BDNF* (blue) vs low *BDNF* expression levels (red). It is evident that the difference in slopes of cognitive decline between the high levels of *BDNF* expression (blue) and low levels of *BDNF* expression (red lines) is much greater for the dashed lines (high AD pathology) as compared to the solid lines (low AD pathology). AD = Alzheimer disease; *BDNF* = brain-derived neurotrophic factor; path = pathology.

of a summary measure for AD pathology (results not shown).

Next, we added a 3-way interaction term to the previous model (table 3) to determine whether *BDNF* expression modified the association of AD pathology with cognitive decline. Higher *BDNF* expression reduced the effect of AD pathology on the rate of cognitive decline (estimate = 0.023, SE = 0.009, $p = 0.015$).

Figure 2 illustrates that the cognitive slowing associated with higher *BDNF* expression was most striking for individuals with the highest levels of AD pathology (90th percentile). Thus, for 2 individuals with high AD pathology, cognitive decline was 40% slower in an individual with 90th percentile *BDNF* expression (blue dotted line) vs 10th percentile (red dotted line).

***BDNF* brain expression, Val66Met, brain pathology, and cognitive decline.** Polymorphism of the *BDNF* gene, Val66Met (rs6265), may influence cognition in old age.¹⁸ Therefore, we examined the relationship of Val66Met (rs6265) with *BDNF* expression levels. Of the subset of 503 cases that had genotype data,

332 (66.0%) had 0 copy of the T allele, 154 (30.6%) had 1 copy, and 17 (3.4%) had 2 copies.

Analysis of variance shows that the *BDNF* expression level did not differ by the genotype ($p = 0.804$). In a linear regression model adjusted for age, sex, and education, we did not find an association of Val66Met with brain *BDNF* expression (estimate = -0.062 , SE = 0.092, $p = 0.498$). Separately, in a linear mixed model adjusted for demographics, we did not find evidence of an association of the polymorphism with the rate of cognitive decline (estimate = 0.008, SE = 0.010, $p = 0.405$). Both results were unchanged when we adjusted for neuropathologies.

DISCUSSION In more than 500 older adults, a higher level of brain *BDNF* expression was associated with a slower rate of cognitive decline across a wide range of cognitive abilities during an average of 6 years before death. This association was strongest in individuals diagnosed with dementia proximate to death compared to those with MCI or NCI. While brain *BDNF* expression was associated with AD pathology, its levels showed an independent association with cognitive decline in a model adjusting for common age-related brain pathologies. Further analyses showed that the relation of AD pathology with the rate of cognitive decline varied by *BDNF* expression. Thus, higher *BDNF* expression reduced the effect of AD pathology on the rate of cognitive decline. These data suggest that a higher level of brain *BDNF* expression is associated with slower cognitive decline and may provide reserve against the effects of AD pathology in older adults.

BDNF promotes neurogenesis and angiogenesis in the CNS. Its role in modulating interactions between neuronal activity and synaptic plasticity is essential for regulating cellular processes that underlie cognition and other complex behaviors. While these functions underscore *BDNF*'s potential utility for treating AD, recent work suggests that *BDNF* may have a role in the pathogenesis of AD.³ β -Amyloid peptide, which is increased in AD, may interact with *BDNF* and suppress its expression. In addition, *BDNF* may downregulate the production of β -amyloid.^{19,20} Loss of *BDNF* in AD may contribute to synaptic failure leading to impaired cognition. Furthermore, some reports suggest that *BDNF* polymorphisms such as Val66Met might be associated with cognitive decline and an increased AD risk.²¹ However, much of the existing work on *BDNF* and AD derives from animal models. Given the complex and varied actions of *BDNF* in the CNS, examining the association of its brain RNA expression levels with the rate of cognitive decline during life in a wide spectrum of older adults both with and without clinical dementia is essential to understand the link of *BDNF* with late-life cognitive impairment.

The current study provides human data showing that a higher level of brain *BDNF* expression is associated with a slower rate of cognitive decline across a wide range of cognitive abilities in community-dwelling older adults. *BDNF* expression levels modified the association of clinical diagnosis with the rate of cognitive decline, being most striking for individuals with dementia. It is possible that the failure to find a robust effect of *BDNF* among participants without cognitive impairment is a result of a smaller rate of change in cognition that limits power. A larger study of individuals with NCI and MCI with longer follow-up may be needed to show the association.

The current study found that *BDNF* expression was independently associated with the rate of cognitive decline. Some prior studies in humans with AD have reported that brain *BDNF* levels are reduced and others have reported increased levels.³ Because of its unique design, the current study was able to compare *BDNF* expression in individuals with and without clinical AD, as well as to examine the relationship of *BDNF* expression with postmortem indices of both AD and other common age-related pathologies. *BDNF* expression was inversely related to AD pathology, but it was not associated with other common age-related pathologies. Thus, individuals with clinical dementia and postmortem evidence of AD pathology had lower levels of *BDNF* expression.

While *BDNF* expression was independently associated with cognitive decline, the current study also found that *BDNF* expression modified and reduced the association with AD pathology and cognitive decline (figure 2). Thus, for each level of AD pathology, an individual with a higher level of *BDNF* expression (blue lines) had a slower rate of cognitive decline. Thus, despite lower *BDNF* expression in persons with more AD pathology, the protective effect of *BDNF* was most striking among individuals with the highest burden of AD pathology (figure 2). This finding is analogous and complementary with the finding that the effect modification of *BDNF* expression and cognitive decline was strongest in individuals with dementia (figure e-1). That reserve is most striking in cases with more pathology has been noted previously for other cognitive reserve indicators.²² This most likely reflects the fact that reserve is most necessary for individuals with more pathology and greater cognitive impairment. Thus, in addition to an association between *BDNF* expression and the rate of cognitive decline, *BDNF* expression may also provide reserve, which mitigates the deleterious effects of AD pathology on cognitive decline.²³

These results have potential translational consequences. Prior reports of cognitive reserve have been difficult to translate into the clinical setting because the mechanisms linking behaviors such as education

or purpose in life with cognitive decline are unclear.^{22,24} By contrast, this study identified a known neurotrophin whose biology has been extensively studied. Further work is needed to replicate these findings and determine the direction of causality and whether strategies that increase brain *BDNF* expression might one day be used to protect or slow the rate of cognitive decline in older adults.

The study has strengths that lend confidence in the findings. All participants were recruited from the community and underwent an annual detailed cognitive assessment. Uniform, structured clinical and postmortem procedures were followed. Autopsy rates were very high and all postmortem evaluations were performed by examiners blinded to all clinical data. The availability of several postmortem indices provided an opportunity to examine the specificity of the association of *BDNF* expression with AD pathology.

This study has important limitations. First, participants were selected by their willingness to participate in these studies and do not represent the general population. *BDNF* expression was obtained from only one brain region and expression likely varies in different brain regions. Nonetheless, the associations of *BDNF* levels in the current study did not vary with AD pathology measured in 8 cortical regions. Observation over a longer period of time and in a larger number of older individuals would likely improve the estimation of individual patterns of progressive cognitive decline and provide more details on the relationship of *BDNF* expression in older adults with NCI.

AUTHOR CONTRIBUTIONS

Drafting/revising manuscript for content: A.S.B., L.Y., P.A.B., J.A.S., P.L.D., D.A.B. Study concept or design: A.S.B., L.Y. Analyses or interpretation of the data: A.S.B., L.Y., P.A.B., J.A.S., P.L.D., D.A.B. Acquisition of data: A.S.B., P.A.B., P.L.D., D.A.B. Statistical analysis: A.S.B., L.Y. Study supervision or coordination: A.S.B., J.A.S., P.L.D., D.A.B. Obtaining funding: A.S.B., P.A.B., J.A.S., P.L.D., D.A.B.

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DISCLOSURE

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