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SHORT REPORT

Body composition and plasma total-tau, neurofilament light chain, and amyloid-β: A population-based study

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Abstract

A higher body mass at older age has been linked to a lower risk of dementia. This unexpected trend may be explained by age-related lean mass depletion, or methodological issues such as the long preclinical phase of dementia or competing risks. Focusing on preclinical markers of dementia may overcome these issues.

Between 2002 and 2005, body composition and plasma total-tau, neurofilament light chain (NfL), amyloid-β40, and amyloid-β42 were measured in 3408 dementia-free participants from the population-based Rotterdam Study. The cross-sectional associations between body composition and plasma markers were determined using linear regression models.

Whole body and fat mass, but not lean mass, were positively associated with total-tau, while all these measures were inversely associated with NfL. Apart from an inverse association between lean mass and amyloid-β40, body composition measures were not associated with plasma amyloid-β.

Our findings suggest distinct effects of body composition on neurodegeneration.

KEYWORDS
adiposity, amyloid, dementia, lean mass, neurofilament light chain, tau

1 | INTRODUCTION

Obesity during midlife is a key determinant of dementia,[1,2] which could be explained by the effects of adipose tissue on cardiometabolic health.[3] Although adiposity presumably confers such effects throughout the life course, a higher body mass at older age has been linked to a lower risk of dementia.[4] Given that the aging process is often accompanied by weight loss due to lean mass depletion,[5] failing to differentiate between fat and lean mass has been thought to explain at least part of this seemingly protective effect.[6,7] Other explanations include methodological issues of studies showing these associations, such as weight loss caused by preclinical dementia or mortality precluding a dementia diagnosis.[8] Focusing on preclinical markers of dementia may overcome these issues.

Currently, the most accessible preclinical blood biomarkers of dementia are total-tau, neurofilament light chain (NfL), and amyloid-β (Aβ).[9] Tau and NfL are building blocks of neurons and are thought to reflect neuronal breakdown when detected in plasma.[10] Amyloid plaques consist predominately of aggregated Aβ42 and to a lesser extent of Aβ40. In the early preclinical phase of dementia, Aβ production is thought to be increased, leading to elevated plasma concentrations. During later stages, Aβ42 plasma may decrease due to deposition.[11]

To further elucidate the complex link between body composition and dementia, we determined the association of body, fat, and lean mass with plasma total-tau, NfL, Aβ40, and Aβ42 among older adults.

2 | METHODS

2.1 | Study setting and population

This study was conducted within the Rotterdam Study, a prospective population-based cohort in the Netherlands.[12] The original study was established in 1990 with 7983 participants aged 55 years and older and expanded in the year 2000 with an additional cohort of 3011 participants who had turned 55 years of age or moved into the study area. Extensive follow-up examination rounds take place every 4 to 5 years through home interviews and various physical and laboratory checks at the dedicated research center.

Between 2002 and 2005, corresponding to the fourth examination round of the original cohort and the second examination round of the second cohort, plasma samples were collected from 5069 participants (84.6% of the surviving participants) and stored at −80°C. In 2018, the plasma samples were utilized to assess total-tau, NfL, Aβ40, and Aβ42 concentrations. From these participants, 1540 were excluded because they had missing data on body composition, primarily due to technical issues and time constraints. We further excluded 109 participants with invalid data on all plasma biomarkers, and 12 participants with prevalent dementia, leaving a total of 3408 participants for analysis.

RESEARCH IN CONTEXT

1. **Systematic review**: We have searched the literature using PubMed and Web of Science databases. Overall, a lower body mass index during midlife is considered protective for dementia, while the opposite trend is generally seen in older populations. This unexpected trend may be attributed to age-related lean mass reduction, reverse causality, and competing risk. Such challenges may be addressed by differentiating between fat and lean mass, and focusing on preclinical dementia biomarkers instead of dementia as ultimate outcome.
2. **Interpretation**: We found that a higher body and fat mass were associated with higher plasma total-tau, whereas the reverse pattern was seen for neurofilament light chain. Apart from a reverse link between lean mass and amyloid-β40, plasma amyloid-β was not associated with body composition measures. These findings may suggest distinct effects of body composition on neurodegeneration.
3. **Future directions**: Future research is warranted to validate these results using biomarkers measured in cerebral spinal fluid and to assess the temporality of these associations.

2.2 | Body composition

Total body mass in kilograms was measured using a digital scale and body height using a stadiometer, while participants were wearing indoor clothes without shoes. Dual X-ray Absorptiometry (DXA; Prodigy and iDXA devices, GE Healthcare, Chicago, United States) scans were performed to determine fat and lean mass (excluding bone mineral content). From these data, we calculated body mass index as total body mass in kilograms divided by height in meters squared, fat mass index as total fat mass in kilograms divided by height in meters squared, and lean mass index as lean mass in kilograms divided by height in meters squared.

2.3 | Assessment of plasma total-tau, NfL, Aβ40, and Aβ42

Plasma samples were collected in EDTA tubes, aliquoted and stored at −80°C according to standard procedures. Measurements were conducted in two separate batches at Quanterix (Lexington, MA, USA) on a Simoa HD-1 analyzer platform.[13] Total-tau, Aβ40, and Aβ42 were assessed using the Simoa Human Neurology 3-Plex A assay (N3PA) and NfL using the Simoa NF-light advantage kit.[14] Samples were analyzed in duplicate and two quality control samples were run on each plate for each analyte. Data were considered as not valid if duplicates were missing, if the concentration coefficient of variation between the two measurement exceeded 20%, or if a control sample was out of range. Detailed descriptions of the concentration coefficient of variation are provided in Table S 1.

2.4 | Covariables

Data on educational attainment, smoking status, and alcohol consumption were collected through home interviews. Apolipoprotein E (*APOE*) genotype was obtained using polymerase chain reaction of coded DNA samples[15] for the original cohort and with bi-allelic TaqMan assay for the second cohort.[16] Depressive symptoms were assessed using the validated Center for Epidemiology Depression Scale.[17] Physical activity in metabolic equivalent of task (MET) hours was assessed using a modified version of the Zutphen Study Physical Activity Questionnaire.[18] Estimated glomerular filtration rate was calculated with the Chronic Kidney Disease Epidemiology Collaboration formula using creatinine level, age, sex, and ethnicity.[19] Mild cognitive impairment (MCI) was defined as having self-reported subjective cognitive complaints in combination with having objective cognitive impairment as assessed using a cognitive test battery, comprising a letter-digit substitution task, Stroop test, word fluency test, and 15-word learning test.[20] From these cognitive tests, a global cognitive factor was

TABLE 1 Characteristics of the study population.

	Total study population ($n = 3408$)
Age, years	72.7 ± 6.9
Sex, women	1960 (58)
Educational attainment	
Primary	391 (12)
Lower	1487 (44)
Intermediate	1040 (31)
Higher	433 (13)
Smoking status	
Never	982 (29)
Former	1857 (56)
Current	501 (15)
APOE genotype	
Non-carriers	2344 (73)
ε4 heterozygosity	826 (26)
ε4 homozygosity	55 (2)
Alcohol intake, grams/day	7.1 [19.3]
CES-D, score	3 [7]
Physical activity, MET-hours/week	81 [55]
Estimated glomerular filtration rate, mL/min/1.73 m^2	75.4 (13.5)
Mild cognitive impairment	314 (10)
Global cognitive factor	0 (1)
Body composition measures	
Height, cm	166.8 ± 9.2
Body mass, kg	76.5 ± 13.3
Body mass index, kg/m^2	27.5 ± 4.0
Fat mass, kg	26.4 ± 8.7
Fat mass index, kg/m^2	9.6 ± 3.4
Lean mass, kg	47.1 ± 9.3
Lean mass index, kg/m^2	16.8 ± 2.1
Plasma biomarkers	
Total-tau, pg/mL	2.4 [1.1]
Neurofilament light chain, pg/mL	13.7 [8.4]
Amyloid-β40, pg/mL	261.3 [62.8]
Amyloid-β42, pg/mL	10.3 [4.2]

Note. Data are shown for non-imputed data and are presented as mean ± standard deviation for normally distributed continuous variables, median [interquartile range] for skewed continuous variables, and number (percentages) for categorical variables. Data were missing for the following percentages of covariables: 8.7% for estimated glomerular filtration rate, 5.4% for *APOE* ε4 genotype, 5.3% for depressive symptoms, 3.6% for physical activity, and less than 2% for all other covariables.

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; MET, metabolic equivalent of task; *n*, number of participants.

determined by taking the first unrotated component of a principal component analysis, explaining 55.7% of the variance in the cognitive test scores. Dementia diagnosis was established through a linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental healthcare. Additionally, comprehensive screenings were conducted during research center visits.[21] For more detailed descriptions of MCI and dementia ascertainment, see the Supplementary Methods section in the Supporting Information. Serum concentrations of glucose, total cholesterol, and high-density lipoprotein (HDL) cholesterol were measured in mmol/L using fasting blood samples. Systolic and diastolic blood pressure, measured in mmHg, were assessed by taking the average of two readings on the right arm while the participant was in a sitting position, utilizing a random zero sphygmomanometer. Information on the use of blood glucose-, lipid-, and blood pressure-lowering medication was obtained through home interviews.

2.5 | Statistical analysis

Total-tau, NfL, Aβ40, and Aβ42 plasma concentrations had a right-skewed distribution and were therefore $\log_2$ transformed to obtain an approximately normal distribution and standardized to facilitate comparison across the different markers. Using multivariable linear regression models, we examined the cross-sectional association of each of the body composition measures per standard deviation increase with $\log_2$ concentrations of total-tau, NfL, Aβ40, and Aβ42. All models were adjusted for assay batch number, height in meters squared, age, and sex (Model I), and further for educational attainment, smoking status, *APOE* ε4 genotype, alcohol intake, depressive symptoms, physical activity, and the estimated glomerular filtration rate (Model II). In models considering Aβ40 as outcome, we further adjusted for Aβ42 and vice versa in an additional model (Model III). Missing values on covariables (8.7% for estimated glomerular filtration rate, 5.4% for *APOE* ε4 genotype, 5.3% for depressive symptoms, 3.6% for physical activity, and less than 2% for all other covariables) were handled using fivefold multiple imputation. Analyses were conducted using the five different datasets, and pooled estimates are provided. To check whether associations deviate from linearity, we repeated the analyses after including splines to the body composition measures and tested whether this improved the fit of the model using analysis of variance (ANOVA). We confirmed that somewhat extreme body composition measures did not drive the associations by plotting body composition measures against corresponding residuals for visual inspection. We stratified the analyses for sex, age, and *APOE* ε4 status, to investigate potential effect modification. In sensitivity analyses, to minimize the risk of residual confounding, we repeated all analyses after excluding participants with MCI and while correcting for the global cognitive factor. To gain insights into the extent to which cardiometabolic health may contribute to this association, we also repeated all analyses while additionally adjusting for cardiometabolic markers, including serum concentrations of glucose, total cholesterol, and HDL cholesterol, systolic and diastolic blood pressure, and the

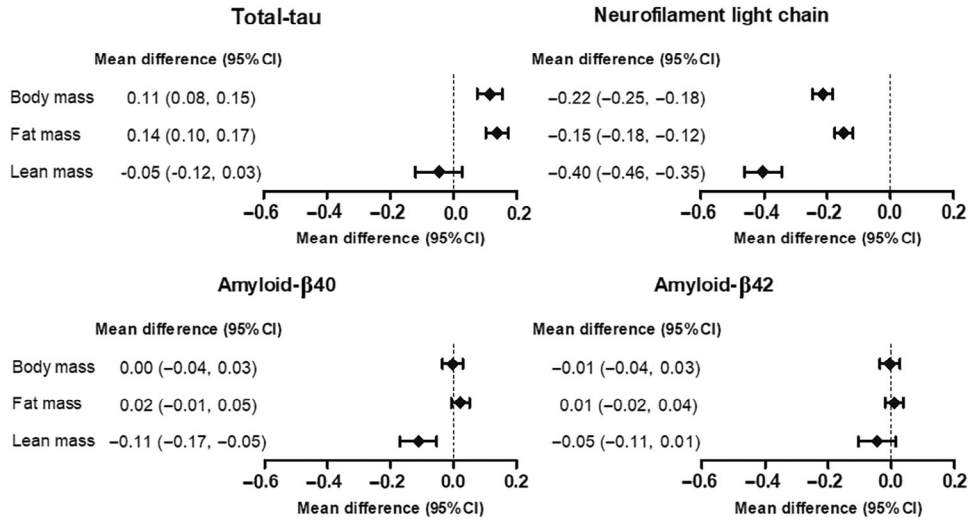

FIGURE 1 Body composition and plasma total-tau, neurofilament light chain, and amyloid-β (Aβ). Mean difference represents the association between body composition measures per standard deviation increase and standardized $\log_2$ plasma levels. All models are adjusted for assay batch number, height in meters squared, age, sex, educational attainment, smoking status, *APOE* ε4 status, alcohol intake, depressive symptoms, physical activity, and estimated glomerular filtration rate. Models with Aβ40 as outcome are additionally adjusted for Aβ42 and vice versa. *APOE*, apolipoprotein E; CI, confidence interval.

use of blood glucose-, lipid-, and blood pressure-lowering medications. Moreover, in our main analyses, we refrained from utilizing ratios to mitigate the risk of generating spurious correlations.[22] However, to facilitate comparability with other studies, we repeated all analyses by first using relative body composition measures as exposure (ie, body mass index, fat mass index, and lean mass index) instead of the crude measures; and second, by using the ratio between Aβ42/40 as the outcome variable. All analyses were performed using R statistical software 4.0.4.

3 | RESULTS

The characteristics of the study population are provided in Table 1. Participants were on average 72.7 years old (standard deviation: 6.9) and 58% were women. The characteristics of the study population were similar to those of the excluded participants, regardless of whether the exclusion was due to missing body composition data or other factors (Table S 2). Body mass was positively correlated with fat ($r = 0.68$) and lean mass ($r = 0.72$), while no correlation was observed between fat and lean mass ($r = -0.01$). The body composition measures followed a somewhat normal distribution as depicted in Figure S1.

A higher body and fat mass, but not lean mass, were associated with higher standardized $\log_2$ total-tau levels (mean difference [95% confidence interval (CI)] per standard deviation increase: 0.11 [0.08, 0.15], 0.14 [0.10, 0.17], and −0.05 [−0.12, 0.03], respectively; Figure 1). Including splines with two knots to $\log_2$ levels of total-tau revealed that the associations with body and fat mass were nonlinear (p-value < 0.00 and 0.02, respectively; Figure 2). Moreover, all body composition measures were inversely associated with standardized $\log_2$ levels of NfL (mean difference [95% CI]:−0.22 [−0.25, −0.18] for body mass, −0.15 [−0.18, −0.12] for fat mass, and −0.40 [−0.46, −0.35] for lean mass; Figure 1). A higher lean mass was associated with lower standardized $\log_2$ Aβ40 levels (mean difference [95% CI]: −0.11 [−0.17, −0.05]). All other body composition measures were not associated with levels of either Aβ40 or Aβ42. Associations were robust across all formulated statistical models, wherein adjustments were made for various covariables (Figure S2).

Stratified analyses uncovered effect modification by sex in the relationship between lean mass and total-tau (Figure S3), primarily driven by a nonlinear association with distinct inflection points occurring at circa 40 kg for women and 60 kg for men (Figure S4). No additional effect modification was observed for sex, *APOE* ε4 carriership, or age. Body composition measures as well as total-tau and Aβ42 plasma concentrations were similar for participants with and without MCI, while NfL and Aβ40 concentrations were somewhat higher in participants with MCI (Table S 3). Excluding the 314 participants with MCI did not affect the results, nor did correcting for the global cognitive factor (Figure S5). Results were also similar after correcting for cardiometabolic markers. Furthermore, repeating all analyses using relative body composition measures (ie, body mass index, fat mass index, and lean mass index) resulted in similar effect estimates as for absolute body composition measures (Figures S6 and S7). Body composition measures were not associated with the Aβ42/40 ratio (Figure S8).

4 | DISCUSSION

In this population-based study, higher body and fat mass, but not lean mass, were associated with higher plasma levels of total-tau, which were driven by excessive adipose tissue as suggested by the

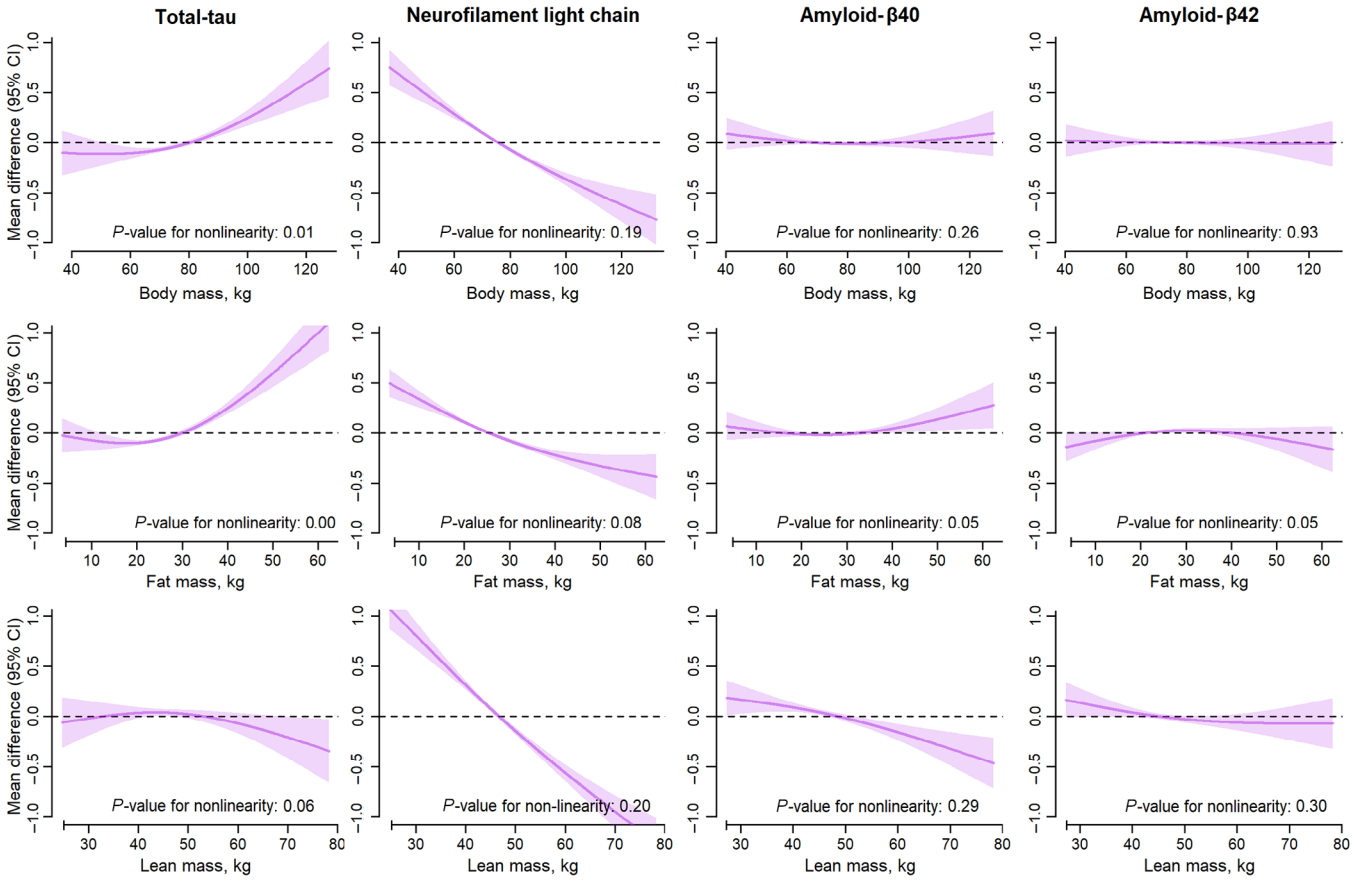

FIGURE 2 Non-linear associations of body composition with plasma total-tau, neurofilament light chain, and amyloid-β (Aβ). Mean differences represent the association between body composition measures and standardized $\log_2$ plasma levels. Splines with two knots are added to the body composition measures. All models are adjusted for assay batch number, height in meters squared, age, sex, educational attainment, smoking status, *APOE* ε4 status, alcohol intake, depressive symptoms, physical activity, and estimated glomerular filtration rate. Models with Aβ40 as outcome are additionally adjusted for Aβ42 and vice versa. *APOE*, apolipoprotein E; CI, confidence interval.

nonlinearity of the association. In contrast, higher body, fat, and lean mass were associated with lower NfL levels. Apart from an inverse association between lean mass and Aβ40, body composition measures were not associated with plasma levels of Aβ40 or Aβ42.

Given that plasma total-tau and NfL both reflect neurodegeneration,[10] our findings of higher total-tau and lower NfL levels in those with a higher body mass are contradictory, but corroborate previous studies.[23–28] More specifically, previous cross-sectional studies consistently demonstrated an association between a higher body mass index and lower NfL concentrations, irrespective of the participants' health stage and age.[23–27] However, longitudinal research revealed a gradual weakening of this association over time among obese individuals.[28] Moreover, a prior cross-sectional study found a positive link between body mass index and total-tau concentrations,[23] whereas a longitudinal study showed an increase in total-tau levels among obese individuals during a 10-year follow-up period.[28] We extend these findings by differentiating between fat and lean mass, and showed that the positive link of a higher body mass with lower total-tau is driven by excessive adipose tissue, while the inverse association with NfL is driven by both fat and lean mass.

Cardiometabolic dysregulations may underlie the association between fat mass and total-tau levels.[3] More specifically, adiposity is a well-established risk factor of insulin resistance, dyslipidemia, hypertension, and inflammation,[29] which are in turn hallmarks of dementia.[30] Conversely, tau pathology may trigger insulin resistance,[31] suggesting that the association could be bidirectional. Nevertheless, we found that associations were independent of cardiometabolic health markers, which could imply the involvement of alternative pathways, such as inflammatory responses.[32]

The observed contrasting directions of effect estimates for total-tau and NfL may be explained by the affected brain regions. Although the clinical implications of total-tau and NfL remain largely unclear,[33] tau is most abundant in the cerebral cortex, while NfL is mainly present in the cerebral white matter.[34] White matter consists mainly of myelinated axons, a lipid-rich material, which could possibly be affected by adipose tissue depletion.[35]

Even though we studied preclinical markers of dementia, weight loss caused by neurodegeneration may also explain part of the inverse link between body composition measures and NfL. Increased plasma levels of NfL can, in contrast to total-tau, be detected up to 10 years before

diagnosis and correlate with disease severity.[11,36] Similarly, a decline in body mass index has been observed 6 to 8 years prior to a dementia diagnosis.[37–39]

With a higher body mass generally corresponding to more blood volume,[40] prior studies have suggested blood volume as an alternative explanation for the inverse link between body mass and NfL through dilution.[24] Our findings that associations with NfL were most pronounced for lean mass may support this hypothesis, because muscle tissue is more perfused than adipose tissue.[40] Dilution may also explain the finding that individuals with more lean mass had lower levels of Aβ40. Moreover, a better physiological status reflected by higher lean mass may contribute to this phenomenon.[5] Lean mass was not associated with total-tau and Aβ42, suggesting negligible dilution effects on these plasma levels, potentially attributed to their substantially lower concentrations compared to NfL and Aβ40.[5]

The absence of an association between body composition measures other than lean mass and Aβ should be interpreted with caution, as amyloid can also be produced by tissues of non-neurological origin, like platelets and vascular wall endothelium.[41] In addition, plasma concentrations of Aβ are highly dynamic across the different preclinical dementia stages, which presents a substantial challenge in detecting associations.[11]

Strengths of this study include the population-based design, use of DXA scans to differentiate between fat and lean mass, and the highly sensitive assay used to determine plasma biomarkers. Limitations are the cross-sectional design, hampering causal inference due to the potential for reverse causality and common causes, and the lack of data on biomarkers measured in cerebrospinal fluid, which provide a more accurate reflection of brain pathology.[10]

Taken together, these findings may suggest distinct effects of body composition on neurodegeneration, but factors of non-neurological origin may also explain part of the observed associations. This study could serve as a basis for the design of future studies to further elucidate the complex link between body composition at old age and brain health. More specifically, we encourage future research to validate these results using biomarkers measured in cerebral spinal fluid and to assess the temporality of these associations.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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