ABSTRACT

Objective: To test whether plasma tau is altered in Alzheimer disease (AD) and whether it is related to changes in cognition, CSF biomarkers of AD pathology (including β-amyloid [Aβ] and tau), brain atrophy, and brain metabolism.

Methods: This was a study of plasma tau in prospectively followed patients with AD (n = 179), patients with mild cognitive impairment (n = 195), and cognitive healthy controls (n = 189) from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) and cross-sectionally studied patients with AD (n = 61), mild cognitive impairment (n = 212), and subjective cognitive decline (n = 174) and controls (n = 274) from the Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably (BioFINDER) study at Lund University, Sweden. A total of 1,284 participants were studied. Associations were tested between plasma tau and diagnosis, CSF biomarkers, MRI measures, 18F-fluorodeoxyglucose-PET, and cognition.

Results: Higher plasma tau was associated with AD dementia, higher CSF tau, and lower CSF Aβ42, but the correlations were weak and differed between ADNI and BioFINDER. Longitudinal analysis in ADNI showed significant associations between plasma tau and worse cognition, more atrophy, and more hypometabolism during follow-up.

Conclusions: Plasma tau partly reflects AD pathology, but the overlap between normal aging and AD is large, especially in patients without dementia. Despite group-level differences, these results do not support plasma tau as an AD biomarker in individual people. Future studies may test longitudinal plasma tau measurements in AD. Neurology® 2016;87:1827-1835

GLOSSARY

Aβ = β-amyloid; AD = Alzheimer disease; ADAS = Alzheimer’s Disease Assessment Scale—Cognitive subscale; ADNI = Alzheimer’s Disease Neuroimaging Initiative; BioFINDER = Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably; CI = confidence interval; CN = cognitively healthy control; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised; EPIC = European Prospective Investigation Into Cancer and Nutrition; FDG = 18F-fluorodeoxyglucose; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; P-tau = phosphorylated tau; T-tau = total tau.

Brain accumulation of β-amyloid (Aβ) and phosphorylated tau (P-tau) in Alzheimer disease (AD) may be monitored by CSF and PET biomarkers. These technologies have revolutionized clinical research and trials and are rapidly transforming clinical practice. However, they are hampered by their relative invasiveness and high costs. There is a great unmet need...
for less invasive and cheaper biomarkers of AD pathology. Plasma tau is a candidate because tau is a brain-specific protein that may be expected to leak from brain interstitial fluid to the plasma compartment in AD. Most studies of plasma tau in AD have been small, including up to 150 participants, with one study including 273 participants. The results have been contradictory, showing clearly elevated levels in AD (several studies from one group), mild elevations in AD, no difference between patients with AD and controls, or reduced levels in AD.

To clarify the role of plasma tau in AD, we used an ultrasensitive digital ELISA method in 2 large cohorts with 563 participants from a prospective North American study and 721 participants from a cross-sectional Swedish study. We tested the hypotheses that plasma tau is elevated in AD dementia, correlates with reduced CSF Aβ42 and increased CSF total tau (T-tau) and P-tau (biomarkers of AD pathology), and correlates with cognitive impairment, brain atrophy, and reduced brain metabolism.

**METHODS ADNI study design.** As noted on the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database, “Data were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. For up-to-date information, see www.adni-info.org” (http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_DSP_Policy.pdf). ADNI participants have been recruited from 50 sites across the United States and Canada. For the current study, we used data accessed at the ADNI database on November 11, 2015.

**ADNI participants.** Our ADNI cohort consisted of all cognitively healthy controls (CNs), patients with mild cognitive impairment (MCI), and patients with AD dementia with available baseline plasma tau samples from ADNI-1. Inclusion and exclusion criteria were described in detail previously. Briefly, all ADNI-1 participants were between the ages of 55 and 90 years, had completed at least 6 years of education, were fluent in Spanish or English, and had no significant neurologic disease other than AD. CNs had a Mini-Mental State Examination (MMSE) score ≥24 and Clinical Dementia Rating score of 0. Patients with MCI had an MMSE score ≥24, objective memory loss tested by delayed recall of the Wechsler Memory Scale Logical Memory II (>1 SD below the normal mean), a Clinical Dementia Rating score of 0.5, preserved activities of daily living, and absence of dementia. Patients with AD dementia fulfilled the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria for probable AD and had an MMSE score of 20 to 26 and Clinical Dementia Rating score of 0.5–1.0.

**ADNI measurements.** Several of the ADNI procedures have been described previously. CSF Aβ42, T-tau, and P-tau were measured with the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with the INNOBIA AlzBio3 kit (Fujirebio, Ghent, Belgium). Participants were classified as Aβ-positive or -negative with the use of a previously established cutoff (CSF Aβ42 <192 pg/mL). Using this cutoff, we excluded 9 patients with AD dementia who were Aβ-negative and therefore likely misdiagnosed. Cognition was assessed by MMSE and Alzheimer’s Disease Assessment Scale–Cognitive subscale (ADAS-cog; at screening and 6, 12, 18, 24, 36, and 48 months; n: CNs, 189, 181, 175, 0, 168, 157, and 102; MCI, 195, 188, 182, 167, 154, 130, and 68; AD, 179, 167, 151, 4, 131, 12, and 3). Structural brain images were acquired with 3T MRI scanners (at screening and 6, 12, 18, 24, 36 and 48 months; n: CNs, 193, 176, 164, 0, 150, 125, and 86; MCI, 195, 180, 169, 151, 133, 96, and 54; AD, 177, 156, 136, 1, 101, 2, and 1) with T1-weighted MRI scans using a sagittal volumetric magnetization prepared rapid gradient echo sequence. FreeSurfer was used for quantification of volumes. Right and left hippocampi were averaged. Fluorodeoxyglucose (FDG)-PET image data were acquired (at screening and 6, 12, 18, 24, 36 and 48 months; n: CNs, 186, 80, 73, 0, 71, 61, and 51; MCI, 96, 90, 88, 80, 72, 57, and 29; AD, 91, 83, 71, 1, 55, 1, and 1) as described previously. For FDG-PET, we averaged counts of the lateral and medial frontal, anterior, and posterior cingulate, lateral parietal, and lateral temporal regions. The data were obtained from 2005 to 2014.

**BioFINDER study design, participants, and measurements.** From the Swedish 4-center Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably (BioFINDER) study, we included CNs, patients without dementia with mild cognitive symptoms characterized as having subjective cognitive decline or MCI, and patients with AD dementia. Inclusion/exclusion criteria have been described elsewhere. CNs were originally enrolled from the population-based European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort. The inclusion criteria were age ≥60 years, MMSE score of ≥28 to ≤30, and fluent in Swedish. Quality criteria were the presence of subjective cognitive impairment, significant neurologic or psychiatric disease, dementia, or MCI. Patients with subjective cognitive decline and MCI were recruited consecutively and were assessed by physicians with special competence in dementia disorders. The inclusion criteria were as follows: referred to the memory clinics because of cognitive impairment, not fulfilling the criteria for dementia, MMSE score of ≥24 to ≤30, age of 60 to 80 years, and fluent in Swedish. The exclusion criteria were cognitive impairment that without doubt could be explained by another condition (other than prodromal dementia), severe somatic disease, and refusing lumbar puncture or neuropsychological investigation. The classification was based on a neuropsychological battery and the assessment of a senior neuropsychologist. Patients with a clinical syndrome of AD dementia met the DSM-III-R criteria for dementia and the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria for AD. All participants with plasma tau data were included. CSF sampling was done at baseline, following the Alzheimer’s Association Flow Chart. CSF samples were analyzed by ELISAs.
### Table 1: Demographics

| ADNI cohort | BioFINDER cohort | p Value |
|-------------|-----------------|---------|
| CN          | ADNI cohort     | BioFINDER cohort |
| Age, y      | 75.9 (4.9)      | 74.7 (7.5)  | 0.63    |
| MF (% female) | 75.2 (7.4)   | 70.1 (5.8)  | 0.0099  |
| Education, y | 129.8 (48)     | 125.6 (39)  | 0.0017  |
| Plasma tau, ng/L | 2.58 (1.19) | 2.71 (1.32)  | 0.0016  |
| CSF Aβ42, ng/L | 72.9 (4.9)    | 70.1 (5.8)  | 0.0009  |
| MRI ventricle volume, mL | 139.0 (50)   | 94.0 (101)  | 0.0017  |
| MRI hippocampal volume, mL | 134.0 (26) | 134.0 (26)  | 0.0016  |
| FDG-PET      | 1.31 (0.12)     | 1.20 (0.14) | 0.0016  |

#### Plasmatic tau measurements
Plasma tau was measured using the Human Total Tau kit (research use only grade, Quanterix, Lexington, MA) on the Simoa HD-1 analyzer (CE marker). This is an updated version of the assay described previously with a monoclonal capture antibody that reacts with a linear epitope in the midregion of all tau isoforms and a detection antibody that reacts with a linear epitope in the N-terminal region of T-tau. The same method (2 different lots) was used for BioFINDER and ADNI. ADNI samples were analyzed at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, and BioFINDER samples were analyzed at Quanterix.

Plasma tau was higher in BioFINDER (mean 5.53 ng/L, SD 2.99 ng/L, median 5.11 ng/L, interquartile range 3.78–6.57 ng/L) than in ADNI samples (mean 2.80 ng/L, SD 1.35 ng/L, median 2.65 ng/L, interquartile range 1.88–3.44 ng/L). Three ADNI participants (1 CN and 2 MCI; plasma tau >10 ng/L) and one BioFINDER participant (CN; plasma tau 48.7 ng/L) were extreme outliers and were excluded from all analyses. BioFINDER samples had undergone slightly different sample handling than ADNI samples with one less freeze-thaw cycle.

#### Statistical analysis
First, we tested associations between plasma tau and demographic factors using Mann-Whitney U and Spearman correlation. Second, we tested associations between plasma tau and diagnosis using linear regression adjusted for confounders (with plasma tau as outcome). Third, we tested associations between plasma tau and CSF biomarkers using linear regression adjusted for confounders (with plasma tau as predictor). Fourth, we tested associations between plasma tau and cognition, brain structure, and brain metabolism with longitudinal data using linear mixed-effects models. These models had random intercepts and slopes for time and an unstructured covariance matrix for the random effects and included the interaction between (continuous) time and plasma tau as predictor with adjustment for confounders. To test whether variables related to study dropout (missing data for cognition, MRI and FDG-PET), we used a generalized mixed-effects model with a binomial response, with plasma tau as predictor of missing data (a missing indicator, true/false, for each study visit). We evaluated interactions between predictors and diagnosis. If they were significant, we performed subgroup analyses within diagnostic groups.

All continuous outcome variables were standardized to facilitate comparisons between modalities. Beta coefficients (which are presented with 95% confidence intervals [CIs]) from linear regressions and linear mixed effects therefore refer to standardized effects ($\beta=1$ implies a 1-ng/L increase in plasma tau was associated with a 1-SD increase in the dependent variable).

We checked model assumptions by inspecting residuals (normality, histograms, q-q plots, linearity, heteroscedasticity, leverage, influence, correlations with fitted values, and predictors of interest). For linear mixed-effects models, we evaluated marginal residuals and conditional residuals. All tests were 2 sided. Significance was determined at $p < 0.05$. All statistics were done with R (version 3.2.3, The R Foundation for Statistical Computing).

**Standard protocol approvals, registrations, and patient consents.** Regional ethics committees of all institutions approved the ADNI study. The Regional Ethics Committee in...
RESULTS Table 1 provides demographics. High plasma tau was associated with missing data for MMSE ($p = 0.0017$), ADAS-cog ($p = 0.00047$), and MRI ($p = 0.036$). This was driven by the patients with AD dementia, who had high plasma tau levels and shorter follow-up than the other groups (see above). The effects of plasma tau on longitudinal cognition and volume may therefore be slightly underestimated, although mixed-effect models are robust to missing data associated with covariates.$^{22}$

Plasma tau and demographic factors. Plasma tau did not correlate with age (ADNI: $p = 0.042$, $p = 0.32$; BioFINDER: $p = -0.012$, $p = 0.74$), sex (ADNI: median 2.67 ng/L for men vs 2.64 ng/L for women, $p = 0.51$; BioFINDER: 4.95 ng/L for men vs 5.24 ng/L for women, $p = 0.16$) or education (ADNI: $p = -0.067$, $p = 0.11$; BioFINDER: $p = -0.044$, $p = 0.24$). Plasma tau was slightly increased in $APOE$ $e4$ carriers compared with noncarriers in ADNI (2.75 vs 2.55 ng/L, $p = 0.022$) but not in BioFINDER (5.10 vs 5.11 ng/L, $p = 0.70$).

Plasma tau in different diagnostic groups. In ADNI, plasma tau was higher in patients with AD dementia (figure 1A) compared with CNs and patients with MCI. In contrast, plasma tau did not differ between patients with MCI and CNs ($\beta = -0.11$, 95% CI $-0.38$ to $0.17$, $p = 0.44$) or between patients with progressive MCI (diagnosed with AD dementia during the 9-year follow-up, $n = 105$) and CNs ($\beta = -0.12$, 95% CI $-0.42$ to $0.17$, $p = 0.41$; results from a model restricted to progressive participants with MCI and CNs). All comparisons were done with linear regressions adjusted for $APOE$ $e4$, age, and sex.

Plasma tau and biomarkers of $A\beta$ pathology. High plasma tau correlated weakly with low CSF $A\beta_{42}$ in ADNI (figure 1B, table 2). There was no interaction between plasma tau and diagnosis of CSF $A\beta_{42}$; thus, we did not test effects within diagnostic groups. However, in the whole study cohort, we compared model testing the effect of the combination of diagnostic group and $A\beta$ status to predict plasma tau, adjusted for $APOE$ $e4$, age, and sex. Patients with AD had higher plasma tau levels than $A\beta$-negative CNs ($\beta = 0.62$, 95% CI 1.07–0.17), $A\beta$-positive CNs ($\beta = 0.67$, 95% CI 1.16–0.18), $A\beta$-negative patients with MCI ($\beta = 0.90$, 95% CI 1.37–0.42), and $A\beta$-positive patients with MCI ($\beta = 0.43$, 95% CI 0.78–0.081), and $A\beta$-positive patients with MCI had higher plasma tau levels than $A\beta$-negative patients with MCI ($\beta = 0.47$, 95% CI 0.90–0.031).
Plasma tau and cognition, atrophy, and brain metabolism. Associations between plasma tau and MMSE score, ADAS-cog, ventricular volume, hippocampal volume, and FDG-PET in ADNI are presented in table 2 and figure 2. High plasma tau was associated with accelerated decline of MMSE score, high (poor) baseline ADAS-cog and accelerated increase, large baseline ventricular volume and accelerated increase, accelerated decrease of hippocampal volume, and accelerated decline of FDG-PET. Interactions for plasma tau by diagnostic group were significant for MMSE, ADAS-cog, and ventricular volume. We therefore tested models within diagnostic groups for these outcomes. High plasma tau was associated with low baseline MMSE score in AD (β = −0.062, 95% CI −0.11 to 0.019, p = 0.0055) and accelerated decline of MMSE score in MCI (β = −0.063, 95% CI −0.11 to 0.018, p = 0.0068), high baseline ADAS-cog (β = 0.82, 95% CI 0.24–1.40, p = 0.0059) and accelerated increase of ADAS-cog in AD (β = 0.81, 95% CI 0.28–1.35, p = 0.0031), and accelerated increase of ventricular volume in AD (β = 0.026, 95% CI 0.013–0.040, p < 0.001). All linear mixed-effects models were adjusted for diagnosis, education, age, sex, and APOE ε4.

Plasma tau in the BioFINDER cohort. In BioFINDER, plasma tau did not vary by diagnosis (p = 0.16–0.83 for comparisons between different groups) or CSF Aβ42 (p = 0.89) but correlated with CSF T-tau and P-tau (β = 0.039, 95% CI 0.013–0.065, p = 0.0033; and β = 0.032, 95% CI 0.0054–0.059, p = 0.019; figure 3). To determine whether the associations between plasma tau and CSF biomarkers differed by diagnostic group, we tested the interaction between plasma tau and diagnosis, which was present for AD and CSF T-tau (p = 0.0051), and there was a tendency for an association between AD and CSF P-tau (p = 0.051). This indicated that the relationship between plasma tau and CSF tau biomarkers differed between CNs and AD, and we found associations only in AD dementia (CSF T-tau, β = 0.13, 95% CI 0.039–0.22, p = 0.0057; CSF P-tau, β = 0.093, 95% CI 0.00058–0.19, p = 0.049). Plasma tau was not associated with MMSE score (p = 0.77). Models were adjusted for age, sex, APOE ε4, diagnosis, and (for MMSE) education.

DISCUSSION We evaluated an ultrasensitive method for tau in plasma and found several associations supporting that plasma tau partly reflects brain pathology. High plasma tau was found in patients with AD dementia compared to CNs and patients with MCI (in ADNI), was associated with low CSF Aβ42 (in ADNI), was associated with high CSF tau biomarkers (in BioFINDER), was found in APOE ε4 carriers (in ADNI), and was associated with poor cognition at baseline and accelerated worsening of cognition (in ADNI), large ventricular volumes at baseline and accelerated atrophy (in ADNI), and accelerated decrease in cortical glucose metabolism.

| Table 2: Associations between plasma tau and Alzheimer disease hallmarks in the Alzheimer’s Disease Neuroimaging Initiative |
|---------------------------------|-----------------|------------|
| Outcome                        | β Coefficient (95% CI) | p Value |
| CSF Aβ42                       | −0.087 (−0.15 to −0.024) | 0.0071   |
| CSF T-tau                      | 0.063 (0.0092 to 0.14)  | 0.087    |
| CSF P-tau                      | 0.047 (−0.025 to 0.12)  | 0.20     |
| MMSE L                         | −0.017 (−0.041 to 0.0063) | 0.15       |
| MMSE L                         | −0.063 (−0.090 to −0.037) | <0.001   |
| ADAS-cog BL                    | 0.064 (0.034 to 0.094)  | <0.001   |
| ADAS-cog L                     | 0.060 (0.035 to 0.085)  | <0.001   |
| Ventricular volume BL          | 0.059 (0.0074 to 0.11)  | 0.027    |
| Ventricular volume L           | 0.018 (0.010 to 0.025)  | <0.001   |
| Hippocampal volume BL          | 0.0035 (−0.039 to 0.046) | 0.87     |
| Hippocampal volume L           | −0.0063 (−0.013 to −0.00047) | 0.049   |
| FDG-PET BL                     | −0.016 (−0.081 to 0.049) | 0.63     |
| FDG-PET L                      | −0.039 (−0.060 to −0.019) | <0.001   |

Abbreviations: Aβ42 = β-amyloid-42; ADAS-cog = Alzheimer’s Disease Assessment Scale-Cognitive subscale; BL = baseline; CI = confidence interval; FDG = 18fluorodeoxyglucose; L = longitudinal; P-tau = phosphorylated tau; T-tau = total tau.

Results are for linear regression (CSF Aβ42, CSF T-tau, and CSF P-tau) and linear mixed-effects models (MMSE, ADAS-cog, ventricular volume, hippocampal volume, FDG-PET). Plasma tau was the predictor, adjusted for age, sex, diagnostic group, APOE ε4, and education plus intracranial volume (for ventricular and hippocampal volume). All outcome measures are standardized to facilitate comparison between estimates.
No associations were seen in unexpected or illogical directions. The results suggest that plasma tau partly reflects AD pathology, but the mild associations and the varying results between the cohorts suggest that plasma tau alone is insufficient as an AD biomarker. This is different from CSF tau, which has high diagnostic accuracy for AD.23

Patients with AD had increased plasma tau in ADNI, but this was not replicated in BioFINDER. The small increase in patients with AD was similar to that in a previous study on another cohort,7 while other studies failed to detect differences between CNs, patients with MCI, and patients with AD9 or found reduced plasma tau in patients with AD compared with CNs, patients with MCI,5 or those with vascular dementia.5 One group used an immunomagnetic reduction assay for plasma tau with high separation between CNs and patients with AD (sensitivity and specificity >90%).3,6,8 Those findings await replication by independent groups.

Plasma tau was associated with CSF biomarkers of Aβ and tau. The associations were weak and differed between ADNI and BioFINDER. In ADNI, high plasma tau was associated with low CSF Aβ42, and patients with AD had higher plasma tau than all other groups, including Aβ-positive patients with MCI, who had higher plasma tau than Aβ-negative patients with MCI. The association with Aβ was not seen in BioFINDER, in which high plasma tau was instead associated with slightly increased CSF T-tau and P-tau. In ADNI, there was a tendency for an association between plasma tau and CSF T-tau. Together,

Longitudinal data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI). Plasma tau was associated with significantly greater decline of Mini-Mental State Examination (MMSE) over time (A), lower Alzheimer’s Disease Assessment Scale–Cognitive subscale (ADAS-cog) at baseline and greater increase in ADAS-cog over time (B; y axis reversed to facilitate comparisons), slightly greater decline of hippocampal volume over time (C), greater ventricular volume at baseline and greater increase in ventricular volume over time (D; y axis reversed to facilitate comparisons), and greater decline in FDG-PET over time (E). The error bars are 95% confidence intervals of the mean effects. All measures were standardized to facilitate comparisons between modalities. All results are from linear mixed-effects models, adjusted for diagnosis, APOE ε4, education, age, sex, and (for hippocampus and ventricles) intracranial volume. Plasma tau was used as a continuous predictor, but for visualization purposes, the graphs show results for quartiles (Q1, plasma tau <1.88 ng/L; Q2, plasma tau <2.65 ng/L; Q3, plasma tau <3.44 ng/L; Q4, plasma tau >8.89 ng/L).
These findings suggest that plasma tau captures some information about AD pathology. Previous smaller studies failed to find associations between plasma tau and CSF tau or PET Ab biomarkers. High plasma tau was associated with cognitive impairment, brain atrophy, and brain hypometabolism in ADNI. The associations were significant at baseline (for ADAS-cog and ventricular volume) and over time (for MMSE, ADAS-cog, hippocampal volume, ventricular volume, and FDG-PET) and were seen mainly in AD and MCI. This suggests that elevated plasma tau is related to disease activity particularly in late clinical stages. Few studies have reported these analyses for plasma tau. One study using the immunomagnetic reduction assay found associations between high plasma tau and small volume of gray matter, hippocampus, and amygdala, but it is not clear if those associations were corrected for diagnostic group.

This study is the largest published on plasma tau, but it is not without limitations. ADNI and BioFINDER samples were handled with different protocols and analyzed at different laboratories with different kit lots, which may have contributed to the varying results. Some ADNI participants had plasma tau below the lower limit of quantification of the assay (14 CNs, 11 patients with MCI, 10 patients with AD). These measurements are uncertain but they were included because excluding them would have biased the data toward higher plasma tau (excluding them did not change the main results, data not shown). Another limitation is that we used only one plasma tau assay. It is possible that other assays capture tau fragments that are less sensitive to peripheral degradation and more likely to reflect AD pathology. A final limitation is that we did not covary for copathologies that may affect plasma tau levels.

We found associations between elevated plasma tau and AD hallmarks, but the associations were mild and differed between cohorts. Our longitudinal data suggest that high plasma tau is associated with rapid progression in later disease stages. The large study sample supports generalization of these results. Future studies should include longitudinal measurements to explore whether plasma tau is sensitive to intraindividual changes during the progression of AD and an assessment of plasma tau across neurodegenerative diseases. This would increase the usability of plasma tau as an AD biomarker, particularly in clinical trials for patient enrichment and stratification.

**AUTHOR CONTRIBUTIONS**

Drafting the manuscript: N.M. Revising the manuscript for content: all authors. Study concept or design: N.M., O.H., D.B., C.A.T.H., K.B., H.Z. Analysis or interpretation of data: N.M., O.H., K.B., H.Z. Contribution of vital reagents/tools/patents: D.H., A.J., C.A.T.H., D.B., L.S. Acquisition of data: U.A., S.P., D.H., A.J., E.S., J.Q.T., L.M.S., L.S. Statistical analysis: N.M. Study supervision or coordination: N.M., O.H., K.B., U.A. Obtaining funding: N.M., O.H., D.B., C.A.T.H., K.B., H.Z., M.W.W.

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DISCLOSURE

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