CSF proteins and resting-state functional connectivity in Parkinson disease

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ABSTRACT

Objective: The purpose of this study was to investigate the relationship between disruption of MRI-measured resting-state functional connectivity (rs-fcMRI) brain networks and CSF levels of potentially pathogenic proteins that reflect brain pathology in Parkinson disease (PD).

Methods: PD participants without dementia ($n = 43$) and age-matched controls ($n = 22$) had lumbar punctures to measure CSF protein levels, Pittsburgh compound B (PiB)-PET imaging, and rs-fcMRI while off medication. Imaging analyses focused on 5 major resting-state networks as well as the striatum.

Results: Participants with PD had significantly reduced sensorimotor functional connectivity, which correlated with reduced CSF levels of α -synuclein. The PD group also had significantly stronger default mode network functional connectivity that did not correlate with CSF β -amyloid ($A\beta$)₄₂ or PiB uptake. In contrast, default mode network functional connectivity in the control group did correlate with CSF $A\beta$ ₄₂ levels. Functional connectivity was similar between groups in the dorsal attention, control, and salience networks.

Conclusion: These results suggest that abnormal α -synuclein accumulation, but not $A\beta$, contributes to the disruption of motor-related functional connectivity in PD. Furthermore, correlating CSF protein measures with the strength of resting-state networks provides a direct link between abnormal α -synuclein metabolism and disrupted brain function in PD. *Neurology*® 2015;84:2413-2421

GLOSSARY

A β = β -amyloid; **AD** = Alzheimer disease; **ANCOVA** = analysis of covariance; **BP** = binding potentials; **CDR** = Clinical Dementia Rating; **DAN** = dorsal attention network; **DMN** = default mode network; **MCCBP** = mean cortical binding potentials; **MMSE** = Mini-Mental State Examination; **PD** = Parkinson disease; **PiB** = Pittsburgh compound B; **QA** = quality assurance; **ROI** = region of interest; **rs-fcMRI** = resting-state functional connectivity MRI; **RSN** = resting-state network; **SMN** = sensorimotor network; **TE** = echo time; **TR** = repetition time; **UPDRS-III** = Unified Parkinson's Disease Rating Scale, Part III.

Pathologic accumulation of α -synuclein contributes to nigrostriatal dopamine loss and the subsequent motor and nonmotor manifestations in Parkinson disease (PD). However, most PD studies focus on the nigrostriatal dopamine system despite evidence that pathologic α -synuclein and β -amyloid ($A\beta$) deposition extends to cortical areas.¹ Interrogation of cortical and subcortical brain networks through MRI measures of resting-state functional connectivity (rs-fcMRI) reveals disruption of not only corticostriatal motor, but also default mode (DMN) and dorsal attention networks (DAN) in PD.²⁻¹⁰ In Alzheimer disease (AD) biomarker studies, DMN topography and strength correspond with cortical $A\beta$ deposition.^{11,12} Furthermore, CSF $A\beta$ ₄₂ correlates with in vivo measures of $A\beta$ deposition¹³ and with DMN functional connectivity.^{14,15} Although α -synuclein neuroimaging markers are not yet available, CSF α -synuclein levels are lower in PD^{16,17} and may reflect synuclein brain pathology. Thus, determining the relationship between CSF levels of potentially pathogenic proteins and resting-state networks (RSNs) could link brain pathology and cortical

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dysfunction, providing key insights into the relationship between synucleinopathy and brain dysfunction in PD.

Therefore, in the present study, we investigated the relationships between functional connectivity and CSF α -synuclein, $A\beta_{42}$, and tau in PD. We hypothesized that CSF α -synuclein correlates with motor-related RSNs and that CSF $A\beta_{42}$ and $A\beta$ PET (Pittsburgh compound B [PiB]) binding correlate with DMN functional connectivity. To test these hypotheses, participants with PD and controls had rs-fcMRI, PiB-PET scans, and lumbar punctures to measure CSF proteins while off PD medications. Functional connectivity analyses, including rigorous quality control for movement,^{18,19} focused on 5 major RSNs^{20,21} and striatal connectivity.²²

METHODS **Standard protocol approvals, registrations, and participant consents.** The Washington University in St. Louis Human Research Protection Office and Radioactive Drug Research Committee approved this study and participants provided written informed consent.

Participants. Participants with PD ($n = 68$) were recruited through the Washington University in St. Louis Movement Disorders Center and the community between January 2006 and December 2013. Age-matched controls ($n = 27$) were recruited through the participants with PD (e.g., spouses/partners, friends). Clinical diagnosis of idiopathic PD was based on modified United Kingdom PD Society Brain Bank clinical diagnostic criteria with clear motor response to levodopa.²³ Exclusion criteria included head injury with loss of consciousness >5 minutes, neurologic diagnosis other than PD, severe psychiatric disorders (e.g., schizophrenia), treatment with dopaminergic blocking or depleting drug, or inability to complete MRI. Based on evidence of altered rs-fcMRI with mood disorders,²⁴ participants who reported high levels of current depression symptoms on the 15-item Geriatric Depression Scale (scores ≥ 6)²⁵ were excluded (7 PD, 3 control). Controls had a normal neurologic examination and no family history of PD.

Dementia evaluation. Participants completed the Clinical Dementia Rating (CDR)²⁶ and Mini-Mental State Examination (MMSE) with experienced raters. PD participants with CDR ≥ 1 or MMSE <24 were considered to have cognitive decline with functional impairment, meeting criteria for PD dementia²⁷ and were excluded ($n = 4$). PD participants with CDR of 0.5 have cognitive impairment insufficient to meet dementia criteria²⁷ and were included. All controls had normal cognition (CDR = 0 and MMSE ≥ 24).

Motor assessments. Movement disorder specialists rated motor severity using the Unified Parkinson's Disease Rating Scale motor evaluation (UPDRS-III²⁸) in the practically defined "off" state, after overnight withdrawal of PD medications. See appendix e-1 on the *Neurology*[®] Web site at Neurology.org for motor subtype classification and calculations.

CSF protein measures. Participants completed lumbar punctures within 1 year of rs-fcMRI scans. CSF was collected and processed as described.¹⁶ CSF α -synuclein, $A\beta_{42}$, and tau were measured using standard, commercially available ELISA kits.¹⁶ The CSF data represent a subset of published data,¹⁶ including only participants with rs-fcMRI.

PiB-PET imaging. Participants completed [¹¹C]-PiB-PET imaging as described.^{29,30} PiB binding potentials (BP) were calculated from the tracer distribution volume (DV) as $BP = DV - 1$. Mean cortical BP (MCPB) (average of prefrontal cortex, gyrus rectus, lateral temporal cortex, and precuneus) were calculated for each participant; higher scores indicate more cortical fibrillar $A\beta$. MCPB ≥ 0.18 is considered abnormally elevated.³¹ To ensure controls did not have preclinical AD,³² controls with elevated PiB ($n = 1$) were excluded. Portions of these PET data have been reported.^{29,30}

Resting-state fMRI. Neuroimaging was performed using a 3T Siemens Trio scanner (Erlangen, Germany) with a standard 12-channel head coil. Participants with PD were imaged after overnight withdrawal of PD medications. Structural scans included the following: T1-weighted magnetization-prepared rapid gradient echo MRI scan (repetition time [TR] = 2,400 milliseconds [ms], inversion time = 1,000 ms, echo time [TE] = 16 ms, flip angle = 8°, 0.9 mm³ voxels) and T2-weighted MRI scan (TE = 455 ms, TR = 3,200 ms, 1 mm³ voxels). Participants completed up to 3 rs-fcMRI runs (200 volumes/run, TE = 27 ms, TR = 2,200 ms, field of view = 256 mm, flip angle = 90°, 4 mm³ voxels), with eyes closed but awake. To control for movement confounds, participants were observed throughout scan acquisitions; rs-fcMRI runs with observable sustained tremor, dyskinesia, or dystonia were excluded.

Resting-state fcMRI data were processed as previously described.⁷ Preprocessing included compensation for systematic, slice-dependent time shifts, elimination of systematic odd-even slice intensity differences due to interleaved acquisition, rigid-body correction for head motion, and normalization of signal intensity (all voxels in all volumes of each run) to obtain a mode value of 1,000. fMRI scans were registered to an atlas-representative template representing equal numbers of PD and control participants to minimize registration bias.^{7,33} Additional preprocessing before seed-based correlation mapping included spatial smoothing (6 mm full width at half maximum in each direction) and temporal low-pass filtering retaining frequencies <0.1 Hz. Signals treated as nuisance regressors included (1) 6 rigid body parameters derived from head motion correction, (2) signals extracted from regions of interest (ROIs) in white matter and CSF, and (3) the mean over the whole brain.

MRI quality assurance measures. Rigorous quality assurance (QA) measures were applied to minimize the impact of motion artifacts and movement confounds.^{18,19} fMRI runs in which head motion exceeded 0.6 mm root mean square or the voxel-wise temporal SD averaged over the brain (after full preprocessing) exceeded 0.5% were excluded. Volumes with large changes in signal intensity (DVARs $>0.5\%$)¹⁹ were excluded. Participants with more than 15% volumes removed were excluded. Only participants with at least 2 usable rs-fcMRI runs, as determined by QA measures, were included. One control and 14 participants with PD were excluded on the basis of these QA measures. In the retained data, QA measures were equivalent between PD and control groups.

Network-level functional connectivity. Network-level functional connectivity analyses focused on 5 previously defined RSNs (DMN, dorsal attention [DAN], control, salience, and sensorimotor [SMN]).^{20,21} ROIs (table e-1) were defined as 5-mm-radius spheres centered on Talairach atlas coordinates.²¹ The time series for each ROI was extracted and correlated with all other brain voxels. Individual correlation maps for each seed were converted to Fisher z -transformed correlation maps and then averaged across groups. Functional connectivity between ROI pairs was evaluated as the mean Fisher z -transformed correlation value over expanded seed regions surrounding the second member of each pair.²¹ Expanded seed regions were defined as voxels satisfying $|z| > 3$ in Fisher z -transformed correlation maps averaged over the entire cohort (figure 1). Composite scores representing within-RSN functional connectivity were computed as the average over diagonal blocks of ROI pairs,²¹ as illustrated in figure 2B.

Striatal functional connectivity. Striatal functional connectivity was compared between groups using previously defined seeds in dorsal caudate and anterior and posterior putamen.²² For striatal seeds (figure 1B), the group averaged Fisher $z(r)$ maps were compared using random-effects analysis. Significant clusters, based on extent and z -score thresholds, were determined by bootstrapped Monte Carlo simulations (10,000 iterations) at a $p = 0.05$ significance level to control for multiple comparisons across all brain voxels.⁷ Fisher $z(r)$ correlation coefficients for significant clusters (seed-cluster pairs) were extracted for additional correlation analyses with CSF and disease-severity measures.

Statistical analyses. First, group differences in RSN composite scores and CSF protein levels were established with one-way analyses of variance. To test the primary hypothesis of correlations between CSF protein levels and functional

connectivity in PD, Pearson partial correlations, controlling for the potential effects of age on protein levels and functional connectivity, were computed separately for each group. Correlation analyses also tested associations among disease severity, RSN composite scores, and CSF protein levels. Nonparametric Spearman correlations were used for the UPDRS-III rank-order motor ratings. Data were analyzed with PASW version 22 (IBM, Chicago, IL). Extreme values (>3 SD) were excluded as statistical outliers. All tests were 2-tailed and $p \leq 0.05$ was considered statistically significant.

RESULTS Participants. Forty-three PD participants without dementia and 22 controls had usable rs-fMRI data after applying QA measures (see table 1). For these participants, QA measures did not differ across groups ($p > 0.25$). PD and control groups had similar ages ($p = 0.55$), but the PD group was slightly more educated ($F_{1,63} = 6.68$, $p = 0.01$) and had more men ($\chi^2 = 4.09$, degrees of freedom [df] = 1, $p = 0.04$). Therefore, education and sex were included as covariates for between-group analyses.

RSN functional connectivity differences. Topographically, PD and control groups displayed the typical RSN connectivity patterns (figure 2A). However, the PD group exhibited reduced functional connectivity within the SMN (analysis of covariance [ANCOVA], education and sex as covariates; $F_{1,61} = 6.20$, $p = 0.02$; figure 2, B and C) and stronger DMN functional connectivity after excluding one control

Figure 1 RSN and striatal functional connectivity seeds

The expanded RSN seeds for each network are in the top panel of images (A). Colors indicate the respective RSNs as follows: blue = DMN; red = DAN; green = CON; purple = SAL; teal = SMN. See table e-1 for complete list of seed regions. The bottom panel of images (B) shows the striatal seeds of the DC (Talairach: $-12.76, 10.83, 11.64$, left; $12.04, 10.56, 12.18$, right), DCP ($-26.89, -2.23, 4.88$, left; $26.53, -2.81, 6.05$, right), and DRP ($-24.12, 4.35, 8.17$, left; $23.58, 3.83, 9.21$, right). CON = control network; DAN = dorsal attention network; DC = dorsal caudate; DCP = dorsal caudal putamen; DMN = default mode network; DRP = dorsal rostral putamen; RSN = resting-state network; SAL = salience network; SMN = sensorimotor network.

Figure 2 RSN functional connectivity for PD and control groups

Both groups display the typical functional connectivity patterns for each RSN, as shown by the Fisher $z(r)$ correlation maps representing each RSN (A) and network correlation matrices (B). Each network is bound by a different color box, as follows: blue = DMN; red = DAN; green = CON; purple = SAL; teal = SMN. The group difference correlation map represents the control group - PD group. Warm colors represent positive correlations and cool colors represent negative ("anti-correlations") correlations. (C) Scatterplots demonstrate the significant differences (as indicated by asterisks; $p < 0.05$) between PD (circles) and control (squares) groups in SMN and DMN functional connectivity. Open symbols indicate outliers. CON = control network; DAN = dorsal attention network; DMN = default mode network; PD = Parkinson disease; RSN = resting-state network; SAL = salience network; SMN = sensorimotor network.

outlier (ANCOVA; $F_{1,60} = 4.12$, $p = 0.05$; figure 2, B and C). Composite RSN scores did not differ between groups for DAN (ANCOVA; $p = 0.57$), control network (ANCOVA; $p = 0.26$), or salience network (ANCOVA; $p = 0.25$) (figures 2B and e-1). Additional internetwork connectivity comparisons are presented in appendix e-1.

Striatal functional connectivity. Based on striatal seeds, dorsal caudate functional connectivity differed between groups, with significant clusters in cerebellum and temporal-parietal junction (figure 3). For control participants, the left dorsal caudate positively correlated with the cerebellum and negatively correlated with the

temporal-parietal junction; in contrast, the PD group exhibited a relative lack of any correlation between left dorsal caudate and these regions. None of the other striatal seeds yielded significant group differences.

CSF protein level differences. Participants with PD had lower CSF α -synuclein (ANCOVA; $F_{1,61} = 5.05$, $p = 0.03$) and $A\beta_{42}$ (ANCOVA; $F_{1,61} = 4.35$, $p = 0.04$) than controls, but CSF tau did not differ between groups (ANCOVA; $p = 0.95$) even after excluding outliers (ANCOVA; $p = 0.95$) (figure e-2).

CSF proteins and functional connectivity in PD. Partial correlations, controlling for age, tested the relationship

Table 1 Participant demographic and clinical information

	Control group (n = 22)	PD group (n = 43)	Group comparison
Age, y	64.6 ± 10.3 (49-90)	66.0 ± 7.6 (49-82)	$p = 0.55$, NS
Sex, M/F	8/14	27/16	$p = 0.04$
Education, y	14.6 ± 2.3 (12-19)	16.3 ± 2.7 (12-20)	$p = 0.01$
Duration since PD diagnosis, y	—	4.2 ± 3.6 (0-18)	—
UPDRS-III OFF total score	—	20.6 ± 7.5 (4.5-36.5)	—

Abbreviations: NS = not significant; PD = Parkinson disease; UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III.

Values represent means ± SD (range).

between CSF protein levels and RSN composite scores. For participants with PD, CSF α -synuclein correlated with SMN functional connectivity ($r = 0.32$, $df = 40$, $p = 0.04$), such that participants with lower CSF α -synuclein had reduced SMN functional connectivity (figure 4). The DAN composite score also correlated with CSF α -synuclein ($r = -0.36$, $df = 40$, $p = 0.02$; figure 4). CSF $A\beta_{42}$ did not correlate with the DMN ($p > 0.60$; figure 4) or any other RSN ($p > 0.14$). CSF tau levels did not correlate with DAN ($r = -0.30$, $df = 39$, $p = 0.06$) or any other RSN ($p > 0.34$). CSF protein levels did not correlate with the significant left dorsal caudate seed-cluster pairs ($p \geq 0.10$).

CSF proteins and functional connectivity in controls. For controls, CSF $A\beta_{42}$ correlated with the DMN composite score ($r = 0.48$, $df = 18$, $p = 0.03$; figure 4) after excluding one control outlier, even though all controls had normal CSF $A\beta_{42}$. CSF $A\beta_{42}$ did not correlate with any other RSN ($p > 0.17$). Furthermore, CSF α -synuclein did not correlate with any RSN ($p > 0.43$; figure 4). CSF tau levels did not correlate with DMN ($r = 0.41$, $df = 18$, $p = 0.08$) or any RSN after excluding one control outlier ($p \geq 0.28$). None of the CSF proteins correlated with the left dorsal caudate seed-cluster pairs ($p > 0.35$).

PiB and functional connectivity. PiB MCBP did not correlate with the DMN for PD or control groups

Figure 3 Striatal functional connectivity differences between PD and control groups for the left dorsal caudate

Top 2 rows are the group average Fisher $z(r)$ correlation maps for the left dorsal caudate seed. The bottom row of images (group contrast effect) represent the gaussianized t statistic (z score) thresholded at $|z| = 2.0$ from the between-group random-effects analysis. Significant group difference clusters are determined by computing threshold-extent criteria using Monte Carlo simulations for multiple comparison correction. Significant group difference clusters in the temporal-parietal junction ($z = 3.3$, $p = 0.05$) (A) and cerebellum ($z = 2.2$, $p = 0.05$) (B) are circled. Warm colors indicate higher correlations in the control group and cool colors indicate higher correlations in the PD group. PD = Parkinson disease.

Figure 4 CSF protein levels and resting-state network functional connectivity

Top row of figures are the PD group (circles) correlations. CSF α -synuclein significantly correlated with SMN and DAN functional connectivity for the PD group. Bottom row of figures are the control group (squares) correlations. CSF A β_{42} significantly correlated with DMN functional connectivity for the control group (squares). Open symbols indicate outliers. A β = β -amyloid; DAN = dorsal attention network; DMN = default mode network; PD = Parkinson disease; SMN = sensorimotor network.

($p > 0.48$). Only 7 (16.3%) participants with PD had abnormally elevated PiB binding (PiB⁺).

Correlations with disease severity. We also investigated the correlation between motor severity, as determined by duration of PD, UPDRS-III OFF total and motor subscale scores, and RSNs or CSF protein levels. The motor subscale analyses are provided in appendix e-1. UPDRS-III ratings did not correlate with any RSN ($p > 0.16$), including the SMN ($r = -0.26$, $df = 41$, $p = 0.10$), or seed-cluster pairs ($p > 0.11$). Similarly, CSF protein levels did not correlate with motor severity measures ($p > 0.11$).

DISCUSSION Disruption of SMN functional connectivity in PD correlated with reduced CSF levels of α -synuclein. Participants with PD with the lowest CSF α -synuclein levels had the greatest reduction in SMN functional connectivity. This relationship was unique to the PD group and was not found for the control group. In contrast, DMN functional connectivity did not correlate with either CSF A β_{42} or PiB binding in PD; instead, CSF A β_{42} correlated with DMN functional connectivity only in the control group. These results suggest that abnormal α -synuclein accumulation contributes to disruption of particular RSNs in PD.

The relationship between CSF α -synuclein and functional connectivity provides new evidence for the functional significance of α -synuclein in the pathophysiology of PD. Since CSF levels of α -synuclein likely reflect abnormal brain deposition of α -synuclein, the correlation between CSF levels and SMN

coherence indicates that α -synuclein may directly disrupt cortical function. Disruption of striatal functional connectivity for the dorsal caudate did not correlate with CSF protein levels. Given that direct dopaminergic denervation occurs mostly in striatum and CSF levels correlate with other resting-state cortical networks, these findings may indicate that the effects of α -synuclein extend beyond nigrostriatal dopaminergic denervation. This also offers a possible explanation for reports of disrupted motor network functional connectivity in PD while on medication.⁷ Of note, DAN functional connectivity negatively correlated with CSF α -synuclein, which may reflect increased reliance on external information frequently observed in PD³⁴ since DAN activity is associated with externally directed cognition.³⁵ This finding suggests that even in PD without dementia, changes in α -synuclein metabolism influence nonmotor cortical functional connectivity networks. Thus, combining CSF protein measures and rs-fMRI in the present study provides a link between α -synuclein metabolism and disrupted brain function in PD.

However, DMN functional connectivity did not correlate with A β measures in PD. Despite significantly lower CSF A β_{42} , the PD group surprisingly had stronger DMN functional connectivity than controls. Of note, DMN functional connectivity correlated with CSF A β_{42} levels only in the control group despite all control participants having normal cortical PiB binding and CSF A β_{42} (CSF A $\beta_{42} > 500$ pg/mL).¹³ These data suggest that the strength of DMN functional connectivity in our control

participants correlates with the variability of CSF A β ₄₂ levels within the normal range but does not necessarily indicate that this reflects preclinical AD in these controls. People with preclinical AD may be more likely to have elevated A β deposition several years before symptom onset, at least if the findings in familial AD can be extrapolated to sporadic AD³²; therefore, we excluded controls with abnormally elevated PiB binding. Thus, our findings indicate either that A β ₄₂ relates to DMN function in normal aging or that this relationship can develop many years before onset of sporadic AD. Nevertheless, our findings of stronger DMN functional connectivity in PD despite lower CSF A β ₄₂ levels directly contrast with findings in preclinical and symptomatic AD in which disruption of DMN correlates with reductions in CSF A β ₄₂. These results reinforce the notion that A β deposition has a different role in PD pathophysiology than in AD. Alternatively, the lack of an association between CSF A β ₄₂ and DMN functional connectivity in PD may reflect differences between the specific types of A β plaques that occur in AD and PD. Neuritic plaques are a prominent pathologic feature of AD, whereas diffuse plaques are more common in PD.³⁶ Given that relatively few participants with PD had abnormally elevated PiB binding, it remains possible that A β plaque deposition must exceed a threshold level to disrupt DMN functional connectivity.

Overall, these results raise an interesting question about the role of soluble α -synuclein as measured in CSF vs insoluble, fibrillar α -synuclein aggregates found in Lewy bodies. Animal models of synucleinopathy demonstrate that α -synuclein oligomers impair synaptic function and long-term potentiation.^{37,38} For example, mice overexpressing oligomeric forms of α -synuclein have greater synaptic and dendritic loss than α -synuclein wild-type mice that express monomers, oligomers, and fibrillar α -synuclein.³⁷ Similarly, AD animal models also demonstrated that A β oligomers impair synaptic function.³⁹ Identification of the specific roles of the various forms of α -synuclein in PD requires more advanced biochemical and neuroimaging methods.

This study has several important strengths. We investigated the relationships between CSF pathogenic protein levels and disruption of RSNs and found that CSF α -synuclein, but not A β ₄₂, correlate with the strength of some cortical RSNs in PD. None of our control participants had evidence of preclinical AD, as indicated by normal PiB scans and CSF A β ₄₂ levels.^{13,31} Equally important, we rigorously controlled for movement in the rs-fcMRI analyses as a behavioral confound and for motion-related artifacts. Finally, functional connectivity analyses extended

beyond the more traditional seed-based approach and used a network-level analysis strategy to examine functional connectivity within the major RSNs.

The principal limitation of the present study is the small number of participants with PD who had elevated PiB binding, thus hindering the ability to adequately test for group differences in DMN functional connectivity based on abnormally elevated A β burden. Treating CSF and PiB A β as continuous measures, however, revealed no correlations between DMN functional connectivity and either CSF A β ₄₂ or PiB binding in the PD group. The current study also did not control for possible PD-related atrophy; however, all previous studies that measured atrophy failed to find an association between disrupted functional connectivity and atrophy in PD.^{4,8,9,40}

Combining protein measures and rs-fcMRI affords a greater understanding of the pathologic basis for motor impairment in PD. This approach could also provide valuable insight into nonmotor features of PD. Determination of the utility of these measures to detect and predict PD progression requires longitudinal studies incorporating CSF measures and rs-fcMRI.

AUTHOR CONTRIBUTIONS

Study concept and design: M.C.C., J.S.P. Analysis and interpretation of data: M.C.C., J.M.K., P.T.K., C.B., A.Z.S., J.S.P. Drafting/revising the manuscript for content: M.C.C., J.M.K., P.T.K., C.B., A.Z.S., J.S.P.

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DISCLOSURE

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