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Journal

SLEEP, 47(6)

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Publication Date

2024-06-13

DOI

10.1093/sleep/zsae007

Peer reviewed

SLEEP, 2024, 47, 1–12
https://doi.org/10.1093/sleep/zsae007
Advance access publication 5 January 2024
Original Article

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Comorbid neurotrauma increases neurodegenerative-relevant cognitive, motor, and autonomic dysfunction in patients with rapid eye movement sleep behavior disorder: a substudy of the North American Prodromal Synucleinopathy Consortium

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Abstract

Study Objectives: Rapid eye movement sleep behavior disorder (RBD) is strongly associated with phenoconversion to an overt synucleinopathy, e.g. Parkinson's disease (PD), Lewy body dementia, and related disorders. Comorbid traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD)—henceforth "neurotrauma" (NT)—increase the odds of RBD by ~2.5-fold and are associated with an increased rate of service-connected PD in Veterans. Thus, RBD and NT are both independently associated with PD; however, it is unclear how NT influences neurological function in patients with RBD.

Methods: Participants ≥18 years with overnight polysomnogram-confirmed RBD were enrolled between 8/2018 to 4/2021 through the North American Prodromal Synucleinopathy Consortium. Standardized assessments for RBD, TBI, and PTSD history, as well as

Submitted for publication: October 11, 2023; **Revised:** December 13, 2023

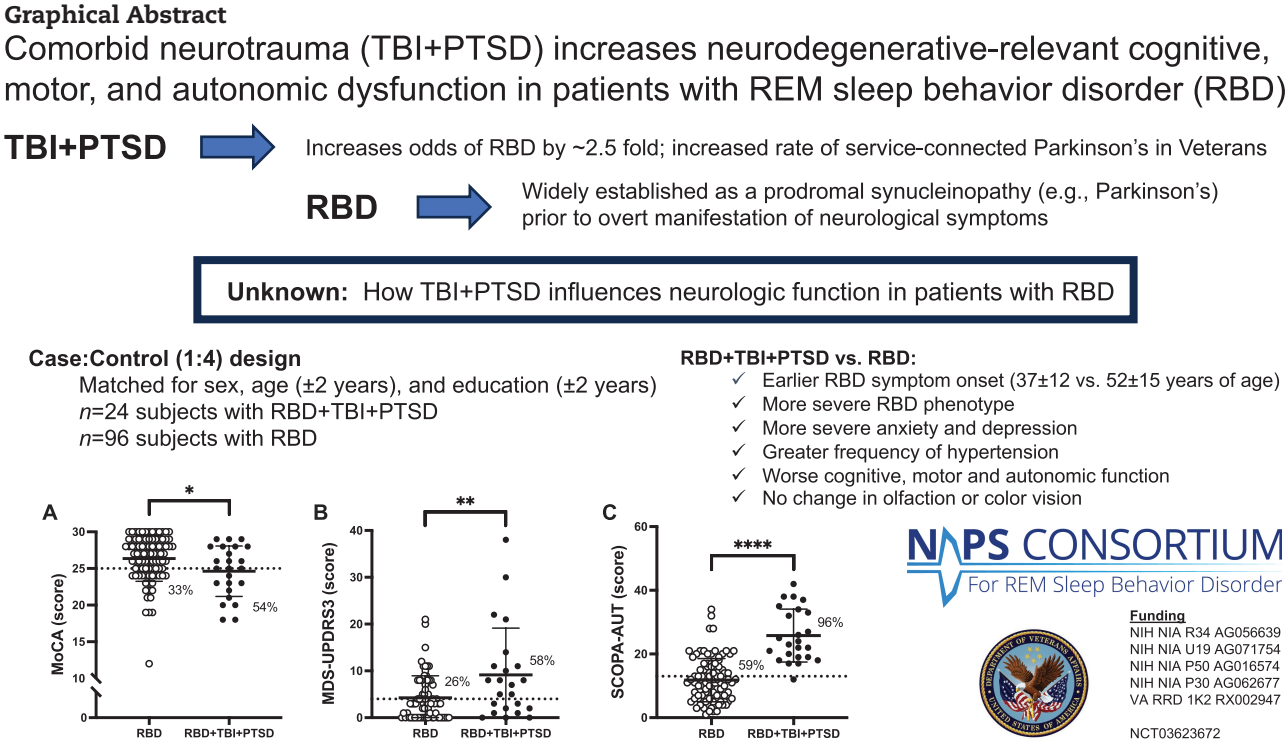
cognitive, motor, sensory, and autonomic function, were completed. This cross-sectional analysis compared cases (n = 24; RBD + NT) to controls (n = 96; RBD), matched for age (~60 years), sex (15% female), and years of education (~15 years).

Results: RBD + NT reported earlier RBD symptom onset (37.5 ± 11.9 vs. 52.2 ± 15.1 years of age) and a more severe RBD phenotype. Similarly, RBD + NT reported more severe anxiety and depression, greater frequency of hypertension, and significantly worse cognitive, motor, and autonomic function compared to RBD. No differences in olfaction or color vision were observed.

Conclusions: This cross-sectional, matched case:control study shows individuals with RBD + NT have significantly worse neurological measures related to common features of an overt synucleinopathy. Confirmatory longitudinal studies are ongoing; however, these results suggest RBD + NT may be associated with more advanced neurological symptoms related to an evolving neurodegenerative process.

Key words: RBD; REM sleep without atonia; Parkinson's disease; synucleinopathy; traumatic brain injury; posttraumatic stress disorder; trauma-associated sleep disorder

Graphical Abstract



Statement of Significance

Individuals with comorbid traumatic brain injury and posttraumatic stress disorder (PTSD), i.e. neurotrauma (NT), show increased rates of rapid eye movement sleep behavior disorder (RBD). RBD is a prodromal synucleinopathy, and NT is also an independent risk factor for Parkinson's disease and dementia, as well as other disorders and pathophysiologic processes (e.g. chronic traumatic encephalopathy, TDP-43-associated neurodegeneration, and neuroinflammation). However, how patients with comorbid NT and RBD differ from idiopathic RBD is unknown. In this cross-sectional case:control study, we show individuals with comorbid NT and RBD demonstrate significantly worse cognitive, motor, and autonomic function compared to those with RBD without NT, even after matching for age, sex, and years of education. Although confirmatory longitudinal studies are still ongoing, these results suggest RBD + NT may be associated with a more advanced state of neurological symptoms related to an evolving neurodegenerative process.

Introduction

Idiopathic RBD was first described in 1986 [1] and is characterized by lack of muscle atonia during rapid eye movement (REM) sleep (i.e. REM sleep without atonia; RSWA) and overt dream enactment behavior [2]. Beyond the impaired quality of life, RBD is widely regarded as a prodromal synucleinopathy reflecting one of the earliest and best predictors for phenoconversion to an overt synucleinopathy such as Parkinson's disease (PD), dementia with Lewy bodies, or multiple system atrophy. Indeed, it is estimated that 40%–70% of individuals with RBD will phenoconvert to an overt synucleinopathy within 5–10 years [3–5], with a recent systematic review and meta-analysis calculating a phenoconversion rate of 96% within 14 years [6]. The economic footprint associated with such synucleinopathies is enormous [7], and currently, there are no treatments to prevent severe disability and death [8, 9]. The incipient neurodegenerative progression of synuclein deposition

is such that by the time overt motor or cognitive symptoms warrant a clinical diagnosis, the pathologic framework is already well advanced [10]. Accordingly, the patient with RBD population is potentially a high-yield target with the goal of establishing biomarkers for detecting and tracking prodromal synucleinopathies at an earlier time when neuroprotective interventions may be more effective (i.e. by way of slowing, altering, or preventing neuropathologic progression) [11]. Toward this goal, in 2018 the North American Prodromal Synucleinopathy (NAPS) Consortium for RBD (https://www.naps-rbd.org) was founded comprising a coordinated effort across nine sites in North America to establish a cohort of RBD participants to be prospectively and longitudinally assessed by standardized neurologic assessments and biomarker collection protocols.

Idiopathic RBD (iRBD) is generally thought to be nosologically distinct from other REM-related parasomnias, in particular—neurotrauma-associated RBD (also referred to as trauma-associated sleep disorder; TASD) [12–15]. It is thought to be clinically important to make a distinction between these two conditions because the implication is that neurotrauma-associated RBD (e.g. TASD) is not necessarily a prodromal synucleinopathy (or tauopathy in the context of chronic traumatic encephalopathy), but rather, simply an extension or variant of PTSD nightmares [12, 13]. However, while many longitudinal cohort studies exist for iRBD, there have been no reports to date examining longitudinal or neurodegenerative outcomes in individuals with TASD. Furthermore, as an additional factor analysis in this study, genetic profiles that confer increased risk for neurodegeneration after neurotrauma (e.g. apolipoprotein ε [*APOE*] genotype and microtubule-associated protein tau [*MAPT*] haplotypes) were also examined [16–19].

Neurotrauma, including traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD), has been widely reported to result in chronic and debilitating sleep disturbances [20–26]. Chronic sleep disruption contributes directly to neurodegenerative pathology, including aggregates of alpha-synuclein, amyloid-beta, and tau relevant to Parkinson's and related dementias [27–31]. However, not all individuals with neurotrauma go on to develop sleep disturbances or RBD [32]. It appears that individuals with *comorbid* TBI + PTSD have higher rates of sleep disturbances as well as higher rates of RBD—synergistic and more than additive effects of TBI or PTSD alone [23, 32]. Combined TBI + PTSD also synergistically leads to worsened neurobehavioral symptoms and disability compared to either TBI or PTSD in isolation [23, 32–34]. While recent epidemiological studies have shown a direct association between combined TBI + PTSD and risk of neurodegeneration [35, 36], it is still unknown whether combined TBI + PTSD together with associated sleep disruption confers higher neurodegenerative risk.

RBD is not only more prevalent among individuals with neurotrauma (NT) [32], and because NT itself increases the risk of PD [35, 37–43], it logically follows that RBD in addition to NT (henceforth RBD + NT) may further increase the risk of phenoconversion to an overt neurodegenerative condition. However, this has not yet been demonstrated. Furthermore, it is unclear whether RBD + NT is a variant of PTSD nightmares without increased risk for neurodegenerative conditions, or associated with a prodromal neurodegenerative proteinopathy. We attempted to provide some closure to this gap by analyzing data collected within the NAPS Consortium. In this cross-sectional, case:control analysis, we compared neurological scores from individuals with RBD to individuals with RBD plus NT (RBD + NT), while matching for age, sex, and education. Given the prior strong evidence that NT is an independent risk factor for eventual PD, dementia, and other neurodegenerative conditions or processes (e.g. chronic traumatic encephalopathy, abnormal TDP-43 deposition, neuroinflammation), we hypothesized that RBD + NT participants would demonstrate worse neurologic function across cognitive, motor, sensory, and autonomic neurologic domains compared to those with only RBD. Cross-sectional findings reported herein lend some missing evidence to pinpoint NT's role in potentiating neurodegenerative processes, potentially manifested by interim RBD.

Materials and Methods

Overview

Participants in the NAPS consortium, i.e. those ≥18 years of age with overnight video polysomnogram-confirmed RBD by International Classification of Sleep Disorders-3 criteria [44] without a diagnosis of PD [45], dementia of any type [46], multiple system atrophy [47], or narcolepsy [48] were enrolled from nine sites across North America from August 2018 to April 2021. A total of $n = 361$ participants were enrolled: Washington University School of Medicine ($n = 26$; IRB #20171205), Mayo Clinic Rochester ($n = 50$; IRB# 18-004722 00), University of Minnesota ($n = 30$; IRB# study00003927), Center for Advanced Research in Sleep Medicine at the *Hôpital du Sacré-Coeur de Montréal* ($n = 94$; IRB# MP-32-2019-1652), Harvard/Massachusetts General Hospital ($n = 26$; IRB# 2018P002080), Emory University ($n = 32$; IRB# 104229), University of California Los Angeles ($n = 32$; IRB# 18-000801), Stanford University ($n = 20$; IRB# 53655), and the VA Portland Health Care System ($n = 51$; IRB # STUDY00020615 via Oregon Health and Science University). Participants from a tenth site, at Banner Sun Health, are not included in this analysis. This study was performed according to the *Declaration of Helsinki* and approved by the Institutional Review Boards at each enrollment site. All participants provided written and verbal informed consent prior to participation.

Data collection procedures and practices were rigorously standardized across sites, which included structured interviews and questionnaires on health history, structured neurological and physical examinations, an objective test battery of cognitive, motor, autonomic, and sensory function, and venous blood sampling for genetic analyses. A detailed description of the broader NAPS cohort and study design is presented in a separate publication [49].

RBD and sleep measures

A NAPS-specific structured interview queried for RBD symptoms, frequency, severity, treatments, and possible temporal relationship with any antidepressant or other medications. Diagnoses of sleep apnea (obstructive or central), restless legs syndrome, and periodic limb movement were determined during the clinician's structured interview. Other sleep-related measures included the Epworth Sleepiness Scale to measure daytime sleepiness [50] and the Scales for Outcomes in PD-Sleep (SCOPA-Sleep) which queries nighttime sleep quality and daytime sleepiness [51].

TBI, PTSD, and health history

Participants' history for TBI was based on self-reports during standardized clinician assessments [52]. Provisional diagnosis for PTSD was assessed via the PTSD checklist for DSM-5 (PCL-5). This survey includes 20 questions, each response on a 0 to 4 Likert scale (maximum = 80; higher = worse PTSD) [53], and is subdivided into four clusters: B-Intrusion, 1–5; C-Avoidance, 6–7;

D-Mood/Cognition, 8–14; and E-Arousal, 15–20. PTSD was determined by a PCL-5 score ≥ 33 and positive "cluster criteria" (i.e. rating of ≥ 2 for 1 B item, 1 C item, 2 D items, and 2 E items; as well as affirmative for criterion A), as is standard. All participants in the "Neurotrauma" (NT) group (RBD + NT) met diagnostic criteria for both TBI and PTSD (no participants in the "RBD only" group met criteria for either TBI or PTSD).

Additional demographic and health history, including comprehensive family history, were obtained via structured interviews and following standardized forms, including those from the Uniform Data Set version 3 (UDS3), from the National Alzheimer Coordinating Center (https://naccdata.org/data-collection/forms-documentation/uds-3) and custom NAPS-specific forms. Questionnaires assessing neuropsychiatric function included the Beck Anxiety Inventory (BAI), Patient Health Questionnaire-9 (PHQ-9) for depression, and an informant-completed Neuropsychiatric Inventory-Questionnaire (NPI).

Neurological and neurobehavioral assessment

Participants underwent a broad neurological test battery including objective tests of cognitive, motor, autonomic, and sensory (color vision and smell) function. Cognitive assessments included the psychometric battery from the UDS3 standard and Lewy body dementia modules: Montreal Cognitive Assessment (MoCA), the Craft Story 21 (immediate and delayed), the Benson Complex Figure Copy (immediate and delayed), Number Span Test Forward and Backward, Trail Making Test (TMT) parts A and B, categorical and phenomic verbal fluency (animals, vegetables, words beginning with F and L), Multilingual Naming Test (MINT), the Speeded Attention Task, and the Noise Pareidolia Task.

Motor function was assessed via the timed up-and-go, Purdue Pegboard, and Alternate Tap tests. Collectively, these assessments evaluated participants' gross motor function, ability to sit/stand/walk, fine motor control and coordination of the limbs and digits, and overall reaction/movement speed. Additionally, the Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) was administered, and part 3 of this assessment includes a clinician-quantified rating of gross and fine motor function. Scores of >4 were defined as abnormal on the MDS-UPDRS part 3.

Autonomic function was measured with orthostatic blood pressure, in which blood pressure was measured after lying supine for 5 minutes, then 1, 2, and 3 minutes after standing. Orthostatic hypotension was defined as a sustained ≥20 mm Hg decrease in systolic blood pressure and/or a ≥10 mm Hg decrease in diastolic blood pressure at 3 minutes after standing. Severe orthostatic hypotension was defined as ≥30 mm Hg decrease in systolic blood pressure and/or a ≥15 mm Hg decrease in diastolic blood pressure. Additionally, subjective autonomic function was assessed using the Scales for Outcomes in PD—Autonomic Dysfunction (SCOPA-AUT).

The 12-item Brief Smell Identification Test (BSIT; Version A, Sensonics Inc. NJ, USA) assessed overall olfaction and scent discrimination, with higher scores indicating better olfactory function. Sex- and age-adjusted cutoffs were used to define abnormal results; however, in general scores ≤8 typically indicate impaired olfaction. The Farnsworth-Munsell 100 Color Hue test (FM-100) assessed participants' color discrimination ability, with higher scores indicating worse color vision. Age-adjusted cutoffs were used for FM-100 scores; however, in general scores > 100 suggest poor color discrimination. In addition, participants self-reported any color blindness or subjective smell impairment.

Genetic analysis

The library preparation for whole-genome sequencing was performed using the Illumina DNA PCR-Free Prep workflow and the Illumnia NovaSeq sequencing platform with 150-bp paired-end reads at the McGill Genome Center. Each sample had a minimum of depth of coverage of 30×. VerifyBamId was applied (https://genome.sph.umich.edu/wiki/VerifyBamID) on the single-chromosome alignment files to exclude lanes with a FreeMix value above 0.03. Samples with more than one problematic lane were excluded. Hardware-accelerated Illumina DRAGEN Bio-IT Platform was used along with the DRAGON joint genotyping pipeline (Illumina, Inc.) to identify SNPs and indels in genomic data. Samples were aligned to GRCh38. We then performed standard quality control procedures were also performed. Samples with sex mismatch, missingness > 5%, and heterogeneity outliers were removed. Variant-level quality control excluded SNPs with call rate < 5%, missingness by haplotype $p < 0.0001$, and controls deviating from Hardy-Weinberg equilibrium ($p < 0.0001$). The genotype of *APOE* e4 and the *MAPT* H2 haplotype were determined based on the genotype of the *APOE* SNPs: rs7412 and rs429358 and the *MAPT* SNP: rs1052553.

Statistical analyses

Statistical analyses were performed with SPSS and GraphPad Prism v9, with alpha defined a priori at 0.05. Data are presented as mean ± standard deviation, or as the number and percentage of the whole. Comparing groups (i.e. RBD + NT vs. RBD) utilized an unpaired two-tailed Student's t-test, Mann–Whitney U test, or Fischer Exact tests, as appropriate (Tables 1–3; Figure 1). Overall family-wise error rate, i.e. correcting for multiple testing, across all comparisons was not done in an effort to not obscure otherwise potentially meaningful clinical differences. Throughout the presentation of results, p values should be interpreted accordingly. However, key outcome variables for each major neurologic domain of interest (e.g. Cognition, MoCA/Craft story; Motor, MDS-UPDRS III/Alternate Tap Test; Sensory, Brief Smell Identification Test/FM-100; Autonomic Function, SBP/SCOPA-AUT) were adjusted for potential confounders including age, hypertension, and obstructive sleep apnea via multiple logistic regression with adjusted p values presented. Adjusted p values are specified in the written text by stating "adjusted." Case:control matching was implemented in a standardized sequential manner. All participants were ordered according to the date of enrollment, and separated based on group status (i.e. case = RBD + NT vs. control = RBD only). One control participant was sequentially matched to each case before advancing on to matching the second, third, and fourth control. Matching criteria were prioritized according to (1) sex, (2) age, and (3) years of education (age and education ± 2 years).

Results

Demographics and general health

Table 1 Validating the case:control design to match for age, sex, and years of education, there were no statistically significant differences in these variables between the RBD versus RBD + NT groups. The RBD and RBD + NT groups were approximately 60 years of age, 15% female, and reported 15 years of education. Demographically, the only significant difference between these groups was a higher proportion of Hispanic/Latinx participants in the RBD + NT group ($p = 0.0078$).

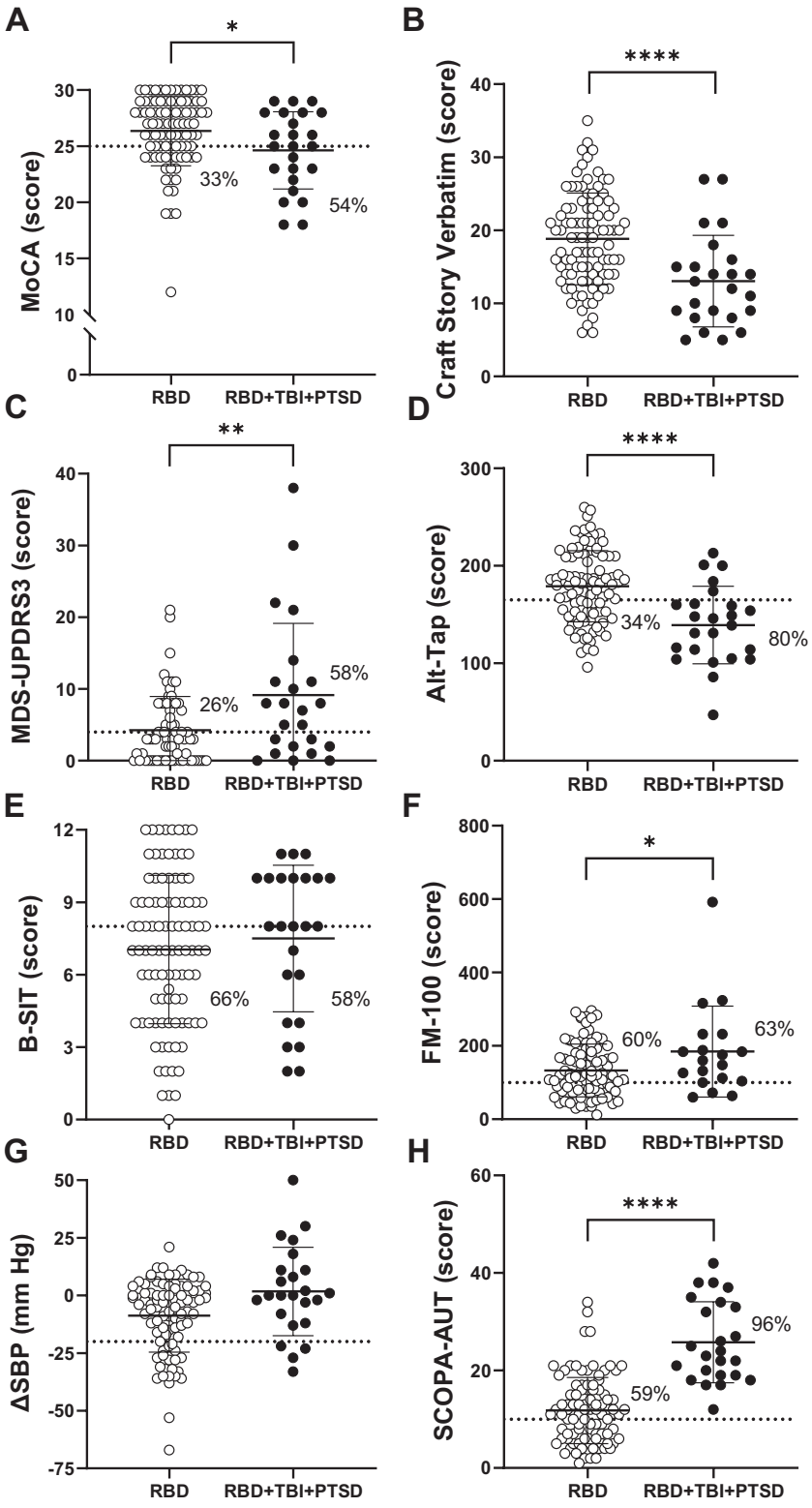


Figure 1. Data for the RBD + NT and the RBD groups from (A) The Montreal Cognitive Assessment (MoCA), (B) Craft Story Verbatim, (C) The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale 3 (MDS-UPDRS III), (D) The Alternative Tap Test (Alt Tap), (E) The Brief Smell Identification Test (BSIT), (F) The Farnsworth-Munsell 100-Hue test (FM-100), (G) change in systolic blood pressure between supine to after 3 minutes of standing (ΔSBP), and (H) The Scale for Outcomes in Parkinson's disease-Autonomic Test (SCOPA-AUT). Data are mean ± standard deviation with the percent abnormal listed above/below the dashed line appropriate to the directionality for each outcome. Comparisons were unpaired with two-tailed t-tests.

Table 1. Demographic and General Health Outcomes

	RBD; *n* = 96	RBD + NT; *n* = 24
Age, *years*	62.5 ± 10.0	60.7 ± 11.8
Sex, *males*	85.4%	83.3%
Education, *years*	15.8 ± 2.3	14.9 ± 2.1
Race and ethnicity		
Ethnicity, *Hispanic/Latinx*	0.0%	12.5%*
Race, *White*	92.7%	79.2%
Race, *Black or African American*	3.1%	4.2%
Race, *other*	4.2%	4.2%
General health		
Hypercholesterolemia	32.3%	29.2%
Arthritis	27.1%	12.5%
Thyroid disease	9.4%	4.2%
Type II diabetes	6.3%	12.5%
Cardiovascular and cerebrovascular		
Hypertension	25.0%	54.2%*
Atrial fibrillation	8.3%	4.2%
Myocardial infarction	7.3%	4.2%
Stroke	2.1%	4.2%
Mental health		
BAI, *score*	5.9 ± 6.1	27.5 ± 14.6*
PHQ-9, *score*	3.5 ± 3.5	16.8 ± 6.0*
PCL-5, *score*	6.4 ± 7.8	52.0 ± 10.4*
Genotype/haplotype		
APOE ε4+	29%	40%
MAPT H2+	43%	37%

Data are mean standard deviation. BAI, Beck Anxiety Inventory; PHQ-9, Patient Health Questionnaire-9; PCL-5, Posttraumatic stress disorder checklist for DSM-V. * = $p < 0.05$ versus RBD.

General cardiovascular and cerebrovascular health outcomes were largely similar between the RBD and RBD + NT, the exception being a higher frequency of hypertension in the RBD + NT group (54% vs. 25%, $p = 0.0119$). Self-reported anxiety and depression, via the BAI (27.5 ± 14.6 vs. 5.9 ± 6.1, $p < 0.0001$) and PHQ-9 (16.8 ± 6.0 vs. 3.5 ± 3.5, $p < 0.0001$), were both significantly higher in the RBD + NT group. Consistent with the criteria for PTSD, the RBD + NT group also showed higher PCL-5 scores (52.0 ± 10.4 vs. 6.4 ± 7.8, $p < 0.0001$). These scores equate to moderate-severe clinical ranges for anxiety, depression, and PSTD-related symptoms in the RBD + NT group, compared to no clinically meaningful scores in the RBD group.

No significant association was found with either the *APOE* genotype ($p = 0.561$) or *MAPT* haplotype ($p = 0.785$) genetic profile comparing the RBD + NT and RBD groups. This was further explored as additional predictor variables in multiple logistic regression models describing our primary outcomes within each neurologic domain and no effect from either *APOE* genotype or *MAPT* haplotype was observed.

RBD characteristics and sleep disturbances

Table 2. There was a significantly earlier age of self-reported RBD symptom onset in the RBD + NT compared to RBD group (37.5 ± 11.9 vs. 52.2 ± 15.1 years of age, $p < 0.0001$). Additionally,

Table 2. RBD Behavior and Sleep Disorders

	RBD; *n* = 96	RBD + NT; *n* = 24
RBD history		
Earliest age of onset, *years*	52.2 ± 15.1	37.5 ± 11.9*
RBD behavior: injured self, *ever*	40.6%	75.0%
RBD behavior: injured self, *past 6 mo*	18.8%	50.0%*
RBD behavior: injured bed partner, *ever*	35.4%	79.2%*
Other sleep disorders		
Obstructive sleep apnea	50.0%	75.0%*
Central sleep apnea	3.1%	4.2%
Restless legs syndrome	14.6%	29.2%
Insomnia	15.6%	50.0%*
Periodic limb movements	9.4%	8.3%
Sleep questionnaires		
SCOPA-Sleep, *score*	10.6 ± 5.9	21.1 ± 9.6*
Epworth Sleepiness Scale, *score*	5.6 ± 4.1	8.7 ± 6.2*

Data are presented as mean ± standard deviation, or % of total. SCOPA, Scales for Outcomes in Parkinson's disease. * = $p < 0.05$ versus RBD.

the RBD + NT group demonstrated characteristics consistent with more severe RBD symptoms. For example, the RBD + NT group reported a higher rate of regularly occurring RBD behavior despite medication usage, a higher rate of self-inflicted injury related to their RBD behavior in the last 6 months (50.0% vs. 18.8%, $p = 0.0081$), and a higher rate of having injured their bed partner as a result of their RBD behavior (79.2% vs. 35.4%, $p = 0.0002$).

Other sleep disorders were also more common in the RBD + NT group, including higher rates of obstructive sleep apnea (75.0% vs. 50.0%, $p = 0.0382$), and higher rates of insomnia (50.0% vs. 15.6%, $p = 0.0101$). Lastly, the RBD + NT group also self-reported greater sleep impairment and daytime sleepiness via higher SCOPA-sleep scores (21.1 ± 9.6 vs. 10.6 ± 5.9, $p < 0.0001$), and higher Epworth Sleepiness Scale scores (8.7 ± 6.2 vs. 5.6 ± 4.1, $p = 0.0038$).

Neurologic function

Table 3. There were many observed cognitive, motor, and sensory differences between the RBD + NT and the RBD group. With respect to cognition, the RBD + NT group exhibited lower MoCA scores (24.6 ± 3.5, 54% abnormal vs. 26.4 ± 4.9, 33% abnormal); however, this effect was obscured post-adjustment via multiple logistic regression (adjusted $p = 0.068$, $\beta = 0.88$, 95% CI = 0.76 to 1.01), potentially driven by the presence of hypertension ($p = 0.01$, $\beta = 0.26$, 95% CI = 0.09 to 0.71). In contrast, lower scores on the Craft Story immediate (13.0 ± 6.3 vs. 18.8 ± 6.5) did persist post-adjustment via multiple logistic regression (adjusted $p = 0.0007$, $\beta = 0.85$, 95% CI = 0.76 to 0.92) with the only other significant predictor being OSA status ($p = 0.023$, $\beta = 0.26$, 95% CI = 0.07 to 0.78). Additional cognitive relevant outcomes where the RBD + NT group performed worse were the Craft Story Delay (10.6 ± 4.0 vs. 13 ± 5.5, $p = 0.0269$), the Number Span Test Backward (5.9 ± 2.6 vs. 7.1 ± 2.6, $p = 0.0409$), and the TMT A (46.3 ± 28.0 vs. 34.1 ± 14.3, $p = 0.0029$) and TMT B (107.7 ± 64.9 vs. 82.1 ± 42.3, $p = 0.0104$). Additionally, the RBD + NT group scored lower on the categorical and phonetic verbal fluency subtests, F words (11.3 ± 4.7 vs.

Table 3. Cognition, Motor, Autonomic, and Sensory Function

	RBD; *n* = 96	RBD + NT; *n* = 24
Cognition		
Montreal cognitive assessment	26.4 ± 4.9 (33%)	24.6 ± 3.5* (54%)
Craft story 21		
Immediate recall	18.8 ± 6.5	13.0 ± 6.3*
Delay recall	13.3 ± 5.5	10.6 ± 4.0*
Benson complex figure copy		
Immediate	15.6 ± 2.6	15.9 ± 1.4
Delay	11.6 ± 3.9	10.8 ± 2.9
Number span		
Total forward	8.4 ± 2.6	7.9 ± 2.6
Total backward	7.1 ± 2.6	5.9 ± 2.6*
TMT A, *seconds*	34.1 ± 14.3	46.3 ± 28.0*
TMT B, *seconds*	82.1 ± 42.3	107.7 ± 64.9*
Multilingual naming test uncued	26.4 ± 4.9	24.3 ± 3.5
Phonemic/categorical verbal fluency		
F words	13.6 ± 5.1	11.3 ± 4.7*
L words	12.6 ± 5.5	11.5 ± 5.0
Animals	20.8 ± 5.5	18.2 ± 5.1*
Vegetables	14.2 ± 4.5	12.3 ± 3.6*
Motor		
MDS-UPDRS part 3, *score*	4.3 ± 2.4 (26%)	9.1 ± 1.9* (58%)
Purdue pegboard, *dominant hand*	11.2 ± 2.5 (11%)	10.4 ± 2.8 (17%)
Alternate tap test, *dominant hand*	179.0 ± 44.4 (34%)	139.2 ± 39.7* (80%)
Timed up and go, *seconds*	8.6 ± 2.9 (6%)	11.0 ± 4.9* (21%)
Autonomic		
Supine SBP/DBP, *mm Hg*	134.6 ± 18.5/79.2 ± 10.1	141.7 ± 16.1/81.3 ± 10.7
Standing SBP/DBP, *mm Hg*	126.0 ± 17.7/79.8 ± 10.0	141.6 ± 12.8*/89.3 ± 16.8*
ΔSBP/ΔDBP, *mm Hg*	-8.8 ± 15.6/0.5 ± 8.5	0.1 ± 16.2*/8.0 ± 13.1
Supine heart rate, *bpm*	63.0 ± 9.7	66.1 ± 9.4
3 min standing heart rate, *bpm*	73.7 ± 11.6	77.5 ± 12.2
ΔHR, *bpm*	10.5 ± 7.7	11.4 ± 7.6
ΔHR/ΔSBP	2.47 ± 3.63	2.32 ± 4.52
Supine hypertension	30%	56%*
SCOPA-AUT, *total raw score*	11.8 ± 6.8 (59%)	25.4 ± 9.0* (100%)
Gastrointestinal, *subscale*	10.6 ± 12.0	33.7 ± 15.8*
Bowel, *subscale*	18.0 ± 16.5	31.0 ± 19.4*
Urinary, *subscale*	27.8 ± 17.3	42.6 ± 24.8*
Cardiovascular, *subscale*	6.1 ± 10.6	26.9 ± 20.2*
Thermoregulatory, *subscale*	10.8 ± 12.4	37.2 ± 21.1*
Visual, *subscale*	13.5 ± 24.0	52.8 ± 36.7*
Sexual, *subscale*	27.3 ± 31.2	40.3 ± 38.0
Urinary incontinence, *%*	12.5%	26.1%*
Bowel incontinence, *%*	3.1%	4.4%
Sensory		
Farnsworth-munsell color vision test	132.9 ± 76.2 (60%)	184.5 ± 133.8* (63%)
Brief smell identification test	7.1 ± 6.8 (66%)	7.5 ± 3.0 (58%)

Data are presented as mean ± standard deviation. SBP, systolic blood pressure; DBP, diastolic blood pressure; TMT, Trail Making Test; HR, heart rate; bpm, beats per minute. If applicable, the % of each group meeting clinical criteria for abnormal scores is reported in parentheses. Criteria for abnormality: Montreal Cognitive Assessment, ≤25; Movement Disorders Society Uniform Parkinson's Disease Rating Scale (MDS-UPDRS) part 3, >4; Purdue Pegboard, <9; Alternate Tap Test, <165; Timed Up and Go, ≥13.5 seconds; Farnsworth-Munsell Color Vision Test, >100; Brief Smell Identification Test, ≤8. SCOPA-AUT, Scales for Outcomes in Parkinson's disease-autonomic function, ≥13 (subscales normalized). * = $p < 0.05$ vs. RBD with respect to average score when % abnormal is also present.

13.6 ± 5.1, $p = 0.0351$), animals (18.2 ± 5.1 vs. 20.8 ± 5.5, $p = 0.0255$) and vegetables (12.3 ± 3.6 vs. 14.2 ± 4.5, $p = 0.0427$) compared to the RBD group.

Overall motor function was also worse in the RBD + NT group, with higher MDS-UPDRS part 3 scores (9.1 ± 1.9, 58% abnormal vs. 4.3 ± 2.4, 26% abnormal, adjusted $p = 0.0112$, $\beta = 1.11$, 95% CI = 1.03 to 1.22), with other significant predictors being age ($p = 0.028$, $\beta = 1.11$, 95% CI = 0.89 to 0.99) and hypertension ($p = 0.011$, $\beta = 0.22$, 95% CI = 0.06 to 0.69). Additional motor-relevant outcomes where the RBD + NT group performed worse were the Alternate Tap Test with their dominant hand (139.2 ± 39.7, 80% abnormal vs. 179.0 ± 44.4, 34% abnormal, $p < 0.0001$), and timed up and go scores (11.0 ± 4.9, 21% abnormal, vs. 8.6 ± 2.9, 6% abnormal, $p = 0.0020$) compared to the RBD group. The only motor assessment that was not significantly different between groups with the Purdue Pegboard test.

The objective assessment of autonomic cardiovascular parameters revealed comparable function across the RBD + NT and RBD groups. For example, SBP and DBP were both maintained after 3 minutes of standing in both the RBD + NT and RBD groups. Standing SBP and DBP were higher in the RBD + NT group (141.6 ± 12.8, $p < 0.0001$ and 89.3 ± 16.8, $p = 0.0006$, respectively) compared to RBD (126.0 ± 17.7 and 79.8 ± 10.0, respectively), potentially consistent with their greater rate of hypertension. Toward this point, the RBD + NT group showed a higher rate of supine hypertension (56% vs. 30%) compared to the RBD group. The relative lack of objective differences in cardiovascular autonomic function contrasted with a consistently greater degree of self-reported autonomic dysfunction in the RBD + NT group. SCOPA-AUT scores, reflecting global autonomic dysfunction, were higher in the RBD + NT (25.4 ± 9.0, 100% abnormal vs. 11.8 ± 6.8, 59% abnormal, adjusted $p < 0.0001$, $\beta = 1.25$, 95% CI = 1.15-1.39). compared to RBD group. Furthermore, 6 of the 7 subscores of the SCOPA-AUT, reflecting system-specific autonomic dysfunction, were significantly worse in the RBD + NT group. Specifically, there was greater gastrointestinal (33.7 ± 15.8 vs. 10.6 ± 12.0, $p < 0.0001$), bowel (31.0 ± 19.4 vs. 18.0 ± 16.5, $p = 0.0012$), urinary (42.6 ± 24.8 vs. 27.8 ± 17.3, $p = 0.0011$), cardiovascular (26.9 ± 20.2 vs. 6.1 ± 10.6, $p < 0.0001$), thermoregulatory (37.2 ± 21.1 vs. 10.8 ± 12.4, $p < 0.0001$), and visual (52.8 ± 36.7 vs. 13.5 ± 24.0, $p < 0.0001$) autonomic dysfunction in RBD + NT (scores normalized for each subscale). Furthermore, the frequency of self-reported urinary incontinence in the RBD + NT group was higher than in the RBD group (26.1% vs. 12.5%, respectively).

In contrast, olfaction and color vision were largely unchanged between groups. Although the RBD + NT group had worse Farnsworth-Munsell Color Vision Test (FM-100) scores (184.5 ± 133.8, 63% abnormal, adjusted $p = 0.0281$, $\beta = 1.01$, 95% CI = 1.00 to 1.02) compared to RBD (132.9 ± 76.2, 60% abnormal) there was no difference in proportion of participants scoring in the abnormal range.

Discussion

In this retrospective, cross-sectional, case–control study within the NAPS Consortium (1:4 case:control ratio—matched for sex, age, and years of education; both ± 2 years), participants with RBD + NT ("cases") compared to RBD (i.e. "controls") showed a significantly earlier onset of RBD symptoms, increased RBD symptom severity, worsened general health (e.g. increased rate of hypertension), and generally worsened neurological function across cognitive, motor, and subjective autonomic domains with no influence by *APOE* genotype or *MAPT* haplotype genetic profiles. Although confirmatory longitudinal studies are still ongoing, results suggest RBD + NT may be associated with a more advanced state of neurological symptoms related to an evolving neurodegenerative-related process. Following these same participants over time will be critical to establish whether this increased neurological impacts in RBD + NT is a harbinger of phenoconversion to an overt synucleinopathy or related neurodegenerative condition.

Traditionally, individuals with an earlier age of RBD onset (e.g. <50 years of age) are often considered at reduced risk for phenoconversion compared to typical (e.g. >50 years of age) RBD. However, this is based primarily on existing longitudinal data that, by default, included only individuals > 50 years of age (cf., Galbiati et al. [6]) who more commonly presented with RBD. Thus, little is known about the potential risk factors and the neuropathologic progression toward phenoconversion in those with early RBD symptom onset. Nevertheless, there is recognition that substantial variability in the duration of this prodromal period exists. Claasen et al., reported a case series of 27 patients who experienced isolated RBD for at least 15 years before phenoconversion, showing a median interval of 25 years between RBD symptom presentation and neurologic onset [54]. Although the median age for RBD symptom presentation was 49 years, there were 15 (56%) individuals who were 50 years of age or younger. In the present study, participants in the RBD + NT group were effectively ~23 years post-RBD symptom onset, whereas the RBD group was only ~8 years post-RBD symptom onset. The fact that the RBD + NT group has had RBD for a significantly longer duration of time than the RBD alone group could indicate fundamental differences in pathogenesis. While at face value, it appears that the RBD + NT group had greater neurological impairment compared to age-matched RBD, it is also possible that these individuals had greater resilience to phenoconversion, since they have not yet phenoconverted. Another possibility is that NT potentially unmasked a preexisting vulnerability to RBD in a subset of individuals with preexisting risk for synucleinopathy—a similar, but yet unproven, argument has also been made for antidepressant-associated RBD [55–58].

An alternative explanation to participants with NT presenting with a more advanced neuropathologic state could be that this observation is purely correlational. Indeed, TBI and/or PTSD are independently known to negatively impact general health, as well as cognition, motor, autonomic, and sensory function [25, 26, 59–61]. Similarly, mood (specifically, depression, and anxiety) has also been shown to be associated with generally worse neurologic function on cognitive, motor, and autonomic testing. Including these variables (i.e. both BAI and PHQ-9 score) in our multiple logistic regression models that adjusted key outcome variables for age, hypertension, and OSA status was not possible due to the inclusion of these outcomes resulting in perfect separation. Adjusting for PHQ-9 or BAI individually did obscure significant differences in cognitive outcomes (i.e. MoCA and Craft Story) but did not impact motor (i.e. MDS-UPDRS III and Alternate Tap Test) or autonomic function (i.e. SCOPA-AUT scores).

It is also possible that TBI and/or PTSD in the context of worse neurologic function is being driven by non-synuclein-related neurodegeneration (e.g. tau, TDP-43), and/or generalized neuroinflammation, alone or in combination with each other. If the underlying explanation for RBD + NT participants demonstrating worse neurologic function is indeed due to neurodegeneration, then it remains likely to be a synuclein-specific process in light of

the very strong association between RBD and synucleinopathies. However, without synuclein-specific biomarkers (e.g. plasma/skin biopsies, genetic synuclein risk data), or longitudinal data, this issue will remain equivocal in the present analyses. Other biomarkers of general health and injury, including other biomarkers of neurodegeneration (e.g. neurofilament light chain) may help to distinguish general decline of function from a synuclein-, tau- or other neurodegenerative-specific process. Additional work interrogating the relationship between TBI/PTSD and risk for the future development of RBD and neurodegeneration is needed.

It could be interpreted that participants with NT in this study would be categorized as having TASD, rather than RBD. TASD has recently been proposed as a distinct nosological entity but has not yet been formally acknowledged by the International Classification of Sleep Disorders [12, 13, 62]. Proposed clinical criteria to distinguish TASD from RBD include (1) a history of dream mentation related to a specific prior inciting traumatic experience, and (2) evidence of autonomic hyperarousal (i.e. tachycardia or tachypnea) not due to sleep-disordered breathing during periods of RSWA [12, 13]. There is no biological or scientific basis yet to believe that TASD and RBD are mutually exclusive categories; thus, in this study, the most parsimonious diagnosis of RBD was assumed (e.g. participants met AASM-specified diagnostic criteria for RBD). Regardless of whether NT participants would be categorized as TASD versus RBD, this group presented with worse neurodegenerative-relevant function compared to the non-NT (i.e. RBD only) group. This finding effectively leapfrogs the ongoing clinical debate between TASD versus RBD, and provides a compelling argument that further longitudinal examination of the RBD + NT cohort is warranted. Nevertheless, distinguishing whether the neuropathologic mechanism underpinning RBD with/without comorbid TBI/PTSD is different remains a high priority and will ultimately resolve this debate.

Finally, it is critical to interpret these data and discuss them in the appropriate context. Central to this analysis is the presence–absence of neurotrauma, defined herein as a history of TBI and PTSD. Although PTSD was provisionally diagnosed according to PCL-5 scores (see Materials and Methods), TBI status was limited to a single yes/no question collected via self-report. There are several different approaches to capturing participant TBI history, including structured clinical interviews, medical record review, etc. each of which comes with their own pros and cons. Based on prior work from our group [52], self-reported TBI likely underestimates the actual frequency but does not systematically over-predict the presence of TBI. Thus, although additional confirmatory measures of TBI status would strengthen this analysis, our prior data would suggest the presence of TBI in RBD + NT participants is accurate, with the main question mark being whether or not there were TBI-positive participants unknowingly included in the control population.

Several remaining questions will require further investigation. For example, not all NT-exposed individuals become symptomatic with respect to sleep, cognition, mood disturbances, and the plethora of other associated sequela. It remains unknown whether manifesting symptoms is indicative of unmasking a baseline altered/accelerated prodromal state. Additionally, regardless of NT exposure, not all individuals with RSWA show dream enactment, and vice versa. Despite these individuals only having isolated RSWA and therefore not meeting clinical criteria for RBD, their long-term neuropathological progression remains unknown. Finally, it remains possible that genetic risk factors or environmental exposures could influence the neuropathological trajectory in NT-exposed individuals, with or without RBD—outside of *APOE* genotype and *MAPT* haplotype profiles, these risk factors were not addressed in the present study.

Although these data stem from a large multi-center (and multi-national) research effort with rigorous standardized procedures, there still remain a number of limitations that should be acknowledged. The sample of NT-exposed individuals included 24 participants, spanning five of the nine research sites (Portland VA, Washington University in St. Louis, University of California Los Angeles, Emory, and McGill University) with the majority being from the Portland VA (16/24). Sub-analyses on key outcome variables did not show differences when comparing participants from the Portland VA to the other four sites (data not shown); nevertheless, site-related biases cannot be completely excluded. There were no non-RBD control participants in the NAPS registry baseline study, although controls will be enrolled during the longitudinal phase of the study (i.e. NAPS2, which began in 2021; NIH U19 AG071754), and the longitudinal portion will include more extensive and specific outcomes related to synucleinopathy impacts, e.g. quantitative Dopamine transporter scans, magnetic resonance imaging, synuclein amplification assays, and other emerging synucleinopathy biomarkers.

Conclusions

The present cross-sectional prospective study reports a case:-control analysis of participants with RBD and a history of TBI/PTSD (cases, $n = 24$; RBD + NT), compared to individuals with RBD only (controls, $n = 96$; RBD). In this case:control analysis followed a 1:4 ratio, matching based on sex, age, and years of education (both ± 2 years) in a standardized sequential fashion. The results show that the RBD + NT group reported a significantly earlier age of RBD symptom onset, and demonstrated significantly worse neurodegenerative-relevant function across cognitive, motor, autonomic, psychiatric, and sleep domains, potentially. These data suggest that individuals with RBD + NT may be fundamentally different from RBD without NT, and could be consistent with a phenotype of either advanced neurological progression or functional resilience with a protracted prodromal phase. Longitudinal follow-up studies, currently underway via NAPS2, are warranted to definitively examine potential differences in rates of phenoconversion and neuropathologic progression in RBD + NT.

Acknowledgments

The authors would like to express their sincere appreciation and gratitude for the participation of our research participants, and to the entire NAPS consortium. Financial support from NIH grants R34 AG056639, U19 AG071754, P50 AG016574, P30 AG062677; VA RRD 1K2 RX002947; and Canadian support via Research Chair in Cognitive Decline in Pathological Aging. Dr. Lim takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; has full access to all the data; and has the right to publish all data separate and apart from any sponsor.

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Disclosure Statements

Financial disclosure: None. *Nonfinancial disclosure:* The interpretations and conclusions expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs, the National Institute of Health, or the United States government.

Author Contribution

(1) Conception and design of the study. JEE, MML. (2) Acquisition and analysis of data. JEE, BRL, MDBE, ATK, KLMP, CO, LN, RBP, AP, JFG, ZG, EY, LL, EKSL, LKF, JAF, OAR, DEH, DLB, AYA, MJH, CHS, JM, SRC, AV, EHD, MGM, DRS, JKLI, BFB, YSJ, MML. (3) Drafting a significant portion of the manuscript or figures (i.e., a substantial contribution beyond copy editing and approval of the final draft, which is expected of all authors). JEE, MML.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author once institutional data use and/or other relevant consortium and institutional agreements have been approved.

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