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Original Article

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Sleep quality and efficiency in adults with post-acute sequelae of COVID-19

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Abstract

Study Objectives: Sleep disruptions are associated with adverse mental and physical health outcomes. Individuals with post-acute sequelae of COVID-19 (PASC) commonly report worsened sleep. This study examined sleep quality and efficiency and their associations with neuropsychiatric symptoms and fatigue in non-hospitalized individuals with PASC.
Methods: Sixty-one participants (73.8 percent female; $\bar{x}_{age} = 45.4$) who reported being infected with COVID-19 ≥ 2 months before enrollment, non-hospitalized, and experiencing ≥3 symptoms since infection were eligible. The Pittsburgh Sleep Quality Index was used to measure self-reported sleep quality, and the Fitbit Charge-4 to assess sleep efficiency. Participants completed the Beck Anxiety Index, Beck Depression Index, Post-Traumatic Stress Disorder-Checklist Civilian Version, and the Fatigue Severity Scale. We conducted multivariable linear regressions to examine associations controlling for age, sex, time since first COVID-19 infection, pre-COVID sleep disorders, and sleep aids.
Results: Pittsburgh Sleep Quality Index scores were not associated with objective sleep efficiency. Nearly 97 percent of PASC participants reported poor sleep quality, 85 percent indicated that sleep difficulties interfered with their daily functioning, and 93.9 percent achieved optimal sleep efficiency. Higher Beck Depression Index scores were linked to worse sleep quality, while Beck Anxiety Index, Post-Traumatic Stress Disorder-Checklist Civilian Version, and Fatigue Severity Scale scores were not. However, Beck Anxiety Index and Fatigue Severity Scale scores were related to distinct Pittsburgh Sleep Quality Index components. None were associated with sleep efficiency.
Conclusion: Individuals with PASC experience significant sleep difficulties impacting daily functioning. Although they showed adequate sleep efficiency, most participants perceived their sleep as inefficient, which correlated with worse depressive symptoms. Therefore, sleep is a modifiable factor that could enhance the quality of life for patients with PASC.

Key words: long-COVID; anxiety; depression; behavioral sleep medicine; SARS-CoV-2; mood

Statement of Significance

Millions of people worldwide experience post-acute sequelae of COVID-19 (PASC), with most reporting worsened sleep post-infection. However, sleep patterns, both subjective and objective, in non-hospitalized individuals who had mild-to-moderate COVID-19 symptoms remain underexplored despite representing a significant PASC subgroup. This study examined self-reported sleep quality, objective sleep efficiency, and their associations with fatigue and neuropsychiatric symptoms in young-to-middle-aged adults with PASC. Objective measurements showed adequate sleep efficiency, yet many participants felt their sleep was inefficient and significantly interfered with daily activities. This perceived poor quality was associated with higher depression symptoms. Findings highlight the need to assess sleep in PASC to develop effective interventions. Addressing sleep, a modifiable factor, could improve the quality of life for millions of individuals.

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Introduction

Over 775 million cases of SARS-CoV-2 have been reported globally, with more than 10 percent of those infected experiencing post-acute sequelae of COVID-19 (PASC), commonly referred to as long-COVID, representing a significant clinical and public health challenge [1–5]. PASC is defined as new, ongoing, or relapsing symptoms persisting for over 30 days after the initial infection [2]. These symptoms are often disabling and severely impact people's quality of life and ability to work [2]. Sleep disturbances are among the most frequently reported symptoms in the PASC, with nearly 70 percent of people reporting new onset or worsening insomnia, sleep-disordered breathing, parasomnias, or circadian rhythm sleep–wake disorders after COVID-19 infection [5, 6]. The PASC has also been linked to changes in sleep architecture, including reduced REM sleep, potentially due to the persistent inflammation characteristic of the PASC [6, 7]. These changes in sleep raise significant health concerns, as disrupted sleep is associated with increased risk for chronic illnesses such as cardiovascular disease and diabetes, compromised immune function, and cognitive difficulties [8, 9].

Disrupted sleep is also closely tied to mood disturbances, including a higher risk of depression and anxiety, which are also highly prevalent in the PASC [8, 10–14]. Individuals with mood or anxiety disorders frequently experience altered sleep patterns, such as hypersomnia, insomnia, delayed sleep onset, or fragmented sleep [9, 15]. Sleep-related issues like nightmares and difficulties with sleep initiation and maintenance are also core symptoms of post-traumatic stress disorder (PTSD) [16, 17]. A single-center study of individuals with PASC found a significant association between self-reported reduced sleep quality and greater severity of depression, anxiety, and PTSD among patients referred to a post-COVID-19 recovery clinic after hospital discharge or from the community [18]. However, much of the current research focuses on individuals with severe COVID-19 or those hospitalized, leaving a gap in understanding how non-hospitalized individuals—who represent a substantial portion of PASC cases—experience these symptoms [19]. Investigating sleep and neuropsychiatric symptoms among non-hospitalized individuals with PASC is critical, as these symptoms can severely affect daily functioning, mental health, and overall quality of life.

Sleep encompasses both subjective (i.e. sleep quality) and objective aspects (i.e. sleep efficiency). Sleep quality is an individual's perception of how restful and satisfying their sleep is [20, 21]. It covers factors like self-reported sleep efficiency, sleep latency (the time it takes to fall asleep), sleep duration, and wakefulness after sleep onset [20, 21]. In contrast, sleep efficiency can be objectively measured and reflects the proportion of time spent asleep relative to the total time spent in bed [22, 23]. This metric, often assessed through polysomnography, actigraphy, or wearable devices, reflects how effectively one's time in bed is used for actual sleep, with 85 percent or higher generally considered efficient [21, 22, 24]. Interestingly, studies indicate that self-reported sleep quality doesn't always align with objectively measured sleep efficiency [25–27]. For instance, individuals might feel their sleep is poor even when objectively it's adequate, or vice versa. Further, sleep quality and efficiency are often distinctly associated with health outcomes. For instance, poor sleep quality has been linked to mood symptoms like depression and anxiety, while low sleep efficiency has been more closely tied to physical health issues such as cardiovascular and metabolic conditions [28, 29]. By investigating both subjective and objective aspects of sleep, researchers will be able to identify targeted interventions to improve the quality of life for people with PASC. While it is largely recognized that people with PASC endorse significant sleep changes since before infection, less is known about subjective and objective sleep quality and efficiency in young- and middle-aged adults, who are disproportionally affected by PASC.

This study aimed to assess both self-reported sleep quality and objectively measured sleep efficiency, alongside their impact on daily functioning and association with mood symptoms, in young-to-middle-aged non-hospitalized adults with PASC. We hypothesized that most participants with PASC would report poor self-reported sleep quality compared to healthy controls and show reduced objective sleep efficiency, that these sleep issues would interfere with daily activities, and that worse sleep would be associated with higher symptom severity for depression, anxiety, and PTSD.

Materials and Methods

Participants

Participants were enrolled in an investigator-initiated clinical trial titled "Randomized, placebo-controlled parallel group clinical trial of nicotinamide riboside to evaluate NAD+ levels in individuals with persistent cognitive and physical symptoms after COVID-19 illness" (NCT04809974) or a cross-sectional study that required a single visit. The study was conducted at the Massachusetts General Hospital. Baseline data from this clinical trial and from the cross-sectional studies were used to address the aims of this study. Participants with PASC met the following criteria to be eligible for the study: (1) History of PCR+ SARS-CoV-2 infection at least 2 months before study entry and PCR/antigen test- at study entry; (2) Report currently experiencing "brain fog" and at least 2 other symptoms caused by SARS-CoV-2 infection (e.g. anosmia, headaches); (3) Was not intubated or in the intensive care unit during infection; (4) Ages 18–65 years; (5) Able to read and write in English or Spanish; (6) No diagnosis of a neurocognitive disorder prior to SARS-CoV-2 infection; (7) No history of neurodegenerative disease; (8) No unstable psychiatric disorder (i.e. current suicidal ideation, history of suicide attempt, or psychotic episode in <2 years); (9) No history of alcohol or other substance abuse or dependence within <2 years; and (10) >18 on the Mini-Mental State Examination. Participants who met the following criteria were ineligible for the study: (1) Clinically significant unstable medical condition; (2) History of neuroimaging with evidence of major infarction, injury, infection, or other focal lesions that may be related to cognitive dysfunction; (3) Significant systemic illness that could affect safety or study compliance; (4) Laboratory abnormalities that may contribute to cognitive dysfunction (i.e. Vitamin B12, Thyroid Stimulating Hormone, or hematologic, hepatic or renal function tests); (5) Current use of medications with psychoactive properties that in the opinion of the principal investigator, may deleteriously affect cognition; (6) Known hypersensitivity to nicotinamide riboside, or its principal metabolite, nicotinamide mononucleotide; (7) Consumption of dietary supplements containing more than 100 mg of niacin, nicotinamide riboside, or nicotinamide mononucleotide as the primary agents 30 days prior to baseline and for the duration of the trial; (8) Use of other investigational agents or interventions one month prior to entry and for the duration of the trial; and (9) Pregnant women or women who were planning to become pregnant within 7 months from study entry. Individuals in the healthy control group met the same criteria as those in the PASC group, except that they did not experience residual COVID-19 symptoms (i.e. fully recovered).

Participants were recruited through Rally, an online research recruitment platform developed by Mass General Brigham, flyers, clinicaltrials.gov, physician referrals and from the community. Individuals who expressed interest were first screened by phone. Those who met the eligibility criteria at this stage were scheduled for the screening visit based on the person's availability. These individuals then completed an in-person screening assessment. Participants who met all the eligibility criteria at the screening visit were scheduled for a baseline visit. Recruitment primarily targeted individuals in Boston and surrounding areas in Massachusetts. However, people from other states were also eligible if they could attend the in-person assessments in Boston.

All study procedures included in this study were approved by the Institutional Review Board of the Mass General Brigham. All participants provided written informed consent before participating in any procedures.

Clinical assessments

Medical history. A comprehensive medical history was obtained by a licensed clinician from the study team. Participants were inquired about comorbidities diagnosed before SARS-CoV-2 infection, including any sleep-related diagnosed condition or complaint such as insomnia, obstructive sleep apnea, and hypersomnia. They were also asked about their vaccination status. Fully vaccinated individuals were defined as those who had received either two doses of the Moderna or Pfizer vaccine or one dose of the J&J vaccine, considering the moment during the pandemic when this happened. This interview also involved detailed questions about medication usage accounting for over-the-counter medications and herbal supplements.

Sleep symptom severity and interference with daily activities. Participants rated the severity of PASC symptoms using a self-administered questionnaire. They were asked to indicate whether they had experienced any of the 24 symptoms listed in the past 2 weeks, including shortness of breath, fatigue, muscle aches, altered smell/taste, headaches, hair loss, rash, discoloration of fingers, dizziness, nausea, neuropathy, cough, sore throat, loss of appetite, abdominal pain, chest pain, constipation, loose stools, brain fog, insomnia, sleeping more than usual, changes in vision, tachycardia, and feeling hot or cold, or other. Specifically, participants were asked to rate the severity of the symptom on a five-point scale based on the past 2 weeks: 1 = no, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe. They were then asked to rate the frequency with which the symptom interfered with their daily activities on a four-point scale: 1 = never, 2 = sometimes, 3 = often, 4 = very often. Here, we report the severity and the frequency with which each sleep-related symptom (i.e. insomnia, sleeping more than usual, or hypersomnia) interfered with the person's daily activities. Participants in the non-PASC group did not complete this questionnaire.

Beck Anxiety Inventory. Symptoms of anxiety were measured using the Beck Anxiety Inventory (BAI), a 21-item self-report questionnaire that has been validated in this age group [30]. Participants were instructed to indicate how much they have been bothered by the symptoms during the past month, including today. Each item was scored on a scale of 0–3. A score of 0–7 indicates minimal anxiety, 8–15 mild, 16-25 moderate, or 26–63 severe anxiety [30].

Beck Depression Inventory. Symptoms of depression were measured using the Beck Depression Inventory (BDI), a 21-item self-report questionnaire [31]. Participants were instructed to indicate the statement that best described how they had been feeling in the past week, including today. Each item was scored on a scale of 0–3. Scores between 0–13 indicate minimal symptoms of depression, 14–19 mild symptoms, 20–28 moderate symptoms, and >29 severe symptoms [31].

Post-Traumatic Stress Disorder-Checklist Civilian Version. Symptoms of Post-Traumatic Stress Disorder (PTSD) were measured using the Post-Traumatic Stress Disorder-Checklist Civilian Version (PCL-C). The PCL-C is comprised of 17 items, with each item being scored on a scale of 1–5. Total scores range from 17 to 85, and scores above 44 are considered indicative of possible PTSD [32].

Fatigue Severity Scale. The Fatigue Severity Scale is a 9-item self-report questionnaire that assesses the severity and impact of fatigue on daily functioning over the past week. Participants are asked to rate each item on a 7-point Likert scale, ranging from 1 (no fatigue or impact) to 7 (severe fatigue with significant impact). Higher scores indicate more severe fatigue. The maximum score is a seven. A score of six or seven reflects severe, debilitating fatigue that significantly impairs daily functioning [33].

Pittsburgh Sleep Quality Index. The Pittsburgh Sleep Quality Index (PSQI) is a self-report questionnaire that measures self-reported sleep quality during the past month [20]. The PSQI generates seven component scores that include self-reported sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A higher score denotes greater sleep difficulties. The scores for each component were added to yield a global score that represents overall sleep quality. The total score ranges from 0 to 14, and a global score ≥5 indicates poor sleep quality [20].

Wearable activity tracker. The Fitbit Charge 4, a wearable technology that assesses sleep–wake patterns, was used to measure sleep efficiency [34–36]. Fitbits calculate sleep efficiency by tracking movement and heart rate to identify different sleep stages and moments of wakefulness. Only participants with PASC wore the Fitbit, as it was part of the clinical trial design and not the cross-sectional studies that the healthy control group completed. Participants began using the Fitbit 2 weeks prior to completing the PSQI, resulting in an overlap between the Fitbit data and the last 2-week period referenced in the PSQI. Participants were instructed to wear the Fitbit for 14 consecutive days and to engage in activities as usual. They were also asked to remove it only when showering or when charging it while they engaged in a sedentary activity such as reading or watching TV. Sleep efficiency was calculated by dividing the total time asleep by the total time in bed in minutes and multiplying the ratio by 100 to obtain a percent [23]. We averaged the sleep efficiency data obtained over any 5 consecutive days of valid nighttime data on each participant since most participants were missing data for 14 consecutive days. Fitbits were distributed on the same visit in which the PSQI was administered. In addition, we first conducted all analyses with those who had sleep data from at least seven consecutive days ($n = 40$) and compared it to results from 5 days. The results were not different. As such, we only report data for 5 days since the sample size was larger. A percentage of 85 or higher was considered to indicate good sleep efficiency [22, 23]. Participants without at least 5 consecutive days of valid nighttime data were excluded from the analysis. Valid nighttime data were defined as data recorded during start and end times that correspond to a full night's sleep, consistent with typical circadian rhythms. We excluded any short lapses of sleep recorded outside these hours, whether they occurred during nighttime or daytime, to focus exclusively on coherent nighttime sleep patterns. Total time asleep in minutes, total time in bed in minutes, and total time of REM sleep were also evaluated.

Statistical analyses

Descriptive statistics were calculated for sociodemographic characteristics, sleep-related medical history (i.e. insomnia, hypersomnia, obstructive sleep apnea), sleep efficiency percentage, sleep-related symptom severity and interference with daily activities, and PSQI, BAI, BDI, and PCL-C scores. PASC symptom duration was determined by calculating the number of days between acute infection and study enrollment. Group differences in demographic variables were measured using two-tailed independent sample *t*-tests for continuous variables and chi-square tests for categorical variables. Effect sizes were estimated using Cohen's *d*.

Pearson correlation coefficients were calculated to measure the relationship between self-reported sleep quality and sleep efficiency measured with Fitbit. Medications and supplements used to improve sleep quality or treat sleep disturbances were included in this analysis. Reported sleep aids included serotonin receptor antagonists and reuptake inhibitors, antihistamines, sedative-hypnotics, benzodiazepines, and supplements such as melatonin, magnesium, and medical cannabis. We created a dichotomous variable with all individuals taking sleep aids categorized in one group and those who do not take sleep aids in another.

Analysis of covariance was conducted to measure differences between PASC and healthy control groups in the PSQI seven components and global scores controlling for age, sex, time since infection, and use of medications and supplements for sleep. Multivariable linear regression models were conducted to estimate beta coefficients (β) to examine associations between the PSQI global score and sleep efficiency percent as measured with the Fitbit with the BAI, BDI, and PCL-C total scores controlling for age, sex, time since infection, diagnosis of a sleep disorder, use of any sleep aid. An analogous analysis was also conducted to examine associations between total minutes asleep, total minutes in bed, and total minutes of REM sleep measured with the Fitbit with the BAI, BDI, and PCL-C total scores controlling for the previously mentioned confounders. Additionally, a sub-analysis examined fatigue severity as a predictor of sleep quality and sleep efficiency, and each PSQI component scores using multivariable linear regression models, adjusting for the previously listed confounders.

A *p*-value of <.05 was deemed statistically significant for all analyses. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC). Visualizations were conducted using GraphPad Prism 10.0.2 for Mac OS X, Boston, MA, United States.

Results

Participants characteristics

A total of 61 individuals with PASC and 28 healthy controls participated in the study. Their sociodemographic characteristics are summarized in Table 1. Participants with PASC were predominantly female, based on their sex assigned at birth, with a mean age in the mid-40s and an average duration of symptoms of 471 days. Most identified as non-Hispanic White, had at least a college-level education, and were employed at the time of the assessment. Additionally, most participants reported being fully vaccinated against COVID-19 by the time of the study visit. Similarly, healthy controls were predominantly female, with a mean age in the mid-40s, and were infected with COVID-19 an average of 639 days before data collection. Most identified as non-Hispanic White, had at least a college-level education, and were employed at the time of the assessment. Most were also fully vaccinated against COVID-19. Groups did not differ in age ($p=.431$), sex assigned at birth ($p=.626$), or education level ($p=.250$). Time since infection in the group with PASC was significantly shorter compared to healthy controls ($t(86)=-2.66$, $p=.006$, Cohen's $d=-.67$).

Sleep quality, efficiency, and interference with daily functioning

Table 2 presents data on self-reported sleep quality, Fitbit sleep efficiency, and scores on the BAI, BDI, and PCL-C. A diagnosis or complaint of a sleep disorder before COVID-19 infection was reported by 31.2 percent of PASC participants, including insomnia, obstructive sleep apnea, or hypersomnia. In the healthy control group, 11 percent reported insomnia before COVID-19 infection, but no other sleep disorder.

Of those in the group with PASC who endorsed experiencing insomnia in the past 2 weeks, 44 percent reported that insomnia interfered "sometimes" with daily activities, 30 percent reported that it interfered "often," and 14 percent "very often". Moreover, of those who reported that hypersomnia interfered with daily activities, 59.3 percent reported that it "sometimes" interfered, 22.2 percent reported that it interfered "often," and 7.4 percent "very often". In addition, 35 percent of participants reported both some degree of hypersomnia and some degree of insomnia (Table S1). One participant (1.7 percent) reported severe or very severe symptoms of both, with interference in daily activities occurring "often" due to hypersomnia and "very often" due to insomnia.

On the PSQI, 96.7 percent of the participants with PASC and 39 percent of healthy controls reported experiencing poor overall sleep quality (Fig. 1). On individual index scores, the PASC group self-reported worse sleep quality ($F(1, 78)=25.256$, $p<.001$, partial $\eta^2=0.245$), a longer sleep latency ($F(1, 78)=32.708$, $p<.001$, partial $\eta^2=0.295$), more sleep disturbances ($F(1, 78)=5.886$, $p=.018$, partial $\eta^2=0.070$), and greater daytime dysfunction such as having trouble staying awake and maintaining enthusiasm to get things done ($F(1, 78)=26.278$, $p<.001$, partial $\eta^2=0.254$) compared to the healthy control group. Groups did not significantly differ in their self-reported sleep duration ($p=.509$), efficiency (p=.050), or the frequency with which they used sleep medications ($p=.095$) (Fig. 1).

A total of 93.9 percent of participants with PASC had an optimal sleep efficiency of >85 percent, as measured with the Fitbit (x$\bar{x}=88.2$; SD = 2.6). There was no significant association between self-reported global sleep quality on the PSQI and sleep efficiency measured with the Fitbit ($r=-0.065$, p=.659).

Severity of neuropsychiatric symptoms

The group with PASC reported significantly higher scores on the BAI ($F(1, 81)=17.134$, $p<.001$, partial $\eta^2=0.175$), BDI ($F(1, 81)=37.193$, $p<.001$, partial $\eta^2=0.315$), and PCL-C ($F(1, 81)=16.111$, $p<.001$, partial $\eta^2=0.166$) compared to the healthy control group. In the group with PASC, 52.5 percent of participants reported experiencing mild to moderate anxiety symptoms on the

Table 1. Demographics and clinical characteristics

	PASC* (*n* = 61)	Healthy controls (*n* = 28)
	%	
Sex assigned at birth (Female)	73.8	73.3
Age (Mean, SD)	45.4 (15.5)	44.7 (17.9)
Race		
American Indian or Alaska Native Islander	1.6	0
Asian, South Asian, Southeast Asian	3.3	0
Black or African American	3.3	0
Hispanic or Latino	8.2	46.4
Non-Hispanic White	90.2	53.57
Education		
High school or GED	3.3	7.1
Some college	11.5	10.7
Associate or technical degree	9.8	3.6
College	47.5	50
Professional studies (MD, JD, MS, PhD)	27.9	21.4
Vaccination status		
Not vaccinated	8.3	13.6
At least one dose	1.7	36.4
Fully vaccinated†	90.0	50.0
Vaccine booster		
Not boosted	10.0	6.25
At least one booster	50.0	6.25
Boosted twice	26.7	31.25
Boosted >2	13.3	56.3
Pre-COVID sleep disorder‡	31.2	10.7
Mini-Mental State Examination (Mean, SD)	29.1 (1.4)	28.8 (1.5)
Days Since COVID-19 Infection (Mean, SD)	471 (261.5)	639.0 (317.3)

*PASC, post-acute sequelae of COVID-19. †A study participant was considered "Fully Vaccinated" if they had two doses of Moderna or Pfizer vaccine; 1 dose of J&J. We did not have data about vaccination history for 7 healthy controls. ‡Pre-COVID-19 sleep disorder included a diagnosis or complaint of insomnia, obstructive sleep apnea, or hypersomnia prior to the COVID-19 infection.

Table 2. Neuropsychiatric symptoms and sleep

	Mean (SD) or %
BAI*	
Total score	16.6 (10.8)
Minimal anxiety (%)	23.0
Mild anxiety (%)	34.4
Moderate anxiety (%)	18.0
Severe anxiety (%)	24.6
BDI†	
Total score	13.8 (7.0)
Minimal depression (%)	44.3
Mild depression (%)	32.8
Moderate depression (%)	23.0
PCL-C‡	
Total score	34.3 (12.6)
Unlikely PTSD (%)	82.0
Possible PTSD (%)	18.0
PSQI§	
Total score	10.1 (3.4)
Total score > 5 (poor sleep quality) (%)	96.7
Fitbit sleep efficiency‖	88.2 (2.6)
Participants with equal or >85% sleep efficiency (%)	93.9
Fitbit total minutes asleep‖	418. 4 (65.1)
Fitbit time minutes in bed‖	473.1 (73.9)
Fitbit total minutes of REM sleep‖	90.3 (18.9)

*BAI, Beck Anxiety Inventory. A score of 0–7 is considered minimal, 8–15 mild, 16–25 moderate, or 26–63 severe anxiety. †BDI, Beck Depression Inventory. Scores between 0–13 indicate minimal symptoms of depression, 14–19 mild symptoms, 20–28 moderate symptoms, and equal or >29 severe symptoms. ‡PCL-C, PTSD (Post-Traumatic Stress Disorder)-Checklist Civilian Version. Total scores range from 17 to 85, and scores above 44 are considered indicative of possible PTSD. §PSQI, Pittsburgh Sleep Quality Index. The total score ranges from 0 to 14, and a global score of ≥5 indicates poor sleep quality. ‖Sleep efficiency, total minutes asleep, time in bed, and total minutes of Rapid Eye Movement (REM) sleep were measured using Fitbit. A value of 85 percent or greater is considered an indicator of good sleep efficiency. *n* = 49 for sleep efficiency, total minutes asleep, total minutes in bed, and total minutes of REM sleep.

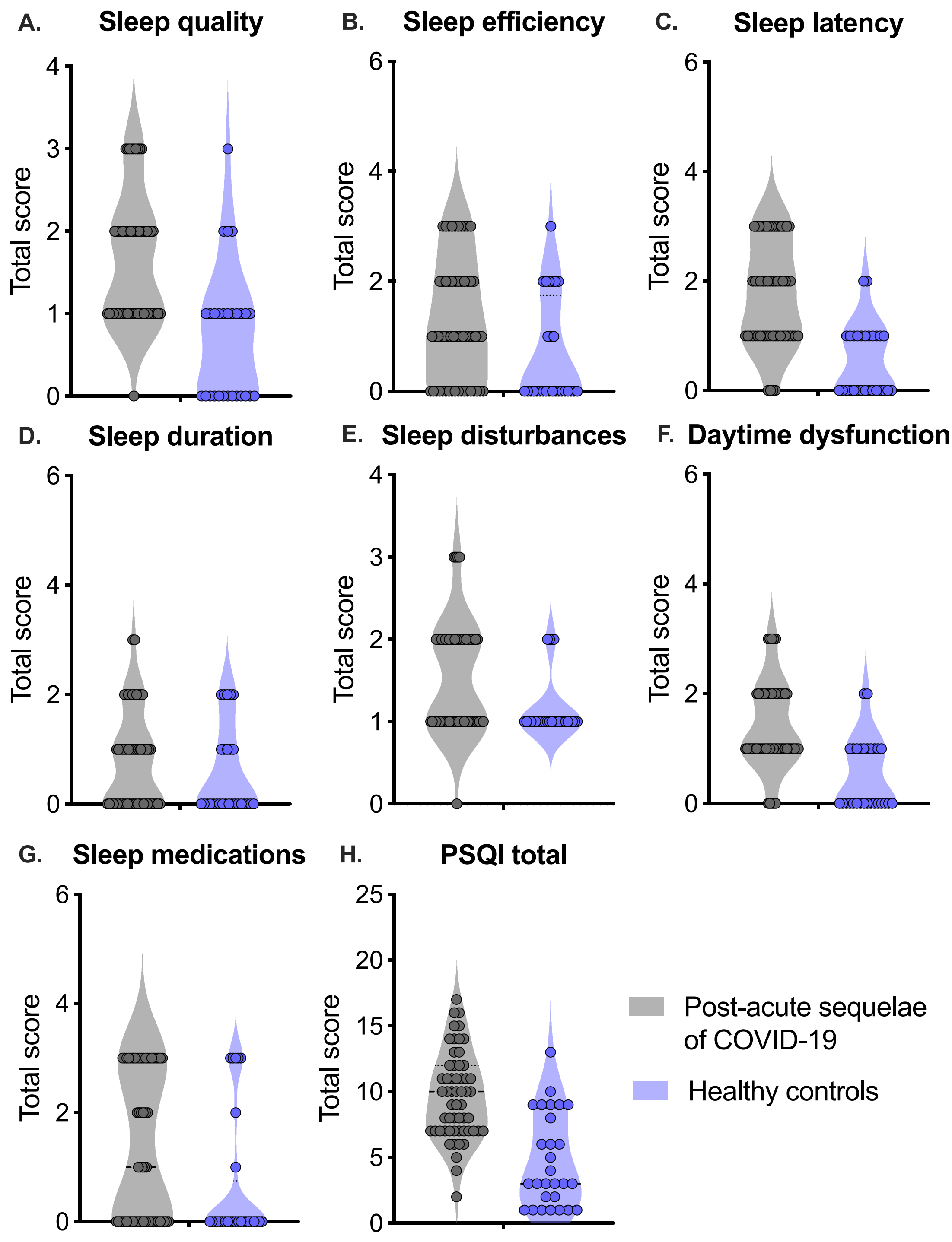

Figure 1. Pittsburgh Sleep Quality Index Scores. Violin plots demonstrate the mean and standard deviation for each PSQI component per group, and circles represent individual values.

BAI, 23.0 percent moderate depression symptoms on the BDI, and 18 percent scored on the PCL-C at a level that is often seen in individuals with a PTSD diagnosis.

Association between sleep quality and sleep efficiency and severity of neuropsychiatric symptoms

Greater depression symptoms were associated with reduced self-reported sleep quality ($\beta = 0.148$; SE = 0.060) after adjusting for age, sex, time since infection, pre-COVID-19 sleep disorder, and use of sleep aid (Table 3; Fig. 2). There were no statistically significant relationships between self-reported sleep quality and symptoms of anxiety ($\beta = 0.077$; SE = 0.041), PTSD ($\beta = 0.062$; SE = 0.034), or fatigue severity ($\beta = 0.024$; SE = 0.033) after adjusting for the previously listed confounders (Table 3; Fig. 2; Table S2). The sub-analysis examining the distinct PSQI components, showed that worse PTSD symptoms were significantly associated with greater sleep duration ($\beta = 0.022$; SE = 0.009). Worse symptoms of anxiety and fatigue severity were significantly associated with greater sleep disturbances ($\beta = 0.025$, SE = 0.007; $\beta = 0.013$; SE = 0.006,

Table 3. Associations between sleep quality and sleep efficiency and severity of neuropsychiatric Symptoms

	β	SE	P-value	95% CI
Self-reported sleep quality				
BAI*				
Unadjusted	0.051	0.040	.211	−0.030, 0.132
Adjusted‡	0.077	0.041	.068	−0.006, 0.159
BDI§				
Unadjusted	0.155	0.060	.012	0.035, 0.274
Adjusted‡	0.148	0.060	.016	0.028, 0.267
PCL-C‖				
Unadjusted	0.055	0.034	.112	−0.013, 0.124
Adjusted‡	0.062	0.034	.077	−0.007, 0.130
Sleep efficiency				
BAI				
Unadjusted¶	0.019	0.041	.651	−0.065, 0.102
Adjusted#	0.007	0.045	.886	−0.085, 0.098
BDI				
Unadjusted¶	0.078	0.052	.143	−0.027, 0.182
Adjusted#	0.062	0.055	.266	−0.049, 0.174
PCL-C				
Unadjusted¶	0.034	0.032	.292	−0.030, 0.099
Adjusted#	0.019	0.035	.585	−0.052, 0.091

All the adjusted models included age, sex, time since infection, pre-COVID sleep complaint or disorder, and pharmacologic and non-pharmacologic sleep aids. Pre-COVID-19 sleep disorder included a diagnosis or complaint of insomnia, obstructive sleep apnea, or hypersomnia prior to the COVID-19 infection. *$n = 60$.
‡BAI, Beck Anxiety Inventory. §BDI, Beck Depression Inventory. ‖PCL-C, PTSD (Post-Traumatic Stress Disorder)-Checklist Civilian Version. ¶$n = 49$. #$n = 48$.

respectively), and worse fatigue severity was significantly associated with greater daytime dysfunction ($\beta = 0.027$; SE = 0.007) in adjusted models (Table S3).

Sleep efficiency measured with the Fitbit was not significantly associated with symptoms of depression ($\beta = 0.062$; SE = 0.055), anxiety ($\beta = 0.007$; SE = 0.045), PTSD ($\beta = 0.019$; SE = 0.035), or fatigue severity ($\beta = -0.020$; SE = 0.029) (Table 3; Fig. 2; Table S2). The average REM sleep duration among participants with PASC was 90.3 min (Table 2). Symptoms of anxiety, depression, PTSD, or fatigue severity were not associated with other objectively assessed sleep parameters such as minutes asleep, time in bed, and time spent on REM sleep (Table 4; Table S2).

Discussion

Sleep disruptions have been linked to various negative outcomes, including increased cognitive difficulties and a heightened risk for hypertension, diabetes, obesity, depression, heart attack, and stroke [37]. Poor sleep quality is also closely linked to reduced quality of life, particularly among individuals with comorbid mood and anxiety symptoms [21]. Individuals with PASC frequently report worsening sleep difficulties following COVID-19 infection. As such, assessing sleep in individuals with PASC is essential for developing effective therapies that can improve sleep health in this population. Further, young- and middle-aged adults are disproportionately affected by PASC, particularly neurological symptoms, yet less is known about sleep in this population. This study examined the relationship between self-reported sleep quality and objective sleep efficiency and their association with neuropsychiatric symptoms in individuals with young and middle-aged adults with PASC who were never hospitalized during infection, underscoring the significance of addressing these challenges due to their profound impact on daily functioning and overall quality of life.

Our findings show that poor sleep quality is highly prevalent in young-to-middle-aged adults with PASC who were never hospitalized during COVID-19 infection and most of whom did not have a history of sleep difficulties prior to COVID-19 infection. Over 90 percent reported experiencing poor sleep quality compared to individuals who were infected with COVID-19 and fully recovered. While the duration of sleep and frequency of use of sleep aids did not differ between individuals with PASC and those who fully recovered from COVID-19 illness, individuals with PASC reported less efficient sleep, including a longer time to fall asleep and waking up more frequently during the night and early morning. Notably, some individuals reported experiencing both insomnia and hypersomnia or sleeping more than usual. This highlights the complexity of sleep disturbances in PASC and possible disruption of sleep–wake regulation. In addition, individuals with PASC reported having more trouble keeping up the enthusiasm to get things done and staying awake while driving, eating meals, or engaging in social activities. Over 85 percent reported that sleep difficulties interfere with their daily activities from sometimes to very often. However, while the perceived sleep quality in the group with PASC was poor, most demonstrated good sleep efficiency on an objective measure. Participants spent an average of 90 min or 22 percent of their time asleep in the REM stage, which is considered to be within the normal range (90–120 min) [38]. Consistent with these findings, we did not observe an association between self-reported sleep quality and objectively measured sleep efficiency. In addition, we found that worse depression symptoms, but not symptoms of anxiety or PTSD, were significantly associated with decreased self-reported sleep quality but not objective sleep efficiency, independent from age, sex, time since infection, pre-COVID sleep disorder, and use of sleep aids.

These findings are consistent with prior research supporting that sleep disturbances and poor sleep quality are prevalent among patients with PASC and further add that the perceived sleep difficulties significantly interfere with daily activities [39–41]. A systematic review and meta-analysis involving 13 935 patients with PASC across 29 studies estimated a pooled prevalence of poor sleep quality of 56 percent [39], which is comparable

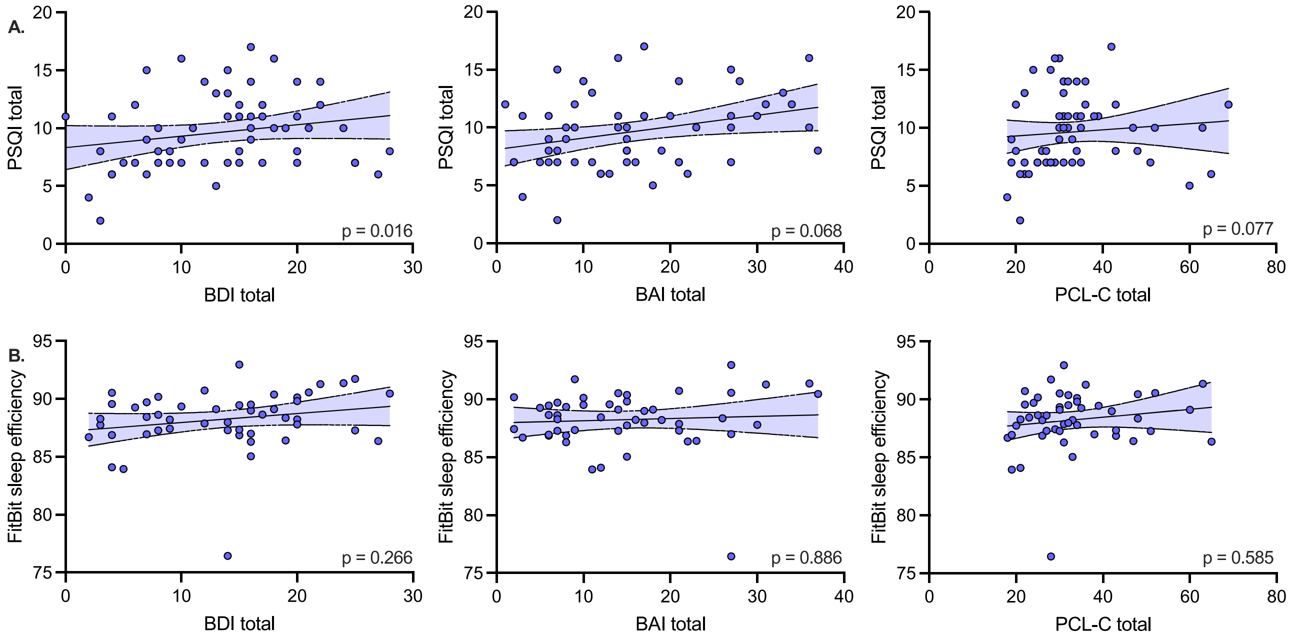

Figure 2. Association between sleep quality and sleep efficiency and severity of neuropsychiatric symptoms in post-acute sequelae of COVID-19. (A) Represent associations between the PSQI total score and the BAI, BDI, and PCL-C total scores; (B) Represent associations between sleep efficiency measured with the Fitbit and the BAI, BDI, and PCL-C total scores; and shaded areas represent confidence intervals.

Table 4. Associations between other objectively measured sleep parameters and severity of neuropsychiatric symptoms

	β	SE	P-value	95% CI
Total minutes asleep				
BAI*				
Unadjusted†	−0.360	1.062	.7364	−2.496, 1.777
Adjusted‡	−0.389	1.151	.737	−2.711, 1.933
BDI§				
Unadjusted†	0.569	1.359	.677	−2.165, 3.304
Adjusted‡	1.154	1.417	.420	−1.705, 4.014
PCL-C‖				
Unadjusted†	−0.539	0.829	.519	−2.207, 1.128
Adjusted‡	−0.236	0.9899	.794	−2.049, 1.578
Total minutes in bed				
BAI				
Unadjusted†	−0.809	1.201	.504	−3.225, 1.607
Adjusted‡	−0.747	1.296	.568	−3.363, 1.869
BDI				
Unadjusted†	0.095	1.545	.951	−3.014, 3.204
Adjusted‡	0.852	1.608	.599	−2.392, 4.096
PCL-C				
Unadjusted†	−0.910	0.936	.336	−2.792, 0.972
Adjusted‡	−0.466	1.013	.648	−2.510, 1.579
Total minutes of REM sleep				
BAI				
Unadjusted¶	0.069	0.320	.831	−0.576, 0.714
Adjusted#	−0.043	0.363	.906	−0.778, 0.691
BDI				
Unadjusted¶	0.177	0.404	.663	−0.637, 0.991
Adjusted#	0.105	0.437	.812	−0.781, 0.990
PCL-C				
Unadjusted¶	−0.083	0.267	.757	−0.623, 0.456
Adjusted#	−0.121	0.295	.683	−0.718, 0.476

All the adjusted models included age, sex, time since infection, pre-COVID sleep complaint, or disorder, and pharmacologic and non-pharmacologic sleep aids. Pre-COVID-19 sleep disorder included a diagnosis or complaint of insomnia, obstructive sleep apnea, or hypersomnia prior to the COVID-19 infection. *$n=49$. †$n=48$. ‡BAI, Beck Anxiety Inventory. §BDI, Beck Depression Inventory. ‖PCL-C, PTSD (Post-Traumatic Stress Disorder)-Checklist Civilian Version. ¶$n=45$. #$n=44$.

to the prevalence of poor sleep quality among our participants with PASC, despite the low prevalence of sleep disorders pre-COVID in the group. Consistent with our findings, a study found that depression symptoms were a predictor of poor sleep quality among patients with mild PASC, and anxiety was associated with poor sleep quality among patients who were hospitalized and in the intensive care unit during acute infection [40].

Our data also highlight a discordance between perceived sleep quality and objectively measured sleep efficiency. Most participants had high sleep efficiency, meaning they spent the majority of their time in bed asleep with few awakenings or interruptions—an indicator of healthy sleep. They also did not show abnormal time spent in REM sleep, which is important for memory consolidation and emotion regulation, among others [42, 43]. However, their subjective experience diverged; despite objectively good sleep, participants did not feel rested and perceived their sleep as inefficient. Discrepancies between subjective and objective sleep metrics are well-documented and may have significant implications for understanding sleep physiology and potential adverse health outcomes [44–46]. For instance, subjective perceptions of sleep quality are often associated with psychological factors, such as stress or mood, that do not always align with objective sleep measurements like actigraphy. This discordance may arise from overestimations or underestimations of sleep dimensions (e.g. duration, quality, efficiency), potentially linking these misperceptions to psychophysiological mechanisms associated with poor health outcomes. This perceived poor sleep quality was associated with worse symptoms of depression. This is not surprising as poor sleep and depression are closely interconnected in a bidirectional relationship, where each can worsen or trigger the other. Research consistently shows that people with insomnia or other sleep disturbances have a significantly increased risk of developing depression, and those with depression frequently experience poor sleep quality, characterized by difficulty falling asleep, maintaining sleep, or experiencing restorative rest [47, 48]. These findings underscore the importance of prioritizing patients' subjective sleep experiences when developing therapeutic strategies to address sleep disturbances in patients with PASC, ultimately aiming to enhance their sleep health and overall quality of life.

We did not observe a relationship between sleep quality and efficiency and symptoms of anxiety or PTSD. It is possible that anxiety may be more predictive of poor sleep quality, primarily among patients with PASC who experienced severe COVID-19 episodes, with hospitalized cases showing a greater vulnerability to anxiety-related sleep disturbances [40]. Similarly, PTSD is reported to be more prevalent among those hospitalized for COVID-19 [49]. As our participants were not hospitalized and experienced milder acute COVID-19 symptoms, they were likely at a reduced risk for PTSD. Consequently, the low number of participants with a PCL-C score indicative of possible PTSD reduced the likelihood of detecting associations between PTSD symptoms and sleep quality in this sample. However, when we examined distinct components of sleep from the PSQI, we found that greater symptoms of anxiety were associated with increased sleep disturbances, and that more severe PTSD symptoms were linked to longer sleep duration. These findings are consistent with sleep studies in other populations. For instance, some studies have shown that anxiety's impact on sleep health may be driven by specific PSQI components, particularly sleep disturbances, even when global sleep quality scores remain unaffected [50]. In turn, worse PTSD symptoms have been associated with greater sleep duration variability [51]. Given that anxiety and PTSD symptoms were associated with specific domains of self-reported sleep quality rather than overall sleep quality, these findings may have important implications for tailoring sleep interventions in individuals with PASC.

Sub-analyses also revealed that greater fatigue severity was associated with higher self-reported sleep disturbances and daytime dysfunction. However, no significant associations were observed with global sleep quality. Prior studies have documented that fatigue and sleep disturbances are prevalent symptoms among individuals with PASC [52–54]. Our findings build on this literature by examining the contribution of specific symptom domains and their potential interrelationship. These results highlight the importance of a comprehensive assessment of fatigue and sleep-related symptoms in individuals with PASC.

Preventing and treating sleep disturbances offers an opportunity to address a modifiable risk factor with a broad impact on health and well-being. Although the acute phase of the COVID-19 pandemic has passed, its enduring effects on population health continue to unfold, particularly in ongoing research among patients with PASC worldwide. This study highlights the substantial impact of the PASC on sleep quality among never-hospitalized individuals, revealing how sleep disruptions can significantly hinder daily functioning. Evidence-based behavioral interventions, such as Cognitive Behavioral Therapy for insomnia, may offer effective strategies for alleviating these sleep difficulties in patients with PASC, potentially enhancing quality of life and reducing depressive symptoms [55]. Nevertheless, intervention studies are needed to test this hypothesis.

Several limitations of our study should be acknowledged. We used Fitbit devices to measure sleep efficiency, which, while effective for estimating time in bed and sleep duration, may lack the precision of medical-grade devices such as polysomnography. Additionally, we did not include a control group with Fitbit data, limiting our ability to identify potential differences in sleep architecture between individuals with PASC and those who recovered from COVID-19. Further, we did not assess for other sleep parameters, such as number of awakenings or wake after sleep onset, and did not include a validated measure of insomnia. Future research with reliable measures of these parameters and disorder is needed to gain a deeper understanding of sleep disturbances in the PASC. Notably, the PSQI requires individuals to consider their average sleep quality during the past month. Future studies may consider collecting 1 month of Fitbit data to align with the time frame referenced in the PSQI. However, it is likely that 2 weeks of Fitbit data captures sleep patterns that are representative of a full month. This study was also observational and cross-sectional, restricting our capacity to establish causality. Furthermore, most participants in the group with PASC were enrolled in a clinical trial and were actively seeking intervention for their symptoms, introducing a selection bias that may affect assessments of mood and sleep symptom severity. Most of our study sample with PASC were highly educated participants who identified as non-Hispanic White. Future studies should also include a larger representation of individuals from diverse sociodemographic backgrounds to better represent the community of individuals affected by the PASC.

Our study also had many strengths. First, we evaluated both subjective and objective sleep quality, which provides essential insights for developing effective therapeutic interventions. We utilized the Fitbit wearable device to assess average sleep patterns over multiple consecutive nights for each individual, providing insights into their typical sleep behaviors. Beyond assessing sleep characteristics in this population, we examined the impact of sleep disturbances on daily functioning related to the PASC. We also investigated associations between prevalent neuropsychiatric symptoms—including anxiety, depression, and PTSD—and sleep quality and efficiency in non-hospitalized patients with PASC, a substantial subset about whom little is known regarding sleep. In addition, we collected comprehensive histories of sleep disorders and medication use, along with detailed information on COVID-19 symptoms and other medical conditions. Neuropsychiatric symptoms and sleep quality were measured using validated and widely used instruments, and we controlled for potential confounding variables, including an exhaustive list of pharmacological and non-pharmacological sleep aids.

Conclusion

Poor sleep quality is highly prevalent in young-to-middle-aged, never-hospitalized individuals with PASC and no prior history of sleep difficulties. Sleep difficulties were reported to significantly interfere with daily functioning. While sleep duration and use of sleep aids were comparable to those who recovered fully from COVID-19, participants with PASC reported longer sleep latency, more frequent nighttime awakenings, and greater difficulty staying alert during daily tasks. Interestingly, most participants with PASC showed good sleep efficiency on an objective measure of sleep. However, despite good objective sleep efficiency, participants felt their sleep was inefficient, an impression linked to greater depression symptoms. These results help address the knowledge gap regarding the impact of the PASC on sleep health, particularly its association with neuropsychiatric symptoms, among individuals who were never hospitalized. They also underscore the need to prioritize patients' subjective sleep experiences in therapeutic strategies for the PASC. Evidence-based behavioral therapies for insomnia may help alleviate sleep difficulties and potentially reduce depressive symptoms, though further research is required to confirm these benefits.

Supplementary material

Supplementary material is available at *SLEEP Advances* online.

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Author contributions

Leidys Gutierrez-Martinez (Conceptualization [Equal], Formal analysis [Lead], Writing—original draft [Lead]), William Reynolds (Data curation [Equal], Investigation [Supporting], Writing—original draft-Supporting), Edmarie Guzmán-Vélez (Conceptualization [Equal], Data curation [Supporting], Formal analysis [Supporting], Funding acquisition [Lead], Investigation [Lead], Methodology [Lead], Project administration [Lead], Resources [Lead], Supervision [Lead], Visualization [Supporting], Writing—original draft-Equal), Steven Arnold (Conceptualization, Funding acquisition, Writing—original draft [Supporting]), Isabel Abril (Data curation, Writing—original draft [Supporting]), Gabriel Gonzalez-Irizarry (Data curation, Writing—original draft [Supporting]), Perla Ortiz-Acosta (Data curation, Writing—original draft [Supporting]), Janet Mullington (Conceptualization, Writing—original draft [Supporting]), Jonathan Rosand (Funding acquisition, Writing—original draft [Supporting]), Rudolph E. Tanzi (Funding acquisition, Writing—original draft [Supporting])

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Data availability

Requests for access to the data may be considered on a case-by-case basis and should be directed to the corresponding author at eguzman-velez@mgh.harvard.edu.

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