https://doi.org/10.5664/jcsm.11322

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Sleep and long COVID: preexisting sleep issues and the risk of post-acute sequelae of SARS-CoV-2 infection in a large general population using 3 different model definitions

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Study Objectives: Insomnia, poor sleep quality, and extremes of sleep duration are associated with COVID-19 infection. This study assessed whether these factors are related to post-acute sequelae of SARS-CoV-2 infection (PASC).

Methods: Cross-sectional survey of a general population of 24,803 United States adults to determine the association of insomnia, poor sleep quality, and sleep duration with PASC. Three definitions of PASC were used based on post COVID-19 clinical features: COVID-19 Outbreak Public Evaluation Initiative (COPE) (≥ 3), National Institute for Health and Care Excellence (NICE) (≥ 1), and Researching COVID to Enhance Recovery (RECOVER) (scoring algorithm).

Results: Prevalence rates of PASC were 21.9%, 38.9%, and 15.5% for COPE, NICE, and RECOVER PASC definitions, respectively. PASC was associated with insomnia in all 3 models after full adjustment with odds ratios and 95% confidence intervals (CIs) ranging from 1.30 (95% CI: 1.11–1.52, $P \leq .05$, RECOVER PASC score) to 1.52 (95% CI: 1.34–1.71, $P \leq .001$, NICE). Poor sleep quality was related to PASC in all models with adjusted odds ratios ranging from 1.77 (95% CI: 1.60–1.97, $P \leq .001$, NICE) to 2.00 (95% CI: 1.77–2.26, $P \leq .001$, COPE). Sleep < 6 hours was associated with PASC with adjusted odds ratios between 1.59 (95% CI: 1.40–1.80, $P \leq .001$, RECOVER PASC score) and 1.70 (95% CI: 1.53–1.89, $P \leq .001$, COPE). Sleep ≥ 9 hours was not associated with PASC in any model. Although vaccination with COVID-19 booster decreased the likelihood of developing PASC, it did not attenuate associations between insomnia, poor sleep quality, and short sleep duration with PASC in any of the models.

Conclusions: Insomnia, poor sleep quality, and short sleep duration are cross-sectionally associated with PASC and may be potential risk factors. Further longitudinal studies should be conducted.

Keywords: long COVID, PASC, insomnia, poor sleep quality, sleep duration, post-acute sequelae of SARS-CoV-2 infection

Citation: Quan SF, Weaver MD, Czeisler MÉ, et al. Sleep and long COVID: preexisting sleep issues and the risk of post-acute sequelae of SARS-CoV-2 infection in a large general population using 3 different model definitions. *J Clin Sleep Med*. 2025;21(2):249–259.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Insomnia, poor sleep quality, and extremes of sleep duration have been associated with a higher likelihood of COVID-19 infection. However, evidence implicating an association with the development of post-acute sequelae of SARS-CoV-2 infection is scant.

Study Impact: Results indicate that insomnia, poor sleep quality, and sleep duration ≤ 6 hours are associated with an increase in the prevalence of post-acute sequelae of SARS-CoV-2 infection among persons who have previously had a COVID-19 infection. The findings provide support further research into the impact of unhealthy sleep in the development of post-acute sequelae of SARS-CoV-2 infection.

INTRODUCTION

As the COVID-19 pandemic has evolved into global endemic status, the emergence of persistent and/or relapsing-remitting physical, cognitive and mental health symptoms commonly known as "long COVID" or more formally as post-acute sequelae of SARS-CoV-2 infection (PASC) has become an increasingly important public health concern.[1–4] Risk factors for the development of PASC include greater severity of initial COVID-19 illness, multiple infections, female sex, and preexisting health conditions.[2,5] Recently, obstructive sleep apnea (OSA) has been demonstrated in 2 large studies to be associated with the development of PASC.[6,7] Although poor sleep quality and short sleep duration are associated with an increased risk of

acute COVID-19 infection,[8,9] it is uncertain whether they also are related to a higher likelihood of PASC.

Estimates of the prevalence of PASC are imprecise, ranging from 7.5–41%.[10] In part, this imprecision is related to the lack of a generally accepted definition of this syndrome. Several definitions have been proposed that include the use of various combinations of duration of time postinfection, number of symptoms, and a scoring system that weights some symptoms more than others.[6,11–14] However, there are few data that have prospectively tested or compared definitions to each other, control groups and long-term outcomes.

In this cross-sectional analysis, we aimed to determine in a large general population cohort whether preexisting insomnia, poor sleep quality, and short or long sleep duration are associated with the development of PASC using 3 different model definitions of the syndrome. In addition, we compared the prevalence of PASC among these models.

METHODS

Study design and participants

From March 10–October 15, 2022, the COVID-19 Outbreak Public Evaluation (COPE) Initiative[15] administered 5 successive waves of identical surveys focused on accumulating data on the prevalence and sequelae of COVID-19 infection in the United States (U.S.). Dates of administration were Wave 1 (March 10–30, 2022), Wave 2 (April 4–May 1, 2022), Wave 3 (May 4–June 2, 2022), Wave 4 (August 1–18, 2022), and Wave 5 (September 26–October 15, 2022). Each wave consisted of approximately 5,000 unique participants who were recruited to create samples that approximated population estimates for age, sex, race, and ethnicity based on the 2020 U.S. census. Surveys were conducted online by Qualtrics, LLC (Provo, Utah, and Seattle, Washington, U.S.), using their network of participant pools with varying recruitment methodologies. Informed consent was obtained electronically. The 5 survey waves were combined into a single cross-sectional analytic cohort. The study was approved by the Monash University Human Research Ethics Committee (Study #24036).

Survey items

Participants self-reported demographic, anthropometric, and socioeconomic information including age, race, ethnicity, sex, height and weight, education level, employment status, and household income. In addition, they provided information on several current and past medical conditions by answering the question: "Have you ever been diagnosed with any of the following conditions?" In addition to insomnia, opportunity was provided to endorse OSA, high blood pressure, cardiovascular disease (eg, heart attack, stroke, angina), gastrointestinal disorder (eg, acid reflux, ulcers, indigestion), cancer, chronic kidney disease, liver disease, sickle cell disease, chronic obstructive pulmonary disease, and asthma. Possible responses to each condition were "Never," "Yes I have in the past, but don't have it now," "Yes I have, but I do not regularly take medications or receiving treatment," and "Yes I have, and I am regularly taking medications or receiving treatment."

The following 2 questions pertaining to sleep quality were asked of the participants:

1. "Thinking about the past month, to what extent has poor sleep troubled you in general?" Possible responses were "Not at all," "A little," "Somewhat," "Much," and "Very Much."
2. From the Pittsburgh Sleep Quality Index,[16] "During the past month, how would you rate your sleep quality overall?" Possible responses were "Very good," "Fairly good," "Fairly bad," and "Very bad."

Sleep duration was assessed using a question from the Pittsburgh Sleep Quality Index.[16] Responses were rounded to the nearest hour; those < 3 hours or > 12 hours were excluded as improbable estimates (n = 987). In addition, sleep duration was stratified as short sleep (≤ 6 hours), recommended sleep (7–8 hours) and long sleep (≥ 9 hours).

Symptoms of OSA were obtained from responses to the Pittsburgh Sleep Quality Index and included items related to roommate or bedpartner reported "loud snoring" and "long pauses between breaths while you sleep."[16] In addition, sleepiness was assessed from the following item in the questionnaire: "During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity." Possible responses to all 3 items were "not during the past month," "less than once a week," "once or twice a week," or "3 or more times a week." As done in our previous studies, participants were considered to have symptoms of OSA if they had either of the following combination of symptoms: (1) snoring "3 or more times a week" and witnessed apnea or sleepiness "once or twice a week"; (2) witnessed apnea and sleepiness "once or twice a week."[6,17]

Each survey contained identical items related to COVID-19 infection status and the number of COVID-19 vaccinations participants had received. Ascertainment of past COVID-19 infection was obtained using responses to the following questions related to COVID-19 testing or the presence of loss of taste or smell:

1. "Have you ever tested positive?"
2. "Despite never testing positive, are you confident that you have had COVID-19?"
3. "Despite never testing positive, have you received a clinical diagnosis of COVID-19?"
4. "Have you experienced a problem with decreased sense of smell or taste at any point since January 2020?"

Participants who endorsed having had any of the aforementioned items #1–4 were asked if they had experienced any of the general health, cognitive, or mental health symptoms listed in the supplemental material (**Table S1** in the supplemental material) more than 2 weeks after their infection. For each symptom, participants who endorsed having experienced the symptom more than 2 weeks after their COVID-19 infection or indicated that they were currently having the symptom were asked how long their symptoms persisted after their infection.

COVID-19 vaccination status was ascertained by asking "How many COVID-19 vaccine doses have you received? (If you have had 2 doses of 1 brand and 1 of another, please select 3)." Participants were allowed to respond from 0–4.

Statistical analyses

Exposures

Based on our previous analyses in this cohort, we defined a positive history of COVID-19 infection as an affirmative response to having tested positive for COVID-19, a clinical diagnosis of COVID-19, or loss of taste or smell.[6,9,17] Participants were classified as having OSA if they affirmed currently having the condition whether treated or not or if they had 2 or more symptoms of OSA.[6,9,17] Insomnia was present if endorsed by participants irrespective of treatment status. Poor sleep quality was defined as being troubled by poor sleep "Much" or "Very Much" or rating their sleep quality as "Fairly Bad" or "Very Bad."[9]

Vaccination status was dichotomized as Boosted (> 2 vaccinations) or Not Boosted (≤ 2 vaccinations). Comorbid medical conditions were defined as currently having the condition whether treated or untreated. The effect of comorbid medical conditions was evaluated by summing the number of conditions reported by the participant (minimum value 0, maximum value 9).[6,9,17] Body mass index was calculated using self-reported height and weight as kg/m^2. Socioeconomic covariates were dichotomized as follows: employment (retired vs not retired), education (high school or less vs some college) and income in U.S. Dollars (< $50,000 vs ≥ $50,000).

Outcomes

Based on previous analyses of this cohort, PASC was defined as the presence of 3 or more symptoms commonly associated with PASC for at least 3 months after their COVID-19 infection (COPE).[6] For comparison, 2 other definitions of PASC were also used: (1) a PASC score ≥ 12 modified from the Researching COVID to Enhance Recovery (RECOVER) cohort proposal,[13] and (2) 1 or more symptoms commonly associated with PASC for at least 3 months after their COVID-19 infection as suggested by the United Kingdom's National Institute for Health and Care Excellence (NICE).[12] Because the COPE survey did not contain a few items comparable to those in the RECOVER cohort, we substituted symptoms contained in the COPE survey which were correlated[13] or similar as follows: sore throat for thirst, sleep problems for sexual function, headache for dizziness, and other aches for abnormal movements.

Analytics

Summary data for continuous or ordinal variables are reported as their respective means and standard deviations and for categorical variables as their percentages. Comparisons of comorbid medical, demographic, and social characteristic variables stratified by presence or absence of PASC were performed using Student's unpaired *t* test for continuous or ordinal variables and χ^2 for categorical variables.

Multivariable modeling using logistic regression was utilized to determine whether insomnia, poor sleep quality, and sleep duration were associated with the COPE, RECOVER, and NICE models of PASC. For each definition, a baseline model was constructed using only insomnia, poor sleep quality, and sleep duration stratified as short (≤ 6 hours), recommended (7–8 hours),[18] and long (≥ 9 hours) sleep. We then developed increasingly complex models by sequentially including demographic factors, comorbidities, boosted vaccination status, socioeconomic factors, and other sleep conditions. Inasmuch as the sleep conditions evaluated in the models may have been correlated, diagnostic tests for collinearity were performed; the variance inflation factor was less than 10 and the tolerance was greater than 0.1 for all variables. However, because poor sleep quality can be considered a component of insomnia, models for insomnia were not adjusted for poor sleep quality. Conversely, models for poor sleep quality were not adjusted by insomnia. Results of the logistic regression models are presented as unadjusted or adjusted odds ratios (aORs) and their 95% confidence intervals (CIs).

To determine whether our definition of COVID-19 infection status influenced our results, we performed sensitivity analyses with stricter (ie, using COVID-19 infection as a positive test or loss of taste or smell) and broader (ie, our original definition plus assumed positive for COVID-19 without a positive test or clinical diagnosis as an indicator of a past COVID-19 infection).

All analyses were conducted using IBM SPSS version 28 (Armonk, New York). A $P < .05$ was considered statistically significant.

RESULTS

There were 24,803 participants with evaluable data from the 5 COPE initiative surveys from which a positive history of COVID-19 infection (see Methods) was reported in 10,324 (41.6%), which represented the analytic sample. **Table 1** presents the demographic, anthropometric, comorbid medical and social characteristics of these COVID-19 positive participants in the COPE cohort stratified by PASC status for the 3 models of PASC analyzed in this study. Characteristics of participants positive for PASC were generally similar for all 3 models. Those who were PASC positive were younger and more likely to be Hispanic, not retired, and have a higher income. They were less likely to have received a COVID-19 booster vaccination (COPE: 24.2% vs 29.3%; NICE: 23.7% vs 31.0%; PASC score: 24.5% vs 28.8%; all $P < .01$). In terms of sleep, 3,452 (45.6%) participants reported having slept the recommended 7–8 hours, 2,973 (36.9%) screened positive for poor sleep quality, 1,671 (20.7%) screened positive for insomnia, and 1,697 (21.0%) screened positive for OSA. Compared with participants who did not experience PASC, those with PASC had a higher prevalence of OSA, insomnia, and poor sleep quality. In addition, they were more likely to report a short sleep duration whereas there was a slight tendency for those with PASC to report a long sleep duration.

The prevalence of PASC as defined in the COPE, NICE, and PASC score models is shown in **Table 1**. The most restrictive model was the PASC score (15.3%) followed by the COPE (21.9%) and NICE (38.9%) models.

In **Table 2** are logistic regression analyses describing among participants with a positive history of COVID-19 infection the association between insomnia and PASC in all 3 PASC models at baseline and subsequently in partially and fully adjusted models. The aORs in the fully adjusted models were comparable with narrow CIs ranging from 1.30 (95% CI: 1.11–1.52, $P \leq .05$,

Table 1—Associations between PASC status and insomnia, poor sleep quality, sleep duration, comorbid medical, demographic, and social characteristics.

	COPE (≥ 3 Symptoms)				NICE (≥ 1 Symptom)				PASC Score (≥ 12)				Overall	
	PASC Negative		PASC Positive		PASC Negative		PASC Positive		PASC Negative		PASC Positive			
	n = 8,067 (78.1%)		n = 2,257 (21.9%)		n = 6,310 (61.1%)		n = 4,014 (38.9%)		n = 8,747 (84.7%)		n = 1,577 (15.3%)		n = 10,324	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	41.9	16.6	37.4*	13.6	43.1	17.0	37.6*	13.9	41.6	16.5	37.0*	13.1	40.9	16.1
BMI (kg/m^2)	27.6	6.2	27.5	6.6	27.5	6.1	27.7	6.6	27.6	6.2	27.7	6.8	27.6	6.3
No. comorbidities	1.6	2.5	3.7*	3.5	1.4	2.2	3.3*	3.4	1.8	2.6	3.8*	3.5	2.1	2.9
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex														
Male	3951	49.5	1056	47.6	3121	49.9	1886	47.7†	4251	49.1	756	48.7	5007	49.1
Female	4034	50.5	1164	52.4	3129	50.1	2069	52.3	4403	50.9	795	51.3	5198	50.9
Race/ethnicity														
White	4763	59.0	1269	56.2*	3792	60.1	2240*	55.8	5140	58.8	892†	56.6	6032	58.4
Black	805	10.0	251	11.1	609	9.7	447	11.1	866	9.9	190	12.0	1056	10.2
Asian	429	5.3	84	3.7	355	5.6	158	3.9	464	5.3	49	3.1	513	5.0
Hispanic	1728	21.4	536	23.7	1278	20.3	986	24.6	1900	21.7	364	23.1	2264	21.9
Other	342	4.2	117	5.2	276	4.4	183	4.6	377	4.3	82	5.2	459	4.4
Employment														
Retired	1230	15.2	152	6.7*	1079	17.1	303	7.5*	1272	14.5	110	7.0*	1382	13.4
Not retired	6837	84.8	2105	93.3	5231	82.9	3711	92.5	7475	85.5	1467	93.0	8942	86.6
Education														
High school or less	2129	26.4	541	24.0†	1661	26.3	1009	25.1	2290	26.2	380	24.1	2670	25.9
Some college	5938	73.6	1716	76.0	4649	73.7	3005	74.9	6457	73.8	1197	75.9	7654	74.1
Income (yearly)														
< $50,000	3292	42.2	844	38.2*	2576	42.4	1560	39.6*	3535	41.8	601	38.7†	4136	41.3
≥ $50,000	4506	57.8	1367	61.8	3496	57.6	2377	60.4	4922	58.2	951	61.3	5873	58.7
Vaccination boosted														
No (≤ 2 vaccinations)	5524	70.7	1683	75.8*	4206	69.0	3001	76.3*	6028	71.2	1179	75.5*	7207	71.9
Yes (> 2 vaccinations)	2285	29.3	538	24.2	1890	31.0	933	23.7	2441	28.8	382	24.5	2823	28.1
OSA														
Yes	1697	21.0	1131	50.1*	1071	17.0	1757	43.8*	2011	23.0	817	51.8*	2828	72.6
No	6370	79.0	1126	49.9*	5239	83.0	2257	56.2	6736	77.0	760	48.2	7496	27.4

(continued on following page)

Table 1 (*continued*)—Associations between PASC status and insomnia, poor sleep quality, sleep duration, comorbid medical, demographic, and social characteristics.

	COPE (≥ 3 Symptoms)				NICE (≥ 1 Symptom)				PASC Score (≥ 12)				Overall	
	PASC Negative		PASC Positive		PASC Negative		PASC Positive		PASC Negative		PASC Positive			
	n = 8,067 (78.1%)		n = 2,257 (21.9%)		n = 6,310 (61.1%)		n = 4,014 (38.9%)		n = 8,747 (84.7%)		n = 1,577 (15.3%)		n = 10,324	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Insomnia														
Yes	1671	20.7	991	43.9*	1090	17.3	1573	39.2*	1968	22.5	695	44.1*	2663	25.8
No	6395	79.3	1266	56.1	5220	82.7	2441	60.8	6779	77.5	882	55.9	7661	74.2
Poor sleep quality														
Yes	2973	36.9	1367	60.6*	2140	33.9	2200	52.8*	3386	38.7	954	60.5*	4340	42.0
No	5094	63.1	890	39.4	4170	66.1	1814	45.2	5361	61.3	623	39.5	5984	58.0
Sleep duration (hourly)														
3	234	3.1	142	7.1*	160	2.7	216	6.1*	281	3.4	95	6.8*	376	3.9
4	532	7.0	250	12.5	380	6.3	402	11.3	607	7.4	175	12.5	782	8.2
5	955	12.6	341	17.0	724	12.0	572	16.1	1066	13.0	230	16.5	1296	13.5
6	1563	20.7	370	18.5	1250	20.8	683	19.2	1683	20.6	250	17.9	1933	20.2
7	1647	21.8	295	14.7	1367	22.7	575	16.2	1747	21.4	195	14.0	1942	20.3
8	1805	23.9	388	19.4	1483	24.7	710	20.0	1913	23.4	280	20.1	2193	22.9
9	433	5.7	90	4.5	355	5.9	168	4.7	460	5.6	63	4.5	523	5.5
10	244	3.2	75	3.7	186	3.1	133	3.7	256	3.1	63	4.5	319	3.3
11	39	0.5	16	0.8	31	0.5	24	0.7	42	0.5	13	0.9	55	0.6
12	110	1.5	36	1.8	75	1.2	71	2.0	115	1.4	31	2.2	146	1.5
Sleep duration (categorical)														
≤ 6 hours	3284	43.4	1103	55.1*	2514	41.8	1873	52.7*	3637	44.5	750	53.8*	4387	45.9
7–8 hours	3452	45.6	683	34.1	2850	47.4	1285	36.2	3660	44.8	475	32.1	4135	43.2
≥ 9 hours	826	10.9	217	10.8	647	10.8	396	11.1	873	10.7	170	12.2	1043	10.9

†$P < .05$, *$P < .01$ vs corresponding placebo group. BMI = body mass index, COPE = The COVID-19 Outbreak Public Evaluation, NICE = National Institute for Health and Care Excellence, OSA = obstructive sleep apnea, PASC = post-acute sequelae of SARS-CoV-2 infection, SD = standard deviation.

Table 2—Association of self-reported insomnia with 3 models of PASC.

	COPE (≥ 3 Symptoms)		NICE (≥ 1 Symptom)		PASC Score (≥ 12)	
Model	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
Baseline	2.94§	2.71–3.31	3.58§	3.22–3.73	3.58§	3.23–3.96
+Demographics	2.89§	2.61–3.20	3.20§	2.99–3.45	3.21§	2.89–3.57
+Comorbidities	1.75§	1.55–1.98	1.79§	1.63–1.96	1.63§	1.43–1.86
+Socioeconomic	1.74§	1.54–1.97	1.78§	1.62–1.95	1.61§	1.42–1.84
+Sleep factors	1.46§	1.28–1.68	1.52§	1.34–1.71	1.30§	1.11–1.52

Models adjusted as follows (see text for definitions): Demographics: age, sex, race; Comorbidities: body mass index, number of the following conditions: diabetes, asthma, sickle cell disease, cardiovascular disease, hypertension, cancer, chronic kidney disease, liver disease, chronic obstructive pulmonary disease, boosted vaccination status; Socioeconomic: education, income, employment; Sleep factors: sleep duration, obstructive sleep apnea. §$P < .001$. aOR = adjusted odds ratio, CI = confidence interval, COPE = COVID-19 Outbreak Public Evaluation, NICE = National Institute for Health and Care Excellence, PASC = post-acute sequelae of SARS-CoV-2 infection.

PASC score) to 1.52 (95% CI: 1.34–1.71, $P \leq .001$, NICE). In none of the models did boosted vaccination affect the relationship between insomnia and PASC (insomnia × boosted vaccination aORs were not significant, data not shown).

Table 3 describes the association of poor sleep quality with PASC among participants with a positive history of COVID-19 infection. For all 3 models, poor sleep quality was related to an increased probability of PASC; aORs at baseline were comparable ranging from 2.36 (95% CI: 2.18–2.56, $P \leq .001$, NICE) to 2.63 (95% CI: 2.39–2.90, $P \leq .001$, COPE). Subsequent adjustment for demographic and socioeconomic factors, and sleep conditions as well as comorbidities attenuated these associations, but all remained significant in fully adjusted models with aORs ranging from 1.77 (95% CI: 1.60–1.97, $P \leq .001$, NICE) to 2.00 (95% CI: 1.77–2.26, $P \leq .001$, COPE). In none of the models did boosted vaccination affect the relationship between poor sleep quality and PASC (poor sleep quality × boosted vaccination aORs were not significant, data not shown).

In Table 4 are shown the relationships between the full distribution of hourly sleep duration (3–12 hours) with 3 models of PASC among participants with a positive history of COVID-19 infection. For all 3 models, the unadjusted aORs suggested that both short and long sleep durations were associated with PASC in comparison to the recommended 7–8 hours of sleep. For sleep durations less than 7–8 hours, these findings were attenuated, but remained significant after full adjustment. However, for sleep durations greater than 7–8 hours, the association with PASC was no longer present with the solitary exception of 11 hours in the PASC score model.

Shown in Table 5 are the associations of short sleep (≤ 6 hours) and long sleep (≥ 9 hours) with PASC among participants with a positive history of COVID-19 infection. In comparison to recommended hours of sleep (7–8 hours; n = 3,452), short sleep (n = 3,284) was associated with a greater likelihood of PASC. The aORs at baseline were comparable for all 3 models and ranged from 1.59 (95% CI: 1.40–1.80, $P \leq .001$, PASC score) to 1.70 (95% CI: 1.53–1.89, $P \leq .001$, COPE). These associations were attenuated but remained significant in fully adjusted models with aORs of 1.17 (95% CI: 1.01–1.36, $P \leq .05$, PASC score), 1.23 (95% CI: 1.08–1.41, $P \leq .001$, COPE), and

Table 3—Association of poor sleep quality with 3 models of PASC.

	COPE (≥ 3 Symptoms)		NICE (≥ 1 Symptom)		PASC Score (≥ 12)	
Model	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
Baseline	2.63§	2.39–2.90	2.36§	2.18–2.56	2.42§	2.17–2.71
+Demographics	2.56§	2.32–2.82	2.27§	2.09–2.47	2.36§	2.11–2.64
+Comorbidities	2.13§	1.91–2.38	1.92§	1.75–2.11	1.99§	1.75–2.25
+Socioeconomic	2.11§	1.89–2.37	1.92§	1.75–2.12	1.98§	1.75–2.25
+Sleep factors	2.00§	1.77–2.26	1.77§	1.60–1.97	1.89§	1.64–2.18

Models adjusted as follows (see text for definitions): Demographics: age, sex, race; Comorbidities: body mass index, number of the following conditions: diabetes, asthma, sickle cell disease, cardiovascular disease, hypertension, cancer, chronic kidney disease, liver disease, chronic obstructive pulmonary disease, boosted vaccination status; Socioeconomic: education, income, employment; Sleep factors: sleep duration, obstructive sleep apnea. §$P < .001$. aOR = adjusted odds ratio, CI = confidence interval, COPE = COVID-19 Outbreak Public Evaluation, NICE = National Institute for Health and Care Excellence, PASC = post-acute sequelae of SARS-CoV-2 infection.

Table 4—Odds ratio (adjusted) for association of self-reported hourly sleep duration with 3 models of PASC.

Sleep Duration#	n	COPE (≥ 3 Symptoms)				NICE (≥ 1 Symptom)				PASC Score (≥ 12)			
		Unadjusted		Fully Adjusted†		Unadjusted		Fully Adjusted†		Unadjusted		Fully Adjusted†	
		aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
3 hours	376	3.07§	2.45–3.84	1.56&	1.18–2.05	2.99§	2.42–3.71	1.49&	1.15–1.94	2.61§	2.03–3.35	1.40¶	1.04–1.89
4 hours	782	2.38§	2.00–2.82	1.57§	1.28–1.92	2.35§	2.01–2.74	1.57§	1.30–1.89	2.22§	1.83–2.70	1.55§	1.24–1.95
5 hours	1296	1.81§	1.56–2.09	1.23¶	1.03–1.48	1.75§	1.54–1.99	1.25&	1.07–1.46	1.66§	1.40–1.97	1.15	0.94–1.41
6 hours	1933	1.20¶	1.04–1.38	1.05	0.89–1.24	1.21§	1.08–1.36	1.09	0.95–1.25	1.15	0.97–1.35	0.99	0.82–1.20
7–8 hours	4135	Reference		Reference		Reference		Reference		Reference		Reference	
9 hours	523	1.05	0.83–1.34	0.96	0.71–1.28	1.05	0.86–1.28	0.92	0.72–1.17	1.06	0.80–1.40	0.92	0.66–1.30
10 hours	319	1.55§	1.18–2.04	1.15	0.83–1.61	1.59§	1.26–2.00	1.20	0.90–1.59	1.90§	1.42–2.54	1.34	0.94–1.92
11 hours	55	2.07¶	1.15–3.73	2.05	0.97–4.34	1.72¶	1.00–2.94	1.56	0.76–3.19	2.39&	1.27–4.48	2.45¶	1.13–5.31
12 hours	146	1.65&	1.12–2.43	1.15	0.73–1.82	2.10§	1.51–2.92	1.47	0.98–2.19	2.08§	1.38–3.12	1.53	0.95–2.46

#Self-reported sleep duration (3–12 hours); reference is 7–8 hours. †Fully adjusted model includes age, sex, race, body mass index, insomnia, number of comorbidities, education, income and employment, insomnia, obstructive sleep apnea, and poor sleep quality. ¶$P < .01$; §$P < .001$. aOR = adjusted odds ratio, CI = confidence interval, COPE = COVID-19 Outbreak Public Evaluation, NICE = National Institute for Health and Care Excellence, PASC = post-acute sequelae of SARS-CoV-2 infection.

1.23 (95% CI: 1.10–1.37, $P \leq .001$, NICE). Long sleep (n = 826) also was associated with a higher probability of PASC at baseline in all 3 models with aORs ranging from 1.33 (95% CI: 1.12–1.58, $P \leq .001$, COPE) to 1.50 (95% CI: 1.24–1.82, $P \leq .001$, PASC score). However, in contrast to short sleep, adjustment for demographic and socioeconomic factors, and sleep conditions as well as comorbidities negated these associations in fully adjusted models. The associations between short and long sleep, and all 3 models of PASC were not mitigated by having received a COVID-19 booster (sleep duration × boosted vaccination aORs were not significant, data not shown).

In sensitivity analyses, using a stricter definition of COVID-19 that required a positive test or loss of taste or smell, the positive associations between insomnia, poor sleep quality, and short sleep duration remained (data not shown). Similarly, using a less stringent definition of COVID-19 that allowed for a positive diagnosis for any unconfirmed report of infection did not alter these relationships (data not shown).

DISCUSSION

In this study, the prevalence of PASC among participants with a positive history of COVID-19 infection was estimated in a large U.S. general population cohort using 3 different models of PASC and found to range between 15.3% and 38.9%. In all 3 models, insomnia, poor sleep quality, and sleep shorter than recommended levels were highly prevalent and associated with PASC after adjustment for demographic, anthropometric, and socioeconomic factors, and comorbid medical conditions. In contrast, sleep longer than recommended was not related to PASC.

Although it is generally acknowledged that a substantial proportion of persons who develop acute COVID-19 infection have a multitude of lingering symptoms, there is no agreement on a unifying definition of PASC. Such a definition is important for public health case identification as well as for guiding future research. However, several definitions have been proposed using different requirements for number of symptoms and time elapsed after acute infection. In the current study, we estimated the prevalence of PASC using a definition proposed by NICE in the United Kingdom[12] and another modified from the RECOVER cohort in the U.S.[13] and compared them to one we developed for the COPE Initiative.[6] We found that among participants with a positive history of COVID-19 infection, prevalence estimates of PASC were 21.9%, 38.9%, and 15.3% using the COPE, NICE, and RECOVER models, respectively. In contrast, prevalence rates of 21.21% and 8.68% were observed using the NICE and PASC score definitions in a survey of the adult population of Mexico.[19] Analysis of the Behavioral Risk Factor Surveillance System (BRFSS) found a 21.7% prevalence using the NICE definition.[20] The prevalence of PASC in the RECOVER cohort was 23%,[13] but a much higher rate of 61% was noted in a study from the International COVID Sleep Study II (ICOSSII) group using the World Health Organization definition of at least 1 symptom lasting at least 3 months.[21] Notably, a meta-analysis of a heterogeneous array of 33 studies found an overall prevalence of 37% 30 days after infection with

Table 5—Association of self-reported sleep duration with 3 models of PASC.

	COPE (≥ 3 Symptoms)		NICE (≥ 1 Symptom)		PASC Score (≥ 12)	
Model	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
Sleep ≤ 6 hours#						
Unadjusted	1.70§	1.53–1.89	1.62§	1.51–1.81	1.59§	1.40–1.80
+Demographics	1.66§	1.49–1.85	1.61§	1.47–1.76	1.56§	1.37–1.76
+Comorbidities	1.52§	1.35–1.72	1.48§	1.33–1.64	1.41§	1.23–1.63
+Socioeconomic	1.55§	1.37–1.75	1.51§	1.36–1.68	1.43§	1.24–1.65
+Sleep factors	1.23§	1.08–1.41	1.23§	1.10–1.37	1.17§	1.01–1.36
Sleep ≥ 9 hours#						
Unadjusted	1.33§	1.12–1.58	1.36§	1.18–1.56	1.50§	1.24–1.82
+Demographics	1.20¶	1.01–1.43	1.22&	1.05–1.41	1.35&	1.11–1.64
+Comorbidities	1.05	0.86–1.28	1.05	0.89–1.24	1.18	0.95–1.48
+Socioeconomic	1.12	0.92–1.38	1.11	0.94–1.32	1.25	0.99–1.56
+Sleep factors	1.12	0.91–1.37	1.12	0.94–1.33	1.24	0.99–1.55

Models adjusted as follows (see text for definitions): Demographics: age, sex, race; Comorbidities: body mass index, number of the following conditions: diabetes, asthma, sickle cell disease, cardiovascular disease, hypertension, cancer, chronic kidney disease, liver disease, chronic obstructive pulmonary disease, boosted vaccination status; Socioeconomic: education, income, employment; Sleep factors: insomnia, obstructive sleep apnea, sleep quality. #Referent is 7–8 hours. ¶$P \leq .05$; &$P \leq .01$; §$P < .001$. aOR = adjusted odds ratio, CI = confidence interval, COPE = COVID-19 Outbreak Public Evaluation. NICE = National Institute for Health and Care Excellence, PASC = post-acute sequelae of SARS-CoV-2 infection.

a 95% CI between 26% and 49%.[22] The explanation for the considerable heterogeneity in PASC prevalence rates is not entirely clear, but investigations differed in both methods used to ascertain COVID-19 positivity and definition of PASC as well as in the population evaluated. Most studies utilized self-report of both COVID-19 infection and PASC associated symptoms,[6,20,21,23,24] but in some, objective documentation of infection was required resulting in lower prevalence rates.[13,19] To our knowledge, this is the first study in the U.S. to estimate prevalence rates of PASC using different definitions in the same cohort. The most appropriate definition to ultimately use may depend on which one best predicts clinical outcomes or responses to therapy although the simplicity of using either the COPE or NICE definitions argue for adoption by clinicians. However, by requiring only 1 PASC associated symptom, the NICE definition may be overly sensitive but is more consistent with the definition recently proposed by the U.S. National Academies of Sciences, Engineering, and Medicine.[14] In contrast, the RECOVER definition is more complex, but is likely more specific; the COPE definition may be a compromise among simplicity, sensitivity, and specificity.

We observed that among participants with a positive history of COVID-19 infection, both insomnia and poor sleep quality were strongly associated with PASC in all 3 of the models evaluated. With respect to insomnia, our results are consistent with data from a longitudinal study of 2,759 Italians in which higher pre-COVID-19 insomnia severity index scores were found to predict greater risk of individual symptoms of PASC 1–3 months after COVID-19 infection.[25] Our findings extend this previous report by demonstrating in a larger cohort that insomnia is associated with several global definitions of PASC. Additionally, our results related to poor sleep quality are supported by data from the aforementioned Italian cohort study which showed that higher scores on the Pittsburgh Sleep Quality Index predicted a greater risk for developing symptoms associated with PASC.[25] Furthermore, in a study of 1,581 persons from the United Kingdom who were surveyed concerning their sleep quality 1 month before their COVID-19 infection, persons who reported average to very poor sleep quality were 2.4–3.5 times more likely to self-report having "long COVID."[24] Our study extends these previous observations by using a more precise definition of poor sleep quality as well as more formal definitions of PASC.

Sleep duration ≤ 6 hours per night in comparison to recommended levels of 7–8 hours was found to be associated with PASC in all 3 models. Our findings replicate those noted in analyses of the BRFSS dataset in which < 7 hours of sleep were also associated with higher odds of PASC.[20] However, they differ from a report from the ICOSSII group who noted increased likelihood of PASC in those sleeping < 6 hours per night only among individuals who had pre-existing medical comorbidities; no association was observed in the absence of medical comorbidities.[21] In contrast to the strong association between short sleep duration and PASC, no such linkage was observed in our study for long sleep duration. Thus, our results with respect to long sleep duration are consistent with reports from the BRFSS and ICOSSII studies which also did not find increased odds of PASC with longer than recommended sleep duration.[20,21]

We observed that for all 3 PASC models, the prevalence of having received a COVID-19 booster vaccination was lower in persons with PASC. This finding is consistent with a meta-analysis of 18 studies[26] as well as with a recent large retrospective matched cohort study demonstrating that COVID-19 vaccination decreased the risk of developing PASC.[27] Previous results from

the COPE initiative indicated that receiving a COVID-19 booster vaccination reduced the risk of COVID-19 hospitalization attributable to OSA.[17] In contrast, we did not find that boosted vaccination for COVID-19 affected the odds of developing PASC related to insomnia, poor sleep quality or short sleep duration.

There are several mechanisms that could explain the association between insomnia, poor sleep quality, and short sleep duration, and PASC. Insomnia and most likely poor sleep quality are characterized by a state of stress and hyperarousal.[28] This can lead to alterations in the hypothalamic-pituitary-adrenal axis related to inflammation; in a meta-analysis, sleep disturbance was associated with higher levels of C reactive protein and interleukin-6.[29] Reduced sleep can result in an increase in transcriptional pathways and greater cellular production of inflammatory cytokines from monocytes.[30] Furthermore, it has been suggested that inflammatory processes are important in the pathogenesis of the dysautonomia, endothelial dysregulation, and neurocognitive impairments observed with PASC.[31] Sleep disturbances also have been implicated in dysfunction of the immune system. Chronic sleep loss and disturbed sleep promote not only a proinflammatory state, but also affect the number and function of immune regulating cells[32,33] and prolong shedding of SARS-CoV-2 after infection.[34] Both factors may promote viral persistence in tissues which is hypothesized as a mechanism resulting in PASC.[31,35]

Our findings that sleep disruption is associated with a greater likelihood of PASC suggest interventions improving sleep may mitigate or reduce the impact of PASC on overall public health. For example, information pertaining to the benefits of healthy sleep could be disseminated to persons who develop COVID-19 infection. Inasmuch as the prevalence of PASC in our study as well as others ranges between 26% and 49%,[22] even a small reduction in the incidence of PASC could have profound public health importance.

There are several limitations to the interpretation of our findings. First, sleep disturbances can occur de novo after acute COVID-19 infection particularly in hospitalized patients.[36–39] Our analyses are cross-sectional. Therefore, it is possible that the association between sleep disturbances and PASC observed in this study is largely a function of COVID-19 infection or PASC producing disturbed sleep. Second, sleep duration was self-reported. Self-reported sleep has historically overestimated sleep duration compared with the gold-standard objective measurement by polysomnography.[40] However, inasmuch as both 3 and 4 hours of sleep in this study were associated with PASC, it is unlikely that any overestimates of sleep duration would have been sufficiently extreme to alter our findings of an association between short sleep duration and PASC. Third, the sample could be susceptible to misclassification bias with respect to history of COVID-19 infection, as infection with COVID-19 was based on self-report and included dyssomnia and dysgeusia. However, in sensitivity analyses our findings were robust when incorporating less and more stringent criteria. Fourth, ascertainment of OSA as well as other covariates in our models was self-reported. Although this may have resulted in some misclassification of these factors, we have no reason to believe that it was differential. Therefore, to the extent that some misclassification existed, this would have biased our findings to the null. Finally, the COPE survey did not include all of the symptoms included in the RECOVER PASC score, which had not been published at the time the COPE survey was developed and initially administered. Nevertheless, the findings observed with our modification of the PASC score were consistent with the COPE and NICE definitions suggesting that they were similarly representative of participants with PASC.

In summary, the prevalence of PASC ranged between 15.3% and 38.9% in persons who previously had a COVID-19 infection. Insomnia, poor sleep quality, and short sleep duration are highly prevalent and associated with higher odds of PASC. Boosted vaccination for COVID-19 did not affect these observations. These findings emphasize the importance of sleep disturbance in COVID-19 infection and PASC. Further longitudinal studies are indicated to determine whether sleep disturbances are risk factors for the development of PASC.

ABBREVIATIONS

aOR, adjusted odds ratio
BRFSS, Behavioral Risk Factor Surveillance System
CI, confidence interval
COPE, COVID-19 Outbreak Public Evaluation
NICE, National Institute for Health and Care Excellence
ICOSSII, International COVID Sleep Study II
OSA, obstructive sleep apnea
PASC, post-acute sequelae of SARS-CoV-2 infection
RECOVER, Researching COVID to Enhance Recovery
U.S., United States

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ACKNOWLEDGMENTS

Author contributions: Concept and design: S.F.Q. Data collection: M.D.W., M.É.C., M.E.H. Data analysis and interpretation: S.F.Q., M.E.H., C.F.M., M.L.J., M.E.H. Drafting of the manuscript: S.F.Q. Critical feedback and revision of manuscript: S.F.Q., M.D.W., M.É.C., L.K.B., L.A.B., M.E.H., M.L.J., R.L., C.F.M., A.R., R.R., P.V., S.M.W.R., C.A.C.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication June 24, 2024
Submitted in final revised form September 12, 2024
Accepted for publication September 13, 2024
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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Conflicts of Interest: M.D.W. reports institutional support from the United States Centers for Disease Control and Prevention, National Institutes of Occupational Safety and Health, and Delta Airlines as well as consulting fees from the Fred Hutchinson Cancer Center and the University of Pittsburgh. L.K.B. reports institutional support from the United States Centers for Disease Control and Prevention, National Institutes of Occupational Safety and Health, Delta Airlines, and the Puget Sound Pilots as well as honorariums from the National Institutes of Occupational Safety and Health, University of Arizona, and University of British Columbia. M.É.C. reported personal fees from Vanda Pharmaceuticals Inc., research grants or gifts to Monash University from WHOOP, Inc., Hopelab, Inc., CDC Foundation, and the Centers for Disease Control and Prevention. S.M.W.R. reported receiving grants and personal fees from Cooperative Research Centre for Alertness, Safety, and Productivity, receiving grants and institutional consultancy fees from Teva Pharma Australia and institutional consultancy fees from Vanda Pharmaceuticals, Circadian Therapeutics, BHP Billiton, and Herbert Smith Freehills. S.F.Q. has served as a consultant for Best Doctors, Bryte Foundation, Jazz Pharmaceuticals, Apnimed, and Whispersom. R.R. reports personal fees from SleepCycle AB; Rituals Cosmetics BV; Sonesta Hotels International, LLC; Ouraring Ltd; AdventHealth; and With Deep, LLC. C.A.C. serves as the incumbent of an endowed professorship provided to Harvard Medical School by Cephalon, Inc. and reports institutional support for a Quality Improvement Initiative from Delta Airlines and Puget Sound Pilots; education support to Harvard Medical School Division of Sleep Medicine and support to Brigham and Women's Hospital from: Jazz Pharmaceuticals PLC, Inc., Philips Respironics, Inc., Optum, and ResMed, Inc.; research support to Brigham and Women's Hospital from Axome Therapeutics, Inc., Dayzz Ltd., Peter Brown and Margaret Hamburg, Regeneron Pharmaceuticals, Sanofi SA, Casey Feldman Foundation, Summus, Inc., Takeda Pharmaceutical Co., Ltd., Abbaszadeh Foundation, CDC Foundation; educational funding to the Sleep and Health Education Program of the Harvard Medical School Division of Sleep Medicine from ResMed, Inc., Teva Pharmaceuticals Industries, Ltd., and Vanda Pharmaceuticals; personal royalty payments on sales of the Actiwatch-2 and Actiwatch-Spectrum devices from Philips Respironics, Inc.; personal consulting fees from Axome, Inc., Bryte Foundation, With Deep, Inc., and Vanda Pharmaceuticals; honoraria from the Associated Professional Sleep Societies, LLC for the Thomas Roth Lecture of Excellence at SLEEP 2022, from the Massachusetts Medical Society for a New England Journal of Medicine Perspective article, from the National Council for Mental Wellbeing, from the National Sleep Foundation for serving as chair of the Sleep Timing and Variability Consensus Panel, for lecture fees from Teva Pharma Australia PTY Ltd. and Emory University, and for serving as an advisory board member for the Institute of Digital Media and Child Development, the Klarman Family Foundation, and the United Kingdom Biotechnology and Biological Sciences Research Council. C.A.C. has received personal fees for serving as an expert witness on a number of civil matters, criminal matters, and arbitration cases, including those involving the following commercial and government entities: Amtrak; Bombardier, Inc.; C&J Energy Services; Dallas Police Association; Delta Airlines/Comair; Enterprise Rent-A-Car; FedEx; Greyhound Lines, Inc./Motor Coach Industries/FirstGroup America; PAR Electrical Contractors, Inc.; Puget Sound Pilots; and the San Francisco Sheriff's Department; Schlumberger Technology Corp.; Union Pacific Railroad; United Parcel Service; Vanda Pharmaceuticals. C.A.C. has received travel support from the Stanley Ho Medical Development Foundation for travel to Macao and Hong Kong; equity interest in Vanda Pharmaceuticals, With Deep, Inc., and Signos, Inc.; and institutional educational gifts to Brigham and Women's Hospital from Johnson & Johnson, Mary Ann and Stanley Snider via Combined Jewish Philanthropies, Alexandra Drane, DR Capital, Harmony Biosciences, LLC, San Francisco Bar Pilots, Whoop, Inc., Harmony Biosciences LLC, Eisai Co., LTD, Idorsia Pharmaceuticals LTD, Sleep Number Corp., Apnimed, Inc., Avadel Pharmaceuticals, Bryte Foundation, f.lux Software, LLC, Stuart F. and Diana L. Quan Charitable Fund. Dr. Czeisler's interests were reviewed and are managed by the Brigham and Women's Hospital and Mass General Brigham in accordance with their conflict of interest policies. No other disclosures were reported.

Preprint Information: A preprint of this manuscript has posted on medRxiv.
Funding Information: This work was supported by the Centers for Disease Control and Prevention. Dr. M. Czeisler was supported by an Australian-American Fulbright Fellowship, with funding from The Kinghorn Foundation. The salaries of Dr. Barger, Dr. Czeisler, Dr. Robbins, and Dr. Weaver were supported, in part, by National Institute for Occupational Safety and Health R01 OH011773 and National Heart, Lung, and Blood Institute (NHLBI) R56 HL151637. Dr. Robbins also was supported in part by NHLBI K01 HL150339.