Risk of post-acute sequelae of SARS-CoV-2 infection associated with pre-coronavirus disease obstructive sleep apnea diagnoses: an electronic health recordbased analysis from the RECOVER initiative

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Abstract

Study Objectives: Obstructive sleep apnea (OSA) has been associated with more severe acute coronavirus disease-2019 (COVID-19) outcomes. We assessed OSA as a potential risk factor for Post-Acute Sequelae of SARS-CoV-2 (PASC).

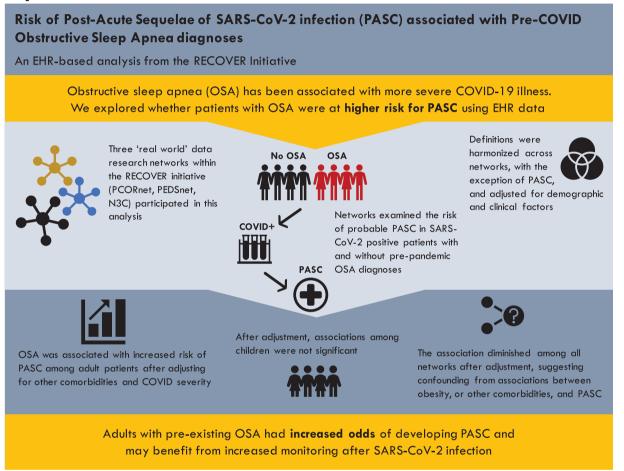
Methods: We assessed the impact of preexisting OSA on the risk for probable PASC in adults and children using electronic health record data from multiple research networks. Three research networks within the REsearching COVID to Enhance Recovery initiative (PCORnet Adult, PCORnet Pediatric, and the National COVID Cohort Collaborative [N3C]) employed a harmonized analytic approach to examine the risk of probable PASC in COVID-19-positive patients with and without a diagnosis of OSA prior to pandemic onset. Unadjusted odds ratios (ORs) were calculated as well as ORs adjusted for age group, sex, race/ethnicity, hospitalization status, obesity, and preexisting comorbidities.

Results: Across networks, the unadjusted OR for probable PASC associated with a preexisting OSA diagnosis in adults and children ranged from 1.41 to 3.93. Adjusted analyses found an attenuated association that remained significant among adults only. Multiple sensitivity analyses with expanded inclusion criteria and covariates yielded results consistent with the primary analysis.

Conclusions: Adults with preexisting OSA were found to have significantly elevated odds of probable PASC. This finding was consistent across data sources, approaches for identifying COVID-19-positive patients, and definitions of PASC. Patients with OSA may be at elevated risk for PASC after SARS-CoV-2 infection and should be monitored for post-acute sequelae.

Key words: Post-acute sequelae COVID-19; Long COVID; Chronic COVID-19 Syndrome; Late sequelae of COVID-19; Long haul COVID-19; Long-term COVID-19; Post COVID-19 syndrome; Post-acute COVID-19; Post-acute sequelae of SARS-CoV-2 infection; Sleep Apnea; Obstructive.

Graphical Abstract



Statement of Significance

Recent studies have identified a positive association between obstructive sleep apnea (OSA) and acute coronavirus disease-2019 (COVID-19) outcomes, but few studies have examined outcomes beyond acute illness. This is the first large-scale, multi-cohort collaboration to examine the role of preexisting OSA on risk for Post-Acute Sequelae of SARS-CoV-2 (often referred to as Long COVID). Notably, our analysis was conducted across multiple data sources, employed different approaches for identifying COVID-19-positive patients, and used multiple definitions of Long COVID. While we found consistent evidence of elevated risk for Long COVID among adults with preexisting OSA, additional research is needed to elucidate the role of severity, and treatment.

Introduction

Post-Acute Sequelae of SARS-CoV-2 infection (PASC) refers to ongoing, relapsing, or new symptoms, or other health effects occurring after the acute phase of SARS-CoV-2 infection (i.e. present four or more weeks after the acute infection). Recent studies

estimate that between 7% and 54% of coronavirus disease-2019 (COVID-19) patients may develop PASC, and that risk may vary by sex, age, and certain preexisting conditions [1–3]. However, the impact of preexisting conditions on the risk of developing PASC is not well elucidated.

Obstructive sleep apnea (OSA) has been proposed as a potential risk factor for PASC, warranting further research [4]. OSA is characterized by repeated obstruction of airways during sleep, resulting in disrupted breathing, interrupted sleep, and blood oxygen desaturation. OSA is highly prevalent, affecting approximately twenty percent of adults in the United States, and is associated with a high risk of a number of comorbidities including obesity, hypertension, and diabetes [5].

Recent studies have identified a positive association between OSA and acute COVID-19 outcomes [6–8]. In a 2022 meta-analysis, Hu et al. found that patients with OSA were at higher risk for fatal COVID-19 after adjusting for age and acute infection hospitalization status [7]. Similarly, Hariyanto and Kurniawan identified a significant association between OSA and severe COVID-19, intensive care unit admission, ventilation, and mortality in a meta-analysis of 21 studies [6]. Looking beyond acute outcomes, Labarca et al. identified significantly higher rates of abnormal pulmonary function and mental impairment among COVID-19 survivors with versus without preexisting comorbid OSA one year after COVID-19 infection [4], and multiple studies found increased sleep-related symptoms or disordered sleep in PASC patients [9, 10].

Prior studies have demonstrated that algorithms designed to identify patients with an OSA diagnosis from electronic health records (EHRs) have excellent validity. For example, in a multisite analysis of six institutions, Keenan et al reported a positive predictive value of 97.1 and negative predictive value of 95.5 using a diagnosis-based computable phenotype (CP) [11]. As part of the National Institutes of Health (NIH)-funded REsearching COVID to Enhance Recovery (RECOVER) Initiative, three "real-world data analysis" research teams collaborated to assess the impact of pre-existing OSA on the risk for PASC in adults and children, through a harmonized analysis across all three RECOVER EHR research networks [12].

Methods

Participating institutions

RECOVER is a large NIH-funded initiative designed to investigate the long-term effects of COVID-19. RECOVER includes projects leveraging real-world data from EHRs to develop and validate algorithms to detect PASC for clinical and epidemiological characterization, risk factor prediction, and investigation of prevention and treatment opportunities. RECOVER's EHRbased efforts include research teams from three participating research networks: the National COVID Cohort Collaborative (N3C); the National Patient-Centered Clinical Research Network (PCORnet) limited to adults aged 18 and older; and PCORnet's pediatric population, anchored in PEDSnet, a pediatric learning health system within PCORnet. These networks are coordinated by a clinical science core (CSC) at NYU Langone Health. For this study, the RECOVER EHR networks and CSC collaborated to produce a harmonized analysis investigating the impact of preexisting OSA on the risk of probable PASC. N3C drew analyses from over 15 million patients across 77 data partners in the N3C Enclave [13]. Of the 77 participating sites, 13 were removed due to data quality issues. PCORnet selected from 11 million patients from 19 sites including institutions within the INSIGHT, ReachNet, OneFlorida, STAR, Greater Plain Collaborative, and PaTH Clinical Research Networks, and PEDSnet selected from 8.5 million patients across eight pediatric health systems.

Analysis Plan

For this study, in collaboration with the CSC, each network independently generated distinct CP definitions to identify probable PASC patients (Table 1) and applied those definitions in a harmonized analysis to examine the risk of probable PASC in patients

Network	Approach	PASC computable phenotype
N3C	Machine- learning- based definition	 Adult patients with all of the following within 100 to 190 days after the index date: ≥18 years old ≥2 days of data ≥1 diagnosis and ≥1 medication in the pre-/post-index period Who are likely to have PASC based on a model trained to identify patients who have previously visited a Long COVID clinic
PCORnet	Rules- based definition	 Adult patients with all of the following: ≥1 diagnosis and ≥1 medication in the pre-/post-index period. ≥1 incident diagnosis belonging to a list of 25 CCSR codes within 30 to 180 days after the index date (truncated at end of study period) with no prior diagnosis recorded before the index date. The 25 CCSR codes are established to have higher incidence rates in COVID positive patients, derived through prior literature and clinician review.
PEDSnet	Rules- based definition	 Pediatric patients with any of the following within 28 to 179 days after the index date: Clinician-assigned PASC or MIS-C diagnosis. ≥2 occurrences of diagnosis codes for one of the following: Abnormal liver enzymes Myocarditis Anosmia Myositis Dysgeusia Pericarditis Chest pain Thrombophlebitis/thromboembolism COVID-19

 Table 1. PASC Computable Phenotype Definition Across Three EHR Networks

Networks took different approaches to identify patients with probable PASC within the EHR. CCSR, Clinical Classifications Software Refined; MIS-C, Multisystem Inflammatory Syndrome in Children.

with and without evidence of an OSA diagnosis prior to pandemic onset. CPs included a machine learning definition trained on patients who previously visited a Long COVID clinic [14], and rules-based definitions involving clinical diagnoses, labs, and medications.

Patients were eligible for inclusion in this analysis if they had a documented COVID-19 infection within the study period (March 1, 2020–February 28, 2022), as determined by a positive SARS-CoV-2 polymerase chain reaction or antigen test. If there were multiple indicators of positivity for COVID-19 infection within the period, we considered the earliest instance to be the index event. We excluded patients with sparsely populated records, requiring all patients included to have two or more visits within the health system within the two years before their index event. As sufficient time is necessary to develop PASC after an acute infection, we also excluded patients if they died within 30 days of the index event. To clearly differentiate results for adults and children, N3C and PCORnet restricted their analyses to adults aged 21 and older, while PEDSnet was restricted to children under age 21 (Supplementary Figure 1).

Given challenges in leveraging polysomnography and symptom questionnaire data within multisite EHR-based analyses, we identified patients as having preexisting OSA if they had documentation of at least two records of any relevant International Statistical Classification of Diseases and Related Health Problems - Clinical Modification (ICD-10-CM) diagnostic codes (G47.30, G47.33, G47.39; ICD-9-CM: 327.20, 327.23, 327.29, 780.51, 780.53, and 780.57) or the equivalent Systematized Nomenclature of Medicine - Clinical Terms (SNOMED-CT) codes on separate days. This approach has been leveraged for prior analyses [11, 15] and demonstrated success over multiple sites. We sought evidence of OSA within two years prior to the study period (March 1, 2018– March 1, 2020), the duration of historical EHR data that was consistently available across all three cohorts.

Statistical analysis

We estimated unadjusted and adjusted odds ratios (ORs) using logistic regression models with 95% confidence intervals to evaluate the association between a preexisting diagnosis of OSA and probable PASC. We developed three adjusted models: (1) adjusting for age group (N3C and PCORnet: ([21-35, 36-45, 46-55, 56-65, and ≥65], PEDSnet [0-4, 5-9, 10-15, and 16-20]), sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, other, and unknown), (2) additionally adjusting for hospitalization status during the index SARS-CoV-2 infection as a proxy for infection severity, a risk factor for PASC [16], with documentation of hospitalization and COVID-19 or nonspecific active infection within one day prior to 16 days following the index event (not hospitalized, hospitalized, or hospitalized with evidence of Intensive Care Unit admission, ventilator use, or vasopressors), and (3) additionally adjusting for obesity (N3C and PCORnet: body mass index ≥30 or >1 diagnosis code, PEDSnet: body mass index percentile ≥ 95th using NHANES norms) and comorbidities (N3C and PCORnet: Charlson Comorbidity Index [CCI [17]], PEDSnet: Pediatric Medical Complexity Algorithm [PMCA [18]]) within two years prior to the index event. For this study, OSA codes were excluded from the PMCA.

As a sensitivity analysis, we then repeated our analyses using a wider set of eligibility criteria, identifying patients as COVID-19 positive based on lab results in addition to one inpatient or two outpatient instances of code U07.1 (ICD-10-CM). We also varied our initial models to investigate whether adjusting for (1) preexisting hypertension and diabetes instead of comorbidity score, (2) SARS-CoV-2 variant epoch of the index infection, or (3) pediatric asthma influenced the association, in addition to an interaction analysis by sex.

Results

We have summarized demographic characteristics of patients identified through positive lab tests from each network in Table 2. The N3C network comprised 1 783 940 COVID-19 patients. A total of 3.9% of N3C patients had preexisting OSA and 4.9% were identified as having probable PASC. The PCORnet network comprised 333 642 patients, of which 5.1% had preexisting OSA and 16.6% were identified with probable PASC. Finally, the PEDSnet network comprised 106 262 pediatric patients, of which 1.8% had preexisting OSA and 4.6% were identified as having probable PASC.

We estimated ORs for probable PASC by comparing patients with and without a preexisting OSA diagnosis (Table 3 and Supplementary Figure 2). The unadjusted odds of probable PASC were 1.41–3.93 times greater among adults with a preexisting OSA diagnosis than those without evidence of OSA (N3C, OR: 3.93, 95% CI: 3.84, 4.02; PCORnet, OR: 1.41, 95% CI: 1.36, 1.46). The association was attenuated yet still elevated after successively adjusting for demographic factors, hospitalization, obesity, and comorbidities.

Results followed a similar pattern in children (PEDSnet unadjusted OR: 3.28, 95% CI: 2.85, 3.76). This association was attenuated yet still elevated after adjusting for demographic factors alone and together with hospitalization. After additionally adjusting for obesity and comorbidities, no significant difference in the odds of probable PASC was found when comparing children with and without OSA (PEDSnet: 1.05, 95% CI: 0.89, 1.24).

In a subsequent sensitivity analysis, we reexamined the association between preexisting OSA and probable PASC development among patients with either a positive lab test or a diagnosis indicating COVID-19, to assess the impact of the inclusion criteria on the study outcome (Supplementary Table 1). Through this expanded inclusion criteria, an additional 2999 PEDSnet patients, 78 103 PCORnet patients, and 185 928 N3C patients were included in the analysis. The resulting ORs from the three sites generated similar results to those of the primary analysis: the odds of developing probable PASC were higher among patients with preexisting OSA compared to those without preexisting OSA after adjusting for sex, race/ethnicity, age group, and hospitalization at the time of the index infection.

Further sensitivity analyses, additionally adjusting for pediatric asthma or variant epoch of the index infection, did not meaningfully change the results (Supplementary Table 2). When adjusting for hypertension and diabetes instead of comorbidity score, the association changed minimally for adults though was no longer significant in PCORnet (1.03, 95% CI: 1.00, 1.07 vs. 0.91, 95% CI: 0.88, 0.95). Within the pediatric population, this modification strengthened the association (PEDSnet: 1.07, 95% CI: 0.92, 1.25 vs. 1.95 vs. 95% CI: 1.67, 2.27).

Finally, interaction analysis results were not significant in PEDSnet or PCORnet. In N3C, results indicated that evidence of OSA in men increases odds of PASC by 59%, compared with an 89% increase in women (p < .001).

Table 2. Patient Characteristics by EHR Network

	N3C	PCORnet	PEDSnet
Total	1 783 940	333 642	106 262
Age			
D4	_	_	37 852 (35.62%)
5–9	_	_	23 937 (22.53%)
10–15	_	_	28 374 (26.7%)
16–20	_	_	16 099 (15.15%)
21–35	493 596 (27.67%)	86 503 (25.93%)	_
36-45	328 361 (18.41%)	57 766 (17.31%)	_
46–55	327 465 (18.36%)	56 181 (16.84%)	_
56–65	310 112 (17.38%)	58 837 (17.63%)	_
≥66	324 406 (18.18%)	74 355 (22.29%)	_
Sex			
Male	678 446 (38.03%)	133 161 (39.91%)	54 679 (51.46%)
Female	1 104 905 (61.94%)	200 393 (60.06%)	51 577 (48.54%)
Unknown	589 (0.03%)	88 (0.03%)	6 (0.01%)
Race/ethnicity			
Non-Hispanic white	1 215 790 (68.15%)	167 431 (50.18%)	45 953 (43.24%)
Non-Hispanic black	229 908 (12.89%)	60 424 (18.11%)	23 404 (22.02%)
Hispanic	189 593 (10.63%)	45 544 (13.65%)	17 684 (16.64%)
Non-Hispanic Asian	28 251 (1.58%)	10 881 (3.26%)	3717 (3.5%)
Native Hawaiian or Other Pacific Islander	_	533 (0.16%)	_
American Indian or Alaska Native	_	834 (0.25%)	_
Other	29 360 (1.65%)	10 509 (3.15%)	7998 (7.53%)
Missing/Unknown	91 038 (5.10%)	37 486 (11.24%)	7506 (7.06%)
Hospitalization ^a			
Hospitalized	149 308 (8.37%)	59,056 (17.70%)	5009 (4.71%)
Hospitalized with ICU level care	17 578 (0.99%)	15,838 (4.75%)	949 (0.89%)
Jariant epoch of index infection			
Alpha (Oct 1, 2020–Jun 30, 2021)	687 524 (38.54%)	119 952 (35.95%)	6230 (5.86%)
Ancestral (Mar 1, 20/20–Sept 30, 2020)	175 714 (9.85%)	55 393 (16.60%)	34 135 (32.12%)
Delta (Jul 1, 2021–Nov 30, 2021)	346 083 (19.40%)	48 562 (14.56%)	21 661 (20.38%)
Omicron (Dec 1, 2021–Present)	574 619 (32.21%)	109 735 (32.89%)	44 236 (41.63%)
PASC			
Has probable PASC	86 966 (4.87%)	55 219 (16.55%)	4902 (4.61%)
PMCA body system count ^b			
)	_	_	74 645 (70.25%)
1	_	_	20 001 (18.82%)
2	—	—	6187 (5.82%)
3-4	_	_	3586 (3.37%)
5-17	_	_	1843 (1.73%)
CCI score ^c			_
Mean ± SD	1.00 (1.88)	0.52 (1.11)	_
Clinical conditions	•	· · ·	
Preexisting obstructive sleep apnea	69 590 (3.90%)	17 126 (5.13%)	1860 (1.75%)

Table 2. Continued

	N3C	PCORnet	PEDSnet
Obesity ^d	458 025 (25.67%)	102 963 (30.86%)	16 583 (15.61%)
Essential hypertension ^e	493 321 (27.65%)	107 915 (32.34%)	1292 (1.22%)
Diabetes ^f	228 701 (12.82%)	53 722 (16.10%)	877 (0.83%)
Asthma ^g	_	_	1134 (1.07%)

Clinical and demographic characteristics of patients meeting the study inclusion criteria. CCI (Charlson Comorbidity Index).

^aHospitalized with no indication of severe illness, or hospitalization with evidence of ventilation, admittance to the Intensive Care Unit, or vasopressors. Hospitalization must have taken place on the day prior through 16 days following the index event, with COVID-19 diagnosis, or other indication of active infection documented during the same timeframe.

^bPediatric Medical Complexity Algorithm (PMCA) Body System Count was used as a measure of comorbidities in children.

°CCI Score was used as a measure of comorbidities in adults.

^dMultiple diagnosis codes or a Body Mass Index > 30 (adults), or Body Mass Index > 95th percentile per Centers for Disease Control and Prevention guidelines (children), within two years prior to the index event.

^eEncompasses essential hypertension in adults or children within two years prior to the index event.

Encompasses Type 2 Diabetes in adults, and Type 1 or 2 Diabetes in children, within two years prior to the index event.

«For pediatric patients aged ≥5 years at their most recent diagnosis or medication prescription, asthma within two years prior to the index event. Asthma status was determined using a computable phenotype described by Ashfar et al. [19] and modified for application to PEDSnet data. Patients were identified as having asthma if they met the following criteria: Either (1) asthma diagnoses on two separate dates, or (2) an asthma diagnosis code and asthma medication.

Table 3. Association of preexisting OSA and PASC by EHR Ne
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Prior OSA	With PASC	Without PASC	Unadjusted OR (95% CI)	Model 1ª OR (95% CI)	Model 2 ^b OR (95% CI)	Model 3º OR (95% CI)
Yes	N3C: 10 756 (15.5%) PCORnet: 3681 (21.5%) PEDSnet: 247 (13.3%) N3C: 76 210 (4.4%) PCORnet: 51 538 (16.3%) PEDSnet: 4655 (4.5%)	N3C: 58 834 (84.5%) PCORnet: 13 445 (78.5%) PEDSnet: 1613 (86.7%) N3C: 1 638 140 (95.6%) PCORnet: 264 978 (83.7%) PEDSnet: 99 747 (95.5%)	N3C: 3.93 (3.84, 4.02) PCORnet: 1.41 (1.36, 1.46) PEDSnet: 3.28 (2.85, 3.76)	3.15 (3.08, 3.22) 1.22 (1.18, 1.27) 3.26 (2.83, 3.73)	2.92 (2.85, 2.99) 1.17 (1.13, 1.22) 2.24 (1.92, 2.61)	1.75 (1.71, 1.80) 1.12 (1.08, 1.16) 1.05 (0.89, 1.24)

Odds ratios and 95% CI for association of preexisting OSA and probable PASC. CI, Confidence Interval.

^aAdjusted for age group, sex, and race/ethnicity.

^bAdjusted for age group, sex, race/ethnicity, and hospitalization status.

Adjusted for age group, sex, race/ethnicity, hospitalization status, obesity, and comorbidities.

Discussion

In this harmonized analysis, we found that preexisting OSA was associated with increased risk of PASC-like conditions among adult patients in the RECOVER EHR research networks, despite different approaches for identification of probable PASC patients. The positive associations between preexisting OSA and probable PASC among adults were attenuated but remained significant after adjusting for other comorbidities. In contrast, associations among children were no longer significant after comorbidity adjustment. Sensitivity analyses modifying covariates did not meaningfully alter the results for adults. However, sensitivity analyses for children demonstrated the susceptibility of the association to the potential confounding influence of various comorbidities, with different effect estimates when adjusting for asthma, PMCA, or hypertension and diabetes.

Indeed, we observed that the strength of the association diminished among all three networks after adjusting for obesity and comorbidities, which suggests that the observed risk may in part be due to confounding from underlying associations between obesity, or other comorbidities, and PASC. Obesity is a particularly well-known risk factor for both OSA and severity of acute COVID infections, and was most prevalent in PCORnet, suggesting that obesity may account for some of the apparent difference in OSAassociated risk for PASC outcomes between networks [20, 21].

A notable strength of our study is the consistency of positive associations between OSA and PASC risk among adults across multiple data sources, approaches for identifying COVID-19-positive patients, and definitions of probable PASC. Because identification of PASC within patient populations has proved challenging due to heterogeneity of symptoms and lack of an accepted case definition, this study included a range of PASC definitions that were either more sensitive or more specific to examine the association [22].

Our analysis had several limitations. First, COVID diagnoses may not be well documented within the EHR, especially given limited availability of testing during early months of the pandemic, lower testing accuracy among women and people under 40 [23], and, more recently, increasingly widespread use of at-home testing.

Second, our analysis did not adjust for COVID vaccination status, as few EHR data networks adequately capture this, and the networks in this collaboration are still establishing data linkages to statewide vaccination registries to improve COVID vaccination data quality. Race and ethnicity data also varied in completeness across networks, which is consistent with prior studies [24, 25]. After initial exploratory analysis, we chose not to pursue whether active treatment of OSA altered findings, due to concerns that continuous positive airway pressure (CPAP) machine orders are not being routinely transmitted from participating sites to EHR networks and would be more reliably explored using claims data. Finally, our CP could only identify patients with diagnosed OSA, and OSA severity could not be ascertained due to the lack of polysomnography and sleep-specific symptom data. This means that results may not be generalizable across the spectrum of OSA severity or phenotype.

We also noted that the prevalence of OSA in our analyses was lower than in some published studies [15], though consistent with estimated prevalence of OSA in EHR-based data warehouses and claims databases [26]. This discrepancy may be due to the limited (two year) lookback period that was used for this analysis. It is possible that individuals diagnosed with sleep apnea prior to a SARS-CoV-2 infection are more likely to seek care from a Long COVID clinic or be diagnosed with PASC, due to increased encounters with the healthcare system. Nevertheless, OSA is often underdiagnosed in clinical practice and therefore might be present in patients not detected by our computable phenotyping strategy.

PASC is not one cohesive condition, but rather multiple constellations of symptoms or sub-phenotypes [27]. This analysis did not determine what symptoms were most prevalent in patients with OSA who develop probable PASC, but future research could examine the association of OSA and other preexisting conditions with specific PASC variations and the trajectory of impacted patients. The RECOVER Initiative also includes the recruitment and longitudinal follow-up of large cohorts of adult and pediatric participants with and without history of SARS-CoV-2 infection (>10 000 participants in each cohort) [28]. In these cohorts, patient history of OSA prior to SARS-CoV-2 infection and the development of probable PASC will be assessed directly without relying solely on EHR diagnoses. Nonetheless, these findings suggest that patients with OSA may be at elevated risk for PASC after SARS-CoV-2 and should be monitored for post-acute infection sequelae.

Supplementary Material

Supplementary material is available at SLEEP online.

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Author Contribution

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Data Availability

The N3C data transfer to NCATS has been performed under a Johns Hopkins University reliance protocol (IRB00249128) or individual site agreements with the NIH. The N3C Data Enclave is managed under the authority of the NIH; more information can be found at ncats.nih.gov/n3c/resources. All data is available in the N3C Data Enclave to those with an approved protocol and data use request from an institutional review board. Data access is governed under the authority of the National Institutes of Health; more information on accessing the data can be found at https://covid.cd2h.org/for-researchers. Please send all other data access requests to the corresponding author, who will direct them accordingly.

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