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Editorial

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Obstructive sleep apnea association with post-acute sequelae of Severe acute respiratory syndrome coronavirus 2: insights from the NIH researching coronavirus disease 2019 to enhance recovery initiative and a call for action

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Post-Acute Sequelae of SARS-COV-2 (PASC) continues to represent a global public health burden, yet to be understood, in which a substantial number of patients experience a myriad of debilitating symptoms that last beyond 4 weeks after SARS-COV-2 acute onset infection [1]. Sleep disturbances and fatigue are ranked in the top three PASC symptoms afflicting approximately 30% of the over 100 million individuals infected in the United States and this number continues to rise [2]. The scope of PASC-related sleep disturbance is vast and of high priority given the alarming societal, personal, and estimated economic costs compared to the $14.5 billion/annum estimated health care costs for myalgicence encephalomyelitis and chronic fatigue syndrome [3]. Obstructive sleep apnea (OSA) has been associated with worse coronavirus disease 2019 (COVID-19) clinical outcomes [4], however our understanding of the relationship of OSA and PASC remains limited. Recent literature reflects a high prevalence of 41% of moderate to severe sleep disturbances in patients with PASC; however, a significant association of objective sleep study measures of antecedent sleep apnea and hypoxia was not observed—likely due to small sample size [5].

In this issue of *SLEEP*, we welcome the study of *Mandel* et al. which is the largest multi-cohort study investigating the association of OSA as a possible risk factor for developing probable PASC in adults and children. Investigators analyzed three large clinical cohorts (~2.2 million individuals) from research networks that are part of the NIH researching COVID to enhance recovery (RECOVER) Initiative [6] which leverages data from Electronical Health Records. Data from both adult and pediatric research networks were included, i.e. PCORnet Adult, PCORnet Pediatric, and the National COVID Cohort Collaborative (N3C])utilizing a harmonized analytic approach. Machine learning and rules-based definitions were used to define probable PASC. The reported prevalence of preexisting OSA was 3.9%–5.1% and PASC prevalence was 4.9%–16.6%. In the pediatric cohort, the prevalence of preexisting OSA was 1.8%–4.6% for probable PASC. Adult patients with preexisting OSA had an increased odds for probable PASC compared to those without OSA. However, in the pediatric cohort, there was no significant difference in PASC between those with versus without OSA. In a sensitivity analysis after adjusting for hypertension and diabetes, the association of preexisting OSA with the risk of probable PSC was no longer significant in one of the adult cohorts; however, in the pediatric population, the association became stronger in models adjusted for confounders. Sex-specific differences were observed such that OSA in men increased odds of PASC by 59%, compared to 89% increased odds in women ($p < .001$).

The authors conclude that preexisting OSA is associated with the development of probable PASC. There are several important points to consider in the interpretation of these findings. First, even though the usage of three different large RECOVER networks is a major strength as it provides a large sample size, the lack of standardized PASC and OSA definitions may have resulted in heterogeneity among all three samples, likely biasing the results towards the null. Registry-based research using electronic medical record data is also prone to relative under-diagnosis when based upon International Classification Disease codes resulting in a likely underestimate and less stringency in OSA exposure ascertainment. Also, the inability to specify PASC symptom subtypes and OSA phenotypes prevents the ability to understand which pathophysiologic correlates of OSA may contribute to specific subtypes of PASC. Second, previous studies have reported a PASC prevalence with range from 35% to 87% based on the follow-up period, reported symptoms, and hospitalization status [7–9]. However, the reported PASC prevalence in this study is

lower, which may be explained by the variability across datasets, possible under-recognition of PASC, and potentially attributable to different algorithms used to extract the data. Third, the lack of association of preexisting OSA and probable PASC in children likely is explained by high prevalence of obesity as previous data have shown that obesity is associated with PASC in children and adolescents [10]. Fourth, OSA severity could not be ascertained due to lack of polysomnographic data, thereby precluding ability to characterize dose–response relationships with PASC and association of sleep-related hypoxia, the latter observed to be associated with worse clinical outcomes and mortality in COVID-19 [4]. Fifth, lack of treatment data limits effective interpretation of findings and would be expected to also bias to the null. Sixth, the prevalence of non-Hispanic black individuals in the largest of the cohorts (N3C) was 12.9% and there was missingness of data specific to race/ethnicity which may have limited ability to detect race-specific interactions. Amassing data underscore racial disparities in PASC with black and Hispanic Americans experiencing greater symptoms and health issues secondary to PASC compared to white individuals [11]. Likewise, recent data have shown that black race is associated with worse sleep-specific PASC symptoms [5]. However, the underlying explanation for this symptom variation based on race remains unclear. We hope that further studies focus on race-specific differences including those specific to structural racism to address this important knowledge gap.

The study by Mendel et al [12] corroborates a biological conceptual basis for OSA, likely in part via intermittent hypoxia, sleep fragmentation, and augmented systemic inflammation, to create a macroenvironment conducive to development of PASC. (Figure 1) For example, we have shown that biomarkers of systemic inflammation including C-reactive protein and interleukin-6 may serve as important mediators of sleep-related hypoxia and increased COVID-19 morbidity and mortality [4]. Whether these pro-inflammatory mechanisms operate in concert with immune-mediate responses to contribute to changes in neurobiology resulting in sleep disturbances including fatigue and hypersomnia in PASC remains unclear. The role of the circadian rhythm also warrants further investigation particularly as circadian disruption from the interplay of altered immune response and the inflammatory state in the central nervous system resulting from SARS-CoV-2 infection has been cited; however, the role of sleep-related hypoxia in this paradigm also remains unclear [13].

These results are of clinical relevance to inform risk stratification strategies it suggests benefit of increased monitoring of those with OSA after developing COVID-19 given elevated odds of developing PASC. This study also unveils an imminent, critical need, and challenge. Without rigorous, prospective collection of objective measures of sleep disorders including OSA integrated with other key measures such as blood samples and autonomic measures to glean mechanistic inter-relationships, we will be left without critical knowledge to definitively inform management of our patients with COVID-19—and even future pandemics involving post-viral syndromes which adversely impact sleep and result in fatigue, sleepiness, and decrements in quality of life. Such measures should include detailed repeated objective sleep and circadian rhythm assessments to understand longitudinal trajectories in PASC. Without this information, the profound negative impact on patient functional status and economic burden of PASC-related sleep disturbance continues unabated. Without key studies to understand the mechanisms such as immune-mediated and inflammatory responses incited by or leading to sleep disturbance in COVID-19 and PASC, we will not be able to uncover key biologic insights to identify novel targetable biomarkers. Fortunately, ongoing efforts from the NIH RECOVER cohort implementing a tiered approach of progressive deeper level of phenotyping including objective sleep testing offers the opportunity

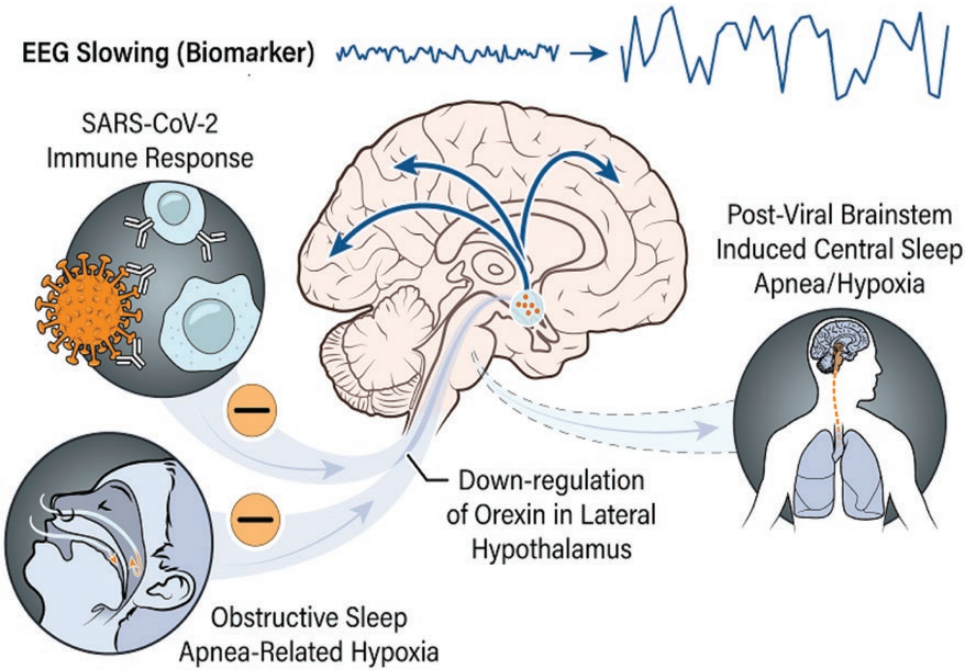

Figure 1. Conceptual model of autoimmune and hypoxic mechanisms in PASC-related sleep disturbance. Autoimmune pathways (post-viral and post-vaccine) have been implicated in the destruction of alerting orexinergic neurons of the lateral hypothalamus. Hypoxic mechanisms, as occurs in sleep apnea, identified as a risk for COVID-19 morbidity and mortality, also inhibit orexin. As orexin is responsible for maintaining alertness, autoimmune and hypoxic pathways may contribute to PASC-related sleep disturbance, hypersomnia, and fatigue. Moreover, post-viral immune-mediated responses may induce PASC-alterations in ventilatory control. (Illustration by Erika Woodrum).

to shed key insights into understanding sleep disturbance and PASC mechanistic underpinnings. Moreover, patients are in need of interventions for PASC-related sleep disturbance and it is crucial to understand which sleep and circadian-specific interventions in our current armamentarium are effective. The NIH has assembled RECOVER clinical trials working groups including one specific to PASC-sleep disturbance to inform a rubric for these interventions. As such, there is a call to action given the closing window of opportunity to identify and refine optimal approaches to treat PASC-related sleep disturbances to improve outcomes for our patients.

Disclosure Statement

None declared.

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