SLEEP, 2022, 1–3

https://doi.org/10.1093/sleep/zsac116
Advance Access Publication Date: 14 May 2022
Editorial

EDITORIAL

Sleep and circadian phenotypes: risk factors for COVID-19 severity?

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Emerging evidence has implicated specific sleep phenotypes such as excessive daytime sleepiness and napping as independent risk factors for hospitalization or mortality after COVID-19 [1]. This is biologically plausible given that disrupted sleep is known to affect many physiological functions, including the immune system [2] and clotting function [3], two suspected etiologies in COVID-19 outcomes [4]. However, whether common sleep phenotypes are causally linked to COVID-19 susceptibility and severity, e.g. need for hospitalization, critical care support, or death remains unclear.

In *SLEEP*, Zheran Liu et al. [5] address this issue by analyzing epidemiological and genetic data from the community-based UK Biobank and the COVID-19 Host Genetic Initiative using Mendelian randomization (MR) analyses. This study is notable given the large number of participants enrolled (>500 000) with both phenotypic and genotypic data acquired at baseline between 2006 and 2010. COVID-19 results were derived from Public Health England's surveillance systems from the start of the pandemic through multiple waves in the United Kingdom between January 21, 2020 and December 30, 2020. These were linked to participant inpatient hospital data from England, Scotland, and Wales. Liu et al. examined the associations of five sleep and circadian phenotypes: habitual sleep duration (reported in hours during a 24-h period), insomnia symptoms (trouble falling asleep at night or waking in the middle of the night), daytime sleepiness (likelihood of falling asleep during daytime activities), daytime napping and chronotype (preference for morning or evening), with two COVID-19 outcomes: susceptibility (positive vs negative) and severity (positive cases resulting in hospitalization vs those who avoided hospitalization). Only significant associations were further tested for causality using MR analyses.

Liu et al. noted an association between "sometimes having daytime napping" and increased COVID-19 susceptibility and hospitalization compared to those reporting never having daytime napping. In addition, "often having excessive daytime sleepiness" was associated with increased COVID-19 hospitalization. They further examined these associations by performing subgroup and sensitivity analyses. MR analyses confirmed that daytime sleepiness was associated with a higher risk of COVID-19 hospitalization using inverse-variance weighted (IVW) weighted-median estimator (WME) and MR-Egger methods. A secondary MR analysis where COVID-19 severity was restricted to focus on hospitalization requiring critical respiratory illness (death or respiratory support) showed that daytime sleepiness remained associated with severity. The associations between daytime napping and COVID-19 outcomes were not significant in MR analyses.

The findings of Liu et al. build on prior work linking sleep to both COVID outcomes [1] and presenting conditions linked to severity [6, 7]. This is also in keeping with prior association studies linking obstructive sleep apnea (OSA) and COVID-19 severity [8, 9], given the potential overlap in symptomatology. Therefore, these findings provide novel evidence that excessive daytime sleepiness is likely on a causal pathway leading to poorer outcomes after COVID-19. This has important implications since excessive daytime sleepiness may be a symptom of OSA [10, 11], or precede causal intermediates, such as future increases in BMI, hypertension, or heart failure [12], which are established clinical risk factors for COVID-19 severity. Additionally, there are multiple disorders with immunopathology (e.g. rheumatoid arthritis [13], inflammatory bowel disease [14], etc.) and a diverse range of psychiatric medications [15] (e.g. steroids, opioids, sedatives,

antipsychotics, or sleep aids) that can also contribute to both excessive daytime sleepiness and napping. Ideally, both fatigue and excessive daytime sleepiness should be distinguished as symptoms of OSA [16], but data from the UK Biobank contained a fatigue question within their pain questionnaires that was only introduced in a third of their cohort. However, there is also a primary care/hospital episode diagnostic code for chronic fatigue, so this may be of further interest for future studies.

In addition to daytime sleepiness, long sleepers (more than 9 h) and those usually having insomnia complaints were also associated with hospitalization in a prior study from the UK Biobank [1]. However, it must be noted that prior work included all patients hospitalized within 7 days of a positive result. In contrast, Liu et al. better refined the outcome of interest by including only those admitted with COVID-19 as a primary diagnosis. This is an important strength since increased testing may have contributed to many incidental positive results, biasing the prior findings away from specific COVID effects [17]. Another study from the UK Biobank found that shift workers were associated with COVID-19 susceptibility [18]. However, Liu et al. did not find that sleep phenotypes conferred an increased risk for acquiring COVID-19. Nor did they find that chronotype preference affected COVID-19 susceptibility or severity. Although chronotype links to the outcome were an important negative finding, this is more of a marker of diurnal preference rather than a measure of the circadian clock. None of the phenotypes assessed in this study were true circadian measures.

Although these results are compelling, Liu et al. findings reflect self-reported sleep phenotypes up to 14 years before COVID-19. As the authors noted, Mendelian analyses were conducted using summary-level data rather than individual-level data, which prevented confirmation that associations were independent of some known confounding variables. These results suggest that sleep is related to COVID severity. The MR work by this group strengthens the argument that sleep is on the causal pathway, but whether sleep is the final step cannot be definitively answered. This may limit generalizability and knowledge of downstream causal intermediates without accounting for follow-up health assessments. For example, OSA is likely underreported in the UK Biobank, although the authors did adjust for comorbid conditions, such as obesity and hypertension at the time of sleep assessment. The value of knowing these associations will depend on the clinical situation. If early sleep intervention can halt conditions, such as cognitive decline or Alzheimer's disease many years prior [19], this information would still be clinically relevant, even if the ultimate causal factor was improved cardiovascular profile. Using this information clinically in COVID will likely need more proximal sleep assessment. Since COVID is an ongoing disease for the foreseeable future, this work brings public attention to the potential importance of sleep/circadian health in COVID outcomes, which motivates further follow-up work.

Although Liu et al. have made a significant step forward, these findings still need replicating in an independent dataset, ideally considering follow-up sleep and health assessment proximal to COVID-19 as others have done with other diseases related to sleep [7]. Further studies incorporating objective sleep measures (collected more recently in 2013–2015 in the UK Biobank), to understand further how sleep and circadian phenotypes contribute to COVID-19 severity are ongoing. For now, a prior history of daytime sleepiness in someone who tests positive for COVID-19 may be an additional risk factor for hospitalization that warrants further attention.

Funding

This work was supported by National Institutes of Health (R03AG067985 to L.G.).

Disclosure Statement

Financial disclosure: the authors report no financial arrangements or connections.

Non-financial disclosure: the authors report no potential conflicts of interest.

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