



LETTER TO THE EDITOR

Poor sleep behavior burden and risk of COVID-19 mortality and hospitalization

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Dear Editor,

Despite the unprecedented efforts in vaccinations, the COVID-19 pandemic will likely continue to affect those most vulnerable [1], and the need to identify modifiable risk factors remains [2]. Poor sleep behavior traits have been linked to multisystemic disruptions [3], but whether this is linked to COVID-19 severity remains unknown. Using the UK Biobank, a population-based cohort of >500 000 participants recruited between 2006 and 2010 [4], we determined the associations of poor sleep behavior burden with mortality, and need for hospitalization after a positive COVID-19 result.

This study was restricted to 46 535 participants tested between March and December 2020 (age: 69.4 ± 8.3 years [mean \pm standard deviation]; female: 53.3%). Sleep behavior traits (duration, daytime sleepiness, insomnia, and chronotype) were assessed between 2006 and 2010. Scores of 0 (if sleep duration between 6 and 9 h, “never/rarely” daytime sleepiness/insomnia, or non-evening chronotype), 1 (if short <6 h, or long sleeper >9 h, “sometimes” experience daytime sleepiness/insomnia, or evening chronotype), and 2 (if “often/all the time” experience daytime sleepiness, or “usually” have insomnia) were assigned, and summed to obtain a *sleep behavior score* ranging from 0 to 6, where higher scores are indicative of multiple domains of poor

sleep behavior traits. We used this to classify poor *sleep behavior burden* as follows: “none” (0), “mild” (1), “moderate” (2–3), and “significant” (4–6).

8422 participants tested positive (COVID+), defined as the earliest result from PCR tests, provided by Public Health England. If tested but never positive (COVID–; $n = 38\,113$), the earliest test date was used. Primary outcome was 30-day mortality, matched to death registry dates. The interaction effect between sleep behavior burden and COVID positivity/negativity on mortality was also tested.

Finally, hospitalization within 7 days of a positive test was extracted by matching dates with hospital admission data (7146 positive cases available). We included test results that were reported up to 4 days after death or hospitalization, per the UK Biobank's guidance over testing-to-result time frames; thus, we excluded 11 participants with a date of death and/or hospitalization more than 4 days before test results were released.

Logistic regression models were used to determine the associations of sleep with binary COVID-19 outcomes (dead/alive, and separately, hospitalized/not). The primary model (A) was adjusted for age, sex, education, and ethnicity. We further adjusted for lifestyle factors including Townsend deprivation index (TDI), physical activity level, body mass index (BMI),

alcohol, and smoking (model B), and comorbidities including presence/absence of cardiovascular risks/disease (CVD; hypertension, high cholesterol, diabetes, and ischemic heart disease), cancer, chronic obstructive pulmonary disease (COPD), and sleep apnea (model C). For mortality models, an interaction term between poor sleep behavior burden and COVID+/- groups was included. Statistical tests were two-sided and significance was defined as $\alpha < 0.05$.

Cases of 30-day mortality were 499 (5.9%) and 670 (1.8%), respectively, in COVID+ and COVID- groups. In COVID+ participants, moderate (odds ratio [OR] = 1.50, 95% confidence interval [CI]: 1.09–2.07, $p = 0.013$) and significant (OR = 2.31, 95% CI: 1.47–3.63, $p = 0.0003$) poor sleep burdens were associated with increased mortality. The association was specific to COVID+ participants compared to COVID- patients (p for interaction < 0.001 ; Figure 1). After adjusting for demographics and risk factors (socioeconomic status, physical activity, BMI, alcohol, and smoking), the significant burden group still saw an almost doubled mortality risk (OR 1.93, 95% CI: 1.22–3.06, $p = 0.005$), while the moderate group was borderline associated (OR 1.34, 95% CI: 0.97–1.86, $p = 0.079$). In the fully adjusted model C, the significant burden group remained significantly associated (OR 1.76, 95% CI: 1.11–2.82, $p = 0.017$).

1317 participants were hospitalized within 7 days after a positive test. Both moderate (OR 1.27, 95% CI: 1.04–1.57, $p = 0.022$) and significant (OR 1.56, 95% CI: 1.12–2.17, $p = 0.008$) burden groups were associated with needing hospitalization (model C).

For individual sleep behavior traits, the ORs of sleep duration (long or short vs. normal sleepers) were greater than 1, but did not reach significance for mortality. However, long sleepers remained at increased risk for hospitalization (OR 1.70, 95% CI: 1.13–2.54) in model C. Often having daytime sleepiness was associated with both mortality (OR 1.74, 95% CI: 1.17–2.67, $p = 0.006$) and hospitalization (OR 1.43, 95% CI: 1.03–1.99, $p = 0.03$). Similarly, usually having insomnia saw increased mortality (OR 1.33, 95% CI: 1.01–1.78, $p = 0.047$) and hospitalization (OR 1.30, 95% CI: 1.08–1.57, $p = 0.006$). Late chronotype was borderline associated with mortality (OR 1.39, 95% CI: 0.98–1.93, $p = 0.054$), but not hospitalization beyond the core model (OR 1.17, 95% CI: 0.93–1.48, $p = 0.18$).

Sleep disruption is rarely diagnosed and is a growing public health concern. Our results provide novel evidence that poor sleep up to 14 years prior, is an independent risk factor for mortality and hospitalization after COVID-19. This is compelling, particularly for those that fall into the group with significant poor sleep burden (sum score = 4–6), given that recently established risk factors such as obesity, smoking, CVD, COPD and sleep apnea were adjusted for. It is also worth noting that even those with two occasional, or one frequent poor sleep behavior trait (i.e. in the moderate group) were at higher risks for hospitalization and death (although borderline significant) and would benefit from confirmation in future analysis.

Many pathophysiological pathways may link poor sleep patterns to worse COVID-19 outcomes. For example, poor sleep is

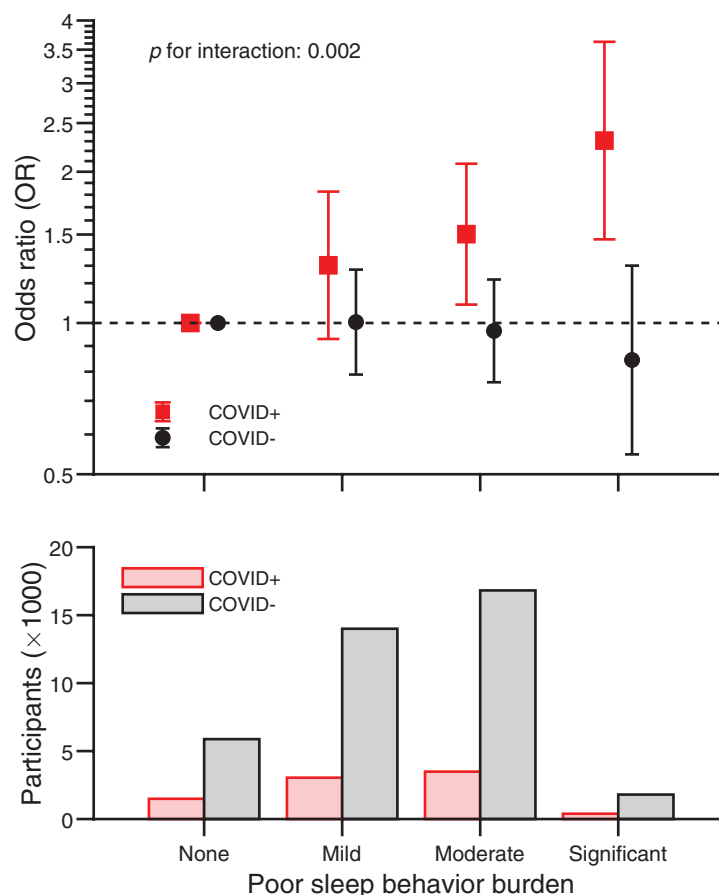


Figure 1. Risk of mortality and number of participants. Mortality ORs increase with poorer sleep behavior burden (top). Number of participants by different poor sleep behavior burdens (bottom). Error bars represent ORs and 95% CIs based on logistic regression models adjusted for age, sex, education, and ethnicity, with participants in the “None” group as reference.

known to affect the immune system [5] and clotting function [6], two suspected etiologies in COVID-19 mortality [7]. Sleep disturbances can also disrupt the synchrony between the circadian rhythms of these important physiological functions. This can be exacerbated by misalignments between societal demands of work or schooling and our internal body clocks [8], commonly seen in shiftworkers [9], which has just been shown to increase the likelihood for COVID-19 positivity [10]. Constant exposure to these stressors over time might have contributed to some of the maladaptive inflammatory or coagulation cascades specific to COVID-19.

Two potential limitations of our study should be considered. While information on outcomes were obtained from quality administrative sources and recorded in real-time, they reflect data from a single country. Sleep behaviors were based on self-report such that the estimates of risk are likely underestimated due to misclassification.

In summary, tracking sleep behavior may have importance in identifying those at increased risk for COVID-19 mortality and hospitalization. Future studies should extend to objective, more contemporary assessment of sleep, and whether sleep health optimization offers resilience to severe forms of COVID-19.

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Conflict of Interest

FAJLS has received lecture fees from Sentara HealthCare 2017, Philips 2017, Vanda Pharmaceuticals 2018, and Pfizer Pharmaceuticals 2018. MR has received a speaker fee from Novo Nordisk.

Disclosure Statement

None declared.

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