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## Brief Communication

## Circadian misalignment is associated with Covid-19 infection

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## ABSTRACT

**Background:** Circadian system contributes to the regulation of inflammatory processes, but the role of circadian misalignment as a risk factor for contracting Covid-19 has up to now been poorly studied. The aim of this study was to explore the relationship between circadian misalignment (chronic disturbance of the circadian system) and the risk of Covid-19 infection in a population of subjects suspected of contact or infection with SARS-CoV-2.

**Methods:** Cross-sectional single-center study conducted during a period without lockdown in winter 2021. Recruitment took place in a Covid-19 outpatient testing center. Subjects between 18 and 45 years old were included whether they were symptomatic or not, healthcare workers or not, in contact with a Covid-19 case or not. To determine social jetlag, a proxy of circadian misalignment, they were asked about their usual sleep-wake behaviors. Usual sleep duration and sleep-wake timing were explored on workdays and free days. Social jetlag was defined as at least 2 h shift of circadian alignment (defined as the difference between mid-sleep on workdays and mid-sleep on free days, mid-sleep as the median between bedtime and rise time).

**Results:** One thousand fourteen subjects were included (sampling rate: 10.8%, 39% men, mean age  $28 \pm 8$ ) with 56 subjects positive for Covid-19 (positivity rate: 5.5%). Usual mean sleep duration was equivalent in both groups (7h47 versus 7h49,  $p = 0.733$ ). Social jetlag greater than 2 h comprised 33.3% of subjects in the Covid-19 group versus 20.6% in the control group ( $p = 0.026$ ). After adjustment on age, gender, BMI and work schedules, subjects presenting with social jetlag greater than 2 h had a 2.07-fold higher likelihood to test positive than subjects who had identical sleep-wake timing on workdays and free days (OR = 2.07, 95%CI = [1.12–3.80],  $p = 0.024$ ).

**Conclusion:** Circadian misalignment not only is present in subjects infected by Covid-19 but could also be responsible for a higher likelihood of being infected. The chronobiological impact on the immune system or a higher likelihood of being exposed to social contacts during nocturnal activities could explain our findings, which need to be confirmed in a future large cohort study. Regular sleep-wake timing could ultimately become a target for preventing Covid-19 infection.

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## 1. Background

The Covid-19 epidemic has massively disrupted sleep-wake behaviors in western society [1]. Social distancing has disturbed

daily life routines, increasing worry, isolation, stress, and screen time, which are known contributors to impaired sleep [2,3]. However, circadian clocks contribute to the regulation of inflammatory processes (control the function of our immune system, virus replication and the severity of infections) which are particularly important in this context of a pandemic [4]. Indeed, a recent study found that the expression of 30% of 332 human proteins that interact with SARS-CoV-2 proteins shows circadian oscillation [5], and that most potential drug targets exhibit robust 24-h oscillation in at least one organ or tissue in mammalian systems [6]. Moreover,

Abbreviations: BMI, Body Mass Index; OR, Odds-Ratio; CI, Confidence Interval; RT-PCR, Reverse Transcription-Polymerase Chain Reaction.

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people with circadian misalignment/disruption (a chronic disturbance of the circadian system) due to internal (age, blindness) or external (shift work, social jetlag) have a weaker immune system and could be more susceptible to such viral respiratory diseases [6]. Social jetlag is a chronic misalignment between internal circadian clocks and external time (social time). Taken together, these results support the hypothesis that circadian misalignment could promote SARS-CoV-2 infection [6–8]. Nevertheless, usual circadian misalignment as a risk factor for contracting Covid-19 has up to now been poorly studied. Only a 2021 study showed that night work, which involves circadian disruption, was associated with an 1.85-fold increased risk of Covid-19 infection [9]. Therefore, the aim of this study was to explore the relationship between usual circadian misalignment (described by social jetlag) and the risk of Covid-19 infection in the general population.

## 2. Methods

We conducted a cross-sectional single-center study during a period between February and April 2021 without lockdown but with very stringent socio-economic restrictions including curfew from 6 p.m. to 6 a.m. Recruitment took place at the entering of the Covid-19 outpatient testing center at Bordeaux University Hospital (southwest of France). Strict compliance with barrier gestures from investigators and participants was required. Patients between 18 and 45 years old who accepted to participate were included whether they were symptomatic or not, healthcare workers or not, in contact with a Covid-19 case or not. Following their test, participants answered an internet-based questionnaire on their sociodemographic data (age, gender, body mass index (BMI), profession and work schedules), their current symptoms and their medical background. Participants were asked about their usual sleep-wake timing. They were asked what time they usually go to bed (bedtime) and get up (rise time) on workdays and on free days, and how many hours of actual sleep they get (sleep duration) [10]. Mean sleep duration was defined as the average sleep duration over a full week, including workdays and free days. We then used these answers to estimate a proxy of their circadian misalignment: social jetlag (defined as the difference between mid-sleep on workdays and mid-sleep on free days, mid-sleep as the median between bedtime and rise time [11]). Short mean sleep duration was defined as fewer than the 7 h per night recommended by the National Sleep Foundation [12] and social jetlag as at least 2 h shift [13].

### 2.1. Statistical analysis

The primary endpoint was the SARS-CoV-2 detection using RT-PCR on nasopharyngeal samples (positive/negative) performed in a hospital-accredited center following the recommendations of the French Ministry of Health. Socio-demographical data and sleep-wake behaviors were compared between the Covid-19 group and the control group using a  $\chi^2$  test for qualitative variables or the t-test for quantitative variables. Adjusted odds-ratio (OR), 95% confidence interval (CI) and p-value were then assessed using a logistic regression with age, gender, BMI, and work schedules as covariates. The threshold of 0.05 was used to determine significance.

## 3. Results

### 3.1. Population

Out of 9419 patients (41% of men, mean age of  $28 \pm 8$ ) tested in the center during the study period and meeting the inclusion criteria, 1014 participants were included since they were tested and interviewed during the work shifts of the student nurses assigned

to the project (sampling rate: 10.8%). The population interviewed was representative of the whole sample in terms of age and sex (39% men, mean age  $28 \pm 8$ ). Out of the 1014 subjects recruited, 56 participants tested positive for Covid-19 (5.5%). This positivity rate was similar to the department's data over the period (from 4.3% on March 12 to 7.5% on April 23). Table 1 describes socio-demographic and clinical patterns of the Covid-19 group and the control group. A total of 20.6% of participants were overweight, including 6% obese, 27.5% had shifted schedules including 18.3% with consecutive hours of more than 12 h, 29.1% were healthcare workers and 39.5% were students. Cough, fatigue, fever, headache, sore throat, aches, loss of taste and/or smell, shortness of breath and chest pain were more frequent in the Covid-19 group than in the control group. Presence of at least one chronic disease was equivalent in both groups (10.7% versus 10.2%).

### 3.2. Circadian misalignment

Two-hundred eleven participants (20.8%) had social jetlag. Fig. 1 describes the sleep-wake timing of participants according to their social jetlag. Usual bedtime and rise time were 11:15 p.m. and 7:00 a.m. on workdays and 1:00 a.m. and 10:00 a.m. on free days in participants with social jetlag, versus 11:30 p.m. and 7:15 a.m. on workdays and 12:00 p.m. and 9:00 a.m. on free days for others (respectively,  $p = 0.450$ ,  $p = 10^{-9}$ ,  $p = 0.089$  and  $p = 10^{-16}$ ). Social jetlag was present in 33.3% of participants in the Covid-19 group versus 20.6% of the control group ( $p = 0.026$ ). In other words, the positivity rate was 8.5% (18/211) in subjects with social jetlag while the positivity rate was 4.6% (36/782) in subjects with regular sleep-wake timing on workdays and free days.

### 3.3. Sleep duration

Usual sleep duration before workdays and free days were equivalent in both groups: 7h18 and 9h00 in the Covid-19 group and 7h27 and 8h52 in the control group (respectively,  $p = 0.476$  and  $p = 0.204$ ) as usual mean sleep duration (7h47 in the Covid-19 group versus 7h49 in the control group,  $p = 0.733$ ).

### 3.4. Association between usual social jetlag, sleep duration and Covid-19 status

Social jetlag was significantly associated with Covid-19 infection after adjustment for age, gender, BMI, and usual work schedules (OR = 2.07, 95%CI = [1.12–3.80],  $p = 0.024$ ). Mean sleep duration was not associated with Covid-19 infection after adjusting for age, gender, BMI and work schedules (OR = 0.66, 95%CI = [0.27–1.59],  $p = 0.331$ ).

## 4. Discussion

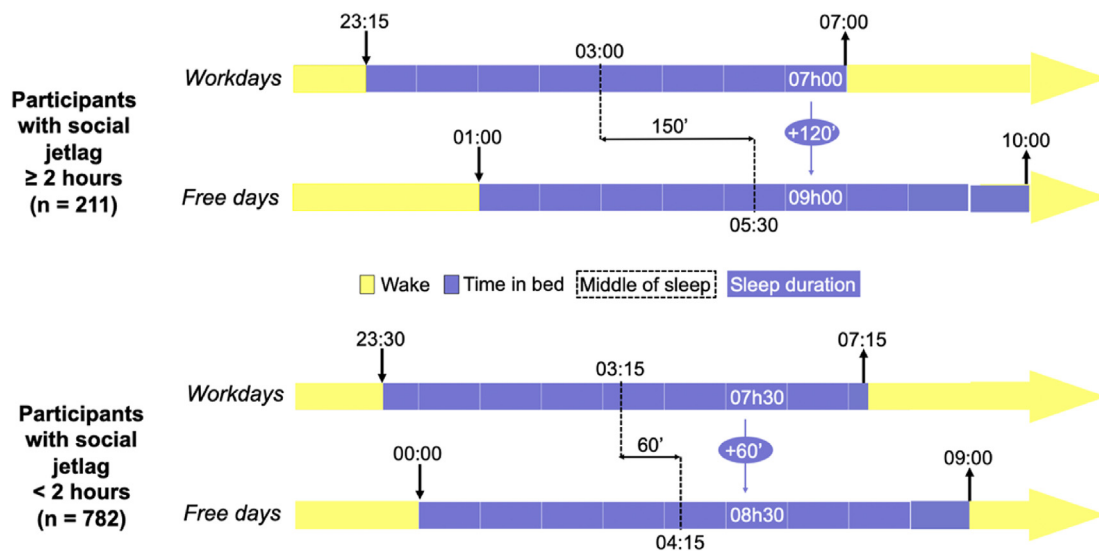
Our study shows that usual social jetlag, a proxy of circadian misalignment, is frequent (20.8%) and significantly associated with Covid-19 infection in the general population, and it suggests that chronic circadian disruption could weaken the immune system and promote infection [6,7]. This result is in line with the conclusions of a 2022 review which conclude that alterations of circadian rhythms have been identified as possible new risk factors for alteration of physiologic metabolism, including immunity [14]. Although the study period included a curfew from 6 p.m. to 6 a.m., one cannot exclude social gatherings in apartments and homes, which could explain the higher rate of contamination in subjects with a delayed sleep onset [15,16]. On the other hand, usual sleep duration was not associated with Covid-19 infection. Many studies have found a link between sleep deprivation and immunity, and particularly Covid-

**Table 1**  
Characteristics of study population.

Variables	Covid-19 Positive (n = 56)	Covid-19 Negative (n = 958)
<b>Age</b>	28.9 ± 8.4	28.0 ± 8.3
<b>Gender = Female (%)</b>	36 (64.3%)	587 (61.3%)
<b>BMI</b>		
<18	4 (7.1%)	22 (2.3%)
[18–25]	40 (71.4%)	741 (77.4%)
[25–30]	6 (10.7%)	142 (14.8%)
>30	6 (10.7%)	53 (5.5%)
<b>Work schedules</b>		
Fixed day work	48 (85.7%)	664 (69.3%)
Fixed night work	1 (1.8%)	21 (2.2%)
Shifted without consecutive 12 h	2 (3.6%)	92 (9.6%)
Shifted with consecutive 12 h	5 (8.9%)	181 (18.9%)
<b>Healthcare workers = Yes (%)</b>	12 (21.4%)	282 (29.3%)
<b>Students = Yes (%)</b>	20 (35.7%)	381 (39.8%)
<b>Symptoms</b>		
Cough	29 (51.2%)	150 (15.7%)
Fatigue	40 (71.4%)	251 (26.2%)
Fever	19 (33.9%)	64 (6.7%)
Headache	34 (60.7%)	195 (20.3%)
Sore throat	25 (44.6%)	166 (17.3%)
Aches	23 (41.1%)	94 (9.8%)
Loss of taste and/or smell	14 (25.0%)	15 (1.6%)
Shortness of breath	8 (14.3%)	35 (3.7%)
Chest pain	3 (5.4%)	18 (1.9%)
<b>Medical background</b>		
Any	6 (10.7%)	98 (10.2%)
Endocrine disease (diabetes, dysthyroid)	0	12 (1.3%)
Chronic inflammatory bowel disease	0	8 (0.8%)
Mood disorder (depression, bipolarity)	0	7 (0.7%)
Sleep apnea	1 (1.8%)	5 (0.5%)
Chronic obstructive pulmonary disease	2 (3.6%)	2 (0.2%)
Multiple sclerosis	0	2 (0.2%)
Chronic renal failure	1 (1.8%)	0
Others	3 (5.4%)	54 (5.6%)
<b>Mean sleep duration<sup>a</sup></b>	07h47 ± 50'	07h49 ± 56'
<b>Social jetlag<sup>b</sup> (≥2 h)</b>	18 (33.3%)	193 (20.6%)

<sup>a</sup> 11 missing data (n = 1003).

<sup>b</sup> 21 missing data (n = 993).



**Fig. 1.** Sleep-wake timing of participants according to their social jetlag.

19 infection [17–20]. The lack of association in this sample may be due to the low prevalence of significant deprivation (sleep duration less than 6 h per night on workdays: 5.2% versus 35.9% in a 2019 French study conducted before the outbreak [21]). Indeed, sleep

duration has increased significantly since the beginning of the Covid-19 epidemic in western society [22].

The study has some limitations. First, the subjects were included on a voluntary basis, although their characteristics were quite similar

to the source population, except for a high proportion of students. However, supplementary analyses showed that the association between social jetlag and Covid-19 infection was consistent across both groups (students: 31.6% of social jetlag in the Covid-19 group versus 21.2% in the control group and non-students: 34.3% versus 20.1%). Second, the design was cross-sectional, although we focused on usual sleep-wake timing, which limited reverse causality. A large cohort study is now required to confirm our findings. Finally, the formula used to calculate social jetlag does not take into account sleep latency as described by Roenneberg et al. and could lead to an erroneous estimate [11].

In conclusion, circadian misalignment, ie, a chronic disturbance of the circadian system observed frequently in shift workers and evening subjects with sleep-wake timing constrained by work, could prove to be another risk factor for Covid-19 infection in the general population due to continuing social constraints. Defining the most appropriate schedules for (tele)-working or staying at home to maintain a healthy body and circadian clock could help to reduce the risk of infection and rapid transmission and manage the dynamics of the current pandemic and future ones. Thus, 'temporal' social interventions need to be considered along with 'spatial' social distancing to help curb the spread of SARS-CoV-2.

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### Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2022.03.015>.

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