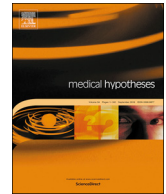




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## Are night shift workers at an increased risk for COVID-19?

Rachel K. Lim<sup>a,\*</sup>, Carlos G. Wambier<sup>b</sup>, Andy Goren<sup>c</sup>

<sup>a</sup> Brown University, Providence, RI, United States

<sup>b</sup> Department of Dermatology, Alpert Medical School of Brown University, Providence, RI, United States

<sup>c</sup> Applied Biology, Inc., Irvine, CA, United States



### ABSTRACT

Recent data has revealed an association between coronavirus disease-19 (COVID-19) incidence and seasonally regulated androgen sensitivity. This potential relationship between SARS-CoV-2 infection and clock genes, coupled with previously reported effects of night shift work on health, leads us to hypothesize that night shift workers may be at an increased physiological risk of coronavirus disease-19 (COVID-19).

Shift work, especially night shift work, has long been associated with several chronic health conditions. The mechanisms that drive these associations are not well understood; however, current literature suggests that the disruption of circadian rhythms may cause downstream hormonal and immune effects that render night shift workers more susceptible to disease. First, circadian rhythms may play a role in the mechanism of viral infection, as viral vaccines administered in the morning elicit greater immune responses than those administered in the afternoon. Next, increased exposure to light at night may inhibit the production of melatonin, which has been observed to enhance DNA repair and shown to upregulate expression of *Bmal1*, an established inhibitor of herpes simplex virus and influenza. Finally, abnormal immune cell and cytokine levels have been observed following night-shift work. These data suggest that further research is warranted and that high-risk occupations should be taken into consideration as public health policies are introduced and evolve.

### Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of the *Coronaviridae* family that was first documented in December of 2019 [1]. Since it was first identified, SARS-CoV-2 has infected millions of people globally leading to the COVID-19 pandemic. The rates of diagnosis and hospitalizations associated with COVID-19 infection have been closely monitored. Viral respiratory infections are known to follow a seasonal outbreak cycle, but it is not known whether COVID-19 infections follow a similar pattern [2]. In a recent communication, we hypothesized that clock genes may drive the seasonal variation observed so far in COVID-19 due to a positive relationship between COVID-19 and androgen sensitivity [3,4]. Androgen sensitivity is mediated by the seasonal expression of specific genes and proteins [5]. Clock genes regulate a set of anticipatory responses to changes in the environment which are referred to as circadian rhythms. Circadian rhythms are regulated by an internal time-keeping system, though they can also adjust to exogenous signals such as light or heat. Endogenous molecular clocks acting out of phase have been implicated in the literature to exacerbate or increase the risk of a wide range of disorders and diseases [6].

### The Hypothesis

Due to the regular disruption of the 24-hr sleep-wake cycle, a notable circadian rhythm in humans, we hypothesize that night shift workers may be at higher risk for COVID-19 infection. Several studies have suggested that night shift work may be associated with cancer and other chronic health conditions [7]. In particular, night shift work has been associated with greater risks of metabolic syndrome, obesity, and diabetes, as well as breast cancer and prostate cancer [8–12].

### Evaluation of the Hypothesis

#### *The Role of Circadian Rhythms*

One theory explaining the increased risk of conditions like obesity and type II diabetes is that disruption of the circadian rhythm alters the regulation of endocrine signaling. Qin et al. analyzed plasma samples of medical students who led diurnal or nocturnal lifestyles. The nocturnal lifestyle group displayed lower peak concentrations of melatonin, a hormone that regulates the sleep-wake cycle, and leptin, a hormone that inhibits hunger, than the diurnal lifestyle group. Plasma glucose increased after all meals in both groups, but glucose concentrations remained high while insulin secretion decreased in the nocturnal lifestyle group between midnight and early morning [13]. These findings

\* Corresponding author at: 69 Brown St, Box 5523, Providence, RI 02912, United States.

E-mail address: [rachel\\_lim@brown.edu](mailto:rachel_lim@brown.edu) (R.K. Lim).

suggest that nocturnal lifestyles may be associated with higher risk of type II diabetes and obesity which in turn are risk factors for many other health conditions.

Additionally, circadian rhythms have specifically been linked to viral infection [14]. This has notably been demonstrated through studies of the efficacy of viral vaccination. In an early study, Phillips et al. observed that patients immunized in the morning developed greater antibody responses to both hepatitis A and influenza vaccines [15]. More recently, Long et al. conducted a large randomized trial that showed that morning vaccination significantly increased viral specific antibody responses compared with afternoon vaccination [16]. Furthermore, mouse models of herpes and influenza A showed enhanced infections when circadian rhythms were disrupted by removing the clock gene *Bmal1* [17]. Viruses can also act to sabotage circadian regulation to increase viral replication, exemplified by the suppression of *Bmal1* by HSV-1 and influenza [17,18].

### The Role of Melatonin

A prominent theory explaining elevated cancer risk in night shift workers is that melatonin may be suppressed by prolonged exposure to light at night, leading to downstream signaling effects. This is particularly relevant to breast cancer, as a decrease in melatonin production upregulates the gonadal axis, increasing the levels of circulating estrogen following night shift work [19]. Conversely, increased melatonin has also been shown in several experimental and epidemiological studies to have an inhibitory effect on breast and other cancers [20]. At the cellular level, melatonin may prevent DNA damage by carcinogenic agents by acting as a free radical scavenger directly or indirectly via activation of the glutathione or related antioxidative pathways and has been observed to enhance DNA repair [21]. Melatonin may also play a role in protecting against viral infections, as it has been shown to up-regulate expression of *Bmal1*, an established inhibitor of herpes simplex virus and influenza [10].

Suppression of melatonin may also result in alterations in immune activity, rendering night shift workers at a greater risk of infection. In one study, a bimodal rhythmic cytokine secretion was found to phase-shift 4.5–6 hours earlier in peripheral blood mononuclear cells from people who had undergone simulated night shift work conditions than in those collected from people examined following simulated day shift work conditions [22]. Another study found that the average number of monocytes was 1.15 times higher in night-shift workers, and that night-shift workers who had worked night-shifts in the past three days had higher mean numbers of lymphocytes, T cells, and CD8 + T cells [23]. These alterations in immune response and cell subpopulations might also contribute to the increased risk for autoimmune diseases, cardiovascular and metabolic disorders, and cancer reported in night shift workers.

### Discussion

Taken together, the role of circadian rhythms in viral infection and hormone regulation and the immune system irregularities in night shift workers as a result of circadian rhythm disruption strongly suggest that night shift workers may face an increased risk of COVID-19 infection. As economies worldwide begin to reopen amidst a global pandemic, high-risk occupations must be identified and considered as new public health policies take shape. The number of COVID-19 cases and related hospitalizations continues to increase, and it is more important than ever to devise and implement new protocols to protect high-risk populations and their contacts.

Although many occupations have transitioned to remote settings during the pandemic, certain “essential” workers such as health care workers, food industry workers, and police officers have continued to work in-person. It would be interesting to test this hypothesis through a large-scale survey of essential shift workers who have continued to

work night shifts as the COVID-19 pandemic began and progressed. Comparing the incidence of COVID-19 infections among night shift and day-shift workers will shed light upon this topic.

### Perspectives and Conclusions

In conclusion, because several viral infections, including influenza, are closely linked to circadian rhythms, and night shift workers regularly disrupt their circadian rhythms, it is likely that night shift workers are at a greater risk of COVID-19 infection and further research is warranted.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110147>.

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