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RESEARCH ARTICLE

Understanding the association between sleep, shift work and COVID-19 vaccine immune response efficacy: Protocol of the S-CORE study

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Summary

This protocol describes an innovative study to investigate the relationship between sleep, shift work and the immune response to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2; coronavirus disease 2019 [COVID-19]) vaccination. As the COVID-19 pandemic is a global crisis with devastating health, social and economic impacts, there is a pressing need for effective vaccination programmes. Previous influenza and hepatitis vaccination studies suggest that lack of sleep can negatively alter immune responsiveness, while circadian misalignment most likely may also play an important role in the immune response to vaccination. Our present study will be the first to address this question in actual shift workers and in relation to COVID-19 vaccination. We hypothesise that the occurrence of recent night shifts and diminished sleep will negatively alter the immune response to vaccination in shift workers compared to dayworkers. We aim to recruit 50 shift workers and 50 dayworkers. Participants will receive an mRNA-based vaccination, through the Dutch vaccination programme. To assess immune responsiveness, blood will be drawn at baseline (before first vaccination), 10 days after first vaccination, the day prior to the second vaccination; and 28 days, 6 and 12 months after the second vaccination. Actigraphy and daily sleep e-diaries will be implemented for 7 days around each vaccination to assess sleep. The Pittsburgh Sleep Quality Index will be used to monitor sleep in the long term. Optimising the efficacy of the COVID-19 vaccines is of outmost importance and results of this study could provide insights to develop sleep and circadian-based interventions to enhance vaccination immunity, and thereby improve global health.

KEYWORDS
circadian misalignment, immune response, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), Shift work, sleep loss, vaccination

1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was discovered in Wuhan, China, during a recent epidemic of pneumonia in December 2019 (Wu et al., 2020). Since then, the virus has spread all over the world, and as of July 19, 2021, >4 million deaths have been reported to the World Health Organization (2021). The coronavirus SARS-CoV-2 disease (coronavirus disease 2019 [COVID-19]) pandemic is the most significant global health challenge of this era, with ongoing devastating health, social and economic impacts. To overcome this pandemic, worldwide COVID-19 vaccines have been developed and are now the most important and widely used public health intervention. Since the beginning of 2021, the first COVID-19 vaccines 'BioNTech/Pfizer' and 'Moderna' approved by the European Medicines Agency (EMA), are now predominantly used for the broader public in the Netherlands. Optimising the efficacy of the COVID-19 vaccines is of outmost importance and sleep and circadian rhythms could play an important role to enhance vaccination-induced immunity.

Emerging evidence suggests that immune functioning is hampered in people with poor sleep and sleep deprivation (for reviews see Faraut et al. (2012) and Besedovsky et al. (2019)). Moreover, a few human studies available provide convincing evidence that efficient sleep supports vaccination outcomes. The first human laboratory study in this context found that sleep-deprived male participants who were restricted to 4 hr sleep/night (4 nights before and 2 nights after vaccination against influenza), displayed roughly a 50% reduction in antibody production 10 days post-immunisation, compared to control participants who were allowed to keep their usual sleep duration of ~8 hr (Spiegel et al., 2002). In a sleep-deprivation laboratory study by Lange et al. (2003), healthy adults were randomised to be either completely sleep deprived for the night after hepatitis A vaccination (HAV) or had the ability to sleep normal the night after the vaccination. Those who were allowed to sleep had a nearly twofold higher antibody titre 4 weeks later, relative to participants staying awake throughout that night (Lange et al., 2003). In a more recent study, Lange et al. (2011) also measured HAV-specific Th cell responses besides antibody levels. They found that total sleep loss on the night following a HAV resulted in significantly fewer antibodies and HAV-specific Th cells after 8 and 16 weeks, compared to the response when sleep was normal following the HAV (Lange et al., 2011). Another laboratory study showed that 24-hr sleep deprivation immediately after a Swine flu vaccination resulted in a reduced number of antibodies 5 days after the vaccination in men. However, among women no differences were found in antibodies between the sleep-deprivation group or those who were able to sleep for 8 hr (Benedict et al., 2012). These laboratory studies suggest that sleep deprivation immediately after vaccination hampers the formation of antigen-specific immune defence as reflected by antibody production, whether sleep prior to vaccination also plays a role still needs more research. These laboratory-based results were strengthened by field studies, which have found that shorter sleep durations were related to reduced vaccine responses to influenza (Prather et al., 2021) and hepatitis B in healthy young adults (Prather et al., 2012).

In addition to sleep, other factors have previously been associated with antibody responses to vaccination. Biological variables, including genetics and sex, and psychological stress account for variation in antibody responses to several vaccines (Klein & Flanagan, 2016; Pedersen et al., 2009; Scepanovic et al., 2018). A recent field study investigated sensitive periods of sleep loss in relation to immune response to vaccination and found that shorter sleep duration on the 2 closest nights prior to vaccination, was significantly related to lower antibody responses at 1 and 4 months after vaccination. These associations remained statistically significant after adjustment for baseline antibody levels, age, and sex (Prather et al., 2021). Noteworthy, the two field studies of Prather et al. only found significant effects for sleep duration, self-reported sleep efficiency and subjective sleep quality measures were not associated with antibody responses. Taylor et al. (2017) did reveal that poor global sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI), predicted poor influenza vaccination response across both insomniacs and non-insomniacs (Taylor et al., 2017).

Sleep insufficiency is a major problem affecting night and rotating shift workers (Akerstedt, 2003; Kecklund & Axelsson, 2016). The ability to remain awake throughout a wake episode during the day and to have a consolidated sleep episode at night is regulated by a complex interaction between the circadian timing system and a homeostatic sleep process (Borbely, 1982; Daan et al., 1984). However, night workers must be awake at night (when their circadian system is promoting sleep), and they must try to sleep during the day (when their circadian system promotes wakefulness). In addition, shift workers tend to have greater irregularity of their sleep timing than dayworkers because of switching between night shifts and day or evening shifts, and from adopting a day-wake, night-sleep schedule on days off. Together, these atypical and/or irregular sleep–wake schedules result in misalignment between the circadian drive for sleep and the timing of the shift worker's sleep. This misalignment typically results in shorter and less consolidated sleep during the day (Foster & Wulff, 2005), and increased sleepiness and performance decrements during night shifts (Reinberg & Ashkenazi, 2008), and when severe is classified as shift work disorder (Wickwire et al., 2017).

Empirical evidence suggest that shift work is associated with negative health outcomes related to metabolic and cardiovascular health, cancer, and mental health (James et al., 2017). It is thought that the immune system may be affected by shift work, as immune responses are under influence of circadian rhythms, and might play a role in the higher risk of health problems (Almeida & Malheiro, 2016; Zhuang et al., 2017). A recent study showed that night shift workers had a higher number of monocytes than non-shift workers, and night shift workers who recently worked night shifts had significantly more lymphocytes, T cells and $CD8^+$ T cells compared to non-shift workers (Loef et al., 2019). Furthermore, Fatima et al. showed that night shift workers that have circadian misalignment are at high

risk of COVID-19 infection irrespective of their occupational group (Fatima et al., 2021).

Taken together, the limited human studies available provide convincing evidence that efficient sleep and circadian alignment supports vaccination outcomes. There is a pressing need to understand the importance of these factors for COVID-19 vaccination efficacy (Benedict & Cedernaes, 2021; Kow & Hasan, 2021). Therefore, we propose a protocol to investigate the association between sleep and circadian (mis)alignment in relation to immune response to COVID-19 vaccination.

2 | OBJECTIVES AND HYPOTHESIS

The primary objective of this S-CORE study is to investigate the immune response to COVID-19 vaccination in shift workers, a vulnerable group facing chronic sleep deprivation and circadian misalignment and compare these results to a group of dayworkers with sufficient sleep duration and regular sleep times. We hypothesise that the presence of recent night shifts and limited and mistimed sleep in shift workers will show a lower level of antibody response to a COVID-19 vaccination compared to dayworkers.

In addition to our main objective, we will address two secondary objectives: first, to determine the long-term anti-SARS-CoV-2 immune responses over time in both shift workers and dayworkers; and secondly to evaluate anti-SARS-CoV-2 specific T-cell responses in shift workers and dayworkers.

3 | METHODS

3.1 | Participants

A total of 50 shift workers and 50 dayworkers, aged between 18 and 50 years, will be recruited to ask if they are interested in participation. Subjects will complete an online screening survey and their eligibility will be determined by the research team. Inclusion criteria for shift workers will be: (a) work schedules of ≥20 hr a week; (b) work hours outside the conventional 9:00 a.m. to 5:00 p.m. working day, i.e. shift work (Costa, 2003), including night shifts (defined as ≥6 hr between 10:00 p.m. and 7:00 a.m.) or rotating shifts (morning, evening and night shifts); (c) 6–12 hr shift durations; and (d) ≥3 months history of working rotating shift work or night shifts prior to the study. Inclusion criteria for dayworkers will contain: (a) an average habitual sleep duration of ≥7 hr; (b) regular sleep times on workdays, average bedtimes between 9:00 p.m. and 1:00 a.m. and rise times between 5:00 a.m. and 9:00 a.m.; and (c) no history of consistent night or rotating shift work in the last 6 months.

In addition, potential subjects who meet any of the following exclusion criteria will be excluded from participation: (a) indication of prior exposure to COVID-19; (b) pregnant or have a wish to become pregnant within 6 months; (c) regular medication regimen known to affect sleep (e.g. hypnotics) or alertness (e.g. antihistamines); and (d) diagnosed with an immunodeficiency syndrome, any auto-immune or auto-inflammatory disease except atopic disease.

3.2 | Research design

Participants will be vaccinated according to the Dutch National COVID-19 vaccination programme, where they will receive two SARS-CoV-2 mRNA vaccinations, with a 28-day interval. We expect shift workers to be vaccinated predominantly with one type, either BioNTech/Pfizer or Moderna.

Samples will be obtained at six points in time (Figure 1). Baseline measurements (T0) will take place around the scheduled first vaccination day. When consistent with their work schedule, vaccination for shift workers will take place prior to working at least two consecutive night shifts. For all participants, blood will be drawn for baseline levels of antibodies against SARS-CoV-2 (i.e. to rule out prior exposure) and to assess circadian clock phase. At 3 days prior to the first vaccination day, participants will start wearing an activity

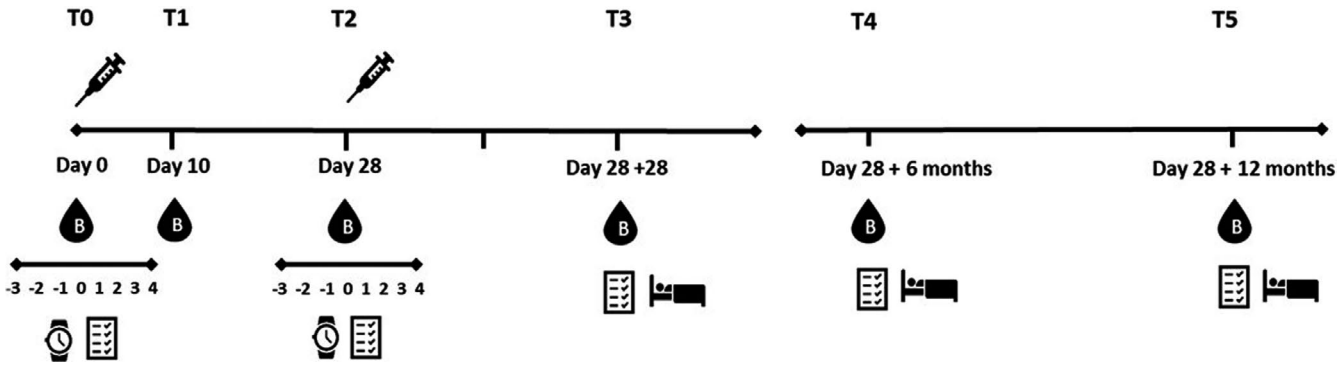

FIGURE 1 Schematic overview of study protocol. Participants will be vaccinated twice, 28 days apart. A total of six blood draws take place, i.e. before the first vaccination, ~10 days after the first vaccination, at the day of the second vaccination and 28 days, 6 and 12 months after the second vaccination. At 3 days before each vaccination, sleep will be measured for 7 days using actigraphy and daily e-diaries (T0, T2), and a follow-up questionnaire will be completed at T3–T5

monitor (wrist-worn accelerometer) for 7 days to measure objective sleep duration, and simultaneously report their sleep and work activities in a daily electronic diary. Approximately 10 days after the first vaccination, blood will be drawn again (T1).

At 3 days prior to the scheduled second vaccination day (T2), participants will be asked to monitor their sleep again for 7 days by wearing an activity monitor and complete daily e-diaries. Prior to the second vaccination, blood will be drawn again to assess the immune response.

To assess the immune response over time, all participants will be asked to give blood after 28 days (T3), 6 months (T4) and 12 months (T5) following the second vaccination day. At the same points in time, short comprehensive questionnaires will be used to monitor sleep duration and sleep quality, including assessment of occurrence and severity of COVID-19 (re-)infections and stress over time.

3.3 | Outcome measures

The key objective of the study is to measure sleep, circadian misalignment, and the immune response against SARS-CoV-2 after vaccination in night shift workers and dayworkers. Blood will be taken before the first vaccination, 10 days after the first vaccination, at the second vaccination timepoint, and 28 days, 6 months and 12 months after the second vaccination timepoint. For each blood draw, 10 ml of blood will be obtained by venepuncture to quantify antibody titres and T-cell responses to the vaccine components.

- SARS-CoV-2-specific humoral response: to rule out previous exposures, anti-SARS-CoV-2 total immunoglobulin (Ig) will be determined by an anti- receptor-binding domain (RBD) enzyme-linked immunosorbent assay (ELISA; Beijing Wantai Biological Pharmacy Enterprise Co., Ltd.) as described previously (GeurtsvanKessel et al., 2020). Optical density (OD) ratios >1.0 are interpreted as positive as indicated by the manufacturer. In this assay, ratios >10 are indicative of the presence of neutralising antibodies. In post-vaccination sera, SARS-CoV-2 specific antibodies will be measured by a quantitative assay directed against the S antigen (Liaison SARS-CoV-2 TrimericS IgG assay), which has shown to correlate well to virus neutralisation by plaque reduction neutralisation test (PRNT).
- SARS-CoV-2-specific T-cell response: At baseline (before vaccination), 10 and 28 days after the first vaccination, and 28 days after the second vaccination, T-cell responses will be evaluated by whole-blood interferon γ (IFN-γ) release assay (IGRA). Briefly, 1 ml LiHep anticoagulated blood will be incubated with four different antigens (T-cell antigen 1, T-cell antigen 2, mitogen control and negative control, QuantiFERON, Qiagen). After overnight incubation at 37 °, plasma is obtained by centrifugation and subsequently assessed for the presence of IFN-γ by ELISA. Presence of other cytokines can subsequently be assessed.
- Sleep measurements: Participants will wear an activity monitor on their non-dominant wrist to record rest-activity over the 24-hr for 7 days, beginning ≥2 days before each SARS-CoV-2 vaccination. Actigraphy data will be collected in 60-s epochs and actigraphy software will be used to score the sleep and wake periods. At the same time, electronic sleep diaries ~1 hr after awakening are completed. Participants will report sleep/wake timing, use of naps, subjective sleep quality, whether they woke during the sleep episode, and whether they were awake prior to final out of bed time. Daily e-diaries will be sent at designated times by secure email. The electronic diary is constructed in Castor and will be completed on participants' own device (by phone, tablet, or laptop). To assess sleep in the long term, the validated sleep questionnaire the PSQI will be administered at T3, T4 and T5 (Buysse et al., 1989).
- Circadian clock parameters: Using recently published algorithms is it possible to estimate circadian clock phase and amplitude using a single timepoint transcriptomics sample (Braun et al., 2018; Laing et al., 2017; Wittenbrink et al., 2018). To assess the level of circadian (mis)alignment of shift workers and dayworkers, we will estimate internal circadian time by analysing the circadian transcriptome, as determined by RNA sequencing of whole blood samples collected at baseline (T0).

Furthermore, age, sex, body mass index (BMI) and stress, variables which have previously shown to be related to antibody responses to other immunisations will be assessed (Cohen et al., 1983).

3.4 | Ethics and confidentiality

This study has been approved by the medical ethical committee of Erasmus MC and the Central Committee on Research Involving Human Subjects as this study is subject to the Medical Research Involving Human Subjects act (WMO). The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (64th version, October 2013) and are consistent with the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines. All data will be treated according to the privacy regulations applicable for Europe and the Erasmus MC privacy regulations. All data gathered during the course of the study will be stored online using a secure network server.

3.4.1 | Risks and benefits

All vaccines will be administered according to their respective Summary of Product Characteristics registration as part of the National vaccination programme. Blood draws and other study procedures provide minimal burden and low risks.

3.4.2 | Consent

The ICH/GCP guidelines will be followed in informing the participant and obtaining consent. Participants who volunteer to participate will be given written informed consent before enrolment in the study.

3.5 | Data analysis

Descriptive analysis will be performed for all study outcomes. Continuous variables will be presented as mean ± standard deviation in case of a normal distribution or median (interquartile range) in case of non-normal distribution. Characteristics of each group will be compared using linear mixed models or Mann–Whitney *U* test (whichever appropriate based on variable distribution) for continuous variables and Pearson chi-square test for categorical variables. Covariates, such as time of day and sex will be taken into account. Significance tests will be two-tailed and at $p \leq 0.05$ level. When appropriate, Bonferroni adjustments will be used to account for multiple comparisons. All analysis will be performed using the Statistical Package for the Social Sciences (SPSS) or Statistical Analysis System (SAS) 9.4 software (SAS Institute Inc., Cary, NC, USA).

Participants who will have at least one vaccination and at least one actigraphy period completed will be included in the statistical analyses. The SAS software handles missing data, therefore incomplete data will remain in the statistical models.

4 | DISCUSSION

The magnitude of the ongoing COVID-19 vaccination programme offers a unique opportunity to explore the relation between sleep, circadian misalignment, and vaccination responsiveness. The present paper describes the protocol of an innovative project to achieve this goal. To our knowledge, there are no publications addressing sleep and shift work in relation to immune response to COVID-19 vaccination, yet the scientific community recently expressed the necessity for this kind of information (Benedict & Cedernaes, 2021; Kow & Hasan, 2021).

There are several strengths to our study. First, we will be the first to study the association of sleep, shift work, and antibody responses to the COVID-19 vaccination. Second, we will aim to investigate night shift workers, where sleep insufficiency and misaligned circadian rhythms are prevalent. Although previous studies have looked at sleep deprivation and vaccine responsiveness, none of these studies targeted shift workers. Third, this will be a natural field study, measuring objective and subjective sleep parameters, where we will carry out as much as possible remotely, i.e. with the use of e-sleep diary and actigraphy. Fourth, we will aim for an equal distribution of men and women among groups to explore possible sex differences. Studies including male and female participants either found no sex differences (Lange et al., 2003) or a significant difference between sex, such that the sleep manipulation affected only men (Benedict et al., 2012). Furthermore, the study will provide comprehensive information, such as serostatus at baseline, (re-)infections monitoring, work schedules, and timing of vaccinations in the context of shift work. Last, we aim to investigate long-term associations by follow-up measurements of immune response and sleep after 6 months and 1 year after vaccinations are completed. The persistence of the sleep-related effects on antibodies varied between the described studies in the introduction, some studies failed to reveal any statistical differences at ≥4 weeks after vaccination (Benedict et al., 2012; Spiegel et al., 2002), whereas others did (Lange et al., 2003, 2011). One study found a pronounced sleep effect on antigen-specific T-cell response 1 year after the initial vaccination (Lange et al., 2011). Although these discrepancies might be related to differences in vaccinations against different virus types and study designs, the few human studies available provide convincing evidence that efficient sleep supports vaccination outcomes.

Our protocol also has limitations. First, the accelerated speed of vaccination programmes in the Netherlands might limit successful recruitment, as a large group have already been vaccinated and could limit us in our attempt to aim for an equal distribution of occupation, sex, and age range among participants within each group. Second, stress related to occupation and/or COVID-19 might vary between shift workers and day workers. To take this into account, the perceived stress scale will be administered (Cohen et al., 1983).

To conclude, this proposed research is innovative, as (a) we will be the first to study the association of sleep and antibody responses to the COVID-19 vaccination; and (b) investigate this in a vulnerable population, shift workers. Successful completion of this proposal will advance our understanding of sleep, shift work, and immune response to the COVID-19 vaccine, addressing an important knowledge gap directly relevant to all humans facing a global COVID-19 pandemic. These insights are critically necessary to further improve the efficiency of future vaccination programmes, where targeted interventions to improve sleep and circadian misalignment could positively influence vaccination efficacy, and thereby improve global health.

CONFLICT OF INTEREST

The authors have nothing to disclose, and there are no conflict of interest regarding this manuscript.

AUTHOR CONTRIBUTIONS

HLvdH, GJL, GTJvdH, IC, RDdV, CGvK, BK, HvdK designed the research, drafted, and edited the manuscript. All co-authors have read the final manuscript and gave approval for submission.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets have been generated yet or analysed in the present study.

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REFERENCES

Akerstedt, T. (2003). Shift work and disturbed sleep/wakefulness. *Occupational Medicine (Oxford)*, *53*, 89–94. https://doi.org/10.1093/occmed/kqg046

Almeida, C. M., & Malheiro, A. (2016). Sleep, immunity and shift workers: A review. *Sleep Science*, *9*, 164–168. https://doi.org/10.1016/j.slsci.2016.10.007

Benedict, C., Brytting, M., Markström, A., Broman, J.-E., & Schiöth, H. B. (2012). Acute sleep deprivation has no lasting effects on the human antibody titer response following a novel influenza A H1N1 virus vaccination. *BMC Immunology*, *13*, 1. https://doi.org/10.1186/1471-2172-13-1

Benedict, C., & Cedernaes, J. (2021). Could a good night's sleep improve COVID-19 vaccine efficacy? *Lancet Respiratory Medicine*, *9*, 447–448. https://doi.org/10.1016/S2213-2600(21)00126-0

Besedovsky, L., Lange, T., & Haack, M. (2019). The sleep-immune crosstalk in health and disease. *Physiological Reviews*, *99*, 1325–1380. https://doi.org/10.1152/physrev.00010.2018

Borbely, A. A. (1982). A two process model of sleep regulation. *Human Neurobiology*, *1*, 195–204.

Braun, R., Kath, W. L., Iwanaszko, M., Kula-Eversole, E., Abbott, S. M., Reid, K. J., … Allada, R. (2018). Universal method for robust detection of circadian state from gene expression. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, E9247–E9256. https://doi.org/10.1073/pnas.1800314115

Buysse, D. J., Reynolds, C. F. 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*, 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, *24*, 385–396. https://doi.org/10.2307/2136404

Costa, G. (2003). Shift work and occupational medicine: An overview. *Occupational Medicine*, *53*, 83–88. https://doi.org/10.1093/occmed/kqg045

Daan, S., Beersma, D. G., & Borbely, A. A. (1984). Timing of human sleep: Recovery process gated by a circadian pacemaker. *American Journal of Physiology*, *246*, R161–R183. https://doi.org/10.1152/ajpregu.1984.246.2.R161.

Faraut, B., Boudjeltia, K. Z., Vanhamme, L., & Kerkhofs, M. (2012). Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. *Sleep Medicine Reviews*, *16*, 137–149. https://doi.org/10.1016/j.smrv.2011.05.001

Fatima, Y., Bucks, R., Mamun, A., Skinner, I., Rosenzweig, I., Leschziner, G., & skinner, T. (2021). Shift work is associated with increased risk of COVID-19: Findings from the UK Biobank cohort. *Journal of Sleep Research*, *30*, e13326. https://doi.org/10.2139/ssrn.3684452

Foster, R. G., & Wulff, K. (2005). The rhythm of rest and excess. *Nature Reviews Neuroscience*, *6*, 407–414. https://doi.org/10.1038/nrn1670

GeurtsvanKessel, C. H., Okba, N. M. A., Igloi, Z., Bogers, S., Embregts, C. W. E., Laksono, B. M., … Koopmans, M. (2020). An evaluation of COVID-19 serological assays informs future diagnostics and exposure assessment. *Nature Communications*, *11*, 3436. https://doi.org/10.1038/s41467-020-17317-y

James, S. M., Honn, K. A., Gaddameedhi, S., & Van Dongen, H. P. A. (2017). Shift work: Disrupted circadian rhythms and sleep-implications for health and well-being. *Current Sleep Medicine Reports*, *3*, 104–112. https://doi.org/10.1007/s40675-017-0071-6

Kecklund, G., & Axelsson, J. (2016). Health consequences of shift work and insufficient sleep. *BMJ*, *355*, i5210. https://doi.org/10.1136/bmj.i5210

Klein, S. L., & Flanagan, K. L. (2016). Sex differences in immune responses. *Nature Reviews Immunology*, *16*, 626–638. https://doi.org/10.1038/nri.2016.90

Kow, C. S., & Hasan, S. S. (2021). Do sleep quality and sleep duration before or after COVID-19 vaccination affect antibody response? *Chronobiology International*, *38*, 941–943. https://doi.org/10.1080/07420528.2021.1900216

Laing, E. E., Möller-Levet, C. S., Poh, N., Santhi, N., Archer, S. N., & Dijk, D. J. (2017). Blood transcriptome based biomarkers for human circadian phase. *eLife*, *6*, e20214. https://doi.org/10.7554/eLife.20214

Lange, T., Dimitrov, S., Bollinger, T., Diekelmann, S., & Born, J. (2011). Sleep after vaccination boosts immunological memory. *The Journal of Immunology*, *187*, 283–290. https://doi.org/10.4049/jimmunol.1100015

Lange, T., Perras, B., Fehm, H. L., & Born, J. (2003). Sleep enhances the human antibody response to hepatitis A vaccination. *Psychosomatic Medicine*, *65*, 831–835. https://doi.org/10.1097/01.PSY.0000091382.61178.F1

Loef, B., Nanlohy, N. M., Jacobi, R. H. J., van de Ven, C., Mariman, R., van der Beek, A. J., … van Baarle, D. (2019). Immunological effects of shift work in healthcare workers. *Scientific Reports*, *9*, 18220. https://doi.org/10.1038/s41598-019-54816-5

Pedersen, A. F., Zachariae, R., & Bovbjerg, D. H. (2009). Psychological stress and antibody response to influenza vaccination: a meta-analysis. *Brain, Behavior, & Immunity*, *23*, 427–433. https://doi.org/10.1016/j.bbi.2009.01.004

Prather, A. A., Hall, M., Fury, J. M., Ross, D. C., Muldoon, M. F., Cohen, S., & Marsland, A. L. (2012). Sleep and antibody response to hepatitis B vaccination. *Sleep*, *35*, 1063–1069. https://doi.org/10.5665/sleep.1990

Prather, A. A., Pressman, S. D., Miller, G. E., & Cohen, S. (2021). Temporal links between self-reported sleep and antibody responses to the influenza vaccine. *International Journal of Behavioral Medicine*, *28*, 151–158. https://doi.org/10.1007/s12529-020-09879-4

Reinberg, A., & Ashkenazi, I. (2008). Internal desynchronization of circadian rhythms and tolerance to shift work. *Chronobiology International*, *25*, 625–643. https://doi.org/10.1080/07420520802256101

Scepanovic, P., Alanio, C., Hammer, C., Hodel, F., Bergstedt, J., Patin, E., … Fellay, J. (2018). Human genetic variants and age are the strongest predictors of humoral immune responses to common pathogens and vaccines. *Genome Medicine*, *10*, 59. https://doi.org/10.1186/s13073-018-0568-8

Spiegel, K., Sheridan, J. F., & Van Cauter, E. (2002). Effect of sleep deprivation on response to immunization. *JAMA*, *288*, 1471–1472.

Taylor, D. J., Kelly, K., Kohut, M. L., & Song, K. S. (2017). Is insomnia a risk factor for decreased influenza vaccine response? *Behavioral Sleep Medicine*, *15*, 270–287. https://doi.org/10.1080/15402002.2015.1126596

Wickwire, E. M., Geiger-Brown, J., Scharf, S. M., & Drake, C. L. (2017). Shift work and shift work sleep disorder: Clinical and organizational perspectives. *Chest*, *151*, 1156–1172. https://doi.org/10.1016/j.chest.2016.12.007

Wittenbrink, N., Ananthasubramaniam, B., Münch, M., Koller, B., Maier, B., Weschke, C., … Kramer, A. (2018). High-accuracy determination of internal circadian time from a single blood sample. *Journal*

of Clinical Investigation, *128*, 3826–3839. https://doi.org/10.1172/JCI120874

World Health Organization. (2021). Retrieved from https://covid19.who.int/

Wu, F., Zhao, S. U., Yu, B., Chen, Y.-M., Wang, W., Song, Z.-G., … Zhang, Y.-Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, *579*, 265–269. https://doi.org/10.1038/s41586-020-2008-3

Zhuang, X., Rambhatla, S. B., Lai, A. G., & McKeating, J. A. (2017). Interplay between circadian clock and viral infection. *Journal of Molecular Medicine (Berlin)*, *95*, 1283–1289. https://doi.org/10.1007/s00109-017-1592-7

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