Responses to Participants' Questions

This document provides responses* to questions raised by webinar participants related to the following presentations:

- **Presentation 1: *The Sleep-Immune Connection: Implications for COVID Recovery***
  Monika Haack, PhD
- **Presentation 2: *Sleep-Circadian Dysregulation and PASC***
  Sairam Parthasarathy, MD
- **Presentation 3: *Sleep Apnea: Potential to Moderate COVID-19 and PASC Outcomes***
  Susan Redline, MD, MPH
- **Discussant: *Janet Mullington, PhD***

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. What is the effect of shift work (switching from days to nights to evenings) on the immune system?

Response:

Unidentified panelist: What's been shown is that mistimed sleep, including shift work and jet lag, disturbs the rhythms of major physiological processes, including diurnal rhythms of immune cells and mediators. When simulating shift work in the laboratory, for example, about 70% of rhythmic transcripts are reduced in their amplitude, and key biological processes affected are immune cell processes. This may be a potential molecular mechanism underlying the negative health consequences, such as cancer, of shift work sleep.

Q. Unrefreshing sleep may be caused by mitochondrial dysfunction. So, why not test all Long-COVID patients for mitochondrial dysfunction? If a correlation is established, then mitochondrial dysfunction could be used as a biomarker and a means to monitor patient progress.

Response:

Unidentified panelist: Yes, mitochondrial dysfunction may be one of multiple potential mechanisms that contribute to the development and persistence of Long COVID, and I expect it will be addressed in future studies.

Indeed, there is some evidence of protein upregulation in Long COVID that points to activation of anti-inflammatory efforts and mitochondrial stress.

Q. Have Long-COVID cases further exacerbated the alcohol/substance-mediated inflammatory response resulting in sleep disturbances/disorders?

Response:

Dr. Redline: There isn't a lot of data on this, but we do know that sleep disorder breathing, because of the effects on mood and cognition, may increase the opportunity for substance use disorders. What's important is that alcohol and other substances may make sleep apnea and sleep worse. It's possible to get into vicious cycles where disturbed sleep may promote substance use disorders and those substances themselves may exacerbate sleep disturbances, which causes this upward spiral that we really need to look at.

Q. Do you think that increased sleep pressure seen during acute COVID infection may be a functional change to promote humoral response and conversion to positive receptor-binding domain?

Response:

Dr. Parthasarathy: That's a complex question. I think the increase in sleep pressure, as I elucidated in my talk, may be associated with an attenuated humoral response. But I also think that the process goes to some of the work that my colleagues, Dr. Haack and Aric Prather, have done with regard to how sleep adversely affects T cell and B cell functioning. So, with regard to how this excess of sleep pressure causes the immune dysfunction, it's possibly the other way around in terms of the infection causing the dysregulated T cell and B cell function, which is then affecting sleep patterns. Consequently, this may be a situation of reverse causation. But we don't have the data to prove this, other than the preclinical experimental data that Dr. Haack shared, as well as what others have published. Now, connecting that to RBD, that's a tough stretch. Both Drs. Haack and Mullington are working in the autoimmune area and they … can comment on whether they believe there's autoimmune-mediated neural damage that may be responsible for the observed cases of receptor-binding domain. Or is this a manifestation of neurodegeneration? Or is this not a situation of neurodegeneration?

Dr. Haack: We'll need more research in this area. What is clear is that insomnia is an independent risk factor for many autoimmune diseases. Something is going on with sleep disturbances that's involving autoimmune processes and there has been work done on autoreactive T cells, but we still need more work in this area. This is very important given the associations reported in the epidemiology on insomnia and autoimmune diseases.

Dr. Mullington: Certainly, the bidirectionality is coming through in all this work. Sleep is affected by pain and by sleep apnea and other disrupting factors. The immune factor may be a bit homeostatic in its response, potentially

to increase sleep and slow wave sleep when the immune system needs it. This bidirectionality may be functional. The research opportunities are there, and this is very interesting work.

Webinar Slides

To request a copy of the R3 Webinar slides, please email RECOVER_ACC@rti.org

To Learn More

- Information about RECOVER research and to volunteer for studies: https://recovercovid.org/research
- Frequently Asked Questions about RECOVER and PASC: https://recovercovid.org/faqs
- CDC information: Information for the general public and for healthcare providers about post-COVID conditions: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/