Obesity & Cancer Webinar Series

Sleep and Circadian Rhythm Assessment in Obesity and Cancer Research Webinar
December 3, 2020, 12:00 noon – 1:30 p.m. (Eastern Time)

Frequently Asked Questions

Panelists:

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1. **Are there any validated metabolomic or transcriptomic measures of circadian phase or insufficient sleep in adult and pediatric/adolescent populations?**

   Kenneth P. Wright, Jr., Ph.D.: Several transcriptomic biomarkers (e.g., slides 21-23 in recording) have been tested, mostly under controlled laboratory conditions. These and other biomarkers (e.g., metabolomic) under development need validation studies in adult and/or pediatric/adolescent populations. These tests represent an important research opportunity.

2. **What is known about the impact or use of microbiome on sleep/circadian biomarker discovery?**

   Kenneth P. Wright, Jr., Ph.D.: The integration of sleep and circadian rhythms with the microbiome, with regard to biomarkers and metabolic health, is at the forefront of research. We published a paper in the April 2021 issue of *Current Opinion in Endocrine and Metabolic Research* that highlights recent developments (Withrow et al., 2021). See also the following published articles: Matenchuk et al., 2020; Mahaqi and Gozal, 2020; Broussard and Devkota, 2016; Reynolds et al., 2017.

3. **How can we use information about timing between dim light melatonin onset (DLMO) and sleep onset, midsleep, or sleep offset to inform whether circadian rhythms may be misaligned or use other information about circadian phase in adult and/or pediatric populations?**

   Kenneth P. Wright, Jr., Ph.D.: For healthy adults who obtain adequate sleep, the DLMO occurs on average about 2 hours prior to bedtime, and for younger children who obtain such sleep, the DLMO takes place closer to bedtime. There are individual differences in the timing of DLMO to bedtime, and thus, there is a range (e.g., Wight et al., 2005; Duffy and Wright, 2005; Sletten et al., 2010; Burgess et al., 2003; Lazar et al., 2013; LeBourgeois et al., 2013; Akacem et al., 2015; Crowey et al., 2014). Extremes outside these ranges could represent misalignment. In addition, high melatonin levels existing within individuals for many hours after waketime (i.e., dim light melatonin offset occurring after waketime) can be associated with metabolic impairment (e.g., Eckel et al., 2015; Simon et al., 2019). We are in the early stages of being able to assess misalignment between central and peripheral clocks, and this area of inquiry is important.

4. **When real-world conditions make DLMO assessment impossible, can you suggest alternative methods that would validate a blood biomarker of circadian phase in adult and/or pediatric populations?**

   Kenneth P. Wright, Jr., Ph.D.: There are current efforts to estimate DLMO/circadian phase with blood-based biomarkers, and these efforts need to be validated out of the laboratory and within various populations. (See the answer to question #1.) Currently, at-home DLMO testing is feasible.

5. **Is it in any way detrimental to health to conduct saliva melatonin sampling for DLMO when the collection times interfere with nocturnal sleep? What are the considerations for keeping a sick patient awake during their usual sleep time to collect a sample(s)?**

   Kenneth P. Wright, Jr., Ph.D.: To assess DLMO, we recommend sampling to start about 7 hours prior to habitual bedtime and to end about 1 hour after habitual bedtime. Thus, sleep disturbance would be minimal. Within a laboratory setting, melatonin can also be assessed from blood samples collected during sleep with indwelling IV and extended (e.g., 12-foot) tubing so that sleep can be minimally disturbed.

6. **Could polysomnography (PSG) underestimate sleep due to in-lab disruption of sleep?**

   Susan Redline, M.D., M.P.H.: That phenomenon is referred to as a “1st-night” effect and is a reason that some studies bring individuals into the laboratory for 2 to 3 nights, discarding the 1st night as a habituation night. Full PSG can also be done in home settings, where a 1st night or laboratory effect would likely be minimal (Iber et al., 2004). Nonetheless, contextual factors can influence measurement and should be considered when interpreting

the data. For these reasons, certain parameters potentially susceptible to environmental disturbance, such as sleep efficiency and duration, are often estimated using multi-day (home-based) actigraphy rather than PSG. Although actigraphy has measurement bias, it may provide a more representative estimate for each studied individual than a single-night PSG study.

7. **Are there research findings regarding whether drugs, such as exogenous melatonin or Ambien, can modify the associations between sleep/circadian disruption and obesity- or cancer-disease outcomes?**

   Susan Redline, M.D., M.P.H.: I am not aware of any specific studies of such effect modification. Keep in mind that indication biases need to be considered when interpreting potential drug effects.

8. **Has anyone studied whether time-restricted eating without changing insufficient sleep improves health?**

   Susan Redline, M.D., M.P.H.: Flanagan and colleagues (2020) extensively reviewed the topic of time-restricted eating. Carefully conducted laboratory studies have shown the beneficial cardiometabolic effects of timed eating when sleep was controlled (Wehrens et al., 2017). Larger clinical trials, to my knowledge, have not explicitly addressed the potential modifying or confounding by sleep on time-restricted eating. This issue is important, as there are complex inter-relationships among chronotype (and circadian misalignment), sleep duration, and meal timing. For example, short sleepers tend to have more irregular meals but also tend to eat earlier in the day (Dashti et al., 2015). In considering both meal timing and circadian rhythms, several studies identified the potential interaction with chronotype. (For example, larks who eat earlier and owls who eat later have improved metabolism.)

9. **Among shift-working populations, it is common to revert to daytime-based schedules on non-workdays due to family needs and responsibilities. Given this, are there any technologies or other approaches to limit the degree of circadian disruption experienced by these populations?**

   Susan Redline, M.D., M.P.H.: There are several strategies for minimizing the adverse effects of shift work (Reid & Abbott, 2015). The strategies include optimizing the scheduling of sleeping, napping, shift work (e.g., regular shifts or those that rotate clockwise), and eating; the use of appropriate light at the workplace and darkness after the shift; and the use of melatonin or melatonin agonists.

10. How has the general population's average sleep duration changed over time? How (if at all) has this situation affected the need for new measurement approaches over time?

Susan Redline, M.D., M.P.H.: There are conflicting data on this issue. It is often quoted that sleep duration has declined by 1 minute per year over the last 100 years. However, systematic reviews—all based on self-reported data—have not confirmed significant changes in sleep duration across large communities, at least over the last 50 years (e.g., Youngstedt et al., 2016). The marked effect of sampling and differences in estimates due to how questions are asked and data analyzed make it challenging to confidently estimate long-term trends. Moreover, from equity issues, a key question is whether sleep has declined differentially in certain populations more than others (as discussed in the review of the Alameda, California, data showing shorter sleep patterns increasing in prevalence more in blacks than among other groups.