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Editorial

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Biomarkers of sleep and insomnia—challenges and opportunities

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Accumulating evidence support links between poor sleep health, including insomnia, and increased risk for negative age-related health conditions, such as cardiovascular and cardiometabolic disorders, among others. While the underlying biological mechanisms remain to be fully elucidated, many have turned to the biomarkers of the immune system, particularly markers of inflammation, as prime candidates. A meta-analytic review of 72 studies supports a fairly consistent association between sleep disturbances, including insomnia symptoms, with elevated circulating levels of inflammatory markers interleukin (IL)-6 and C-reactive protein (CRP) [1]. However, sleep disturbances and acute sleep loss have also been associated with alterations in other aspects of the innate and adaptive immune system ranging from a downregulation in natural killer (NK) cell cytotoxicity [2] to impairment in antigen-specific antibody production in response to vaccination [3].

To date, most studies that have integrated biomarkers into sleep research have been limited in scope, relying on a handful of usual suspects (e.g. IL-6, CRP). Such an approach, while practical and straightforward, likely obscures important immunologic complexities. The paper by Bakewell et al. [4] takes a more comprehensive approach by using data from the Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY)-Sleep substudy, which is comprised of participants 50 years or older diagnosed with HIV, 50 years or older demographically similar matched control group without HIV, and a younger sample of participants with HIV. All participants completed questionnaires about their sleep health, including insomnia symptoms, and wore a wrist actigraph and fingertip oximetry device for 1 week. A blood samples were processed to quantify concentrations of 31 biomarkers that covered 8 distinct inflammatory pathways.

One clear strength of this study is the breadth of biomarkers assessed. However, a challenge faced by all who wade into the high-dimensional biomarker space is how best to facilitate data reduction. The authors employed principal components analysis (PCA) and unsupervised agglomerative hierarchical cluster analysis (AHCA) to create three data driven clusters that the authors found reflected "gut/immune activation," "neurovascular," and an undifferentiated cluster they called "reference." Using these clusters, they tested whether rates of HIV positivity differed by cluster and found that higher proportions of HIV were observed in the "neurovascular" cluster than in "gut/immune activation' or "reference" cluster. This is not surprising as HIV has been linked to elevated chronic inflammation in several studies [5]. Thanks to more effective antiretroviral therapies, viral suppression is allowing people living with HIV (PLWH) to live substantially longer, healthier lives. However, chronic HIV is considered a state of persistent inflammation that is implicated in the development of atherosclerosis and cardiovascular disease (CVD). Indeed, CVD is one of the leading causes of mortality and morbidity among PLWH [6], at least in high-resourced countries.

Reports of sleep disturbance, including insomnia, are often elevated in PLWH, which has been previously documented in the POPPY sample [7]. Proinflammatory mediators have the capacity to impact the brain and alter sleep homeostasis, setting up a vicious cycle through which sleep disturbance contributes to enhanced, and dysregulated, inflammatory activity that further disrupts sleep [8]. Interestingly, Bakewell et al. reported no differences in rates of insomnia, as defined by an Insomnia Severity Index (ISI) score of ≥15, across the three clusters. Examination of secondary sleep outcomes, including those derived from actigraphy, revealed only a couple significant differences of low clinical relevance.

The largely null sleep findings presented by Bakewell et al. are likely a bit disappointing for sleep and circadian scientists committed to understanding how peripheral blood-based biomarkers may be used to inform prediction and treatment; however, there are several considerations that may increase one's optimism for future investigations. First, while the sample was fairly large (n = 465), only 82 participants were classified as having insomnia based on an ISI ≥15. It is possible that the inclusion of more participants with "insomnia" or participants with insomnia ascertained through a more comprehensive method (e.g. structured clinical interview) would have revealed otherwise elusive biomarker differences. Another consideration is related to the method used for classifying inflammatory clusters. As noted, the authors identified three clusters using PCA and AHCA; however, this method accounted for only 41.5% of the variance in inflammatory activity, leaving an additional 58.5% of variance in the data. As new methods are developed, tested,

and validated there may be opportunities to continue to interrogate immunological phenotypes in the context of sleep health.

Observational and experimental data demonstrate that insomnia and insufficient sleep can affect the immune system in ways that may accelerate inflammatory disease processes. However, our understanding of how and when this occurs remains to be clarified. Collaboration with basic scientists, including immunologists, are critical to advancing our understanding of how sleep and circadian disruption can promote disease. At present, research in humans indicates that disrupted sleep can routinely affect systemic markers of inflammation, but that is likely only a fraction of what is perturbed. Nevertheless, because we know how to improve sleep, researchers are employing interventions to reduce or better regulate inflammatory functioning. Indeed, prior work suggests cognitive behavioral therapy for insomnia, as well as tai chi, can reduce systemic levels of chronic inflammation and modulate inflammatory gene expression in older adults with insomnia [9]. Moreover, there is an ongoing clinical trial (NCT04721067) testing the effects of digital cognitive behavioral therapy for insomnia on markers of inflammation in patients with HIV.

Biomarker discovery can facilitate and inform a better understanding of sleep health and circadian function, which could be used for diagnosis of sleep disorders, assessment of risk for sleep-related health outcomes, and potentially to evaluate the adequacy or appropriateness of a therapy [10]. Advances in biotechnology, including high throughput, high-dimensional bioassays, coupled with robust and replicable computational methods have the potential to accelerate progress across all domains of science and medicine, including the sleep and circadian sciences. The study by Bakewell et al. represents an important step forward in this regard, but hopefully just the first of many.

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