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Uncovering the role of sleep on human health

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A large-scale, phenome-wide study enables a holistic view of the role of sleep on human health, highlighting its potential as a modifiable risk factor for chronic disease.

Sleep is fundamental for maintaining overall health, influencing nearly every physiological system. However, most sleep studies are performed in the context of single systems, such as the cardiovascular, endocrine or neurological system. Although valuable, this single-system approach obscures the ubiquitous role of sleep and the broader interplay between health and sleep. In this issue of *Nature Medicine*, Kohn et al.[1] seek to address this limitation with their report of a large-scale, phenome-wide analysis of sleep characteristics. The data are derived from multi-night assessments and incorporate a broad range of phenotypes across 16 body systems — characterized by measurements such as blood pressure, dietary logging and gut microbiome mapping, among others (Fig. 1) — as part of the Human Phenome Project (HPP)[2]. Phenome-wide association studies are often conducted to examine how genetic variants influence a broad range of phenotypes to identify pleiotropic effects[3]. Because sleep is a pervasive function that affects most (if not all) body systems, a similar rationale can be adopted to examine how variation in sleep influences a wide variety of human body system traits. In this manner, Kohn et al.[1] have established a framework for a more holistic understanding of the role of sleep.

The authors' main findings reinforce established associations between sleep characteristics and cardiometabolic traits, such as strong correlations between the peripheral apnea hypopnea index (pAHI, a marker of obstructive sleep apnea) and body composition features — including body mass index and visceral adipose tissue (VAT), as well as blood lipids and markers of glucose metabolism.

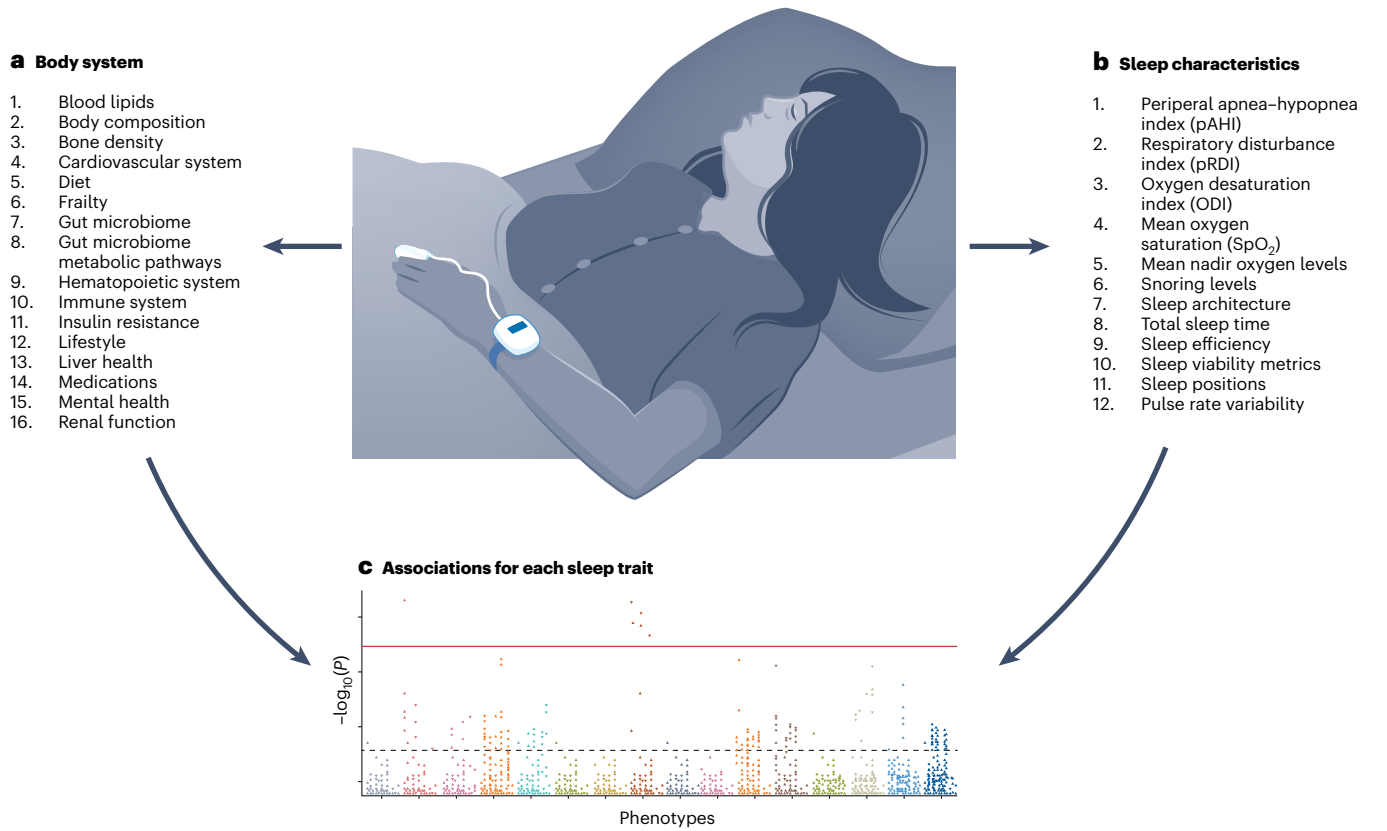

Fig. 1 | Sleep characteristics and their associations with 16 body systems. The figure summarizes the framework used by Kohn et al.[1] in their analysis of the interplay of nightly sleep characteristics and body system health, utilizing data from the HPP cohort. **a**, A total of 16 body systems were analyzed to provide a comprehensive view of possible health associations. The body systems were qualified using measurements from the HPP study. **b**, Nightly sleep characteristics were compiled from a three-night monitoring period using the WatchPAT 300 home sleep test device, which tracks features such as respiratory events, pulse rate variability, oxygen saturation and sleep architecture. **c**, Kohn et al.[1] performed association studies attempting to link nightly sleep characteristics with body system health. Their results corroborated well-established findings and prompted areas for future investigation.

Other relevant findings included known sex-specific associations between sleep architecture and age, mostly driven by menopausal status. As well as confirming known associations between sleep characteristics and body system traits, Kohn et al.[1] generated new insights that highlight the utility of this approach, paving the way for additional studies that leverage data from the HPP and similar cohorts. They also demonstrate the potential of sleep as a modifiable risk factor for conditions of public health relevance.

First, the authors focused on sleep measurements that extend beyond sleep duration, such as sleep architecture, surrogate measurements of respiratory events, and pulse rate variability. Sleep is a highly dynamic process, and focusing on such physiological surrogates provides insights into associations with a wide range variety of human traits, offering deeper understanding than would be gained from studying sleep duration alone. To accomplish this, Kohn et al.[1] used a non-invasive, simple to set-up, wrist-worn home sleep apnea-monitoring device based on pulse arterial tonometry, which reliably estimates sleep characteristics in a natural setting. However, the lack of electroencephalogram (EEG) and airflow channels prevented the authors from deriving even more detailed sleep features[4]. Future research should explore other similarly straightforward set-ups, but with additional signals to provide further insights into the role of EEG biomarkers beyond sleep architecture.

Second, the data were collected across multi-night assessments, with an average of almost three nights of recording per participant. This approach helps to minimize intraindividual variability in sleep behaviors that can otherwise obscure associations. By contrast, understanding the sources of intraindividual variability may help to characterize which behaviors could positively affect sleep and help to prevent associated conditions. Although the authors did not leverage sleep variability as a potential predictor in this investigation — probably because it would have required more longitudinal data — they established a framework that could guide future studies to do so. Notably, studies that explore variability in sleep duration using wearables[5,6] or simplified surrogates of the severity of obstructive sleep apnea derived from under-the-mattress sensors[7,8] have shown significant detrimental effects on cardiometabolic[7] and mental health[5,6] among those with greater sleep variability. These findings suggest a potential area for future studies, exploring multi-night averaged and variable data along with additional sleep measures.

Third, the authors' main findings reinforced the role of sleep in metabolic functions, reporting associations with VAT and insulin resistance. These findings are relevant in the context of new weight-loss pharmacological therapies based on dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) agonists[9]. These therapies demonstrate important cardiometabolic benefits[9], and whether this is partially mediated by changes in sleep remains an open question. Recent evidence that suggests that the dual GLP-1 and GIP agonist tirzepatide may improve moderate-to-severe obstructive sleep apnea[10] hints at an interesting relationship between sleep and metabolic health. This raises intriguing questions about the potential effects of these medications on sleep, as well as whether improved sleep health may enhance their benefits.

Finally, Kohn et al.[1] successfully leveraged a cohort with comprehensive deep phenotyping, the HPP. Deep cohorts such as this are extremely challenging to establish and follow up but can provide unprecedented data that can further our understanding of the role of sleep in health. Sleep research is a field that has been fortunate in the context of data availability, with resources such as the US-based National Sleep Research Resource (NSRR), a repository of datasets containing detailed physiological, epidemiological and clinical data related to sleep[11]. Cohorts like the HPP and those that are available within the NSRR could be leveraged to further extend phenome-wide investigations like that of Kohn et al.[1]. However, many relevant clinical data elements are still lacking in such resources, such as direct integration of electronic health record (EHR) data[12]. Sleep data are still not consistently integrated within EHRs — even within clinical sleep laboratories in academic medical centers — largely owing to the lack of standardized harmonization frameworks[12]. Data harmonization is a fundamental step for phenome-wide studies. Ultimately, the integration of deep phenotyping cohorts, EHRs and consumer-generated data (for example, from wearables or 'nearables'), along with other environmental and geographical resources, may provide the ideal framework for creating a dataset that expands beyond the diversity limitations of the HPP to form a representative and diverse deep phenotype cohort. Such a dataset could apply the holistic analysis of associations between body systems and sleep put forth by Kohn et al.[1] to better understand and test the relationships identified in this study.

Looking ahead, the study by Kohn et al.[1] lays the groundwork for understanding the complex interplay between sleep characteristics and systemic health through a phenome-wide association framework. The study highlights the potential of sleep as a modifiable risk factor for chronic disease. Future work should focus on diverse longitudinal cohorts to investigate causal pathways and integrate advanced artificial intelligence-driven models to tease out complex relationships. As sleep becomes recognized as essential for systemic health, studies like this set the stage for using sleep characteristics as an important intervention in personalized medicine and to improve public health.

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Competing interests

The authors declare no competing interests.