

## **Circadian rhythms and mental health: detecting reliable associations via wearable sensing at scale.**

Circadian rhythms are physiological and behavioral processes that typically recur over 24-hour periods. The 2017 Nobel Prize for Physiology or Medicine was awarded to investigators who described the molecular mechanisms of circadian regulation, highlighting their central importance to human health. In this issue of *The Lancet Psychiatry*, Laura Lyall and colleagues show that circadian disruption, a marked break in normal 24-hour cycles of sleep and activity behaviour, has robust cross-sectional associations with mood disorders, subjective wellbeing and cognitive function<sup>1</sup>. Using the UK Biobank prospective cohort, the authors derived objective circadian disruption measures in a large sample of 91,105 participants who wore activity monitors<sup>2</sup> between 2013 and 2015. For context, previous efforts to objectively measure circadian disruption have only included a few hundred participants. The authors were then able to link this information to a 2016 online mental health questionnaire<sup>3</sup> where participants were classified as meeting criteria for lifetime major depressive disorder and bipolar disorder. This online questionnaire also allowed the authors to categorise subjective happiness and health satisfaction. In addition, UK Biobank participants underwent an initial baseline assessment<sup>4</sup> between 2006-2010, where a touchscreen questionnaire was used to assess subjective loneliness, neuroticism status, and cognitive function (via reaction times in a card game similar to 'Snap'). Using this information, Lyall and colleagues found that adverse activity profiles, characterised by having restless sleep at night and/or much inactivity in the day, were associated with lifetime major depressive disorder and lifetime bipolar disorder. Circadian disruption was also associated with greater mood instability, higher neuroticism scores, more subjective loneliness, lower happiness, lower health satisfaction, and reduced cognitive function. The presented associations remained after adjustment for a wide range of covariates including demographic, lifestyle, education, activity, BMI, and childhood trauma measures.

The study is cross-sectional and therefore cannot provide insights on causal directions. Does circadian disruption cause a decline in mental health status, or vice-versa? Answering this question is challenging as a randomised controlled trial would be prone to ascertainment bias due to the difficulties in blinding participants to behavioural interventions. Observational studies would need very long periods of follow-up to account for reverse causation, where individuals potentially alter their activity profiles before poor health becomes symptomatic. The authors point out that genetic instrument variables and mendelian randomization might provide some insight on causal directions in the near future. In UK Biobank, all participants have been genotyped with imputation to reference panels<sup>5</sup>, and variants have already been discovered for sleep and daily activity status<sup>6</sup>. Further enhancement is also scheduled to include exome sequencing, and eventually whole genome sequencing<sup>7</sup>. This offers a rich genetic discovery resource to support robust mendelian randomization studies on the potential causal relationship between circadian disruption and a variety of psychiatric outcomes.

It is important to highlight Lyall's use of objective exposure measurement for circadian disruption. A traditional advantage of subjective measures of circadian activity is their ease of interpretability and ability to categorise lifetime exposure status; however the measures are typically crude, unreliable, and not particularly sensitive<sup>8</sup>. In UK Biobank participants

were asked to wear a wrist-worn sensor, called an accelerometer, for seven days. This clearly relies on the assumption that seven days are representative of overall circadian rhythm status for this period in an individual's life. For each participant, 180 million "raw" device measurement values were cleaned and then collapsed into average minute-by-minute values. This helped identify the most active ten-hour and the least active five-hour windows in each day, which were subsequently combined into a ratio. This is quite an intuitive measure as one can see that a hypothetically "healthy" person, who is active during the day (high ten hour activity) and sleeps soundly (low five hour activity), is assigned a favourable score. As an important first step this simple measure makes for easier communication to clinical and other non-technical health policy readers. However, one can imagine future studies that include more sophisticated parametric and non-parametric time-series measurements of circadian rhythm exposure status. It will be intriguing to assess whether these more elaborate methods confirm the strong associations between circadian disruption and the measures of mental health status reported by Lyall and colleagues.

While UK Biobank is one of the most valuable medical resources worldwide, the study population (median age = 62, IQR = 54-68) is not ideal to examine the causes of mental health, given 75% of disorders start before the age of 24<sup>9</sup>. As the authors note, the circadian system undergoes developmental change during adolescence, which is also a common time for onset of mood disorders. It may be that UK Biobank provides the template and impetus for a resource of a similar scale in adolescents and younger adults to help transform our understanding of the causes and consequences, prevention and treatment of mental health disorders.

Aiden Doherty

Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford; Nuffield Department of Population Health, BHF Centre of Research Excellence, University of Oxford; NIHR Biomedical Research Centre, Oxford

[aiden.doherty@ndph.ox.ac.uk](mailto:aiden.doherty@ndph.ox.ac.uk)

*I declare no competing interests.*

1. Lyall, L. M. *et al.* Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing and cognitive function: a cross-sectional study of 91 105 participants in the UK Biobank cohort. *Lancet Psychiatry* (**in press**), (2018).
2. Doherty, A. *et al.* Large Scale Population Assessment of Physical Activity Using Wrist Worn Accelerometers: The UK Biobank Study. *PLoS One* **12**, e0169649 (2017).
3. Davis, K. A. S. *et al.* Mental health in UK Biobank: development, implementation and results from an online questionnaire completed by 157 366 participants. *BJPsych Open* **4**, 83–90 (2018).
4. Sudlow, C. *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* **12**, e1001779 (2015).
5. Bycroft, C. *et al.* Genome-wide genetic data on ~500,000 UK Biobank participants. *bioRxiv* 166298 (2017). doi:10.1101/166298
6. Doherty, A. *et al.* GWAS identifies 10 loci for objectively-measured physical activity

and sleep with causal roles in cardiometabolic disease. *bioRxiv* 261719 (2018). doi:10.1101/261719

7. Genome sequencing of first 50,000 UK Biobank participants - News - Medical Research Council. Available at: <https://mrc.ukri.org/news/browse/genome-sequencing-of-first-50000-uk-biobank-participants/>. (Accessed: 19th April 2018)
8. Firth, J. *et al.* The Validity and Value of Self-reported Physical Activity and Accelerometry in People With Schizophrenia: A Population-Scale Study of the UK Biobank. *Schizophr. Bull.* (2017). doi:10.1093/schbul/sbx149
9. Kessler, R. C. *et al.* Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* **62**, 593 (2005).