

Sleep Regularity and Mortality: A Prospective Analysis in the UK Biobank

Reviewed Preprint

Revised by authors after peer review.

[About eLife's process](#)

Reviewed preprint version 2

November 3, 2023 (this version)

Reviewed preprint version 1


July 3, 2023

Posted to medRxiv

April 17, 2023


Sent for peer review

April 14, 2023

Lachlan Cribb, Ramon Sha, Stephanie Yiallourou, Natalie A Grima, Marina Cavuoto, Andree-Ann Baril, Matthew P. Pase 

Turner Institute for Brain and Mental Health, Monash University, Melbourne Australia • National Ageing Research Institute, Melbourne, Australia • Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada • Harvard T.H. Chan School of Public Health, Harvard University, MA, USA

 https://en.wikipedia.org/wiki/Open_access

 Copyright information

Abstract

Background

Irregular sleep-wake timing may cause circadian disruption leading to several chronic age-related diseases. We examined the relationship between sleep regularity and risk of all-cause, cardiovascular disease (CVD), and cancer mortality in 88,975 participants from the prospective UK Biobank cohort.

Methods

The sleep regularity index (SRI) was calculated as the probability of an individual being in the same state (asleep or awake) at any two time points 24 hours apart, averaged over 7-days of accelerometry (range 0-100, with 100 being perfectly regular). The SRI was related to the risk of mortality in time-to-event models.

Findings

The mean sample age was 62 years (SD, 8), 56% were women, and the median SRI was 60 (SD, 10). There were 3010 deaths during a mean follow-up of 7.1 years. Following adjustments for demographic and clinical variables, we identified a non-linear relationship between the SRI and all-cause mortality hazard (p [global test of spline term] < 0.001). Hazard Ratios, relative to the median SRI, were 1.53 (95% confidence interval [CI]: 1.41, 1.66) for participants with SRI at the 5th percentile (SRI = 41) and 0.90 (95% CI: 0.81, 1.00) for those with SRI at the 95th percentile (SRI = 75), respectively. Findings for CVD mortality and cancer mortality followed a similar pattern.

Conclusions

Irregular sleep-wake patterns are associated with higher mortality risk.

Funding

National Health and Medical Research Council of Australia (GTN2009264; GTN1158384), National Institute on Aging (AG062531), Alzheimer's Association (2018-AARG-591358), and the Banting Fellowship Program (#454104).

eLife assessment

This manuscript provides **fundamental** findings on the association between sleep regularity and mortality in the UK Biobank, which is a popular topic in recent sleep and circadian research in population-based studies. The study is based on a large accelerometer study with validated follow-up of incident diseases and deaths, and the data quality and large sample size are **convincing** and strengthen the credibility of the conclusion. This will be of wide interest to researchers in the sleep study field, epidemiologists, practicing clinicians and the general public.

Introduction

Circadian rhythms are endogenous cycles in physiological, hormonal, and behavioral processes largely synchronized to the external 24-hour light-dark cycle. The sleep-wake cycle is perhaps the most notable biological process that follows the 24-hour circadian rhythm.¹ The timing of light exposure is the primary external driver of circadian rhythms. Therefore, rapid changes in sleep timing can cause circadian misalignment through fluctuating light-dark exposure.²

Circadian misalignment is associated with several age-related diseases, including cancer and cardiovascular disease (CVD).^{3–5} However, the health impacts of irregular sleep wake timing are still emerging. This remains an important area of study since modern societal and lifestyle trends, including exposure to artificial and blue light at night, longer work hours, shift work, and the 24-7 lifestyle have blurred the distinction between day and night, increasing the propensity for circadian disruption.⁶ The present study assessed the relationship between sleep regularity and the risk of incident all-cause mortality, cancer mortality, and CVD mortality in the UK Biobank (UKB). We measured sleep regularity via accelerometry to calculate the sleep regularity index (SRI), a new metric sensitive to differences in sleep-wake timing on a circadian timescale.

Methods

Participants

Over 500,000 adults aged 40 to 69 years were recruited to the UKB cohort between 2006 and 2010 across 22 assessment centers. Participants were invited by the UK National Health Service patient registers, resulting in a 5.5% participation rate. Respondents were more likely to be older, female, and less likely to live in socioeconomically deprived areas than the general population.⁷

Baseline demographics, medical history, lifestyle, vitals, and blood samples were collected. A total of 106,053 participants completed a 7-day wrist-worn accelerometer study through random selection between February 2013 and December 2015.

Measurement of sleep regularity

Accelerometry data were collected using a wrist-worn device (Axivity AX3, United Kingdom) over a 7-day/night period. Estimated sleep status (awake or asleep) at a given time was calculated using the open-source R package GGIR version 2.7-1,⁸ using available algorithms.^{9, 10} To distinguish sleep from sustained periods of inactivity without reference to a sleep diary (not available in the UKB), GGIR uses an algorithm to determine a daily ‘sleep period time window’ for each participant.¹¹ This defines the time window between the onset and end of the main daily sleep period, during which periods of sustained inactivity are interpreted as sleep. The algorithm does not, by default, detect bouts of sleep outside of this window and hence is not able to identify naps. Accelerometry data of low quality were removed using established UKB criteria (Appendix 1).¹² Most participants (88%) provided complete accelerometry data. Participants with fewer than two valid SRI measurements (i.e., less than 2 contiguous 24-hour wear periods; <1%) were excluded. In total, 88,975 (84%) participants provided valid SRI data and were included in the study.

The SRI captures the probability of a participant being in the same state (asleep or awake) at any two time points 24 hours apart.¹² An individual who sleeps and wakes at precisely the same time each day would have an index of 100, whereas an individual who sleeps and wakes at entirely random times would have an index of 0. Each participant provided $k-1$ SRI measurements (where k is the number of valid 24-hour periods), one for each contiguous two-day pair. These SRI measurements were averaged using a linear mixed effects model with a random intercept for the participant and fixed effects for the day of the week and daylight savings transition. The average SRI was standardized over the day of the week and daylight savings transitions, so all SRI results were comparable.

Mortality ascertainment

Mortality occurrence was identified through linkage with NHS Digital for participants from England and Wales and the NHS Central Register for participants from Scotland, with complete records available until January 2022. Death records included the date of death and the ICD-10 code for the primary cause. ICD-10 codes I00-I99 and C00-C97 defined CVD and cancer mortality, respectively.

Ascertainment of disease status at baseline

Past or prevalent cancer (ICD-10 codes D00-D09 and D37-D48), diabetes (codes E10-E14), mental and behavioral disorders (codes F00-F99), nervous system disorders (codes G00-G99), and CVD (codes I00-I99) at the time of the accelerometry study were ascertained through self-report at the UKB baseline session and through linkage with hospital inpatient records using the above ICD-10 codes. Linkage with hospital inpatient records was also used to identify disease occurrence between the UKB baseline session and the time of the accelerometry study.

Data Analysis

Data analysis was performed using R version 4.2.1. Cox proportional hazards models were used to examine associations between the SRI and incident all-cause mortality, CVD mortality, and cancer mortality. Surveillance for mortality commenced from the time of accelerometry (2013-2015) until the end of follow-up (January 2022), with a median follow-up time of 7.1 years (Q1, Q3: 6.6, 7.6). Non-events were censored at the last date they were known to be alive. For CVD and cancer mortality, deaths from competing causes were censored at the time of death. The SRI and all continuous confounders were modeled with restricted cubic splines with knots at the 10th, 50th,

and 90th percentiles to allow for departures from linearity. Effect modification was assessed by adding product terms to Cox models. Missing data were infrequent (< 2%) for most confounder variables and were imputed (10 imputations) by predictive mean matching using the `aregImpute` function of R package *Hmisc*.¹³

In addition to Cox models, discrete-time hazards models, including an interaction between SRI and time (aggregated into 3-month intervals and modeled with a restricted cubic spline with knots at the 5th, 35th, 65th, and 95th percentiles), were fitted to relax the assumption of proportionality and allow hazard ratios (HRs) to vary over time.¹⁴ The SRI by time interaction in this model provided a test of proportionality (a small *p* value would indicate strong evidence against the proportional hazards assumption). Time-varying HRs were then displayed visually. In cases where HRs showed clear time-variation (i.e., hazards were non-proportional), we nonetheless present HRs from the Cox models as these can be interpreted as a weighted average of the time-varying HRs.¹⁵

The discrete-time hazards model for all-cause mortality was also used to estimate standardized cumulative incidence (risk) across levels of SRI, with confidence intervals obtained by bootstrapping.¹⁶ To reduce computation demand, only single imputation was used for the discrete-time hazards models.

All models were adjusted for the following variables that were selected using a directed acyclic graph (Appendix, **Figure S1**): age, sex, ethnicity (White, Asian, mixed race, Black, or other), Townsend deprivation index, retirement status (retired vs. all other work arrangements), shift work (shift worker vs. non-shift worker), sick or disabled (self-reported employment category), household income (ordinal with 5 levels), highest level of education (ordinal with 6 levels), smoking status (current, former, never), smoking (pack years), and use of sedative, antidepressant, or antipsychotic medication.

Sensitivity analyses

We fitted a second statistical model to determine whether the observed associations were independent of sleep time and disruption. Therefore, Model 2 included additional adjustments for overnight sleep duration and wake after sleep onset (WASO), averaged across accelerometry days (plus primary model covariates). In the second sensitivity analysis (Model 3), we adjusted for past or prevalent disease at baseline (cancer, CVD, mental and behavioural disorders, nervous system disorders, diabetes), in addition to the variables in the primary model. These variables were included as part of a sensitivity analysis as it is unclear whether they may be mediators or confounders of the SRI-mortality relationship. Long-standing irregular sleep may lead to prevalent disease (or a history of disease) at baseline and influence disease risk factors,^{17–20} indicating that these disease variables may play a mediating role (and consequently should not be adjusted). Conversely, past or prevalent disease may have effects disruptive to regular sleep and these variables may therefore confound the SRI-mortality relationship. Disease risk factor variables body mass index (BMI), moderate and vigorous physical activity (accelerometry-derived), systolic blood pressure (BP), and use of BP lowering medication, in addition to the variables in Model 3, were included in a final sensitivity analysis (Model 4), as it is similarly unclear whether they may confound or mediate the SRI-mortality relationship.

Comparison of SRI with other regularity measures

Preliminary reports which identified irregular sleep as a potential CVD risk factor measured sleep regularity as the amount of deviation in sleep patterns from an individual's average (i.e., the standard deviation [SD] of nocturnal sleep duration and sleep onset time).^{21, 22} To contrast these SD-based metrics with the SRI, we fitted independent Cox models (each with primary model covariates) and estimated HRs for all-cause mortality for each of the three measures. Additionally,

we added the SRI to a model containing both SD-based regularity measures (alongside primary model covariates) to test whether the SRI contained additional mortality risk information beyond that captured by the two SD metrics.

Results

Table 1 displays sample characteristics. The final sample size was 88,975. There were 3010 all cause deaths during a median follow-up of 7.1 years (Q1, Q3: 6.6, 7.6). The most common primary cause of death was cancer ($n = 1701$, 57%) followed by CVD ($n = 616$, 20%).

SRI and all-cause mortality

We identified a non-linear association between the SRI and all-cause mortality hazard (p [global test of spline term] < 0.001) (**Figure 1**). Compared to the sample median (SRI = 61), mortality rates were highest among those with the most irregular sleep and decreased almost linearly as SRI approached its median, after which the decrease began to plateau (**Figure 1**). HRs, relative to the median SRI, were 1.53 (95% CI: 1.41, 1.66) for participants with SRI at the 5th percentile (SRI = 41) and 0.90 (95% CI: 0.81, 1.00) for those with SRI at the 95th percentile (SRI = 75), respectively. Standardized cumulative incidence curves for all-cause mortality are displayed for the SRI at the 5th percentile, median, and 95th percentile in **Figure 2**. There was little indication that hazard ratios varied according to age (p interaction = 0.48), sex ($p = 0.36$), household income ($p = 0.62$), sleep duration ($p = 0.47$), moderate to vigorous physical activity ($p = 0.13$), past or prevalent CVD ($p = 0.48$), or past or prevalent cancer ($p = 0.29$).

There was strong evidence against the proportionality assumption in the discrete-time hazards model (p [time x SRI interaction] < 0.001). Time-varying HRs for the 5th and 95th SRI percentiles compared to the median are displayed in the appendix (**Figure S2**). For the 5th percentile relative to the median, HRs were greatest in the earliest period of follow-up (HRs > 2), declining until approximately 2.5 years, after which they remained approximately stable with a HR of around 1.5. There was no clear time variation in the HR for the 95th percentile of SRI vs. the median.

CVD-specific mortality

The SRI was associated with CVD-specific mortality in the primary model (p [global] < 0.001 ; **Figure 1**). HRs, relative to the median SRI, were 1.88 (95% CI: 1.61, 2.21) and 0.93 (95% CI: 0.73, 1.20) for the 5th and 95th percentiles, respectively. There was no evidence of non-proportional hazards in the discrete-time hazards model (p [time x SRI interaction] = 0.57). There was little indication that HRs varied according to age (p interaction = 0.17), household income ($p = 0.30$), sleep duration ($p = 0.69$), moderate to vigorous physical activity ($p = 0.95$), past or prevalent CVD ($p = 0.16$), or past or prevalent cancer ($p = 0.24$). HRs for low SRI were larger for males than females (p interaction = 0.006; **Figure S4**).

Cancer-specific mortality

The SRI was associated with cancer mortality in the primary model (p [global] < 0.001). HRs, relative to the median SRI, were 1.36 (95% CI: 1.22, 1.53) and 0.89 (95% CI: 0.77, 1.02) for the 5th and 95th percentiles, respectively. There was strong evidence of non-proportional hazards in the cancer-mortality discrete-time hazards model (p [time x SRI interaction] < 0.001). HRs, for the 5th percentile vs. the median, were large at the beginning of follow-up (HRs > 2) and declined until approximately four years, after which they were small (~ 1.05) and compatible with the null (Appendix, **Figure S3**). There was no indication that HRs for the 95th SRI percentile relative to the median varied over follow-up. There was little indication that hazard ratios varied according

Characteristic	SRI tertile		
	< 56.8 n = 29,361	56.8 to 65.2 n = 29,361	>65.2 n = 30,252
Sex (male), n (%)	16,429 (56%)	12,747 (43%)	9,691 (32%)
Age (years)	62.3 (7.8)	61.8 (7.8)	61.6 (7.9)
BMI	27.8 (4.9)	26.6 (4.3)	25.8 (4.1)
Ethnicity, n (%)			
Asian	1,199 (4.1%)	1,110 (3.8%)	1,114 (3.7%)
Black	159 (0.5%)	107 (0.4%)	76 (0.3%)
Mixed race	1,024 (3.5%)	831 (2.8%)	658 (2.2%)
White	26,621 (91%)	27,070 (93%)	28,210 (93%)
Other	233 (0.8%)	145 (0.5%)	129 (0.4%)
Townsend deprivation index (score units)	-1.36 (3.01)	-1.79 (2.76)	-2.01 (2.63)
Household income* (thousands), n (%)			
<18	4,917 (19%)	3,601 (14%)	3,266 (12%)
18-30	6,665 (25%)	6,225 (24%)	6,450 (24%)
31-50	7,352 (28%)	7,741 (29%)	7,843 (29%)
51-100	5,888 (22%)	6,816 (26%)	7,280 (27%)
>100	1,633 (6.2%)	1,994 (7.6%)	2,159 (8.0%)
Retired, n (%)	9,467 (32%)	8,984 (31%)	9,442 (31%)
Shift worker, n (%)	1,869 (6.4%)	1,146 (3.9%)	912 (3.0%)
Smoking status, n (%)			
Current	2,790 (9.5%)	1,863 (6.4%)	1,451 (4.8%)
Former	10,956 (37%)	10,587 (36%)	10,367 (34%)
Never	15,526 (53%)	16,830 (57%)	18,361 (61%)
Sedative medication, n (%)	334 (1.1%)	231 (0.8%)	216 (0.7%)
Antidepressant medication, n (%)	2,217 (7.6%)	1,543 (5.3%)	1,385 (4.6%)
Past or prevalent cancer, n (%)	3,941 (13%)	3,800 (13%)	3,897 (13%)
Past or prevalent CVD, n (%)	13,949 (48%)	11,602 (40%)	10,727 (35%)
Past or prevalent diabetes, n (%)	1,976 (6.7%)	1,059 (3.6%)	724 (2.4%)
Past or prevalent neurological disease, n (%)	3,946 (13%)	3,380 (12%)	3,467 (11%)
Past or prevalent mental/behavioural disorder, n (%)	3,521 (12%)	2,482 (8.5%)	2,184 (7.2%)
Average night time sleep duration (hours; actigraphy-derived)	6.33 (0.97)	6.59 (0.78)	6.79 (0.66)
Average night time wake after sleep onset (hours; actigraphy-derived)	0.86 (0.30)	0.80 (0.26)	0.70 (0.23)
Sleep duration SD, hours	1.33 (0.64)	1.11 (0.52)	0.94 (0.48)
Sleep onset time SD, hours	1.41 (1.12)	0.96 (0.64)	0.72 (0.51)
SRI, score units	48.5 (7.3)	61.2 (2.4)	70.3 (3.7)
Data are mean (SD), unless specified otherwise. *pounds. SRI = sleep regularity index; CVD = cardiovascular disease.			

Table 1

Sample characteristics (n = 88,975)

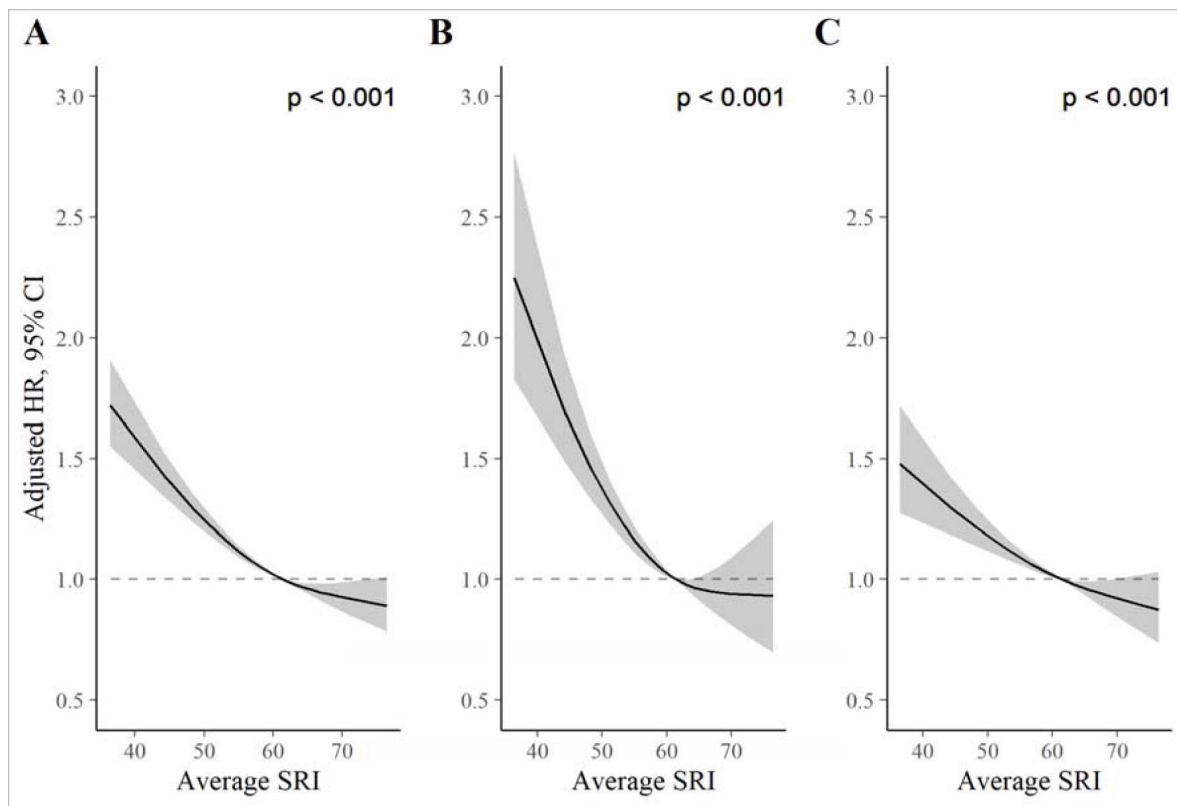


Figure 1.

Adjusted hazard ratios for all-cause (A), CVD (B), and cancer (C) mortality.

P values from global (2 degree of freedom) test of spline term. Hazard ratios (HR) are relative to the median SRI (SRI = 60). HRs for all-cause mortality, CVD mortality, and cancer mortality were estimated using Cox proportional hazards models, adjusted for age, Townsend deprivation index, sex, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category). All continuous confounders and the SRI were modeled with restricted cubic splines (knots at 10th, 50th, and 90th percentiles) to allow for departures from linearity.

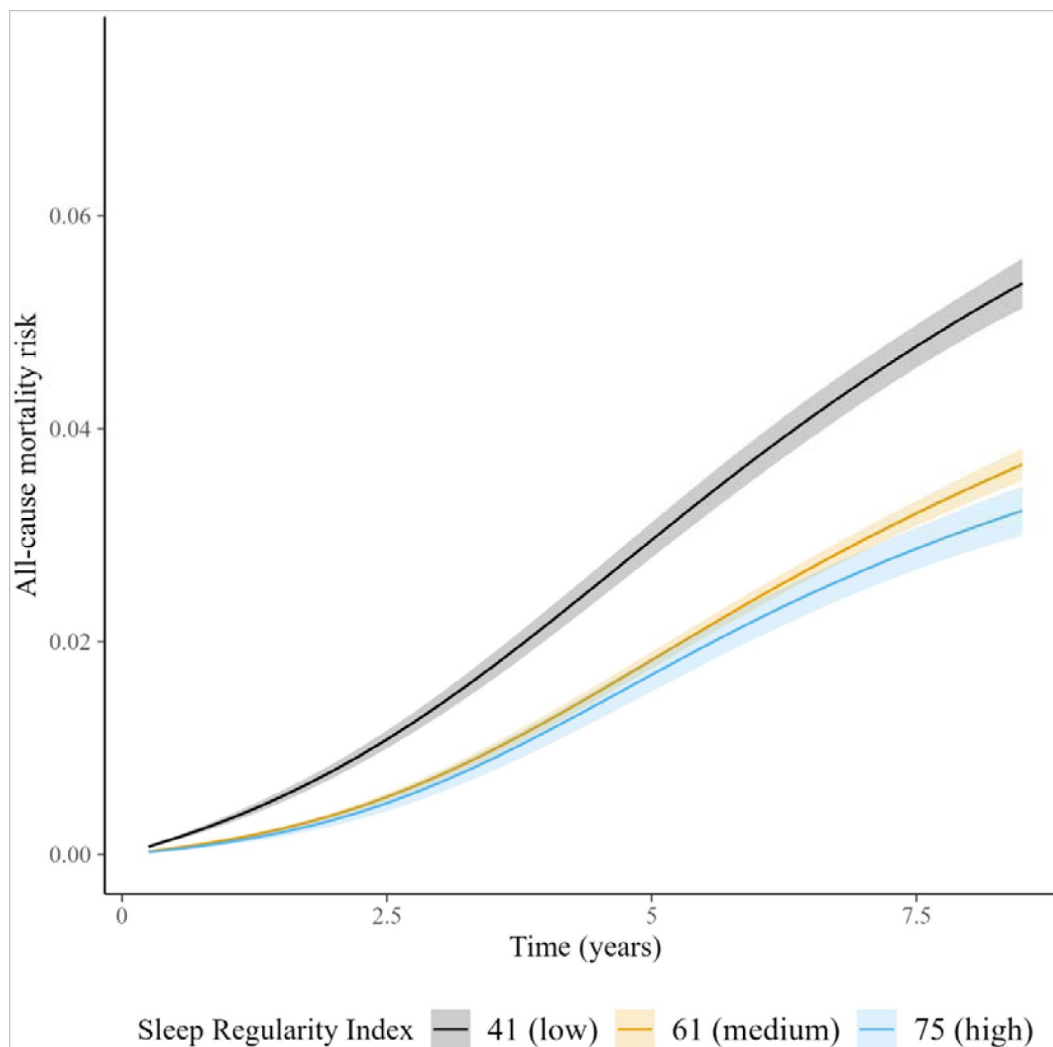


Figure 2.

Cumulative incidence of all-cause mortality across SRI.

Standardized cumulative incidence of all-cause mortality for SRI at 41 (5th percentile), 61 (median), and 75 (95th percentile). Estimates from a discrete-time hazards models including an interaction between SRI and time (aggregated into 3-month intervals and modeled with a restricted cubic spline with knots at the 5th, 35th, 65th, and 95th percentiles) and primary model covariates. Confidence intervals were obtained by bootstrapping.

to age (p interaction = 0.48), sex (p = 0.36), household income (p = 0.62), sleep duration (p = 0.49), moderate to vigorous physical activity (p = 0.42), past or prevalent CVD (p = 0.82), or past or prevalent cancer (p = 0.12).

Sensitivity analyses

Sensitivity analyses are displayed in the appendix (**Figures S5**–**7**). Overall, results were similar and not meaningfully altered following adjustments for sleep time and WASO (Model 2) or past or prevalent baseline disease, including cancer and CVD (Model 3). The SRI remained associated with mortality after further adjustments for past or prevalent diseases, BMI, systolic BP, BP treatment, and physical activity (Model 4), though effect sizes were attenuated. For example, when comparing the 5th percentile to the median, HRs were 1.22 (95% CI: 1.07, 1.39) for all-cause, 1.43 (95% CI: 1.21, 1.69) for CVD, and 1.15 (95% CI: 1.01, 1.29) for cancer mortality.

Comparison of SRI with sleep duration SD and sleep onset time SD

The SRI was modestly negatively correlated with the sleep duration SD (-0.32) and sleep onset time SD (-0.42; see correlation matrix in **Table S1**). **Figure 3** displays HRs, relative to the median, for the SRI, sleep duration SD, and sleep onset time SD. For each measure, greater sleep irregularity (i.e., lower SRI or higher SD representing more day-to-day variability) was associated with an increased all-cause mortality rate in independent models (all p [global] < 0.001). HRs, for low regularity compared to the median, were largest for the SRI (**Figure 3**). The addition of the SRI to a model containing both SD metrics (alongside primary model covariates) improved model fit (p [likelihood ratio test] < 0.001). Conversely, the addition of sleep duration SD and sleep onset time SD to a model containing the SRI (and primary model covariates) did not meaningfully improve model fit (p [likelihood ratio test] = 0.10).

Discussion

Among 88,975 individuals followed for a median of 7.1 years, there was a non-linear association between sleep regularity and the risk of mortality; mortality rates were highest in persons with the most irregular sleep and decreased approximately linearly as sleep regularity approached its median, after which the decrease began to plateau. Our findings were independent of past or prevalent illness (including cancer and CVD at baseline), sleep duration, sleep fragmentation, and other confounding factors. Overall, these data indicate a relationship between sleep regularity and longevity in a large community-based cohort.

Physiological processes associated with CVD and cancer are under circadian control. Mutations or deletions to circadian clock genes such as *CLOCK*, *PER*, and *BMAL1* influence BP, endothelial function, and glucose homeostasis.^{23–26} Both major (e.g., chronic shift work) and minor (e.g., daylight savings transitions) stressors to the circadian system have been associated with a higher risk of CVD.^{3, 5} Similarly, circadian misalignment has also been implicated in the pathogenesis of cancer. For example, circadian clocks are critical to the orchestration of cell division²⁷, and altered clock function can precipitate aberrant cell proliferation²⁸ as well as growth and DNA damage in cancer cells.²⁹ Many systems are under circadian influence, including the sleep-wake cycle, and less clear has been the extent to which differences in sleep regularity are related to negative health outcomes. We extend this research by demonstrating that differences in sleep regularity are associated with the risk of mortality from both CVD and cancer.

Whereas sleep regularity has not been examined with respect to incident cancer or mortality, the current findings extend research showing that greater sleep-wake variability, as measured by the SD of sleep onset or duration, was independently associated with a higher risk of incident CVD in the multi-ethnic study of atherosclerosis but not the UK Biobank.^{21, 22} We demonstrate that

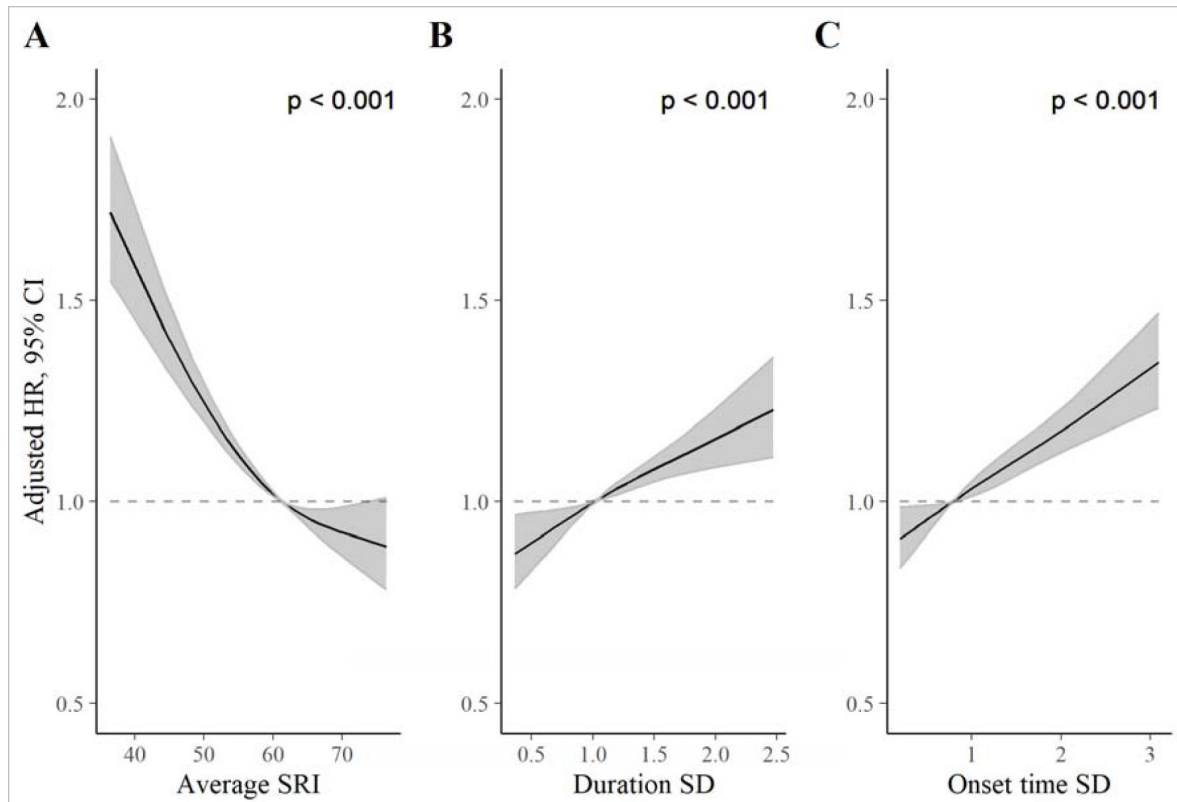


Figure 3.

Adjusted hazard ratios for all-cause mortality for the SRI (A), sleep duration SD (B), and sleep onset SD (C) measures.

P values from global (2 degree of freedom) test of exposure spline term. Hazard ratios (HR) are relative to the median SRI (SRI = 60). HRs were estimated using Cox proportional hazards models, adjusted for age, Townsend deprivation index, sex, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category). All continuous confounders and the sleep regularity metrics were modeled with restricted cubic splines (knots at 10th, 50th, and 90th percentiles) to allow for departures from linearity.

the SRI contains information about mortality risk beyond that contained in the SD of sleep duration and onset, whereas the converse was not the case. The SRI may be superior to the SD-based metrics because the SRI captures rapid changes in sleep patterns across consecutive days, as compared to the SD-based metrics which only calculate deviation from an individual's average. Rapid changes in sleep timing have been hypothesised as being principally challenging for the circadian system to accommodate¹² which may, in turn, produce negative health outcomes.

We found evidence that hazard rates across levels of SRI were non-proportional (i.e., varied across the follow-up period) for all-cause and cancer mortality (which accounted for most deaths), though not for CVD mortality. For cancer mortality, HRs for low SRI compared to the median were largest in the earliest follow-up period and decreased thereafter. One plausible interpretation of this finding is that irregular sleep may be a manifestation of the underlying physiological processes of cancer itself or of cancer treatment (i.e., the SRI-cancer mortality association may be due to reverse causation). However, this thesis is challenged by the fact that associations between the SRI and cancer mortality remained similar after adjusting for past or prevalent cancer at baseline. In the case of CVD mortality, no such evidence of a decline in HRs over follow-up time was evident; a potential causal role of irregular sleep on CVD death cannot be easily ruled out.

Sleep of insufficient or excessive duration is associated with many adverse health outcomes, including increased mortality risk.³⁰ As of 2022, sleep duration was included by the American Heart Association in their Essential Eight guidelines for CVD prevention.³¹ However, sleep is far more complex than its habitual duration and quality, with sleep regularity receiving comparatively little attention. As sleep-tracking wearables become more accessible, objective measurement of sleep regularity has the potential for public and clinical use. Much like sleep duration, replicating the current findings across different samples will be necessary for establishing population norms and clinical targets. Furthermore, identifying the determinants of poor sleep regularity may be of import, not only considering biological factors, but broader social determinants that impact circadian rhythmicity (e.g., racial/ethnic disparities³², neighbourhood factors³³) and consequently overall health.

Our study is not without limitations. Firstly, the study was observational. We are, therefore, unable to establish cause and effect. Although we performed extensive analyses to control for confounding, we cannot exclude the possibility that our results are explained by residual confounding. As such, although therapies exist for improving sleep regularity, it's not clear if these interventions are able to extend the lifespan. Second, sleep and wake were estimated through activity patterns from accelerometry. As compared to polysomnography, there is the potential to misclassify sleep and wake, although accelerometry is more suited to estimate circadian patterns over several days; there are several strengths to using accelerometry (e.g., days of continuous recording, minimal technical apparatus affecting sleep quality), making it the recommended clinical tool for assessing circadian rhythms.³⁴ In addition, sleep diaries in the UKB were not available. Consequently, the algorithm we used to determine sleep and wake relied on the identification of a main 'sleep period time window' and did not identify napping.

Circadian rhythms have a major influence on health and disease. Although sleep wake timing is under circadian control, research on sleep regularity as a risk factor for mortality was equivocal. These data suggest sleep regularity as an important correlate of longevity, independent of sleep duration, fragmentation, and quality.

Future work is needed to determine the underlying mechanisms to inform possible interventions to extend the lifespan.

Funding

Dr. Pase is supported by a National Health and Medical Research Council of Australia Investigator Grant (GTN2009264) with sleep research funding from the National Health and Medical Research Council of Australia (GTN1158384), National Institute on Aging (R01 AG062531) and Alzheimer's Association (2018-AARG-591358). Dr. Baril is funded by the Banting Fellowship Program (#454104). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Data Availability

Data from the UK Biobank are available, pending application approval from:
<https://www.ukbiobank.ac.uk/>

Acknowledgements

This research has been conducted using the UK Biobank Resource under project ID 70607.

Data sharing

Data from the UK Biobank are available, pending application approval from: <https://www.ukbiobank.ac.uk/>

Appendix 1: Methods. Removal of low-quality accelerometer data

Accelerometry data of low quality were removed using established UKB criteria;

incongruity of self-reported wear time and accelerometer wear time data (5%); insufficient wear time (< 72 hours; 5%); and poorly calibrated data (<1%). Lastly, data were removed for participants in which GGIR was unable to determine a sleep window (5%) and for participants providing less than two valid SRI measurements (i.e., 2 24-hour wear periods; <1%). In total, 88,975 (84%) participants provided valid sleep regularity index data and were included in the study.

Appendix 2: STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

Item

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (see title) (b) Provide in the abstract an informative and balanced summary of what was done and what was found (see pg 2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (pg 3)
Objectives	3	State specific objectives, including any prespecified hypotheses (pg 3)
Methods		
Study design	4	Present key elements of study design early in the paper (Pg 3)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Pg 3)
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Pg 3-4) (b) For matched studies, give matching criteria and number of exposed and unexposed NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Pg 4)
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Pg 3-4)
Bias	9	Describe any efforts to address potential sources of bias (pg 5)
Study size	10	Explain how the study size was arrived at (pg 3 and appendix)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (pg 5)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (pg 4-5, Figure S1) (b) Describe any methods used to examine subgroups and interactions NA (c) Explain how missing data were addressed (pg 4-5) (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses (pg 5)
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Pg 3) (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram Not considered necessary but can be created upon request
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Table 1 (b) Indicate number of participants with missing data for each variable of interest Missing data were infrequent, as described in methods (c) Summarise follow-up time (eg, average and total amount) (pg 5)
Outcome data	15*	Report numbers of outcome events or summary measures over time (pg 5)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Figures and Appendix figures (b) Report category boundaries when continuous variables were categorized NA (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Figure 2

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (pg 6)
Discussion		
Key results	18	Summarise key results with reference to study objectives (pg 7)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (pg 8)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (pg 8)
Generalisability	21	Discuss the generalisability (external validity) of the study results (pg 7-8)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (pg 8)
<p>*Give information separately for exposed and unexposed groups.</p> <p>Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.</p>		

Regularity measure	Sleep regularity index	Sleep duration SD	Sleep onset SD
Sleep regularity index	1	-0.32	-0.42
Sleep duration SD	-0.32	1	0.55
Sleep onset SD	-0.42	0.55	1

Table S1

Correlation between sleep regularity index and standard deviation-based regularity metrics

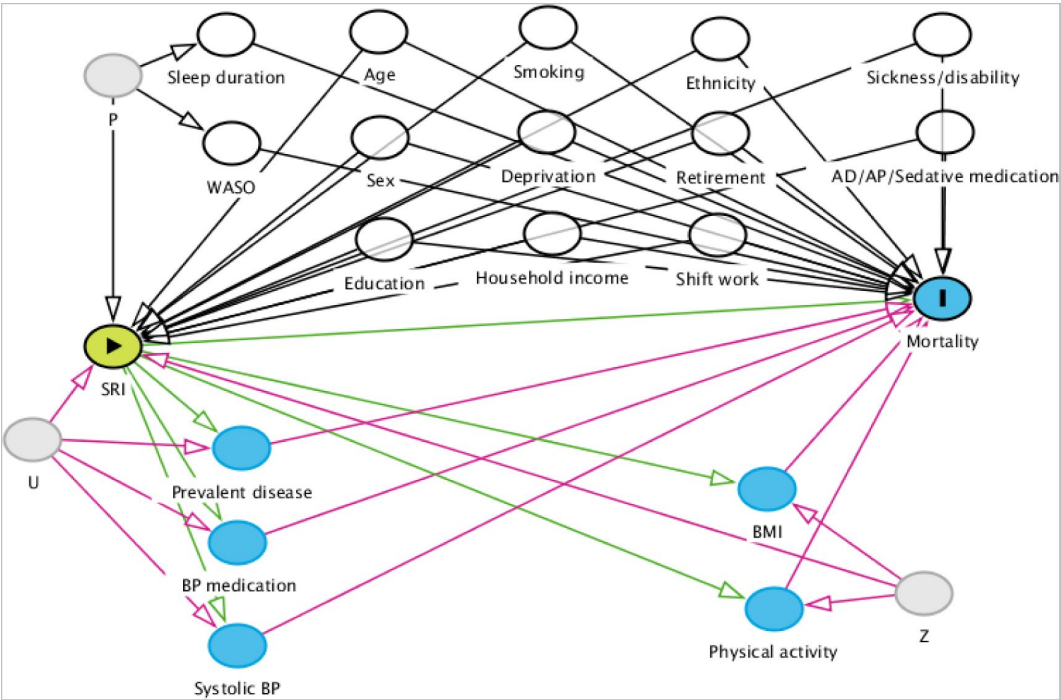


Figure S1.

Directed acyclic graph for identification of adjustment variables.

The green node indicates the exposure variable (*SRI*), and the blue node (*Mortality*) is the outcome variable. Pale grey nodes indicate unobserved variables; white nodes indicate a variable which has been conditioned on (by regression adjustment or restriction). Paths in red are biasing paths. Arrows indicate the direction of causal effect between two nodes. *P* is an unobserved variable representing unmeasured causes of sleep habits (e.g., genetics). *U* is an unobserved variable representing unmeasured causes of disease and cardiovascular dysfunction (e.g., genetics, biological ageing). *Z* is an unobserved variable representing unmeasured causes of health behaviours (e.g., personality factors, genetics). Green paths from *SRI* to *Prevalent disease*, *BP medication*, *Systolic BP*, *BMI*, and *Physical activity* and from these nodes to *Mortality* represent potential mediation of an *SRI* effect. Conversely, red paths indicate potential sources of confounding (e.g., a backdoor path from *Mortality* to *Prevalent disease* to *SRI* via *U*). Given the current evidence base, we are unable to determine whether and to what extent variables such as *Prevalent disease* act as mediators or confounders (via *U*) of the *SRI*-mortality association. AP = anti-psychotic; AD = antidepressant; BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; Deprivation = the Townsend deprivation index; *SRI* = sleep regularity index; WASO = wake after sleep onset.

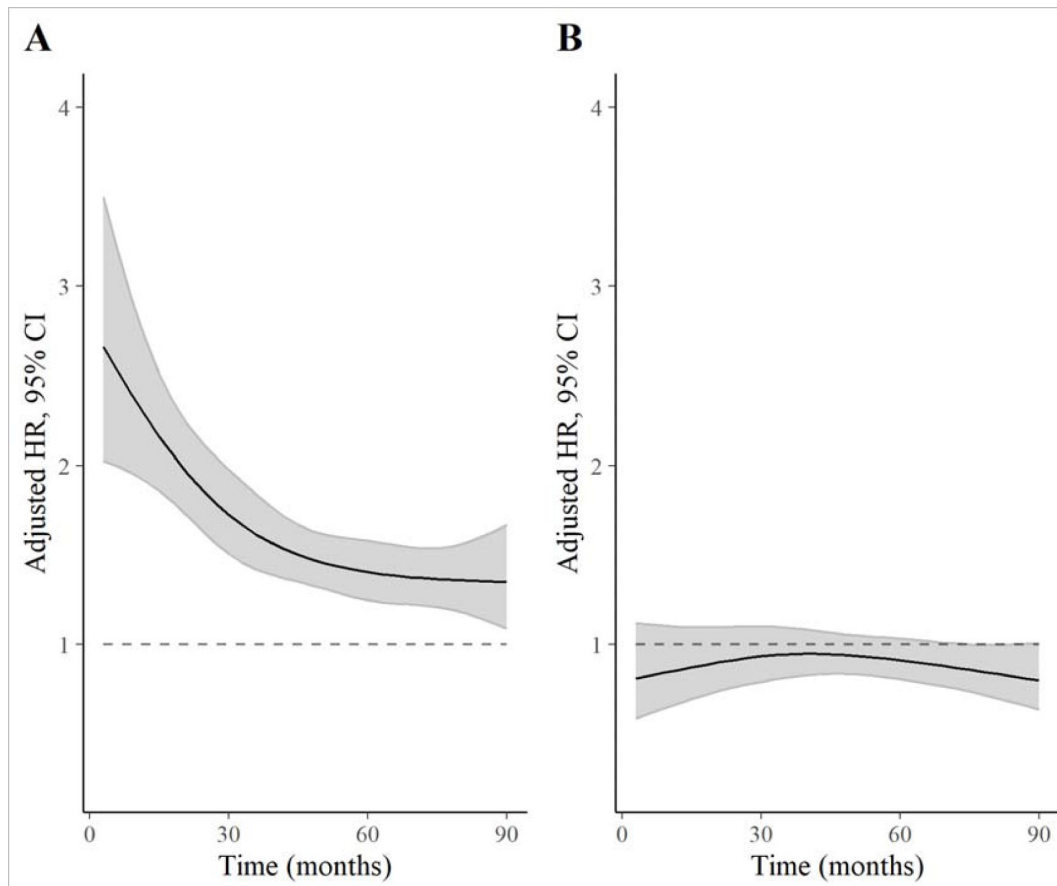


Figure S2.

Time-varying HRs for 5th and 95th percentiles of SRI (relative to median) for all-cause mortality.

A: Hazard ratios for 5th percentile vs median SRI; **B:** Hazard ratios for 95th percentile vs median SRI. Discrete time hazards model including time (aggregated into 3-month intervals and modelled with a restricted cubic spline with knots at the 5th, 35th, 65th, and 95th percentiles), SRI, and an SRI by time interaction. Adjusted for age, Townsend deprivation index, sex, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category). All continuous confounders and the SRI were modelled with restricted cubic splines (knots at 10th, 50th, and 90th percentiles) to allow for departures from linearity. There was strong evidence of an interaction between time and SRI (p [interaction] < 0.001).

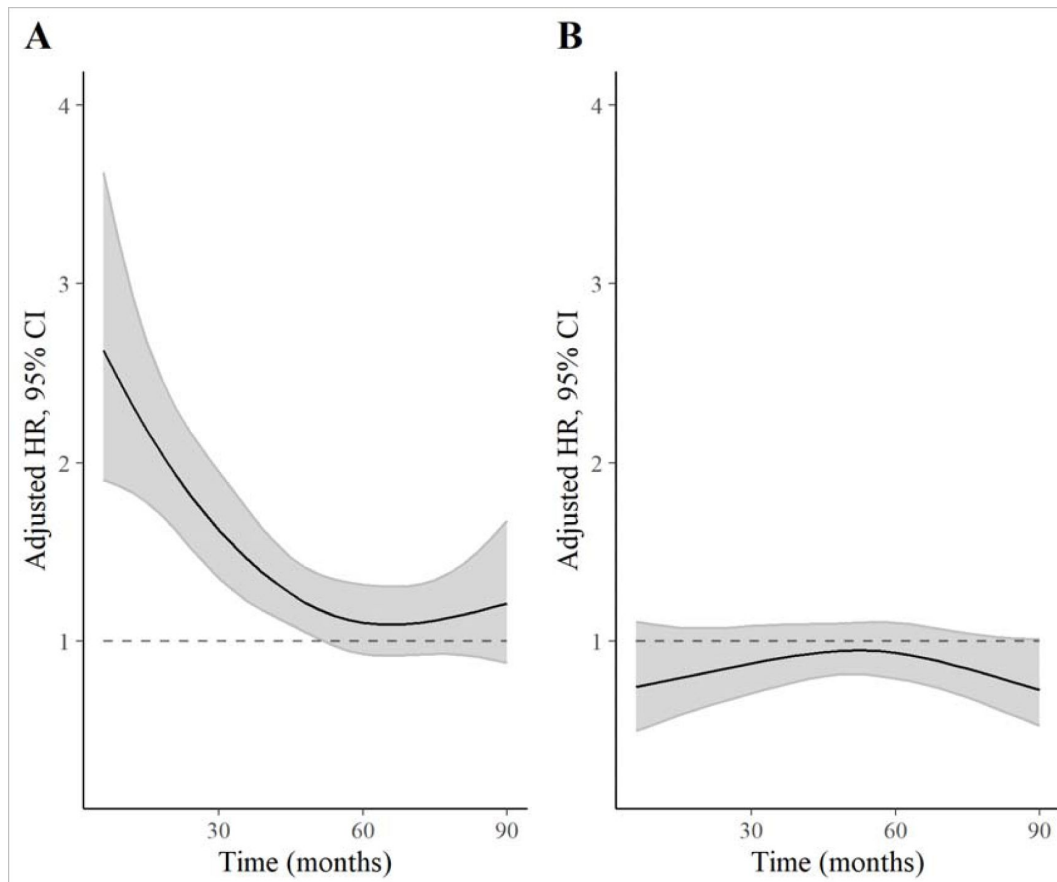


Figure S3.

Time-varying HRs for 5th and 95th percentiles of SRI (relative to median) for cancer-mortality.

A: Hazard ratios for 5th percentile vs median SRI; **B:** Hazard ratios for 95th percentile vs median SRI. Discrete time hazards model including time (aggregated into 3-month intervals and modelled with a restricted cubic spline with knots at the 5th, 35th, 65th, and 95th percentiles), SRI, and an SRI by time interaction. Adjusted for age, Townsend deprivation index, sex, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category). All continuous confounders and the SRI were modelled with restricted cubic splines (knots at 10th, 50th, and 90th percentiles) to allow for departures from linearity. There was strong evidence of an interaction between time and SRI (p [interaction] < 0.001).

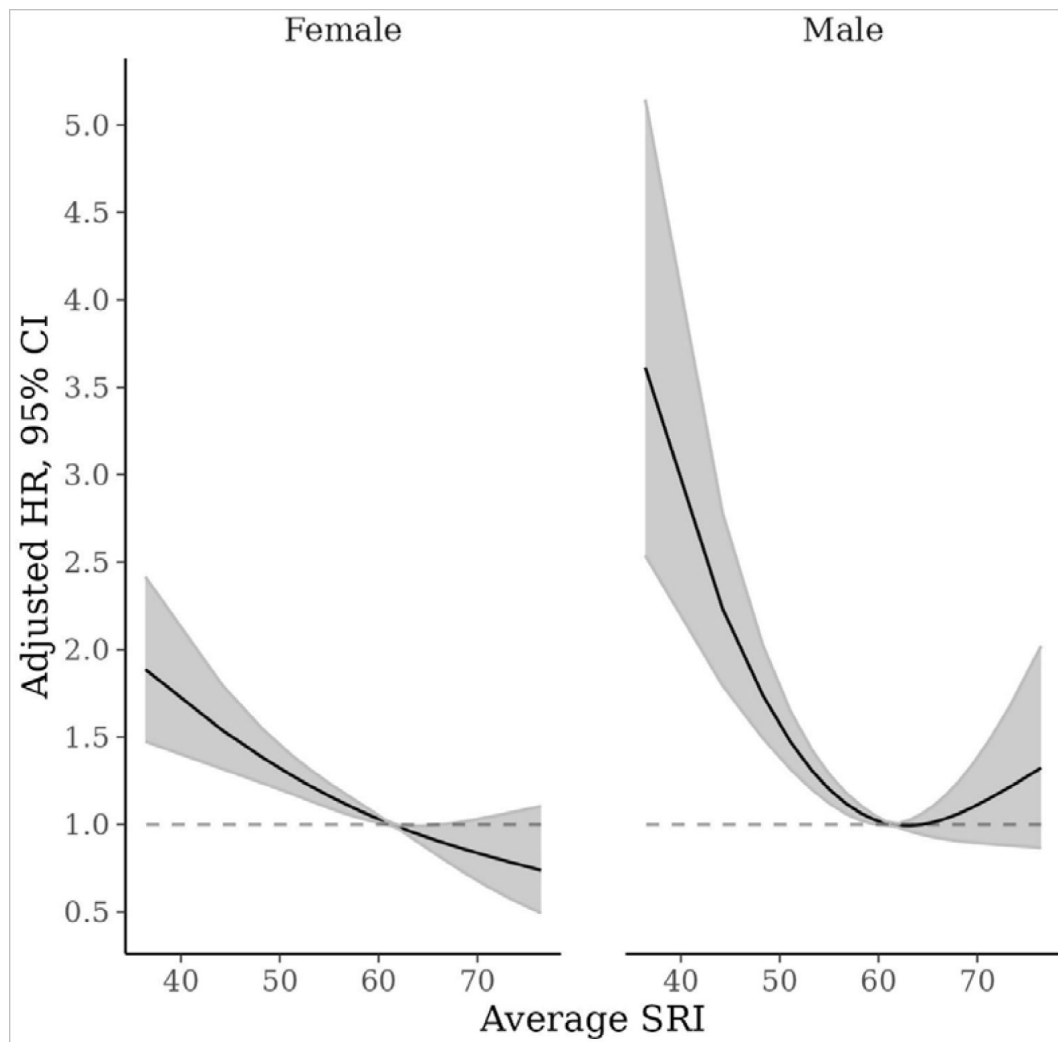


Figure S4.

SRI and CVD-specific mortality by sex.

Adjusted for age, Townsend deprivation index, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category). Hazard ratios are relative to the median SRI (SRI = 60).

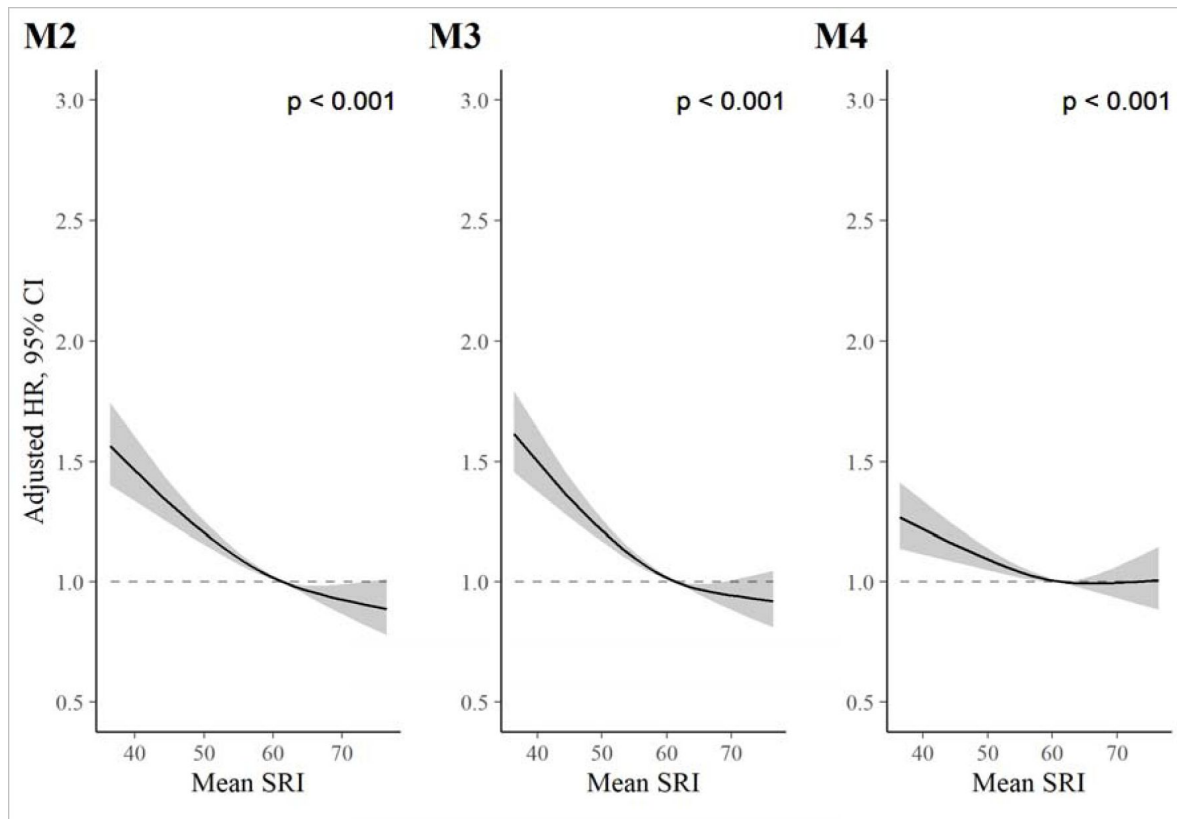


Figure S5.

SRI and all-cause mortality in sensitivity analyses.

P values from global (2 degree of freedom) test of spline term. Hazard ratios are relative to the median SRI (SRI = 60).

Model 2 (M2) adjustments: Adjusted for age, Townsend deprivation index, sex, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category), average sleep time, and average wake after sleep onset time. **M2 results:** HRs, relative to the median SRI, were 1.42 (95% CI: 1.31, 1.55) and 0.90 (95% CI: 0.80, 1.00) for SRI at the 5th and 95th percentiles, respectively.

Model 3 (M3) adjustments: Adjusted for age, Townsend deprivation index, sex, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category), and past or prevalent diabetes, cancer, mental and behavioural disorder, neurological illness, and cardiovascular illness. **M3 Results:** HRs, relative to the median SRI, were 1.46 (95% CI: 1.35, 1.58) and 0.93 (95% CI: 0.83, 1.03) for the 5th and 95th percentiles of SRI, respectively.

Model 4 (M4) adjustments: Model 3 with additional adjustment for BMI, moderate and vigorous physical activity, systolic blood pressure, and blood pressure medication. **M4 results:** HRs, relative to the median SRI, were 1.20 (95% CI: 1.11, 1.31) and 1.00 (95% CI: 0.90, 1.12) for the 5th and 95th percentiles, respectively.

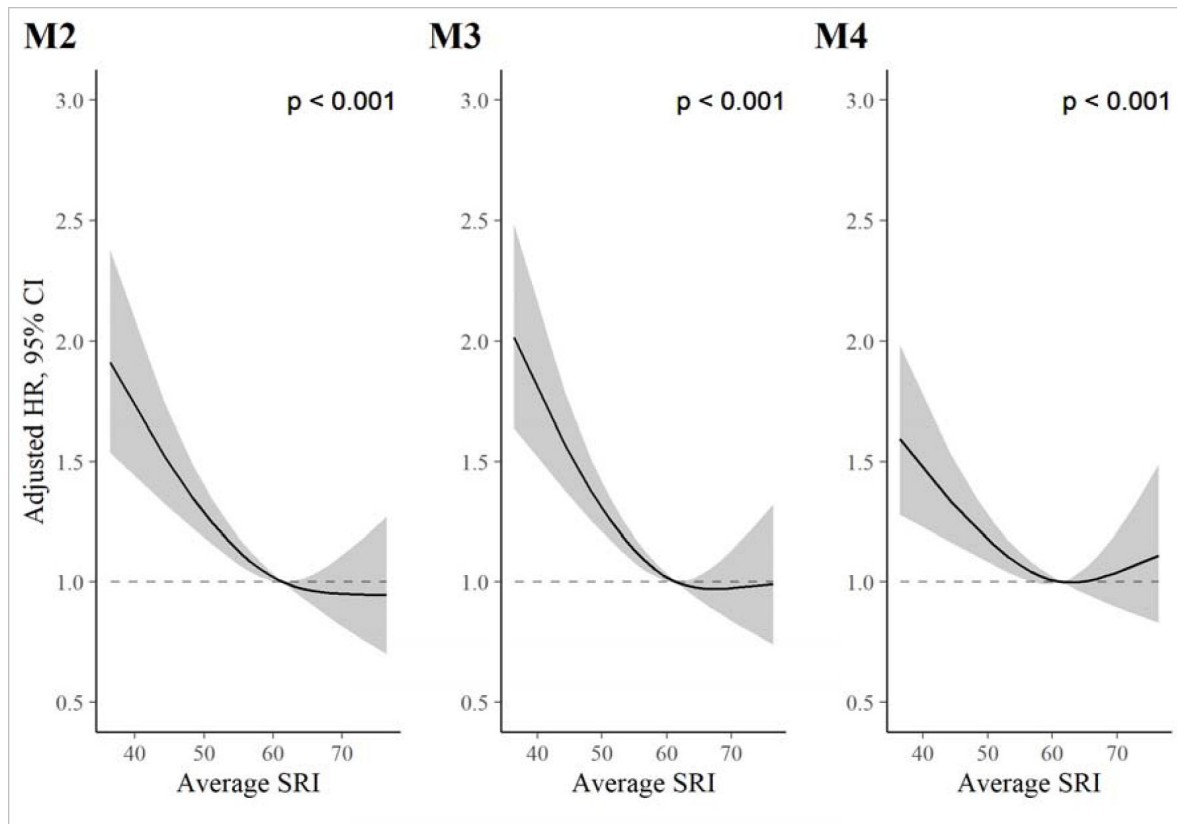


Figure S6.

SRI and CVD-mortality in sensitivity analyses.

P values from global (2 degree of freedom) test of spline term. Hazard ratios are relative to the median SRI (SRI = 60).

Model 2 (M2) adjustments: Adjusted for age, Townsend deprivation index, sex, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category), average sleep time, and average wake after sleep onset time. **M2 results:** HRs were 1.66 (95% CI: 1.40, 1.96) and 0.95 (95% CI: 0.73, 1.22) for the 5th and 95th percentile vs. the median SRI, respectively.

Model (M3) adjustments: Adjusted for age, Townsend deprivation index, sex, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category), and past or prevalent diabetes, cancer, mental and behavioural disorder, neurological illness, and cardiovascular illness. **M3 results:** HRs were 1.73 (95% CI: 1.47, 2.02) and 0.99 (95% CI: 0.77, 1.26) for the 5th and 95th percentiles, respectively.

Model 4 (M4) adjustments: Model 3 with additional adjustment for BMI, moderate and vigorous physical activity, systolic blood pressure, and blood pressure medication. **M4 results:** HRs were somewhat attenuated: 1.43 (95% CI: 1.21, 1.69) and 1.09 (95% CI: 0.85, 1.40), for the 5th and 95th percentiles, respectively.

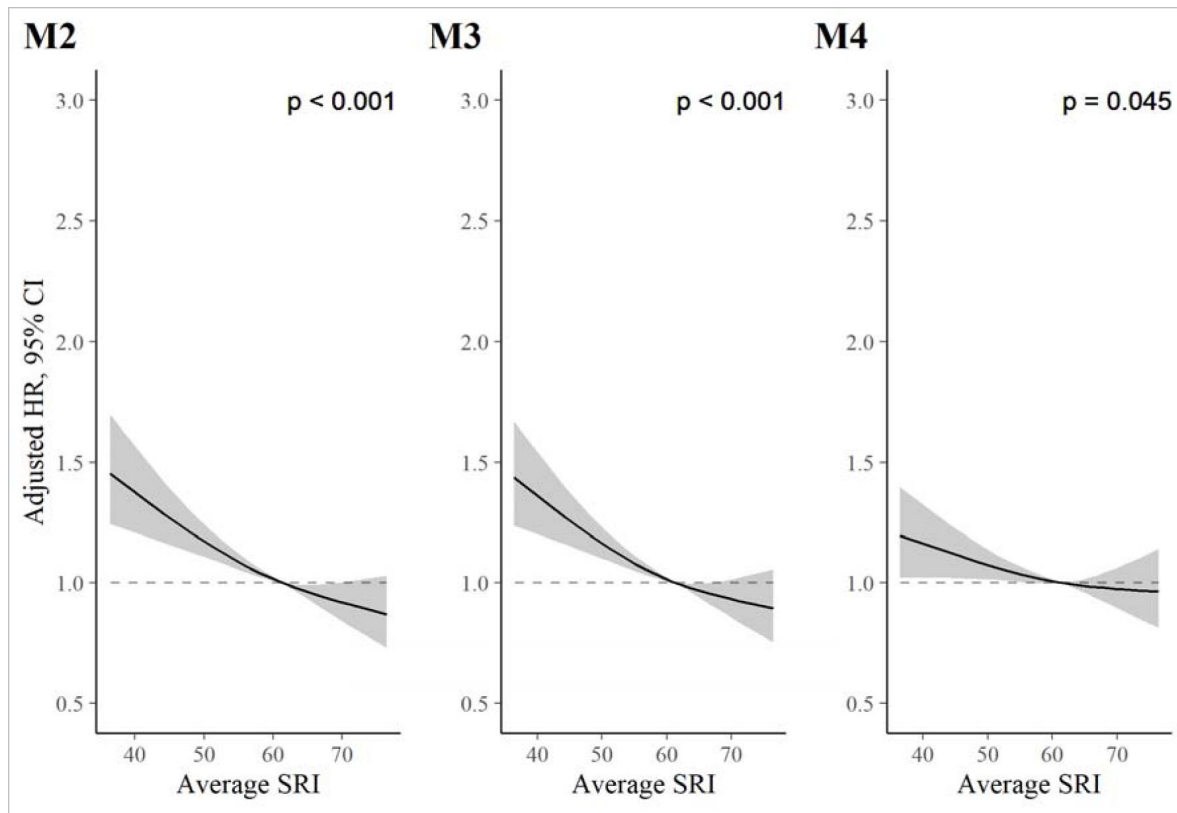


Figure S7.

SRI and cancer-mortality in sensitivity analyses.

P values from global (2 degree of freedom) test of spline term. Hazard ratios are relative to the median SRI (SRI = 60).

Model 2 (M2) adjustments: Adjusted for age, Townsend deprivation index, sex, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category), average sleep time, and average wake after sleep onset time. **M2 results:** HRs were 1.35 (95% CI: 1.20, 1.52) and 0.88 (95% CI: 0.76, 1.02) for the 5th and 95th percentile vs. the median SRI, respectively.

Model 3 (M3) adjustments: Adjusted for age, Townsend deprivation index, sex, antidepressant, antipsychotic, and sedative medication, ethnicity, household income, education, smoking status (former, current, never), smoking pack years, shift work, retirement status, and sick or disabled (self-reported employment category), and past or prevalent diabetes, cancer, mental and behavioural disorder, neurological illness, and cardiovascular illness. **M3 results:** HRs were 1.33 (95% CI: 1.19, 1.49) and 0.90 (95% CI: 0.78, 1.04) for the 5th and 95th percentiles, respectively.

Model 4 (M4) adjustments: Model 3 with additional adjustment for BMI, moderate and vigorous physical activity, systolic blood pressure, and blood pressure medication. **M4 results:** HRs were 1.15 (95% CI: 1.02, 1.30) and 0.97 (95% CI: 0.84, 1.12) for the 5th and 95th percentiles, respectively.

References

1. Zee PC, Vitiello MV (2009) **Circadian Rhythm Sleep Disorder: Irregular Sleep Wake Rhythm Type** *Sleep Med Clin* **4**:213–8
2. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C (2000) **Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression** *J Physiol* **526**:695–702
3. Torquati L, Mielke GI, Brown WJ, Kolbe-Alexander T (2018) **Shift work and the risk of cardiovascular disease. A systematic review and meta-analysis including dose-response relationship** *Scand J Work Environ Health* **44**:229–38
4. International-Agency-for-Research-on-Cancer (2010) **Painting, firefighting, and shiftwork** *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* **98**
5. Janszky I, Ljung R (2008) **Shifts to and from Daylight Saving Time and Incidence of Myocardial Infarction** *New England Journal of Medicine* **359**:1966–8
6. Walker WH, Walton JC, DeVries AC, Nelson RJ (2020) **Circadian rhythm disruption and mental health** *Translational Psychiatry* **10**
7. Fry A, Littlejohns TJ, Sudlow C, et al. (2017) **Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population** *Am J Epidemiol* **186**:1026–34
8. Migueles JH, Rowlands AV, Huber F, Sabia S, van Hees VT (2019) **GGIR: a research community-driven open source R package for generating physical activity and sleep outcomes from multi-day raw accelerometer data** *Journal for the Measurement of Physical Behaviour* **2**:188–96
9. Van Hees VT, Sabia S, Anderson KN, et al. (2015) **A novel, open access method to assess sleep duration using a wrist-worn accelerometer** *PloS one* **10**
10. van Hees VT, Sabia S, Jones SE, et al. (2018) **Estimating sleep parameters using an accelerometer without sleep diary** *Scientific reports* **8**:1–11
11. van Hees VT, Sabia S, Jones SE, et al. (2018) **Estimating sleep parameters using an accelerometer without sleep diary** *Scientific reports* **8**
12. Phillips AJ, Clerx WM, O'Brien CS, et al. (2017) **Irregular sleep/wake patterns are associated with poorer academic performance and delayed circadian and sleep/wake timing** *Scientific reports* **7**:1–13
13. Jr FE Harrell, Jr MFE Harrell (2019) **Package 'hmisc'** *CRA*
14. Singer JD, Willett JB (2003) **Applied Longitudinal Data Analysis**
15. Stensrud MJ, Hernán MA (2020) **Why Test for Proportional Hazards?** *JAMA* **323**:1401–2
16. Hernán MA, Robins JM. (2010) **Causal inference**

17. Fritz J, Phillips AJK, Hunt L, et al. (2021) **Cross-sectional and prospective associations between sleep regularity and metabolic health in the Hispanic community Health Study/Study of Latinos** *Sleep* **44**
18. Huang T, Redline S (2019) **Cross-sectional and prospective associations of actigraphy-assessed sleep regularity with metabolic abnormalities: the multi-ethnic study of atherosclerosis** *Diabetes care* **42**:1422–9
19. Huang W-C, Chang S-H, Hsueh M-C, Liao Y (2022) **Relationship of sleep regularity with device-based sedentary behavior time and physical activity time in working adults** *Sleep Health*
20. Zuraikat FM, Makarem N, Redline S, Aggarwal B, Jelic S, St-Onge M-P (2020) **Sleep regularity and cardiometabolic health: is variability in sleep patterns a risk factor for excess adiposity and glycemic dysregulation?** *Current diabetes reports* **20**:1–9
21. Nikbakhtian S, Reed AB, Obika BD, et al. (2021) **Accelerometer-derived sleep onset timing and cardiovascular disease incidence: a UK Biobank cohort study** *European Heart Journal - Digital Health* **2**:658–66
22. Huang T, Mariani S, Redline S (2020) **Sleep Irregularity and Risk of Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis** *J Am Coll Cardiol* **75**:991–9
23. Viswambharan H, Carvas JM, Antic V, et al. (2007) **Mutation of the Circadian Clock Gene Per2 Alters Vascular Endothelial Function** *Circulation* **115**:2188–95
24. Curtis AM, Cheng Y, Kapoor S, Reilly D, Price TS, Fitzgerald GA (2007) **Circadian variation of blood pressure and the vascular response to asynchronous stress** *Proc Natl Acad Sci U S A* **104**:3450–5
25. Anea CB, Zhang M, Stepp DW, et al. (2009) **Vascular disease in mice with a dysfunctional circadian clock** *Circulation* **119**:1510–7
26. Rudic RD, McNamara P, Curtis AM, et al. (2004) **BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis** *PLoS Biol* **2**
27. Reddy AB, Wong GK, O'Neill J, Maywood ES, Hastings MH (2005) **Circadian clocks: neural and peripheral pacemakers that impact upon the cell division cycle** *Mutat Res* **574**:76–91
28. Wang Q, Ao Y, Yang K, Tang H, Chen D (2016) **Circadian clock gene Per2 plays an important role in cell proliferation, apoptosis and cell cycle progression in human oral squamous cell carcinoma** *Oncol Rep* **35**:3387–94
29. Gery S, Komatsu N, Baldjyan L, Yu A, Koo D, Koeffler HP (2006) **The circadian gene per1 plays an important role in cell growth and DNA damage control in human cancer cells** *Mol Cell* **22**:375–82
30. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA (2010) **Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies** *Sleep* **33**:585–92
31. Lloyd-Jones DM, Allen NB, Anderson CAM, et al. (2022) **Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association** *Circulation* **146**:e18–e43

32. Chung J, Goodman M, Huang T, et al. (2021) **Racial-ethnic Differences in Actigraphy, Questionnaire, and Polysomnography Indicators of Healthy Sleep: The Multi-Ethnic Study of Atherosclerosis** *Am J Epidemiol*
33. Richardson AS, Troxel WM, Ghosh-Dastidar M, et al. (2021) **Violent crime, police presence and poor sleep in two low-income urban predominantly Black American neighbourhoods** *J Epidemiol Community Health* **75**:62–8
34. Smith MT, McCrae CS, Cheung J, et al. (2018) **Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment** *J Clin Sleep Med* **14**:1209–30

Article and author information

Lachlan Cribb

Turner Institute for Brain and Mental Health, Monash University, Melbourne Australia
ORCID ID: [0000-0001-5276-5249](https://orcid.org/0000-0001-5276-5249)

Ramon Sha

Turner Institute for Brain and Mental Health, Monash University, Melbourne Australia

Stephanie Yiallourou

Turner Institute for Brain and Mental Health, Monash University, Melbourne Australia

Natalie A Grima

Turner Institute for Brain and Mental Health, Monash University, Melbourne Australia

Marina Cavuoto

Turner Institute for Brain and Mental Health, Monash University, Melbourne Australia, National Ageing Research Institute, Melbourne, Australia

Andree-Ann Baril

Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada

Matthew P. Pase

Turner Institute for Brain and Mental Health, Monash University, Melbourne Australia, Harvard T.H. Chan School of Public Health, Harvard University, MA, USA

For correspondence: matthewpase@gmail.com

Copyright

© 2023, Cribb et al.

This article is distributed under the terms of the [Creative Commons Attribution License \(https://creativecommons.org/licenses/by/4.0/\)](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use and redistribution provided that the original author and source are credited.

Editors

Reviewing Editor

Edward Janus

University of Melbourne, Australia

Senior Editor

Eduardo Franco

McGill University, Canada

Reviewer #1 (Public Review):

This manuscript provides important evidence on the association between sleep regularity and mortality in the UK Biobank, which is a popular topic in recent sleep and circadian research in population-based studies. The analysis reported robust associations between sleep irregularity and increased total, CVD and cancer mortality, and provided evidence to support the role of sleep and circadian health in disease progression and longevity in human populations. The Sleep Regularity Index (SRI) used in this study is a novel metric that quantifies the consistency in rest-activity rhythms over consecutive 24 hour periods, thus providing objective assessment of potential circadian disruption. The study is based on a large accelerometer study with validated follow-up of incident diseases and deaths. The data quality and large sample size strengthen the credibility of the conclusion. Overall, the analyses are appropriately done and the manuscript is clearly written.

Reviewer #2 (Public Review):

This interesting research commendably revealed irregular sleep-wake patterns are associated with higher mortality risk. However, as authors acknowledged, the analysis can not to accurately identify the cause and effect. In my opinion, the causality is important for this topic, cuz, sleep regularity and health (e.g. chronic disease) were long-term simultaneous status. especially given the participants are older. I suggest that the author could utilize MR analysis to find out for more evidence.

Author Response

The following is the authors' response to the original reviews.

Note to reviewer and editor:

In the previous version of the manuscript, we referred to 'prevalent' disease at baseline (e.g., prevalent cardiovascular disease). We have since changed this throughout the manuscript to 'past or prevalent' disease. This is a more accurate description as we ascertained diseases which occurred prior to baseline but may have been resolved by the time of the accelerometry study.

Responses to reviewer 1:

• I assume that not every participant provided data on all 7 nights. Did the authors exclude those who had fewer number of nights with accelerometer data (e.g., only 2-3 days), as the SRI based on fewer nights may not reliably reflect sleep regularity compared with SRI based all 7 consecutive nights?

It is correct that not every participant provided complete accelerometry data. Most participants (88%) provided complete data. We only included participants who provided at least 2 valid measurements of the SRI (requiring valid data for at least 2 pairs of contiguous 24-hour periods). This is described in the appendix, but we have additionally now added this detail to the main text:

“Most participants (88%) provided complete accelerometry data. Participants with fewer than two valid SRI measurements (i.e., less than 2 contiguous 24-hour wear periods; <1%) were excluded.”

We would also like to note that our statistical analysis accounted, to some extent, for the lower reliability of SRI estimates in those with fewer nights of data. In those with sparse data, their estimated average SRI value would be pulled towards the overall sample average relatively more than for those with complete data. This is a consequence of the ‘partial pooling’ of the linear mixed effects model.

• *The primary analysis and results were based on restricted cubic spline models that allow assessment of nonlinearity. This is different from the usual strategy that starts with the simpler linear relationship and further explores potential nonlinear relationships. Did the authors have a strong rationale for a nonlinear dose-response relationship between sleep regularity and mortality, so that the assessment of linear relationships was skipped?*

We chose to model the SRI with a restricted cubic spline for two reasons. Firstly, we did expect non-linearity to be present a-priori. Partly this was because other sleep exposures (especially sleep time) have known non-linear relationships with health outcomes. We also thought that it is plausible that a ‘plateau’ might be present, which we wanted to capture. Secondly, we decided that our primary model should be sufficiently flexible from the outset in order that we did not need to make data-driven adjustments to our model specification (e.g., adding non-linear terms depending on the results of hypothesis tests). This approach we believe to be generally safer as making data-driven changes can undermine the validity of standard errors and p-values.¹

• *Was the proportional hazards assumption violated in the Cox modeling? Were discrete-time hazard models used to address the violation of the modeling assumption? Please clarify.*

Yes, the proportional hazards assumption was violated for all models except for the cardiovascular disease death model. This was the rationale for the use of the discrete time hazards model. They allowed for the inclusion of a flexible time by SRI interaction, allowing the hazard ratio to vary over the follow-up period. We have made this clearer in our revision. The following text has been added to the statistical methods:

“In addition to Cox models, discrete-time hazards models, including an interaction between SRI and time (aggregated into 3-month intervals and modeled with a restricted cubic spline with knots at the 5th, 35th, 65th, and 95th percentiles), were fitted to relax the assumption of proportionality and allow hazard ratios (HRs) to vary over time. The SRI by time interaction in this model provided a test of proportionality (a small p value would indicate strong evidence against the proportional hazards assumption).”

• *Please provide correlations between different sleep regularity measures. Although different measures lead to the same conclusion, it is interesting that SRI appeared to provide stronger signals with mortality than the other two SD measures. In addition to*

what was discussed by the authors, another possibility is that SRI also captures the regularity of napping during the day which is common in older populations.

Thank you for this helpful suggestion. We have added a correlation matrix for the different sleep regularity measures (Table S1). We have additionally added the following text to the Results:

“The SRI was modestly negatively correlated with the sleep duration SD (-0.32) and sleep onset time SD (0.42; see correlation matrix in Table S1).”

Regarding napping during the day, the algorithm we used to make determinations of sleep and wake unfortunately is not able to identify napping. This is because, in the absence of a sleep diary, it is very difficult to distinguish napping from inactivity in accelerometry data. The algorithm that we used requires the estimation of a ‘sleep period time window’, defining the period from the beginning to the end of the main sleep bout, in which sleep can be identified. Any sleep outside of this window is treated as inactivity. While some methods have been developed to estimate napping time from accelerometry without a sleep diary, we are not aware of any that are validated for adults using wrist worn accelerometers.

This is something that was not sufficiently clear from the current manuscript. We have had added the following text to ensure this is clear in the revised version.

Methods:

“To distinguish sleep from sustained periods of inactivity without reference to a sleep diary (not available in the UKB), GGIR uses an algorithm to determine a daily ‘sleep period time window’ for each participant.¹¹ This defines the time window between the onset and end of the main daily sleep period, during which periods of sustained inactivity are interpreted as sleep. The algorithm does not, by default, detect bouts of sleep outside of this window and hence is not able to identify naps.”

Discussion:

“In addition, sleep diaries in the UKB were not available. Consequently, the algorithm we used to determine sleep and wake relied on the identification of a main ‘sleep period time window’ and did not identify napping..”

• Table 1 - I would suggest adding additional columns showing the variable distributions across quantiles of the SRI, which can help understand the confounding structure and the covariate associations with SRI.

We agree that this is a good idea and we have adjusted Table 1 accordingly.

• Figure 1 and related supplemental Figures: it would be good to label in the figure the specific HR estimate and 95% CI mentioned in the manuscript.

Thank you for this suggestion. We agree that this would be helpful. After some consideration, we have decided to leave the figures as they are for one primary reason. This is that we want to avoid over-emphasising the 5th and 95th quantiles. As discussed above, we chose to present HRs for these quantiles as they would provide a complement to the Figures which would assist in communication (for some readers, the key results might be easier to glean from these numeric summaries than from the Figures). However, we don’t wish to overemphasise these quantiles when the full ‘dose-response’ function we believe to be of the greatest interest.

- *Additional stratified analyses by main sociodemographic factors (age, sex, SES, etc) and sleep variables (sleep duration and sleep quality) would be informative to understand the population heterogeneity in the association between sleep regularity and mortality*

Thank you for this suggestion. We have assessed effect modification across a range of key background variables (age, sex, household income, sleep duration, moderate to vigorous physical activity, prevalent CVD, and prevalent cancer). This has been added to the results. Where meaningful evidence of effect modification was noted, we have presented results within strata of the effect modifier.

- *Some brief discussion on socioeconomic aspects of sleep is needed (the authors focused on the biological mechanisms underlying the observed association), as emerging evidence suggests that sleep health is not only a biological but also a social construct. For example, a recent study in the US found that sleep regularity is the most important contributor to racial/ethnic disparities in sleep health (see PMID: 34498675).*

We agree that sleep health is both a biological and social construct. We have added the following text to the discussion to address this comment:

Discussion:

“Furthermore, identifying the determinants of poor sleep regularity may be of import, not only considering biological factors, but broader social determinants that impact circadian rhythmicity (e.g., racial/ethnic disparities³², neighbourhood factors³³) and consequently overall health.”

References

1. Harrell FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. vol 608. Springer; 2001.