Sleep regularity and major adverse cardiovascular events: a device-based prospective study in 72 269 UK adults

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ABSTRACT

Background This study examines the associations between device-measured sleep regularity and the risk of major adverse cardiovascular events (MACE), and aims to determine whether sufficient sleep duration attenuates or eliminates the effects of irregular sleep on MACE risk.

Methods A prospective cohort study of adults aged 40–79 years from the UK Biobank who wore wrist-attached accelerometers for 7 days was conducted. Sleep Regularity Index (SRI) scores were calculated for each participant using a validated algorithm, and categorised as irregular (SRI <71.6), moderately irregular (SRI between 71.6 and 87.3), and regular (SRI >87.3 (reference group)). Information on MACE and its subtypes (myocardial infarction, heart failure, stroke) was obtained from inpatient hospitalisation and death records.

Results We analysed data from 72 269 individuals followed for 8 years, without a previous history of MACE and without an event in the first year of follow-up. Irregular (HR 1.26, 95% CI 1.16 to 1.37) and moderately irregular sleepers (HR 1.08, 95% CI 1.01 to 1.70) were at higher risk of MACE compared with regular sleepers. Dose-response analyses treating SRI as a continuous measure showed that SRI was associated with MACE risk in a near-linear fashion, with a steeper MACE risk reduction at higher (better) SRI scores. Joint SRI and sleep duration analyses showed that meeting the age-specific sleep duration recommendation offsets MACE risk for moderately irregular sleepers (HR 1.07, 95% CI 0.96 to 1.18), but not for irregular sleepers (HR 1.19, 95% CI 1.06 to 1.35).

Conclusions Irregular sleep was strongly associated with higher MACE risk. Adequate sleep duration was not sufficient to offset these adverse effects among irregular sleepers. This study supports the inclusion of sleep regularity in public health guidelines and clinical practice as a risk factor for cardiovascular disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Most observational studies on sleep have focused on the associations between self-reported sleep duration and health outcomes. There is increased research interest on the effects of sleep regularity, defined as the intraindividual variability in sleep-wake timing, on health. Although the literature in this field is limited, the general consensus is that daily regularity in sleep timing is important for health. However, the available evidence relies heavily on cross-sectional studies and uses self-reported sleep.

WHAT THIS STUDY ADDS

⇒ In this prospective cohort study comprising 72 269 adults wearing wrist-attached accelerometers and followed up for 7.8 years, irregular sleep was associated with significantly higher major adverse cardiovascular events (MACE) risk, regardless of whether individuals met sleep duration recommendations or not.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More attention needs to be paid to sleep regularity in public health guidelines and clinical practice due to its role in cardiovascular health. Future studies are needed to explore whether interventions aimed at improving sleep regularity might improve cardiovascular health.

INTRODUCTION

Most observational studies on sleep have focused on the associations between self-reported sleep duration and health outcomes.[1] There is increased research interest on the effects of sleep regularity, defined as the intraindividual variability in sleep-wake timing, on health. Although the literature in this field is limited, the general consensus is that daily regularity in sleep timing is important for health.[2 3] However, the evidence base relies heavily on cross-sectional studies that use self-reported sleep.[2 3]

Cardiovascular disease (CVD) is the leading cause of death globally, and there is a growing number of hospital admissions for acute manifestations of cardiovascular events such as heart failure and stroke.[4] A recent prospective analysis of 60 977 UK Biobank participants showed that sleep regularity is a stronger predictor of mortality than sleep duration.[5] Analyses in smaller samples (~2000 participants) have indicated that sleep irregularity may be associated with narrow CVD outcomes such as measures of subclinical atherosclerosis,[6] and with incident CVD.[7] MACE (major adverse cardiovascular events) is a widely used composite clinical

endpoint in medical and clinical research that combines non-fatal and fatal key cardiovascular endpoints, including stroke and myocardial infarction, that are responsible for the majority of CVD burden in the population.[8]

It is established that unhealthy sleep characteristics tend to cluster and often have interactive effects. For example, individuals with insufficient sleep commonly also have irregular sleep patterns and report insomnia symptoms.[9] However, it is unknown whether healthy sleep duration can mitigate or even eliminate the adverse effects of irregular sleep patterns on cardiovascular health. Understanding the independent and joint associations of sleep regularity and sleep duration with major cardiovascular endpoints is critical for informing clinical practice and public health guidelines, and for expanding options for lifestyle-based interventions.

Using the largest wrist-accelerometry database available, we examined the associations between device-measured sleep regularity and MACE risk in a population-based sample of middle-aged and older adults. An additional aim was to examine whether sufficient sleep duration mitigates or eliminates the effects of irregular sleep on MACE risk. We hypothesised that irregular sleep would be associated with higher MACE risk and that adequate (age-specific) sleep duration would not offset the adverse effects of irregular sleep patterns on MACE risk.

METHODS

Study design and participants

The UK Biobank is a large, population-based prospective cohort of adults recruited across the UK between 2006 and 2010. Around 9.2 million invitations were mailed to recruit 502 616 adults (response rate 5.5%) aged 40–69 years from 22 centres across the UK to reflect a diverse socioeconomic demographic and mixture of urban and rural residents. Detailed information on study methods has been published elsewhere.[10] The present analysis relies on a subset of UK Biobank participants who were part of the accelerometry sub-study. We thus excluded participants who did not have accelerometry data, participants with insufficient wear time, those who did not wear the monitor to sleep, and those with missing covariate data. We also excluded participants with a previous history of MACE at accelerometry baseline or earlier, and those who had an event in the first year of follow-up. The final analytical sample comprised 72 269 adults with a mean (SD) follow-up duration of 7.8 (1.3) years. A flowchart of participants included in the present study is presented in figure 1.

Sleep regularity and sleep duration

Sleep was accelerometer-measured in a subsample of participants (n=103 660) using data from the Axivity AX3 accelerometer (Newcastle on Tyne, UK) worn on the dominant wrist for 24 hours/day for 1 week. The accelerometers were initialised to collect data with a sampling frequency of 100 Hz and a dynamic range between ±8 g. We used previously established procedures[11 12] to calibrate data and identify non-wear time and only included participants with at least five valid monitoring days (including at least 3 weekdays and 2 weekend days). Monitoring days were considered valid if wear time was >16 hours. Participants had a median (IQR) of 23.5 (23.4–23.9) hours of valid wear time a day. The Sleep Regularity Index (SRI),[13] a metric that compares sleep-wake patterns between consecutive days, was assessed using an open-source algorithm[14] that calculates sleep-wake states at the epoch level and allows multiple sleep bouts per day (fragmented sleep, or awakenings to be correctly factored into the SRI calculation). More information about the

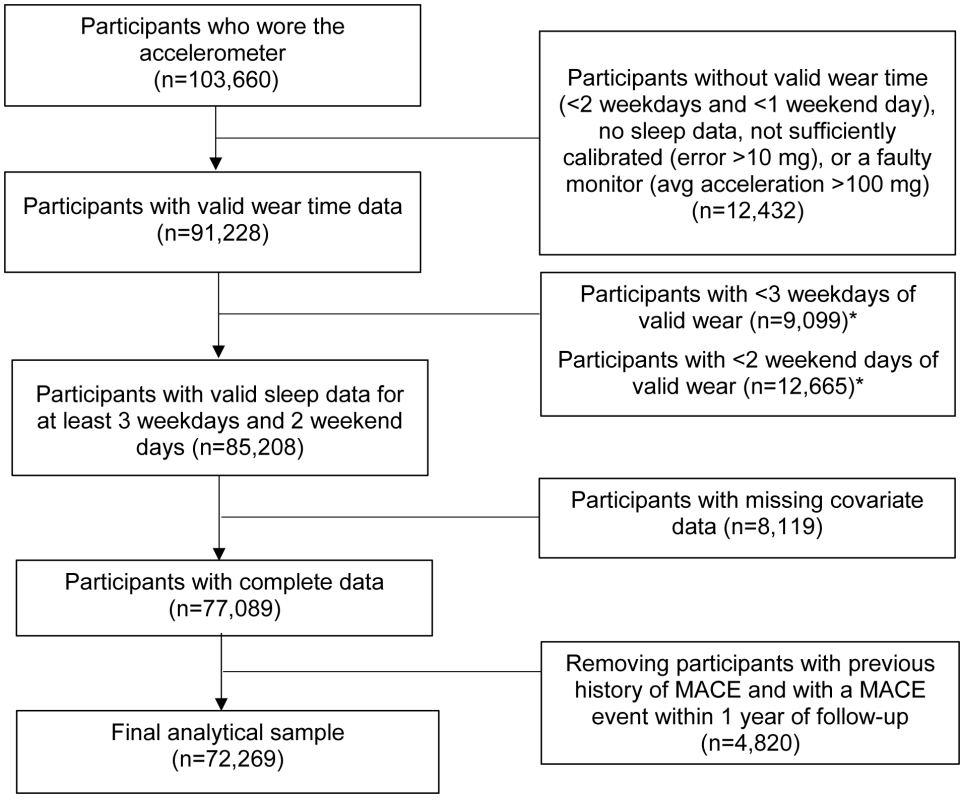

Figure 1 Flowchart of participants included in the study. *There are overlapping participants in both groups. MACE, major adverse cardiovascular events.

Table 1 Baseline characteristics of participants stratified by sleep regularity index (SRI) group

Baseline characteristic	Regular (SRI >87.3) (n=17 918)	Moderately irregular (SRI 71.6–87.3) (n=36 602)	Irregular (SRI <71.6) (n=17 749)	Full sample (n=72 269)
Follow-up (years), mean (SD)	7.8 (1.2)	7.8 (1.2)	7.7 (1.4)	7.8 (1.3)
Age at enrolment (years), mean (SD)	62.6 (7.6)	61.6 (7.8)	62.3 (7.8)	62.1 (7.7)
Male sex, n (%)	8226 (45.9)	15 952 (43.6)	6839 (38.5)	31 017 (42.9)
White ethnicity, n (%)	17 084 (95.3)	34 113 (93.2)	16 510 (93.0)	67 707 (93.7)
Townsend area deprivation index, mean (SD)*	−2.1 (2.6)	−1.8 (2.8)	−1.6 (2.9)	−1.8 (2.8)
Moderate-to-vigorous physical activity (min/day), mean (SD)†	44.0 (31.7)	41.3 (30.9)	36.7 (29.1)	40.8 (30.8)
Discretionary screen time (hours/day), mean (SD)‡	3.6 (1.9)	3.7 (2.0)	3.9 (2.1)	3.7 (2.0)
Fruit and vegetable intake (servings/day), mean (SD)§	8.1 (4.4)	8.0 (4.5)	8.1 (4.5)	8.0 (4.5)
Coffee intake per day, n (%)				
No coffee	4492 (25.1)	9807 (26.8)	4952 (27.9)	19 251 (26.6)
1–3 cups	10 197 (56.9)	19 911 (54.4)	9377 (52.8)	39 485 (54.6)
3+ cups	3229 (18.0)	6884 (18.8)	3420 (19.3)	13 533 (18.7)
Alcohol consumption (units/week), mean (SD)¶	13.2 (14.1)	14.0 (15.3)	13.8 (15.8)	13.7 (15.2)
Smoking status, n (%)				
Never	11 057 (61.7)	21 000 (57.4)	9829 (55.4)	41 886 (58.0)
Former	6109 (34.1)	13 226 (36.1)	6553 (36.9)	25 888 (35.8)
Current	752 (4.2)	2376 (6.5)	1367 (7.7)	4495 (6.2)
Mental health issues, n (%)**	5038 (28.1)	11 924 (32.6)	6354 (35.8)	23 316 (32.3)
Medication use (cholesterol, diabetes, blood pressure), n (%)	3508 (19.6)	7620 (20.8)	4018 (22.6)	15 146 (21.0)
Family history of CVD, n (%)	9909 (55.3)	19 894 (54.4)	9843 (55.5)	39 646 (54.9)
Family history of cancer, n (%)	5695 (31.8)	11 382 (31.1)	5491 (30.9)	22 568 (31.2)
Employment shift, n (%)				
Retired/not in the workforce	7997 (44.6)	14 413 (39.4)	7711 (43.4)	30 121 (41.7)
Employed not in shift work	9040 (50.5)	19 411 (53.0)	8290 (46.7)	36 741 (50.8)
Employed in night shift work	350 (2.0)	1234 (3.4)	982 (5.5)	2566 (3.6)
Employed in day shift work	531 (3.0)	1544 (4.2)	766 (4.3)	2841 (3.9)
Sleep problems, n (%)††	9081 (50.7)	19 785 (54.1)	10 189 (57.4)	39 055 (54.0)
Sleep duration, n (%)‡‡				
Meeting guidelines	10 918 (60.9)	21 665 (59.2)	8488 (47.8)	41 071 (56.8)
Not meeting guidelines	7000 (39.1)	14 937 (40.8)	9261 (52.2)	31 198 (43.2)
MACE, n (%)	1112 (6.2)	2397 (6.5)	1378 (7.8)	4887 (6.8)
Heart failure, n (%)	198 (1.1)	449 (1.2)	285 (1.6)	932 (1.3)
Myocardial infarction, n (%)	718 (4.0)	1531 (4.2)	859 (4.8)	3108 (4.3)
Stroke, n (%)	196 (1.1)	417 (1.1)	234 (1.3)	847 (1.2)

*Townsend area deprivation index assigns each participant a score based on postcodes. Higher scores represent greater socioeconomic deprivation.
†Accelerometer-derived moderate-to-vigorous physical activity.
‡Daily discretionary screen time is calculated as the sum of TV viewing time plus (non-occupational) leisure time computer use.
§Self-reported daily intake of fruits and vegetables served as a proxy for dietary quality by asking, for example, 'about how many pieces of fresh fruit would you eat per day?'.
¶Self-reported alcohol consumption was converted into UK unit (1 unit=10 mL of alcohol).
**Mental health issues were defined as the self-reported history by asking, 'have you ever seen a general practitioner (GP) for nerves, anxiety, tension, or depression?'.
††Self-reported sleep issues including insomnia symptoms, daytime sleepiness, and snoring.
‡‡Participants were categorised as meeting the sleep duration recommendations (7–9 hours/day for adults aged 18–64 years and 7–8 hours/day for adults aged 65 years and older) or not.
CVD, cardiovascular disease; MACE, major adverse cardiovascular events; SRI, Sleep Regularity Index.

SRI calculation can be found elsewhere.[5] The SRI captures day-to-day variability in bedtime, wake-up time, sleep duration, and awakenings during sleep,[15] and is scored from 0 (sleep and wake times at random) to 100 (perfectly regular sleep-wake patterns). Based on the SRI distribution in the UK Biobank and recent research,[14] participants were categorised as follows: irregular (SRI <71.6; percentile 0–25%), moderately irregular (SRI between 71.6 and 87.3; percentile 25–76%), and regular (SRI >87.3; percentile 76–100%). Sleep duration was assessed with an algorithm developed and validated in 3752 British participants with sleep diary data and 28 patients with polysomnography data.[16] The sleep period time window derived from the algorithm was 11 min and 3 min longer compared with a sleep diary in men and women, respectively. Daily sleep durations were derived in the same study days used to calculate SRI scores, and average sleep duration for each participant was calculated. Participants were categorised as meeting, or not meeting, the sleep duration recommendations[17 18] (7–9 hours/day for adults aged 18–64 years and 7–8 hours/day for adults aged 65 years and older).

Major adverse cardiovascular events (MACE)

The main outcome measure for this study was MACE (binary variable; event/no event). Participants were followed through 30 November 2022 using linked death registry from the National Health Service (NHS) Digital of England and Wales or the NHS Central Register and National Records of Scotland. Inpatient

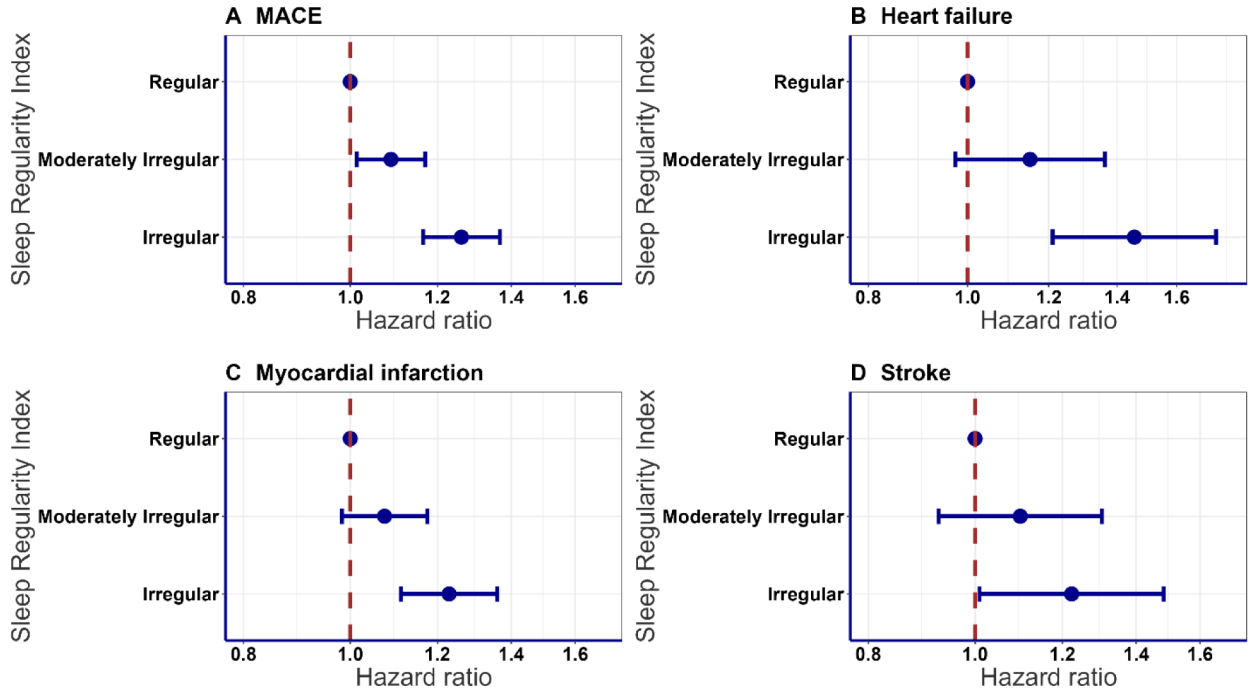

Figure 2 Associations between Sleep Regularity Index (categorised) and major adverse cardiovascular events (MACE) and its subtypes in UK adults. Data are presented as hazard ratios with 95% confidence intervals. Adjusted for age, sex, ethnicity, Townsend area deprivation index, moderate-to-vigorous physical activity (accelerometer-derived), discretionary screen time, fruit and vegetable intake, coffee intake, alcohol consumption, smoking status, mental health issues, medication use (cholesterol, blood pressure, diabetes), family history of cardiovascular disease or cancer, shift work, and self-reported sleep problems (insomnia symptoms, daytime sleepiness, snoring). We removed participants with a previous history of MACE and who had an event in the first year of follow-up. (A) All MACE (n=72 269, events: 4887). (B) Heart failure (n=68 519, events=932). (C) Myocardial infarction (n=70 490, events=3108). (D) Stroke (n=68 229, events=847). Three groups were used for Sleep Regularity Index (SRI): regular (SRI >87.3), moderately irregular (SRI between 71.6 and 87.3), and irregular (SRI <71.6) sleepers.

and hospitalisation data were provided by either the Hospital Episode Statistics for England, the Patient Episode Database for Wales, or the Scottish Morbidity Record for Scotland. As previously reported,[4 19] MACE was defined as any fatal cardiovascular events, or incidence of non-fatal ST-elevated or non-ST-elevated myocardial infarction (International Classification of Diseases version 10: I21, I23, I24, I25, I26, I30, I31, I33, I34, I35, I38, I42, I45, I46, I48), or stroke (I60, I61, I63, I64, I67), or heart failure (I11, II13, I50, I51) (whatever occurred first). We explored associations of total MACE and its subtypes (ie, myocardial infarction, heart failure and stroke).

Covariates

Potential confounders were selected a priori due to their documented association with sleep and MACE. They included age, sex, ethnicity, Townsend area deprivation index, moderate-to-vigorous physical activity (accelerometer-derived), discretionary screen time, fruit and vegetable intake, coffee intake, alcohol consumption, smoking status, mental health issues, medication use (cholesterol, diabetes, blood pressure), family history of CVD or cancer, shift work status (day shift work, night shift work, employed not in shift work, retired/not in the workforce), and self-reported sleep problems (insomnia symptoms, daytime sleepiness, snoring). Of note, body mass index was not included as a covariate in the models because it is a mediator of the association between sleep irregularity and MACE risk (ie, it is in the causal pathway). Details on how these variables were assessed and classified are included in online supplemental eTable 1.

Statistical analysis

Baseline characteristics of participants in the full sample and stratified by levels of SRI are presented. We examined whether there was a sex-by-SRI interaction with MACE risk and found no significant interaction; therefore, pooled analyses were conducted. We used multivariable-adjusted Cox proportional hazards regression models to examine the associations between SRI and MACE, with regular sleep (SRI >87.3) as the reference category. Follow-up time (in years) was used as the time scale for all survival models, and started 1 year after study entry. We used the Fine-Grey subdistribution method to account for competing risks from non-CVD deaths. Models were adjusted for the above-mentioned covariates. To reduce the possibility of reverse causation through prodromal/undiagnosed disease, all analyses excluded adults with a previous history of MACE and who had an event within the first year of follow-up. Proportional hazards assumptions were tested using Schoenfeld residuals and no violations were observed. Additionally, we tested sleep regularity as a continuous dose-response association with knots set based on main exposure (SRI/sleep duration) sampling distributions (10th, 33rd, and 67th percentiles), and estimated the adjusted dose-response risk using the same knots. Departure from linearity was assessed using a Wald test. Hazard ratios (HR) and 95 confidence intervals (95% CI) are presented. To provide conservative point estimates, we calculated the 'minimal dose', defined as the SRI score associated with 50% of the optimal risk reduction. We also present point estimates (HR and 95% CI) associated with the median SRI value. Finally, we conducted an

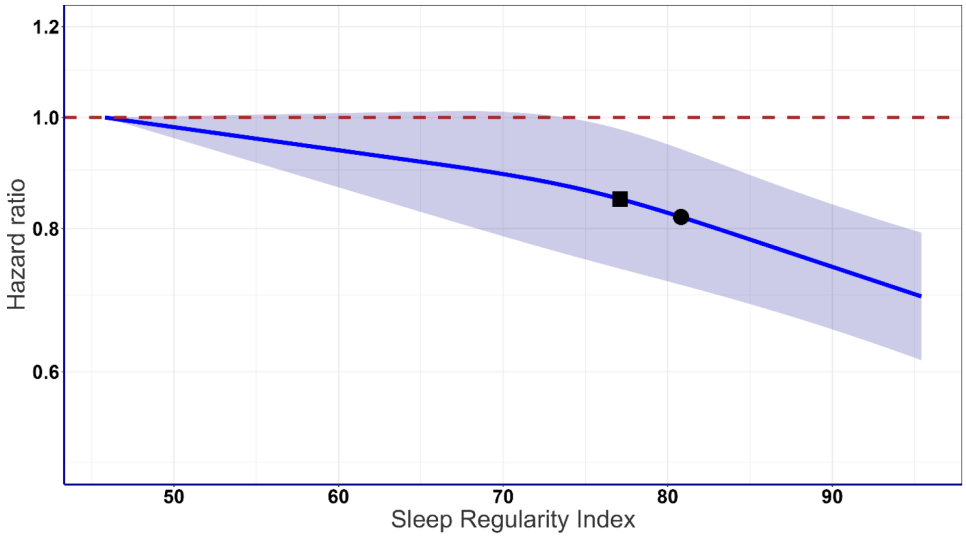

Figure 3 Dose-response associations between Sleep Regularity Index (continuous) and major adverse cardiovascular events (MACE) in UK adults (n=72 269, events 4887). The shaded region represents the 95% confidence intervals (95% CI). The solid line that lies within the shaded region represents the hazard ratios (HR). Adjusted for age, sex, ethnicity, Townsend area deprivation index, moderate-to-vigorous physical activity (accelerometer-derived), discretionary screen time, fruit and vegetable intake, coffee intake, alcohol consumption, smoking status, mental health issues, medication use (cholesterol, blood pressure, diabetes), family history of cardiovascular disease or cancer, shift work, and self-reported sleep problems (insomnia symptoms, daytime sleepiness, snoring). We removed participants with a previous history of MACE and who had an event in the first year of follow-up. Square: minimal dose, as indicated by the ED50 statistic which estimates the Sleep Regularity Index (SRI) associated with 50% of optimal risk reduction (SRI=77.1 and HR 0.85, 95% CI 0.74 to 0.98). Circle: HR associated with the median SRI value (SRI=80.8 and HR 0.82, 95% CI 0.71 to 0.94).

adjusted joint analysis (six group exposures) for the combination of SRI groups (regular; moderately regular; irregular) and sleep duration groups (two groups; meet/do not meet recommended sleep duration) with MACE risk. All analyses were performed using R version 4.2.3 with RMS (version 6.3.0) and survival packages (version 3.5.5).

Patient and public involvement

Patient and public involvement in the UK Biobank study is integral to its ethical and effective operation. It includes comprehensive participant engagement through informed consent and feedback mechanisms, ensuring participants are well-informed and can voice their experiences. Governance and oversight are strengthened by an independent Ethics and Governance Council and an Access and Oversight Committee, both including public representatives to review ethical aspects and research applications. Public engagement is maintained through regular outreach, transparent communication, and public consultations to align research priorities with public health concerns. Continuous improvement is facilitated by feedback loops, ensuring the study remains participant-friendly and ethically sound.

RESULTS

Our analysis involved a cohort of over 70 000 adults who underwent accelerometry assessment between 1 June 2013 and 23 December 2015 (figure 1). A comparison between the baseline characteristics of individuals in our primary analysis sample and those excluded due to incomplete or missing data is provided in online supplemental eTable 2. Baseline descriptive characteristics of participants (full sample) and stratified by SRI group is shown in table 1. The mean (SD) age at enrolment was 62.1 (7.7) years, and the mean (SD) duration of follow-up was 7.8 (1.3) years. A greater proportion of regular sleepers met the recommended sleep duration than irregular sleepers (60.9% vs 47.8%, respectively).

In multivariable-adjusted models, moderately irregular sleepers (HR 1.08, 95% CI 1.01 to 1.70) and irregular sleepers (HR 1.26, 95% CI 1.16 to 1.37) were at higher risk of MACE compared with regular sleepers (see figure 2 and online supplemental eFigure 1). Analyses examining MACE subtypes showed clearer associations for irregular sleepers only for risk of heart failure (HR 1.45, 95% CI 1.21 to 1.75), myocardial infarction (HR 1.23, 95% CI 1.11 to 1.36) and stroke (HR 1.22, 95% CI 1.01 to 1.48).

Adjusted dose-response curves of continuous SRI scores showed that SRI was associated with MACE risk in a near-linear fashion, with steeper MACE risk reduction at higher SRI scores (figure 3 and online supplemental eFigure 2). The minimal dose, or the SRI dose associated with 50% of optimal risk reduction in MACE, was 77.1, corresponding with a 15% reduction in MACE risk (HR 0.85, 95% CI 0.74 to 0.98). The median SRI score of 80.8 was associated with 18% reduction in MACE risk (HR 0.82, 95% CI 0.71 to 0.94). Dose-response curves of the constituent MACE sub-types were in agreement with the main analysis, but with wider confidence intervals due to fewer event numbers (online supplemental eFigure 3).

Joint SRI and sleep duration analyses showed that sufficient sleep duration offsets MACE risk for moderately irregular sleepers (HR 1.07, 95% CI 0.96 to 1.18), but not for irregular sleepers (HR 1.19, 95% CI 1.06 to 1.35) (figure 4 and online supplemental eFigure 4). Analyses with MACE subtypes were in agreement with the main analysis, but with wider confidence intervals due to small event numbers in each sleep category (online supplemental eFigure 5). We also repeated the joint analysis by keeping only individuals not employed in shift work (n=36 741) and the results were similar (online supplemental eFigure 6).

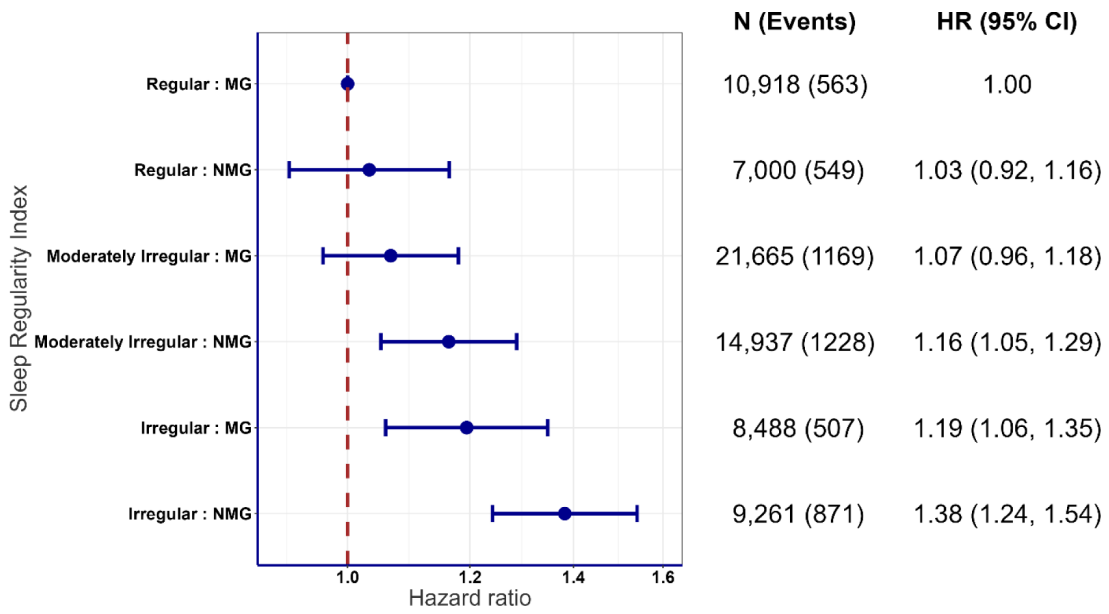

Figure 4 Joint associations between Sleep Regularity Index (categorised) and sleep duration (categorised) with major adverse cardiovascular events (MACE) (n=72 269, events 4887). Data are presented as hazard ratios (HR) with 95% confidence intervals (95% CI). Adjusted for age, sex, ethnicity, Townsend area deprivation index, moderate-to-vigorous physical activity (accelerometer-derived), discretionary screen time, fruit and vegetable intake, coffee intake, alcohol consumption, smoking status, mental health issues, medication use (cholesterol, blood pressure, diabetes), family history of cardiovascular disease or cancer, shift work, and self-reported sleep problems (insomnia symptoms, daytime sleepiness, snoring). We removed participants with a previous history of MACE and who had an event in the first year of follow-up. Three groups were used for Sleep Regularity Index (SRI): regular (SRI >87.3), moderately irregular (SRI between 71.6 and 87.3), and irregular (SRI <71.6) sleepers. Participants were also categorised as meeting the sleep duration guidelines (MG) (7–9 hours/day for adults aged 18–64 years and 7–8 hours/day for adults aged 65 years and older) or not meeting the guidelines (NMG).

DISCUSSION

Findings from this large prospective cohort study of wearable device data-computed SRI suggest that irregular sleep is strongly associated with MACE risk in adults. More importantly, our results suggest that sleep regularity may be more relevant than sufficient sleep duration in modulating MACE risk. Indeed, joint analyses revealed that irregular sleep was associated with significantly higher MACE risk, regardless of whether individuals met sleep duration recommendations or not. Our study prompts for a stronger focus on sleep regularity in public health guidelines and clinical practice relevant to CVD prevention.

The literature on sleep regularity and CVD risk is limited, but available studies suggest an adverse effect of irregular sleep. For example, sleep irregularity has been found to be associated with subclinical atherosclerosis in a recent cross-sectional study.[6] Sleep irregularity and the incidence of CVD has also been recently investigated in the Multi-Ethnic Study of Atherosclerosis.[7] Individuals with the most irregular sleep had more than a twofold risk of developing CVD over a follow-up of under 5 years compared with individuals with the most regular sleep patterns.[7] However, the small samples used in the above studies (n=~2000 participants) precluded investigators from conducting dose-response analyses or joint analyses to answer the question of whether sufficient sleep duration attenuates or eliminates the adverse effects of irregular sleep. Moreover, instead of using a validated Sleep Regularity Index, they defined sleep regularity as the standard deviation of sleep across measurement days—an approach that is not recommended for use in research because it only measures variability without accounting for alignment with circadian rhythms or day-to-day patterns.[3 15] Our study not only addresses important methodological limitations and knowledge gaps in the field, but also provides practical information to inform policy and clinical practice.

Although steeper MACE risk reductions occurred at the upper end of the SRI distribution in our study, there were continuing MACE risk reductions in a near-linear fashion. A minimum SRI of 77.1 was associated with a 15% reduction in MACE risk. The median SRI score of 80.8 was associated with a 18% reduction in MACE risk. These findings suggest that the benefits of sleep regularity on cardiovascular outcomes are observed on a continuum of risk, and individuals should aim for an SRI >80, with greater benefits the closer they get to 100. An SRI ≥80 corresponds to approximately half of the UK Biobank sample, and best strategies to improve sleep regularity include maintaining a consistent sleep schedule, establishing a relaxing bedtime routine, and creating a sleep-conducive environment.[2 3]

A key question our study tried to address was to determine whether sufficient sleep duration attenuates or eliminates the effects of irregular sleep on MACE risk. We observed that irregular sleep was associated with significantly higher risk of MACE, irrespective of whether individuals met the sleep duration recommendation or not. We also observed that sufficient sleep duration offsets MACE risk among moderately irregular sleepers, but not among irregular sleepers. This finding emphasises the importance of sleep regularity in cardiovascular health, which is further supported by results from a recent study showing that sleep regularity, as assessed with the SRI, was more strongly associated with mortality risk than sleep duration.[5] Irregular sleep-wake patterns have also been shown to be associated with higher mortality risk in another recent study that relied on the SRI.[20] However, these studies did not examine the joint SRI-sleep duration associations with mortality, which is essential for

understanding whether sufficient sleep duration mitigates the effects of irregular sleep on mortality.

Circadian misalignment, resulting from sleep irregularity, disrupts the synchronisation between the internal biological clock and external environmental cues, potentially leading to adverse health effects. Plausible mechanisms explaining the association between sleep irregularity and impaired cardiovascular health include disruptions in circadian rhythms, hormonal regulation, meal timing, inflammation, and immune function.[21] Irregular sleep patterns can lead to dysregulation of glucose and lipid metabolism, insulin resistance, and heightened sympathetic nervous system activation.[21] These disturbances contribute to a cascade of adverse effects, including increased stress hormone release, elevated blood pressure, impaired endothelial function, and a greater risk of developing CVD and metabolic disorders.[21] Furthermore, it is possible that irregular sleep-wake patterns may reflect variability in the timing of light exposure and timing of meals and physical activity, all contributors to circadian disruption.[22 23] The intricate interplay of these mechanisms underscores the importance of maintaining regular sleep-wake patterns for overall cardiometabolic health.

The recent consensus statement from the National Sleep Foundation in the USA stipulates that sleep regularity is important for health and performance.[3] The panel also recommended that one common metric should be used consistently in studies for the assessment of sleep regularity to facilitate comparisons across studies. Although consensus will be required for this common metric, the panel recommended that metrics of day-to-day variability such as the SRI should be prioritised over less precise survey methods of sleep patterns on work days versus non-work days.[3 15] Furthermore, it is worth noting that the American Heart Association's construct of cardiovascular health, called Life's Essential 8, now includes sleep duration as one of the metrics.[24] The addition of sleep to this construct is certainly good news and recognises the importance of sleep in cardiovascular health. The association between the Life's Essential 8 score and cardiovascular health has recently been examined in recent studies,[25 26] supporting the inclusion of sleep to this metric. Future studies will be instrumental in determining whether sleep regularity may be a better marker of sleep health than sleep duration for Life's Essential 8.

Several strengths and limitations need to be discussed when interpreting the findings from this study. First, this study is the first to examine the longitudinal association between sleep regularity and MACE risk in a large population sample. We also examined for the first time whether sufficient sleep duration offsets the adverse effects of irregular sleep on cardiovascular outcomes. The finding that sufficient sleep does not offset MACE risk for irregular sleepers, but appears to do so for moderately irregular sleepers, is novel and provides tangible information for guidelines and clinical interventions development. We used device data-based computation instead of self-reported instruments to measure sleep regularity and relied on SRI, as per current research recommendations.[3 15] Lastly, our analyses were adjusted for a multitude of potential confounders, thus providing greater confidence in the internal validity of the results.

Nevertheless, it is important to acknowledge several limitations inherent in this study. First, while the study's sample size was large, the UK Biobank's response rate was low and may not accurately reflect the broader population.[27] However, a recent analysis of the UK Biobank showed that the multivariable-adjusted associations concerning health-related behaviours remained relatively unaffected by poor representativeness.[28] Second, covariate assessments were conducted at a single time point, and covariates were not treated as time-varying.[29] The median lag between the UK Biobank baseline, when covariate measurements were taken, and the accelerometry sub-study was 5.5 years. However, previous reports indicate that the covariates remained stable over time, except for medication use.[30 31] Third, while longitudinal studies are well suited for assessing potentially causal associations, randomised experiments are needed to strengthen causal inference. Fourth, as is typical with accelerometry assessment in population-based studies,[1–3] the assessment of sleep was conducted over a single week. It is thus possible that individuals may have altered their usual sleep patterns during the observation period. However, recent evidence shows that a week of sleep assessment provides reliable estimates of habitual sleep patterns in adults.[32] Furthermore, the SRI algorithm did not detect napping, only the longest sleep period. Finally, a well-known limitation of actigraphy in assessing sleep/wake states is its inability to distinguish accurately between quiet wakefulness and sleep, leading to potential misclassification errors. Future studies should try to incorporate sleep efficiency into statistical models when testing joint SRI and sleep duration associations with outcome measures. For example, it is possible that sleep duration within the recommended range and sleep efficiency >85% could offset the MACE risk in individuals with irregular SRI scores.

CONCLUSIONS

In a study of 72 269 adults wearing wrist accelerometers, who were followed up for 7.8 years, irregular sleep was associated with significantly higher MACE risk, regardless of whether individuals met sleep duration recommendations or not. Sufficient sleep offsets MACE risk for moderately irregular sleepers, but not for irregular sleepers. Findings from this study suggest that more attention needs to be paid to sleep regularity in public health guidelines and clinical practice due to its potential role in cardiovascular health. Future studies are needed to explore whether interventions aimed at improving sleep regularity might improve cardiovascular health.

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Contributors J-PC, RKB, MA and ES designed the study. RKB conducted the statistical analyses and had full access to the dataset. J-PC prepared the first manuscript draft and ES thoroughly edited the draft. All authors critically revised the manuscript for important intellectual content. All authors take final responsibility for the decision to submit the article for publication. RKB, ES and MA had full access to all the data in the study and take responsibility in the integrity of the data and the accuracy of the data analysis. RKB is the guarantor.

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Competing interests PAC has an appointment as an endowed Academic Chair at the University of Sydney that was created from ResMed funding; he receives no personal fees, and this relationship is managed by an Oversight Committee of the University. Additionally, he has received research support from ResMed, SomnoMed, and Bayer, and is a consultant/adviser to SomnoMed, ResMed, and Sunrise Medical. SMWR declared grants or contracts from Vanda Pharmaceuticals, WA Police and the Centers for Disease Control and Prevention, consulting fees from Roche and Circadian Therapeutics, honoraria from Roche, a patent for a digital application for sleep in shift workers (application no. 17/799206), and acts as Chair of the Sleep Health Foundation and the International Association of Circadian Health Clinics. The other authors declared no competing interests.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and all participants provided written informed consent for data collection, analysis, and linkage and ethical approval was obtained from the UK National Health Service (NHS), National Research Ethics Service (reference No. 11/NW/0382). Only de-identified data were provided to researchers for this analysis. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. The UK Biobank data that support the findings of this study can be accessed by researchers on application (https://www.ukbiobank.ac.uk/register-apply/). The data that support the findings of this study are available on reasonable request from Dr Raaj Kishore Biswas (raaj.biswas@sydney.edu.au). The dataset used in this study is not publicly available due to UK Biobank access restrictions.

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