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# Sleep timing irregularity in midlife: association with incident major adverse cardiac events and cardiovascular disease mortality over a 10-year follow-up

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## Abstract

**Background** Sleep timing reflects daily routines and lifestyle patterns, which influence cardiovascular health through circadian mechanisms that regulate cardiovascular processes. Wearable devices enable sensor-based assessment of sleep timing, offering insights into daily behavior. This cohort study examined how the regularity of wearable device-determined sleep timing (bedtime, wake-up time, and sleep midpoint) predicts incident major adverse cardiac event (MACE) and cardiovascular disease (CVD) mortality over a 10-year follow-up in midlife.

**Methods** The study included 3,231 participants (39.5% men) from the Northern Finland Birth Cohort 1966 who attended the 46-year follow-up in 2012–2014. Participants were followed until December 31, 2023, or until a MACE (acute myocardial infarction, unstable angina, stroke, heart failure hospitalization, or CVD death) or were censored due to moving abroad or dying from a non-cardiovascular cause. Sleep timing regularity was assessed via 7-day standard deviation for bedtime, wake-up time, and sleep midpoint, categorized into tertiles: regular, fairly regular, and irregular. Cox proportional hazards models estimated hazard ratios (HRs) with 95% confidence intervals (CIs), adjusting for gender, employment status, body mass index, systolic blood pressure, glycated hemoglobin, low-density lipoprotein cholesterol, and total physical activity. Analyses were stratified by sleep duration below or above the group median (7 h 56 min).

**Results** In total, 128 participants (4.0%) experienced MACEs during the follow-up period. Irregular sleep timing was associated with an elevated risk, but this association was observed only among participants whose sleep period was shorter than the group median. Individuals with irregular bedtimes had a 2.01-fold higher risk of MACEs compared to those with regular bedtimes (HR = 2.01, 95% CI: 1.00–4.01,  $p = 0.049$ ), and those with irregular sleep midpoints had a 2.00-fold higher risk compared to those with regular midpoints (HR = 2.00, 95% CI: 1.01–3.98,  $p = 0.048$ ).

**Conclusions** Among the participants with sleep durations under eight hours, irregular sleep timing was a significant risk factor for MACEs. Specifically, variability in bedtime and sleep midpoint, but not in wake-up time, was associated

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with increased risk. These findings highlight the importance of consistent sleep behavior, particularly regular bedtimes, as a potential target for health promotion.

**Keywords** 24-h activity rhythm, sleep consistency, sleep regularity, physical activity, chronotype, circadian health

## Background

The 24-hour internal circadian rhythm is an important factor in human biology, regulating the circadian rhythms that influence sleep, metabolism, and cardiovascular function [1]. Critically, disruptions in circadian alignment, such as those caused by evening chronotype, shift work, irregular sleep timing, and late meal timing, have been associated with adverse cardiometabolic health [2–6]. These findings suggest that behavioral patterns affecting circadian stability may play an important role in cardiometabolic health.

Research has shown that any amount of physical activity could be beneficial for cardiovascular health [7, 8] and, relatedly, that higher physical activity level is associated with reduced risk of cardiovascular disease (CVD) and mortality [9, 10]. In addition to physical activity, both short and long sleep durations have been linked to increased risk of CVD [11, 12], with adequate sleep duration and quality being considered important in maintaining cardiometabolic health [9, 13–15].

Sleep health, however, is multidimensional. In addition to sleep duration and quality, regularity of sleep and sleep timing could also be predictors of health outcomes. Recent studies have increasingly emphasized the role of regularity in sleep and activity behaviors in promoting cardiometabolic health [5, 6, 16, 17]. In a recent statement, the American Heart Association emphasized the multidimensionality of sleep health, listing sleep duration, regularity, timing, continuity, satisfaction, daytime functioning, sleep architecture, and the absence of sleep disorders as essential elements contributing to healthy cardiovascular functioning [15].

Emerging research has also highlighted the potential causal relationships between sleep-related factors, such as chronotype, sleep duration, and insomnia symptoms, and cardiometabolic outcomes, including blood pressure, cholesterol levels, and type 2 diabetes [18–20]. Inconsistent sleep rhythms and shorter sleep durations have additionally been associated with elevated cardiometabolic mortality risk [5]. Indeed, a large-scale longitudinal study from the UK Biobank found that higher night-to-night variation in sleep duration was associated with increased risk of myocardial infarction and stroke, independent of genetic risk [21].

Notably, the increasing availability of wearable devices offers new opportunities to assess sleep and activity behaviors in everyday life with increased temporal resolution and objectivity, enabling more accurate evaluations of these factors' long-term health implications [22].

This advancement has, in turn, facilitated the quantification and computation of different metrics reflecting the regularity of sleep patterns and timing. Device-based metrics, such as the sleep regularity index, interdaily stability, and standard deviation (SD) of sleep timing, have shown consistent associations with cardiometabolic biomarkers, including blood pressure, waist circumference, and lipid profiles [16, 23–26]. These metrics, though, are not identical, and their related interpretations and implications may differ. First, the sleep regularity index quantifies the probability that an individual is in the same sleep or wake state at any two time points in time 24 h apart, averaged over multiple days [27]. Interdaily stability, meanwhile, measures the stability of rest-activity rhythms across multiple days, indicating how consistent a person's daily pattern is over time [28]. In contrast, SD of sleep timing provides a direct measure of variability in specific behaviors (e.g. bedtime or wake-up time) offering a simple yet informative indicator of sleep routine consistency. While the sleep regularity index and interdaily stability capture general rhythmicity and alignment with the 24-hour cycle, they are composite measures that do not isolate specific behavioral components.

To complement these composite metrics and better understand the role of specific sleep timing behaviors in cardiovascular health, this study focused on sleep timing regularity. By examining the consistency of bedtime, wake-up time, and the midpoint of the sleep period, we aimed to capture direct measures of routine variability that may be more interpretable and actionable in clinical and public health contexts. This study investigated whether sleep timing regularity measures predict incident major adverse cardiac events (MACEs) and CVD mortality over a 10-year follow-up in a middle-aged population from the Northern Finland Birth Cohort 1966. Sleep timing regularity was assessed based on the regularity of bedtime, wake-up time, and the midpoint of the sleep period.

## Methods

### Study population

This study draws on data from the Northern Finland Birth Cohort 1966 (NFBC1966). NFBC1966 is a population-based cohort comprising all individuals born in Northern Finland in 1966 ( $N = 10,331$ ) [29, 30]. Since birth, participants have been followed prospectively through a series of clinical examinations, interviews, and comprehensive questionnaire-based assessments.

The present analyses included NFBC1966 participants who took part in the latest follow-up at 46 years of age (2012–2014), consented to wear accelerometer-based activity monitors, and provided sufficient accelerometer data. The 46-year follow-up involved completion of postal questionnaires on health-related behaviors ( $n = 7,146$ ; 69.2%), attendance at a clinical examination for fasting blood sampling and anthropometric measurements ( $n = 5,832$ ; 56.5%), and continuous 24-hour accelerometer monitoring of daily activity over two weeks ( $n = 5,624$ ; 54.5%). The 46-year data collection protocol has been described in detail elsewhere [29, 30]. The study protocol was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District in Oulu, Finland (94/2011). This study is reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

## Measurements

### Questionnaires and clinical measurements

Participants self-reported their smoking status (non-smoker, former smoker, or current smoker), education level, marital status, and alcohol consumption. Alcohol consumption in grams per day was calculated from responses to six questionnaire questions. Heavy alcohol consumption was classified based on national guidelines issued by the Finnish Institute for Health and Welfare, with thresholds of  $\geq 40$  g/day for men and  $\geq 20$  g/day for women [31]. Based on the question about their work schedule, the participants were divided into three groups: shift work, day work, and not working or no information available. The questions used for obtaining this information are shown in Additional file 1. Chronotype was assessed using the shortened Morningness–Eveningness Questionnaire, and participants were classified as morning-type, day-type, or evening-type individuals [32, 33].

Participants attended the clinical examination following a 12-hour overnight fast and abstention from smoking and coffee consumption. Trained nurses measured height and weight, from which body mass index (BMI, kg/m<sup>2</sup>) was calculated. After at least 10 min of seated rest, blood pressure was measured on the right upper arm using an automated monitor (Omron M10-IT; Omron Healthcare Europe BV, Netherlands). Blood pressure values were calculated as the mean of three consecutive measurements. Plasma low-density lipoprotein cholesterol was assessed from fasting blood samples.

### Device-based measurement of sleep and physical activities

At the clinical examination, participants were asked to continuously wear an accelerometer-based activity monitor (Polar Active; Polar Electro Oy, Kempele, Finland) on their nondominant wrist continuously for 14 consecutive days, including during [29]. The device records metabolic

equivalents (METs) at 30-second intervals using participant-specific background information (height, weight, age, and sex). The Polar Active monitor has demonstrated good validity for estimating daily energy expenditure when compared with the doubly labeled water method ( $R^2 = 0.78$ ) [34]. Participants did not receive feedback from the device regarding their sleep or physical activity patterns.

### Sleep period and sleep regularity

Sleep periods were derived from Polar Active MET data using a previously developed sleep-detection algorithm [16, 35]. This algorithm identifies bedtime as the start of a prolonged low-activity period and wake-up time as the end of that period. In a previously published study, we demonstrated the validity of this algorithm, showing that it estimates bedtime and wake-up time with approximately 20-minute accuracy compared with self-reported sleep diaries and approximately 5-minute accuracy compared with smart ring-derived sleep periods [35]. Notably, smart rings have demonstrated high validity in sleep measurement when evaluated against polysomnography, the clinical gold standard [36].

Sleep regularity was examined from three measures: bedtime (defined as the start of the sleep period), wake-up time (defined as the end of the sleep period), and sleep midpoint (calculated as the halfway point between bedtime and wake-up time). Sleep regularity was quantified as the standard deviation (SD) of each measure (bedtime, wake-up time, and sleep midpoint) across the first seven consecutive days of monitoring. A seven-day monitoring period was selected to capture both weekdays and weekend days, providing a representative estimate of habitual sleep variability, consistent with prior evidence indicating that 5–6 nights are sufficient for reliable assessment [37]. A day was considered valid if the non-wear time was less than 2.5 h, with non-wear time defined as continuous periods with intensity levels below 1 MET.

### Physical activity

Physical activity during non-sleep periods were calculated using the MET values provided by Polar Active for each day, and the daily means for total physical activity were calculated for each participant. Total physical activity, defined as all activity with an intensity of  $\geq 2$  METs, was calculated by multiplying each MET value by its corresponding duration and expressed as MET-minutes per day (total PA [MET min/day]) [33, 38]. Activity intensity thresholds followed the manufacturer's specifications, which have demonstrated better alignment compared to the traditional intensity thresholds originally defined for hip-worn devices [39]. For instance, Polar Active's  $< 2$  MET threshold for sedentary behavior has been found to yield comparable results to the  $< 100$  counts-per-minute

criterion used by the ActiGraph GT3X, which is a widely accepted threshold for identifying sedentary time [40].

### **Morbidity and mortality**

Data on hospital visits, including discharge diagnoses from inpatient care, were obtained from the Finnish Care Register for Health Care. This nationwide register aggregates information from hospitals operated by municipalities, joint municipal authorities, and the central government, as well as from major private healthcare providers. New MACEs were identified as the first hospital admission or outpatient visit occurring after the conclusion of physical activity monitoring, attributed to any of the following conditions: acute myocardial infarction (ICD-10 codes: I21, I22), unstable angina pectoris (I20), stroke (I63), hospitalization for heart failure (I50), or CVD death (I00–I99). Mortality data, including deaths due to CVD were obtained from Statistics Finland. Incident cases and causes of death were determined based on the primary diagnosis. Participants were followed until December 31, 2023, unless they experienced an earlier MACE or were censored due to moving out of the study area or dying from a non-cardiovascular cause. The study included only participants residing in Finland. Because information on individuals who moved abroad after 2021 was unavailable, censoring for residence outside Finland beyond that point could not be applied. The research data was obtained from Findata, the Finnish Social and Health Data Permit Authority, with data permit THL/6250/14.05.00/2024. Findata was responsible for the pseudonymization of the data and ensuring the anonymity of the final results.

### **Statistical analyses**

Only participants with a SD less than 6 h in each sleep regularity variable were included; values  $\geq 6$  h were excluded as extreme outliers. This was done because it is unclear whether such high variability reflects true behavior or measurement artefact, given that this level of variability substantially exceeds that reported in comparable population-based actigraphy studies [24–26]. These observations were excluded to avoid potential distortion of the results. Bedtime, wake-up time, and midpoint regularities were recoded to three equally sized groups and labelled as tertiles: regular, fairly regular, and irregular.

The distributions of sleep-related, sociodemographic, lifestyle, and cardiovascular risk factors were calculated separately for participants with and without a MACE during the 10-year follow-up. The statistical significance of the group differences was analyzed using chi-square tests for normally distributed data and Mann-Whitney U tests for skewed data. For categorical variables, group differences were assessed using chi-square tests.

Post-hoc comparisons were adjusted using the Bonferroni correction.

Cox proportional hazards models were conducted to estimate the hazard ratios (HRs) of MACE incidence with 95% confidence intervals (CIs), with these models being created separately for bedtime regularity, wake-up time regularity, and midpoint regularity. Based on previous studies, this study considered the following variables as covariates: total physical activity (MET min/day), sedentary time (min/day), gender (male/female), alcohol use, smoking status, employment status (employed/unemployed), low-density lipoprotein (LDL) cholesterol (mmol/L), BMI ( $\text{kg}/\text{m}^2$ ), glycated hemoglobin (mmol/mol), systolic blood pressure (mmHg), chronotype (morning, day, or evening type), and sleep-period duration [41–44]. These covariates were selected because they are known to be related to CVD. Variables significantly associated with survival in univariate analyses were entered simultaneously into the multivariable Cox models using the enter method (gender, employment status, BMI, systolic blood pressure, LDL cholesterol, and total physical activity), given the limited number of events and to reduce the risk of overfitting. Participants with missing data in one or more covariates were excluded from the multivariable analyses. The analyses were based on a complete-case approach because less than 10% of participants had missing values in any of the covariates. When performing proportional hazards analysis, complete case analysis can provide good estimates of coefficients without imputation when the proportion of missing data is relatively small [45].

The proportional hazards assumption was assessed visually and with scaled Schoenfeld residuals. Sleep period did not meet the proportional hazards assumption. Therefore, Cox models were stratified by sleep period duration. Separate models were constructed for participants with sleep period duration at or below the group median (7 h 56 min) and those above it, referred to as the below-median and above-median sleeper groups. Stratification by the median was chosen because it approximates the recommended sleep duration. More groupings were not possible, as the number of events per group was low. Due to the violation of the proportional hazards assumption, employment status was included as a stratification variable in the Cox model. For total physical activity, a time-varying coefficient model using the  $\text{tt}()$  transformation in the Cox regression [46] was applied, as the proportional hazards assumption was not met.

Kaplan–Meier survival curves were generated separately for the below-median and above-median sleeper groups to examine the association between sleep regularity and survival. For each group, separate curves were plotted for strata of regularity (regular, fairly regular,

and irregular) across three variables: bedtime regularity, wake-up time regularity, and midpoint regularity.

Sensitivity analyses were performed to test the stability of the main findings. The associations of sleep regularity may be prone to the problem of reverse causality bias. To address this problem, participants who experienced a MACE within the first 2 years of follow-up were excluded to reduce potential reverse causality, as early events may reflect preclinical cardiovascular disease present at baseline. Second, shift workers were excluded to account for the confounding effect of irregular work schedules. In both cases, fully adjusted Cox models were re-estimated using the same covariates as in the main analysis.

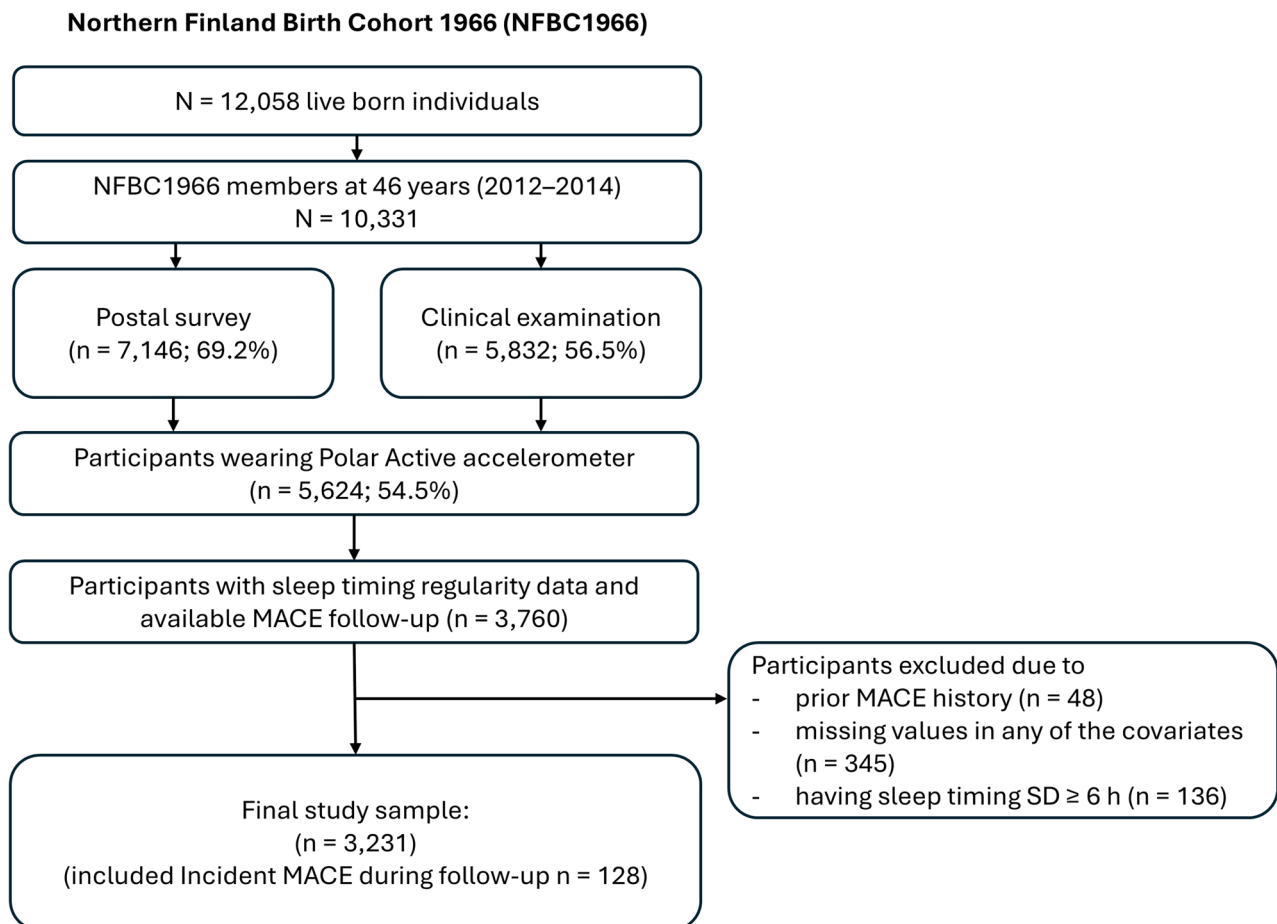
All data were analyzed using R version 4.3.1 [47]. Survival analyses were performed with the survival package, version 3.8.3, and survival plots were created with the R survminer package, version 0.5.0. Statistical significance was set at  $p < 0.05$ .

### Results

The final study sample included 3,231 middle-aged participants whose sleep regularity was measured over 7 consecutive nights, resulting in a total of 22,617 recorded

nights. During the over-10-year follow-up, 128 participants experienced a MACE. The average follow-up time was 130.1 (interquartile range (IQR) of 10.8) months. This corresponds to a cumulative incidence of 4.0% over a median follow-up of 130.1 months. The flow of participants from the original cohort to the final sample is shown in Fig. 1.

Table 1 presents the main characteristics of the study population. Covariates that indicated association with MACEs included gender (57.0% of men vs. 38.8% of females), employment status (25.8% of those unemployed vs. 17.7% of those employed). Among continuous variables, participants who experienced a MACE had higher median BMI (28.2 kg/m<sup>2</sup> vs. 25.7 kg/m<sup>2</sup>), systolic blood pressure (131.0 mmHg vs. 123.0 mmHg), glycated hemoglobin (5.6 mmol/mol vs. 5.4 mmol/mol), and LDL cholesterol levels (3.7 mmol/L vs. 3.3 mmol/L) compared to those without a MACE. Statistically significant differences in BMI and systolic blood pressure were observed between participants included in the final analyses and those excluded ( $n=393$ ) due to missing data in one or multiple covariates or a prior MACE ( $p=0.024$ ; Mann-Whitney U test) but not in other covariates (all  $p > 0.05$ ;



**Fig. 1** Participant selection and inclusion flow diagram

**Table 1** Characteristics of the study population of the Northern Finland Birth Cohort 1966 (N = 3,231)

Variable	Major adverse cardiac event or cardiovascular disease-related death			p-value
	All (N = 3, 231)	Yes (n = 128)	No (n = 3,103)	
Follow-up time, number of months	130.1 (10.8)	83.8 (84.1)	130.4 (10.5)	<b>&lt; 0.001</b>
Factors related to sleep				
Bedtime [hh: mm]	23:13 (01:24)	23:17 (01:15)	23:12 (01:24)	0.302
Wake-up time [hh: mm]	07:12 (01:18)	07:16 (01:21)	07:12 (01:18)	0.219
Midpoint of sleep period [hh: mm]	03:11 (01:13)	03:18 (01:14)	03:11 (01:13)	0.296
Sleep period duration [hh: mm]	07:56 (01:11)	07:54 (01:14)	07:56 (01:11)	0.990
Below-median sleep sleeper ( $\leq 7$ h 56 min), (n [%])	1614 (50.0)	66 (51.6)	1548 (49.9)	0.719
Bedtime regularity (n [%])				
Regular	1077 (33.3)	34 (26.6)	1043 (33.6)	
Fairly regular	1077 (33.3)	43 (33.6)	1034 (33.3)	
Irregular	1077 (33.3)	51 (39.8)	1026 (33.1)	
Wake-up time regularity (n [%])				
Regular	1077 (33.3)	33 (25.8)	1044 (33.6)	0.180
Fairly regular	1077 (33.3)	48 (37.5)	1029 (33.2)	
Irregular	1077 (33.3)	47 (36.7)	1030 (33.2)	
Midpoint regularity (n [%])				
Regular	1077 (33.3)	32 (25.0)	1045 (33.7)	0.067
Fairly regular	1077 (33.3)	43 (33.6)	1034 (33.3)	
Irregular	1077 (33.3)	53 (41.4)	1024 (33.0)	
Chronotype (n [%])				
Morning-type	1322 (40.9)	56 (43.0)	1266 (40.8)	0.775
Day-type	1733 (53.6)	66 (51.9)	1667 (53.7)	
Evening-type	176 (5.4)	6 (5.2)	170 (5.5)	
Work schedule (n [%])				
Day work	2121 (65.6)	77 (60.2)	2044 (65.9)	0.066
Shift work with night shifts	527 (16.3)	18 (14.1)	509 (16.4)	
Not working/no information available	583 (18.0)	33 (25.8)	550 (17.7)	
Sociodemographic and lifestyle factors				
Male (n [%])	1277 (39.5)	73 (57.0)	1204 (38.8)	<b>&lt; 0.001</b>
High education (n [%])	871 (28.9)	34 (28.8)	837 (28.9)	1.000
Employed (n [%])	2648 (82.0)	95 (74.2)	2553 (82.3)	<b>0.025</b>
Marital status: living alone (n [%])	721 (22.4)	37 (28.9)	685 (22.1)	0.083
Current smoker (n [%])	688 (21.3)	32 (25.0)	656 (21.1)	0.321
Heavy alcohol drinkers* (n [%])	249 (7.7)	11 (8.5)	238 (7.7)	0.736
Total physical activity [MET min/day]	1056.0 (415.5)	1017.9 (464.9)	1056.8 (413.3)	0.058
Sedentary time [min/day]	580.2 (121.6)	596.3 (125.5)	579.7 (121.3)	0.294
Cardiovascular risk factors				
BMI [kg/m <sup>2</sup> ]	25.8 (6.0)	28.2 (6.5)	25.7 (5.9)	<b>&lt; 0.001</b>
Systolic blood pressure [mmHg]	123.3 (20.7)	131.0 (19.0)	123.0 (20.3)	<b>&lt; 0.001</b>
Glycated hemoglobin [mmol/mol]	5.5 (0.5)	5.6 (0.6)	5.4 (0.5)	<b>&lt; 0.001</b>
Low-density lipoprotein cholesterol [mmol/L]	3.4 (1.2)	3.7 (1.5)	3.3 (1.2)	<b>&lt; 0.001</b>

The table presents the characteristics of the study population, stratified by the occurrence of major adverse cardiac events (MACE) or cardiovascular disease (CVD)-related death during the follow-up period from 2012 until the end of 2023. The data are shown separately for participants who experienced a cardiovascular event or death and those who did not. Values are presented as median with interquartile range (IQR), unless otherwise specified. The variables include demographic factors, lifestyle behaviors, clinical measurements, and relevant biomarkers. Statistically significant results ( $p < 0.05$ ) are shown in bold. \*Heavy alcohol drinkers: men  $\geq 40$  g/day; women  $\geq 20$  g/day [31]

Mann-Whitney U and chi-square tests, data not shown). There were no statistically significant differences in median bedtime, wake-up time, sleep midpoint, or time in bed between participants who experienced a MACE and those who did not. Similarly, the distribution of sleep

timing regularity categories did not differ significantly between the groups.

Median variability values for sleep timing across regularity groups were as follows (Table 1). For bedtime

regularity, the median variability was 33 min (IQR 13) in the regular group, 59 min (IQR 15) in the fairly regular group, and 108 min (IQR 55) in the irregular group. For wake-up time regularity, the corresponding values were 41 min (IQR 19), 73 min (IQR 15), and 114 min (IQR 41), respectively. For the sleep midpoint regularity, the median variability was 33 min (IQR 13) in the regular group, 55 min (IQR 11) in the fairly regular group, and 93 min (IQR 40) in the irregular group.

Table 2 presents HRs with 95% CIs, standard errors, and p-values for MACEs in relation to sleep period regularity variables (bedtime, wake-up time, and midpoint regularity). In participants with the below-median sleep periods ( $\leq 7$  h 56 min), irregular bedtime regularity was associated with an increased risk of MACEs compared to regular bedtime (adjusted HR = 2.01, 95% CI: 1.00–4.01,  $p = 0.049$ ). Similarly, irregular midpoint regularity was linked to a higher risk of experiencing a MACE (adjusted HR = 2.00, 95% CI: 1.01–3.98,  $p = 0.048$ ). No significant associations were observed for wake-up time regularity or among participants in the above-median sleeper group ( $> 7$  h 56 min). The results are also presented as forest plots in Fig. 2, which visualizes the HRs and 95% CIs across categories of regularity based on both univariate and adjusted Cox models. The figure highlights the increased risk associated with irregular bedtime and sleep midpoint compared to the reference group, observed only among participants in the below-median sleeper group ( $\leq 7$  h 56 min).

The results of the sensitivity analyses supported the robustness of our findings. First, excluding 12 participants with early MACE events within the first 2 years

yielded result's similar to those observed in the full sample (data not shown). Second, excluding 527 shift workers, it yielded results comparable to those observed in the full sample. In the below-median sleeper group, irregular bedtime was associated with a higher risk of a MACE compared to regular bedtime (adjusted HR = 2.29, 95% CI: 1.02–5.12,  $p = 0.044$ ). Likewise, greater variability in sleep midpoint was linked to increased risk of a MACE (adjusted HR = 2.25, 95% CI: 1.01–5.01,  $p = 0.047$ ). (Table 3).

Figure 3 shows individual Kaplan–Meier survival curves for the below-median and above-median sleeper groups to examine the association between sleep regularity and survival. Among below-median sleepers ( $\leq 7$  h 56 min), significant group differences were observed in bedtime regularity ( $p = 0.036$ ) and midpoint regularity ( $p = 0.048$ ). In both cases, the survival curve for the irregular group declined earlier and more steeply compared to the regular and fairly regular groups.

### Discussion

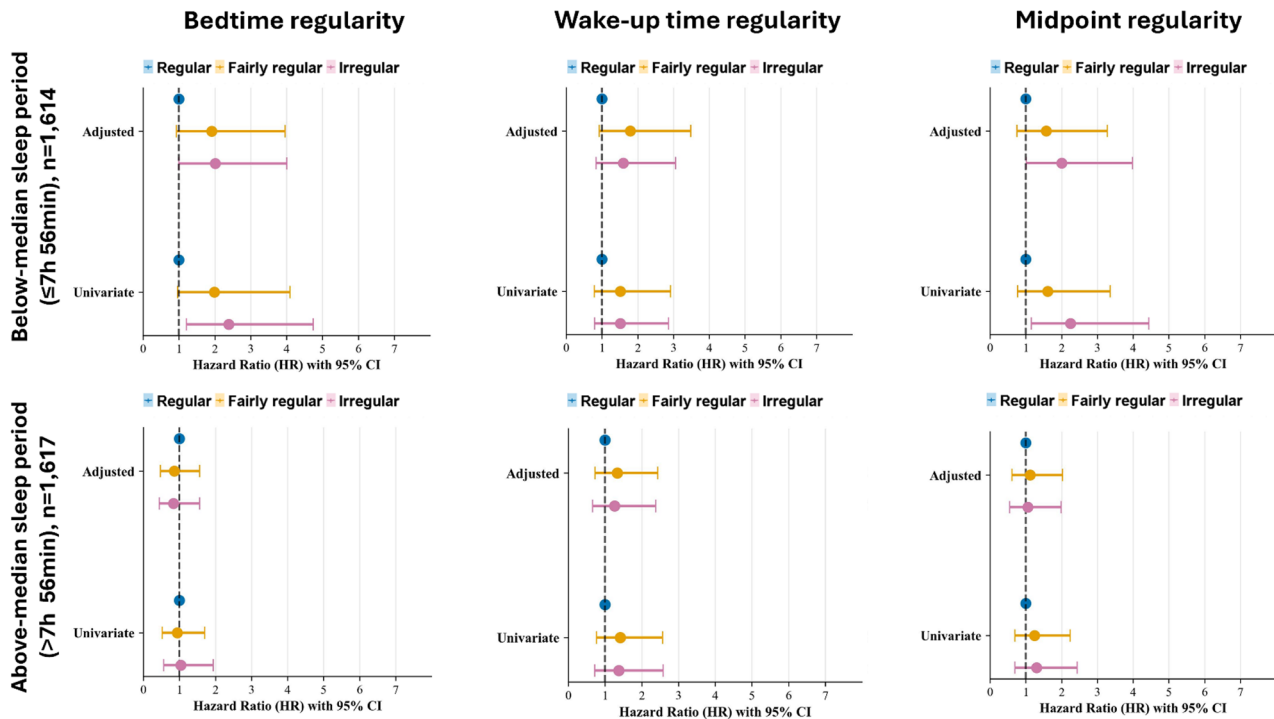
This population-based study examined the relationship between sleep timing regularity and the risk of MACEs over a 10-year follow-up period among 3,231 middle-aged adults. Average sleep timing and duration were not statistically different between those who experienced an event and those who did not. Conversely, irregular sleep patterns were associated with increased cardiovascular risk among participants with below-median sleep periods ( $\leq 7$  h 56 min). In this subgroup, individuals with irregular bedtimes or sleep midpoints had a twofold higher risk

**Table 2** Hazard ratios for major adverse cardiac events by sleep regularity and sleep period duration

Variable	Bedtime regularity			Wake-up time regularity			Midpoint regularity		
	HR (95% CI)	SE	p-value	HR (95% CI)	SE	p-value	HR (95% CI)	SE	p-value
Below-median sleep period ( $\leq 7$ h 56 min), $n = 1,614$									
Univariate model									
Fairly regular vs. Regular	1.99 (0.96–4.10)	0.37	0.063	1.51 (0.78–2.92)	0.34	0.221	1.61 (0.77–3.36)	0.38	0.205
Irregular vs. Regular	<b>2.39 (1.21–4.74)</b>	<b>0.35</b>	<b>0.012</b>	1.51 (0.79–2.86)	0.33	0.211	<b>2.25 (1.15–4.44)</b>	<b>0.34</b>	<b>0.019</b>
Adjusted model									
Fairly regular vs. Regular	1.91 (0.93–3.96)	0.37	0.079	1.79 (0.92–3.48)	0.34	0.088	1.57 (0.75–3.28)	0.38	0.231
Irregular vs. Regular	<b>2.01 (1.00–4.01)</b>	<b>0.35</b>	<b>0.049</b>	1.59 (0.83–3.06)	0.33	0.163	<b>2.00 (1.01–3.98)</b>	<b>0.35</b>	<b>0.048</b>
Above-median sleep period ( $> 7$ h 56 min), $n = 1,617$									
Univariate model									
Fairly regular vs. Regular	0.94 (0.52–1.70)	0.30	0.838	1.41 (0.77–2.57)	0.31	0.266	1.24 (0.69–2.24)	0.30	0.478
Irregular vs. Regular	1.04 (0.56–1.94)	0.31	0.890	1.37 (0.72–2.58)	0.32	0.334	1.30 (0.69–2.44)	0.32	0.412
Adjusted model									
Fairly regular vs. Regular	0.86 (0.47–1.56)	0.30	0.623	1.33 (0.73–2.44)	0.31	0.352	1.12 (0.61–2.03)	0.31	0.719
Irregular vs. Regular	0.83 (0.44–1.56)	0.33	0.555	1.26 (0.66–2.38)	0.33	0.487	1.05 (0.55–1.99)	0.33	0.884

Hazard ratios (HR) with 95% confidence intervals (CIs), standard errors (SEs), and p-values are presented for major adverse cardiac events and cardiovascular disease mortality in relation to 3 sleep period regularity variables: bedtime regularity, wake-up time regularity, and midpoint regularity. Analyses were conducted separately for participants with sleep period durations equal to or below and above the median value of 7 h 56 min ( $N = 3,231$ ). Statistically significant results ( $p < 0.05$ ) are shown in bold. The model was adjusted for gender (male/female), employment status (employed/unemployed), body mass index ( $\text{kg}/\text{m}^2$ ), systolic blood pressure (mmHg), low-density lipoprotein cholesterol (mmol/L), glycosylated hemoglobin (mmol/mol), and total physical activity (MET min/day)

Abbreviations HR hazard ratio, SE standard error, CI confidence interval



**Fig. 2** Hazard ratios for sleep regularity by sleep period duration. Forest plots showing hazard ratios (95% CI) for sleep regularity categories, with “regular” serving as the reference group. Results are presented separately for participants with the below-median sleep periods (≤ 7 h 56 min) and with the above-median sleep periods (> 7 h 56 min). Adjusted models included the following covariates: gender, employment status, BMI, systolic blood pressure, low-density lipoprotein cholesterol, and total physical activity. Data came from the Northern Finland Birth Cohort 1966 (N = 3,231)

**Table 3** Hazard ratios for major adverse cardiac events by sleep regularity (shift workers excluded)

Variable	Bedtime regularity			Wake-up time regularity			Midpoint regularity		
	HR (95% CI)	SE	p-value	HR (95% CI)	SE	p-value	HR (95% CI)	SE	p-value
Below-median sleep period (≤ 7 h 56 min), n = 1,310									
Univariate model									
Fairly regular vs. Regular	1.72 (0.72–4.10)	0.44	0.221	1.33 (0.62–2.84)	0.39	0.462	1.62 (0.68–3.86)	0.44	0.278
Irregular vs. Regular	<b>2.71 (1.23–5.98)</b>	<b>0.40</b>	<b>0.013</b>	1.43 (0.69–2.97)	0.37	0.333	<b>2.46 (1.12–5.42)</b>	<b>0.40</b>	<b>0.025</b>
Adjusted model									
Fairly regular vs. Regular	1.64 (0.68–3.93)	0.45	0.267	1.60 (0.74–3.44)	0.39	0.231	1.59 (0.66–3.79)	0.44	0.300
Irregular vs. Regular	<b>2.29 (1.02–5.12)</b>	<b>0.41</b>	<b>0.044</b>	1.54 (0.73–3.24)	0.38	0.256	<b>2.25 (1.01–5.01)</b>	<b>0.41</b>	<b>0.047</b>
Above-median sleep period (> 7 h 56 min), n = 1,338									
Univariate model									
Fairly regular vs. Regular	1.05 (0.52–2.16)	0.37	0.886	1.66 (0.82–3.36)	0.36	0.161	1.67 (0.83–3.38)	0.36	0.154
Irregular vs. Regular	1.43 (0.71–2.90)	0.36	0.317	1.53 (0.72–3.25)	0.39	0.271	1.67 (0.78–3.55)	0.39	0.183
Adjusted model									
Fairly regular vs. Regular	0.92 (0.45–1.90)	0.37	0.831	1.51 (0.74–3.08)	0.36	0.256	1.45 (0.71–2.96)	0.37	0.314
Irregular vs. Regular	1.04 (0.50–2.16)	0.37	0.917	1.40 (0.65–3.01)	0.39	0.387	1.26 (0.58–2.73)	0.39	0.557

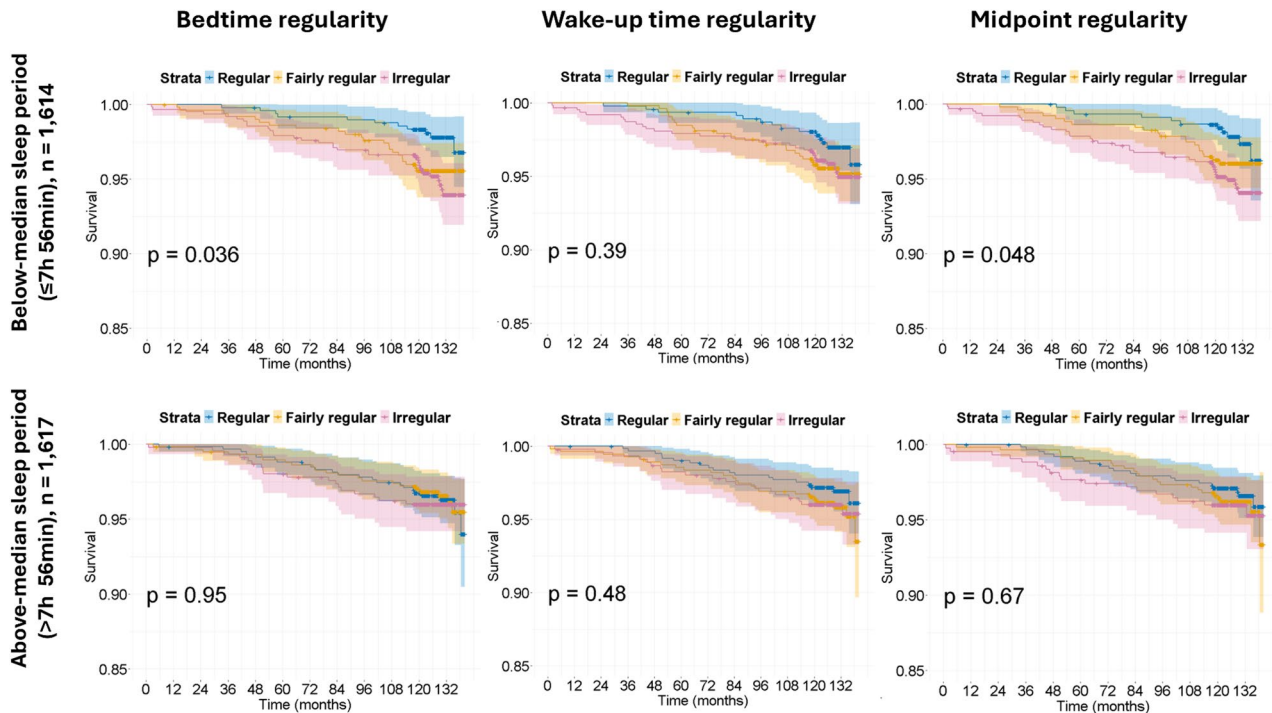
Hazard ratios (HRs) with 95% confidence intervals (CIs), standard errors (SEs), and p-values are presented for major adverse cardiac events and cardiovascular disease mortality in relation to 3 sleep period regularity variables: bedtime regularity, wake-up time regularity, and midpoint regularity. Analyses were conducted separately for participants with sleep period durations equal to or below and above the median value of 7 h 56 min. Shift workers were excluded from the analysis (n = 2,648). Statistically significant results at the level of  $p < 0.05$  are shown in bold. The model was adjusted for gender (male/female), employment status (employed/unemployed), body mass index (kg/m<sup>2</sup>), systolic blood pressure (mmHg), low-density lipoprotein cholesterol (mmol/L), glycated hemoglobin (mmol/mol), and total physical activity (MET min/day)

Abbreviations HR hazard ratio, SE standard error, CI confidence interval

of experiencing a MACE compared to those with regular bedtimes or regular sleep midpoints. These associations remained statistically significant even after adjusting for other known CVD risk factors, such as BMI, systolic

blood pressure, cholesterol levels, glycated hemoglobin levels, employment status, and physical activity.

Our study differs from previous research examining the association between sleep timing regularity and MACEs



**Fig. 3** Kaplan–Meier survival curves by sleep regularity and sleep duration. Kaplan–Meier survival curves with p-values and number-at-risk tables are shown, stratified by sleep regularity tertiles, categorized as regular, fairly regular, and irregular. Figures are presented separately for participants with the below-median sleep periods ( $\leq 7$  h 56 min) and the above-median sleep periods ( $> 7$  h 56 min). Data came from the Northern Finland Birth Cohort 1966 ( $N=3,231$ ), with sleep regularity assessed at midlife. Participants were followed for over 10 years for major adverse cardiac events and cardiovascular disease mortality. Adjusted models included the following covariates: gender, employment status, BMI, systolic blood pressure, low-density lipoprotein cholesterol, and total physical activity

in a crucial way: namely, in how sleep regularity was operationalized. Similar to our study, previous studies have often used accelerometer-measured sleep, but these prior studies used composite indices like the Sleep Regularity Index [5, 26, 48, 49] or sleep duration variability to operationalize sleep regularity [21]. Some studies have further included sleep onset variability with sleep duration variability [17, 24]. While the findings of those studies have collectively highlighted the importance of sleep regularity, they have not specifically emphasized the full set of behaviorally interpretable sleep variables, such as the regularity of initiating and ending one’s sleep period, which may be more actionable from a public health and behavioral intervention perspective. Our study further contributes to this field through its examination of bedtime regularity, wake-up time regularity, and midpoint regularity as distinct behavioral dimensions of sleep timing.

Notably, higher variability in bedtime and sleep midpoint was linked to increased MACE risk among short sleepers, consistent with prior research showing that irregular sleep onset timing and duration is linked with elevated cardiovascular risk [24]. The twofold risk observed in our study between participants with regular and irregular bedtime variability was comparable to

previous findings based on a 7-day accelerometer measurement period, where sleep onset variability  $> 90$  min was associated with more than double the risk of experiencing a CVD event compared to a variability of  $\leq 30$  min over a median follow-up of 4.9 years. Similarly, although derived using a different methodological approach, our findings align with results of previous studies computing the Sleep Regularity Index from wearable accelerometer data, with these studies also demonstrating that higher sleep irregularity is associated with increased risk of a MACE over a mean follow-up of 7.8 years [48].

On the other hand, wake-up time variability was not associated with MACE incidence in participants with either below- or above-than-median sleep period durations. This finding suggests that wake-up time regularity, unlike bedtime or sleep midpoint, may not be a predictor of cardiovascular events. This finding is noteworthy: Despite growing interest in sleep regularity and its health implications, recent large-scale investigations have not specifically examined whether regularity in wake-up time is associated with MACE incidence [50, 51]. However, previous findings have suggested that individuals who report waking up either very early ( $\leq 5$  AM) or late ( $> 7$  AM) may have a higher prevalence of hypertension compared to those whose wake-up times fall between

5 AM and 6 AM [52]. Similar to the findings produced herein, a population study using questionnaire data did not observe a significant link between wake-up time and cardiovascular mortality, although late bedtimes and delayed sleep midpoint were associated with higher mortality risk [51].

Although there is a scarcity of research examining the associations of wake-up time with CVD risk, several large-scale studies have observed that both earlier and later bedtimes (typically defined as before 10 PM or after midnight) may be associated with modestly elevated risks of all-cause and cardiovascular mortality, particularly when compared to bedtimes between 10 PM and midnight [51–53]. A delayed sleep midpoint (typically defined after 3 AM or 4 AM) has also been linked to increased all-cause mortality [51] and hypertension risk [52]. Our findings on timing regularity align with these associations with bedtime and midpoint, indicating that both timing and consistency may contribute to cardiovascular risk. As the human circadian system regulates sleep within a 24-hour rest-activity cycle [1], it is possible that maintaining consistent sleep-onset timing may be more critical for supporting sleep quality and cardiovascular recovery than consistent wake-up time alone. Future research should clarify how both the regularity and timing of bedtime and wake-up time contribute to cardiovascular risk.

No significant associations were observed between sleep timing regularity and MACE incidence among participants with sleep period durations above the sample median. This finding contrasts with that of a recent prospective study using device-measured sleep data, which found that irregular sleep was associated with elevated MACE risk, even among individuals who met sleep duration recommendations. Specifically, sufficient sleep duration did not offset the increased risk among irregular sleepers, whereas moderately irregular sleepers appeared to benefit from longer sleep [48]. A recent study from the Multi-Ethnic Study of Atherosclerosis further supported this finding, showing that objectively measured regular sleep and sufficient duration were associated with a 39%–42% lower mortality hazard compared with irregular and insufficient sleep, independent of sleep disorders and comorbidities [6]. These findings suggest that sleep regularity may play a more critical role than sleep duration in cardiovascular health, possibly due to its influence on circadian alignment and physiological recovery processes [54]. In addition, these findings support the view that adequate sleep is a vital component of healthy sleep behavior and may contribute to physiological recovery and resilience against the adverse effects of circadian irregularity. Nonetheless, further research is needed to clarify these mechanisms and their clinical relevance.

After excluding shift workers, we observed an even more pronounced detrimental association between irregular bedtime and sleep periods and the resulting outcomes. This finding suggests that shift work is not the sole factor shaping sleep behavior. In the present study, a notably high proportion of participants who had MACE events or CVD-related deaths (24.4%) were unemployed or had missing employment data compared to the non-MACE group (17.7%). Relatedly, a recent study has shown that unemployment is independently associated with increased cardiovascular mortality, particularly among vulnerable subgroups such as middle-aged women and the elderly [55]. In particular, associated mental health challenges may contribute to irregular sleep behavior, which in turn can impact cardiovascular health. Indeed, this relationship is somewhat cyclical: Insomnia increases the risk of depression and anxiety, while psychiatric conditions can disrupt sleep patterns [56]. These findings underscore the need to consider broader psychosocial factors, such as unemployment, stress, mental health, and their interactions in understanding the links between sleep behavior regularity and cardiometabolic health.

A major strength of this large-scale population-based study is its comprehensive assessment of sleep timing regularity, including bedtime, wake-up time, and sleep midpoint, in addition to daytime activity behaviors. Another strength of this study stems from its use of comprehensive national health register data, which enabled accurate follow-up regarding cardiovascular events. Unlike many previous studies that have focused specifically on shift workers, our study demographic represents the general middle-aged population across a wide range of socioeconomic and occupational backgrounds, and all participants followed a standardized study protocol. Additionally, despite the length of the study period, moving abroad within the first years of the study proved to be only a minor issue, with only 4 participants doing so. To our knowledge, this is the first population-based study of middle-aged people to study behavioral sleep regularity among a middle-aged population to incorporate an over-10-year follow-up.

This study also has some limitations. The cumulative incidence of MACE (4.0%) over about 10-year was comparable to that reported in other population-based cohorts of adults [21, 24]. Given the relatively young baseline age, a modest event rate was expected. Although 128 events permitted multivariable analyses, the limited number may have reduced the precision of effect estimates, particularly in stratified analyses. The analyses were based on a complete-case approach, and although the proportion of missing data was modest, some degree of selection bias cannot be entirely excluded. Although reverse causality cannot be entirely excluded, removing early events ( $n = 12$ ) did not change the results. The study

sample was homogenous regarding participants' age and ethnicity, which may limit the generalizability of the findings to more diverse populations with different sociodemographic or cultural sleep patterns. Additionally, the methodological limitations of accelerometer-estimated sleep schedules should be acknowledged. Sleep regularity was assessed based on a 7-day consecutive measurement period, which could be considered a relatively short time frame for capturing habitual sleep behavior—though, as mentioned above, previous research has indicated that five to six nights may be sufficient for reliable estimation of habitual sleep [37]. While the mean follow-up duration in this study was 10.8 years, extending the follow-up could increase the number of observed cases. Lastly, due to the potential U-shaped association between sleep duration and cardiovascular outcomes [57], a categorization into < 7 h, 7–9 h (recommended), and > 9 h would have been appropriate [58], but we did not apply this due to the small number of events, which may have limited our ability to fully explore the role of sleep duration in these associations.

## Conclusion

Our findings suggest an association between the variability in bedtime and sleep midpoint and cardiovascular risk, particularly among individuals with below the sample median sleep period duration which was approximately 8 h. Of note, irregular sleep timing was not associated with survival risk when the sleep period exceeded 8 h, indicating that sufficient sleep may offer partial protection regardless of the regularity of sleep timing. Taken together, these results emphasize that consistent sleep behavior, particularly regular bedtimes, should be considered in health promotion to reduce cardiovascular risks.

## Abbreviations

BMI	Body mass index
CVD	Cardiovascular disease
HR	Hazard ratio
MACE	Major adverse cardiac event
SE	Standard error
SD	Standard deviation

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12872-026-05762-4>.

Supplementary Material 1.

Supplementary Material 2.

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## Authors' contributions

LN, MN, RK, and VF participated in the literature search; LN, MN, and VF designed the study; LN, MN, RK, and VF collected the data; LN and MN collected the MACE events and information of CVD related deaths from Finnish registers; LN performed the data analysis; SA performed forest plot figures; LN, MN, RK, and VF interpreted the data; and LN, MN, RK, and VF wrote this manuscript. All the authors read and approved the final manuscript.

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## Data availability

NFBC data is available from the University of Oulu, Infrastructure for Population Studies. Permission to use the data can be applied for research purposes via electronic material request portal. In the use of data, we follow the EU general data protection regulation (679/2016) and Finnish Data Protection Act. The use of personal data is based on cohort participant's written informed consent at his/her latest follow-up study, which may cause limitations to its use. Please, contact NFBC project center (NFBCprojectcenter(at)oulu.fi) and visit the cohort website for more information.

## Declarations

### Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. The 46-year follow-up study was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District in Oulu, Finland (94/2011). The participants and their parents provided written consent for the 1966 study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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