diabetesresearchandclinicalpractice197(2023)110262

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Association of circadian rest-activity rhythms with cardiovascular disease and mortality in type 2 diabetes

Lulu Yang [a,1], Hongliang Feng [a,b,1], Jie Chen [b], Yun Kwok Wing [b], Christian Benedict [c], Xiao Tan [d,e,*], Jihui Zhang [f,g,h,i,*]

[a] Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China
[b] Li Chiu Kong Family Sleep Assessment Unit, Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region
[c] Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden
[d] Department of Big Data in Health Science, Zhejiang University School of Public, Health and Department of Psychiatry, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China
[e] Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[f] Center for Sleep and Circadian Medicine, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China
[g] Guangdong Mental Health Center, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China
[h] Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region
[i] Key Laboratory of Neurogenetics and Channelopathies of Guangdong Province and the Ministry of Education of China, Guangzhou Medical University, Guangzhou, China

ARTICLE INFO

Keywords:
Circadian rhythm
Type 2 Diabetes
Cardiovascular disease
Mortality

ABSTRACT

Aims: To examine the associations of disrupted circadian rest-activity rhythm (CRAR) with cardiovascular diseases and mortality among people with type 2 diabetes.
Methods: A total of 3147 participants with baseline type 2 diabetes (mean age 65.21 years, 39.78% female; mean HbA1c 50.02 mmol/mol) from UK Biobank were included. The following CRAR parameters were derived from acceleration data: interdaily stability (IS), intradaily variability (IV), relative amplitude (RA), most active 10 h period onset (M10 onset), and least active 5 h period onset (L5 onset). We used Cox proportional hazards models to estimate the associations of CRAR with cardiovascular diseases and mortality, adjusting for sociodemographic, lifestyle, and health characteristics.
Results: Participants in the lowest quartile of IS and RA exhibited the greatest risk of developing cardiovascular disease (IS, hazard ratio $[HR]_{Q1\ vs.\ Q4}$ 1.40 [95% confidence interval (CI) 1.04, 1.88]; RA, $HR_{Q1\ vs.\ Q4}$ 2.45 [95% CI 1.73, 3.49]). However, the association between delayed L5 onset and cardiovascular disease risk did not reach statistical significance. Additionally, we found that high IV and low RA were associated with all-cause and cardiovascular mortality.
Conclusion: Objectively determined CRAR disturbances may increase the risk of cardiovascular diseases and mortality among people with type 2 diabetes.

1. Introduction

Growing evidence from the general population has linked circadian rhythm and its manifestations with cardiometabolic health [1]. Experimental studies in humans have found that circadian disruptions impair glucose regulation and increase inflammation [2,3], with potential relevance to cardiovascular disease (CVD) [4]. Epidemiological studies have demonstrated that circadian disruptions such as shift work are significantly associated with an increased risk of type 2 diabetes and cardiovascular events [5,6]. Recently, a cross-sectional study among 52

* Corresponding authors at: Department of Big Data in Health Science, Zhejiang University School of Public Health and Department of Psychiatry, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China (X. Tan). Center for Sleep and Circadian Medicine, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China; or Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region (J. Zhang).
E-mail addresses: xiao.tan@zju.edu.cn (X. Tan), jihui.zhang@cuhk.edu.hk (J. Zhang).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.diabres.2023.110262
Received 27 October 2022; Received in revised form 30 December 2022; Accepted 17 January 2023
Available online 20 January 2023

adults further found that objectively measured circadian rest-activity rhythms were associated with indices of cardiometabolic health (e.g., fasting lipids, C-reactive protein) [7]. Moreover, results from the Multi-Ethnic Study of Atherosclerosis with a 5-year follow-up demonstrated that high day-to-day stability in sleep duration or timing may be novel risk factors for CVD [8]. However, most previous studies have several limitations including being in a non-free-living environment, potential misclassification due to crude measures of exposures, small sample size, cross-sectional nature of the data, and limited metrics of circadian rhythm. In particular, despite the fact that a disrupted circadian rhythm is particularly common among the population with type 2 diabetes [9], prospective high-quality and comprehensive evidence focusing on the associations of objectively determined circadian rhythm disruption with cardiovascular outcomes and mortality in this population is scarce.

The accelerometer is an objective and ambulatory monitoring method for assessing circadian rest-activity rhythm (CRAR), which is the most evident manifestation of circadian rhythm in humans [10–12]. The nonparametric method developed by van Someren et al. for quantifying the CRAR has been used widely [13,14], and the metrics mainly include interdaily stability (IS), intradaily variability (IV), relative amplitude (RA), the least active 5 continuous hours onset (L5 onset), and the most active 10 continuous hours onset (M10 onset). IS stands for the stability of rhythm and a higher IS indicates good synchronization to light and other environmental cues that regulate the biological clock. The IV reflects the fragmentation of the rhythm, and a higher IV would be observed among those who often nap during the daytime and are more frequently awake during the night. The RA is the robustness of rhythm and higher RA reflects increased daytime activity, or more restful sleep, or both. The L5 onset reflects the timing of sleep onset and M10 onset indicates whether a person is most active earlier or later in the day. Disruption of CRAR is characterized by low interdaily stability, high intradaily variability, low relative amplitude, or phase advance or delay.

The UK Biobank is a prospective cohort study and has collected a large objective physical activity dataset to date using wrist-worn accelerometers with links to health records in the UK, which provides an ideal opportunity for us to investigate the circadian rhythm disruption and health risk among the population with type 2 diabetes. Therefore, to address the aforementioned gaps in the literature, we aimed to examine the associations of accelerometer-derived CRAR with the risks of CVD and mortality among people with type 2 diabetes in the UK Biobank over 8.3 years of follow-up.

2. Materials and methods

2.1. Participants and setting

The UK Biobank is a prospective study that recruited over 500 000 participants aged 40 to 73 years between 2006 and 2010 from across the UK. Between 2013 and 2015, data from a subsample of 103 712 participants who wore an Axivity AX3 triaxial accelerometer on their dominant wrist were collected [15]. The UK Biobank accelerometer expert working group conducted data processing and generated physical activity intensity data for 103 682 participants. We excluded participants whose accelerometer data were flagged as being unreliable, or those with accelerometer data for less than 72 h or did not provide data for all 1-h periods within a 24-h cycle. We also excluded those data identified as not well-calibrated, or those data were recalibrated using the previous accelerometer record from the same device worn by a different participant, or those data with a non-zero count of interrupted recording periods, or those data with more than 768 (Q3 + 1.5×IQR) data recording errors. In the current study, 92 614 participants whose data passed quality control were available, among whom 3940 were identified as having probable type 2 diabetes before wearing the accelerometer. Participants were classified as having type 2 diabetes whenever one of three criteria was met: 1) type 2 diabetes indicated by using a validated algorithm [16] based on self-reported disease, medication, and a diagnosis of type 2 diabetes noted in the medical history. 2) HbA1c level ≥48 mmol/mol. 3) Non-insulin-dependent diabetes mellitus diagnoses (International Classification of Diseases, 10th revision (ICD-10) codes E11) were obtained through the linked hospital admission data. Individuals with probable or possible type 1 diabetes or gestational diabetes mellitus identified by the aforementioned algorithm were excluded from the analysis. In addition, we excluded those who had CVD before wearing the accelerometer. A flowchart of participant selection is shown in Supplemental Fig. S1.

The UK Biobank received ethical approval from the NHS (National Health Service) National Research Ethics Service (Ref11/NW/0382). All participants provided written informed consent before enrollment in the study.

2.2. Ascertainment of exposures

Nonparametric models were utilized to estimate the following CRAR parameters from activity intensity data as these are thought to better represent the non-sinusoidal form of the rhythm among older adults [17]. These CRAR parameters: (1) IS, an estimate of the stability/synchronization of the rhythm, wherein 1 signifies a perfect synchronization to the light-dark cycle; (2) IV, an estimate of the fragmentation of the rhythm, where a higher IV indicates a more fragmented rhythm; (3) RA, reflecting the difference between the least and most active periods during the day, hence a higher RA represents a stronger circadian rhythm. (4) L5 onset indicates the phase markers of circadian function corresponding to the offset of activity. (5) M10 onset indicates the phase markers of circadian function corresponding to the onset of activity.

Similar to a previous study [18], IS, IV, and RA were examined based on quartile distributions. Considering the potential U-shaped associations observed and sufficient sample size across the categories, L5 onset, and M10 onset were examined in terms of deviation from the population mean (L5 onset: 01:00 AM, M10 onset: 8:34 AM). “Advanced” participants were defined as having an L5 onset or M10 onset of < -0.5 standard deviations (SD) from the mean (L5 onset: <00:20 AM, M10 onset: <7:49 AM), and “Delayed” participants were defined as having an L5 onset or M10 onset of > +0.5 SD from the mean (L5 onset: >01:41 AM, M10 onset: >9:20 AM). Participants in the reference category had an L5 onset or M10 onset within 0.5 SD of the mean (L5 onset: 00:20 AM-01:41 AM; M10 onset: 7:49 AM-9:20 AM).

2.3. Ascertainment of outcomes

The primary outcome was the incident CVD as IHD and stroke. The secondary outcomes were the incident ischemic heart disease (IHD) and mortality from all-cause and CVD. The incident stroke was not included in the analyses due to its evidently insufficient events according to the rule-of-thumb estimation [19]. The incident CVD events were defined with the ICD-10 codes on the hospital or death records: I20-I25 (angina pectoris; acute myocardial infarction; subsequent myocardial infarction; certain current complications following acute myocardial infarction; other acute ischemic heart diseases; chronic ischemic heart disease) and I60-I64 (subarachnoid hemorrhage; intracerebral hemorrhage; other nontraumatic intracranial hemorrhage; cerebral infarction; stroke, not specified as hemorrhage or infarction). The IHD events were defined as hospital admission or death with the following ICD-10 codes: I20-25. The CVD mortality was defined using the following ICD-10 codes: I00-I99. The date and cause of hospital admissions were obtained through record linkage to health episode statistics (England and Wales) and Scottish morbidity records (Scotland). The date and cause of death were obtained from death certificates held within the NHS Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). At the time of analysis, data were available to September 30, 2021, and we censored the incident events at this date or the date of event in question or death, whichever occurred first.

2.4. Ascertainment of covariates

Age was calculated from the date of birth and accelerometer wear. Sex, ethnic origin, Townsend deprivation index, region, educational level, smoking status, frequency of alcohol intake, and diet-related factors were obtained from touchscreen questions at the time-point closest to the accelerometer. The healthy diet score was calculated using the following factors: vegetable intake at least four tablespoons each day (median); fruits intake at least three pieces each day (median); fish intake at least twice a week (median); unprocessed red meat intake no more than twice a week (median); and processed meat intake no more than twice a week (median). One point was given for each favorable diet factor, with total diet score ranging from 0 to 5. Season when the accelerometer started, sleep duration, and duration of moderate to vigorous physical activity recorded by the accelerometer were included.

2.5. Statistical analyses

To minimize the potential for inferential bias and to maximize the statistical power possible, we conducted multiple imputations to assign any missing covariate values by using the "mice" R package, assuming data were conditionally missing at random. Detailed information on the missing covariates is provided in Supplemental Table S1. Baseline characteristics are presented as number (%) for categorical variables and as the mean ± SD or median [interquartile range] for continuous variables.

Cox proportional hazard regression, with time since accelerometer wearing time as the start of follow-up, was used to model the associations of CRAR with cardiovascular outcomes and mortality, excluding participants with CVD at baseline. The proportionality of hazards assumption was assessed using the Schoenfeld residuals technique and no violation of the assumption was found. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were calculated. The basic model examined the associations of CRAR with multiple outcomes, adjusting for age and sex. Model 2 additionally adjusted for ethnic origin, Townsend deprivation index, recruitment center, education level, and season of accelerometer wear. Model 3 adjusted for these covariates in addition to healthy diet score, smoking status, and alcohol intake. Model 4 adjusted all the covariates in Model 3, in addition to sleep duration and duration of moderate to vigorous physical activity, to examine whether the associations were independent of sleep and physical activity. Collinearity between all covariates included in the analyses was examined using correlation matrix analysis, which revealed no problem of multicollinearity. In addition, we used restricted cubic splines with three knots (percentile 10, 50, 90) to assess the possible linear and non-linear associations between CRAR parameters and multiple outcomes.

Furthermore, we performed five sensitivity analyses to investigate potential sources of bias in our primary results of the associations between CRAR parameters and CVD incidence. First, to interrogate the potential bias from competing risks, Fine-Gray subdistribution hazards were calculated, incorporating death as a competing risk for the incidence of CVD. Second, we restricted the analyses to participants without missing covariate. Third, we excluded events that occurred within the first year of follow-up. Fourth, we excluded those reporting a history of shift work, which were collected by touchscreen questionnaires and online follow-up questionnaires. Fifth, we additionally adjusted for health-related variables potentially on the causal pathway [18,20], including HbA1c, systolic blood pressure, obesity, insomnia, longstanding illness, blood glucose-lowering medications, blood pressure-lowering medications, and cholesterol-lowering medications.

To test the robustness and potential variations in sex subgroups, we repeated the main analyses stratified by sex (Female/Male). All statistical analyses were conducted by using the R software version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS 26.0 (SPSS Inc. Chicago, IL, USA). All statistical tests were two-sided, and a P value of less than 0.05 was regarded as statistically significant.

3. Results

3.1. Characteristics of the study population

Of 3940 individuals with probable type 2 diabetes, 793 were excluded because they were diagnosed with CVD before wearing the accelerometer, leaving 3147 participants for the main analyses (Supplemental Fig. S1). During a follow-up of 8.33 years, 390 participants (12.39%) developed CVD, and 341(10.84%) developed IHD. In addition, 251(7.98%) died from all-cause and 110 (3.50%) died from CVD.

The baseline characteristics of the study population according to the CVD incidence are shown in Table 1. The mean (SD) age was 65.21 (6.85) years, and 1252 (39.78%) were female. Compared with participants without incident CVD, those with incident CVD were more likely to be older, male, materially deprived, and recruited from England, smokers. They also tended to have lower education levels, consume less alcohol, and have short sleep duration and less moderate to vigorous physical activity. In addition, they were more likely to have higher HbA1c and systolic blood pressure, be obese, have insomnia and longstanding illness, and use blood glucose-lowering medications, blood pressure-lowering medications, or cholesterol-lowering medications. The baseline characteristics of the study population by IS, IV, RA, L5 onset, and M10 onset categories were shown in Supplemental Table S2-6.

3.2. Associations of circadian rest-activity rhythms with incident cardiovascular disease among people with type 2 diabetes

Fig. 1 shows that overall, IS, RA, and L5 onset, but not IV or M10 onset, were significantly associated with the risk of CVD. The associations of IS, IV, RA, and M10 onset with CVD incidence were linear, and L5 onset exhibited a non-linear association with CVD incidence. As shown in Table 2, in Model 1, participants in the lowest quartile of IS had a 38% higher risk of developing CVD than those in the highest quartile (HR: 1.38, 95%CI: 1.03-1.84), and these associations remained significant upon multivariable adjustment. A significant linear trend across quartiles was observed, such that a linear increase in the hazards of developing CVD was found with corresponding decrease across quartiles of IS (P for trend = 0.012). In the minimally adjusted model, participants in the lowest quartile of RA exhibited a more than 2-fold risk of CVD than those in the highest quartile (HR: 2.71, 95%CI: 2.00-3.68), and this association remained strong across all models. The linear trend across quartiles was significant. In addition, delayed L5 onset (HR: 1.29, 95% CI: 1.02-1.64), but not advanced onset, was associated with a higher risk of CVD in comparison with the intermediate group after controlling for sociodemographic and lifestyles factors. However, the association of delayed L5 onset and CVD risk did not reach statistical significance after further adjustment for sleep duration and duration of moderate to vigorous physical activity (HR: 1.25, 95%CI: 0.99-1.59). In addition, we did not observe significant associations of IV and M10 onset with the incidence of CVD.

In the sensitivity analyses, all results remained largely unchanged by using competing risk regression, excluding participants with missing data on covariates, excluding events that occurred within the first year of follow-up, or excluding those who reported shift work history (Supplemental Table S7-10). In addition, further adjustment for HbA1c, systolic blood pressure, obesity, insomnia, longstanding illness, use of blood glucose-lowering medications, use of blood pressure-lowering medications, and use of cholesterol-lowering medications slightly attenuated the results, but the associations remained similar (Supplemental Table S11). Subgroup analyses stratified by sex categories revealed similar results despite limited statistical power. Notably, the association between delayed L5 onset and cardiovascular disease seems more prominent among female participants with type 2 diabetes

Table 1
Characteristics of participants at baseline

Characteristic	No. (%)		
	All (n=3147)	No CVD (N=2757)	Incident CVD (n=390)
Age at accelerometry, mean (SD), y	65.21 (6.85)	64.91 (6.90)	67.36 (6.00)
Female	1252 (39.78)	1126 (40.84)	126 (32.31)
White ethnicity	2940 (93.42)	2576 (93.43)	364 (93.33)
Townsend deprivation index, median [IQR]	-1.92 [4.26]	-1.96 [4.25]	-1.70 [4.46]
Recruitment regions			
England	2832 (89.99)	2466 (89.45)	366 (93.85)
Wales	146 (4.64)	140 (5.08)	6 (1.54)
Scotland	169 (5.37)	151 (5.48)	18 (4.62)
Education level			
Degree or above	1109 (35.24)	983 (35.65)	126 (32.31)
Any other qualification	1599 (50.81)	1409 (51.11)	190 (48.72)
No qualification	439 (13.95)	365 (13.24)	74 (18.97)
Season of accelerometer wear			
Spring	669 (21.26)	587 (21.29)	82 (21.03)
Summer	834 (26.50)	729 (26.44)	105 (26.92)
Autumn	957 (30.41)	832 (30.18)	125 (32.05)
Winter	687 (21.83)	609 (22.09)	78 (20.00)
Healthy diet score, mean (SD)	2.55 (1.19)	2.55 (1.18)	2.59 (1.21)
Smoking status			
Never	1437 (45.66)	1271 (46.10)	166 (42.56)
Previous	1469 (46.68)	1276 (46.28)	193 (49.49)
Current	241 (7.66)	210 (7.62)	31 (7.95)
Alcohol consumption			
Not current	325 (10.33)	278 (10.08)	47 (12.05)
Two or less times a week	1714 (54.46)	1508 (54.70)	206 (52.82)
Three or more times a week	1108 (35.21)	971 (35.22)	137 (35.13)
Sleep duration			
< 7 hours/day	1316 (41.82)	1139 (41.31)	177 (45.38)
7-8 hours/day	1232 (39.15)	1090 (39.54)	142 (36.41)
> 8 hours/day	599 (19.03)	528 (19.15)	71 (18.21)
Duration of moderate to vigorous physical activity (mins/week), median [IQR]	55.50 [104.17]	57.83 [106.66]	41.83 [87.54]
HbA1c (mmol/mol)	50.02 (13.24)	49.98 (13.31)	50.29 (12.71)
Obesity (yes)	1600 (50.84)	1368 (49.62)	232 (59.49)
Systolic blood pressure (mmHg)	142.28 (16.93)	142.13 (16.94)	143.31 (16.87)
Insomnia			
Never/rarely	708 (22.50)	644 (23.36)	64 (16.41)
Sometimes	1351 (42.93)	1184 (42.95)	167 (42.82)
Usually	1088 (34.57)	929 (33.67)	159 (40.77)
Longstanding illness (yes)	2348 (74.61)	2042 (74.07)	306 (78.46)
Use of blood glucose-lowering medications (yes)	1705 (54.2)	1477 (53.57)	228 (58.46)
Use of blood pressure-lowering medications (yes)	1722 (54.72)	1483 (53.79)	239 (61.28)
Use of cholesterol-lowering medications (yes)	2014 (64.00)	1749 (63.44)	265 (67.95)

Abbreviation: IQR: interquartile range; SD: standard deviation. Townsend deprivation index was calculated based on the preceding national census output areas prior to participants joining UK Biobank.

(Supplemental Table S12).

3.3. Associations of circadian rest-activity rhythms with incident ischemic heart disease and mortality among people with type 2 diabetes

Supplemental Fig. S2-4 show that overall, IS, RA, and L5 onset, but not IV or M10 onset, were significantly associated with IHD incidence. The associations of IS, IV, RA, and M10 onset with IHD incidence were linear, and L5 onset exhibited a non-linear association with IHD incidence. For mortality, the IV and RA were significantly associated with all-cause and CVD mortality, but not IS, L5 onset, and M10 onset. All CRAR parameters exhibited linear associations with all-cause and CVD mortality.

We examined the CRAR in relation to incident IHD, all-cause mortality, and CVD mortality, and the results are presented in Supplemental Table S13, Table 3, and Table 4. In the fully adjusted model, the lowest quartile of RA was significantly associated with a higher risk of incident IHD ($HR_{Q1VS.Q4}$: 2.49, 95%CI: 1.71-3.64). We also found a trend supporting an association between the lower quartile of IS and higher HRs of incident IHD. In addition, delayed L5 onset (HR: 1.31, 95%CI: 1.01-1.68), but not advanced L5 onset, was associated with a higher risk of developing IHD in comparison with the intermediate group. After further controlling for sleep duration and moderate to vigorous physical activity, the association was attenuated slightly, but the trend remained. No significant associations of IV and M10 onset with IHD incidence were found among people with type 2 diabetes. In terms of all-cause mortality, the highest quartile of IV, lowest quartile of RA, and extreme L5 onset were significantly associated with all-cause mortality, and associations remained significant in final model (IV: $HR_{Q4VS.Q1}$: 1.48, 95%CI: 1.04-2.12; RA: $HR_{Q4VS.Q1}$: 1.75, 95%CI: 1.14-2.71; L5 onset: $HR_{advancedVS.intermediate}$: 1.39, 95%CI: 1.02-1.89, $HR_{delayedVS.intermediate}$: 1.40, 95%CI: 1.03-1.90). No significant associations of IS and M10 onset with all-cause mortality were observed. Similar findings were found for the associations with CVD mortality. There were significant associations of IV and RA with CVD mortality (IV: $HR_{Q4VS.Q1}$: 1.82, 95%CI: 1.07-3.10; RA: $HR_{Q4VS.Q1}$: 3.98, 95%CI: 1.76-9.00), but not IS, L5 onset, and M10 onset.

4. Discussion

In this prospective cohort study among people with type 2 diabetes, we found that disrupted CRAR, objectively quantified by continuous accelerometer recordings, was associated with higher risks of CVD, IHD, and mortality from all-cause and CVD. In detail, low IS (decreased day-to-day consistency in rhythm) and low RA (less robustness in rhythm) were associated with an increased risk of CVD. A series of sensitivity analyses for assessing potential bias provided further support to the robustness of these findings. Similarly, we also found that low RA was associated with the risk of IHD, and those with low IS and delayed L5 onset also demonstrated a slightly higher risk. In addition, high IV (fragmentation in rhythm) and low RA were significantly associated with CVD mortality. Similar patterns were observed for all-cause mortality.

To our knowledge, this is the first study to comprehensively investigate the associations of circadian rest-activity patterns with cardiovascular outcomes and mortality among people with type 2 diabetes. Some epidemiological and prospective studies have linked circadian disruption to cardiometabolic outcomes and mortality in the general population [7,21–24]. Sohail et al. primarily focused on IS measured by accelerometers and found that a higher IS was independently associated with lower odds of numerous cardiometabolic diseases, including metabolic syndrome, diabetes, obesity, hypertension, dyslipidemia, and CVD [21]. Another cross-sectional study with a small sample size (N= 52) demonstrated that IS and IV, but not RA, were associated with cardiometabolic biomarkers [7]. While data from teens with a moderate sample size (N= 778) found that higher RA was strongly associated with

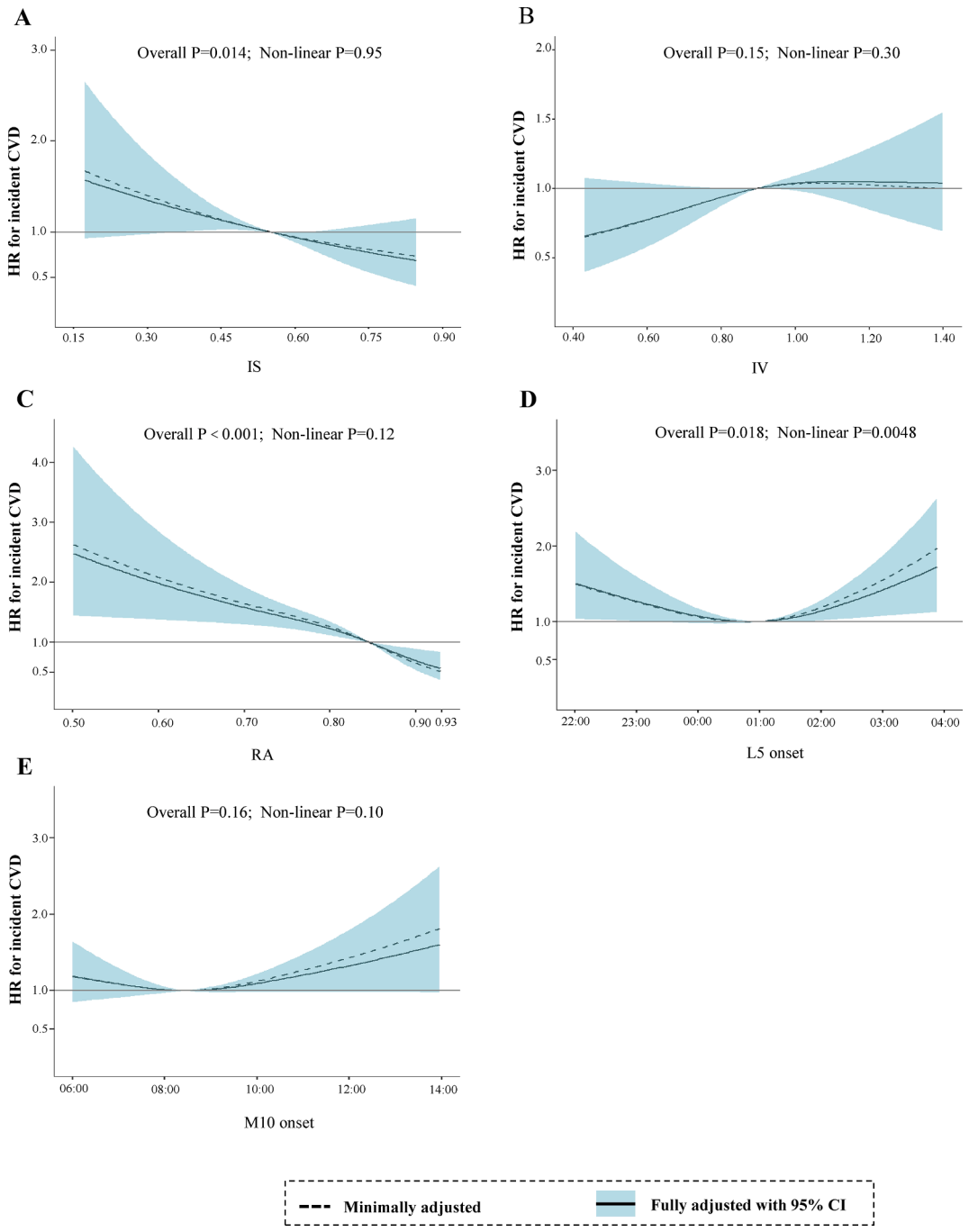

Fig. 1. Associations of circadian rest-activity rhythms with incident cardiovascular disease among people with type 2 diabetes Abbreviation: CI, confidence interval; HR, hazard ratio; IS, interdaily stability; IV, intradaily variability; M10, activity counts of the most active 10 hours of the day; M10 onset, onset of activity during the day; L5, activity counts of the least active 5 hours of the day; L5 onset, offset of activity during the night; RA, relative amplitude. In minimally adjusted models (dash line), analyses were adjusted for age and sex (Model 1). In fully adjusted models (solid line), analyses were adjusted for age, sex, ethnic origin, Townsend deprivation index, recruitment center, education level, season of accelerometer wear, healthy diet score, smoking status, alcohol intake, sleep duration, and duration of moderate to vigorous physical activity (Model 4). Shaded areas represent the 95% CIs in Model 4. Participants with prevalent CVD were excluded.

favorable indices of adiposity and cardiometabolic health [22], which is consistent with our findings. Shift work, which wreaks havoc on the circadian rhythm and decreases the levels of IS and RA [25], was also found to associate with higher risks of cardiometabolic diseases and mortality [23,24]. Notably, our results suggest that CVD incidence is particularly sensitive to decreased day-to-day consistency in rhythm (i.e., low IS) while mortality is more sensitive to fragmentation in rhythm (i.e., high IV) among population with type 2 diabetes. It is possible that IS, representing consistency of the daily circadian signal across days, which may link to the strength of its coupling master clock to stable zeitgebers [26], plays a more important role in developing cardiovascular disease, while IV, relating to the degeneration of the circadian timing system [27], may be a nonspecific health indicator and reflects the presence of different clinical and subclinical diseases [28], which may further contribute to the mortality. However, the underlying mechanism of these differences is still unclear, and further studies are needed to confirm these associations and elucidate exactly which specific pathophysiological processes mediate the link of rest-activity

Table 2
Associations between circadian rest-activity rhythms and Risk of incident cardiovascular disease among people with type 2 diabetes

	No. of events/person-years	Model 1HR (95% CI)	Model 2HR (95% CI)	Model 3HR (95% CI)	Model 4HR (95% CI)
IS					
Q1	104/4937	1.38 (1.03, 1.84)	1.36 (1.01, 1.82)	1.36 (1.01, 1.82)	1.40 (1.04, 1.88)
Q2	107/4911	1.31 (0.99, 1.75)	1.35 (1.01, 1.79)	1.35 (1.01, 1.79)	1.37 (1.03, 1.83)
Q3	93/4947	1.09 (0.81, 1.46)	1.11 (0.83, 1.49)	1.12 (0.83, 1.50)	1.14 (0.85, 1.53)
Q4	86/4947	1[Reference]	1[Reference]	1[Reference]	1[Reference]
P- trend		0.015	0.019	0.020	0.012
IV					
Q1	81/5023	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Q2	99/4885	1.19 (0.89, 1.60)	1.21 (0.90, 1.62)	1.21 (0.90, 1.62)	1.21 (0.90, 1.62)
Q3	105/4892	1.27 (0.95, 1.70)	1.27 (0.95, 1.71)	1.28 (0.96, 1.71)	1.29 (0.96, 1.72)
Q4	105/4943	1.27 (0.95, 1.69)	1.27 (0.95, 1.70)	1.27 (0.94, 1.70)	1.31 (0.97, 1.75)
P- trend		0.10	0.11	0.11	0.071
RA					
Q1	150/4657	2.71 (2.00, 3.68)	2.70 (1.99, 3.67)	2.70 (1.98, 3.67)	2.45 (1.73, 3.49)
Q2	93/4951	1.57 (1.13, 2.18)	1.58 (1.13, 2.19)	1.57 (1.13, 2.18)	1.45 (1.02, 2.07)
Q3	89/4995	1.44 (1.03, 2.00)	1.46 (1.04, 2.03)	1.46 (1.05, 2.04)	1.39 (0.98, 1.96)
Q4	58/5140	1[Reference]	1[Reference]	1[Reference]	1[Reference]
P- trend		< 0.001	< 0.001	< 0.001	< 0.001
L5 onset					
Advanced	115/5805	1.12 (0.88, 1.43)	1.14 (0.89, 1.45)	1.14 (0.89, 1.45)	1.15 (0.90, 1.47)
Intermediate	149/8465	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Delayed	126/5473	1.29 (1.02, 1.64)	1.30 (1.03, 1.65)	1.29 (1.02, 1.64)	1.25 (0.99, 1.59)
P- trend		0.27	0.29	0.32	0.52
M10 onset					
Advanced	113/5746	1.00 (0.79, 1.27)	0.98 (0.77, 1.24)	0.97 (0.77, 1.23)	0.98 (0.77, 1.25)
Intermediate	180/9113	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Delayed	97/4884	1.17 (0.91, 1.50)	1.14 (0.89, 1.47)	1.14 (0.88, 1.46)	1.11 (0.87, 1.43)
P- trend		0.30	0.29	0.29	0.39

Abbreviation: CI, confidence interval; HR, hazard ratio; IS, interdaily stability; IV, intradaily variability; M10, activity counts of the most active 10 hours of the day; M10 onset, onset of activity during the day; L5, activity counts of the least active 5 hours of the day; L5 onset, offset of activity during the night; RA, relative amplitude. **Model 1** was adjusted for age and sex. **Model 2** was adjusted as in model 1 and for ethnic origin, Townsend deprivation index, recruitment center, education level, and season of accelerometer wear. **Model 3** was adjusted as in model 2 and for healthy diet score, smoking status, and alcohol intake. **Model 4** was adjusted as in model 3 and for sleep duration and duration of moderate to vigorous physical activity. Participants with prevalent CVDs were exclude.

Table 3
Associations between circadian rest-activity rhythms and risk of all-cause mortality among people with type 2 diabetes

	No. of events/ person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
IS					
Q1	68/5250	1.21 (0.86, 1.70)	1.20 (0.85, 1.69)	1.19 (0.84, 1.68)	1.28 (0.91, 1.81)
Q2	55/5232	0.87 (0.61, 1.24)	0.87 (0.61, 1.25)	0.88 (0.61, 1.25)	0.92 (0.64, 1.32)
Q3	59/5230	0.88 (0.62, 1.24)	0.88 (0.62, 1.25)	0.89 (0.63, 1.26)	0.91 (0.64, 1.29)
Q4	69/5210	1[Reference]	1[Reference]	1[Reference]	1[Reference]
P- trend		0.33	0.37	0.38	0.20
IV					
Q1	52/5274	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Q2	58/5207	1.06 (0.73, 1.53)	1.05 (0.72, 1.53)	1.05 (0.72, 1.53)	1.06 (0.73, 1.55)
Q3	64/5226	1.16 (0.81, 1.68)	1.15 (0.80, 1.67)	1.14 (0.79, 1.64)	1.15 (0.80, 1.66)
Q4	77/5214	1.45 (1.02, 2.07)	1.43 (1.00, 2.04)	1.40 (0.98, 2.00)	1.48 (1.04, 2.12)
P- trend		0.028	0.037	0.051	0.025
RA					
Q1	107/5086	2.81 (1.93, 4.09)	2.67 (1.82, 3.90)	2.50 (1.70, 3.66)	1.75 (1.14, 2.71)
Q2	59/5241	1.47 (0.94, 2.22)	1.44 (0.95, 2.18)	1.36 (0.90, 2.07)	0.99 (0.63, 1.55)
Q3	48/5281	1.14 (0.74, 1.75)	1.16 (0.75, 1.78)	1.15 (0.74, 1.76)	0.93 (0.60, 1.45)
Q4	37/5315	1[Reference]	1[Reference]	1[Reference]	1[Reference]
P- trend		< 0.001	< 0.001	< 0.001	0.001
L5 onset					
Advanced	81/6197	1.40 (1.03, 1.90)	1.42 (1.05, 1.93)	1.38 (1.01, 1.87)	1.39 (1.02, 1.89)
Intermediate	83/8904	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Delayed	87/5821	1.56 (1.16, 2.11)	1.52 (1.13, 2.06)	1.47 (1.08, 1.99)	1.40 (1.03, 1.90)
P- trend		0.47	0.63	0.67	0.93
M10 onset					
Advanced	72/6098	0.88 (0.66, 1.18)	0.87 (0.65, 1.16)	0.86 (0.64, 1.15)	0.90 (0.67, 1.20)
Intermediate	132/9644	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Delayed	47/5179	0.82 (0.59, 1.15)	0.80 (0.57, 1.13)	0.77 (0.55, 1.08)	0.75 (0.53, 1.05)
P- trend		0.86	0.84	0.73	0.43

Abbreviation: CI, confidence interval; HR, hazard ratio; IS, interdaily stability; IV, intradaily variability; M10, activity counts of the most active 10 hours of the day; M10 onset, onset of activity during the day; L5, activity counts of the least active 5 hours of the day; L5 onset, offset of activity during the night; RA, relative amplitude. **Model 1** was adjusted for age and sex. **Model 2** was adjusted as in model 1 and for ethnic origin, Townsend deprivation index, recruitment center, education level, and season of accelerometer wear. **Model 3** was adjusted as in model 2 and for healthy diet score, smoking status, and alcohol intake. **Model 4** was adjusted as in model 3 and for sleep duration and duration of moderate to vigorous physical activity. Participants with prevalent CVDs were excluded.

Table 4
Associations between circadian rest-activity rhythms and risk of cardiovascular mortality among people with type 2 Diabetes

	No. of events/ person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
IS					
Q1	26/5250	1.19 (0.69, 2.07)	1.14 (0.66, 1.99)	1.17 (0.67, 2.04)	1.27 (0.73, 2.21)
Q2	31/5232	1.27 (0.75, 2.15)	1.28 (0.76, 2.16)	1.30 (0.77, 2.20)	1.39 (0.82, 2.35)
Q3	27/5230	1.05 (0.62, 1.81)	1.08 (0.63, 1.86)	1.12 (0.65, 1.92)	1.16 (0.68, 2.00)
Q4	26/5210	1[Reference]	1[Reference]	1[Reference]	1[Reference]
P- trend		0.41	0.52	0.47	0.30
IV					
Q1	21/5274	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Q2	24/5207	1.08 (0.60, 1.94)	1.09 (0.61, 1.97)	1.10 (0.61, 1.98)	1.11 (0.62, 2.01)
Q3	24/5226	1.08 (0.60, 1.94)	1.05 (0.59, 1.90)	1.04 (0.58, 1.88)	1.08 (0.60, 1.95)
Q4	41/5214	1.88 (1.11, 3.19)	1.79 (1.05, 3.04)	1.73 (1.02, 2.94)	1.82 (1.07, 3.10)
P- trend		0.015	0.029	0.042	0.025
RA					
Q1	58/5086	7.04 (3.36, 14.77)	6.39 (3.03, 13.48)	5.91 (2.79, 12.51)	3.98 (1.76, 9.00)
Q2	25/5241	2.90 (1.31, 6.44)	2.80 (1.26, 6.23)	2.59 (1.16, 5.77)	1.81 (0.78, 4.21)
Q3	19/5281	2.08 (0.91, 4.76)	2.15 (0.94, 4.92)	2.12 (0.92, 4.85)	1.71 (0.74, 3.99)
Q4	8/5315	1[Reference]	1[Reference]	1[Reference]	1[Reference]
P- trend		< 0.001	< 0.001	< 0.001	< 0.001
L5 onset					
Advanced	24/6197	1.36 (0.85, 2.17)	1.40 (0.88, 2.24)	1.33 (0.83, 2.14)	1.34 (0.83, 2.15)
Intermediate	36/8904	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Delayed	40/5821	1.67 (1.06, 2.62)	1.63 (1.04, 2.57)	1.54 (0.98, 2.43)	1.41 (0.89, 2.23)
P- trend		0.35	0.48	0.51	0.77
M10 onset					
Advanced	35/6098	1.01 (0.66, 1.55)	0.98 (0.64, 1.50)	0.96 (0.63, 1.47)	1.00 (0.65, 1.54)
Intermediate	55/9644	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Delayed	20/5179	0.83 (0.50, 1.40)	0.78 (0.47, 1.32)	0.75 (0.45, 1.26)	0.71 (0.42, 1.20)
P- trend		0.52	0.48	0.46	0.28

Abbreviation: CI, confidence interval; HR, hazard ratio; IS, interdaily stability; IV, intradaily variability; M10, activity counts of the most active 10 hours of the day; M10 onset, onset of activity during the day; L5, activity counts of the least active 5 hours of the day; L5 onset, offset of activity during the night; RA, relative amplitude. **Model 1** was adjusted for age and sex. **Model 2** was adjusted as in model 1 and for ethnic origin, Townsend deprivation index, recruitment center, education level, and season of accelerometer wear. **Model 3** was adjusted as in model 2 and for healthy diet score, smoking status, and alcohol intake. **Model 4** was adjusted as in model 3 and for sleep duration and duration of moderate to vigorous physical activity. Participants with prevalent CVD were excluded.

rhythms with cardiovascular disease and mortality. Taken together, the current study converges with these previous studies and extends them by showing that decreased day-to-day consistency, high fragmentation, or reduced robustness in rest-activity patterns might be sensitive biomarkers of cardiovascular outcomes and mortality in a sample of people with type 2 diabetes.

Additionally, the associations of extreme L5 onset with cardiovascular diseases and mortality we observed were similar to the previous reports regarding circadian preference and timing of sleep phase [29–31]. Two cross-sectional studies found that self-reported evening chronotypes were significantly associated with poor cardiovascular health [29,30]. Wallace et al. found that earlier and later sleep midpoints were associated with greater mortality risk in older men [31]. Together with previous studies, this study provides further evidence among the population with type 2 diabetes that extreme sleep timing, that might cause chronic misalignment between internal physiological timing and external behaviors, could play a significant role in health risk. However, we did not detect an association of M10 onset (start time of physical activity) with cardiovascular outcomes and mortality among people with type 2 diabetes, which is consistent with a recent study [32] reporting that the time of day of moderate-to-vigorous physical activity was not associated with all-cause mortality among individuals with type 2 diabetes. However, Qian et al. reported that morning and evening moderate to vigorous physical activity had higher cardiorespiratory fitness than the mixed group while null findings were observed with cardiovascular risk measured by the Framingham risk score in the entire sample of adults with type 2 diabetes, and their associations varied by sex [33]. Therefore, these findings are controversial, and future work is warranted to clarify the health effects of the timing of physical activity among populations with type 2 diabetes.

The observed associations of disrupted CRAR with cardiovascular outcomes and mortality among people with type 2 diabetes may be explained by several mechanisms: First, disrupted rhythms may impact glycemic control through further impairing beta cell function and insulin sensitivity among those with type 2 diabetes [34]. Elevated glucose levels lead to the activation of protein kinase C, nuclear factor κB, and monocyte chemotactic protein-1, all of which contribute to early atherogenesis. Moreover, animal models have demonstrated that a hyperglycemic environment increases glucose uptake in vascular smooth muscle cells, that causes impaired contractility and induction of a proinflammatory and atherogenic vascular [35]. Second, the majority of people with type 2 diabetes reported hypertension [36]. Chronic circadian disruptions, such as night shift work, may further worsen cardiovascular health and increase the risk of cardiovascular events [37]. Third, numerous studies have shown that circadian disruption affects host lipid metabolism through the intestinal microbiome, energy, and hormones. Lipid metabolism abnormalities accelerate the development of obesity, which is a significant contributor to cardiovascular consequences [38]. It is worth mentioning that these three explanations are not necessarily mutually exclusive, and future studies should focus on elucidating the multiple mechanisms that may drive the associations of circadian rhythms with cardiovascular outcomes and mortality among population with type 2 diabetes.

The results of the present study have implications for both risk prediction and prevention of cardiovascular consequences and mortality in type 2 diabetes. We found that accelerometer-measured circadian abnormalities predict the incidence of CVD and mortality among the population with type 2 diabetes, and the accelerometer might be a valuable screening tool to identify at-risk individuals. In addition, the findings of the current study emphasize the important role of circadian rhythm in the development of CVD and mortality among the population with type 2 diabetes. It provides clues for therapeutic strategies, such as lifestyle modifications (e.g. regular sleep timing and meal intake), bright light therapy, or melatonin supplementation [39], targeting the

improvement of circadian rhythm to attenuate the risk of CVD and mortality among those individuals. Further intervention trials are warranted to investigate the effect of those interventions on disease management among population with type 2 diabetes.

The strengths of this study include the relatively large sample size, the prospective study design, long-term follow-up, and a series of sensitivity analyses. In addition, the circadian rest-activity rhythm as the exposure was objectively measured using the accelerometer. Several limitations should be considered when interpreting its results. First, some covariates such as lifestyles were not collected at baseline of the present study (accelerometer mail-out) but at the physical visits to the UK Biobank assessment centers. Nonetheless, responses were generally stable over time [20]. In addition, despite including a wide range of confounders in the analyses, residual or unmeasured confounding cannot be ruled out in our study, such as diabetes duration. Second, as with any observational study, causal inferences could not be made in our study. Despite this limitation, we attempted to minimize this risk by adjusting for potential confounding factors and the results remained similar when we excluded participants with events that occurred during the first year of follow-up. Third, the majority of the participants were of European ancestry, and the generalizability of the study findings to other populations should be evaluated in future studies. Fourth, the study design was limited to people with type 2 diabetes. We have compared the characteristics of the sample in our study and the overall sample in the UK Biobank. Participants in our sample tend to be older, male, materially deprived, have less healthy diet, previous smokers, consume alcohol, and less healthy (details are shown in Supplemental Table S14). It may potentially lead to collider bias although our results were consistent with the associations between circadian rest-activity rhythm and cardiovascular outcomes among other populations [14,22]. Therefore, further studies will be warranted to confirm these associations.

5. Conclusions

In conclusion, we found that CRAR abnormalities, characterized by decreased day-to-day consistency, robustness, or high fragmentation in rhythm, that exist in people with type 2 diabetes may indicate higher risks of cardiovascular outcomes and mortality. Our study provides clues for interventions targeting the regulation of circadian rhythms to improve health among population with type 2 diabetes.

Funding

This work was supported by the National Key R&D Program of China (J.Z.: 2021YFC2501500), the National Natural Science Foundation of China (J.Z.: 82171476; F.H.: 82101558), the China Postdoctoral Science Foundation (F.H.: 2021T140139), Åke Wiberg Foundation (X.T.; M18-0169, M19-0266), and Fredrik and Ingrid Thuring Foundation (X.T.; 2019-00488), H.F. was supported by the International Postdoctoral Exchange Fellowship Program. The funders had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

The UK Biobank data are available from the UK Biobank and can be accessed by researchers on application (www.ukbiobank.ac.uk/).

Acknowledgements

We would like to thank the UK Biobank participants and investigators for their contributions. This research has been conducted using the UK Biobank Resource under Application Number 58082.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110262.

References

[1] Thosar SS, Butler MP, Shea SA. Role of the circadian system in cardiovascular disease. J Clin Invest 2018;128(6):2157–67. https://doi.org/10.1172/JCI80590.
[2] Scheer FA, Hilton MF, Mantzoros CS, et al. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A 2009;106(11):4453–8. https://doi.org/10.1073/pnas.0808180106.
[3] Leproult R, Holmbäck U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. Diabetes 2014;63(6):1860–9. https://doi.org/10.2337/db13-1546.
[4] Meigs JB, Nathan DM, D'Agostino Sr RB, et al. Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. Diabetes Care 2002;25(10):1845–50. https://doi.org/10.2337/diacare.25.10.1845.
[5] Pan A, Schernhammer ES, Sun Q, et al. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. PLoS Med 2011;8(12):e1001141.
[6] Vyas MV, Garg AX, Iansavichus AV, et al. Shift work and vascular events: systematic review and meta-analysis. BMJ 2012;345:e4800.
[7] Hoopes EK, Witman MA, D'Agata MN, et al. Rest-activity rhythms in emerging adults: implications for cardiometabolic health. Chronobiol Int 2021;38(4):543–56. https://doi.org/10.1080/07420528.2020.1868490.
[8] Huang T, Mariani S, Redline S. Sleep irregularity and risk of cardiovascular events: the multi-ethnic study of atherosclerosis. J Am Coll Cardiol 2020;75(9):991–9. https://doi.org/10.1016/j.jacc.2019.12.054.
[9] Dumpala S, Zele AJ, Feigl B. Outer retinal structure and function deficits contribute to circadian disruption in patients with type 2 diabetes. Invest Ophthalmol Vis Sci 2019;60(6):1870–8. https://doi.org/10.1167/iovs.18-26297.
[10] Ancoli-Israel S, Cole R, Alessi C, et al. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003;26(3):342–92. https://doi.org/10.1093/sleep/26.3.342.
[11] Li J, Somers VK, Lopez-Jimenez F, et al. Demographic characteristics associated with circadian rest-activity rhythm patterns: a cross-sectional study. Int J Behav Nutr Phys Act 2021;18(1):107. https://doi.org/10.1186/s12966-021-01174-z.
[12] Feng H, Chen L, Liu Y, et al. Rest-activity pattern alterations in idiopathic REM sleep behavior disorder. Ann Neurol 2020;88(4):817–29. https://doi.org/10.1002/ana.25853.
[13] Van Someren EJ, Swaab DF, Colenda CC, et al. Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. Chronobiol Int 1999;16(4):505–18. https://doi.org/10.3109/07420529908998724.
[14] Sommer R, Yu L, Schneider JA, et al. Disrupted rest-activity rhythms and cerebral small vessel disease pathology in older adults. Stroke 2021;52(7):2427–31. https://doi.org/10.1161/STROKEAHA.120.030870.
[15] Doherty A, Jackson D, Hammerla N, et al. Large scale population assessment of physical activity using wrist worn accelerometers: the UK biobank study. PLoS One 2017;12(2):e0169649. https://doi.org/10.1371/journal.pone.0169649.
[16] Eastwood SV, Mathur R, Atkinson M, et al. Algorithms for the capture and adjudication of prevalent and incident diabetes in UK biobank. PLoS One 2016;11(9):e0162388.
[17] Lysen TS, Luik AI, Ikram MK, et al. Actigraphy-estimated sleep and 24-hour activity rhythms and the risk of dementia. Alzheimers Dement 2020;16(9):1259–67. https://doi.org/10.1002/alz.12122.
[18] Xiao Q, Qian J, Evans DS, et al. Cross-sectional and prospective associations of rest-activity rhythms with metabolic markers and type 2 diabetes in older men. Diabetes Care 2020;43(11):2702–12. https://doi.org/10.2337/dc20-0557.
[19] Peduzzi P, Concato J, Feinstein AR, et al. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48(12):1503–10. https://doi.org/10.1016/0895-4356(95)00048-8.
[20] Strain T, Wijndaele K, Dempsey PC, et al. Wearable-device-measured physical activity and future health risk. Nat Med 2020;26(9):1385–91. https://doi.org/10.1038/s41591-020-1012-3.
[21] Sohail S, Yu L, Bennett DA, et al. Irregular 24-hour activity rhythms and the metabolic syndrome in older adults. Chronobiol Int 2015;32(6):802–13. https://doi.org/10.3109/07420528.2015.1041597.
[22] Quante M, Cespedes Feliciano EM, Rifas-Shiman SL, et al. Association of daily rest-activity patterns with adiposity and cardiometabolic risk measures in teens. J Adolesc Health 2019;65(2):224–31. https://doi.org/10.1016/j.jadohealth.2019.02.008.

[23] Jørgensen JT, Karlsen S, Stayner L, et al. Shift work and overall and cause-specific mortality in the Danish nurse cohort. Scand J Work Environ Health 2017;43(2):117–26. https://doi.org/10.5271/sjweh.3612.
[24] Shan Z, Li Y, Zong G, et al. Rotating night shift work and adherence to unhealthy lifestyle in predicting risk of type 2 diabetes: results from two large US cohorts of female nurses. BMJ 2018;363:k4641. https://doi.org/10.1136/bmj.k4641.
[25] Zhao X, Tang Q, Feng Z, et al. Executive performance is associated with rest-activity rhythm in nurses working rotating shifts. Front Neurosci 2022;16:805039. https://doi.org/10.3389/fnins.2022.805039.
[26] Cavalcanti-Ferreira P, Berk L, Daher N, et al. A nonparametric methodological analysis of rest-activity rhythm in type 2 diabetes. Sleep Sci 2018;11(4):281–9. https://doi.org/10.5935/1984-0063.20180044.
[27] Gonçalves BS, Adamowicz T, Louzada FM, et al. A fresh look at the use of nonparametric analysis in actimetry. Sleep Med Rev 2015;20:84–91. https://doi.org/10.1016/j.smrv.2014.06.002.
[28] Luik AI, Zuurbier LA, Hofman A, et al. Stability and fragmentation of the activity rhythm across the sleep-wake cycle: the importance of age, lifestyle, and mental health. Chronobiol Int 2013;30(10):1223–30. https://doi.org/10.3109/07420528.2013.813528.
[29] Baldanzi G, Hammar U, Fall T, et al. Evening chronotype is associated with elevated biomarkers of cardiometabolic risk in the EpiHealth cohort: a cross-sectional study. Sleep 2022;45(2):zsab226. https://doi.org/10.1093/sleep/zsab226.
[30] Makarem N, Paul J, Giardina EV, et al. Evening chronotype is associated with poor cardiovascular health and adverse health behaviors in a diverse population of women. Chronobiol Int 2020;37(5):673–85. https://doi.org/10.1080/07420528.2020.1732403.
[31] Wallace ML, Stone K, Smagula SF, et al. Which sleep health characteristics predict all-cause mortality in older men? An application of flexible multivariable approaches. Sleep 2018;41(1):zsx189. https://doi.org/10.1093/sleep/zsx189.
[32] Ma T, Xie YJ, Bennett T, et al. Time-of-day moderate-to-vigorous physical activity and all-cause mortality in individuals with type 2 diabetes. J Sports Sci 2022;40(6):614–20. https://doi.org/10.1080/02640414.2021.2009163.
[33] Qian J, Walkup MP, Chen SH, et al. Association of objectively measured timing of physical activity bouts with cardiovascular health in type 2 diabetes. Diabetes Care 2021;44(4):1046–54. https://doi.org/10.2337/dc20-2178.
[34] Mason IC, Qian J, Adler GK, et al. Impact of circadian disruption on glucose metabolism: implications for type 2 diabetes. Diabetologia 2020;63(3):462–72. https://doi.org/10.1007/s00125-019-05059-6.
[35] Almourani R, Chinnakotla B, Patel R, et al. Diabetes and cardiovascular disease: an update. Curr Diab Rep 2019;19(12):161. https://doi.org/10.1007/s11892-019-1239-x.
[36] Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. Lancet 2012;380(9841):601–10. https://doi.org/10.1016/S0140-6736(12)60987-8.
[37] Wang N, Sun Y, Zhang H, et al. Long-term night shift work is associated with the risk of atrial fibrillation and coronary heart disease. Eur Heart J 2021;42(40):4180–8. https://doi.org/10.1093/eurheartj/ehab505.
[38] Li Y, Ma J, Yao K, et al. Circadian rhythms and obesity: Timekeeping governs lipid metabolism. J Pineal Res 2020;69(3):e12682.
[39] Fishbein AB, Knutson KL, Zee PC. Circadian disruption and human health. J Clin Invest 2021;131(19):e148286.