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ORIGINAL RESEARCH

Misalignment Between Circadian Preference and Accelerometer-Derived Sleep-Wake Cycle With Increased Risk of Cardiometabolic Diseases

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ABSTRACT

BACKGROUND The relationship of circadian misalignment, sleep-wake cycle, and cardiometabolic diseases (CMDs) remains unclear.

OBJECTIVES This prospective study investigated the associations between circadian misalignment and CMDs, including type 2 diabetes (T2D), coronary heart disease (CHD), and stroke, and explored potential mechanisms.

METHODS Data from 60,965 participants without pre-existing CMDs from the UK Biobank study and followed for an average of 7.9 years were analyzed. Circadian misalignment was determined by comparing self-reported chronotype and accelerometer-derived sleep timing. Incident CMDs were documented via multiple medical registries and self-reported information. Cox proportional hazards models were applied to estimate HRs and 95% CIs for these associations.

RESULTS A U-shaped relationship between circadian misalignment and both T2D and CHD was observed. Compared to individuals with aligned midsleep and circadian preferences (the third quintile, Q3), those with advanced and delayed circadian misalignment had higher risks of T2D (HR: 1.22 [95% CI: 1.03-1.45] for Q1 and 1.39 [95% CI: 1.18-1.62] for Q5). Delayed circadian misalignment also associated with higher CHD risk (HR: 1.15 [95% CI: 1.01-1.31] for Q4 and 1.16 [95% CI: 1.02-1.33] for Q5). The association between delayed circadian misalignment and CMDs was greater in women (T2D, $P_{interaction} = 0.03$) and younger adults (CHD, $P_{interaction} = 0.02$). Early (HR: 1.19 [95% CI: 1.06-1.34]), rather than late, chronotype was associated with an increased T2D risk.

CONCLUSIONS Both advanced and delayed circadian misalignment were associated with an increased CMD risk, highlighting the potential health benefits of aligning sleep-wake cycles with individual circadian preferences. (JACC Adv. 2024;3:101406) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CMD = cardiometabolic disease

ICD = International Classification of Diseases

MEQ = Horne and Östberg Morningness-Eveningness Questionnaire

T2D = type 2 diabetes

In recent decades, cardiometabolic diseases (CMDs) such as type 2 diabetes (T2D), coronary heart disease (CHD), and cerebrovascular diseases have become major global public health issues.[1] The multifactorial etiology of these diseases involves a complex interplay of genetic, lifestyle, and environmental factors, presenting significant challenges for CMD prevention and prognosis.[2] Therefore, substantial efforts are needed to develop potential preventive strategies for CMDs.

Circadian disruption encompasses a wide range of misalignments in both internal timing and the synchronization between internal and external rhythms.[3] In field-based studies, circadian disruption is typically assessed using metrics such as rest-activity patterns and disrupted sleep behaviors, including social jetlag and shift work.[3] Epidemiological evidence suggests that individuals with a late chronotype (circadian preference), late sleep timing, significant social jetlag (the difference between mid-sleep on work-free and workdays), and those engaged in shift work are more likely to experience circadian disruptions,[4] which are associated with increased risks of CMDs.[5-8] However, commonly used proxies for circadian disruption, such as social jetlag and shift work, either rely heavily on regular work schedules or lack generalizability to the broader population, particularly those with non-shift jobs or those whose internal clocks are less divergent from societal norms.[9] Moreover, most previous epidemiological studies on circadian disruption and CMDs have been cross-sectional in design,[6,10,11] with only a few large-scale prospective analyses conducted.[12] Recent advancements in sensor technology, particularly accelerometers, now allow for objective measurements of sleep-wake cycles, physical activity, and environmental zeitgebers. Unlike biomarkers, which require repeated or invasive procedures to assess circadian rhythms,[13,14] accelerometers offer a noninvasive and consistent method to track rest-activity cycles.[13,14] Notably, over 80% of individuals in the Munich Chronotype Questionnaire database reported using an alarm clock and accumulating sleep debt during the workweek,[15] indicating that a significant portion of the population experiences misalignment between their circadian preferences and actual sleep-wake cycles. However, little is known about the association between this misalignment and CMDs, particularly in large prospective cohort studies.

Thus, utilizing data from the large-scale UK Biobank cohort, we integrated accelerometer-derived sleep-wake cycles, self-reported circadian preferences, and comprehensive disease diagnosis resources to: 1) prospectively analyze the association between circadian misalignment and CMDs, including T2D, CHD, and stroke; and 2) explore the potential mechanisms underlying this relationship through mediation analysis, incorporating plasma biomarkers and anthropometric indices.

METHODS

STUDY DESIGN AND PARTICIPANTS. The UK Biobank, initiated between 2006 and 2010, is a large-scale prospective cohort study that collects comprehensive health data from over half a million adult participants in the United Kingdom. The study received ethical approval from the North West Multi-Center Research Ethics Committee (reference #11/NW/0382), and all research is conducted in accordance with the Declaration of Helsinki.

Of the 502,505 participants enrolled in the UK Biobank at baseline, 74,123 participants with complete and valid data on both the baseline sleep questionnaire and accelerometer-derived information were included. After excluding 7,052 participants with prevalent T2D, stroke, or CHD at the time of activity monitoring, 389 participants with baseline random glucose levels ≥11.1 mmol/L or HbA1c ≥48 mmol/mol, 5,418 participants engaged in shift work, and 299 participants with measured sleep durations <4 hours or >12 hours, a total of 60,965 participants were included in the final analysis (**Figure 1**).

SLEEP ASSESSMENT. Sleep status was assessed using both subjective touchscreen sleep questionnaires and objective actigraphy monitors.

SLEEP QUESTIONNAIRE. At baseline recruitment, data on personal chronotype, 24-hour sleep duration, snoring, insomnia, and daytime sleepiness were collected via a self-administered touchscreen sleep questionnaire (Supplemental Methods). A healthy sleep quality score was calculated based on questionnaire-derived chronotype, insomnia, snoring, daytime sleepiness, and sleep duration (Supplemental Table 1).

ACTIGRAPHY. Between June 2013 and January 2016, physical activity and sleep were measured using a wrist-worn accelerometer (Axivity AX3), a commercial version of the Open Movement AX3 open-source sensor developed by Open Lab at Newcastle University. Detailed data collection and curation processes have been described previously.[16] In brief, participants were instructed to wear the accelerometer upon receipt and continue their normal routines,

attaching it to their dominant wrist. They were informed that the device would activate automatically upon delivery and deactivate after 1 week. At the end of this period, participants returned the device to a central office using a prepaid envelope. The R package GGIR was used for cleaning, calibrating, and deriving data on sleep timing, moderate to vigorous physical activity, and light exposure.[17,18]

ASCERTAINMENT OF CIRCADIAN MISALIGNMENT. Morning-evening preference (chronotype) was assessed using a validated question from the Horne and Östberg Morningness-Eveningness Questionnaire (MEQ)[19] included in the sleep questionnaire. This question showed a strong correlation with the overall MEQ score (r = 0.72).[20] Participants self-reported their chronotype as morning, more morning than evening, more evening than morning, or evening, which were recoded as 1, 2, 3, and 4, respectively, with higher values indicating a stronger evening circadian preference.

Additionally, participants' sleep onset and offset times were recorded using an actigraphy device worn on their dominant wrist for 7 consecutive days, with data processed using the R package GGIR. Nighttime sleep duration was calculated as the difference between the sleep onset and sleep offset times. Midsleep was determined using the following formula, which incorporates the average value of sleep onset and sleep duration.

$$Midsleep = sleeponset + \frac{1}{2}\ sleep\ duration$$

The misalignment between circadian preference (chronotype) and midsleep was calculated as the residuals of midsleep based on chronotype, or as the difference between midsleep and chronotype (subtracting the chronotype group number from midsleep).[21] The residuals of midsleep on chronotype were calculated using specific functions and categorized into quintile (Q) groups or 3 groups: Q1 was designated as the advanced circadian misalignment group, Q2-Q4 as the intermediate group, and Q5 as the delayed circadian misalignment group. This categorization was employed to explore the associations between circadian misalignment and CMDs.

$$\widehat{Midsleep} = \beta_0 + \beta_1 \bullet Chronotype + \epsilon$$

$$Residual = Midsleep - \widehat{Midsleep}$$

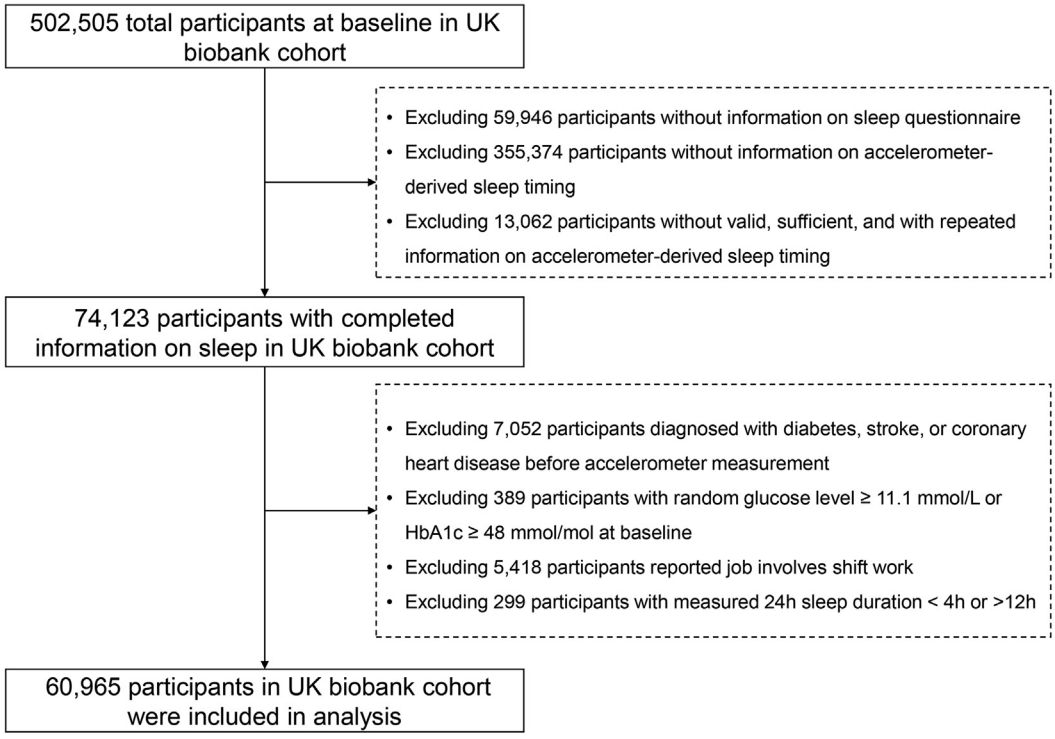
Detailed calculations and categorizations of the difference between midsleep and chronotype can be found in the Supplemental Methods.

CARDIOMETABOLIC OUTCOMES. Newly diagnosed cases of T2D, CHD, and stroke (including ischemic and hemorrhagic stroke subtypes) were individually evaluated and collectively considered when calculating the incidence of CMDs. Data on first occurrences (category 1712) were used to determine the initial diagnosis date. Two primary classification systems for clinical coding were utilized in the linked health data: the International Classification of Diseases (ICD) and Read codes. Information from primary care (Read v2 and Read CTV3), hospital inpatient records (ICD-10 and ICD-9), death registries, cancer registries, and self-reported medical conditions were collected and mapped to 3-character ICD-10 codes to ascertain the source and date of disease onset. Detailed methods can be found here (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/first_occurrences_outcomes.pdf). The ICD codes and field IDs for outcomes were described in Supplemental Table 2. Incident cases were defined as those with a diagnosis date later than the baseline measurement date for information and accelerometer data. Baseline characteristics and other covariates were detailed in the Supplemental Methods.

STATISTICAL ANALYSIS. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc) and R, version 3.4.2. A 2-sided P value <0.05 was considered statistically significant. Descriptive data for participants at baseline were presented as counts (%) for categorical variables and mean ± SD for continuous variables. Please refer to the Supplemental Methods for details on the adjustment of circadian misalignment according to baseline characteristics and the selection of covariates in the subsequent models.

Cox proportional hazards models were employed to investigate the associations between circadian misalignment (quintiles of residuals of midsleep based on chronotype) and incident cardiometabolic events. All Cox models satisfied the proportional hazards assumption as confirmed by the Schoenfeld Residuals Test. Model 1 was adjusted for age (tertiles), sex (men/women), and ethnic group (White British/non-White British). Model 2 was further adjusted for region (urban/town/village), Townsend deprivation index (tertiles), employment status (in-paid employment/retired/without fixed employment), qualifications (college or university degree/A levels or equivalent/O levels or GCSEs or equivalent/none of the above), and ambient noise level (tertiles). Model 3 (the main model) included additional adjustments

FIGURE 1 Study Flow Chart



for smoking status (never/ever/current), drinking status (never/ever/current), tea consumption (<2/2-4/≥5 cups), coffee consumption (0/0-2/≥3 cups), accelerometer-derived moderate to vigorous physical activity (tertiles), and healthy sleep quality score (<2/2-3/>3). All continuous covariates were categorized into tertiles to more clearly illustrate their relationships with circadian misalignment (Supplemental Figure 1) and CMDs. Given that missing values for all covariates were less than 6% (5.9% for healthy sleep quality score, 1.2% for ambient noise level, and less than 0.2% for other covariates), they were imputed using the mode.[11] Plots using restricted cubic splines (with 4 knots at 0.05, 0.35, 0.65, and 0.95) and *P* values for nonlinearity (analysis of variance[22]) were utilized to demonstrate the nonlinear relationship between circadian misalignment and cardiometabolic events. Additionally, the risk of cardiometabolic events was evaluated based on circadian misalignment, using the difference between midsleep and chronotype (advanced/intermediate/delayed groups), as well as analyzing chronotype and midsleep individually. Sensitivity analyses (Supplemental Methods) were conducted to assess the stability of the study results.

In the secondary analysis, causal mediation analyses were conducted using the R package CMAverse.[23] The average total effect HR, natural direct HR, natural indirect HR, and the proportion mediated by potential mediators were reported. Mediators were log-transformed and standardized to present HRs with 95% CIs per SD. For the selection of potential mediators, please refer to the Supplemental Methods. Additionally, subgroup analyses were performed based on age (<57/≥57 years, median), sex (women/men), ethnicity (White British/non-White British), residence (urban/town or village), socioeconomic status (<median/≥median), and healthy sleep quality score (<4/≥4). The multiplicative interaction between these characteristics and circadian misalignment was also assessed by adding an interaction term to the model.

RESULTS

BASELINE CHARACTERISTICS AND RISK FACTORS OF DELAYED CIRCADIAN MISALIGNMENT. A total of 60,965 participants aged 39 to 70 years at baseline were included in the analysis. Compared to the advanced circadian misalignment group, participants

TABLE 1 Baseline Characteristics of 60,965 Study Participants From UK Biobank According to Circadian Misalignment[a]

	Circadian Misalignment[b]		
	Advanced Group (n = 12,358)	**Intermediate Group (n = 36,464)**	**Delayed Group (n = 12,143)**
Basic information and lifestyle factors			
Women (%)	7,088 (57.4)	22,449 (61.6)	7,466 (61.5)
Urban area (%)	10,141 (82.9)	30,038 (83.1)	10,283 (85.6)
Age at baseline (y)	54.4 (8.2)	56.1 (7.8)	57.5 (7.2)
Townsend deprivation index[c]	−1.7 (2.8)	−1.9 (2.7)	−1.5 (2.9)
Level of education (%)			
College or university degree	5,522 (44.7)	17,084 (46.9)	5,231 (43.1)
A levels/AS levels or equivalent	1,674 (13.6)	4,837 (13.3)	1,595 (13.1)
O levels/GCSEs or equivalent	2,504 (20.3)	7,343 (20.1)	2,448 (20.2)
None of the above	2,658 (21.5)	7,200 (19.8)	2,869 (23.6)
White British (%)	11,956 (96.8)	35,551 (97.5)	11,667 (96.1)
Family history of diabetes (%)	2,367 (19.2)	7,019 (19.3)	2,358 (19.4)
Family history of cardiovascular diseases (%)	6,726 (54.,4)	20,796 (57.0)	7,196 (59.3)
On-paid work (%)	8,331 (67.4)	22,289 (61.1)	6,361 (52.4)
Drinking status (%)			
Never drinker	372 (3.0)	952 (2.6)	371 (3.1)
Ever drinker	365 (3.0)	817 (2.2)	382 (3.2)
Current drinker	11,621 (94.0)	34,695 (95.2)	11,390 (93.8)
Smoking status (%)			
Never smoker	7,212 (58.4)	21,802 (59.8)	6,627 (54.6)
Ever smoker	4,302 (34.8)	12,619 (34.6)	4,427 (36.5)
Current smoker	844 (6.8)	2,043 (5.6)	1,089 (9.0)
Daily average coffee intake (cups)	2.0 (2.0)	1.9 (1.9)	2.0 (2.0)
Daily average tea intake (cups)	3.2 (2.7)	3.3 (2.6)	3.4 (2.8)
Mediterranean dietary score (points)	2.9 (1.4)	2.9 (1.4)	2.9 (1.4)
Daily average time on moderate to vigorous physical activity per day[d] (min)	117.0 (53.2)	115.4 (50.5)	104.9 (50.1)
Daily average ambivalent light exposure[e] (lux)	781.2 (161.6)	803.7 (149.0)	788.3 (154.7)
Daily average ambivalent noise[f] (dB)	51.2 (4.2)	51.1 (4.1)	51.2 (4.3)
Circadian and sleep			
Chronotype			
Early	2,960 (24.0)	9,262 (25.4)	3,449 (28.4)
Intermediate early	4,702 (38.1)	14,507 (39.8)	3,936 (32.4)
Intermediate late	3,485 (28.2)	9,944 (27.3)	3,334 (27.5)
Late	1,211 (9.8)	2,751 (7.5)	1,424 (11.7)
Weekly average midsleep[g] (hh:mm)	02:06 (00:48)	03:18 (00:30)	04:24 (00:48)
Midsleep on weekdays (hh:mm)	02:06 (00:54)	03:18 (00:30)	04:36 (00:54)
Midsleep on weekends (hh:mm)	02:12 (01:24)	03:24 (00:48)	04:42 (01:06)
Social jetlag[h] (hours)	0.1 (1.6)	0.2 (0.8)	0.1 (1.2)
Residuals of midsleep on chronotype[b]	−1.2 (0.7)	0.0 (0.4)	1.3 (0.6)
Healthy sleep quality score (points)	3.2 (0.9)	3.3 (0.9)	3.1 (0.9)

Values are n (%) unless otherwise indicated. Circadian misalignment was calculated by the residuals of midsleep on chronotype, while the negative or positive value of circadian misalignment indicated an advanced or delayed real sleep-wake cycle comparing to circadian preference. The first quintile of residuals of midsleep on chronotype was defined as the advanced group, demonstrating an advanced sleep-wake cycle relative to their circadian preference. Conversely, the fifth quintile was defined as the delayed group, which indicated a delayed sleep-wake cycle in comparison to circadian preference. The remaining quintiles (Q2, Q3, Q4) combined together were defined as the intermediate group. [a]Values are mean and standard deviation or number and percentage. [b]Circadian misalignment was calculated using the residuals of midsleep on chronotype, with negative values indicating an advanced real sleep-wake cycle and positive values indicating a delayed cycle compared to circadian preference. The first quintile of residuals was defined as the advanced group, reflecting an advanced sleep-wake cycle relative to their circadian preference. Conversely, the fifth quintile was designated as the delayed group, indicating a delayed sleep-wake cycle. The remaining quintiles (Q2, Q3, Q4) were combined and defined as the intermediate group. [c]The Townsend deprivation index was calculated based on the preceding national census output areas. Each participant was assigned a score corresponding to the output area in which their postcode is located. Higher value indicated a poorer socioeconomic status. [d]Accelerometer-derived time spent in moderate or vigorous activity per day, weighted by weekends and weekdays, was calculated using the R package GGIR(17). [e]Accelerometer-derived mean daily light exposure during waking hours was based on data from the R package GGIR(17). [f]Day-evening-night equivalent noise level represents the A-weighted annual average noise level in the local environment, measured over a 24-hour period. [g]Accelerometer-derived midpoint time between sleep onset and sleep end was derived and weighted by weekends and weekdays using the R package GGIR(17). [h]The difference between accelerometer-derived midsleep times on weekends and weekdays was derived and weighted using the R package GGIR(17).

TABLE 2 Associations Between Quintiles of Circadian Misalignment and Cardiometabolic Outcomes by Cox Proportionate Hazard Models[a]

	Incidence Density (Events/Person-Years)	Model 1[b]	Model 2[c]	Model 3[d]
Type 2 diabetes				
Q1	**300/94,667**	**1.30 (1.10-1.54)**	**1.26 (1.07-1.50)**	**1.22 (1.03-1.45)**
Q2	244/94,046	1.01 (0.84-1.20)	1.01 (0.85-1.21)	1.02 (0.85-1.22)
Q3	243/94,917	Reference	Reference	Reference
Q4	310/96,293	1.19 (1.01-1.41)	1.18 (1.00-1.39)	1.17 (0.99-1.38)
Q5	**429/95,528**	**1.59 (1.36-1.87)**	**1.51 (1.29-1.77)**	**1.39 (1.18-1.62)**
Coronary heart disease				
Q1	423/92,171	1.14 (1.00-1.31)	1.13 (0.99-1.30)	1.12 (0.98-1.29)
Q2	364/91,674	0.98 (0.85-1.13)	0.98 (0.85-1.13)	0.98 (0.85-1.13)
Q3	391/92,489	Reference	Reference	Reference
Q4	**482/93,398**	**1.16 (1.02-1.33)**	**1.15 (1.01-1.32)**	**1.15 (1.01-1.31)**
Q5	**526/92,501**	**1.25 (1.09-1.42)**	**1.22 (1.07-1.39)**	**1.16 (1.02-1.33)**
Stroke				
Q1	130/94,424	1.06 (0.83-1.35)	1.06 (0.83-1.35)	1.04 (0.82-1.33)
Q2	114/93,768	0.91 (0.71-1.17)	0.92 (0.71-1.18)	0.92 (0.72-1.19)
Q3	133/94,636	Reference	Reference	Reference
Q4	160/95,895	1.11 (0.89-1.40)	1.11 (0.88-1.39)	1.10 (0.88-1.39)
Q5	147/95,220	0.99 (0.78-1.25)	0.97 (0.76-1.22)	0.91 (0.72-1.16)
Cardiometabolic events				
Q1	**780/91,496**	**1.16 (1.05-1.29)**	**1.15 (1.03-1.27)**	**1.12 (1.02-1.25)**
Q2	675/91,071	0.98 (0.88-1.09)	0.98 (0.88-1.09)	0.98 (0.89-1.09)
Q3	714/91,852	Reference	Reference	Reference
Q4	**884/92,598**	**1.17 (1.06-1.29)**	**1.16 (1.05-1.28)**	**1.15 (1.04-1.27)**
Q5	**1,031/91,626**	**1.33 (1.21-1.46)**	**1.29 (1.17-1.41)**	**1.21 (1.10-1.33)**

Values are HR (95% CI) unless otherwise indicated. **Bold** values indicate statistical significance. [a]Circadian misalignment was categorized by quintiles of residuals of midsleep on chronotype, with negative values indicating an advanced sleep-wake cycle and positive values indicating a delayed cycle compared to circadian preference. [b]Adjusted for age, sex, and ethnic group. [c]Further adjusted for region, socioeconomic status, employment, education, and ambient noise level. [d]Further adjusted for smoking status, drinking status, tea consumption, coffee consumption, moderate to vigorous physical activity, and healthy sleep quality score (calculated from chronotype, insomnia, snoring, daytime sleepiness, and sleep duration).

in the delayed circadian misalignment group were more likely to be older, women, and non-White British. They were also more likely to reside in urban areas, experience higher ambient noise levels, and have lower education levels and socioeconomic status, often working without pay. In terms of lifestyle, individuals predisposed to delayed circadian misalignment tended to be current smokers and drinkers, engage in less moderate to vigorous physical activity, consume more tea and less coffee, and report poorer sleep quality (**Table 1**, Supplemental Figure 1).

ASSOCIATION BETWEEN CIRCADIAN MISALIGNMENT AND INCIDENT CARDIOMETABOLIC EVENTS. During an average follow-up of 7.86 years, 1,526 (2.50%), 684 (1.12%), and 2,186 (3.59%) participants developed incident T2D, stroke, and CHD, respectively, resulting in a total of 4,084 (6.70%) participants developing CMDs.

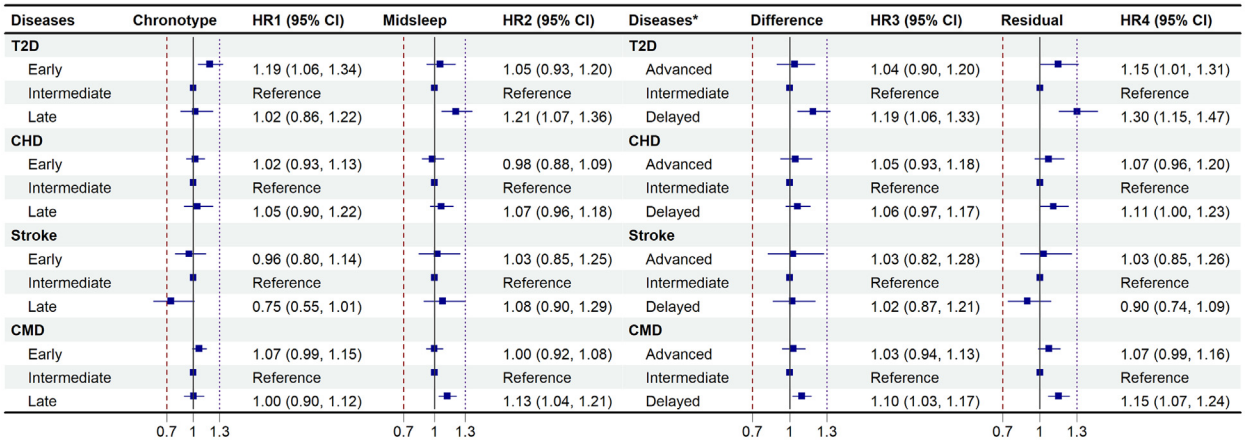
After full adjustment in the main model (Model 3), compared to individuals with aligned midsleep and circadian preferences (Q3), both advanced and delayed circadian misalignment were associated with a higher risk of T2D (HR: 1.22 [95% CI: 1.03-1.45] in Q1 and 1.39 [95% CI: 1.18-1.62] in Q5) and CMDs (HR: 1.12 [95% CI: 1.02-1.25] in Q1 and 1.21 [95% CI: 1.10-1.33] in Q5). However, only delayed circadian misalignment (Q4 and Q5) was significantly associated with an increased risk of CHD: 1.15 [95% CI: 1.01-1.31] in Q4 and 1.16 [95% CI: 1.02-1.33] in Q5) (**Table 2**). Furthermore, circadian misalignment was identified as a significant risk factor for acute myocardial infarction (HR: 1.37 [95% CI: 1.04-1.79] in Q1 and 1.46 [95% CI: 1.12-1.89] in Q5), but not for chronic myocardial infarction (HR: 1.12 [95% CI: 0.96-1.30] in Q1 and 1.12 [95% CI: 0.97-1.29] in Q5) (Supplemental Table 3). It was not associated with the incidence of stroke or its subtypes (**Table 2**, Supplemental Figure 4). When calculating circadian misalignment as the difference between midsleep and chronotype, participants with delayed circadian misalignment had a higher risk of developing T2D (HR: 1.19 [95% CI: 1.06-1.33]) and CMD (HR: 1.10 [95% CI: 1.03-1.17]). Consistently, neither type of circadian misalignment was associated with the incidence of stroke (**Figure 2**).

The "U-shaped" nonlinear associations of circadian misalignment with T2D ($P_{nonlinear} < 0.001$), CHD ($P_{nonlinear} = 0.03$), and CMD ($P_{nonlinear} < 0.001$) were significantly illustrated through restricted cubic spline plots (Supplemental Figure 2). To assess the robustness of the relationship between circadian misalignment and cardiometabolic outcomes, sensitivity analyses were conducted, yielding consistent results (Supplemental Tables 5 and 6, Supplemental Figure 3).

In stratified analyses, consistent results were observed across different ethnic groups, residential areas, socioeconomic statuses, and sleep quality subgroups. Notably, the association between delayed circadian misalignment and CMDs was more pronounced in women (for T2D, $P_{interaction} = 0.03$) and in individuals younger than 57 years (for CHD, $P_{interaction} = 0.02$), compared to their respective counterparts (Supplemental Figure 4).

MEDIATION ANALYSIS ON THE RELATIONSHIP BETWEEN CIRCADIAN MISALIGNMENT AND INCIDENT CARDIOMETABOLIC EVENTS. Mediation analysis revealed that liver function, blood lipids, glucose metabolism, inflammatory markers, and anthropometric indices were independently associated with both circadian misalignment and CMDs, even after adjusting for demographic, socioeconomic,

FIGURE 2 Associations of Circadian Preference, Midsleep, and Circadian Misalignment With cardiometabolic Outcomes



The difference was calculated by subtracting the chronotype group (early, intermediate, and late) from the midsleep group (early, intermediate, and late). The residual was derived from the residuals of midsleep (as a continuous variable) on chronotype. Models were adjusted for age, sex, region, socioeconomic status, employment, education, ethnic group, daily average noise level, smoking status, drinking status, tea consumption, coffee consumption, moderate to vigorous physical activity, and healthy sleep quality score (chronotype was excluded from the healthy sleep quality score when analyzing the association between chronotype and cardiometabolic outcomes). Chronotype and midsleep were also mutually adjusted. *The category of circadian difference and residuals are different from chronotype and midsleep. Participants were categorized into early, intermediate, and late groups according to chronotype and midsleep, whereas they were categorized into advanced, intermediate, and delayed sleep-wake cycle groups based on their chronotype. Abbreviations: CHD = coronary heart disease; CMD = cardiometabolic diseases (incident of any of T2D, CHD, and stroke); T2D = type 2 diabetes.

and lifestyle factors (Supplemental Tables 7 to 9). Among these, anthropometric indices—including body mass index, waist-to-hip ratio, and blood pressure—accounted for the largest proportion of the mediation effect (44.6%) between circadian misalignment and T2D. Liver function, blood lipids, glucose metabolism, and inflammatory markers mediated 12.3%, 24.5%, and 20.0% of the association between circadian misalignment and T2D, respectively (**Table 3**). For CHD, mediation effects were introduced by liver function (8.8%), blood lipids (9.1%), glucose metabolism (13.7%), and anthropometric indices (20.5%) (**Table 3**).

ASSOCIATION BETWEEN OTHER CIRCADIAN RHYTHM PROXIES AND INCIDENT CARDIOMETABOLIC EVENTS. After multiple adjustments, early chronotype (HR: 1.19 [95% CI: 1.06-1.34]) and late midsleep (HR: 1.21 [95% CI: 1.07-1.36]) were both associated with an increased risk of incident T2D. However, neither chronotype nor midsleep was associated with CHD or stroke (**Figure 2**). Notably, the significant association between late chronotype and T2D (HR: 1.22 [1.03-1.44]) disappeared after further adjustment for midsleep (HR: 1.08 [95% CI: 0.91-1.28]). Moreover, late chronotype remained a significant risk factor for T2D (HR: 1.23 [95% CI: 1.03-1.48]) and CHD (HR: 1.20 [95% CI: 1.03-1.40]), independent of sleep duration and overall healthy sleep quality score (Supplemental Table 10).

DISCUSSION

In this large-scale, population-based cohort study, we introduced a new metric for circadian misalignment by calculating the discrepancy between circadian preference and accelerometer-derived actual sleep-wake cycles. We prospectively identified a U-shaped association between circadian misalignment and the risk of T2D and CHD. Our findings suggest that both advanced and delayed sleep-wake cycles, relative to an individual's circadian preference, are associated with increased risks of CMDs, with the association being stronger in the delayed group compared to the advanced group (**Central Illustration**).

Our findings on the relationship between circadian misalignment and CMDs align with previous cross-sectional studies on circadian disruption, including social jetlag,[6] shift work,[10] or alignment between light cycle and sleep cycle,[11] although different metrics were used to measure circadian misalignment. Additionally, the Nurses' Health Study revealed a similar prospective association between circadian misalignment (measured by chronotype and shift work) and

TABLE 3 Multiple Mediation Models of Potential Mediators in the Association Between Circadian Misalignment and T2D as Well as CHD[a]

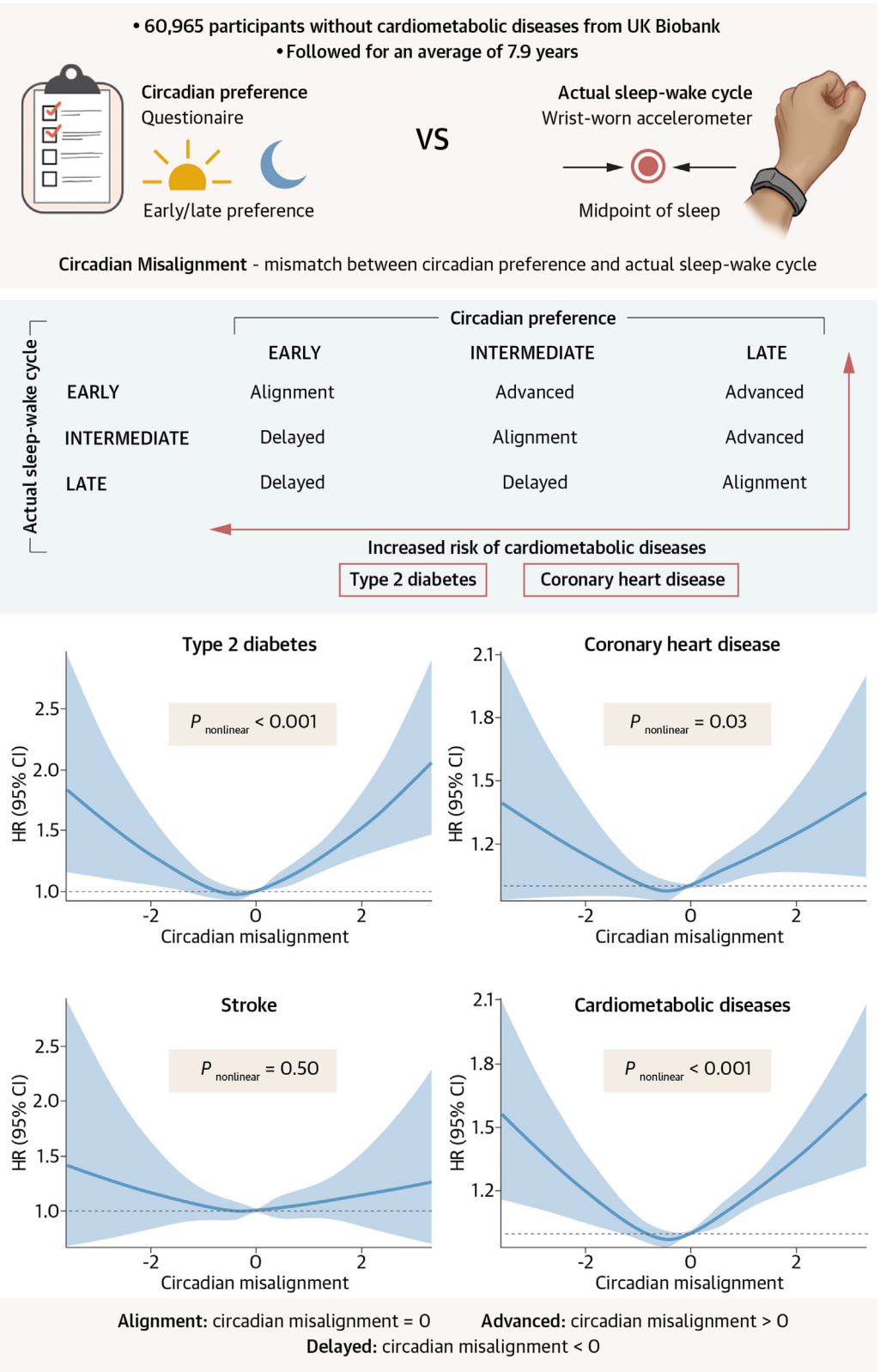
	Total Effect		Natural Direct Effect		Natural Indirect Effect		Proportion Mediated	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	% (95% CI)	*P* Value
T2D								
Liver function								
Alanine aminotransferase (U/L)	1.15 (1.08-1.21)	<0.001	1.14 (1.07-1.20)	<0.001	1.01 (1.00-1.01)	<0.001	6.2 (3.1, 12.6)	<0.001
Alkaline phosphatase (U/L)	1.16 (1.08-1.23)	<0.001	1.15 (1.08-1.22)	<0.001	1.01 (1.00-1.01)	<0.001	4.6 (2.4, 8.4)	<0.001
Aspartate aminotransferase (U/L)	1.15 (1.08-1.23)	<0.001	1.15 (1.08-1.22)	<0.001	1.00 (1.00-1.01)	0.02	3.0 (0.8, 6.0)	0.02
Gamma glutamyl transferase (U/L)	1.15 (1.08-1.21)	<0.001	1.13 (1.06-1.19)	<0.001	1.01 (1.01-1.02)	<0.001	9.1 (5.3, 18.7)	<0.001
Total bilirubin (μmol/L)	1.16 (1.09-1.22)	<0.001	1.16 (1.09-1.21)	<0.001	1.00 (1.00-1.01)	<0.001	2.4 (1.1, 5.0)	0.001
Overall	1.15 (1.09-1.23)	<0.001	1.14 (1.07-1.21)	<0.001	1.02 (1.01-1.02)	<0.001	12.3 (7.1, 20.0)	<0.001
Lipid and glucose metabolism								
HDL-C (mmol/L)	1.17 (1.09-1.23)	<0.001	1.15 (1.08-1.21)	<0.001	1.01 (1.01-1.02)	<0.001	10.0 (6.1, 18.5)	<0.001
Triglycerides (mmol/L)	1.15 (1.09-1.22)	<0.001	1.14 (1.07-1.20)	<0.001	1.01 (1.01-1.02)	<0.001	9.8 (4.8, 20.1)	<0.001
Apolipoprotein A (g/L)	1.16 (1.09-1.23)	<0.001	1.15 (1.08-1.22)	<0.001	1.01 (1.00-1.01)	<0.001	5.9 (3.1, 11.0)	0.001
HbA1c (%)	1.15 (1.07-1.22)	<0.001	1.12 (1.05-1.19)	<0.001	1.02 (1.01-1.04)	<0.001	16.9 (5.2, 34.0)	<0.001
Overall	1.15 (1.09-1.24)	<0.001	1.11 (1.05-1.20)	<0.001	1.03 (1.02-1.05)	<0.001	24.5 (12.3, 41.1)	<0.001
Inflammatory biomarkers								
C-reactive protein (mg/L)	1.16 (1.10-1.22)	<0.001	1.14 (1.07-1.19)	<0.001	1.02 (1.02-1.03)	<0.001	15.5 (11.0, 28.1)	<0.001
White blood cell count ($x10^9$/L)	1.16 (1.09-1.22)	<0.001	1.15 (1.07-1.20)	<0.001	1.01 (1.01-1.02)	<0.001	8.8 (6.2, 17.4)	<0.001
Overall	1.16 (1.09-1.23)	<0.001	1.13 (1.06-1.20)	<0.001	1.03 (1.02-1.04)	<0.001	20.0 (13.9, 37.0)	<0.001
Anthropometric indices								
Systolic blood pressure (mm Hg)	1.16 (1.09-1.23)	<0.001	1.15 (1.08-1.22)	0.02	1.01 (1.00-1.01)	0.02	3.7 (1.1, 8.3)	0.002
Body mass index (kg/m^2)	1.15 (1.07-1.22)	<0.001	1.10 (1.03-1.16)	0.02	1.05 (1.04-1.06)	<0.001	35.2 (23.9, 62.2)	<0.001
Waist-hip ratio	1.16 (1.08-1.23)	<0.001	1.11 (1.04-1.18)	<0.001	1.04 (1.03-1.05)	<0.001	27.1 (17.7, 47.7)	<0.001
Overall	1.15 (1.08-1.23)	<0.001	1.08 (1.01-1.15)	0.02	1.06 (1.05-1.07)	<0.001	44.6 (31.7, 81.8)	<0.001
CHD								
Liver function								
Alanine aminotransferase (U/L)	1.09 (1.03-1.16)	<0.001	1.09 (1.03-1.15)	<0.001	1.00 (1.00-1.00)	<0.001	1.5 (0.3, 4.2)	<0.001
Alkaline phosphatase (U/L)	1.09 (1.03-1.16)	0.02	1.09 (1.03-1.15)	0.02	1.00 (1.00-1.01)	<0.001	4.4 (1.8, 12.7)	0.02
Gamma glutamyl transferase (U/L)	1.09 (1.03-1.16)	<0.001	1.09 (1.03-1.15)	<0.001	1.00 (1.00-1.00)	<0.001	3.4 (1.5, 11.0)	<0.001
Albumin (g/L)	1.10 (1.02-1.16)	0.04	1.09 (1.02-1.16)	0.04	1.00 (1.00-1.00)	<0.001	2.1 (0.5, 6.9)	0.04
Overall	1.09 (1.04-1.15)	<0.001	1.08 (1.03-1.14)	<0.001	1.01 (1.01-1.01)	<0.001	8.8 (5.0, 22.6)	<0.001
Lipid and glucose metabolism								
HDL-C (mmol/L)	1.10 (1.04-1.16)	0.02	1.09 (1.03-1.15)	0.02	1.01 (1.00-1.01)	<0.001	6.2 (2.7, 14.8)	0.02
Triglycerides (mmol/L)	1.10 (1.04-1.16)	0.02	1.09 (1.03-1.16)	0.02	1.01 (1.00-1.01)	<0.001	4.0 (1.6, 9.9)	0.02
Apolipoprotein A (g/L)	1.10 (1.04-1.16)	0.02	1.09 (1.03-1.16)	0.02	1.01 (1.00-1.01)	<0.001	4.5 (1.7, 13.1)	0.02
HbA1c (%)	1.09 (1.03-1.16)	0.02	1.09 (1.03-1.15)	0.02	1.00 (1.00-1.00)	<0.001	2.8 (0.4, 7.5)	0.02
Overall	1.09 (1.04-1.17)	<0.001	1.09 (1.03-1.16)	<0.001	1.01 (1.00-1.01)	<0.001	9.1 (4.5, 20.6)	<0.001
Inflammatory biomarkers								
C-reactive protein (mg/L)	1.10 (1.04-1.16)	<0.001	1.09 (1.03-1.15)	<0.001	1.01 (1.01-1.01)	<0.001	10.7 (6.2, 27.1)	<0.001
White blood cell count ($x10^9$/L)	1.09 (1.04-1.16)	<0.001	1.09 (1.03-1.15)	<0.001	1.01 (1.00-1.01)	<0.001	5.8 (2.7, 14.5)	<0.001
Overall	1.09 (1.03-1.16)	<0.001	1.08 (1.02-1.14)	<0.001	1.01 (1.01-1.02)	<0.001	13.7 (7.1, 38.5)	<0.001
Anthropometric indices								
Systolic blood pressure (mm Hg)	1.10 (1.04-1.16)	0.02	1.09 (1.03-1.16)	0.02	1.00 (1.00-1.01)	0.02	4.6 (0.7, 12.7)	0.04
Body mass index (kg/m^2)	1.09 (1.03-1.16)	0.02	1.08 (1.02-1.14)	0.04	1.01 (1.01-1.02)	<0.001	16.8 (9.3, 44.2)	0.02
Waist-hip ratio	1.09 (1.03-1.16)	0.02	1.08 (1.02-1.15)	0.04	1.01 (1.01-1.01)	<0.001	11.9 (6.0, 29.7)	0.02
Overall	1.09 (1.03-1.15)	0.02	1.08 (1.01-1.13)	0.02	1.02 (1.01-1.02)	<0.001	20.3 (11.5, 63.7)	0.02

[a]Models were adjusted for age, sex, region, ethnic group, socioeconomic status, employment, education, daily average noise level, smoking status, drinking status, tea consumption, coffee consumption, moderate to vigorous physical activity, and healthy sleep quality score. Biomarker levels were natural log-transformed. Mediation analyses were conducted using the R package CMAverse.

CHD = coronary heart disease; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; T2D = type 2 diabetes.

T2D.[12,24] Unlike most studies focusing solely on chronotype[8] or shift work,[7] the Nurses' Health Study[12] was the first large cohort to examine circadian misalignment by analyzing the interaction between chronotype and shift work. This study showed that the increased risk of T2D was most evident in nurses with long night shifts and an early chronotype, as well as in participants working long daytime with a late chronotype. However, it remains unclear whether the mismatch between chronotype and actual sleep-wake cycles is associated with adverse health outcomes, particularly in populations working

CENTRAL ILLUSTRATION **Association Between Misalignment Between Circadian Preference and Accelerometer-Derived Sleep-Wake Cycle and Risk of Cardiometabolic Diseases**



Chen Y, et al. JACC Adv. 2024;3(12):101406.

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non-shift schedules and with less deviation from their internal clocks. By considering both circadian preference and actual sleep-wake cycles, our findings not only align with but also expand on these earlier discoveries, offering a more quantified view of circadian disruption across both men and women population.

We additionally found that an early chronotype, rather than a late chronotype, was associated with an increased risk of T2D, which contrasts with previous evidence.[24,25] Cross-sectional studies[26,27] and a limited prospective cohort study[24] have shown that late or evening chronotypes were associated with a higher risk of disrupted glucose homeostasis and T2D. However, to our knowledge, most existing studies[26,27] did not assess whether the relationship between chronotype and health outcomes was independent of the actual sleep-wake cycle. Our analysis indicated that, after adjusting for the sleep-wake cycle, the risk association of a late chronotype diminished. Similarly, 1 large prospective study revealed that participants identifying as "definite evening" chronotypes were more likely to exhibit unhealthy lifestyle factors, which may largely explain the association with an increased risk of diabetes.[24] Therefore, the relationship between a late chronotype and T2D may be at least partially attributed to a late sleep-wake cycle. Notably, a previous analysis in the UK Biobank population suggested that a "definite morning" chronotype was associated with a higher risk of CMDs when participants were classified into 4 groups (definite morning, morning, evening, definite evening).[28] However, most studies[12,29] generally categorized chronotypes into only 2 or 3 groups, making it challenging to detect the nonlinear relationship between chronotype and health outcomes—an area that requires further investigation in future studies.

On the other hand, our findings align with previous studies showing that preferred sleep-wake timing can conflict with actual sleep-wake patterns, often leading to reduced sleep duration.[5] To date, substantial evidence[30] supports the association between inadequate sleep duration and CMDs. Our analyses revealed that the potential hazards of circadian misalignment and chronotype on CMDs were independent of sleep duration and other sleep characteristics, such as insomnia, snoring, and daytime sleepiness. This highlights the unique public health significance of circadian misalignment. Furthermore, while shift work and social jetlag are the most commonly used proxies for circadian disruption in large-scale population studies,[3] night shifts represent the most strenuous type of work for many individuals. However, the impact of circadian disruption on disease risk among the vast majority of non-shift workers, who experience less extreme disruption, also warrants exploration. Additionally, sleep compensation[31] complicates the accurate calculation of social jetlag, making it less suitable for populations who are retired or not in fixed work schedules. The metric of circadian misalignment used in our analysis, defined by the discordance between self-reported circadian preference and the actual sleep-wake cycle, not only allows for the analysis of circadian misalignment as a continuous variable—revealing the U-shaped relationship with CMDs—but also accommodates non-shift workers, retirees, and those without fixed work.

The potential mechanisms linking circadian misalignment to CMDs remain unclear. A recent compendium highlighted several diurnal and circadian processes underlying cardiovascular and cerebrovascular diseases.[32] Circadian misalignment may impair immune function, promoting systemic inflammation and exacerbating cardiovascular damage.[33] Additionally, evidence suggests that circadian misalignment increases the risk of cardiovascular events by inducing hypoxia, myocardial ischemia-reperfusion injury,[34] and through the interaction of circadian genes with signaling pathways.[35] Our findings indicate that the association between circadian misalignment and CMDs may be partially mediated by liver function, lipid metabolism, inflammatory factors, and, most notably, BMI and waist-to-hip ratio, shedding light on the potential mechanisms linking circadian misalignment with cardiometabolic health outcomes. Furthermore, we observed that sex modified the relationship between circadian misalignment and both CHD and T2D, which may be attributed to sexual dimorphism in metabolism that contributes to

CENTRAL ILLUSTRATION Continued

This study aimed to prospectively investigate the associations of the circadian misalignment with CMDs in UK Biobank. Circadian misalignment was defined as discrepancies between self-reported chronotype and accelerometer-derived midpoint of sleep to detect its association with CMDs. U-shaped associations were found of the circadian misalignment with incident T2D and CHD after adjusting the potential confounders. Compared to individuals with aligned midsleep and circadian preferences, those with advanced and delayed circadian misalignment were both had higher risks of T2D and CHD. Abbreviations as in Figure 2.

differences in CMD risk.[36] Age-related changes in gut microbiota and metabolic profiling[37] may also partially explain the modulatory effect of age on the circadian misalignment-CMD relationship. Additionally, our study revealed that women and older participants were more likely to experience delayed circadian misalignment, which was associated with a higher risk of CMDs.

STRENGTHS AND LIMITATIONS. To our knowledge, this is the first study to examine the association between misalignment of circadian preference and actual sleep-wake cycle with cardiometabolic events. Additionally, we employed validated accelerometers to objectively measure participants' sleep-wake cycles, unlike most previous studies, especially prospective ones, which relied heavily on questionnaires.[38] However, several limitations should be acknowledged:

1. Participants in the UK Biobank tend to be older and have higher socioeconomic status, which may limit the generalizability of the findings.
2. Measurement bias may arise from using accelerometer-derived sleep timing, as accelerometers detect inactivity rather than true sedentary time.[39] Nonetheless, high agreements (89% to 97%) between accelerometer-derived sleep status and polysomnography have been confirmed,[40] and wrist-worn accelerometers offer better accuracy for assessing sleep behaviors compared to waist-worn devices.[41]
3. Self-reported circadian preference was assessed using a single question from the MEQ. As a widely used circadian marker, the validity of the MEQ score in relation to objectively measured circadian markers,[42] and the reliability of this single question relative to the overall MEQ score,[20] have been well investigated.
4. There was an average 5.8-year gap between the measurement of circadian preference and actual sleep-wake cycle. However, research shows that circadian preference is a relatively stable trait in humans.[5] In our sensitivity analysis, we included this time gap as a potential confounder and tested for interaction effects between the gap and key exposures, which did not indicate any effect modification.
5. Since only 1 measurement of the actual sleep-wake cycle was conducted, temporal bias may arise if participants changed their typical sleep-wake patterns during the study period.
6. Using midsleep as a simple time point to represent the sleep-wake cycle may overlook more detailed information about the phase and amplitude of this cycle. However, it is an accessible way to capture sleep-wake patterns and calculate circadian misalignment, making it suitable for large-scale population studies.[15]
7. Given the observational nature of our study and the potential for residual confounding, causality cannot be definitively established.

CONCLUSIONS

Both advanced and delayed circadian misalignment are associated with an increased risk of cardiometabolic events. Populations may benefit from aligning their actual sleep-wake cycles with their circadian preferences. This study introduces a new metric for assessing circadian disruption and may provide insights for the prevention and management of individuals at high risk for developing cardiometabolic conditions. Further research is needed to confirm these findings using objective measurements of personal circadian preference.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Both advanced and delayed sleep-wake cycles, in comparison to individual circadian preferences, are associated with increased risks of CMDs . Notably, early chronotype, rather than late chronotype, is linked to a higher risk of incident T2D, independent of actual sleep-wake cycles. Additionally, age and sex modify the associations between circadian misalignment and CMDs, while liver function, lipid and glucose metabolism, and inflammatory markers partially mediate these associations.

TRANSLATIONAL OUTLOOK: This new perspective on circadian misalignment could provide valuable insights into quantifying human circadian disruption across diverse work schedules and among populations with less deviated circadian rhythms. Maintaining an actual sleep-wake cycle that aligns with individual circadian preferences may benefit overall health.

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APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.