Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Sex-Specific Associations of Late Chronotype and Genetic Risk With Incident Metabolic Syndrome Running Title: Sex Differences of Late Chronotype and Genetic Risk of Metabolic Syndrome

Chun-Yi Lee
National Health Research Institutes
Yi-Wen Wang
National Health Research Institutes
Yii-Der Ida Chen
The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center
Jerome I Rotter
The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center
Wayne Huey-Herng Sheu
whhsheu@vghtc.gov.tw

National Health Research Institutes

Article

Keywords: Sex, Gene, Late chronotype, Metabolic Syndrome

Posted Date: November 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10619944/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

We attempted to evaluate the association between late chronotype and incidental metabolic syndrome differently by sex and menopausal status. Late chronotype was defined as habitual bedtime after midnight while polygenic risk score (PRS) was constructed to assess genetic susceptibility of MetS. By analyzed 35,156 adults (11,885 men and 23,271 women) from the Taiwan Biobank who were free of MetS at baseline and followed for a mean of 4.5 years, we had identified the prevalence of self-reported late chronotype was comparable between men and women. Despite younger age, men with a late chronotype had a higher incidence of MetS than those with an early chronotype (20.6% vs. 18.2%, P = 0.031). A smaller but significant increase was observed in women (15.8% vs. 15.2%, P = 0.011), with a more pronounced association in postmenopausal women (22.4% vs. 20.4%, P < 0.001). Late chronotype and MetS PRS independently increased MetS risk in both sexes. After adjustment for lifestyle factors, late chronotype was associated with higher MetS risk across all PRS tertiles in men, whereas in women the association was evident only in the highest PRS tertile. We conclude that late chronotype is associated with an increased risk of incident MetS, with associations differing according to sex and menopausal status.

Introduction

Metabolic syndrome (MetS) is a highly prevalent cardiometabolic condition associated with substantial morbidity and mortality [1,2]. Although its underlying pathophysiology and modifiable risk factors have been extensively investigated [3–5], emerging evidence has highlighted sleep as an important and potentially modifiable determinant of metabolic health. Multiple aspects of sleep, including short sleep duration, poor sleep quality, fragmented or irregular sleep patterns, and obstructive sleep apnea, have been consistently associated with adverse metabolic outcomes. These sleep-related disturbances may contribute to metabolic dysfunction through complex neuroendocrine and metabolic pathways, underscoring the relevance of sleep timing and regulation in MetS development [6,7].

Beyond sleep duration and quality, the timing of sleep—reflecting underlying circadian regulation—has emerged as an important determinant of metabolic health. Chronotype represents an individual's intrinsic preference for sleep–wake timing and captures interindividual differences in circadian phase. Individuals with a late chronotype (i.e. evening preference), characterized by late sleep timing (sleeping past midnight), are more likely to experience circadian misalignment when social and occupational schedules require early awakening, leading to disrupted hormonal rhythms, altered glucose metabolism, and adverse cardiometabolic profiles. Accumulating evidence has linked late chronotype to obesity, diabetes and cardiovascular disease, suggesting that circadian timing may play a distinct role in the development of metabolic syndrome beyond traditional sleep characteristics [6,8–10].

Recent evidence suggests that genetic susceptibility contributes to the development of MetS [11]. A recent Mendelian randomization study further provided genetic evidence supporting a causal relationshup between late chronotype and MetS, with broadly consistent findings in both the Taiwan Biobank and the

UK Biobank [12]. Importantly, circadian regulation and metabolic homeostasis differ by sex and across the reproductive lifespan. Women experience substantial hormonal fluctuations during the menopausal transition, which are accompanied by changes in sleep timing, circadian alignment, and cardiometabolic risk [13,14]. Sex differences in circadian biology and responses to circadian misalignment have been increasingly recognized and may contribute to differential metabolic vulnerability. [15,16]. For example, women exposed to circadian disruption through shift work exhibit a higher risk of type 2 diabetes mellitus than men [17]. Moreover, individual genetic susceptibility to MetS may further modify the metabolic consequences of circadian misalignment, yet the extent to which genetic risk interacts with chronotype in a sex-specific manner is largely unknown. To address these gaps, we investigated the associations of late chronotype and a polygenic risk score for MetS with incident MetS in a large prospective cohort, with a particular focus on sex- and menopause-specific effects.

Methods

Study population

This was a prospective cohort study. The Taiwan Biobank (TWB) stands as a crucial asset for advancing health and genetic research in Taiwan [18]. The TWB, which gathered comprehensive health data, encompassing genetic information, lifestyle factors, physical exams, as well as blood and urine test results, was launched in 2008 to promote medical research and enhance health policies. A total of 189,131 participants residing in Taiwan were obtained from the TWB database. Among them, 46,561 subjects completed the follow-up assessment. To reduce the impact of serious illness, 82 participants were excluded due to abnormal weight loss. In addition, 11,216 subjects with MetS at baseline and 107 subjects lack of MetS or sleep related data were also excluded. As a result, 35,156 participants with 4.5 years follow-up were included in the current analyses–11,885 were men and 23,271 were women (12,441 before menopause; 10,830 after menopause). The flowchart for selection of subjects is presented in Fig. 1. The study protocol was approved by the Institutional Review Board of National Health Research Institutes (NHRI) and by the TWB Ethics and Governance Council (EGC). The study was conducted in accordance with the Declaration of Helsinki.

Assessment of exposures

Sleep behaviors, including usual bedtime and sleep duration, were assessed for both weekdays and holidays using self-reported questionnaires. Sleep-related information was collected only at follow-up examination. Usual bedtime was determined by responses to the questions, “What time do you usually go to bed on weekdays?” and “What time do you usually go to bed on holidays?”. Late chronotype was defined as a habitual bedtime after midnight based on habitual sleep timing, consistent with our previous study [12]. Because habitual wake time was unavailable in the TWB, this definition was used as a pragmatic indicator of late chronotype. Sleep duration on weekdays and holidays was assessed by asking, “How many hours of sleep did you get on average during weekdays in the past month?” and “How

many hours of sleep did you get on average during holidays in the past month?", respectively. Overall sleep duration was derived from weekday and holiday sleep duration. Sex was self-reported, and menopausal status was determined based on self-reported questionnaire data. Covariates included sociodemographic characteristics (age, sex, education, and employment) and lifestyle factors (current smoking, alcohol consumption, and exercise) [18,19].

Assessment of outcomes

MetS was determined using the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, consistent with our previous TWB study, and was defined as the presence of at least three of the following five criteria [12,20,21]: 1) waist circumference (WC) ≥ 90 cm in men or ≥ 80 cm in women; 2) systolic blood pressure (SBP) ≥ 130 mmHg, diastolic blood pressure (DBP) ≥ 85 mmHg or self-reported hypertension; 3) HDL-cholesterol < 40 mg/dl in men or < 50 mg/dl in women or self-reported hyperlipidemia; 4) triglyceride (TG) level ≥ 150 mg/dl or self-reported hyperlipidemia; 5) fasting blood glucose (FBG) ≥ 100 mg/dl or self-reported type 2 diabetes.

Polygenic risk score (PRS)

The genotyping process and imputation procedures for the TWB were performed in accordance with the methods detailed in previous publications [22]. The PRS of MetS were computed based on the results of genome-wide association analysis of imputed data for MetS while adjusting for age, sex, and the first 10 ancestry principal components. SNPs were clumped according to linkage disequilibrium (LD) with an r^2 threshold 0.1 within a 250 kb region. At *p*-value thresholds of 0.001, 0.005, 10^{-4}, $5*10^{-4}$, $5*10^{-5}$, $5*10^{-6}$, seven PRSs were calculated. The best-fit PRS which accounts for the greatest variance of phenotype using McFadden's pseudo R^2 was chosen (Supplementary Table 1). The above analyses were conducted using PLINK v1.90 [23].

Statistical analyses

Baseline characteristics were age-standardized and compared between participants with early and late chronotypes, stratified by sex and menopausal status. Incident MetS was defined as the presence of metabolic syndrome at the follow-up examination among participants who were free of MetS at baseline. Age-standardized baseline characteristics and cumulative incidence of MetS were estimated. Differences between chronotype groups were assessed using Kruskal-Wallis tests. Cox proportional hazards regression models with age as the underlying time scale were used to examine the associations of late chronotype with incident MetS, with analyses stratified by sex and menopausal status. Participants entered the risk set at their age at baseline examination and exited at their age at the follow-up examination. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated to evaluate the independent and joint associations of late chronotype and the MetS PRS with incident MetS. Effect

modification by genetic risk was assessed using PRS tertiles. To minimize reverse causation, participants with MetS at baseline and those without follow-up data were excluded from the longitudinal analyses. Covariates were selected a priori based on biological plausibility and previously established associations with sleep behaviors and MetS. Multivariable models were adjusted for education, current smoking, alcohol consumption, exercise, and sex or menopausal status, as appropriate. Additional sensitivity analyses further adjusted for sleep duration and the number of MetS components present at baseline. Missing data were handled using complete-case analysis. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Study Population and Baseline Characteristics

The study design and participant flow are outlined in Fig. 1. The final analysis included 35,156 participants, comprising 11,885 men and 23,271 women. Based on chronotype classification, 28.7% of men and 28.4% of women were identified as having a late chronotype. The age-standardized baseline characteristics of the participants, stratified by sex and chronotype, are presented in Table 1. Significant differences between chronotypes were observed in both sexes. Late-chronotype participants were substantially younger than early-chronotype participants across both sexes. Consequently, the proportion of participants aged 20–39 was markedly higher in late-chronotype group for both men (40.1% vs. 17.2%) and women (33.3% vs. 17.6%). Menin the late-chronotype group had slightly higher BMI and WC. A similar trend was observed in women. The late-chronotype group in both sexes reported higher education levels and employment rate. Participants with late chronotype reported shorter sleep duration on weekdays but longer sleep duration on holidays compared with those with non-late chronotype. As a result, average sleep duration across the week was modestly lower among individuals with late chronotype. Furthermore, late chronotype was associated with a higher prevalence of current drinking, current smoking, and a lower prevalence of regular exercise habits (≥ 1.5 h/week) in both sexes. We also found that men with a late chronotype showed a higher incidence of high WC, high TG and low HDL, but a lower incidence of elevated BP and high FBG. In women, a late chronotype was associated with a lower incidence of elevated BP and high FBG.

Table 1
Age standardized baseline characteristics of Late versus Early Chronotypes by sex.

Characteristics	Men		Women	
	Early chronotype	Late chronotype	Early chronotype	Late chronotype
Number of participants (%) [a]	8476 (71.3)	3409 (28.7)	16672 (71.6)	6599 (28.4)
Age (years) [a] **††	**52.0 ± 10.7**	**44.3 ± 10.4**	**50.6 ± 10.0**	**45.3 ± 9.6**
20–39	**17.2**	**40.1**	**17.6**	**33.3**
40–54	**34.8**	**40.3**	**42.3**	**46.9**
55–64	**35.6**	**15.9**	**33.3**	**17.6**
≥65	**12.4**	**3.7**	**6.8**	**2.2**
Follow-up duration (years) [a] *††	**4.5 ± 1.3**	**4.6 ± 1.3**	**4.4 ± 1.3**	**4.5 ± 1.3**
BMI (kg/m^2) **†	**24.5 ± 3.1**	**24.7 ± 3.2**	**23.1 ± 3.4**	**23.4 ± 3.8**
WC (cm) **††	**85.8 ± 8.5**	**86.5 ± 8.6**	**79.8 ± 8.9**	**80.2 ± 9.7**
Education (%) *††				
Middle school or less	**10.2**	**3.6**	**17.2**	**6.7**
High school	**26.6**	**22.0**	**35.5**	**33.3**
College or higher	**63.2**	**74.4**	**47.3**	**60.0**
Employment (%) *††	**69.4**	**83.1**	**57.1**	**67.8**
Current drinking (%) *††	**10.8**	**13.0**	**1.4**	**2.4**
Current smoking (%) **††	**17.4**	**31.2**	**1.5**	**4.9**
Exercise habits (≥ 1.5 h/week, %) **††	**50.2**	**31.5**	**46.2**	**28.3**
Sleep duration (hours) **††	**6.8 ± 1.0**	**6.6 ± 1.1**	**6.8 ± 1.1**	**6.6 ± 1.1**
Sleep duration on weekdays (hours) **††	**6.8 ± 1.0**	**6.3 ± 1.1**	**6.7 ± 1.1**	**6.3 ± 1.1**
Sleep duration on holidays (hours) **†	**7.0 ± 1.2**	**7.1 ± 1.5**	**7.0 ± 1.3**	**7.2 ± 1.6**
Incident high WC (men ≥ 90 cm, women ≥ 80 cm, %) **	**29.5**	**34.6**	47.0	48.5
Incident elevated BP (SBP ≥ 130 mmHg, DBP ≥ 85 mmHg, self-reported HTN, %) **††	**48.4**	**39.0**	**28.2**	**21.4**

Characteristics	Men		Women	
	Early chronotype	Late chronotype	Early chronotype	Late chronotype
Incident high FBG (FBG ≥ 100 mg/dl, self-reported diabetes, %) **†	**24.9**	**21.7**	**13.9**	**13.6**
Incident high TG (≥ 150 mg/dl, self-reported hyperlipidemia, %) **	**24.3**	**31.0**	16.4	16.5
Incident low HDL-C (men < 40 mg/dl, women < 50 mg/dl, self-reported hyperlipidemia, %) *	**18.4**	**21.2**	23.3	24.2
Abbreviations: BMI, body mass index; WC, waist circumference; BP, blood pressure; SBP and DBP, systolic and diastolic blood pressure, respectively; HTN, hypertension; FBG, fasting blood glucose; TG, triglycerides; HDL-C high lipoprotein cholesterol.				
Kruskal-Wallis test was conducted to detect the differences between early chronotype and late chronotype.				
Values are presented as either percentage or mean ± standard deviation, and are standardized to the age distribution of the study population.				
Significantly associated with chronotype: *p < 0.05, **p < 0.001 for men; †p < 0.05, ††p < 0.001 for women.				
[a] Value is not age standardized.				

Baseline Characteristics by Menopausal Status in Women

To investigate the influence of hormonal status, women were further stratified by menopausal status (Supplementary Table 2). In the premenopausal group, 36.3% were late chronotypes, whereas in the postmenopausal group, this proportion was significantly lower at 19.2%. Consistent with the overall population, late chronotypes were younger in both the premenopausal and postmenopausal groups. Late chronotypes in both subgroups also reported higher education levels, higher rates of current smoking and drinking, and lower rates of regular exercise.

Regarding sleep patterns, a late chronotype was associated with shorter sleep duration on weekdays and overall in both premenopausal and postmenopausal women. Interestingly, on holidays, late chronotypes reported longer sleep duration in the premenopausal group (7.5 ± 1.6 vs. 7.3 ± 1.3 h) but not in the postmenopausal group. Premenopausal women with a late chronotype had a lower rate of elevated BP, while postmenopausal women with a late chronotype had a higher chance of high WC, high FBG, and high TG.

Association of Chronotype with Incident MetS

The age-standardized incidence of MetS was higher in individuals with a late chronotype compared to those with an early chronotype (Fig. 2). This association was observed in both men and women (upper panel). When stratified by menopausal status in women (lower panel), the increased incidence of MetS in the late-chronotype group was apparent in both premenopausal and postmenopausal women, with the effect appearing more pronounced in the postmenopausal group.

Association of Late Chronotype with Incident MetS by Menopausal Status

To quantify the risk of incident MetS associated with late chronotype, Cox regression models were used, with results presented in Table 2. Overall, in women, a late chronotype was associated with a 16% increased risk of developing MetS (HR:1.16, 95% CI 1.07–1.26). When stratifying by menopausal status, the association was more prominent and significant in postmenopausal women, who had a 20% increased risk (HR:1.20, 95% CI 1.08–1.34) while in premenopausal women, the trend suggested an 11% increased risk, but this did not reach statistical significance (HR:1.11, 95% CI 0.99–1.25). Analyses based on weekday and holiday chronotypes yielded similar results. Late chronotype on weekdays was significantly associated with incident MetS in both premenopausal and postmenopausal women. Late chronotype on holidays was significantly associated with risk only in postmenopausal women (HR 1.19, 95% CI 1.06–1.32). The primary findings remained largely unchanged after additional adjustment for sleep duration and the number of baseline metabolic syndrome components (Supplementary Table 3).

Table 2
Hazard ratios of late chronotype on incident MetS before and after menopause.

Characteristics	Women	Before menopause	After menopause	p-value [a]
Late chronotype	**1.16 (1.07, 1.26) ****	1.11 (0.99, 1.25)	**1.20 (1.08, 1.34) ****	0.27
Late chronotype on weekdays	**1.18 (1.08, 1.28) ****	**1.13 (1.004, 1.28) ***	**1.20 (1.08, 1.34) ***	0.43
Late chronotype on holidays	**1.14 (1.05, 1.24) ***	1.09 (0.96, 1.22)	**1.19 (1.06, 1.32) ***	0.22
Abbreviations: MetS, metabolic syndrome; SD, standard deviation.				
Cox regression was conducted to estimate the effects of sleep habits on incident MetS.				
Data are reported as the hazard ratios (95% CI).				
Adjusted for education, current smoking, current drinking, exercise and/or menopause.				
Significantly associated with incident MetS: *p < 0.05, **p < 0.001				
[a] Significance of difference before versus after menopause				

Joint Association of Late Chronotype and Genetic Risk with Incident MetS

We next explored the combined effect of behavioral and genetic factors on incident MetS (Table 3). Participants were categorized into low, intermediate, and high genetic risk groups based on their MetS PRS. A late chronotype was associated with an increased risk of incident MetS across all genetic risk groups. In the low genetic risk group, late chronotype conferred a 16% increased risk (HR 1.16, 95% CI 1.03–1.31). This risk was similar in the intermediate group (HR 1.17, 95% CI 1.05–1.30) and highest in the high genetic risk group (HR 1.25, 95% CI 1.13–1.39).

Table 3
Joint associations of late chronotype and PRS of MetS with incident MetS

Characteristics	Genetic risk group	All	Men	Women	p-value [a]
Late chronotype	**Low**	**1.16 (1.03, 1.31) ***	**1.22 (1.003, 1.49) ***	1.15 (0.99, 1.33)	0.06
	Intermediate	**1.17 (1.05, 1.30) ***	**1.21 (1.01, 1.44) ***	1.12 (0.97, 1.29)	**0.03**
	High	**1.25 (1.13, 1.39) ****	**1.31 (1.11, 1.55) ***	**1.19 (1.04, 1.35) ***	**0.01**
Late chronotype on weekdays	**Low**	**1.17 (1.03, 1.32) ***	1.21 (0.99, 1.48)	1.16 (0.99, 1.35)	0.13
	Intermediate	**1.19 (1.07, 1.33) ***	**1.28 (1.07, 1.53) ***	1.12 (0.97, 1.30)	**0.03**
	High	**1.29 (1.16, 1.43) ****	**1.34 (1.12, 1.58) ****	**1.21 (1.06, 1.39) ***	**0.02**
Late chronotype on holidays	**Low**	**1.16 (1.03, 1.30) ***	**1.24 (1.01, 1.50) ***	1.13 (0.97, 1.31)	**0.04**
	Intermediate	**1.16 (1.04, 1.30) ***	**1.21 (1.01, 1.45) ***	1.11 (0.96, 1.28)	**0.03**
	High	**1.23 (1.11, 1.37) ****	**1.31 (1.11, 1.55) ***	**1.16 (1.01, 1.32) ***	**0.009**

Abbreviations: MetS, metabolic syndrome; PRS: Polygenic Risk Score.

Cox regression was conducted to estimate the effects of late chronotype on incident MetS.

Data are reported as the hazard ratios (95% CI).

Adjusted for education, current smoking, current drinking, exercise and/or sex.

Significantly associated with incident MetS: *p < 0.05, **p < 0.001

[a] Significance of sex difference

When stratified by sex, the association between late chronotype and incident MetS was significant in men across all genetic risk strata. In women, the association was only significant in the high genetic risk group (HR 1.19, 95% CI 1.04–1.35). The p-values for sex difference suggested a potential stronger effect in men, particularly in the intermediate and high genetic risk groups. Similar patterns were observed when analyzing late chronotype on weekdays and holidays, with the highest risk consistently seen in individuals with both a late chronotype and high genetic predisposition. Similar associations were observed after additional adjustment for sleep duration and the number of baseline metabolic syndrome components (Supplementary Table 4).

We further examined the independent and interactive effects of late chronotype and MetS PRS on incident MetS (Supplementary Table 5). Both late chronotype (HR 1.19, 95% CI 1.12–1.27) and MetS PRS (HR 1.18, 95% CI 1.15–1.22) were significant independent predictors of incident MetS. The effect of late chronotype appeared stronger in men than in women. Conversely, the effect of MetS PRS was slightly stronger in women than in men, though this difference was not significant. Importantly, the interaction term was not significant, suggesting that the effects of chronotype and genetic risk are additive rather than synergistic.

To further dissect the interplay between chronotype, genetics, and hormonal status, the joint association analysis was repeated in women stratified by menopausal status (Supplementary Table 6). In postmenopausal women, there was a consistent, albeit non-significant, trend of increased MetS risk with late chronotype across all genetic risk groups. For instance, in the high genetic risk group, late chronotype was associated with a 20% increased risk (HR 1.20, 95% CI 0.99–1.46). In premenopausal women, the associations were generally null or weak. The only statistically significant finding was in premenopausal women with high genetic risk, where late chronotype on weekdays was associated with a 22% increased risk of incident MetS (HR 1.22, 95% CI 1.004–1.47). The p-values for the difference between premenopausal and postmenopausal effects were not significant, suggesting no strong statistical interaction with menopausal status in this stratified analysis.

Discussion

In this study, individuals with a late chronotype had a higher incidence of MetS than those with an early chronotype after a mean follow-up of 4.5 years. This association was observed in both sexes but was markedly attenuated in premenopausal women compared with postmenopausal women and men. Moreover, late chronotype and the MetS PRS independently contributed to the development of MetS. When genetic susceptibility was stratified by PRS tertiles, late chronotype was associated with an increased risk of MetS across all genetic risk strata in men, whereas in women this association was evident primarily among those with the highest genetic susceptibility.

Late chronotype reflects circadian misalignment that may adversely affect metabolic regulation, particularly in individuals with greater underlying metabolic vulnerability [8–10]. Individuals with a late chronotype often experience persistent misalignment between internal circadian timing and the social environment, a phenomenon commonly referred to as social jetlag [6,24]. Such circadian misalignment has been associated with increased risks of cardiovascular disease and metabolic disorders, including obesity and type 2 diabetes [9,10]. This increased risk may be partly mediated by adverse health behaviors more prevalent among late chronotypes, such as higher rates of smoking, alcohol consumption, and unhealthy dietary patterns [25,26]. In addition, disruption of circadian regulation may alter physiological rhythms, leading to immune dysregulation, chronic low-grade inflammation, impaired insulin action, disrupted glucose homeostasis, and vascular dysfunction [6]. Supporting these observations, a large

prospective study from the UK Biobank reported that nearly 10% of cardiovascular events in the cohort could be attributed to poor sleep patterns [27].

Previous studies examining sex differences in circadian disruption and metabolic outcomes remain relatively sparse. However, emerging evidence supports sex-specific vulnerability to circadian misalignment. A prior study using both dim light melatonin onset and chronotype questionnaires demonstrated that a later circadian phase was associated with greater adiposity in young men but not in young women, suggesting a relative metabolic protection in premenopausal women [28]. Consistent with this notion, recent work by Shafer et al. further indicated that circadian disruption may promote adverse metabolic trajectories in a sex-dependent manner, particularly among individuals with obesity [29]. Together, these observations align with our findings and support the concept that biological sex modifies the metabolic consequences of circadian disruption.

Several factors may contribute to the higher incidence of MetS observed among individuals with a late chronotype. In the present study, late chronotype was associated with a constellation of adverse lifestyle and metabolic profiles, including higher adiposity, more frequent smoking and alcohol consumption, and lower levels of regular exercise, despite younger age. In men and postmenopausal women, late chronotype was also accompanied by a higher prevalence of multiple MetS components, particularly central obesity and dyslipidemia, which may collectively predispose to MetS development. In contrast, premenopausal women with a late chronotype exhibited a distinct metabolic profile, characterized by lower blood pressure and largely comparable levels of other MetS components relative to their early-chronotype counterparts (Supplementary Table 2). This observation is noteworthy, as late chronotype has been linked to delayed circadian phase and attenuated nocturnal blood pressure dipping, a pattern generally associated with adverse cardiovascular risk [30]. The preserved or even lower blood pressure observed in premenopausal women may therefore reflect sex- and hormone-related buffering effects on circadian and vascular regulation.

The observed sex-specific modification of the association between late chronotype and metabolic syndrome suggests that genetic susceptibility may differentially shape vulnerability to circadian misalignment. In men, the metabolic consequences of late chronotype appear to manifest regardless of underlying genetic risk, whereas in women, greater genetic susceptibility may be required for late chronotype to translate into overt metabolic dysfunction. This pattern is consistent with the concept that biological sex and hormonal milieu influence the buffering capacity of metabolic regulation, potentially modulating the impact of circadian disruption [31]. Together, these findings underscore the importance of considering sex-specific and genetic contexts when evaluating the metabolic implications of sleep timing.

Previous cross-sectional studies have suggested that men are more likely than women to exhibit a late chronotype until approximately 50 years of age [32]. In accordance with that finding, the proportion of late chronotype was quite similar between both sexes among our study participants, whose average age was 50 years (28.7% in men and 28.4% in women). Beyond this, individuals with a late chronotype in both

sexes exhibited shorter sleep duration, a behavioral pattern that has been linked to adverse metabolic outcomes. Supporting this notion, prior population-based studies have shown that habitual short sleep duration is associated with an increased risk of cardiometabolic disorders, including type 2 diabetes [9]. Collectively, these findings suggest that late chronotype may confer metabolic risk partly through concomitant sleep curtailment.

Men and premenopausal women with a late chronotype reported longer sleep duration on holidays but not on weekdays, suggesting partial compensation for shorter weekday sleep. In contrast, this pattern was not observed in postmenopausal women with a late chronotype. Prior literature indicates that women's sleep is significantly impacted by their dual roles in the home and workplace. Such social and professional demands can disrupt sleep timing and circadian rhythmicity, which are recognized to adversely affect cardiometabolic function and overall health [33,34]. In this context, our finding that premenopausal women with high genetic susceptibility to metabolic syndrome exhibited an increased risk of incident MetS when late bedtime occurred on weekdays highlights a potential interaction between behavioral sleep timing, social constraints, and underlying metabolic vulnerability (Supplementary Table 4).

Several limitations of this study should be acknowledged. First, sleep patterns were assessed using a single self-reported questionnaire, which may not fully capture habitual sleep behaviors or temporal variability. Although interviewers were trained and standardized procedures were used, some degree of misclassification is possible. In addition, because habitual wake time was unavailable in the TWB, chronotype was defined according to habitual bedtime after midnight, and individuals with intermediate chronotype characteristics may have been included in the early chronotype group. However, additional adjustment for sleep duration did not materially alter the findings, supporting the robustness of the observed associations. Second, approximately 30% of participants in the TWB reported a late chronotype in both sexes, a proportion higher than that reported in studies using validated chronotype instruments, such as the Nurses' Health Study II [35], in which definite evening chronotype was identified in 11.2% of participants using items from the Morningness–Eveningness Questionnaire. Differences in study populations, age distributions, and chronotype definitions may partly account for this discrepancy. Notably, any nondifferential misclassification of chronotype would be expected to bias the observed associations toward the null, suggesting that the true associations may be underestimated.

Conclusion

This large prospective cohort study from the TWB demonstrates that late chronotype is associated with an increased risk of incident MetS, with effects modified by sex and genetic susceptibility. Late chronotype was associated with elevated MetS risk across all polygenic risk score (PRS) strata in men, whereas in women the association was evident primarily among those with high genetic risk. These findings highlight the importance of considering sex-specific and genetic factors when evaluating the cardiometabolic consequences of sleep timing and support the potential value of integrating behavioral and genomic information in MetS risk stratification.

Declarations

Acknowledgments

The authors thank all the participants from Taiwan Biobank (TWB). This work was supported by the grants MG-112-PP-18, MG-112-SP-09 and MG-113-GP-03 from the National Health Research Institutes in Taiwan and National Science and Technology Council, Taiwan (NSTC 114-2314-B-400-014; NSTC 115-2314-B-400-013-MY2).

Author Contribution

CY Lee contributed the data analysis and interpretation. YW Wang was responsible for data collection, sorting and cleaning. YDI Chen and JI Rotter were responsible for study design and critical review. WHH Sheu was in charge of whole study plan, interpretation and manuscript writing.

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of conflict of interests

All 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.

Ethics Statement

This study was approved by the Institutional Review Board of National Health Research Institutes (NHRI) (approval no. EC1090312-E-R7) and by the Taiwan Biobank Ethics and Governance Council (EGC) (approval no. TWBR11204-04). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants by the Taiwan Biobank.

References

1. Isomaa, B. et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. **24**, 683–689 (2001).
2. Xing, D., Xu, J., Weng, X. & Weng, X. Correlation between estimated glucose disposal rate, insulin resistance, and cardiovascular mortality among individuals with metabolic syndrome: a population-based analysis, evidence from NHANES 1999–2018. *Diabetol. Metab. Syndr.* **17**, 11 (2025).
3. Reaven, G. M. & Banting lecture Role of insulin resistance in human disease. *Diabetes* 37, 1595–1607 (1988). (1988).

4. Liao, C. C., Sheu, W. H., Lin, S. Y., Lee, W. J. & Lee, I. T. The Relationship Between Abdominal Body Composition and Metabolic Syndrome After a Weight Reduction Program in Adult Men with Obesity. *Diabetes Metab. Syndr. Obes.* **13**, 1–8 (2020).
5. Ndumele, C. E. et al. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. *Circulation* **148**, 1636–1664 (2023).
6. Allada, R. & Bass, J. Circadian Mechanisms in Medicine. *N Engl. J. Med.* **384**, 550–561 (2021).
7. Knutson, K. L. & von Schantz, M. Associations between chronotype, morbidity and mortality in the UK Biobank cohort. *Chronobiol Int.* **35**, 1045–1053 (2018).
8. Merikanto, I. et al. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. *Chronobiol Int.* **30**, 470–477 (2013).
9. Noga, D. A. et al. Habitual Short Sleep Duration, Diet, and Development of Type 2 Diabetes in Adults. *JAMA Netw. Open.* **7**, e241147 (2024).
10. Knutson, K. L. et al. Role of Circadian Health in Cardiometabolic Health and Disease Risk: A Scientific Statement From the American Heart Association. *Circulation* **152**, e408–e419 (2025).
11. van Walree, E. S. et al. Disentangling Genetic Risks for Metabolic Syndrome. *Diabetes* **71**, 2447–2457 (2022).
12. Lee, C. Y. et al. Genetic evidence for causality of late chronotype on metabolic syndrome in East Asians and Europeans. *Sleep. Med.* **142**, 108845 (2026).
13. Dashti, H. S. et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat. Commun.* **10**, 1100 (2019).
14. Lok, R., Qian, J. & Chellappa, S. L. Sex differences in sleep, circadian rhythms, and metabolism: Implications for precision medicine. *Sleep. Med. Rev.* **75**, 101926 (2024).
15. Ohayon, M. M., Reynolds, C. F., Dauvilliers, Y. & 3rd & Excessive sleep duration and quality of life. *Ann. Neurol.* **73**, 785–794 (2013).
16. Redline, S. et al. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch. Intern. Med.* **164**, 406–418 (2004).
17. Silva-Costa, A. et al. Gender-specific association between night-work exposure and type-2 diabetes: results from longitudinal study of adult health, ELSA-Brasil. *Scand. J. Work Environ. Health*. **41**, 569–578 (2015).
18. Fan, C. T., Lin, J. C. & Lee, C. H. Taiwan Biobank: a project aiming to aid Taiwan's transition into a biomedical island. *Pharmacogenomics* **9**, 235–246 (2008).
19. Wu, C. S., Hsu, L. Y., Shen, C. Y., Chen, W. J. & Wang, S. H. Validation of Self-reported Medical Condition in the Taiwan Biobank. *J. Epidemiol.* **35**, 141–146 (2025).
20. Expert Panel on Detection. Treatment of High Blood Cholesterol in, A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection,

Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* **285**, 2486–2497 (2001).

21. Hsu, P. W., Chen, Y. R. & Sheu, W. H. MetS-Z: A gender- and age-specific scoring system for predicting type 2 diabetes. *J. Diabetes Investig*. **16**, 907–916 (2025).
22. Wei, C. Y. et al. Genetic profiles of 103,106 individuals in the Taiwan Biobank provide insights into the health and history of Han Chinese. *NPJ Genom Med.* **6**, 10 (2021).
23. Chang, C. C. et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).
24. Sladek, M., Klusacek, J., Hamplova, D. & Sumova, A. Population-representative study reveals cardiovascular and metabolic disease biomarkers associated with misaligned sleep schedules. *Sleep* **46** (2023).
25. Ekiz Erim, S. & Sert, H. The relationship between chronotype and obesity: A systematic review. *Chronobiol Int.* **40**, 529–541 (2023).
26. Arora, T. & Taheri, S. Associations among late chronotype, body mass index and dietary behaviors in young adolescents. *Int. J. Obes. (Lond)*. **39**, 39–44 (2015).
27. Fan, M. et al. Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385 292 UK biobank participants. *Eur. Heart J.* **41**, 1182–1189 (2020).
28. Thomas, J. M. et al. Exploring the role of sex in the association of late chronotype on cardiorespiratory fitness. *Physiol. Rep.* **12**, e15924 (2024).
29. Shafer, B. M. et al. Circadian Alignment, Cardiometabolic Disease, and Sex-Specific Differences in Adults With Overweight/Obesity. *J. Clin. Endocrinol. Metab.* **110**, e1351–e1357 (2025).
30. Shafer, B. M., Christopher, D., Shea, S. A., Olson, R. & McHill, A. W. Later circadian timing and increased sleep timing variability are associated with attenuations in overnight blood pressure dipping among chronic nightshift workers. *Sleep. Health*. **10**, S140–S143 (2024).
31. Mauvais-Jarvis, F. Sex differences in metabolic homeostasis, diabetes, and obesity. *Biol. Sex. Differ.* **6**, 14 (2015).
32. Roenneberg, T. et al. Epidemiology of the human circadian clock. *Sleep. Med. Rev.* **11**, 429–438 (2007).
33. Lee, K. A. & Kryger, M. H. Women and sleep. *J. Womens Health (Larchmt)*. **17**, 1189–1190 (2008).
34. Mallampalli, M. P. & Carter, C. L. Exploring sex and gender differences in sleep health: a Society for Women's Health Research Report. *J. Womens Health (Larchmt)*. **23**, 553–562 (2014).
35. Kianersi, S. et al. Unhealthy Lifestyle, and Diabetes Risk in Middle-Aged U.S. Women: A Prospective Cohort Study. *Ann. Intern. Med.* **176**, 1330–1339 (2023). Chronotype.

Figures

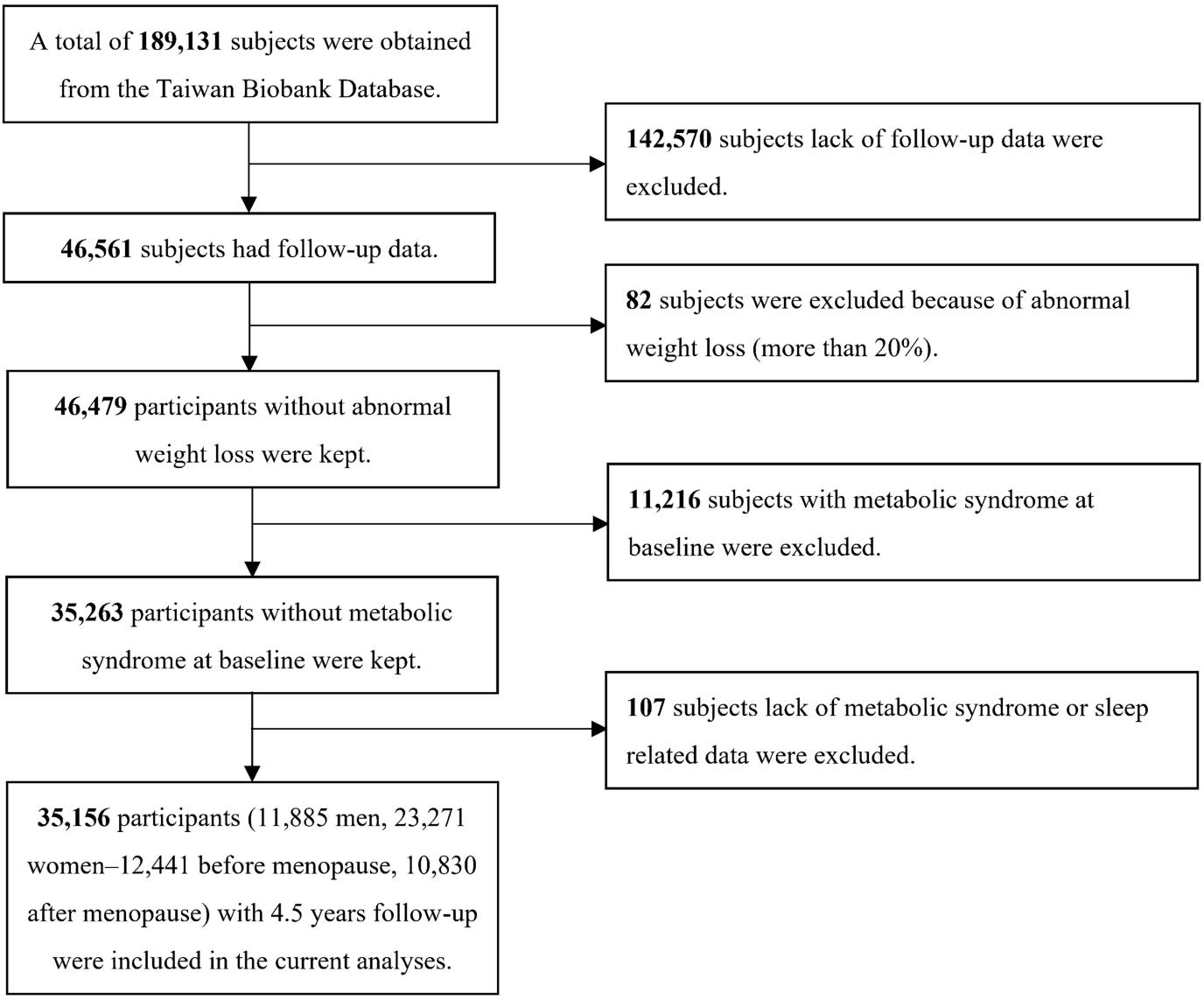


Figure 1

Flowchart of Study Design

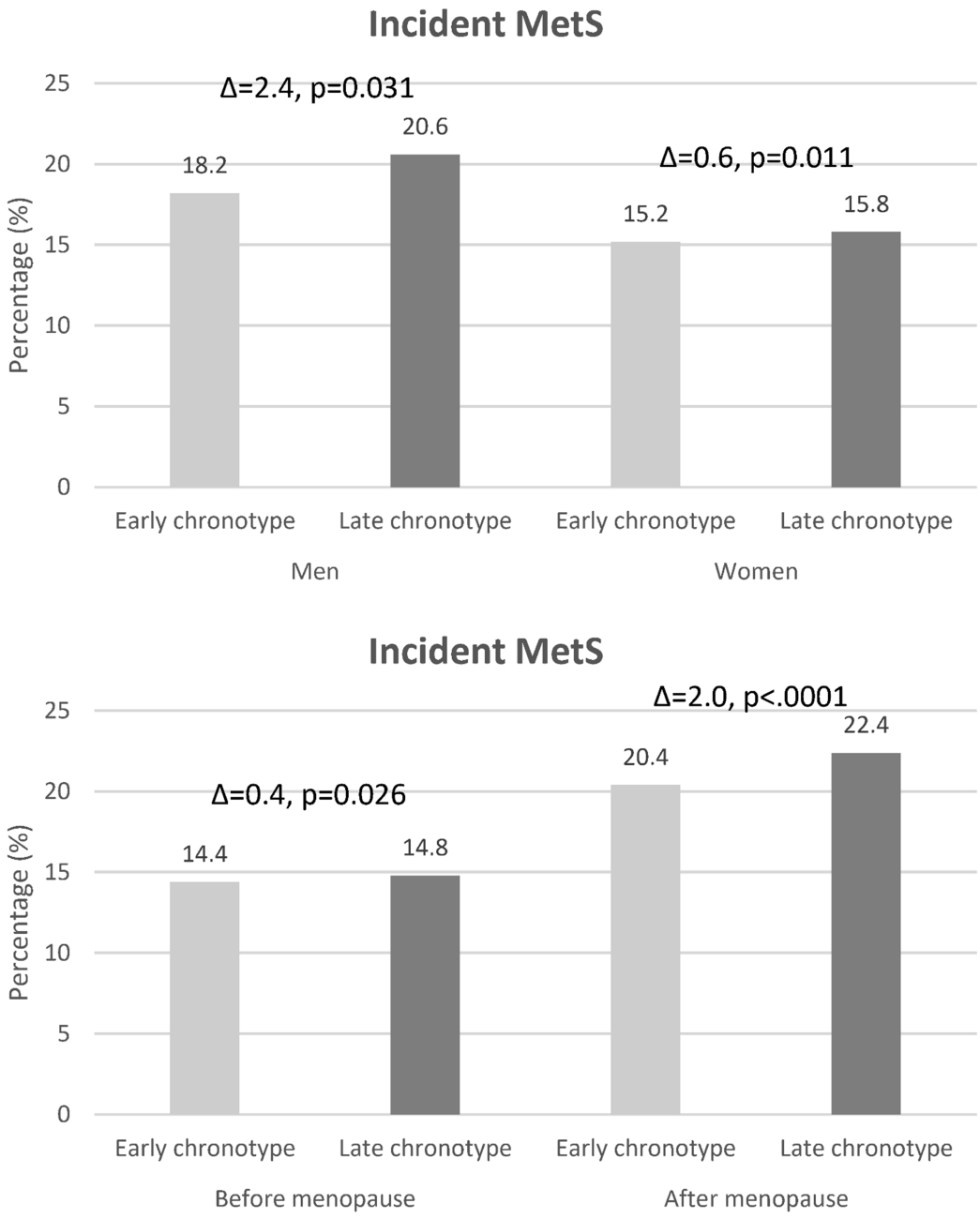


Figure 2

Age standardized incident metabolic syndrome (MetS) by sex (upper panel) and menopausal status (lower panel) in those with early vs. late chronotype. Kruskal-Wallis test was conducted to detect the differences between early chronotype and late chronotype

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 20260721SupplementaryTables.docx