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Original Article

The interaction between circadian syndrome and genetic susceptibility in the risk of incident dementia: A longitudinal cohort study

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ABSTRACT

Background: Despite growing interest in circadian disturbances as potential triggers for dementia, the specific impact of circadian syndrome (CircS) on dementia incidence remains poorly understood. Moreover, the role of genetic susceptibility modulating these effects remains to be explored.

Methods: Dementia-free participants from the UK Biobank cohort were included in the analysis. To evaluate the association between CircS and the incidence of dementia, as well as the modifying influence of genetic susceptibility on this relationship, Cox proportional hazards models were utilized.

Results: During a median follow-up period of 14.55 years, 3,965 incident dementia cases were documented. CircS was found to significantly increased the risk of incident dementia, with a hazard ratio (HR) of 1.401 (95 % confidence interval [CI]: 1.296, 1.516). Compared to a CircS score of ≤3, mild CircS (HR: 1.259, 95 % CI: 1.146–1.383), moderate CircS (HR: 1.667, 95 % CI: 1.461–1.903), and severe CircS (HR: 2.028, 95 % CI: 1.397–2.944) were all significantly associated with an elevated risk of dementia. There were significant multiplicative interactions between CircS and genetic susceptibility ($P_{interaction}$<0.001). Participants with both a high polygenic risk score (PRS) and CircS had the highest risk of incident dementia (HR: 2.551, 95 % CI: 2.169, 3.001), compared to those with a low PRS and no CircS.

Conclusions: CircS was associated with an increased risk of dementia, which might be aggravated by genetic susceptibility.

1. Introduction

Circadian rhythm intricately regulates physiological processes and plays an important role in metabolism. Sleep disruption, depressive symptom, and metabolic alterations are common features of neurodegenerative disorders such as dementia. Recently, circadian disruption has been identified as a significant etiological factor in the development of metabolic syndrome (MetS), promoting the concept of circadian syndrome (CircS). This concept is supported by substantial evidence linking circadian dysregulation to various chronic diseases [1]. CircS encompasses all components of MetS, including central obesity, hypertension, raised triglycerides, elevated fasting glucose levels, and decreased high-density lipoprotein (HDL) cholesterol [2]. In addition, CircS also includes factors such as sleep disruption and depressive symptoms [3]. These additional components are believed to uniquely influence dementia risk, as they interact with neurobiological pathways that are not typically captured by the MetS framework. Additionally, CircS has been associated with cognitive performance and is recognized as a predictor of cognitive decline [4]. CircS represents an expanded metabolic disorder framework that may better predict dementia risk compared to MetS alone.

Dementia is a neurocognitive disorder marked by cognitive impairment. Approximately 78 million people are estimated to develop dementia in 2030 worldwide, posing significant social and economic challenges [5]. Recent studies indicate that MetS and CircS, either independently or in combination, may represent novel risk factors for dementia. However, the precise nature of this relationship remains unclear. A longitudinal cohort study involving 176,249 UK Biobank participants re-

Abbreviations: MetS, metabolic syndrome; CircS, circadian syndrome; HDL, high-density lipoprotein; AD, Alzheimer's disease; APOE, Apolipoprotein E; GWAS, genome-wide association study; PRS, Polygenic risk score; BMI, body mass index; RERI, relative excess risk due to interaction.

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vealed a 12 % increased risk of dementia with MetS [6], while a Korean study reported an 11 % increase [7]. However, a meta-analysis revealed no significant relationship of MetS with the overall risk of dementia or Alzheimer's disease (AD) [8]. Similarly, evidence connecting circadian disruption with dementia is sparse [9]. Although a meta-analysis highlighted a relationship between sleep duration and dementia risk [10], findings on specific sleep disturbances have been inconsistent. For example, insomnia, a common sleep disorder, was not linked to dementia risk in an Italian cohort [11]. In contrast, a Chinese cohort study found an increased dementia risk among individuals with MetS and/or CircS [4].

However, the evidence regarding the relationship between CircS and risk of dementia remains inconclusive, partially due to small sample size (i.e., <20,000 participants) [4,8], variability in the types of sleep disturbances considered [10], and short follow-up durations (typically less than five years) [4,7]. Given the prolonged preclinical phase of dementia, studies with short follow-up periods are vulnerable to reverse causality. While individual components of CircS have been associated with dementia risk [12–14], the combined effects and patterns of these components remain unclear.

Genetic background plays essential roles in the development of dementia, with Apolipoprotein E (APOE)-ε4 allele being the most significant risk factor [15]. Numerous genome-wide association studies (GWASs) have identified additional genetic loci linked to dementia risk [16,17]. The polygenic risk score (PRS), which aggregates the effects of multiple genetic loci, offers a quantitative assessment of cumulative genetic risk and has been shown to predict dementia [18]. For example, in a Chinese cohort, PRS was associated with cerebrospinal fluid biomarkers and the age of dementia onset [19]. PRS can also differentiate between AD patients and cognitively healthy individuals and predict the progression from mild cognitive impairment to AD [20]. While genetic influences are substantial, they may be modified by acquired factors [21]. The combined impact of CircS and polygenic risk on dementia remains underexplored and warrants further investigation.

This study leveraged a population-based UK Biobank (UKB) cohort of 211,982 participants with 15 years of follow-up to investigate the associations between CircS and dementia incidence. A key aspect of our study is the exploration of the interaction between CircS and genetic susceptibility in modifying dementia risk, which has not been extensively studied in previous research. Additionally, we assessed the individual contributions of CircS components to dementia development, providing a more comprehensive understanding of how lifestyle factors and genetic predisposition jointly influence dementia risk.

2. Materials and methods

2.1. Study population

The UKB recruited more than 500,000 participants aged 40 to 69 years between 2006 and 2010, collecting extensive genotypic, clinical, medication, and sociodemographic data. The study was approved by the North West Multi-centre Ethics Committee, and all participants provided written informed consent (Sudlow et al., 2015). This analysis was conducted under UKB project number 106,528.

From the initial cohort of 502,356 participants, we excluded those with pre-existing dementia or missing baseline data on educational level, body mass index (BMI), or household income. We also excluded individuals lacking data on all seven components of CircS and on the APOE-ε4 genotype. Notably, to ensure that only cognitively healthy individuals were included at baseline, individuals diagnosed with "Senile degeneration of the brain" or "Other specified degenerative diseases of the nervous system" were also excluded. As a result, 211,982 dementia-free individuals at baseline were eligible for the analysis. After excluding 442 participants without PRS data, 211,540 participants remained for the PRS analysis. A detailed cohort flow diagram is presented in Fig. S1.

2.2. Definition of circadian syndrome

CircS was defined by the presence of at least four of the following seven factors, with the additional requirement that at least one of these factors be either short sleep or depressive symptoms (Table S1) [3]. The seven factors included: (1) Short sleep: self-reported average daily sleep duration of fewer than 6 h; (2) Depressive symptom: self-reported history of having visited a doctor or psychiatrist for depression, or having sought or received treatment for depression (e.g., medication or therapy); (3) Elevated waist circumference: waist circumference ≥ 88 cm for females or ≥ 102 cm for males; (4) Elevated blood pressure: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, or the use of antihypertensive medication; (5) Elevated triglycerides: triglyceride level ≥ 1.7 mmol/L; (6) Elevated fasting blood glucose: fasting blood glucose ≥5.6 mmol/L, or treatment for elevated blood glucose, or HbA1c ≥39 mmol/mol; (7) Reduced high-density lipoprotein (HDL) cholesterol: HDL cholesterol < 1.3 mmol/L in females or < 1.0 mmol/L in males, or use of lipid-modifying medication [22]. Participants were categorized into two groups based on whether they fulfilled the above definition: (1) no CircS (reference group) and (2) CircS. Detailed medication codes are provided in Tables S2-S4.

2.3. Incident dementia

Dementia was identified through hospital inpatient dementia diagnosis during admission and death registry records using the International Classification of Diseases 10th edition (ICD-10) coding system [23]. The specific ICD-10 codes used to define dementia are provided in Table S5.

2.4. Covariates

Demographic data, including age (in years), gender ("Male," "Female"), and ethnicity ("White,", "Black", "Asian", "Others", "Missing") were collected. BMI was determined as weight (cm)/height $(kg)^2$. Smoking and drinking statuses were self-reported and categorized as "Never," "Previous," "Current," or "Missing". Physical activity was classified into three groups based on the metabolic equivalent (MET)-min/week, calculated from self-reported data on the number of days and duration of physical activity per week: <600, 600–3000, and ≥3000 MET-min/week. Household income in Britain pounds was categorized into five ranges: < 18,000, 18,000–30,999, 31,000–51,999, 52,000–100,000, >100,000 [24]. APOE genotype was determined using the rs7412 and rs429358 single-nucleotide polymorphisms (SNPs), with APOE-ε4 carriers (ε3/ε4 or ε4/ε4) identified through the genetic database.

2.5. Assessment of polygenic risk score

A standard PRS was developed to quantify genetic risk for dementia, using the genotype information from arrays covering more than 800,000 loci across the whole genome [25]. This PRS has demonstrated strong predictive performance for incident all-cause dementia and AD [18]. AD-related genetic loci were selected via meta-analysis of multiple genome-wide association studies (GWASs). A Bayesian approach was used to develop the PRS algorithm, incorporating trait-specific meta-analyses. The PRS for each participant was calculated by summing the posterior effect sizes for each variant, weighted by the allele dosage. Participants were categorized into three PRS groups: low (≤25th percentile), median (25th-75th percentile), and high (>75th percentile).

2.6. Statistical analysis

Baseline characteristics were described as means with standard deviations (SD) for continuous variables, and as frequencies and percentages for categorical variables. Group comparisons between participants with and without CircS were performed using the chi-square test for categorical variables and one-way analysis of variance for continuous variables.

Cox proportional-hazards model was used to evaluate longitudinal associations between CircS and incident dementia. To address the possibility of reverse causation and clarify whether the observed associations reflect true causal relationships, we conducted stratified analyses based on follow-up durations of ≤5 years, 5–10 years, and ≥10 years. To evaluate potential effect modification by gender, smoking status, drinking status, physical activity, and APOE-ε4 carrier status, interaction terms between CircS and each covariate were included in the Cox models. In addition, additive interactions were also evaluated using the relative excess risk due to interaction (RERI). An additive interaction was considered nonsignificant if the 95 % confidence interval (CI) for the RERI included zero.

The association between individual CircS components and incident dementia risk was evaluated using Cox proportional-hazards model. Restricted cubic splines (RCS) were used to assess the dose-response relationships between waist circumference, triglycerides, systolic blood pressure, diastolic blood pressure, fasting blood glucose, and HDL cholesterol as continuous variables and the risk of dementia. In addition, participants were categorized based on the combination of short sleep and/or depressive symptoms with the Mets (defined as the presence of at least three components: elevated waist circumference, elevated triglycerides, elevated blood pressure, elevated fasting blood glucose, and reduced HDL cholesterol). The following categories were considered: (1) Short sleep + MetS: presence of short sleep combined with MetS; (2) Depression + MetS: presence of depressive symptoms combined with MetS; Short sleep + depression + MetS: presence of both short sleep and depressive symptoms, in addition to MetS. Cox proportional hazards models were used to estimate hazard ratios (HR) for dementia risk in these groups.

To explore more refined measures of CircS, we further assigned scores to the CircS factors (excluding short sleep and depressive symptoms) based on previous literature [26–28], as detailed in Table S6. A score of 4–5, with the presence of at least one of either short sleep or depressive symptoms, was classified as 'mild CircS'. A score of 6–7, combined with at least one of short sleep or depressive symptoms, was categorized as 'moderate CircS'. A score of 8–9, with the presence of at least one of short sleep or depressive symptoms, was classified as 'severe CircS'. The association between mild CircS, moderate CircS, and severe CircS and the risk of dementia was assessed using a score of ≤3 as the reference category.

Cox proportional-hazards model was used to evaluate association between PRS and incident dementia. To examine the combined effects of CircS and genetic susceptibility on dementia risk, participants were categorized into six groups based on CircS ("yes" and "no") and PRS level ("low", "median" and "high"). The reference group consisted of participants with no CircS and low PRS. Cox proportional hazards models estimated HR for dementia in the other five groups, including interaction terms for CircS and PRS. The *p*-value for interaction was calculated. Additive interaction between genetic predisposition and CircS was assessed using the RERI.

Sensitivity analyses were conducted to assess the robustness of the results. These included repeating the main analysis while: (1) excluding participants with less than 2 years of follow-up; (2) treating death as a competing risk; and (3) using multiple imputation to address missing data. All analyses adjusted for covariates identified from the literature and preliminary analyses [6], including age, gender, UKB assessment center, ethnicity, smoking status, drinking status, BMI, educational level, household income, physical activity, and APOE-ε4 carrier status. All statistical analyses were performed using R software version 4.3.3, with a significance level set at a two-sided $p < 0.05$.

3. Results

3.1. Characteristics of participants

A total of 211,982 dementia-free individuals at baseline were eligible for the analysis (Fig. S1). The baseline characteristics stratified by CircS is provided in Table 1. The CircS group exhibited a higher likelihood of being older, female, current or previous smokers, having a higher BMI, lower household income levels, engaging in less physically active, and being carriers of the APOE-ε4. During the median follow-up period of 14.55 years, a total of 3965 incident dementia cases were identified.

3.2. Association between CircS and dementia

Participants with CircS exhibited a higher risk of developing dementia (HR: 1.401, 95 % CI: 1.296–1.516, Table 2). This elevated risk persisted across various follow-up periods: ≤5 years (HR: 1.501, 95 % CI: 1.147–1.965), 5–10 years (HR: 1.303, 95 % CI: 1.142–1.488) and >10 years (HR: 1.283, 95 % CI: 1.154–1.425) (Table 2). Compared to a CircS score of ≤3, mild CircS (HR: 1.259, 95 % CI: 1.146–1.383), moderate CircS (HR: 1.667, 95 % CI: 1.461–1.903), and severe CircS (HR: 2.028, 95 % CI: 1.397–2.944) were all significantly associated with an increased risk of dementia (Table 3). These findings underscore a graded escalation in dementia risk with the increasing severity of CircS.

Significant interactions were identified between CircS and APOE-ε4 carrier status concerning dementia risk. No significant interactions were observed between CircS and gender, smoking status, drinking status, or physical activity (Table S7). APOE-ε4 non-carriers with CircS had a higher dementia risk (HR: 1.568, 95 % CI: 1.407–1.748) compared to APOE-ε4 carriers (HR: 1.261, 95 % CI: 1.125–1.413). Notably, the absolute incidence of dementia was greater among APOE-ε4 carriers. The 15-year cumulative dementia incidence was 3.13 % for APOE-ε4 non-carriers with CircS versus 1.68 % without CircS. In contrast, APOE-ε4 carriers showed incidences of 7.18 % with CircS and 5.19 % without CircS. The risk difference was 1.99 % in APOE-ε4 carriers compared to 1.45 % in non-carriers (Fig. S2).

3.3. Joint effects of CircS and PRS on incidence of dementia

Each standard deviation increase in PRS was associated with a 75.3 % higher risk of incident dementia (HR: 1.753, 95 % CI: 1.706–1.801; Table S8). Compared to participants with a low PRS, those with a median PRS had a 42.1 % higher risk of incident dementia (HR: 1.421, 95 % CI: 1.288–1.576), and those with a high PRS had a 270.9 % higher risk (HR: 3.709, 95 % CI: 3.371–4.080) (Table S8). Joint effects models, depicted in Fig. 1, revealed that participants with both high PRS and CircS had a significantly elevated dementia risk (HR = 4.742, 95 % CI: 4.119, 5.460) compared to those with low PRS and no CircS (Fig. 1). A significant multiplicative interaction between PRS and CircS was observed (*p* for interaction < 0.001). However, no additive interaction between PRS and CircS regarding incident dementia risk was observed, the RERI was −0.032 (95 % CI: −0.161, 0.097).

3.4. Association of individual CircS component and dementia

For individual CircS components, elevated waist circumference, elevated blood pressure, elevated fasting blood glucose, reduced HDL cholesterol, short sleep, and depressive symptoms were each associated with a increased risk of dementia (Table 4). However, triglyceride levels did not show a significant association with incident dementia. Additionally, each CircS component, defined by any of the seven factors, was associated with a 13.6 % increase in dementia risk (HR: 1.136, 95 %

Table 1
Baseline characteristics of UKB participants by CircS status (n = 211,982).

Characteristic	Overall (n = 211,982)	CircS		
		No (n = 180,048)	Yes (31,934)	P-value
Baseline age, years	56.49 (8.10)	56.26 (8.18)	57.81 (7.53)	<0.001
Gender, n (%)				<0.001
Female	112,939 (53.28)	94,504 (52.49)	18,435 (57.73)	
Male	99,043 (46.72)	85,544 (47.51)	13,499 (42.27)	
Ethnicity, n (%)				<0.001
White	201,498 (95.05)	171,227 (95.10)	30,271 (94.79)	
Black	2555 (1.21)	2097 (1.17)	458 (1.43)	
Asian	4347 (2.05)	3734 (2.07)	613 (1.92)	
Others	1177 (0.56)	989 (0.55)	188 (0.59)	
Missing	2405 (1.13)	2001 (1.11)	404 (1.27)	
Smoking status, n (%)				<0.001
Never	115,853 (54.65)	100,866 (56.02)	14,987 (46.93)	
Previous	74,070 (34.94)	61,474 (34.14)	12,596 (39.44)	
Current	21,373 (10.08)	17,144 (9.52)	4229 (13.24)	
Missing	686 (0.32)	564 (0.31)	122 (0.38)	
Drinking status, n (%)				<0.001
Never	8564 (4.04)	6782 (3.77)	1782 (5.58)	
Previous	7077 (3.34)	5116 (2.84)	1961 (6.14)	
Current	196,147 (92.53)	168,016 (93.32)	28,131 (88.09)	
Missing	194 (0.09)	134 (0.07)	60 (0.19)	
Body mass index, kg/m^2	27.29 (4.63)	26.68 (4.28)	30.70 (5.05)	<0.001
Physical activity, n (%)				<0.001
<600 MET-min/week	41,277 (19.47)	32,996 (18.33)	8281 (25.93)	
600–3000	106,779 (50.37)	91,376 (50.75)	15,403 (48.23)	
MET-min/week				
≥3000 MET-min/week	63,926 (30.16)	55,676 (30.92)	8250 (25.83)	
Household income				<0.001
<£18,000	41,210 (19.44)	31,851 (17.69)	9359 (29.31)	
£18,000-£30,999	47,301 (22.31)	39,736 (22.07)	7565 (23.69)	
£31,000-£51,999	48,417 (22.84)	42,267 (23.48)	6150 (19.26)	
£52,000-£100,000	37,694 (17.78)	34,050 (18.91)	3644 (11.41)	
>£100,000	9844 (4.64)	9185 (5.10)	659 (2.06)	
Missing	27,516 (12.98)	22,959 (12.75)	4557 (14.27)	
APOE-ε4 status, n (%)				<0.001
Non-carrier	156,936 (74.03)	133,574 (74.19)	23,362 (73.16)	
Carrier	55,046 (25.97)	46,474 (25.81)	8572 (26.84)	

Data are mean (SD) or n (%). Abbreviations: APOE, apolipoprotein; CircS, circadian syndrome; MET, metabolic equivalent of task; SD, standard deviation.

Table 2
Cox proportional-hazards models evaluating the association between CircS and incident dementia across different follow-up periods.

Follow-up period	Case/Population	HR (95 % CI)
Complete follow-up		
No CircS	3067/180,048	1 (Ref.)
CircS	898/31,934	**1.401 (1.296, 1.516)**
≤5 years follow-up		
No CircS	227/2887	1 (Ref.)
CircS	69/703	**1.501 (1.147, 1.965)**
5–10 years follow-up		
No CircS	1101/5881	1 (Ref.)
CircS	278/1291	**1.303 (1.142, 1.488)**
>10 years follow-up		
No CircS	1893/178,886	1 (Ref.)
CircS	397/22,334	**1.283 (1.154, 1.425)**

Model was adjusted for age, sex, UKB assessment center, ethnicity, smoking status, body mass index, drinking status, educational level, household income, physical activity, and APOE-ε4 carrier status. Abbreviations: APOE, apolipoprotein; CI, confidence interval; CircS, circadian syndrome; HR, hazard ratio; Ref., reference group.

Table 3
Cox proportional hazards models evaluating the association between circadian syndrome severity and incident dementia.

CircS severity classification	Case/Population	HR (95 % CI)
Score ≤3	3149/183,181	1 (Ref.)
Mild CircS	525/20,897	**1.259 (1.146, 1.383)**
Moderate CircS	262/7054	**1.667 (1.461, 1.903)**
Severe CircS	29/850	**2.028 (1.397, 2.944)**

Model was adjusted for age, sex, UK Biobank assessment centre, ethnicity, smoking status, body mass index, drinking status, educational level, household income, physical activity, and APOE-ε4 carrier status. Abbreviations: CI, confidence interval; HR, hazard ratio.

CI: 1.106–1.166) (Table 4). Even the presence of three CircS components, regardless of whether they are MetS or non-MetS factors, significantly elevated dementia risk (HR: 1.421, 95 % CI: 1.124–1.796; Fig. S3), highlighting the strong predictive value of CircS components for dementia. Figure S4 presents the associations between continuous variables of waist circumference, triglycerides, blood pressure, fasting blood glucose, and HDL cholesterol with the risk of dementia. The continuous variables of waist circumference, triglycerides, diastolic blood pressure, fasting blood glucose, and HDL cholesterol exhibited nonlinear associations with the risk of dementia ($P_{\text{Nonlinear}}$<0.05), whereas systolic blood pressure did not demonstrate a statistically significant relationship with dementia risk (P_{Total}>0.05).

For participants defined by short sleep + MetS, the HR for dementia was 1.258 (95 % CI: 1.067, 1.482). For those with depression + MetS, the HR was 1.399 (95 % CI: 1.289, 1.519). The highest risk for dementia was observed in participants with short sleep + depressive symptoms + MetS, where the HR was 1.478 (95 % CI: 1.172, 1.864). These results suggest

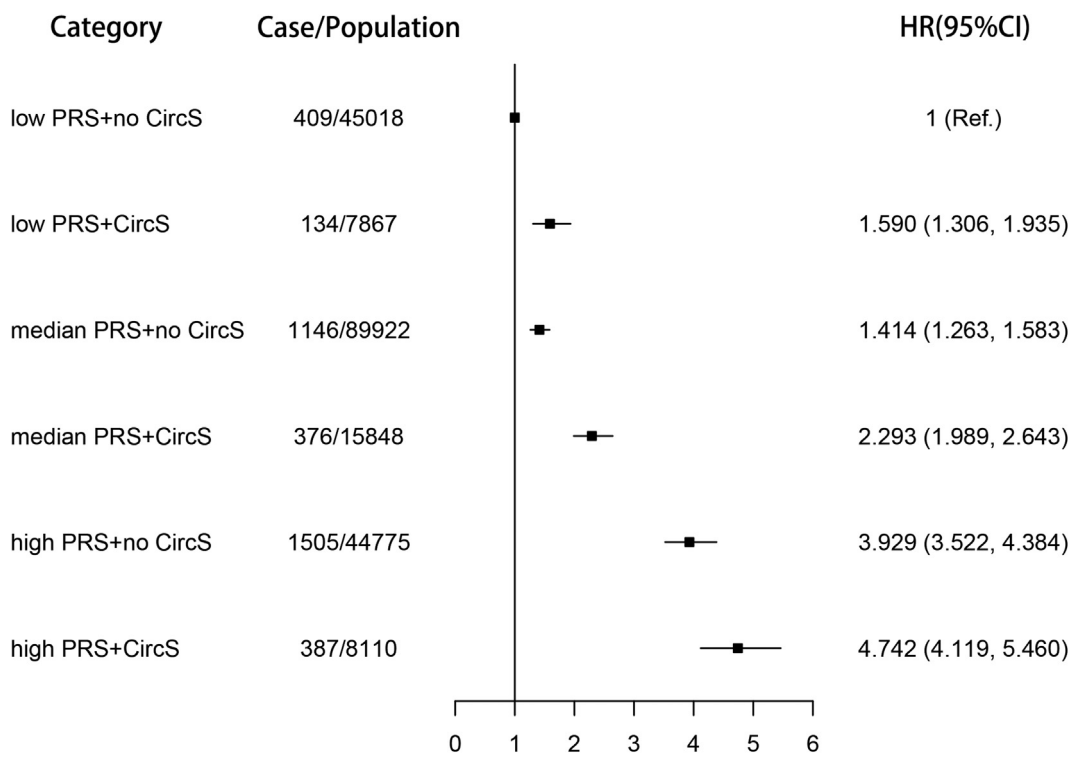

Fig. 1. The joint effects of CircS and PRS on the risk of dementia incidence (n = 211,540). Model was adjusted for age, sex, UKB assessment center, ethnicity, smoking status, body mass index, drinking status, educational level, household income, physical activity, and the scores from the first four axes of genetic principal components. Abbreviations: CI, confidence interval; CircS, circadian syndrome; HR, hazard ratio; PRS, polygenic risk score; Ref., reference group.

that the combination of short sleep and depressive symptoms with MetS components significantly increases dementia risk (Table 4).

3.5. Sensitivity analyses

Results of the sensitivity analyses remained robust after (1) excluding individuals with follow-up time less than 2 years; (2) considering death as a competing risk; and (3) employing multiple imputation to address missing data in the analysis (Table S9).

4. Discussion

This study provides compelling evidence that CircS significantly increases the risk of incident dementia, with a notable multiplicative interaction between genetic susceptibility and CircS in dementia risk. Our findings indicate that a higher PRS for dementia, CircS, and most components of CircS are independently associated with an increased incidence of dementia, with the exceptions of elevated triglycerides. Individuals with CircS combined with a higher PRS exhibited a significantly elevated incidence of dementia, suggesting that genetic predisposition amplifies the impact of CircS on dementia development.

Our findings are in agreement with a previous longitudinal study of 9770 Chinese adults, which demonstrated that CircS is associated with an increased risk of all-cause dementia [4]. Additionally, we observed that APOE-ε4 non-carriers with CircS had a higher dementia risk, consistent with Qureshi et al., who reported that MetS elevates dementia risk in APOE-ε4 non-carriers [6]. Notably, the absolute risk difference between the CircS and no-CircS groups was larger among APOE-ε4 carriers (1.99 %) compared to non-carriers (1.45 %). This suggests that the higher relative risk observed in APOE-ε4 non-carriers may be partly due to the elevated baseline risk in APOE-ε4 carriers, resulting in a relatively smaller increase in dementia risk within the carrier group.

Our analysis also revealed significant additive interactions between smoking and CircS in relation to dementia risk. This association was stronger in smokers and previous smokers compared to never smokers. Smoking is a well-established mediator linking socioeconomic factors and health outcomes, although its role in dementia risk remains debated. Cohort studies without tobacco industry funding have shown a significantly increased risk of AD, whereas tobacco industry-funded studies have found non-significant associations [29]. The Atherosclerosis Risk in Communities study showed 33 % increased risk of incident all-cause dementia in current smokers compared with those who never smoked [30]. Smoking increases oxidative stress and inflammation, both of which are implicated in the pathogenesis of dementia [31]. Additionally, smokers often exhibit other unhealthy lifestyle habits, such as lack of exercise and poor diet [32], which may further exacerbate the risk of CircS and dementia. These findings suggest that smoking may amplify the harmful effects of CircS on dementia risk.

Previous studies have employed PRS to quantitatively examine individual genetic predisposition, highlighting the interaction between acquired risk factors and genetic susceptibility for dementia [33]. In this study, we further investigated the modulating role of genetic predisposition on the relationship between CircS and dementia risk. Our results indicate that CircS and PRS exhibit a multiplicative rather than an additive interaction in relation to dementia risk. Specifically, participants with a high PRS, indicating a greater genetic vulnerability to dementia, exhibited a significantly elevated risk of developing dementia when CircS was present. The presence of a significant multiplicative interaction but no additive interaction indicates that while genetic susceptibility and CircS interact in a way that affects dementia risk differently between CircS categories, their combined effect does not result in an excess risk beyond their individual effects. These results underscore the potential for personalized dementia prevention strategies that account for genetic factors.

Furthermore, our study corroborated that elevated waist circumference, elevated blood pressure, increased fasting glucose levels, reduced HDL cholesterol, short sleep duration, and depressive symptoms are associated with a heightened risk of dementia, consistent with prior stud-

Table 4
Cox proportional-hazards models for the association between CircS components and incident dementia (n = 211,982).

Components	Case/Population	HR (95 % CI)
Per one of CircS components	3965/211,982	**1.136 (1.106, 1.166)**
Elevated waist circumference		
No	2480/143,512	1 (Ref.)
Yes	1485/68,470	**1.114 (1.020, 1.217)**
Elevated triglycerides		
No	2238/127,833	1 (Ref.)
Yes	1727/84,149	0.952 (0.891, 1.016)
Elevated blood pressure		
No	508/55,702	1 (Ref.)
Yes	3457/156,280	**1.111 (1.009, 1.223)**
Elevated fasting blood glucose		
No	2704/172,483	1 (Ref.)
Yes	1261/39,499	**1.335 (1.245, 1.432)**
Reduced HDL-cholesterol		
No	1813/12,6471	1 (Ref.)
Yes	2152/85,511	**1.207 (1.130, 1.289)**
Short sleep		
No	3686/200,462	1 (Ref.)
Yes	279/11,520	**1.218 (1.077, 1.377)**
Depressive symptom		
No	2467/136,665	1 (Ref.)
Yes	1498/75,317	**1.312 (1.228, 1.401)**
Short sleep + MetS		
No	3812/206,954	1 (Ref.)
Yes	132/5028	**1.258 (1.067, 1.482)**
Depression + MetS		
No	3182/183,941	1 (Ref.)
Yes	783/28,041	**1.399 (1.289, 1.519)**
Short sleep + depressive symptoms + MetS		
No	3891/209,574	1 (Ref.)
Yes	74/2408	**1.478 (1.172, 1.864)**

Per one of CircS components refers to the analysis assessing the effect of each individual CircS component (e.g., short sleep, depressive symptoms, or any component of MetS) on the risk of dementia. For example, the model evaluated the increase in dementia risk for each of the seven CircS factors, independently of whether it is a MetS or non-MetS factor.
Model was adjusted for age, sex, UKB assessment center, ethnicity, smoking status, body mass index, drinking status, educational level, household income, physical activity, and APOE-ε4 carrier status. Abbreviations: APOE, apolipoprotein; CI, confidence interval; CircS, circadian syndrome; HDL, high-density lipoprotein; HR, hazard ratio; Ref., reference group.

ies [13,14,34,35]. The association between sleep disturbances and dementia is particularly complex. Xiong et al., found that short sleep duration (<7 h) was linked to a higher risk of dementia in younger-older adults but a lower risk in older-older adults. Additionally, long sleep duration (>8 h) was associated with an increased risk of all-cause dementia and Alzheimer's disease compared to the optimal sleep duration of 7–8 h [13]. These findings suggest that early identification of diverse sleep patterns may aid in recognizing individuals at elevated risk for dementia. In addition, we found non-significant relationship between elevated triglycerides and incident dementia in participants with a mean age < 60 years. Danial Qureshi et al., reported that elevated triglyceride level was associated with lower risk of dementia in individuals aged ≥ 60 years [6], whereas elevated triglycerides were found to be associated with increased risk of dementia at mid-life [36]. Dementia led to metabolism changes, which ultimately affected triglyceride levels among those affected [37]. These inconsistent results may partially due to reverse causation and aggressive medication usages among individuals with elevated triglycerides. As dementia progresses, changes in metabolism and nutritional intake can significantly alter blood lipid levels. Elevated triglycerides in middle-aged individuals may signal an increased future risk of cardiovascular diseases, thus raising the risk of dementia. Conversely, metabolic changes in older adults may obscure this relationship.

Previous studies revealed that increased relative risk could be achieved via increasing the number of components. Danial Qureshi et al., found that the risk of dementia was only significantly elevated among participants with ≥ 4 MetS components [6]. However, Marcos D. Machado-Fragua reported that those with 2 MetS components showed significantly increased risk of dementia compared with those with only 1 MetS component [38]. In our study, CircS was strictly defined to include at least one of short sleep or depressive symptom. We found that the presence of even three CircS components was significantly associated with an elevated dementia risk. Our results are consistent with those of Marcos D. Machado-Fragua, and demonstrate a more substantial predictive role on dementia risk than the study by Danial Qureshi et al. This difference may be attributed to age differences in the samples, as the impact of various components on dementia across the lifespan [39].

The mechanisms underlying the relationship between CircS and dementia are not fully understood. Individual components of CircS, such as short sleep duration and depressive symptoms, are associated with an increased risk of dementia, but the strength of these associations varies across different stages of life [39]. It is critical to clarify whether these associations are driven by CircS as a whole or by specific components. Various biological mechanisms, including vascular injury, neuroinflammation, oxidative stress, and glucose metabolism, are proposed to mediate the effects of different CircS components on dementia development. For instance, chronic sleep deprivation has been shown to exacerbate neuroinflammation and oxidative stress, which are key drivers of neurodegeneration. Depressive symptoms, commonly observed in individuals with CircS, may also contribute to dementia risk through alterations in glucose metabolism and increased vulnerability to vascular injury [40,41]. As the number of CircS components increases, the risk of de-

mentia incidence rises by 13.6 %, suggesting that these components may act both independently and synergistically in enhancing dementia risk.

Our study has several strengths. The large and longitudinal cohort study with comprehensive phenotypic and genotypic information and an average follow-up of nearly 15 years, enabled us to obtain robust association between CircS and dementia. Additionally, we pioneered the introduction of a scoring system for CircS components, enabling the categorization of CircS severity. This approach demonstrated a graded association between CircS severity and dementia risk, with an increased severity of CircS corresponding to a higher risk of dementia, thus offering valuable insights into the relationship between CircS and dementia risk.

Nevertheless, our study has several limitations. First, dementia was identified from the hospital inpatient dementia diagnosis during admission and death registry records, therefore, the number of dementia cases may be underestimated due to the limited record sources. Second, stratified analyses of different dementia subtypes (e.g., AD, vascular dementia) were not performed. Third, medication usage was used to define several CircS components, including elevated blood pressure, increased fasting blood glucose, decreased HDL-cholesterol, and depressive symptom, which may lead to confounding by indication. As individuals prescribed medication for these conditions are likely to have more severe or clinically significant health issues, this could potentially lead to an overestimation of the associations between these CircS components and dementia risk. Fourth, the majority of UKB participants are European descent, which may limit the generalizability of our findings. Finally, the residual confounding may exist even though extensive covariate correction were performed.

In conclusion, our study found that CircS is associated with an increased risk of dementia, with this association remaining consistent over time. The interplay between CircS and genetic susceptibility, particularly in individuals with a high PRS, underscores the need for targeted and personalized prevention strategies in dementia.

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Ethics declarations

Ethics approval and consent to participate

The UK Biobank was approved by the North West Multi-centre Ethics Committee, and written informed consent was provided by all participants. This study was conducted under UK Biobank project number 106528 in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

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.

CRediT authorship contribution statement

Linling Yu: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Wei Liu:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Chenqi Liao:** Writing – review & editing, Resources, Methodology, Conceptualization. **Na Shen:** Writing – review & editing, Supervision, Conceptualization. **Anding Liu:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Liming Cheng:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Xiong Wang:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

Data availability

The usage of UK Biobank data has been approved by UK Biobank Research Team (Application ID: 106528). Data from UK Biobank (https://www.ukbiobank.ac.uk/) are available on application.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100089.

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