BMC Gastroenterology

RESEARCH

Open Access

Association between circadian syndrome and MASLD risk: evidence from a large cross-sectional study

Jihan Sun[1,2], Shuqi Mao[1*] and Caide Lu[1*]

Abstract

Background Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent chronic liver condition closely associated with metabolic syndrome and linked to circadian disruptions. Circadian Syndrome (CircS), a constellation of metabolic and circadian dysregulations, has emerged as a risk factor for metabolic disorders. This study aims to examine the association between CircS and MASLD and to evaluate the potential relevance of CircS in identifying individuals at elevated MASLD risk.

Methods Data from 2,288 participants in the 2017–2018 U.S. National Health and Nutrition Examination Survey (NHANES) cycle were analyzed. Weighted logistic regression models were used to assess the overall association between CircS and MASLD. Restricted cubic spline (RCS) analyses were applied to evaluate the dose–response relationship. Subgroup analyses were conducted to explore potential effect modifiers underlying the CircS-MASLD association.

Results A significant association between CircS and MASLD was observed. Application of weighted logistic regression revealed that individuals with CircS had increased odds of MASLD (adjusted *OR* = 4.123, 95% CI: 2.489–6.832, *P* = 0.001) after adjusting for demographic, lifestyle, and metabolic covariates. The association was consistent across demographic subgroups, with a linear trend showing higher CircS scores correlating with increased MASLD risk.

Conclusion CircS is significantly associated with MASLD and may have potential implications for early risk identification and targeted intervention. However, its clinical utility requires further validation in prospective studies before integration into routine practice.

Keywords Metabolic dysfunction-associated steatotic liver disease (MASLD), Circadian syndrome (CircS), Metabolic dysfunction, NHANES

*Correspondence:
Shuqi Mao
mmmaoshuqi@163.com
Caide Lu
lucaide@nbu.edu.cn
[1]Department of Hepatopancreatobiliary Surgery, The Affiliated Lihuili Hospital, Ningbo University, Ningbo 315041, Zhejiang, China
[2]Université de Franche-Comté, EFS, INSERM, UMR RIGHT, Besançon F-25000, France

Background

Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most prevalent chronic liver diseases worldwide, affecting approximately 29.8% of adults [1]. The pathogenesis of MASLD is complex and multifactorial, in addition to traditional metabolic dysfunctions, recent evidence also highlights the role of endocrine alterations, such as elevated plasma aldosterone concentrations, in MASLD development [2, 3]. Early identification and targeted interventions addressing underlying metabolic dysfunctions are essential for mitigating disease progression and reducing its broader health implications [4].

Circadian Syndrome (CircS) represents the collective metabolic and systemic health consequences of circadian disruption, encompassing hypertension, hyperglycemia, central obesity, dyslipidemia, short sleep duration, and depression [5, 6]. Emerging evidence identifies CircS as a major risk factor for metabolic diseases, highlighting circadian misalignment as a potential driver of these conditions [7, 8]. Previous studies have developed prediction models for related outcomes, such as the risk of type 2 diabetes in obese MASLD patients [9] and the incidence of MASLD in nonobese individuals [10], mainly using traditional metabolic and biochemical indicators. Although circadian rhythm disruptions are linked to various metabolic disorders [11], research specifically examining the relationship between CircS and MASLD remains limited. Circadian rhythms regulate key hepatic functions, including glucose and lipid metabolism and inflammatory responses, all of which are implicated in MASLD pathogenesis. Investigating their disruption may provide new insights into disease mechanisms and support the development of circadian-targeted, personalized management strategies.

This study investigates the association between CircS and MASLD utilizing data from the U.S. National Health and Nutrition Examination Survey (NHANES). The association between CircS and MASLD is validated through weighted and subgroup analyses, including an exploration of potential nonlinear relationships. Using this large, nationally representative dataset, the study assesses the correlation between CircS, an indicator of circadian disruption and metabolic dysregulation, and MASLD risk. These analyses aim to deepen our understanding of the role of circadian health in liver disease, positioning CircS as a potential risk factor for MASLD and offering insights for targeted prevention and intervention strategies.

Methods

Study population

This study utilized data from the 2017–2018 cycle of the NHANES, the only cycle to include comprehensive information on both MASLD and CircS. NHANES is a nationally representative survey that assesses the health and nutritional status of U.S. adults and children through a complex, multistage probability sampling design. The NHANES protocol is approved by the Research Ethics Review Board of the National Center for Health Statistics, with informed consent obtained from all participants. Participant selection followed a systematic process as outlined in Fig. 1. From an initial sample of 9,254 participants, we excluded those with missing MASLD data ($n = 3{,}306$), as controlled attenuation parameter (CAP) measurement using vibration-controlled transient elastography (VCTE) was not administered to all NHANES participants due to logistical constraints and specific eligibility criteria. We further excluded individuals with missing CircS data ($n = 3{,}241$). Several CircS components, particularly sleep duration assessment and depression screening, were administered only to subsets of participants within specialized examination modules. Complete data for all seven CircS components was essential for accurate classification, as missing any component would introduce misclassification bias. Finally, participants with missing covariate data ($n = 419$) were excluded to ensure the integrity of our multivariate models. This approach, consistent with NHANES analytical guidelines, resulted in a final analytical sample of 2,288 participants with complete data. To address potential selection bias, we employed survey weights and design variables in our statistical analysis, ensuring that our results maintained generalizability to the U.S. adult population despite these necessary exclusions.

Assessment of MASLD

In this study, MASLD was defined using the CAP, measured *via* VCTE with the FibroScan 502 Touch device, employed in the NHANES 2017–2018 cycle. This device assesses hepatic steatosis by quantifying ultrasonic attenuation of the echo wave, recorded as the CAP value. Measurements were performed with either a medium or extra-large probe, selected according to participant body habitus. To ensure reliable assessment, the CAP value for each participant was calculated as the median of at least ten valid measurements. CAP values are known to correlate positively with MASLD severity. Based on prior research, a CAP cutoff of 285 dB/m was applied as the threshold for MASLD diagnosis [12].

Assessment of circadian syndrome

Circadian Syndrome was defined as the presence of four or more of the following seven components, as detailed in Table 1. One point was assigned for each component present, resulting in a total CircS score ranging from 0 to 7. The definitions and scoring criteria were based on the methodology described by Shi et al. [13–15].

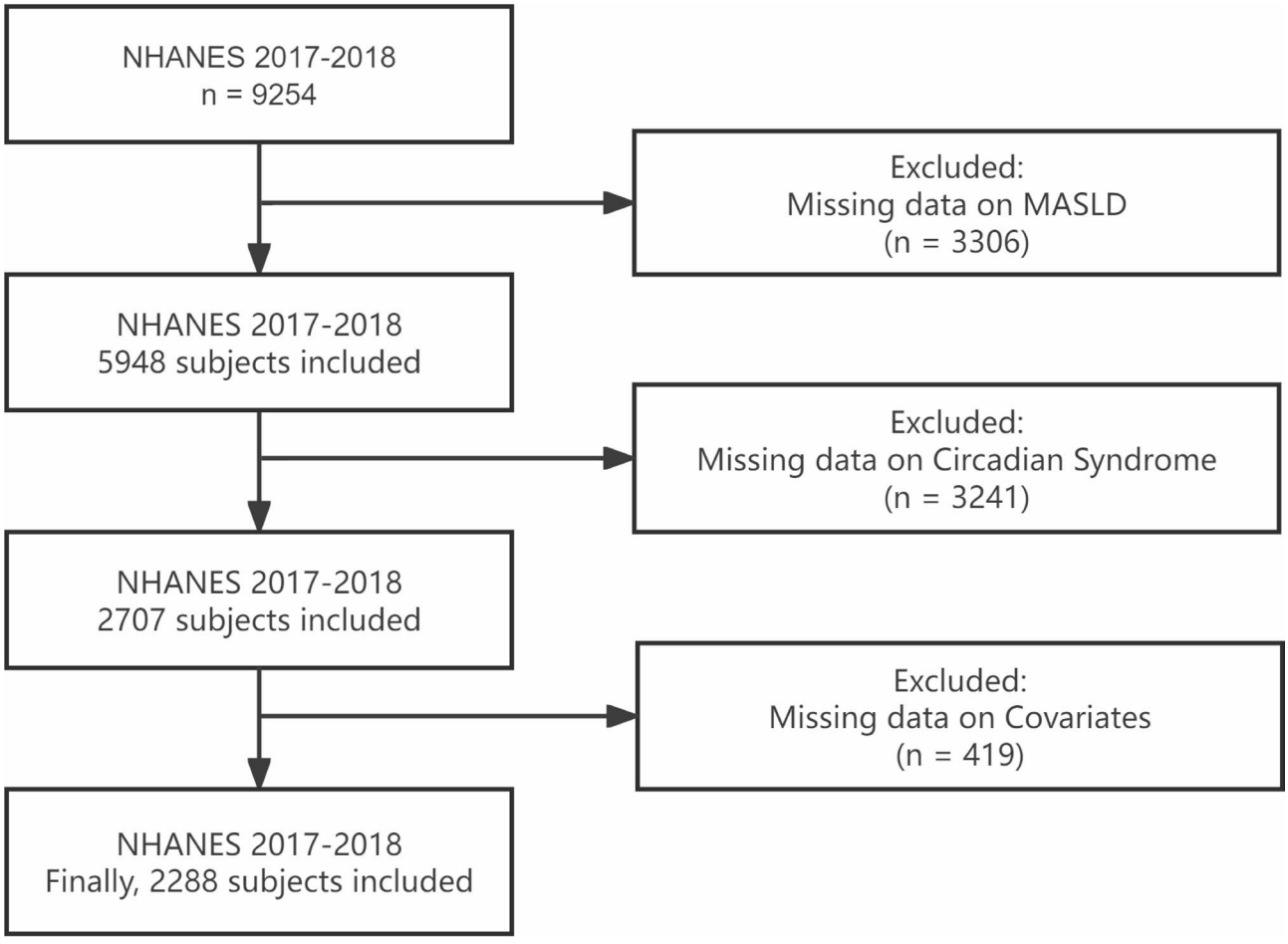

Fig. 1 Screening conditions and process for the study population

Table 1 Diagnostic components and criteria of circadian syndrome

Component	Criteria
a. Elevated triglycerides	Serum triglyceride levels ≥ 150 mg/dL or current use of lipid-lowering medications
b. Central obesity	Waist circumference ≥ 102 cm for men and ≥ 88 cm for women
c. Elevated blood pressure	Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or use of antihypertensive medications
d. Reduced HDL-C	HDL-C < 40 mg/dL in men and < 50 mg/dL in women, or use of prescribed lipid-lowering medications
e. Short sleep duration	Average sleep of ≤ 6 h per night, based on self-reported data
f. Elevated fasting glucose	Fasting glucose level ≥ 100 mg/dL or use of anti-diabetic medications
g. Depressive symptoms	Assessed with the Patient Health Questionnaire (PHQ-9), with a score of ≥ 5 indicating depressive symptoms

Covariates

Covariates were selected based on prior literatures, biological plausibility, and their established relevance to both CircS components and MASLD risk [16, 17]. Covariates in this study included age, gender, race/ethnicity, education level, family income-to-poverty ratio (PIR), smoking status, alcohol consumption, liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) and Healthy Eating Index (HEI). Race/ethnicity was categorized according to NHANES-defined groups, while education level was based on the highest level of schooling completed. PIR, representing economic status, was calculated as the ratio of family income to the federal poverty threshold. Smoking status was determined by asking participants if they had smoked more than 100 cigarettes in their lifetime and if they currently smoked; those answering "yes" to both were classified as current smokers. Alcohol consumption was defined by self-reported intake of at least 12 alcoholic drinks in the past year, with such participants classified as alcohol consumers. These covariates were incorporated into the analysis

to control for potential confounders influencing the association between CircS and MASLD.

Statistical analysis

Given the complex, multi-stage probabilistic sampling design of NHANES, weighted logistic regression was used following the NHANES analysis guidelines (https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx). For descriptive purposes, Table 2 presents unweighted baseline characteristics of the study participants stratified by MASLD status, allowing for clear visualization of the actual study sample composition. Continuous data, which were non-normally distributed, are presented as median (M) and interquartile range (Q1, Q3) and were analyzed using the Mann-Whitney U test. Categorical variables were summarized as frequency (n) and percentage (%) and analyzed with the chi-square test, while ordinal variables were similarly described and analyzed using the Mann-Whitney U test.

To examine the relationship between CircS and MASLD, weighted logistic regression models were employed with three progressively adjusted covariate models. Subgroup and interaction analyses were conducted to assess the stability of these associations, with results visualized through a forest plot. To address potential confounding effects, propensity score matching (PSM) was performed using 1:1 nearest-neighbor matching with a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Covariate balance before and after matching was assessed using standardized mean differences (SMD), with an SMD value below 0.1 considered indicative of adequate balance. Post-matching analyses were conducted using the same logistic regression models to provide adjusted estimates of the CircS-MASLD association in the matched cohorts. Additionally, RCS analysis was performed to explore potential nonlinear relationships between CircS and MASLD. All analyses were conducted using R software version 4.0.0, with statistical significance set at $P < 0.05$.

Results

Characteristics of the study participants

The baseline characteristics of the study participants, stratified by MASLD status, are presented in Table 2. The study included 2,288 participants, of whom 972 (42.49%) were identified with MASLD, while 1,316 (57.51%) were without MASLD. Participants with MASLD were older, with a median age of 57 years (Q1, Q3: 44.00, 67.00), compared with 53 years (Q1, Q3: 35.00, 65.00) for those without MASLD ($P < 0.001$). The proportion of males was significantly higher in the MASLD group (53.09%) compared with the non-MASLD group (47.64%) ($P = 0.010$). In terms of race/ethnicity, a greater percentage of non-Hispanic White (17.80%) and Mexican American (39.71%) individuals were observed in the MASLD group, whereas a higher proportion of Other Race-Including Multi-Racial (25.91%) participants were found in the non-MASLD group ($P < 0.001$). Educational attainment differed significantly, with a lower percentage of college graduates in the MASLD group (20.68%) compared with the non-MASLD group (26.75%) ($P = 0.048$). Smoking status and alcohol consumption also varied by MASLD status, with a lower prevalence of current smokers (14.81% vs. 18.24%, $P = 0.030$) and alcohol consumers (40.02% vs. 44.76%, $P = 0.024$) in the MASLD group. Liver enzymes (ALT and AST) and the CircS score were notably higher in participants with MASLD, indicating potential associations between these variables and MASLD presence ($P < 0.001$). Several components of CircS, including elevated triglycerides, central obesity, elevated blood pressure, reduced high-density lipoprotein cholesterol (HDL-C), elevated glucose, and depression symptoms, were more prevalent among individuals with MASLD (all $P < 0.01$).

Among the initial 2707 eligible participants, 419 individuals were excluded due to missing covariate data. Compared with those included in the final analysis, the excluded participants exhibited a higher proportion of non-drinkers, but did not significantly differ in age, sex, race, education, income, smoking status, liver enzyme levels (ALT and AST), or HEI scores (Supplementary Table 1).

Association between circs and MASLD

Table 3 presented the weighted logistic regression analysis examining the association between CircS and MASLD across three models. In Model 1, with no covariate adjustment, participants with CircS had significantly higher odds of having MASLD ($OR = 4.514$, 95% CI: 3.207–6.354, $P < 0.001$). After adjusting for age, gender, race, education level, and PIR in Model 2, the association remained robust ($OR = 4.567$, 95% CI: 3.212–6.493, $P < 0.001$). Further adjustment in Model 3, which included smoking status, alcohol consumption, ALT, AST, and HEI shown a slight decrease in the *OR*, but the relationship between CircS and MASLD remained significant ($OR = 4.123$, 95% CI: 2.489–6.832, $P = 0.001$). Additionally, several individual components of CircS were independently associated with MASLD. Elevated triglycerides, central obesity, elevated blood pressure, reduced HDL-C, elevated glucose, and depression symptoms all shown significant associations with MASLD across all models ($P < 0.05$), highlighting the strong relationship between CircS and increased MASLD risk. However, short sleep duration did not exhibit a significant association with MASLD in any model ($P > 0.05$). To further validate these associations and address potential confounding, we conducted PSM analysis, which yielded 867 matched pairs of participants

Table 2 Comparison of baseline characteristics between no MASLD and MASLD groups

Variables	Total ($n=2288$)	No MASLD ($n=1316$)	MASLD ($n=972$)	Statistic	*P*
Age, M (Q_1, Q_3)	55.00 (39.00, 66.00)	53.00 (35.00, 65.00)	57.00 (44.00, 67.00)	-5.49	< 0.001
Gender, n (%)				6.62	0.010
Male	1143 (49.96)	627 (47.64)	516 (53.09)		
Female	1145 (50.04)	689 (52.36)	456 (46.91)		
Race, n (%)				49.27	< 0.001
Non-Hispanic White	311 (13.59)	138 (10.49)	173 (17.80)		
Non-Hispanic Black	201 (8.78)	123 (9.35)	78 (8.02)		
Mexican American	827 (36.15)	441 (33.51)	386 (39.71)		
Other Race - Including Multi-Racial	522 (22.81)	341 (25.91)	181 (18.62)		
Other Hispanic	427 (18.66)	273 (20.74)	154 (15.84)		
Education, n (%)				-1.97	0.048
Less Than 9th Grade	152 (6.64)	91 (6.91)	61 (6.28)		
9-11th Grade	249 (10.88)	141 (10.71)	108 (11.11)		
High School Grad/GED or Equivalent	549 (23.99)	302 (22.95)	247 (25.41)		
Some College or AA degree	785 (34.31)	430 (32.67)	355 (36.52)		
College Graduate or above	553 (24.17)	352 (26.75)	201 (20.68)		
PIR, M (Q_1, Q_3)	2.22 (1.22, 4.27)	2.20 (1.22, 4.25)	2.31 (1.24, 4.32)	-0.57	0.567
Smoke, n (%)				4.69	0.030
No	1904 (83.22)	1076 (81.76)	828 (85.19)		
Yes	384 (16.78)	240 (18.24)	144 (14.81)		
Alcohol Use, n (%)				5.12	0.024
No	1310 (57.26)	727 (55.24)	583 (59.98)		
Yes	978 (42.74)	589 (44.76)	389 (40.02)		
ALT, M (Q_1, Q_3)	18.00 (13.00, 26.00)	16.00 (12.00, 23.00)	21.00 (15.00, 31.00)	-12.35	< 0.001
AST, M (Q_1, Q_3)	19.00 (16.00, 24.00)	19.00 (16.00, 23.00)	20.00 (16.00, 26.00)	-4.61	< 0.001
HEI, M (Q_1, Q_3)	49.74 (42.00, 59.05)	50.11 (42.49, 59.74)	49.19 (41.41, 58.01)	Z=-1.49	0.137
CircS Score, M (Q_1, Q_3)	3.00 (2.00, 5.00)	3.00 (1.00, 4.00)	4.00 (3.00, 5.00)	-19.25	< 0.001
CircS, n (%)				245.90	< 0.001
No	1249 (54.59)	903 (68.62)	346 (35.60)		
Yes	1039 (45.41)	413 (31.38)	626 (64.40)		
Elevated triglycerides, n (%)				154.29	< 0.001
No	1209 (52.84)	842 (63.98)	367 (37.76)		
Yes	1079 (47.16)	474 (36.02)	605 (62.24)		
Central obesity, n (%)				345.45	< 0.001
No	864 (37.76)	710 (53.95)	154 (15.84)		
Yes	1424 (62.24)	606 (46.05)	818 (84.16)		
Elevated blood pressure, n (%)				105.77	< 0.001
No	980 (42.83)	684 (51.98)	296 (30.45)		
Yes	1308 (57.17)	632 (48.02)	676 (69.55)		
Reduced HDL-C, n (%)				115.28	< 0.001
No	1172 (51.22)	801 (60.87)	371 (38.17)		
Yes	1116 (48.78)	515 (39.13)	601 (61.83)		
Short sleep, n (%)				3.05	0.081
No	1853 (80.99)	1082 (82.22)	771 (79.32)		
Yes	435 (19.01)	234 (17.78)	201 (20.68)		
Elevated glucose, n (%)				127.05	< 0.001
No	974 (42.57)	692 (52.58)	282 (29.01)		
Yes	1314 (57.43)	624 (47.42)	690 (70.99)		
Depression symptoms, n (%)				10.06	0.002
No	1690 (73.86)	1005 (76.37)	685 (70.47)		
Yes	598 (26.14)	311 (23.63)	287 (29.53)		

Table 3 Association between circs and MASLD analyzed by weighted univariable and multivariable logistic regression analyses

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P*	*OR* (95% CI)	*P*	*OR* (95% CI)	*P*	*OR* (95% CI)	*P*
CircS	4.514 (3.207, 6.354)	< 0.001	4.567 (3.212, 6.493)	< 0.001	4.123 (2.489, 6.832)	0.001	2.880 (2.372, 3.502)	< 0.001
Elevated triglycerides	3.361 (2.538, 4.451)	< 0.001	3.08 (2.31, 4.108)	< 0.001	2.885 (1.855, 4.487)	0.003	2.085 (1.722, 2.527)	< 0.001
Central obesity	8.105 (5.672, 11.581)	< 0.001	9.295 (6.238, 13.851)	< 0.001	7.472 (4.054, 13.773)	0.001	4.850 (3.889, 6.076)	< 0.001
Elevated blood pressure	3.265 (2.408, 4.426)	< 0.001	3.295 (2.363, 4.595)	< 0.001	3.026 (1.916, 4.778)	0.003	1.807 (1.485, 2.200)	< 0.001
Reduced HDL-C	2.397 (1.798, 3.194)	< 0.001	2.266 (1.612, 3.185)	< 0.001	1.974 (1.236, 3.152)	0.016	1.905 (1.575, 2.308)	< 0.001
Short sleep	1.157 (0.740, 1.81)	0.495	1.120 (0.673, 1.866)	0.627	1.161 (0.567, 2.379)	0.594	1.241 (0.977, 1.578)	0.077
Elevated glucose	2.516 (1.681, 3.765)	< 0.001	2.327 (1.507, 3.594)	0.002	2.160 (1.253, 3.724)	0.017	2.120 (1.740, 2.586)	< 0.001
Depression symptoms	1.326 (1.024, 1.717)	0.034	1.379 (1.032, 1.842)	0.033	1.567 (1.115, 2.203)	0.021	1.424 (1.148, 1.767)	0.001

Model 1: No adjustment for any covariates

Model 2: Adjusted for age, gender, race, education level, and PIR

Model 3: Additionally adjusted for smoking, alcohol consumption, ALT, AST and HEI based on Model 2

Model 4: Analysis after PSM for demographic and clinical variables

Table 4 Subgroup analysis and interaction analysis of the relationship between circs and MASLD

Subgroup	OR (95% CI)	*P*	Adjusted *P*	*P* for interaction
Overall	4.123 (2.489, 6.832)	0.001	-	
Gender				0.607
Male	4.453 (2.098, 9.451)	0.004	0.005	
Female	3.848 (2.431, 6.091)	0.001	0.002	
Age				0.358
< 55	5.120 (3.177, 8.253)	< 0.001	0.002	
≥ 55	3.244 (1.473, 7.142)	0.012	0.014	
Smoke				0.601
No	4.257 (2.414, 7.507)	0.001	0.002	
Yes	3.198 (1.274, 8.029)	0.023	0.023	
Alcohol Use				0.589
No	4.550 (2.788, 7.426)	0.001	0.002	
Yes	3.926 (1.919, 8.029)	0.001	0.002	

with and without MASLD. After matching, most covariates achieved good balance with SMD less than 0.1, indicating that the PSM process successfully reduced baseline confounding. In the matched cohort analysis (Model 4, Table 3), CircS remained significantly associated with MASLD, albeit with a more conservative effect size (*OR* = 2.880, 95% CI: 2.372–3.502, *P* < 0.001). These results suggest that CircS, characterized by multiple metabolic and behavioral risk factors, is strongly linked to an elevated likelihood of MASLD, even after accounting for various demographic and lifestyle factors.

Subgroup and interaction analysis

Table 4 presents the results of the subgroup and interaction analysis exploring the association between CircS and MASLD across different demographic and lifestyle categories. As shown, the association between CircS and MASLD remained significant across all subgroups, though the strength of the association varied. For gender, males with CircS had a higher *OR* (*OR* = 4.453, 95% CI: 2.098–9.451, *P* = 0.004) than females (*OR* = 3.848, 95% CI: 2.431–6.091, *P* = 0.001), although the interaction test did not indicate a statistically significant difference between genders (*P* for interaction = 0.607). Age also influenced the association, with participants under 55 showing stronger associations compared with those 55 and older, though the interaction was not significant (*P* for interaction = 0.358). Similar patterns were observed in the smoking and alcohol use subgroups, where non-smokers and non-drinkers shown slightly stronger associations than their counterparts, but these interactions were also not statistically significant (*P* for interaction > 0.05). Subgroup analyses remained consistent after adjustment for multiple comparisons using the Benjamini-Hochberg method, with the overall conclusion unchanged. As shown in Table 4, these subgroup analyses underscore the stability of the association between CircS and MASLD across various population subgroups. Figure 2 provides a visual representation of these results, offering a clearer view of the association strength within each subgroup.

Non-linear associations

Figure 3 illustrates the RCS analysis of the association between CircS score and the risk of MASLD, examining potential nonlinearity in this relationship. Although the test for nonlinearity yielded a marginally significant *P*-value of 0.045, indicating a borderline positive finding for nonlinearity, the visual pattern suggests a predominantly linear trend. As CircS scores increase, the risk of MASLD steadily rises, highlighting a clear dose-response relationship. This linear association implies that higher levels of circadian dysregulation correspond to progressively greater risks of developing MASLD, emphasizing the potential impact of cumulative circadian rhythm disruptions on liver health.

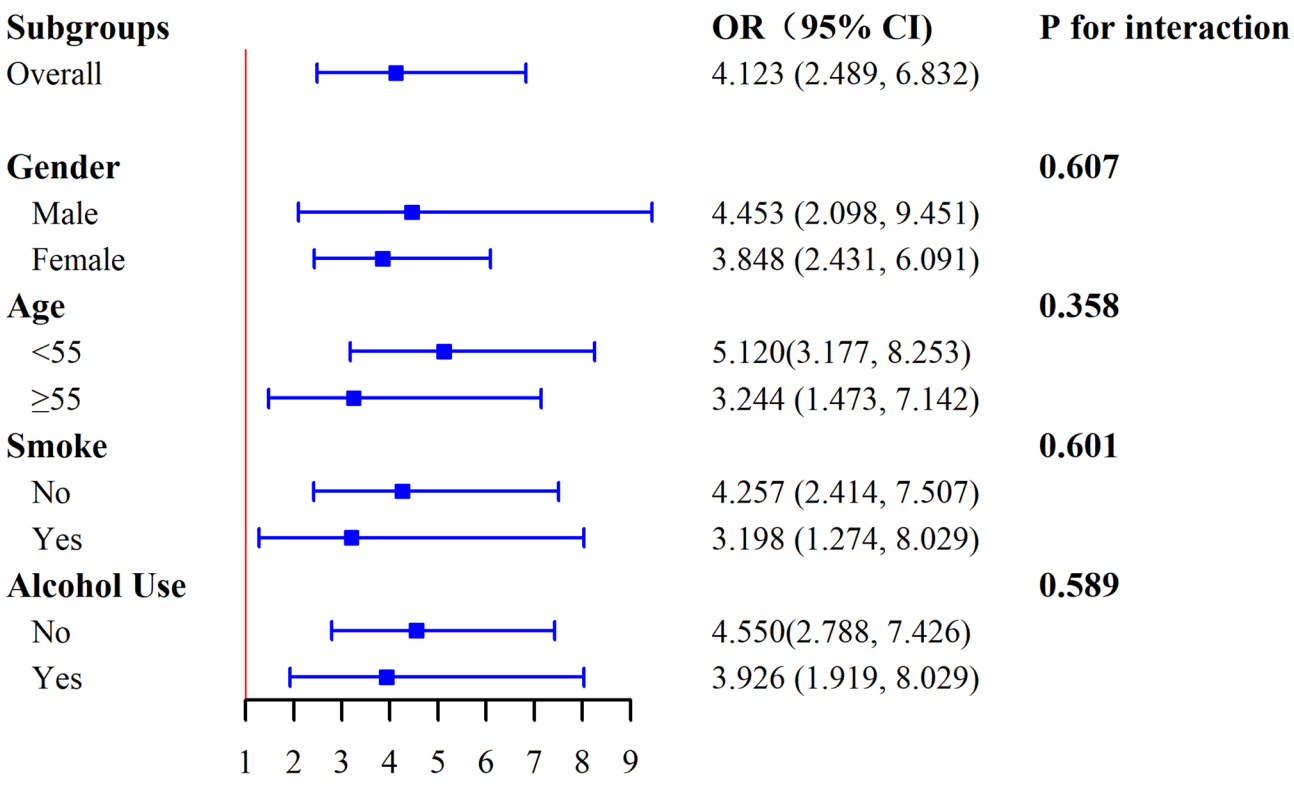

Fig. 2 Forest plot of subgroup analyses and interaction analysis for CircS-MASLD association

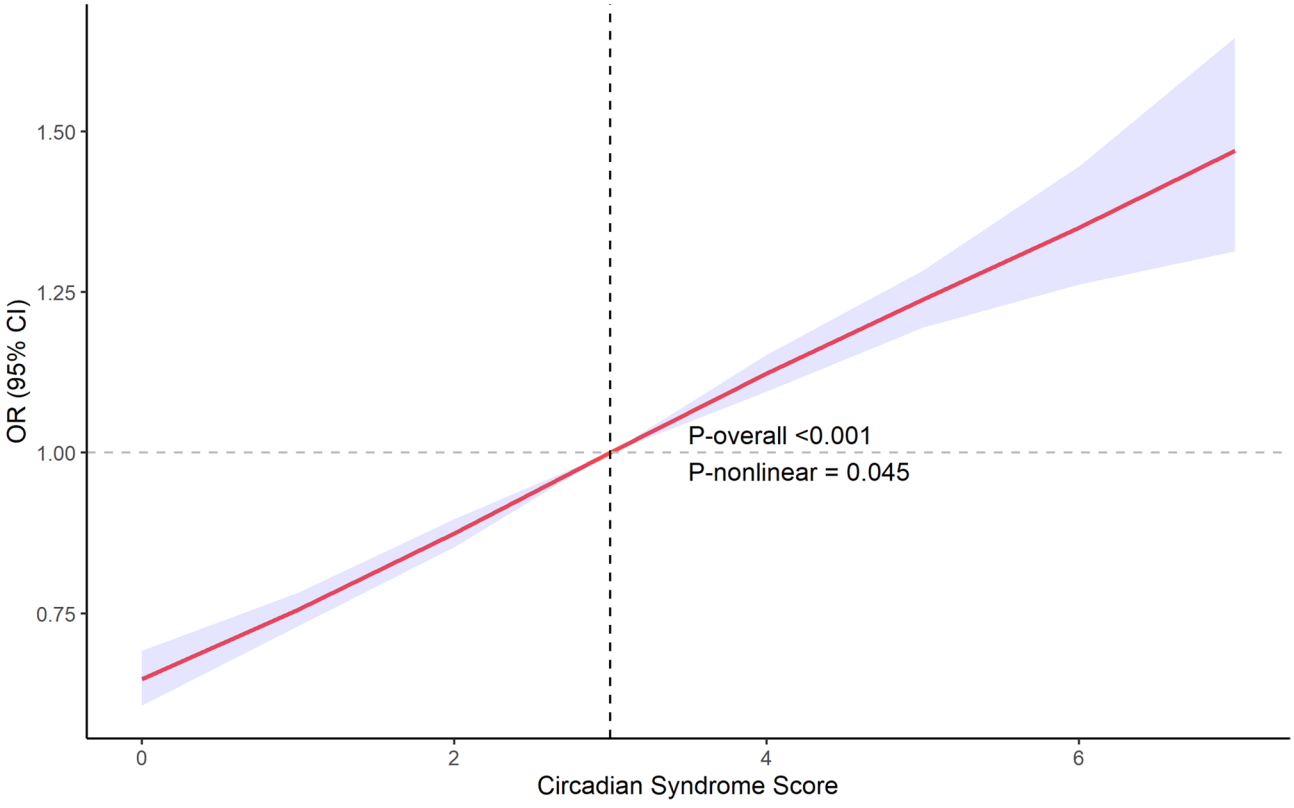

Fig. 3 The non-linear associations between CircS score and MASLD by restricted cubic spline

Discussion

This study revealed a significant positive association between CircS and MASLD, indicating that individuals with CircS face an elevated risk of developing MASLD. CircS, characterized by multiple metabolic and behavioral factors including hypertension, central obesity, elevated triglycerides, reduced HDL-C, elevated glucose, short sleep duration, and depressive symptoms, increases MASLD risk through the cumulative effect of these factors on metabolic dysfunction. These findings highlight CircS as a comprehensive indicator of metabolic health disturbances, where the convergence of these factors increases the likelihood of hepatic fat accumulation and liver inflammation, both critical to MASLD pathogenesis. Weighted logistic regression analysis confirmed these associations, showing that each CircS component, including hypertension, central obesity, and elevated triglycerides, independently contributed to an increased MASLD risk. Notably, central obesity and elevated triglycerides exhibited the strongest associations with MASLD, underscoring their roles as primary contributors to hepatic fat accumulation within the CircS framework. Subgroup analyses further shown that the CircS-MASLD association was consistent across various demographic and lifestyle groups, reinforcing the robustness of this relationship. RCS analysis indicated a predominantly linear association between CircS score and MASLD risk, with higher CircS scores correlating with progressively elevated MASLD risk. These findings suggest a dose-response effect, whereby cumulative circadian and metabolic disruptions associated with CircS lead to a steady increase in MASLD risk.

Interestingly, our analysis revealed that short sleep duration, despite being a core component of CircS, did not show a significant independent association with MASLD. This finding warrants careful interpretation within the broader context of circadian and metabolic disruption. The binary classification of sleep duration (≤ 6 h) used in this study may not fully capture the complex relationship between sleep patterns and liver metabolism. Moreover, sleep's influence on MASLD development may operate through indirect pathways, mediated by other metabolic disturbances such as glucose dysregulation, hypertension, and obesity-components that shown significant associations with MASLD in our analysis [18–20]. Sleep disruption has been shown to affect liver metabolism through inflammatory pathways not directly measured in our study, including alterations in inflammatory markers such as IL-6 and sICAM [21]. This complex interplay suggests that while sleep duration alone may not be directly associated with MASLD risk, its role in the broader context of CircS remains important through its interactions with other metabolic and inflammatory pathways.

Our findings align with existing research linking CircS to other metabolic diseases, such as cardiovascular disease (CVD) and type 2 diabetes [8, 22]. Research indicates that CircS disrupts key metabolic pathways, heightening susceptibility to metabolic syndrome components such as hypertension, obesity, and dyslipidemia [23, 24]. Circadian misalignment is strongly associated with CVD and type 2 diabetes, as it exacerbates systemic inflammation and insulin resistance — key drivers in the pathogenesis of both conditions. These mechanisms support our findings, suggesting that CircS-related risk factors may similarly contribute to MASLD through analogous metabolic pathways.

Multiple studies have highlighted the role of circadian misalignment in MASLD development, demonstrating that metabolic disruptions associated with CircS directly impact liver health. MASLD commonly coexists with metabolic syndrome and is widely regarded as a hepatic manifestation of this condition [25, 26]. The CircS-MASLD association observed in our study aligns with these findings, suggesting that circadian disruption may exacerbate hepatic lipid accumulation and inflammation, thereby elevating MASLD risk. Our study expands on this body of research, demonstrating that CircS, encompassing diverse metabolic and circadian disturbances, is significantly associated with MASLD, underscoring CircS as a relevant risk factor in liver disease.

Metabolic disturbances characteristic of CircS, including hyperglycemia, hyperlipidemia, and central obesity, can induce systemic inflammation that accelerates MASLD progression [27]. Elevated glucose and lipid levels activate pro-inflammatory pathways, triggering cytokine release (e.g., TNF-α and IL-6) that damages hepatocytes and facilitates the transition from simple steatosis to metabolic dysfunction-associated steatohepatitis and fibrosis [28, 29]. Insulin resistance, a core feature of CircS driven by metabolic dysregulation, including elevated glucose and lipid levels, accelerates MASLD progression [30]. Insulin resistance enhances lipolysis, increasing circulating free fatty acids that accumulate in the liver, promoting steatosis and triggering oxidative stress and inflammation, which further damage hepatocytes and contribute to fibrosis [31, 32]. This impairment in glucose and lipid metabolism compounds metabolic strain on the liver, further accelerating disease progression. CircS-associated circadian misalignment disrupts the liver's biological clock, impairing metabolic processes and increasing the risk of hepatic fat accumulation. Hepatic metabolic activities, including lipid and glucose metabolism, are regulated by circadian rhythms; disruptions from irregular sleep or eating patterns disturb metabolic balance, fostering MASLD [33, 34]. Circadian misalignment may interfere with key regulatory genes and proteins in hepatocytes, potentially reducing lipid

processing capacity and amplifying MASLD risk. However, direct assessments of circadian biomarkers such as cortisol, melatonin, or clock gene expression were not available in this study, and these mechanistic pathways remain hypothetical [35, 36]. These findings suggest that systemic inflammation, insulin resistance, and circadian misalignment may collectively contribute to MASLD pathogenesis. Disruptions in circadian regulation of hepatic metabolism, coupled with metabolic stress from hyperglycemia, dyslipidemia, and central obesity, likely accelerate hepatic fat accumulation and inflammatory injury, thereby promoting disease progression.

CircS, which encompasses a range of metabolic and circadian disruptions, closely aligns with the pathophysiology of MASLD, now widely regarded as a hepatic manifestation of metabolic syndrome. CircS assessment may have potential to inform future risk identification strategies for MASLD, pending further validation [37]. Furthermore, this integrated approach could help clinicians optimize healthcare resource utilization by more accurately identifying patients who require additional diagnostic evaluation while reducing unnecessary testing in low-risk individuals. Clinically, CircS assessment may help identify individuals at higher MASLD risk earlier, supporting timely intervention and targeted management strategies. However, further validation in prospective studies is necessary before clinical implementation.

While CircS may offer potential value in identifying individuals at elevated MASLD risk, its clinical applicability may be limited by certain practical challenges. CircS incorporates behavioral and psychological components, such as sleep duration and depressive symptoms, which are not routinely assessed in clinical settings. In contrast, MASLD diagnosis typically relies on imaging and common biochemical tests that are more accessible. The exclusion of a substantial proportion of participants due to missing CircS data further highlights this limitation. Future research should explore simplified CircS assessments and validate their feasibility in clinical practice.

Lifestyle modifications are fundamental in managing CircS and MASLD, as both respond positively to dietary improvements, improved sleep quality, and regular physical activity [38]. Dietary approaches, such as the Mediterranean diet, have demonstrated efficacy in reducing liver fat and improving metabolic markers by aligning eating patterns with circadian rhythms [39]. Given the complex relationship between circadian misalignment and metabolic dysfunction in MASLD, future research should examine how circadian gene expression specifically influences MASLD progression. Such investigations may reveal new therapeutic targets and support the development of personalized lifestyle interventions focused on circadian health, particularly for high-risk individuals with elevated CircS scores.

Prospective cohort studies are essential for clarifying the causal relationship between CircS and MASLD, especially in understanding how circadian disruptions may initiate and worsen MASLD. Studies on circadian gene expression in hepatic cells could reveal novel molecular targets, enhancing the precision of MASLD treatments tailored to circadian health. Furthermore, examining the impact of CircS across diverse populations—such as different age groups, lifestyle profiles, and high-risk categories—would help clarify the generalizability and specificity of the CircS-MASLD association. Personalized, circadian-focused interventions based on these insights may provide an effective nonpharmacological approach to mitigate MASLD risk and progression across diverse patient populations.

Conclusion

This study identifies a significant association between CircS and MASLD, highlighting CircS as a potential risk-associated factor for MASLD. CircS assessment may have potential to inform future risk identification and management strategies for MASLD, pending further validation. These findings highlight the need for future research to explore CircS-informed prevention and intervention approaches aimed at reducing MASLD risk and progression.

Limitations

This study has several limitations. First, as a cross-sectional analysis, it cannot confirm a causal relationship between CircS and MASLD, only an association. Second, the use of self-reported data for certain variables, particularly sleep duration, may introduce information bias due to potential recall inaccuracies. Sleep self-reports may not capture important aspects such as sleep quality, night-to-night variability, or circadian alignment, which could be better assessed through objective measures like actigraphy or polysomnography in future studies. Third, the operational definition of CircS, although used in previous epidemiological studies, includes behavioral components such as short sleep and depressive symptoms, which may not serve as definitive circadian biomarkers. Last, some participants were excluded due to missing covariate data, and a difference in alcohol use between excluded and included participants may limit the generalizability of the findings.

Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CAP	Controlled Attenuation Parameter
CircS	Circadian Syndrome
CVD	Cardiovascular Disease
HDL-C	High-Density Lipoprotein Cholesterol

HEI	Healthy Eating Index
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
NHANES	National Health and Nutrition Examination Survey
PIR	Income-to-poverty Ratio
PSM	Propensity Score Matching
RCS	Restricted Cubic Spline
SMD	Standardized Mean Differences
VCTE	Vibration-controlled Transient Elastography

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03997-7.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
Conceptualization, Jihan Sun and Shuqi Mao; Methodology, Caide Lu; Formal analysis, Jihan Sun; Data curation, Shuqi Mao; Writing—original draft preparation, Jihan Sun; Writing—review and editing, Shuqi Mao and Caide Lu. All authors have read and agreed to the published version of the manuscript.

Funding
This research was supported by the Ningbo Major Research and Development Plan Project (Grant Nos. 2024Z179 and 2023Z160), the Ningbo Natural Science Foundation (2024J393), and Ningbo Top Medical and Health Research Program (2024020818).

Data availability
The dataset supporting the conclusions of this article is available in the National Health and Nutrition Examination Survey (NHANES) repository, https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
The NHANES protocol was approved by the Research Ethics Review Board of the National Center for Health Statistics (NCHS), and informed consent was obtained from all participants. As NHANES data are de-identified and publicly available, this analysis did not require additional ethical review.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 13 March 2025 / Accepted: 15 May 2025
Published online: 21 May 2025

References

1. Le MH, Yeo YH, Li X et al. 2019 Global NAFLD prevalence: A systematic review and Meta-analysis. Clin Gastroenterol Hepatol. 2022;20(12).
2. Shen D, Cai X, Hu J, et al. Associating plasma aldosterone concentration with the prevalence of MAFLD in hypertensive patients: insights from a large-scale cross-sectional study. Front Endocrinol (Lausanne). 2024;15:1451383.
3. Hu J, Cai X, Zhu Q, et al. Relationship between plasma aldosterone concentrations and Non-Alcoholic fatty liver disease diagnosis in patients with hypertension: A retrospective cohort study. Diabetes Metab Syndr Obes. 2023;16:1625–36.
4. Habibullah M, Jemmieh K, Ouda A, et al. Metabolic-associated fatty liver disease: a selective review of pathogenesis, diagnostic approaches, and therapeutic strategies. Front Med (Lausanne). 2024;11:1291501.
5. Akbar Z, Shi Z. Dietary patterns and circadian syndrome among adults attending NHANES 2005–2016. Nutrients. 2023;15(15).
6. Xiao Y, Yin S, Cui J, et al. Association between the prevalence rates of circadian syndrome and testosterone deficiency in US males: data from NHANES (2011–2016). Front Nutr. 2023;10:1137668.
7. Schrader LA, Ronnekleiv-Kelly SM, Hogenesch JB et al. Circadian disruption, clock genes, and metabolic health. J Clin Invest. 2024;134(14).
8. Lemmer B, Oster H. The role of circadian rhythms in the hypertension of diabetes mellitus and the metabolic syndrome. Curr Hypertens Rep. 2018;20(5):43.
9. Cai X, Wang M, Liu S, et al. Establishment and validation of a nomogram that predicts the risk of type 2 diabetes in obese patients with non-alcoholic fatty liver disease: a longitudinal observational study. Am J Transl Res. 2022;14(7):4505–14.
10. Cai X, Aierken X, Ahmat A, et al. A nomogram model based on noninvasive bioindicators to predict 3-Year risk of nonalcoholic fatty liver in Nonobese Mainland Chinese: A prospective cohort study. Biomed Res Int. 2020;2020:8852198.
11. Zhao D, Wang X, Liu H, et al. Effect of circadian rhythm change on gut microbiota and the development of nonalcoholic fatty liver disease in mice. Sleep Med. 2024;117:131–8.
12. Yuan M, He J, Hu X, et al. Hypertension and NAFLD risk: insights from the NHANES 2017–2018 and Mendelian randomization analyses. Chin Med J (Engl). 2024;137(4):457–64.
13. Shi Z, Tuomilehto J, Kronfeld-Schor N, et al. The circadian syndrome predicts cardiovascular disease better than metabolic syndrome in Chinese adults. J Intern Med. 2021;289(6):851–60.
14. Xiao Y, Yin S, Bai Y, et al. Association between circadian syndrome and the prevalence of kidney stones in overweight adults: a cross-sectional analysis of NHANES 2007–2018. BMC Public Health. 2023;23(1):960.
15. Sun L, Huo X, Jia S, et al. The association between circadian syndrome and frailty in US adults: a cross-sectional study of NHANES data from 2007 to 2018. Aging Clin Exp Res. 2024;36(1):105.
16. Zhang Z, Zheng Q, Liu Y, et al. Association between periodontitis and mortality in participants with metabolic dysfunction-associated steatotic liver disease: results from NHANES. BMC Oral Health. 2025;25(1):567.
17. Wang Q, Chen R, Chen S, et al. Exploring the association between dietary indices and metabolic dysfunction-associated steatotic liver disease: mediation analysis and evidence from NHANES. PLoS ONE. 2025;20(4):e0321251.
18. Taheri S, Lin L, Austin D, et al. Short sleep duration is associated with reduced leptin, elevated Ghrelin, and increased body mass index. PLoS Med. 2004;1(3):e62.
19. Kim C-W, Yun KE, Jung H-S, et al. Sleep duration and quality in relation to non-alcoholic fatty liver disease in middle-aged workers and their spouses. J Hepatol. 2013;59(2):351–7.
20. Gu C, Bernstein N, Mittal N, et al. Potential therapeutic targets in obesity, sleep apnea, diabetes, and fatty liver disease. J Clin Med. 2024;13:8.
21. Motivala SJ, Sarfatti A, Olmos L, et al. Inflammatory markers and sleep disturbance in major depression. Psychosom Med. 2005;67(2):187–94.
22. Morris CJ, Yang JN, Garcia JI, et al. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. Proc Natl Acad Sci U S A. 2015;112(17):E2225–34.
23. Shetty A, Hsu JW, Manka PP, et al. Role of the circadian clock in the metabolic syndrome and nonalcoholic fatty liver disease. Dig Dis Sci. 2018;63(12):3187–206.
24. Marhefkova N, Sládek M, Sumová A, et al. Circadian dysfunction and cardio-metabolic disorders in humans. Front Endocrinol (Lausanne). 2024;15:1328139.
25. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes. 2001;50(8):1844–50.
26. Yki-Järvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol. 2014;2(11):901–10.
27. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–7.
28. Tilg H, Moschen AR. Inflammatory mechanisms in the regulation of insulin resistance. Mol Med. 2008;14(3–4):222–31.
29. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology. 2010;52(5):1836–46.
30. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016;65(8):1038–48.
31. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell. 2012;148(5):852–71.

32. Begriche K, Massart J, Robin M-A, et al. Mitochondrial adaptations and dysfunctions in nonalcoholic fatty liver disease. Hepatology. 2013;58(4):1497–507.
33. Poggiogalle E, Jamshed H, Peterson CM. Circadian regulation of glucose, lipid, and energy metabolism in humans. Metabolism. 2018;84:11–27.
34. Manoogian ENC, Chow LS, Taub PR, et al. Time-restricted eating for the prevention and management of metabolic diseases. Endocr Rev. 2022;43(2):405–36.
35. de Assis LVM, Demir M, Oster H. The role of the circadian clock in the development, progression, and treatment of non-alcoholic fatty liver disease. Acta Physiol (Oxf). 2023;237(3):e13915.
36. Saran AR, Dave S, Zarrinpar A. Circadian rhythms in the pathogenesis and treatment of fatty liver disease. Gastroenterology. 2020;158(7).
37. Urias E, Chen VL. Screening for At-Risk nonalcoholic fatty liver disease in the primary care setting. Semin Liver Dis. 2023;43(2):133–41.
38. Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol. 2017;67(4):829–46.
39. Torres-Peña JD, Arenas-de Larriva AP, Alcala-Diaz JF et al. Different dietary approaches, Non-Alcoholic fatty liver disease and cardiovascular disease: A literature review. Nutrients. 2023;15(6).

Publisher's note