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Appropriate sleep duration modifying the association of insulin resistance and hepatic steatosis is varied in different status of metabolic disturbances among adults from the United States, NHANES 2017-March 2020

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A B S T R A C T

Steatosis is the hepatic manifestation of metabolic syndrome (MetS) and its developing is closely associated with insulin resistance. Shortened sleep has adverse effects on hepatic steatosis and the underlying mechanism remains unknown. We conceived to evaluate whether sleep duration was a lifestyle factor modifying the association between insulin resistance and hepatic steatosis and whether it was varied in different status of metabolic disturbances. We performed a cross-sectional analysis on 2264 adults of United States representing a population of 138,319,512 with MetS or pre-MetS from National Health and Nutrition Examination Survey (NHANES) 2017-March 2020. Participants underwent hepatic transient elastography and laboratory tests. The sleep duration was obtained from interviews. Results showed that insulin resistance was significantly associated with hepatic steatosis among participants with metabolic disturbances (OR = 1.85, 95% CI: 1.30–2.65). Significant moderation of sleep duration on the association between insulin resistance and hepatic steatosis was observed when sleep duration was dichotomized by 6.5- (P = 0.042) or 9.5-hour (P = 0.031). The risk of hepatic steatosis associated with insulin resistance was increased when sleep duration was $\leq$ 6.5 h and > 9.5 h. Furthermore, the moderation effect of 6.5-hour sleeping was only significant among participants with pre-MetS while that of 9.5-hour sleeping was only significant among participants with MetS. In conclusion, insufficient or excessive sleep increased the risk of hepatic steatosis associated with insulin resistance. Appropriate sleep duration was advocated and varied in different status of metabolic disturbances. Ensuring adequate sleep should be highlighted before MetS occurs and excessive sleep should be prevented for participants with MetS.

1. Introduction

Metabolic syndrome (MetS) is characterized by the coexistence of multiple metabolic disturbances in an individual including glucose intolerance, hypertriglyceridemia, decreased high-density lipoprotein cholesterol (HDL-C), hypertension, and visceral obesity (Koskinen et al., 2014). Steatosis has been considered as the hepatic manifestation of MetS (Moore, 2010). It is defined as>5% of hepatocytes containing lipid vacuoles in the absence of excessive alcohol ingestion or other causes (Angulo et al., 2015), encompassing a spectrum of histologic changes, ranging from benign steatosis to steatohepatitis, with a relatively high probability of progressing to cirrhosis and hepatocellular carcinoma (Adams et al., 2005). Peoples with hepatic steatosis was less insulin-sensitive than healthy controls (Hoyles et al., 2018). It meant that their liver was less sensitive to the suppressive effects of insulin on hepatic output of glucose and very-low-density lipoprotein which may cause postprandial hyperglycemia and hyperlipidemia. And these are intrinsic features of MetS. Thereby, hepatic steatosis is not only a consequence but also a contributor of MetS (den Boer et al., 2004).

Approved medical therapies for hepatic steatosis are currently lack of

and lifestyle management is recommended (Sheka et al., 2020). Lifestyle modifications including diet, exercise, and weight loss have been advocated. Sleep is a daily routine for human beings with a recommendation of 7 to 9 h per night (Consensus Conference Panel et al., 2015). Its necessity and importance are evident through its contribution to physical growth, metabolism, tissue repair, and memory consolidation. A randomized controlled study showed that experimental sleep restriction promoted visceral fat deposition (Covassin et al., 2022). In a multivariable analysis, there was a significant increasing trend of the risk of prevalent non-alcoholic fatty liver disease (NAFLD) for decreasing sleep duration in the Chinese middle-aged and elderly community population (Peng et al., 2017). Several recent cohort studies revealed a significant association between short sleep duration and increased risk of NAFLD (Kim et al., 2018; Um et al., 2021), but the underlying mechanism remained unknown. Insulin resistance, defined as a state of decreased responsiveness to normal circulating levels of insulin, is one of the most predictive metabolic factors for hepatic steatosis (Claypool et al., 2022). Enhanced lipolysis of visceral adipose tissue owing to insulin resistance may increase the portal delivery of enormous exogenous fatty acids to the liver. Therefore, we sought to examine whether sleep duration was another lifestyle factor that could play a role in the management of hepatic steatosis by modifying the association between insulin resistance and hepatic steatosis among participants with metabolic disturbances.

In the present study, we continued choosing to study sleep duration for the convenience to compare with previous studies and furtherly explored the appropriate sleep duration by moderation analysis using the data of National Health and Nutrition Examination Survey (NHANES) from 2017 to March 2020. It has been suggested that the pre-disease state before MetS could be the best period to carry out effective treatment (Koizumi et al., 2019). Therefore, the moderation effect of sleep duration on the association between insulin resistance and hepatic steatosis was also investigated among participants with MetS and pre-MetS, respectively, to determine whether appropriate sleep duration is varied in different status of metabolic disturbances.

2. Methods

2.1. Study population

The NHANES is a nationally representative cross-sectional study to assess health and nutrition through a complex multistage, stratified, clustered probability and oversampling design. This study utilized 2017-March 2020 data collection before the program was temporally suspended due to the coronavirus disease 2019 pandemic. The pre-pandemic data contained the maximum enrollment of participants received hepatic ultrasound elastography examination so far, which has been validated to classify the presence of steatosis with an absolute cut-off and was feasible for large-scale examination (Castera et al., 2019).

All participants provided written informed consent and the ethics review board of the Centers for Disease Control and Prevention Research approved the survey protocol. MetS was diagnosed according to National Cholesterol Education Program, Adult Treatment Panel III as any three of the following five criteria were satisfied: 1) waist circumference > 102 cm in men or > 88 cm in women; 2) triglyceride (TG) ≥ 150 mg/dL or specific drug treatment; 3) HDL-C < 40 mg/dL in men or < 50 mg/dL in women; 4) systolic or diastolic blood pressure ≥ 130 mmHg or ≥ 85 mmHg, respectively (or receiving medication for hypertension); and 5) glucose ≥ 100 mg/dL (or receiving medication for diabetes) (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2002). Participants with one or two criteria were identified as pre-MetS (Dimitrijevic-Sreckovic et al., 2007). The exclusion criteria were viral hepatitis, autoimmune hepatitis, alcohol-related liver disease, cancer or malignancy, exposure to steatogenic medication for>6 months, pregnancy, type 1 diabetes mellitus, transient elastography or sleep duration data

were missing or incomplete. Of 3158 adults (≥18 years) with MetS or pre-MetS who had valid fasting glucose and insulin values and fasting weights, 894 participants were excluded according to the exclusion criteria, leading to a final cohort of 2264 participants among which 1260 with pre-MetS and 1004 with MetS (Fig. 1).

2.2. Measures

2.2.1. Independent variable: Insulin resistance

Insulin resistance was assessed by homeostasis model assessment of insulin resistance (HOMA-IR), calculated as follows: HOMA-IR = fasting insulin (mU/mL) * fasting glucose (mmol/L)/22.5. Participants with HOMA-IR > 2.5 were defined as insulin-resistant (Lee et al., 2022). Blood samples were collected from participants who have fasted at least 8 h. Vials were stored under appropriate frozen conditions until they were shipped to University of Missouri-Columbia for testing. Insulin levels were measured by two-site immunoenzymometric assay, where insulin in the sample bounded with enzyme-labeled monoclonalantibody in the AIA-PACK and monoclonalantibody immobilized on magnetic beads. Fasting plasma glucose was quantitatively detected with an ultraviolet test using the hexokinase endpoint enzymatic method.

2.2.2. Dependent variable: Hepatic steatosis

Vibration controlled transient elastography was performed in Mobile Examination Centers using a FibroScan® model 502 V2 Touch. The elastography exam was performed by NHANES health technicians, who were trained and certified by NHANES staff and the equipment manufacturer. Exams were considered qualified if there were fasting time of ≥ 3 h, 10 or more complete stiffness measurements and its interquartile range/median < 30% (Ciardullo and Perseghin, 2021). The presence of hepatic steatosis was ascertained by the value of controlled attenuation parameter (CAP) expressed in decibels per meter (dB/m). CAP of 274 dB/m or more was regarded as hepatic steatosis according to a recent landmark study (Eddowes et al., 2019).

2.2.3. Moderation factor: Sleep duration

Sleep duration was self-reported through household interview and calculated by weighted average of workdays and weekends. Although there were questions collecting self-reported sleep habits and disorders, they were lack of validation and their reliability to evaluate the sleep quality could not equal to well-accepted assessment scales. Other questions simplified from Munich ChronoType Questionnaire were incapable to identify the sleep chronotype.

2.2.4. Covariate variables

In the present study, confounders of hepatic steatosis considered as potential covariates included sociodemographic factors of age, gender, race/ethnicity, education and family poverty income ratio, lifestyle factors of smoking status, alcohol consumption, physical activity and sleep duration, anthropometric measurements of height and weight, and laboratory data of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total bilirubin (TB), C-reactive protein (CRP), total cholesterol (TC), triglyceride (TG), HDL-C and uric acid (UA). Sociodemographic and lifestyle variables were obtained from interviews. Race/ethnicity were defined as Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black or other race. Educational status was dichotomized as no high school graduation versus high school graduation (Kim et al., 2022). Family poverty income ratio was dichotomized as ≤ 0.99 (below poverty) or ≥ 1.00 (at or above poverty) (Kim et al., 2022). Alcohol consumption was classified into none, moderate (>0 to ≤ 2 drinks/d for men or > 0 to ≤ 1 drink/d for women), heavy (>2 drinks/d for men or > 1 drink/d for women) or unavailable, whereas smoking status was classified into current (smoked at least 100 cigarettes in life and reported smoking at the time of interview), former (smoked at least 100 cigarettes in life but did not smoke at the time of interview) or never (smoked<100 cigarettes in life)
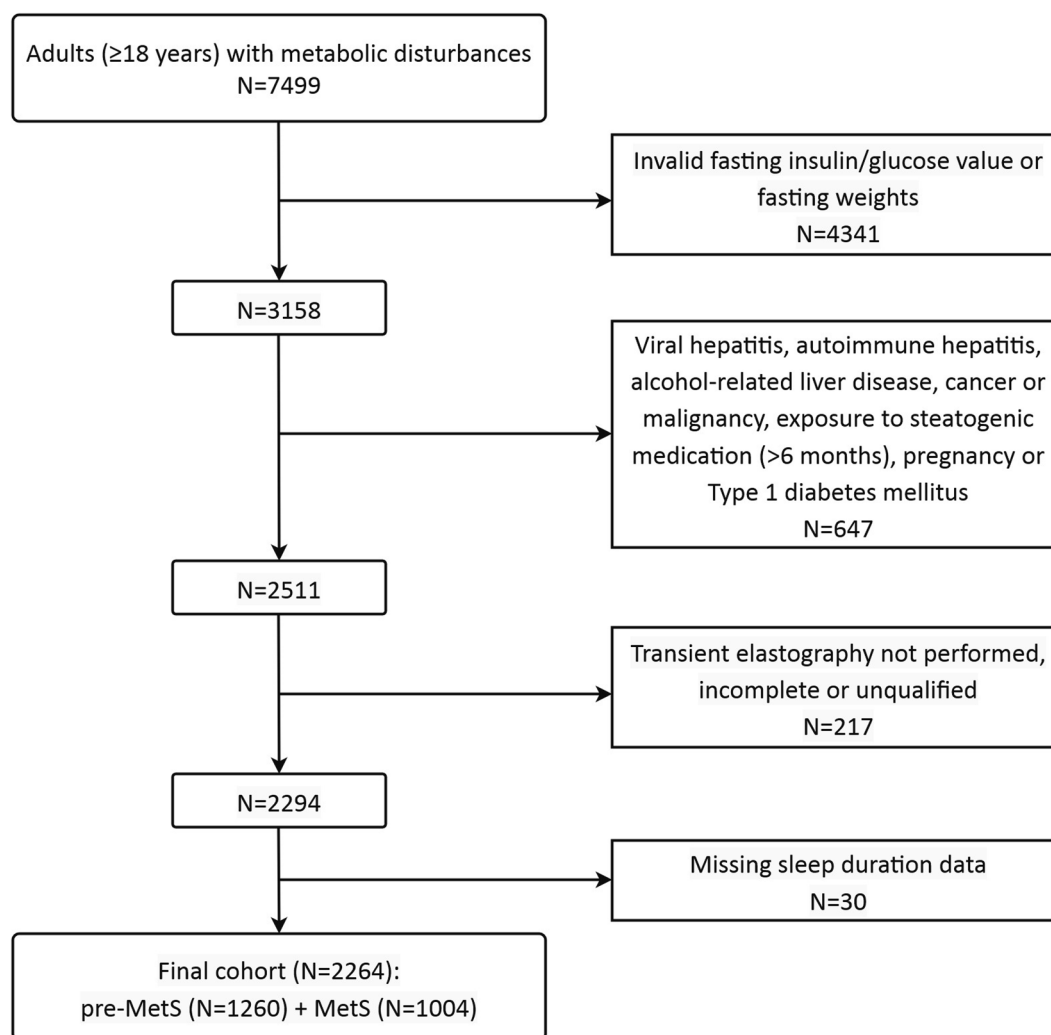
Fig. 1. Flowchart of the study participant inclusion in NHANES 2017-March 2020.

(Unalp-Arida and Ruhl, 2022). Physical activity was labeled as vigorous if positive response was given to any of the following questions: 'does your work involve vigorous-intensity activity' or 'do you do any vigorous-intensity sports, fitness, or recreational activities'. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Laboratory methods of measuring AST, ALT, GGT, TB, CRP, TC, TG and HDL-C were accessible at NHANES website. The NHANES quality assurance and quality control protocols meet the 1988 Clinical Laboratory Improvement Act mandates.

2.3. Statistical analysis

Appropriate strata, cluster, and sample weights for fasting participants were applied to obtain representative population-level data for the entire United States because of the complex sample design of NHANES. Continuous variables were described by weighted means ± standard errors and categorical variables were described by weighted frequencies (95% confidence interval (CI)). Demographic and clinical characteristics were compared between those with and without insulin resistance. Multivariable logistic regression was used to explore the association between insulin resistance and hepatic steatosis. Demographic variables of age, gender, and race/ethnicity were forced into the first multivariable model. Covariates that changed the estimates of insulin resistance on hepatic steatosis by>10% were adjusted for the second model. Moreover, covariates that were significantly associated with hepatic steatosis (p < 0.05) were used to construct a third model in addition to

model 2. Sensitivity analysis was performed using multiple imputation to assess the effect of missing values. Linear trend was estimated by transforming insulin resistance as continuous variable in the models. Stratified analysis by status of metabolic disturbances was also conducted. Possible moderation effects were evaluated using likelihood ratio test among subgroups divided by different sleep durations. Sensitivity analyses were also performed to assess the possible bias caused by sleeping medicine use and weekday-to-weekend sleep differences. All statistical analyses were performed with R (https://www.R-project.org, The R Foundation) and EmpowerStats software (X&Y Solutions, Inc., Boston, MA).

3. Results

3.1. Study population characteristics

Of the weighted participants qualified for the study representing a population of 138,319,512, the mean age was 48.52 ± 0.71 years, 51.24% (95% CI: 48.74–53.73%) were female, 49.92% (95% CI: 47.06–52.79%) had hepatic steatosis, and 58.31% (95% CI: 54.60–61.92%) were insulin-resistant. Characteristics of the study cohorts according to insulin resistance were shown in Table 1. Insulin-resistant participants had higher CAP, ALT, GGT, BMI, CRP, TG, UA and were more likely to have hepatic steatosis compared with non-insulin-resistant participants. They also differed in the levels of TB and HDL-C, the distribution of race/ethnicity, and the percentage of alcohol

Table 1

Characteristics of Adults with Metabolic Disturbances from the United States Based on the Status of Insulin Resistance, NHANES 2017-March 2020.

Characteristics	Insulin-resistant	Non-insulin-resistant	P value
	Weighted mean ± SE / weighted % (95% CI)	Weighted mean ± SE / weighted % (95% CI)	
Age, y	47.95 ± 0.87	49.31 ± 0.93	0.224
Gender, %			0.597
Male	49.91 (44.19, 55.64)	47.15 (41.24, 53.14)	
Female	50.09 (44.36, 55.81)	52.85 (46.86, 58.76)	
Race/ethnicity, %			<0.001
Mexican American	12.91 (9.79, 16.86)	6.08 (4.37, 8.40)	
Other Hispanic	7.40 (5.86, 9.31)	7.53 (5.77, 9.78)	
Non-Hispanic White	56.17 (51.56, 60.67)	65.72 (60.81, 70.31)	
Non-Hispanic Black	12.20 (8.82, 16.64)	11.81 (8.51, 16.16)	
Other	11.31 (8.76, 14.49)	8.86 (6.17, 12.57)	
BMI, kg/m^2	33.17 ± 0.35	27.71 ± 0.27	<0.001
ALT, U/L	24.34 ± 0.59	19.39 ± 0.83	<0.001
AST, U/L	20.87 ± 0.36	20.39 ± 0.52	0.489
GGT, U/L	31.63 ± 1.54	24.73 ± 0.94	0.003
TB, mg/dL	0.47 ± 0.01	0.50 ± 0.01	0.041
CRP, mg/L	5.00 ± 0.29	3.18 ± 0.35	<0.001
TC, mg/dL	186.27 ± 1.79	189.57 ± 2.15	0.242
TG, mg/dL	153.21 ± 4.94	115.66 ± 3.62	<0.001
HDL-C, mg/dL	47.61 ± 0.50	57.39 ± 1.06	<0.001
UA, mg/dL	5.68 ± 0.05	5.21 ± 0.07	<0.001
Sleep duration, h	7.83 ± 0.06	7.71 ± 0.07	0.206
CAP, dB/m	292.96 ± 2.90	250.54 ± 2.18	<0.001
HOMA-IR	6.07 ± 0.25	1.63 ± 0.03	<0.001
Hepatic steatosis, %			<0.001
Yes	63.31 (59.12, 67.31)	31.20 (26.75, 36.02)	
No	36.69 (32.69, 40.88)	68.80 (63.98, 73.25)	
High school graduation, %			0.010
Yes	54.57 (50.09, 58.98)	66.01 (58.70, 72.62)	
No	45.43 (41.02, 49.91)	33.99 (27.38, 41.30)	
Family poverty income ratio, %			0.203
≤0.99	24.28 (19.85, 29.33)	20.67 (16.93, 25.00)	
≥1.00	75.72 (70.67, 80.15)	79.33 (75.00, 83.07)	
Alcohol consumption, %			0.009
None	8.02 (5.90, 10.81)	6.43 (4.36, 9.38)	
Moderate	41.19 (37.11, 45.38)	35.17 (28.61, 42.34)	
Heavy	30.04 (26.23, 34.15)	41.04 (34.59, 47.81)	
Unavailable	20.75 (18.03, 23.77)	17.36 (14.03, 21.29)	
Smoking, %			0.150
Never	60.04 (55.68, 64.26)	55.49 (48.54, 62.24)	
Former	27.10 (24.27, 30.13)	26.07 (20.42, 32.63)	
Current	12.85 (10.38, 15.81)	18.44 (14.67, 22.91)	
Physical activity, %			0.010
None	59.15 (55.80, 62.41)	48.88 (43.21, 54.58)	
Moderate	33.36 (29.80, 37.12)	40.61 (35.40, 46.03)	
Vigorous	7.50 (5.58, 10.00)	10.51 (7.91, 13.85)	
Use of sleeping tablets, %			0.017
Yes	2.71 (1.68, 4.34)	5.75 (3.76, 8.68)	
No	97.29 (95.66, 98.32)	94.25 (91.32, 96.24)	

Values are presented as weighted means ± standard errors (SE) or weighted frequencies (95% confidence interval [CI]).

P-value was determined by *t*-test for continuous variables and Chi-squared test for categorical variables.

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; TB, total bilirubin; CRP, C-reactive protein; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; CAP, controlled attenuation parameter; HOMA-IR, homeostasis model assessment of insulin resistance.

consumption, high school graduation, use of sleeping tablets, and physical activity. In Supplementary Table 1, cohort characteristics classified by hepatic steatosis were compared. The weighted prevalence of insulin resistance was significantly higher in those with hepatic steatosis (73.94%, 95% CI: 69.08%-78.28%) than in those without hepatic steatosis (42.72%, 95% CI: 37.79%-47.79%).

3.2. Results of multivariable logistic regression analysis

Multivariable logistic regression analysis showed that insulin resistance was positively associated with the prevalence of hepatic steatosis in the age-, gender- and race/ethnicity-adjusted model (odds ratio (OR) = 3.94, 95% CI: 2.83–5.49). After BMI, TG, and HDL-C were adjusted in model 2, the OR decreased but remained significant ($P < 0.001$) with insulin-resistant participants being 1.91 times (95% CI: 1.40–2.61) likely to have hepatic steatosis than those without insulin resistance. After adjusting for additional confounders including ALT, GGT, CRP, UA, and physical activity in model 3, the association between insulin resistance and hepatic steatosis did not change markedly (OR = 1.85, 95% CI: 1.30–2.65) (Table 2). Merged ORs of five replications derived from multiple imputation of missing values based on chained equations did not yield appreciable changes in the study results (Supplementary Table 2). HOMA-IR was then categorized into four equal groups and linear trend was tested by entering the median value as continuous variable in the models. When the first quartile was set as reference, significant association was found for the third and fourth quartiles and the risk of hepatic steatosis associated with increasing HOMA-IR was graded in all three models (P for trend < 0.001) (Supplementary Table 3). Subgroup analyses revealed that the association between insulin resistance and hepatic steatosis was also statistically significant in participants with pre-MetS and MetS (Table 3).

3.3. Results of moderation analysis

To identify the sleep duration by which the association between insulin resistance and hepatic steatosis was moderated, sleep duration was dichotomized by varied thresholds defined by every 30-minute-interval from 6.5 to 9.5 h, based on the recommended 7 to 9 h sleeping (Consensus Conference Panel et al., 2015). It was revealed that when either 6.5-hour ($P = 0.042$) or 9.5-hour ($P = 0.031$) was introduced as the threshold, significant moderations were observed on the association between insulin resistance and hepatic steatosis. To be more specific, the positive association between insulin resistance and hepatic steatosis became stronger for the participants with sleep duration ≤ 6.5 h (OR = 3.90, 95% CI: 1.94–7.85), however, this association was attenuated when sleep duration was>6.5 h (OR = 1.66, 95% CI: 1.17–2.34). Conversely, the association was attenuated with sleep duration ≤ 9.5 h (OR = 1.70, 95% CI: 1.24–2.32) but increased (OR = 7.21, 95% CI: 2.06–25.22) when sleep duration was>9.5 h (Fig. 2). Moreover, we further addressed the effect of sleep duration in the subgroups of pre-MetS and MetS, respectively. Results showed that the moderation effect of 6.5-hour sleeping was consistent in participants with pre-MetS ($P = 0.002$) but not in those with MetS ($P = 0.538$). In contrast, significant moderation of 9.5-hour sleeping was consistent in participants with MetS ($P = 0.032$) but absent in those with pre-MetS ($P = 0.251$) (Fig. 3). Similar results were found in sensitivity analyses assessing the possible bias caused by sleeping medicine use (Supplementary Figs. 1 and 2) and weekday-to-weekend sleep inconsistency. (Supplementary Figs. 3 and

Table 2

Associations between Insulin Resistance and Hepatic Steatosis by Multivariable-Adjusted Logistic Regression among Adults with Metabolic Disturbances from the United States, NHANES 2017-March 2020.

	Model 1	Model 2	Model 3
Insulin resistance	OR (95% CI)	OR (95% CI)	OR (95% CI)
No	1	1	1
Yes	3.94 (2.83, 5.49)	1.91 (1.40, 2.61)	1.85 (1.30, 2.65)

Model 1 was adjusted for age, gender and race/ethnicity. Model 2 was adjusted for age, gender, race/ethnicity, body mass index, triglyceride and high-density lipoprotein cholesterol. Model 3 was adjusted for alanine aminotransferase, γ-glutamyltransferase, C-reactive protein, uric acid and physical activity in addition to model 2.

OR, odds ratio; CI, confidence interval.

Table 3
Associations between Insulin Resistance and Hepatic Steatosis Stratified by Status of Metabolic Disturbances among Adults with Metabolic Disturbances from the United States, NHANES 2017-March 2020.

	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Stratified by status			
Pre-MetS	3.04 (2.13, 4.34)	1.88 (1.26, 2.81)	1.86 (1.18, 2.94)
MetS	3.45 (1.89, 6.28)	2.12 (1.26, 3.58)	1.95 (1.21, 3.12)

Model 1 was adjusted for age, gender and race/ethnicity. Model 2 was adjusted for age, gender, race/ethnicity, body mass index, triglyceride and high-density lipoprotein cholesterol. Model 3 was adjusted for alanine aminotransferase, γ-glutamyltransferase, C-reactive protein, uric acid and physical activity in addition to model 2.
OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome.

4).

4. Discussion

In the present study based on the representative samples of NHANES 2017-March 2020, insulin resistance was found to be significantly associated with hepatic steatosis for participants with metabolic disturbances. In addition, significant moderation of sleep duration on the association between insulin resistance and hepatic steatosis was observed when sleep duration was dichotomized by 6.5- and 9.5-hour. The risk of hepatic steatosis associated with insulin resistance was increased when sleep duration was ≤ 6.5 h and > 9.5 h. Furthermore, the moderation effect of 6.5-hour sleeping was only significant among participants with pre-MetS while that of 9.5-hour sleeping was only significant among participants with MetS, which may indicate that appropriate sleep duration was varied in different status of metabolic disturbances. Ensuring adequate sleep should be highlighted before MetS occurs and excessive sleep should be prevented for participants with MetS.

It was revealed in our study that the impact of insulin resistance on the development of hepatic steatosis was aggravated in the presence of sleep duration ≤ 6.5 h or > 9.5 h. The adverse effect of sleep shortage has been verified in previous population-based studies. A cross-sectional evaluation of Japanese men showed that, compared to the group with self-reported sleep duration of < 7 h, the risks for obesity and fatty liver were lower for the group with sleep duration ≥ 7 h (Hsieh et al., 2011). In a study of middle-aged workers and their spouses, the OR for NAFLD comparing self-reported sleep duration ≤ 5 h to the reference (>7h) was 1.59 in women (Kim et al., 2013). Our study furtherly demonstrated that it was partly through moderating the association between insulin resistance and hepatic steatosis that sleep duration took effect. U-shaped associations between actigraphy-measured sleep duration and insulin biomarkers have been reported (Javaheri et al., 2011). Furthermore, the present study proposed that participants with metabolic disturbances should ensure adequate but not excessive sleep with an appropriate sleep duration range of 6.5 to 9.5 h.

As shown in our results, the increased association between insulin resistance and hepatic steatosis with sleep duration ≤ 6.5 h was attributed mainly to participants with pre-MetS, possibly because of the synergism of sleep shortage and insulin resistance at this stage. However, the relationship between insulin resistance and hepatic steatosis may become bidirectional among participants with MetS and hepatic steatosis may facilitate insulin resistance with more complicated pathogenesis including lipid toxicity, oxidative stress, and intestinal flora imbalance (Zhang et al., 2020). On this occasion, resumption of adequate sleep may be incapable of reversing the impact of insulin resistance on hepatic steatosis. As for the significantly increased association found in the participants with MetS sleeping>9.5 h, it is probably caused by the reasons contributing to excessive sleep, for example, obstructive sleep apnea, hypoxemia, reduced physical activity, and

circadian misalignment, which could be more common among participants with MetS (Zhang et al., 2020). Circadian misalignment occurs when the endogenous circadian rhythm cycling misaligned with socially schedule and external environment, which might also lead to appetite-regulating hormones imbalance and impaired metabolic function (McHill et al., 2014).

Lifestyle modification of having appropriate sleep duration should be stressed with regular exercise, mood stability and education about sleep quality to lower the risk of hepatic steatosis for participants with metabolic disturbances. It can be achieved by clinicians using wearable technology to remotely capture patients' data in real time. It is a smart microelectronic device that utilized sensors to detect, transmit, and analyze physiological changes. Its promotion of physical activity and weight loss has been revealed in previous research (Jang et al., 2023; Yen and Chiu, 2019). Clinicians can remind patients to get adequate sleep while encountering sleep shortage, and suggest them to increase physical activity during excessive sleep. The warning threshold could be input according to the status of metabolic disturbances. The validity of lifestyle modification also depends on patients' self-monitoring and education of health behavior, because low compliance is actually a barrier against its sustainability. Hence, personalized coaching such as habit education and motivational interviewing for goal-setting and commitment step may facilitate the maintenance of the new lifestyle. Considering the growing digital health technology, future studies are warranted to conduct on the efficacy and optimization of wearables to achieve appropriate sleep duration.

Recently, to better reflect the complex pathophysiology of NAFLD, the term of metabolic dysfunction–associated fatty liver disease (MAFLD) has been proposed. Instead of the traditional criteria of NAFLD based on exclusion of heavy alcohol consumption, chronic hepatitis and other causes of liver diseases, MAFLD represents a multisystem metabolic disorder that warrants a positive diagnosis. In the present study, both merits of these two definitions were taken into account. Participants with at least one of the components of MetS were included and those with viral hepatitis, autoimmune hepatitis and ALD were ruled out simultaneously, in order to obtain a solid and representative cohort. Utilization of the transient elastography data was another strengths of our study. It was more reliable to assess the histological changes quantitatively compared to the biochemical indices. Hyperinsulinemic-euglycemic clamp is the gold standard of measuring insulin sensitivity but difficult to apply in clinical practice. Alternate methods such as HOMA-IR provide information mainly on hepatic insulin resistance and usually perform well in subjects with obesity and metabolic disturbances. A novel insulin sensitivity index called Fasting Laboratory Assessment of Insulin Sensitivity was developed. It displayed a higher correlation coefficient with hyperinsulinemic-euglycemic clamp than other surrogates in population without metabolic disturbances (Karczewska-Kupczewska et al., 2021). This suggests that the insulin sensitivity index should be chose according to the study population and purpose.

There were several limitations in this study. Firstly, due to the cross-sectional design of the study, inferences on causality was not allowed. Secondly, the confidence intervals were wider in the participants with sleep duration >9 or 9.5 h, partly because of the smaller number of participants with excessive sleep in the present cohort. Thirdly, except sleep duration, other sleep parameters, which have also been correlated with components of MetS, were not measured. For example, it has been reported that worse subjective sleep quality was associated with hypertension (Liu et al., 2022) and longer sleep onset latency was prospectively associated with higher MetS scores (Bowman et al., 2019). Both subjective sleep quality and sleep onset latency were dimensions of Pittsburgh Sleep Quality Index, a well validated, reliable and widely used questionnaire of sleep quality, which also included assessments of habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction (Buysse et al., 1989). Therefore, future investigations with larger sample are needed and should not only focus
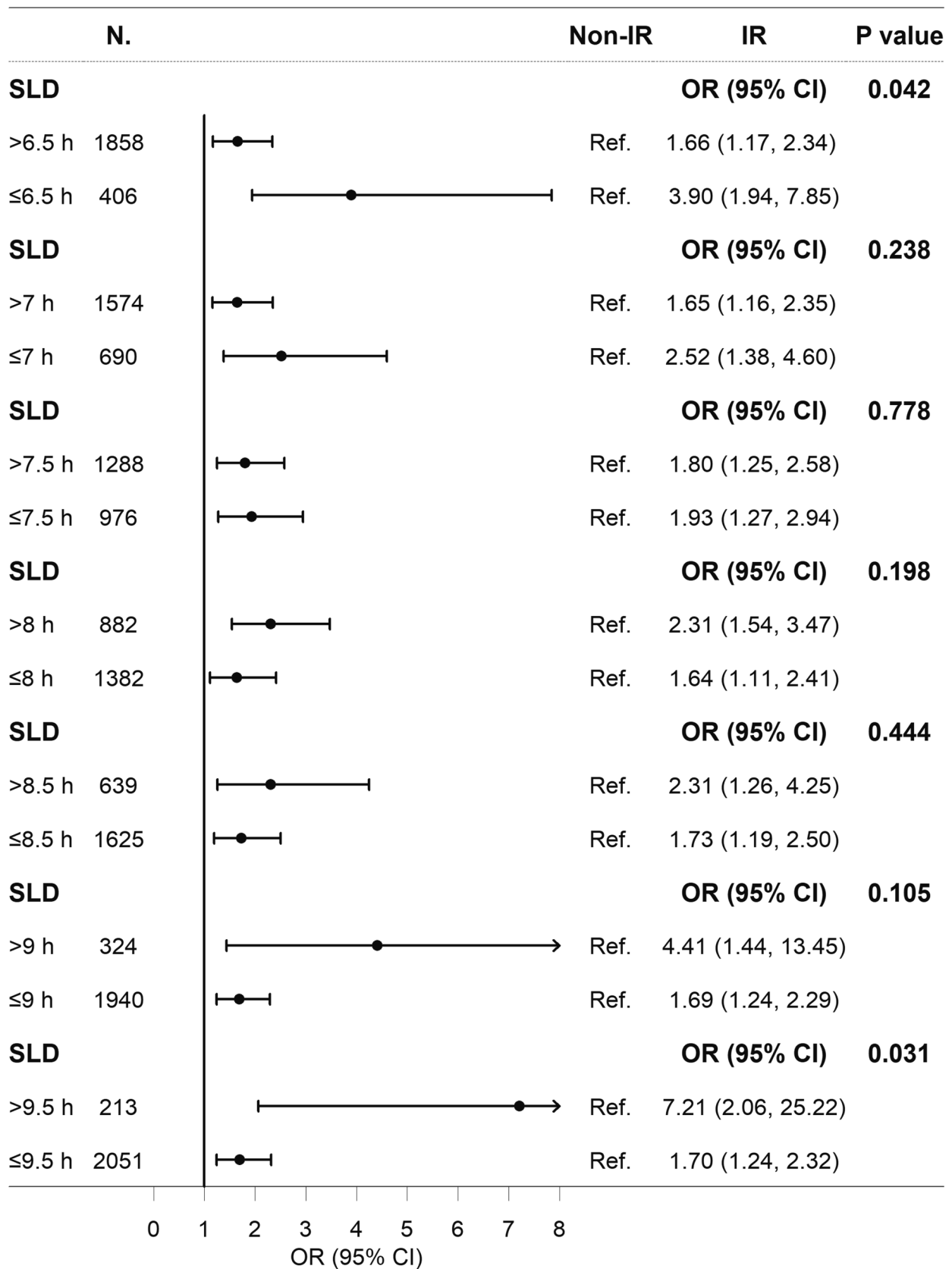
	N.			Non-IR	IR	P value
SLD					OR (95% CI)	0.042
>6.5 h	1858			Ref.	1.66 (1.17, 2.34)	
≤6.5 h	406			Ref.	3.90 (1.94, 7.85)	
SLD					OR (95% CI)	0.238
>7 h	1574			Ref.	1.65 (1.16, 2.35)	
≤7 h	690			Ref.	2.52 (1.38, 4.60)	
SLD					OR (95% CI)	0.778
>7.5 h	1288			Ref.	1.80 (1.25, 2.58)	
≤7.5 h	976			Ref.	1.93 (1.27, 2.94)	
SLD					OR (95% CI)	0.198
>8 h	882			Ref.	2.31 (1.54, 3.47)	
≤8 h	1382			Ref.	1.64 (1.11, 2.41)	
SLD					OR (95% CI)	0.444
>8.5 h	639			Ref.	2.31 (1.26, 4.25)	
≤8.5 h	1625			Ref.	1.73 (1.19, 2.50)	
SLD					OR (95% CI)	0.105
>9 h	324			Ref.	4.41 (1.44, 13.45)	
≤9 h	1940			Ref.	1.69 (1.24, 2.29)	
SLD					OR (95% CI)	0.031
>9.5 h	213			Ref.	7.21 (2.06, 25.22)	
≤9.5 h	2051			Ref.	1.70 (1.24, 2.32)	

OR (95% CI)

Fig. 2. Forest plot investigating the association between insulin resistance and hepatic steatosis stratified by different thresholds of sleep duration among adults with metabolic disturbances from the United States, NHANES 2017-March 2020. Adjusted for age, gender, race/ethnicity, body mass index, triglyceride, high-density lipoprotein cholesterol, alanine aminotransferase, γ-glutamyltransferase, C-reactive protein, uric acid and physical activity. IR, insulin resistance; SLD, sleep duration; N., numbers of participants; OR, odds ratio; CI, confidence interval; Ref., reference.
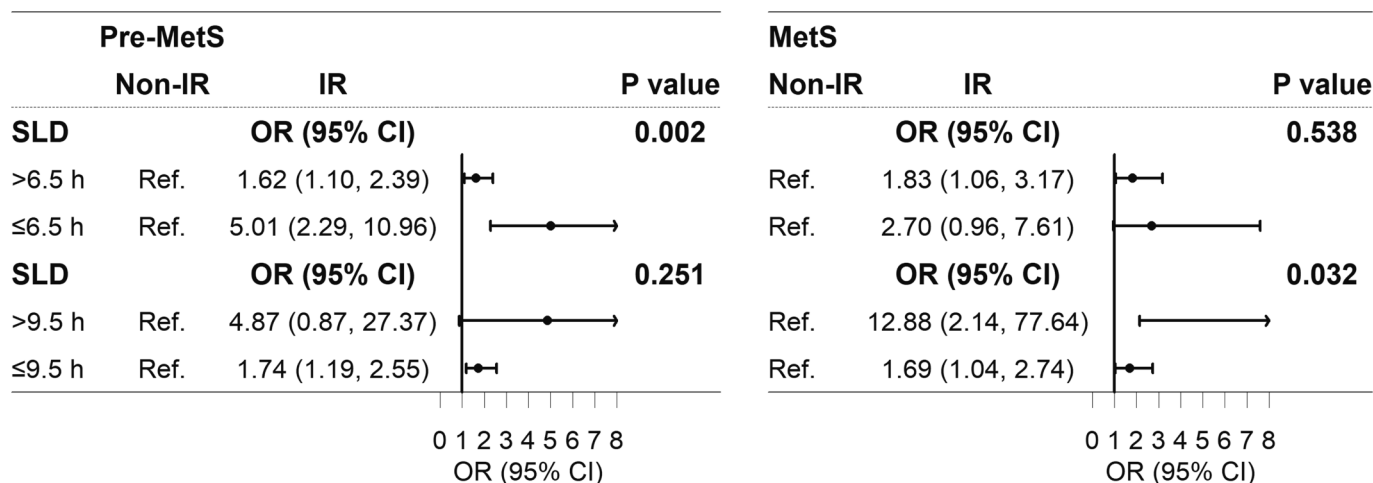
Fig. 3. Forest plot investigating the association between insulin resistance and hepatic steatosis stratified by sleep duration of 6.5 h and 9.5 h for adults with MetS and pre-MetS from the United States, NHANES 2017-March 2020. Adjusted for age, gender, race/ethnicity, body mass index, triglyceride, high-density lipoprotein cholesterol, alanine aminotransferase, γ-glutamyltransferase, C-reactive protein, uric acid and physical activity. IR, insulin resistance; SLD, sleep duration; MetS, metabolic syndrome; OR, odds ratio; CI, confidence interval; Ref., reference.

on sleep duration, but also take sleep quality into account from a multi-dimensional perspective.

5. Conclusion

In conclusion, our study demonstrated a significant moderation of sleep duration on the association between insulin resistance and hepatic steatosis, emphasizing the importance of lifestyle modifications to ensure adequate but not excessive sleep in the management of hepatic steatosis among participants with metabolic disturbances. The significant moderations of 6.5- and 9.5-hour were more likely to be seen among participants with pre-MetS and MetS, respectively. Emphasis of sleep duration demand is varied in different status of metabolic disturbances. Further randomized controlled studies and molecular experiments are needed to clarify the causality of sleep duration moderating the association between insulin resistance and hepatic steatosis and fully decipher the molecular mechanisms in play here.

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Ethics statement

All authors declare that this study on human subjects were conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent and the ethics review board of the Centers for Disease Control and Prevention Research approved the original survey.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Junyan Cao: Conceptualization, Data curation, Writing – original draft. **Weihong Qiu:** Data curation, Methodology, Writing – original draft. **Yuwei Lin:** Data curation, Formal analysis, Software. **Tianyu Liu:** Formal analysis, Software. **Zulin Dou:** Funding acquisition, Methodology, Supervision, Writing – review & editing. **Zhaocong Chen:**

Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2023.102406.

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