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Interaction between the systemic immune-inflammation index and trouble sleeping in nonalcoholic fatty liver disease: a cross-sectional study of the NHANES 2005–2018 data

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Abstract

Background The systemic immune-inflammation index (SII) and trouble sleeping are independent risk factors for nonalcoholic fatty liver disease (NAFLD). Nevertheless, studies investigating the combined effects of the SII and troubled sleeping on NAFLD are lacking. In this study, we investigated the independent relationships and interactions between trouble sleeping and the SII among patients with NAFLD.

Methods Data from seven survey cycles of the National Health and Nutrition Examination Survey (NHANES) (2005–2018) were analyzed. The SII was obtained by counting platelets, neutrophils, and lymphocytes. NAFLD was diagnosed using the US fatty liver index. Trouble sleeping was diagnosed using a sleep disorder questionnaire. The correlation between trouble sleeping and the SII in NAFLD was investigated using multiple regression analysis, subgroup stratification, interaction tests, and restricted cubic spline, and the presence or absence of additive or multiplicative interactions was determined. Additionally, mediation analyses were performed to explore the role of the SII in mediating the effects of trouble sleeping on NAFLD.

Results The survey included 10 963 participants. Multivariate logistic regression revealed that SII (OR: 1.21, 95% CI 1.08–1.35) and trouble sleeping (OR: 1.24, 95% CI 1.05–1.47) were positively correlated with NAFLD. For NAFLD, an additive but not multiplicative interaction was noted between the SII and trouble sleeping. The SII partially mediated the association between trouble sleeping and NAFLD, accounting for approximately 3.11% of the total effect (95% CI 0.01–0.05).

Conclusion The SII and trouble sleeping were independently correlated with NAFLD risk. Furthermore, a combined effect may exist between SII and trouble sleeping, which increases the risk of NAFLD.

Keywords Systemic immune-inflammation index, Nonalcoholic fatty liver disease, Trouble sleeping, NHANES

Background

Nonalcoholic fatty liver disease (NAFLD) is a prevalent chronic liver condition that poses a growing public health challenge because of its widespread occurrence [1, 2]. The prevalence of NAFLD among adults (aged ≥ 15 years) is expected to reach 33.5% by 2030 [3]. To date, no effective

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treatment has been established for NAFLD; hence, appropriate treatment strategies, such as controlling risk factors and lifestyle changes, may be beneficial to prevent the onset of NAFLD.

NAFLD can evolve from basic steatosis to nonalcoholic steatohepatitis, cirrhosis, and finally to hepatocellular carcinoma [4]. This evolution involves complex pathophysiological mechanisms, and some studies have suggested that NAFLD progresses to cirrhosis due to fat deposition in hepatocytes, leading to increased oxidative stress and inflammatory responses [5]. Moreover, oxidative stress drives the development of hepatic lobular inflammation, which is a primary factor in NAFLD progression [6, 7]. Therefore, chronic liver inflammation is a critical factor in NAFLD [6]. The systemic immune-inflammation index (SII) is a recently developed inflammatory marker that reflects both local and overall systemic inflammation [8, 9]. Although previous studies have linked the SII to hepatic steatosis, its association with NAFLD has rarely been explored [10].

Sleep disorders, including sleep apnea, insomnia and restless legs. Evidence suggests that sleep disorders are related to NAFLD, although conclusions remain controversial [11–13]. A decrease in sleep duration and sleep disorders can decrease insulin sensitivity and enhance the release of proinflammatory substances, potentially leading to the onset of NAFLD [14, 15]. A cohort study of 143 306 participants found that inadequate sleep duration, but not sleep quality, was associated with NAFLD risk [11]. Nevertheless, several studies have confirmed that sleep disorders are related to NAFLD [13, 16]. Furthermore, a survey of 33 045 patients revealed that those with sleep disorders had a markedly elevated risk of NAFLD, regardless of whether the disorders were combined with sleep apnea [16]. Although numerous studies have explored the link between sleep and NAFLD, most have focused solely on the length of sleep and sleep-related conditions; few have investigated the impact of trouble sleeping on NAFLD.

A recent study found that sleep disruption increases liver inflammation in NAFLD, which in turn affects sleep disruption, with a bidirectional correlation between them [12]. Therefore, a common pathway may exist between SII and troubled sleeping, which contributes to NAFLD. However, prior research has primarily examined the SII and trouble sleeping separately as potential risk factors for NAFLD. To date, no survey has examined whether the SII and trouble sleeping interact synergistically to increase the risk of NAFLD. Therefore, based on data from the National Health and Nutrition Examination Survey (NHANES), we aimed to explore the relationship between the SII and trouble sleeping in NAFLD and assess the impact of the interaction between high SII levels and trouble sleeping on the risk of NAFLD.

Materials and methods

Study population and design

Data used in this study were obtained from the National Center for Health Statistics (NCHS) [17]. This comprehensive cross-sectional survey aimed to explore the relationship between the SII and trouble sleeping in patients with NAFLD and assess the impact of the interaction between high SII levels and trouble sleeping on the risk of NAFLD through a complex multistage sampling design that enabled the results to be generalized to the majority of the population. The NHANES was designed to collect nutritional and health-related data from non-institutionalized civilians in the United States of America [18]. Ethical approval was obtained from the NCHS Ethics Review Board before conducting this study. All study participants provided written informed consent [19].

Data from seven 2-year NHANES cycles (2005–2018) were used to collect data for this research (Fig. 1). Notably, data on trouble sleeping were available only for specific cycles. In total, 39 749 participants aged 20 years participated in the survey. Participants were excluded based on the following criteria: (i) missing US fatty liver index (USFLI) data (n=23 394); (ii) missing SII data (n=72); (iii) incomplete sleep questionnaire data (n=7); (iv) viral hepatitis diagnosed by positive hepatitis B surface antigen or hepatitis C antibody (n=380); (v) alcohol consumption of 30 g/day in men or 20 g/day in women, defined as excessive drinking (n=2036) [20]; (vi) pregnancy (n=284); (vii) incomplete covariate data (n=2589); and (viii) missing data on alanine aminotransferase (ALT) (n=18) or aspartate aminotransferase (AST) (n=6). In total, 10,963 participants who met the aforementioned criteria were included in the study.

SII

The SII is a composite index calculated from a complete blood count test, including lymphocyte, neutrophil, and platelet counts [21]. A Coulter® DxH 800 analyzer was used for automated blood analysis to determine the SII. To calculate the SII, platelet and neutrophil counts were multiplied and the product was divided by the lymphocyte count [8].

Assessment of trouble sleeping

Trouble sleeping was evaluated using a specifically designed questionnaire. The participants were questioned about previous instances in which they had been advised by a healthcare provider or physician regarding trouble sleeping. Participants who answered "yes" were considered to have experienced trouble sleeping, whereas those who answered "no" were not [22].

Definition of NAFLD

The diagnosis of NAFLD was based on the USFLI. Ruhl et al. [23] initially presented this indicator, which

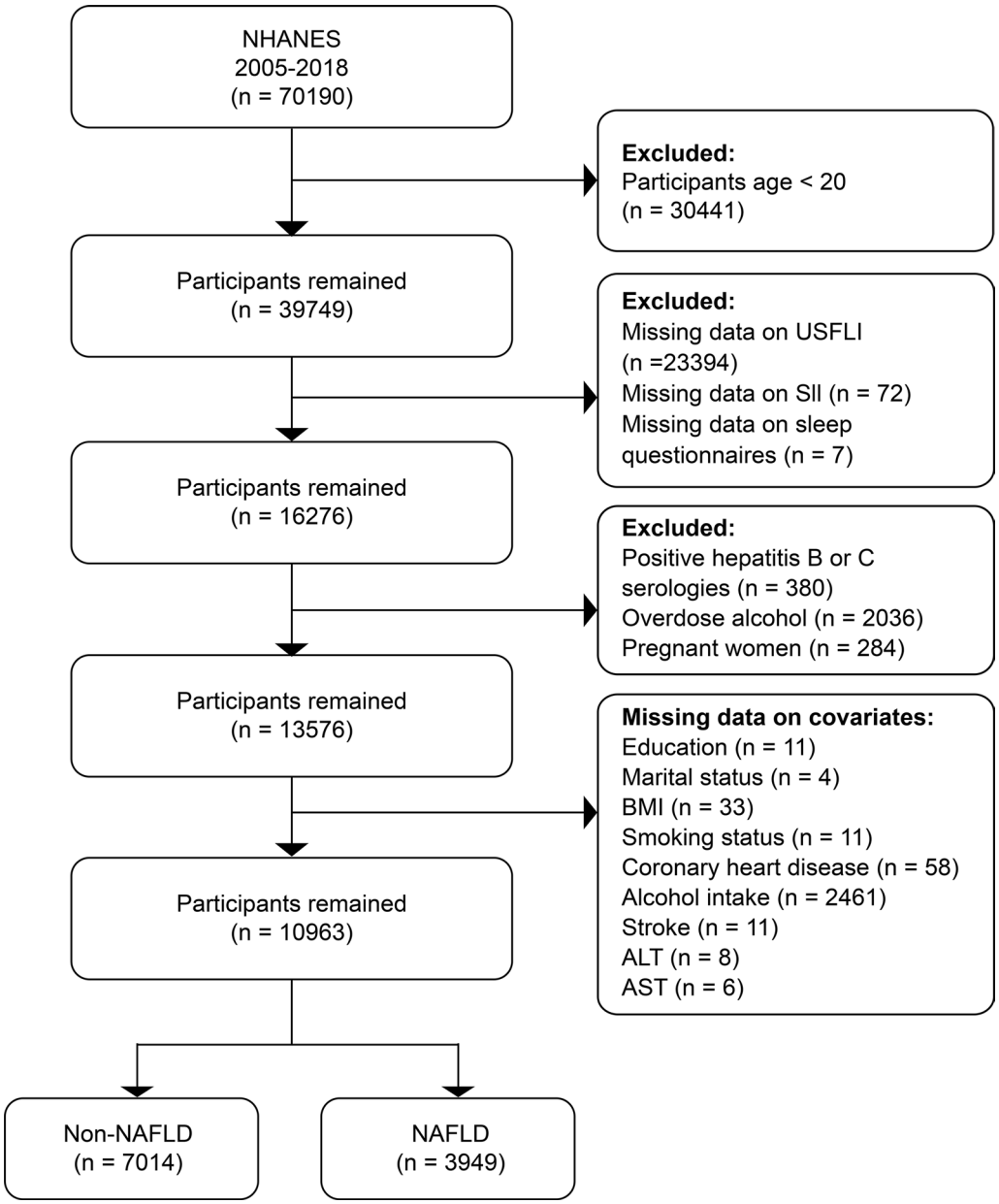

Fig. 1 Study design flowchart

was established using NHANESIII data. Individuals were classified as having NAFLD if their USFLI score was ≥ 30 [24]. The USFLI is based on the following formula [23]:

$$\begin{aligned}\text{USFLI} = e^{(0.6151 \times \log_e(gamma-\text{glutamyl transferase}) + 0.0249 \times \text{waist circumference} - 0.8073} \\ \times \text{non}-\text{Hispanic black} + 0.3458 \times \text{Mexican}-\text{American} + 1.1792 \\ \times \log_e(\text{insulin}) + 0.0093 \times \text{age} + 0.8242 \times \log_e(\text{Glucose}) - 14.7812)/ \\ (1+e(-0.8073 \times \text{non}-\text{Hispanic black} + 0.3458 \times \text{Mexican}-\text{American} + 0.6151 \\ \times \log_e(gamma-glutamyl\ transferase) + 0.0093 \times age + 1.1792 \\ \times \log_e(insulin) + 0.8242 \times \log_e(glu\cos e) + 0.0249 \times waist\ circumference - 14.7812)) \times 100\end{aligned}$$

Covariate assessment

To comprehensively assess the potential impact of variables correlated with NAFLD, data on the following sociodemographic characteristics were collected: age, sex (male/female), ethnicity, level of education (greater than high school/less than or equal to high school), marital status (unmarried/married), physical exercise, alcohol use, tobacco use, waist circumference, and body mass index (BMI).

Information on these variables was obtained through in-person interviews conducted in households. Smoking status was classified as never (< 100 cigarettes ever), former (> 100 cigarettes ever but not presently), or current (> 100 cigarettes ever and still smoking). Total energy and alcohol intake were estimated by calculating the mean of two 24-h dietary recall datasets. Physical activity was categorized according to the American Physical Activity Guidelines established by the Department of Health and Human Services. Individuals were classified as physically active if they participated in 150 min of moderate-intensity physical activity per week, whereas those who failed to meet this standard were deemed physically inactive.

Waist circumference was measured in centimeters by drawing a horizontal line above the uppermost lateral margin of the right ilium. In the statistical analyses, waist circumference was classified into four classes (quartiles: Q1: 56.2–88.7 cm; Q2: 88.8–98.8 cm; Q3: 98.9–109.7 cm; and Q4: 109.8–176.0 cm). BMI, calculated by dividing the weight by height squared, was classified into two categories: < 30.0 and ≥ 30.0 [25].

Comorbidities included hypertension, diabetes, stroke, hyperlipidemia, and coronary heart disease. The diagnosis of hypertension included hypertension medication use, self-reported history of hypertension, and an average of three measurements of blood pressure with systolic values of ≥ 130 mmHg or diastolic values of ≥ 80 mmHg [26]. Similarly, diabetes diagnosis relied on self-reported diabetes, antihyperglycemic medication, and fasting blood glucose levels of > 126 mg/dL or glycated hemoglobin levels of ≥ 6.5% [27, 28]. Hyperlipidemia was diagnosed based on high levels of triglyceride (≥ 150 mg/dL), total cholesterol (≥ 200 mg/dL), low-density lipoprotein (≥ 130 mg/dL), High-density lipoprotein (< 40 mg/dL in men or < 50 mg/dL in women), and the use of lipid-lowering medications [29]. Diagnoses of stroke and coronary heart disease were based on self-reported medical histories. The NHANES was performed using a DxC800 system (Beckman Coulter, Brea, CA, USA) using the kinetic rate method for serum ALT and AST levels and the enzyme rate method for gamma-glutamyl transferase activity [30].

Statistical analysis

Weight was considered when conducting the statistical analysis because the NHANES uses a complex sampling research design. The sampling weight used in this study was that of a 7-year mobile examination center. Survey-weighted means were used to express continuous variables, and survey-weighted percentages were used for categorical variables. Chi-square tests were used to compare baseline characteristics between subgroups for categorical variables, and t-tests were used to compare continuous variables. Additionally, the SII data were right-skewed; hence, log2 transformation was performed before statistical analysis. Values converted through calculations were divided into four quartiles, with the lowest quartile used as the reference.

Logistic regression analysis was used to investigate the potential association between the SII and trouble sleeping and an increased risk of NAFLD across models. Additionally, the effect of trouble sleeping on the SII was assessed using a logistic regression model. Model 1 excluded adjusted variables; in Model 2, adjustments were made for age, sex, and race; and Model 3 included covariates such as education level, marital status, physical activity, waist circumference, BMI, smoking habits, total energy intake, alcohol consumption, ALT, AST, gamma-glutamyl transferase (GGT), diabetes, hypertension, hyperlipidemia, history of stroke, and coronary artery disease. Restricted cubic spline regression was used to explore possible nonlinear associations between the SII and NAFLD. Subgroup analyses were conducted to assess the influence of SII and trouble sleeping on NAFLD in various populations, considering factors such as age, sex, race, waist circumference, BMI, diabetes, hypertension, hyperlipidemia, coronary heart disease, and stroke. A stratified analysis of the subgroup variables was conducted using the fully adjusted Model 3. Interaction analysis was used to assess the variability in associations among subgroups.

An additive interaction model was constructed to evaluate whether the coexistence of the SII and trouble sleeping had a greater effect on the risk of NAFLD than the sum of their independent effects [31]. Additive interactions were determined using three metrics: the relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (SI). The absence of synergy was indicated by the inclusion of zero in the 95% confidence interval for RERI or AP and the inclusion of one in the 95% confidence interval for SI [32, 33]. The odds ratio (OR) was used to measure the multiplicative interaction between the SII and trouble sleeping and its effect on NAFLD risk. A multiplicative interaction was indicated if the 95% confidence interval (CI) for the product term excluded one. An OR value < 1

obtained by the interaction term indicates the existence of antagonism, and an OR value > 1 obtained by the interaction term indicates synergy [33]. Mediation analysis was performed using the mediation package of R software to determine the extent to which the SII mediates the relationship between trouble sleeping and NAFLD. This is an ideal strategy for elucidating pathways and providing statistical evidence for mechanistic analyses. In this study, the direct effect represents the association between trouble sleeping and NAFLF; the indirect effect, which is the association between trouble sleeping and NAFLF, is mediated by the SII; and the mediation ratio represents the percentage of the mediation effect.

Statistical analysis was conducted using R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was set for both groups to determine statistical significance.

Results

Demographic characteristics

Finally, 10,963 participants were selected (weighted n = 65 537 646). Based on the USFLI score, 3949 participants (weighted prevalence of 35.19%) were categorized as having NAFLD, including 2097 males and 1852 females (Table 1). Participants with NAFLD tended to be male and older (aged 52.49 versus [vs.] 46.50 years, respectively), had lower education levels, higher waist circumference, higher BMI, reduced physical activity, were married, and had a history of previous smoking than those without NAFLD. Participants with NAFLD had higher ALT, AST, GGT, and total energy intake than those without NAFLD. In addition, participants with NAFLD were more likely to have metabolic disorders, such as hypertension, hyperlipidemia, and diabetes; a history of coronary heart disease, stroke, and trouble sleeping (34.28% vs. 24.79%); and a higher SII (569.44 vs. 510.84) than participants without NAFLD.

Association between SII and NAFLD

In multivariate logistic regression analysis, the lowest log2-SII level was used as the reference point to assess the correlation between the SII and NAFLD (Additional File 1). When log2SII was expressed as a continuous variable, our findings suggested that a higher SII contributed to increased susceptibility to NAFLD development. This association was significant in Model 1 (OR: 1.39; 95% CI 1.29–1.50) and Model 2 (OR: 1.43; 95% CI 1.31–1.56). The positive correlation between SII and NAFLD remained consistent in Model 3, suggesting that a one-unit increase in the log2-SII score corresponded to a 21% increase in NAFLD risk. The trend $p < 0.05$ indicated statistical significance for all models. A restricted cubic spline (RCS) analysis was performed to elucidate the nonlinear correlation between the SII and NAFLD (Additional File 2). The weighted RCS analysis indicated no significant nonlinear association between the SII and the risk of developing NAFLD ($P_{overall} < 0.001$, $P_{non\text{-}linear} = 0.473$). Analyses were conducted in subgroups to study the correlation between the SII and NAFLD across various demographic characteristics and health states while testing for interactions (Fig. 2). A positive association between the SII and NAFLD was observed among individuals aged 20–39 years. In subgroups stratified by sex, the correlation between the SII and NAFLD was significant in the male population. When stratified by BMI or waist circumference, a positive correlation between SII and NAFLD was observed in participants with a BMI ≥ 30 kg/m^2 or the largest quartile of waist circumference. For the subgroups stratified by diabetes, stroke, and coronary heart disease, positive associations were observed only among participants without these diseases. However, no correlation was observed in the subgroups stratified by hyperlipidemia or hypertension. Interaction tests showed no significant variations in the relationship between the SII and NAFLD across age, sex, race, waist circumference, BMI, hypertension, hyperlipidemia, stroke, and coronary heart disease, suggesting that these variables did not have a significant impact on this relationship.

Association between trouble sleeping and NAFLD

Trouble sleeping was positively associated with NAFLD when no adjustments were made for any variable (Additional file 1). In Model 2, the participants with trouble sleeping had a 1.62-fold increased risk of developing NAFLD. In Model 3, participants with trouble sleeping exhibited a 1.24-fold increased risk of developing NAFLD (OR: 1.24, 95% CI 1.05–1.47). Subgroup analyses were performed in different populations to examine possible links between NAFLD risk and sleeping difficulties (Fig. 2). When stratified by age or sex, the correlation between trouble sleeping and NAFLD did not differ significantly between subgroups. Significant correlations were found between participants with BMIs of ≥ 30 kg/m^2 ($p < 0.05$) but not among those with BMIs of < 30 kg/m^2. Similarly, when stratified by waist circumference quartile, a significant positive correlation was observed among participants in the highest waist circumference quartile. Positive associations were observed between participants without stroke or coronary heart disease and those with hypertension. Interaction tests indicated that the link between trouble sleeping and NAFLD remained stable in all strata, demonstrating the robustness of the study results (all p for interaction > 0.05).

Table 1 Characteristics of NHANES participants during 2005–2018 based on NAFLD status

Variables	Overall	NAFLD		*p*-value
		Yes	No	
Age, years	48.61 (0.28)	52.49 (0.38)	46.50 (0.32)	< 0.001
Age, years, n (%)				< 0.001
20–39	3430 (33.48)	871 (23.72)	2559 (38.78)	
40–59	3611 (37.77)	1366 (39.66)	2245 (36.74)	
≥ 60	3922 (28.74)	1712 (36.61)	2210 (24.47)	
Sex, n (%)				< 0.001
Female	5820 (52.97)	1852 (45.03)	3968 (57.28)	
Male	5143 (47.03)	2097 (54.97)	3046 (42.72)	
Race/ethnicity, n (%)				< 0.001
Non-Hispanic White	4776 (68.34)	1834 (71.03)	2942 (66.89)	
Non-Hispanic Black	2176 (10.24)	454 (5.79)	1722 (12.66)	
Mexican American	1771 (8.56)	944 (12.31)	827 (6.52)	
Other race	2240 (12.86)	717 (10.87)	1523 (13.94)	
Marital status, n (%)				< 0.001
Married	8274 (76.07)	3196 (80.67)	5087 (73.57)	
Unmarried	2689 (23.93)	753 (19.33)	1936 (26.43)	
Education, n (%)				< 0.001
≤ High school	5198 (39.96)	2130 (45.59)	3068 (36.91)	
> High school	5765 (60.04)	1819 (54.41)	3946 (63.09)	
Physical activity, n (%)				< 0.001
Yes	7358 (72.94)	2414 (67.34)	4944 (75.97)	
No	3605 (27.06)	1535 (32.66)	2070 (24.03)	
BMI (kg/m^2), n (%)				< 0.001
< 30	6553 (60.18)	1155 (26.11)	5398 (78.68)	
≥ 30	4410 (39.81)	2794 (73.89)	1616 (21.32)	
Waist circumference quartile (cm)				< 0.001
Quartile 1	2755 (25.96)	96 (1.69)	2659 (39.13)	
Quartile 2	2730 (23.71)	519 (10.51)	2211 (30.88)	
Quartile 3	2741 (24.68)	1220 (29.14)	1521 (22.26)	
Quartile 4	2737 (25.65)	2114 (58.67)	623 (7.73)	
Smoking status, n (%)				< 0.001
Former	2718 (25.13)	1214 (31.60)	1504 (21.62)	
Never	6311 (57.36)	2100 (52.32)	4211 (60.10)	
Now	1934 (17.50)	635 (16.08)	1299 (18.28)	
Hypertension, n (%)				< 0.001
Yes	5845 (49.23)	2747 (68.99)	3098 (38.50)	
No	5118 (50.77)	1202 (31.01)	3916 (61.50)	
Hyperlipidemia, n (%)				< 0.001
Yes	8040 (72.47)	3448 (87.14)	4592 (64.50)	
No	2923 (27.53)	501 (12.86)	2422 (35.50)	
Stroke, n (%)				< 0.001
Yes	469 (3.27)	209 (4.19)	260 (2.77)	
No	10 494 (96.73)	3740 (95.81)	6754 (97.23)	
Coronary heart disease, n (%)				< 0.001
Yes	493 (4.00)	270 (6.36)	223 (2.73)	
No	10 470 (96.00)	3679 (93.64)	6791 (97.27)	
Diabetes, n (%)				< 0.001
Yes	2413 (17.16)	1542 (33.03)	871 (8.54)	

Table 1 (continued)

Variables	Overall	NAFLD		*p*-value
		Yes	No	
No	8550 (82.84)	2407 (66.97)	6143 (91.46)	
Trouble sleeping, n (%)				< 0.001
Yes	2890 (28.13)	1250 (34.28)	1640 (24.79)	
No	8073 (71.87)	2699 (65.72)	5374 (75.21)	
SII (1,000 cells/μl)	531.46 (4.25)	569.44 (6.09)	510.84 (5.26)	< 0.001
SII Quartile				< 0.001
Quartile 1	2741 (22.43)	785 (17.22)	1956 (25.25)	
Quartile 2	2741 (25.77)	981 (24.86)	1760 (26.28)	
Quartile 3	2740 (26.10)	1038 (27.22)	1702 (25.49)	
Quartile 4	2741 (25.70)	1145 (30.70)	1596 (22.98)	
USFLI score	27.06 (0.38)	53.83 (0.46)	12.52 (0.14)	< 0.001
Alanine aminotransferase (U/L)	24.44 (0.18)	30.75 (0.38)	21.02 (0.16)	< 0.001
Aspartate aminotransferase (U/L)	24.26 (0.16)	26.47 (0.29)	23.06 (0.20)	< 0.001
Gamma-glutamyltransferase (U/L)	26.44 (0.44)	39.45 (1.08)	19.37 (0.24)	< 0.001
Total Energy (kcal/day)	2043.68 (10.88)	2100.12 (17.63)	2013.03 (12.10)	< 0.001
Alcohol (g/day)	3.84 (0.24)	3.34 (0.32)	4.11 (0.30)	0.07

Continuous variables are presented as the mean (standard error), and the *P*-value was determined using the Student's t-test. Categorical variables are presented as numbers (percentages), and the *P*-value was determined using the χ2 test

NAFLD: Nonalcoholic fatty liver disease, SII: Systemic immune inflammation index, BMI: Body mass index, NHANES: National Health and Nutrition Examination Survey

Interaction between the SII and trouble sleeping in NAFLD

In the additive interaction model, participants in SII quartiles 1 and 2 were categorized into the normal group, and participants in quartiles 3 and 4 were categorized into the high group. We assessed the existence of additive interactions by calculating the RERI, SI, and AP. The results of the additive interaction model revealed a synergistic effect between high SII and trouble sleeping. In Model 1, the RERI was 2.28 (95% CI 1.46–3.10), AP was 0.56 (95% CI 0.50–0.62), and SI was 3.83 (95% CI 3.31–4.44). These results indicate a synergistic influence of elevated SII combined with trouble sleeping on the risk of developing NAFLD (Table 2). As synergies were still present in Models 2 and 3, the results remained stable (Fig. 3). In Model 3, the AP was 0.27, indicating that 27% of the NAFLD risk in this study sample was caused by interactions between high SII levels and trouble sleeping. No significant multiplicative interaction was identified between SII and trouble sleeping (Model 3, OR: 1.19; 95% CI 0.89–1.59) (Table 2). Logistic regression model analyses showed that trouble sleeping had a significant effect on SII, but the magnitude of the effect varied with model adjustments. Model 1 initially showed that participants with trouble sleeping had a 42.4-fold higher risk of high SII levels than participants without difficulty sleeping ($p < 0.001$). However, after controlling for additional variables in Model 3, the effect of trouble sleeping on SII levels became non-significant ($p = 0.328$) (Additional File 3).

Mediation analysis

In the mediation analyses, trouble sleeping, SII, and NAFLD were considered independent, mediating, and dependent variables, respectively. The results showed a significant direct effect of trouble sleeping on NAFLD (β coefficients: 0.095, 95% CI 0.07–0.12) and a significant indirect effect of trouble sleeping on NAFLD through the SII, with an indirect effect size of 0.0311 ($p < 0.001$) (Additional File 4). This suggests that SII partially mediated the association between trouble sleeping and NAFLD, accounting for approximately 3.11% (95% CI 0.01–0.05) of the total effect; however, the magnitude was much smaller than the direct effect.

Discussion

In this study, we evaluated the association between SII, trouble sleeping, and NAFLD risk based on data from seven NHANES cycles (2005–2018). These findings indicate that SII and trouble sleeping are independently associated with a high risk of developing NAFLD. The results also revealed a synergistic effect of SII and trouble sleeping on NAFLD development. Furthermore, 27% of all patients with NAFLD were affected by the interplay between trouble sleeping and the SII. Additionally, the SII has a mediating role in the positive correlation between trouble sleeping and NAFLD, with a mediation ratio of 3.11%.

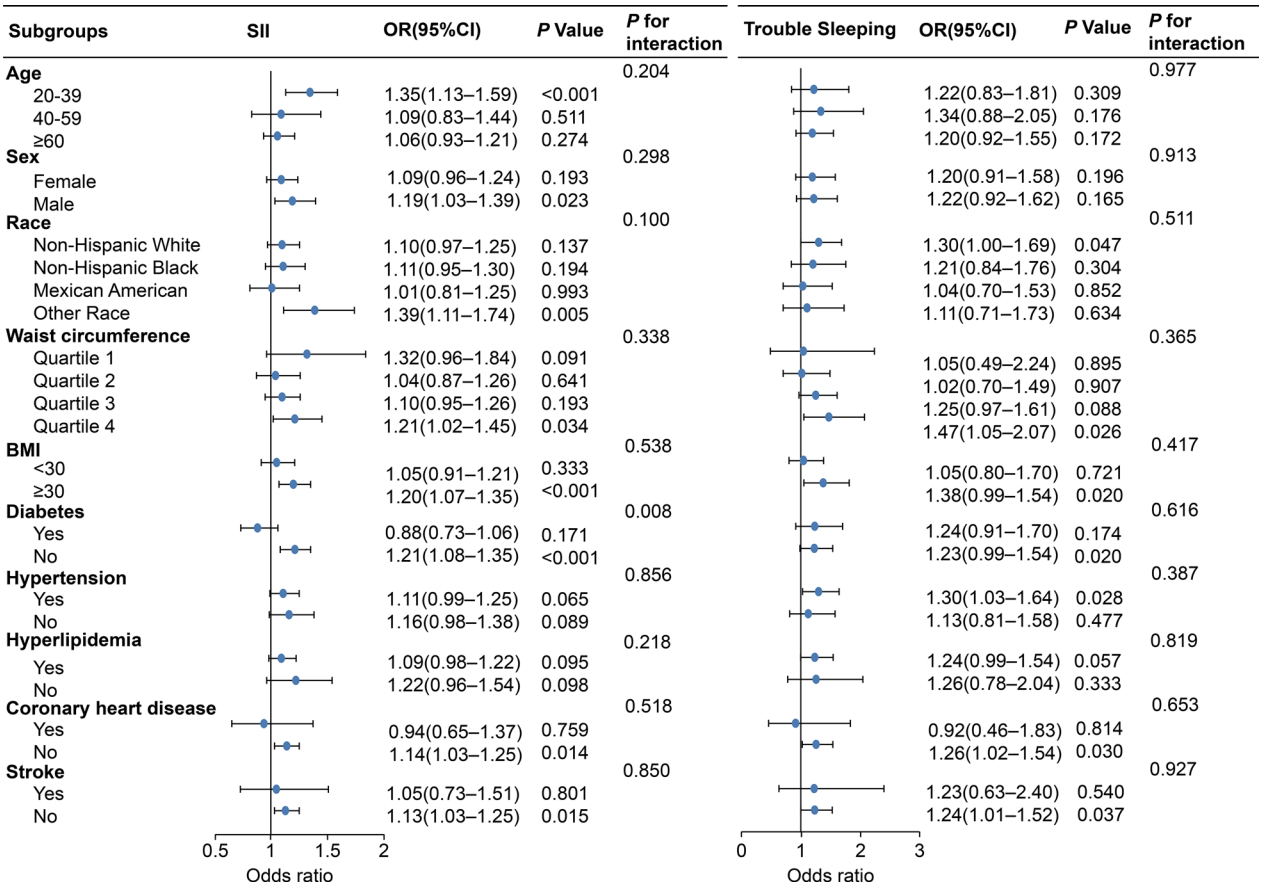

Fig. 2 Forest plot of subgroup analysis between trouble sleeping and systemic immune-inflammation index in NAFLD. Footnotes: Adjusted for age, sex, ethnicity, education, waist circumference, BMI, marital status, smoking status, total energy intake, alcohol intake, physical activity, ALT, AST, GGT, diabetes, hyperlipidemia, hypertension, coronary heart disease, and stroke. Abbreviations: OR: Odds ratio, CI: Confidence interval, SII: Systemic immune-inflammation index, BMI: Body mass index, NAFLD: Nonalcoholic fatty liver disease, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase

The SII is considered a robust indicator of local immune status and overall inflammation in the body [9, 10, 34]. Research has shown that the mechanism underlying NAFLD development is related to insulin resistance and lipotoxicity, which in turn lead to an inflammatory response [35]. This process is believed to be related to elevated neutrophil counts [35]. Indeed, Marques et al. [36] found that increased leukocyte counts, especially neutrophil counts, may increase the risk of developing NAFLD, which is in line with our conclusions. The activation of a range of immune cells and the release of pro-inflammatory factors are also important drivers of NAFLD development [37–39]. Hawkland et al. [40] assessed the histology of blood samples collected from 47 patients with NAFLD. Their results showed significant elevation of several inflammatory factors in patients with NAFLD, which remained high even after adjusting for confounding factors, suggesting that patients with NAFLD have a low-grade systemic inflammatory response [40]. The inflammatory response in NAFLD has also been correlated with several inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and platelet parameters [41–43]. Shavakhi et al. [35] validated the NLR ratio as a predictive marker of NAFLD. An increase in the NLR appears to underlie elevated levels of pro-inflammatory factors, which can be clearly observed from the persistent activation of neutrophils in many patients with NAFLD [41]. Liu et al. [42] investigated the SII, NLR, PLR, and lymphocyte-to-monocyte ratio (LMR) to predict NAFLD risk. Their study confirmed that elevated SII, NLR, and LMR levels were important factors for an increased risk of NAFLD, highlighting the role of systemic immune-inflammatory biomarkers in predicting NAFLD risk [42]. In NAFLD, platelets are highly activated and produce excessive levels of inflammatory cytokines by enhancing thrombosis and promoting an inflammatory response that increases the migration of neutrophils and

Table 2 Interaction analysis between SII and trouble sleeping in patients with nonalcoholic fatty liver disease

SII	Trouble sleeping	Model 1		Model 2		Model 3	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Additive interaction							
Normal-level (n = 5483)	No (n = 8073)	Ref		Ref		Ref	
Normal-level (n = 5483)	Yes (n = 2890)	1.45 (1.28, 1.65)	< 0.001	1.40 (1.20, 1.63)	< 0.001	1.02 (0.84, 1.24)	0.819
High-level (n = 5480)	No (n = 8073)	1.35 (1.23, 1.48)	< 0.001	1.32 (1.19, 1.47)	< 0.001	1.11 (0.96, 1.27)	0.149
High-level (n = 5480)	Yes (n = 2890)	2.08 (1.84, 2.34)	< 0.001	2.05 (1.77, 2.36	< 0.001	1.39 (1.13, 1.63)	0.001
RERI (95% CI)		2.28 (1.46, 3.10)		2.07 (1.18, 2.95)		0.41 (0.05, 0.77)	
AP (95% CI)		0.56 (0.50, 0.62)		0.55 (0.47, 0.62)		0.27 (0.12, 0.41)	
SI (95% CI)		3.83 (3.31, 4.44)		3.86 (3.22, 4.62)		4.17 (1.10, 15.77)	
Multiplicative interaction							
SII × Trouble sleeping		1.06 (0.89, 1.26)	0.519	1.10 (0.90, 1.36)	0.340	1.19 (0.89, 1.59)	0.237

No adjustments were made to Model 1. Model 2 is adjusted for age, sex, and ethnicity. Model 3 was adjusted for the variables in Model 2, including education, waist circumference, body mass index, marital status, smoking habits, total energy intake, alcohol intake, physical activity, ALT, AST, GGT, diabetes, hyperlipidemia, hypertension, coronary heart disease, and stroke

Abbreviations: SII: Systemic immune-inflammation index, CI: Confidence interval, RERI: Relative excess risk of interaction, AP: Attribution proportion, SI: Synergy index, OR: Odds ratio, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase

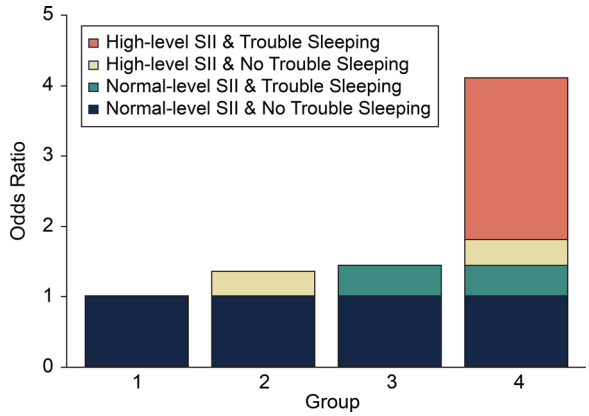

Fig. 3 Interaction between SII and trouble sleeping after adjusting for confounders. Footnotes: Adjusted for age, sex, ethnicity, education, waist circumference, BMI, marital status, smoking status, total energy intake, alcohol intake, physical activity, ALT, AST, GGT, diabetes, hyperlipidemia, hypertension, coronary heart disease, and stroke. Abbreviations: SII: Systemic immune inflammation index, BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase

lymphocytes and induces liver injury [41, 42]. Therefore, the SIIs selected in this study included neutrophils, platelets, and lymphocytes, which could reflect the degree of inflammation and the relationship between the SII and NAFLD.

Recently, improved sleep quality has been suggested to prevent NAFLD [44]. An analysis of 15 studies indicated a significant association between inadequate sleep duration and an increased risk of developing NAFLD, suggesting that adequate sleep may prevent NAFLD [45]. Indeed, Um et al. [46] found that reduced sleep duration or poor sleep quality was linked to a higher risk of NAFLD, emphasizing the importance of sleep quality in reducing the risk of NAFLD [46]. Much of the previous research has focused on evaluating the association between sleep duration, obstructive sleep apnea syndrome, and NAFLD [11, 47, 48]; however, few studies have assessed the impact of trouble sleeping as a major exposure or influencing factor for NAFLD risk. Our findings suggest that patients with trouble sleeping have an increased risk of developing NAFLD. Trouble sleeping may lead to metabolic disorders, such as insulin resistance and fat metabolism disorders, which in turn increase the risk of NAFLD [14]. Trouble sleeping may also interfere with normal neuroendocrine system regulation; this may lead to changes in hormone levels, such as increased cortisol and decreased growth hormone levels, which affects fat metabolism and liver function, thereby increasing the risk of NAFLD [49].

Although the influence of both the SII and trouble sleeping on NAFLD onset is known [11, 50], their synergistic effect remains understudied. The current findings suggest that participants with higher SII scores and trouble sleeping are at higher risk of developing NAFLD. The mechanisms linking trouble sleeping, SII, and NAFLD share several common pathways,

including inflammation and the nervous system [50–52]. Inflammatory mediators may link the SII and sleep problems in NAFLD [10]. Trouble sleeping can activate inflammatory cytokines, cause oxidative stress, and promote the creation of an inflammatory microenvironment within the body, which is associated with the development of NAFLD [53]. Trouble sleeping induces Toll-like 4 receptor (TLR-4) activation in monocytes, leading to an increase in inflammatory cell markers such as interleukin-1β, interleukin-6, and interleukin-17 [53]. Inflammatory mediators may be associated with sleep impairment and NAFLD through multiple pathways. First, inflammatory mediators may interfere with normal sleep patterns and rhythms by affecting central nervous system regulation [54]. Second, inflammatory mediators may act directly on the adipose tissue and liver, leading to fat accumulation, hepatic inflammation, and fibrosis, which may further intensify NAFLD [55]. The SII is also a known marker of inflammatory response [8]. Thus, a high SII may indicate increased inflammation in individuals with sleep disorders [56]. Consistent with a previous study [57], the relationship between the SII and trouble sleeping may be bidirectional and synergistic to promote NAFLD development. Second, trouble sleeping may cause overstimulation of the sympathetic nervous system, resulting in elevated cortisol levels and inflammatory marker levels [58]. A population-based longitudinal cohort study showed that autonomic imbalance, particularly overactivation of sympathetic nervous system activity, was strongly associated with the occurrence of NAFLD [52]. Moreover, a study on patients with sleep disorders found significantly higher IL-6 and CRP levels than in normal controls [59]. These inflammatory mediators can directly or indirectly stimulate sympathetic nervous system activity, leading to increased catecholamine neurotransmitter release, which can influence the development of NAFLD [48]. An overactive sympathetic nervous system may be associated with the development and progression of NAFLD [60]. Sympathetic nerve fibers directly innervate and/or are near hepatocytes, hepatic stellate cells, and hepatic sinusoidal endothelial cells and are involved in the regulation of lipid metabolism, processing of very-low-density lipoproteins, and glucose metabolism, all of which are processes that are closely related to the pathogenesis of NAFLD [60]. Hurr et al. [60] attenuated hepatic steatosis by removing hepatic sympathetic nerves using drugs or phenol. Beta-blockers have also been shown to ameliorate hepatic fat deposition in rats with NAFLD [61]. Sympathetic overactivation induced by sleep disorders plays an important role in NAFLD pathogenesis through direct proinflammatory and intensified metabolic disturbances. Further validation of our proposed mechanisms for the interaction between high SII and trouble sleeping will require additional prospective clinical investigations.

A major strength of this study is the use of a comprehensive sample. Additionally, no previous studies have investigated the interaction between SII levels and trouble sleeping and its impact on NAFLD. Our findings suggest that a synergistic effect exists between high SII and trouble sleeping. However, this study has some limitations. Based on the NHANES study design, trouble sleeping diagnosis was obtained using self-reported questionnaires, which introduced recall bias. However, cross-sectional studies are commonly used in large epidemiological surveys, and self-reported sleep questionnaires are used to examine disease associations. Second, cross-sectional study designs cannot assess causal relationships between variables because of their inherent limitations. Therefore, additional research is required to elucidate the causality. Third, we adopted a higher USFLI threshold as an indicator of NAFLD diagnosis. Whereas the use of higher thresholds may result in the exclusion of more samples due to more stringent criteria, this may affect the representativeness of the analyzed samples. Although the use of strict USFLI thresholds to diagnose NAFLD is a limitation of our study, we believe our findings are valuable and provide a useful reference for further research in the field of NAFLD. However, we emphasize the need to address this issue in future studies and conduct more comprehensive analyses to enhance the definition of the diagnostic criteria for NAFLD. Additionally, within the timeframe of this research, the NHANES dataset did not fully cover chronic viral infection screening, particularly viruses that were uncommon or not of concern at the time, which limited patient identification and may have biased the results, affecting the comprehensiveness and accuracy of the conclusions. Although this study revealed the existence of a synergistic interaction between the SII and trouble sleeping, we did not explore possible mediators of this association. Finally, although our model accounted for as many potential confounders as possible, it did not entirely eliminate the impact of other confounding variables, such as Willson's disease, which may have an impact on study outcomes.

Conclusions

The SII and trouble sleeping were independently associated with an increased risk of NAFLD. A potential combined effect may exist between the SII and trouble sleeping, which increases the risk of NAFLD. Managing inflammatory levels in the body and reducing SII levels, along with ensuring good sleep habits, may help reduce

the risk of NAFLD. However, additional large-scale studies are required to confirm these findings.

Abbreviations

NAFLD	Nonalcoholic fatty liver disease
SII	Systemic immune-inflammation index
NHANES	National health and nutrition examination survey
NCHS	National center for health statistics
USFLI	US fatty liver index
BMI	Body mass index
RERI	Relative excess risk due to interaction
AP	Attributable proportion
SI	Synergy index
OR	Odds ratio
CI	Confidence interval
RCS	Restricted cubic spline
vs.	Versus
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GGT	Gamma glutamyltransferase
STAT	Signal transducer and activator of transcription
TLR-4	Toll-like 4 receptor
NLR	Neutrophil/lymphocyte ratio
PLR	Platelet/lymphocyte ratio
LMR	Lymphocyte-to-monocyte ratio

Supplementary Information

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Additional file 1.

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Author contributions
XY and SZ designed the study and wrote the manuscript; XY and HZ collected, analyzed, and interpreted the data; and TF critically reviewed, edited, and approved the manuscript. All of the authors have read and approved the final version of the manuscript.

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Data availability
The datasets generated and/or analyzed in the current study are available from the NHANES repository (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethical approval and consent to participate
Ethical approval was obtained from the NCHS Ethics Review Board before conducting this study. All the study participants provided written informed consent for their involvement.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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