Insufficient nocturnal sleep was associated with a higher risk of fibrosis in patients with diabetes with metabolic associated fatty liver disease

Jiaping Zheng, Sijie Chen, Yuqing Cai, Su Lin, Sujie Ke and Libin Liu

Abstract

Background: Metabolic associated fatty liver disease (MAFLD) refers to metabolic dysfunction associated with fatty liver disease, and liver fibrosis stage is closely connected with liver-related and all-cause mortality. This study aimed to explore the association of sleep duration with liver fibrosis in the diabetic subgroup of the MAFLD population.

Methods: This retrospective study analyzed 342 patients with MAFLD. Anthropometric measurements, clinical and biochemical markers, and lifestyle parameters were collected. Fibrosis was defined as fibrosis-4 ≥ 1.3. Propensity score matching (PSM) was performed to match cases. Student’s t-test and chi-square tests were applied for group comparisons, and binary regression models were used to explore the independent risk factors of liver fibrosis.

Results: Among the 342 subjects, 87 (25.4%) were diagnosed with fibrosis and 255 (74.6%) without. Baseline characteristic comparisons showed differences in age and diabetes duration between the two groups, and adjustment was made by PSM. Ultimately, the fibrosis group and nonfibrosis group each had 87 patients. The fibrosis group had shorter duration of nocturnal sleep (6.77 ± 1.59 h) than the nonfibrosis group (7.77 ± 1.92 h, p < 0.001). More patients in the fibrosis group stayed up late at night (32.2% versus 14.9%, p < 0.01). Visceral adipose tissue (VAT) areas were larger in the fibrosis group than in the nonfibrosis group (p < 0.001). Glycemic profile, lipid profile, gamma-glutamyl transferase level, and serum uric acid level were not significantly different between the two groups. In the multivariate regression analysis, nocturnal sleep and VAT areas were independently associated with liver fibrosis, with odds ratios of 0.694 [95% confidence interval (CI) 0.551–0.875, p < 0.01] for nocturnal sleep and 1.031 (95% CI 1.014–1.048, p < 0.001) for VAT areas.

Conclusion: Insufficient nocturnal sleep was independently related to a higher risk of fibrosis. Sleep modification might be beneficial in promoting the health of patients with MAFLD.

Keywords: liver fibrosis, metabolic associated fatty liver disease, sleep duration, VAT area

Received: 21 May 2020; revised manuscript accepted: 29 June 2020.
that the overall MAFLD prevalence was 35.36% for men and 26.49% for women in central China.\(^4\) MAFLD may lead to fibrosis and eventually progress to cirrhosis, and enhance the risks of cardiovascular and cerebrovascular diseases.\(^5,6\)

Fibrosis is a common complication of chronic liver disease, and sleep disorder has been shown to promote the progression of liver diseases.\(^7,8\) Sleep disruption contributes to the pathogenesis of hepatic steatosis, and short sleep duration is positively associated with liver stiffness.\(^8\) Furthermore, a study reported that insufficient sleep had negative effects on metabolic disorders including diabetes mellitus (DM), obesity, insulin resistance, and metabolic syndrome.\(^7\) However, the relation between sleeping disorder and progression of MAFLD remains unknown.

In this retrospective study, we collected data of patients with MAFLD with type 2 DM and applied fibrosis-4 (FIB-4) score as an index to define advanced liver fibrosis. This study aimed to explore the association of nocturnal sleep duration with liver fibrosis in the DM subgroup of the MAFLD population.

**Materials and methods**

**Subjects**

Patients with type 2 DM who visited Fujian Medical University Union Hospital from 2018 to 2019 were screened for fatty liver, and those who met the diagnostic criteria of MAFLD were included.\(^2\) This retrospective study was approved by the Ethics Committee of Fujian Medical University Union Hospital (No. 2018KY072), and participants provided written informed consent for personal information collection.

**Definitions**

MAFLD was defined as the presence of hepatic steatosis in addition to one of the following three criteria:\(^2\) overweight/obesity [defined as body mass index (BMI) \(>25\text{ kg/m}^2\)], type 2 DM, or evidence of metabolic dysregulation. Abdominal ultrasonography was performed using a 3.5-MHz transducer (Aplo-400, Toshiba, Kyoto, Japan) by certified radiologists who were blinded to the aim of the study. Ultrasonographic diagnosis of hepatic steatosis was defined by the presence of a diffuse increase in echogenicity of the liver relative to the kidney or spleen parenchyma.\(^9\) The FIB-4 score was obtained using the following formula: \(\text{age (years)} \times \frac{\text{alanine aminotransferase (U/L)}}{\text{platelet (10^9/L)}} \times \sqrt{\frac{\text{aspartate transaminase (U/L)}}{\text{alanine aminotransferase (U/L)}}}\), and fibrosis was defined as FIB-4 \(\geq 1.3.\)\(^10\)

Smoking was defined as smoking at least one cigarette per day for at least 6 months. Physical activity was defined as \(>20\text{ min of exercise per day more than three times a week over the previous 6 months. Late sleep was defined as staying up later than 0:00 am.\)

**Measurements**

Anthropometric measurements (body weight, height, and waist circumference) and lifestyle variables were collected. BMI was calculated as body weight in kilograms divided by the square of height in meters. Waist and hip circumference were measured according to a standard protocol.\(^11\) Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) areas were measured by two experienced nurses using a DUALSCAN HDS-2000 machine (OMRON, Kyoto, Japan). Measurements of fasting plasma glucose (FPG), 2-h postprandial blood glucose (2hPG), fasting and 2-h postprandial C-peptide, glycosylated hemoglobin (HbA1c), alanine aminotransferase, aspartate transaminase, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were performed by standard laboratory methods.

**Statistical analysis**

The distribution of variables was assessed by the Shapiro–Wilk test, and data were represented by \(X \pm SD\) (mean \(\pm\) standard deviation) or percentage, as appropriate. Before statistical analyses, non-normally distributed variables were logarithmically transformed. Comparisons between groups were carried out by Student’s \(t\)-test for continuous variables or chi-square test for categorical variables. Binary logistic regression was performed to evaluate the risk factors of liver disease-related and overall mortality. IBM SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA) was used for analyses. A \(p\) value \(< 0.05\) was considered statistically significant.

**Results**

**Participant characteristics**

A total of 342 patients with MAFLD were enrolled, with 87 (25.4%) in the fibrosis group and 255 (74.6%) in the nonfibrosis group. The fibrosis group was older (64.4 \(\pm\) 7.2 years \textit{versus}
54.5 ± 11.6 years, \( p < 0.001 \) and had longer history of DM (12.2 ± 7.1 years versus 9.6 ± 8.3 years, \( p < 0.05 \)) than the nonfibrosis group.

As age and duration of DM affect the development of fibrosis,\(^{12,13}\) to minimize their influences, propensity score matching (PSM) analysis was performed to adjust for these two factors. Ultimately, the fibrosis group and nonfibrosis group each had 87 patients. The main anthropometric features before and after PSM are reported in Table 1.

**Table 1.** Characteristics of patients with MAFLD before and after PSM.

| Before PSM                      | After PSM                      |
|---------------------------------|---------------------------------|
| **Subjects, n**                 | **Subjects, n**                 |
| Nonfibrosis group               | Fibrosis group                 |
| n                               | 255                            |
| 87                              | 87                             |
| Sex, males, n (%)               | Sex, males, n (%)               |
| Nonfibrosis group               | 146 (57.3%)                    |
| Fibrosis group                  | 50 (57.5%)                     |
| \( p \)                         | 0.972                          |
| Age (years)                     | Age (years)                     |
| 54.5 ± 11.6                     | 64.4 ± 7.2                     |
| \( p \)                         | < 0.001                        |
| Diabetes duration (years)       | Diabetes duration (years)       |
| 9.6 ± 8.3                       | 12.2 ± 7.1                     |
| \( p \)                         | 0.012                          |
| Drug usage, n (%)               | Drug usage, n (%)               |
| Metformin                       | 169 (66.3%)                    |
| (52 (59.8%))                    | 50 (57.5%)                     |
| Lipid-lowering therapy          | 82 (32.2%)                     |
| (40 (46.0%))                    | 17 (19.5%)                     |
| Antplatelet therapy             | 33 (12.9%)                     |
| Insulin therapy                 | 233 (91.4%)                    |
| VAT [cm²]                       | 99.1 ± 7.7                     |
| 99.0 ± 37.5                     | 109.5 ± 30.3                   |
| \( p \)                         | 0.010                          |
| SAT [cm²]                       | 196.5 ± 67.7                   |
| 187.9 ± 49.7                    | 180.3 ± 65.9                   |
| \( p \)                         | 0.279                          |
| Alcohol drinkers, n (%)         | Alcohol drinkers, n (%)         |
| 17 (6.7%)                       | 8 (9.2%)                       |
| HBsAg positive, n (%)           | HBsAg positive, n (%)           |
| 12 (4.7%)                       | 6 (6.9%)                       |
| MetS, n (%)                     | MetS, n (%)                     |
| 186 (72.9%)                     | 56 (64.4%)                     |
| HbA1c (%)                       | HbA1c (%)                       |
| 9.30 ± 2.2                      | 8.59 ± 1.95                    |
| FPG [mmol/L]                    | FPG [mmol/L]                    |
| 9.80 ± 3.41                     | 9.42 ± 3.79                    |
| 2hPG [mmol/L]                   | 2hPG [mmol/L]                   |
| 14.67 ± 4.63                    | 15.19 ± 8.04                   |
| Fasting C-peptide [mmol/L]      | Fasting C-peptide [mmol/L]      |
| 0.77 ± 0.39                     | 0.74 ± 0.40                    |
| Postprandial C-peptide [mmol/L] | Postprandial C-peptide [mmol/L] |
| 1.65 ± 1.00                     | 1.76 ± 1.17                    |
| Albumin [g/L]                   | Albumin [g/L]                   |
| 42.81 ± 4.09                    | 42.09 ± 4.40                   |
| TG [mmol/L]                     | TG [mmol/L]                     |
| 2.32 ± 1.86                     | 2.17 ± 1.78                    |

Data are expressed as means ± standard deviation or medians [interquartile ranges] or numbers [percentage]. 2hPG, 2-h postprandial plasma glucose; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HBsAg, hepatitis B surface antigen; MAFLD, metabolic associated fatty liver disease; MetS, metabolic syndrome; PSM, propensity score matching; SAT, subcutaneous adipose tissue; TG, triglyceride; VAT, visceral adipose tissue.
After PSM adjustment, no significant difference was found in age, sex, DM course, and use of metformin, pioglitazone, antiplatelet therapy, lipid-lowering agents, and insulin therapy between the two groups, which are factors that might influence the progress of MAFLD.14–18 The fibrosis group had larger waist circumference (94.9 ± 13.0 cm versus 91.3 ± 9.4 cm, p < 0.05) and VAT areas (109.5 ± 30.3 cm² versus 90.1 ± 38.5 cm², p < 0.001) than the nonfibrosis group, but SAT areas showed no significant difference (Table 1).

As regards biochemical features (Table 1), glycemic profile (HbA1c, FPG, 2hPG, fasting and postprandial C-peptide values) and lipid profiles (TC, TG, HDL-C, and LDL-C values) were not significantly different between the two groups. Gamma-glutamyltransferase and serum uric acid did not differ between the two groups.

**Association between sleep duration and risks of liver fibrosis in patients with MAFLD**

Lifestyle data are shown in Table 2. The fibrosis group had shorter nocturnal sleep duration than the nonfibrosis group (6.77 ± 1.59 h versus 7.77 ± 1.92 h, respectively, p < 0.001), and more patients stayed up late at night (32.2% versus 14.0%, p < 0.01). Daytime nap was not significantly different between the two groups. As regards dietary intake and other lifestyle factors, no significant differences were found between the groups.
groups in terms of fruit, vegetable, fish, salt, and cigarette consumption as well as physical activities.

Multivariate binary linear regression analysis was performed to assess the influence of sleep on the risk of liver fibrosis (Table 3). Model 1 was adjusted for age, sex, BMI, and DM duration, and the odds ratios (ORs) and 95% confidence interval (CI) of liver fibrosis were 0.709 (0.568–0.883) for nocturnal sleep and 1.032 (1.015–1.049) for VAT areas ($p < 0.01$ and $p < 0.001$, respectively). Model 2 was further adjusted for drug usage, and the association between nocturnal sleep duration and fibrosis remained statistically significant, with ORs (95% CIs) of 0.694 (0.551–0.875) for nocturnal sleep and 1.031 (1.014–1.048) for VAT areas ($p < 0.01$ and $p < 0.001$, respectively).

Table 3. Association between nocturnal sleep and VAT areas and liver fibrosis risks in patients with MAFLD.

|                          | Multivariate OR (95% CI) |
|--------------------------|--------------------------|
|                          | Unadjusted model | Model 1          | Model 2          |
| Waist circumference (cm) | 0.998 (0.963–1.034) | 1.023 (0.976–1.071) | 1.025 (0.978–1.073) |
| VAT (cm²)                | 1.018 (1.006–1.030)**  | 1.032 (1.015–1.049)*** | 1.031 (1.014–1.048)***** |
| Stay up late             | 0.601 (0.259–1.398) | 0.552 (0.224–1.358) | 0.553 (0.215–1.418) |
| Nocturnal sleep duration (h) | 0.742 (0.604–0.912)** | 0.709 (0.568–0.883)** | 0.694 (0.551–0.875)** |

Model 1: Adjusted for age, sex, BMI, and diabetes duration.
Model 2: Additionally adjusted for drug usage in evaluating the association between nocturnal sleep and VAT areas and MAFLD.

**$p < 0.01$, ***$p < 0.001$.

BMI, body mass index; CI, confidence interval; MAFLD, metabolic associated fatty liver disease; OR, odds ratio; VAT, visceral adipose tissue.

Discussion

MAFLD represents a wide spectrum of metabolic pathological states on the basis of hepatic steatosis, the heterogeneity of which renders it necessary to stratify patients when proposing therapies. In this study, we examined features of MAFLD with type 2 DM and searched for the risk factors of advanced liver fibrosis. We found that insufficient nocturnal sleep and larger VAT areas were associated with liver fibrosis, independent of relevant confounders including age, sex, BMI, and DM duration.

Liver fibrosis stage is prognostic to the development of liver-related and all-cause mortality. Factors contributing to the progress of fatty liver disease include enhanced inflammatory levels, dysregulated lipid metabolism, changes in gut microbiota, insulin resistance, etc. The effect of sleep on the liver has been receiving attention in recent years as it regulates a series of endocrine signaling as well as the overall metabolic process. Sleep deprivation has been proven to inhibit energy production and enhance lipogenesis of hepatocytes and consequently induce hepatic steatosis and hepatic insulin resistance. In a recent study, Peng et al. revealed that insufficient night-time sleep and prolonged daytime nap (>30 min) were positively linked to an increased risk of NAFLD prevalence in the middle-aged and older Chinese population. Sleep disturbance or low sleep quality was also related to increased liver stiffness in patients with NAFLD, which was consistent with our findings, whereas optimal sleep (defined as sleep duration $\geq 7$ h and $\leq 9$ h/day) was found to be protective in reducing insulin resistance and liver stiffness.

Sleep plays regulating roles in eating habits, weight gain, neuroendocrine signaling, and glucose homeostasis, and studies reported its link to higher risks of DM and worse control of glycemic levels in patients with DM. Excessive and low-quality sleep was also harmful to metabolic health. Sleeping >9h was shown to increase the risk of DM, cardiovascular disease, coronary heart disease, and obesity. The MAFLD criteria contain a wider spectrum of disease rather than the pathology of an individual organ; impairments in overall metabolic homeostasis would inevitably bring further insult to the liver, and vice
versa. The disruption of the circadian clock is detrimental to liver functions.\textsuperscript{32} Our study revealed that in the case of dysregulated metabolic functions, with multiple influencing factors, sleep duration was still independently related to the progress of fatty liver disease, which highlighted the importance of sleep in regulating liver metabolism and homeostasis of the metabolic environment.

Moreover, the relationship between sleep and liver disease was proven reciprocal. The prevalence of sleep-wake disturbances, such as difficulties in sleep onset and sleep maintenance, daytime sleepiness, and sleep aversion, was higher in patients with liver cirrhosis and fatty liver disease.\textsuperscript{33} If sleep disorder is accompanied by intermittent hypoxia, which happens in obstructive sleep apnea (OSA), the activation of the sympathetic nervous system, increased cortisol secretion, and inflammatory levels would exacerbate the attacks on the liver and further heighten the risks of liver fibrosis and cardiovascular diseases.\textsuperscript{34,35}

In our study, another factor found to be independently related to fibrosis was increased VAT area, which was consistent with the findings of previous studies.\textsuperscript{36,37} Anatomically, VAT is connected closely and drained directly through the portal circulation to the liver, and it was reported to be more inflammatory and metabolically active than SAT, containing a larger number of immune cells and glucocorticoid and androgen receptors.\textsuperscript{38} In obese patients, VAT deposition exposed the liver to increasing amounts of free fatty acids and pro-inflammatory factors, and promoted the development of hepatic insulin resistance and liver steatosis.\textsuperscript{39} The deposition of adipose was also affected by sleep, and short sleep duration and poor sleep quality were positively related with visceral adiposity,\textsuperscript{40} whereas a change from $<6$ h to $7$–$8$ h of sleep was found to be beneficial in reducing VAT deposition.\textsuperscript{41}

This study has several limitations. First, the sleep duration was self-reported. Nonetheless, evidence showed that self-reported sleep duration was well correlated with an objective measurement.\textsuperscript{42} Secondly, we did not include histologic proof of liver fibrosis, but applied the noninvasive index of FIB-4, which was more acceptable by patients. The FIB-4 has a sensitivity of 0.844 and specificity of 0.685 in diagnosing liver fibrosis.\textsuperscript{43} Thirdly, sleep apnea was not screened, as OSA was also a contributing factor to liver damage,\textsuperscript{44} which would be complemented in further research.

In conclusion, our study revealed that insufficient nocturnal sleep and increased VAT area were associated with higher risk of liver fibrosis in patients with MAFLD. Currently, there are limited pharmacological therapies for MAFLD. Exogenous interventions like lifestyle changes have been proved to alleviate disease progression, as supported by various studies.\textsuperscript{45} As sleep pattern influences liver metabolism and systemic metabolic health holistically, optimizing sleep duration and quality might be beneficial in promoting the health of patients with MAFLD.

**Author contributions**

**Jiaping Zheng:** conceptualization; formal analysis; investigation; writing–review and editing.

**Sijie Chen:** data curation; investigation; methodology; writing–review and editing.

**Yuqing Cai:** conceptualization; data curation; software; writing–review and editing.

**Su Lin:** conceptualization; project administration; writing–review and editing.

**Sujie Ke:** data curation; investigation; writing original draft.

**Libin Liu:** conceptualization; funding acquisition; project administration; supervision; writing–review and editing.

**Conflict of interest statement**

The authors declare that there is no conflict of interest.

**Funding**

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The work was supported by the Fujian Science and Technology Innovation Joint Fund Project (Project: Study for multiple risk factors intervention and metabolic model of type 2 diabetes mellitus in Fujian Province; Grant No. 2017Y9060; Clinical registration No. ChiCTR1900028514).

**ORCID iD**

Libin Liu  https://orcid.org/0000-0002-0352-3865
References

1. Eslam M, Sanyal AJ and George J. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* 2020; 158: 1999–2014.e1991.

2. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol* 2020; 73: 202–209.

3. Lin S, Huang J, Wang M, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. *Liver Int*. Epub ahead of print 1 June 2020. DOI: 10.1111/liv.14542.

4. Li H, Guo M, An Z, et al. Prevalence and risk factors of metabolic associated fatty liver disease in Xinxiang, China. *Int J Environ Res Public Health* 2020; 17: 1818.

5. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol* 2019; 71: 793–801.

6. Hazlehurst JM, Woods C, Marjot T, et al. Non-alcoholic fatty liver disease and diabetes. *Metabolism* 2016; 65: 1096–1108.

7. Koren D and Taveras EM. Association of sleep disturbances with obesity, insulin resistance and the metabolic syndrome. *Metabolism* 2018; 84: 67–75.

8. Marin-Alejandre BA, Abete I, Cantero I, et al. Association between sleep disturbances and liver status in obese subjects with nonalcoholic fatty liver disease: a comparison with healthy controls. *Nutrients* 2019; 11: 322.

9. Mathiesen UL, Franzen LE, Aselius H, et al. Increased liver echogenicity at ultrasound examination reflects degree of steatosis but not of fibrosis in asymptomatic patients with mild/moderate abnormalities of liver transaminases. *Dig Liver Dis* 2002; 34: 516–522.

10. Unalp-Arida A and Ruhl CE. Liver fibrosis scores predict liver disease mortality in the United States population. *Hepatology* 2017; 66: 84–95.

11. Wang N, Wang X, Li Q, et al. The famine exposure in early life and metabolic syndrome in adulthood. *Clin Nutr* 2017; 36: 253–259.

12. Klisic A, Abenavoli L, Fagoonee S, et al. Older age and HDL-cholesterol as independent predictors of liver fibrosis assessed by BARD score. *Minerva Med* 2019; 110: 191–198.

13. Roulot D, Roudot-Thoraval F, NKontchou G, et al. Concomitant screening for liver fibrosis and steatosis in French type 2 diabetic patients using Fibroscan. *Liver Int* 2017; 37: 1897–1906.

14. Zhou J, Massey S, Story D, et al. Metformin: an old drug with new applications. *Int J Mol Sci* 2018; 19: 2863.

15. Athyros VG, Alexandrides TK, Bilianou H, et al. The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk. An expert panel statement. *Metabolism* 2017; 71: 17–32.

16. Jiang ZG, Feldbrugge L, Tapper EB, et al. Aspirin use is associated with lower indices of liver fibrosis among adults in the United States. *Aliment Pharmacol Ther* 2016; 43: 734–743.

17. Nascimbeni F, Pellegrini E, Lugari S, et al. Statins and nonalcoholic fatty liver disease in the era of precision medicine: more friends than foes. *Atherosclerosis* 2019; 284: 66–74.

18. Takahashi Y, Sugimoto K, Inui H, et al. Current pharmacological therapies for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol* 2015; 21: 3777–3785.

19. Hagstrom H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. *J Hepatol* 2017; 67: 1265–1273.

20. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. *Hepatology* 2017; 65: 1557–1565.

21. Angulo P, Bugianesi E, Bjornsson ES, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2013; 145: 782–789.e784.

22. Parola M and Pinzani M. Liver fibrosis: pathophysiology, pathogenetic targets and clinical issues. *Mol Aspects Med* 2019; 65: 17–32.

23. Sengupta A, Rhoades SD, Kim EL, et al. Sleep restriction induced energy, methylation and lipogenesis metabolic switches in rat liver. *Int J Biochem Cell Biol* 2017; 93: 129–135.

24. Shigiyama F, Kumashiro N, Tsuneoka Y, et al. Mechanisms of sleep deprivation-induced hepatic steatosis and insulin resistance in mice. *Am J Physiol Endocrinol Metab* 2018; 315: E848–E858.

25. Peng K, Lin L, Wang Z, et al. Short sleep duration and longer daytime napping are associated with non-alcoholic fatty liver disease in Chinese adults. *J Diabetes* 2017; 9: 827–836.
26. Katsagoni CN, Papatheodoridis GV, Papageorgiou MV, et al. A “healthy diet-optimal sleep” lifestyle pattern is inversely associated with liver stiffness and insulin resistance in patients with nonalcoholic fatty liver disease. *Appl Physiol Nutr Metab* 2017; 42: 250–256.

27. Ogilvie RP and Patel SR. The epidemiology of sleep and diabetes. *Curr Diab Rep* 2018; 18: 82.

28. Lee SWH, Ng KY and Chin WK. The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: a systematic review and meta-analysis. *Sleep Med Rev* 2017; 31: 91–101.

29. Rao MN, Neylan TC, Grunfeld C, et al. Subchronic sleep restriction causes tissue-specific insulin resistance. *J Clin Endocrinol Metab* 2015; 100: 1664–1671.

30. Jike M, Itani O, Watanabe N, et al. Long sleep duration and health outcomes: a systematic review, meta-analysis and meta-regression. *Sleep Med Rev* 2018; 39: 25–36.

31. Tan X, Chapman CD, Cedernaes J, et al. Association between long sleep duration and increased risk of obesity and type 2 diabetes: a review of possible mechanisms. *Sleep Med Rev* 2018; 40: 127–134.

32. Mukherji A, Bailey SM, Staels B, et al. The circadian clock and liver function in health and disease. *J Hepatology* 2019; 71: 200–211.

33. Bernsmeier C, Weisskopf DM, Pflueger MO, et al. Sleep disruption and daytime sleepiness correlating with disease severity and insulin resistance in non-alcoholic fatty liver disease: a comparison with healthy controls. *PLoS One* 2015; 10: e0143293.

34. Trzepizur W, Boursier J, Mansour Y, et al. Association between severity of obstructive sleep apnea and blood markers of liver injury. *Clin Gastroenterol Hepatol* 2016; 14: 1657–1661.

35. Trzepizur W, Boursier J, Le Vaillant M, et al. Increased liver stiffness in patients with severe sleep apnoea and metabolic comorbidities. *Eur Respir J* 2018; 51: 1800601.

36. van der Poorten D, Milner KL, Hui J, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. *Hepatology* 2008; 48: 449–457.

37. Eguchi Y, Mizuta T, Sumida Y, et al. The pathological role of visceral fat accumulation in steatosis, inflammation, and progression of nonalcoholic fatty liver disease. *J Gastroenterol* 2011; 46(Suppl. 1): 70–78.

38. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev* 2010; 11: 11–18.

39. du Plessis J, van Pelt J, Korf H, et al. Association of adipose tissue inflammation with histologic severity of nonalcoholic fatty liver disease. *Gastroenterology* 2015; 149: 635–648.e614.

40. Sweat SK, Gower BA, Chieh AY, et al. Sleep quality is differentially related to adiposity in adults. *Psychoneuroendocrinology* 2018; 98: 46–51.

41. Chaput JP, Bouchard C and Tremblay A. Change in sleep duration and visceral fat accumulation over 6 years in adults. *Obesity (Silver Spring)* 2014; 22: E9–E12.

42. Lockley SW, Skene DJ and Arendt J. Comparison between subjective and actigraphic measurement of sleep and sleep rhythms. *J Sleep Res* 1999; 8: 175–183.

43. Sun W, Cui H, Li N, et al. Comparison of FIB-4 index, NAFLD fibrosis score and BARD score for prediction of advanced fibrosis in adult patients with non-alcoholic fatty liver disease: a meta-analysis study. *Hepatol Res* 2016; 46: 862–870.

44. Aron-Wisnewsky J, Minville C, Tordjman J, et al. Chronic intermittent hypoxia is a major trigger for non-alcoholic fatty liver disease in morbid obese. *J Hepatol* 2012; 56: 225–233.

45. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology* 2015; 149: 367–378.e365; quiz e314–e365.