Non-alcoholic fatty liver disease, sleep behaviors, and incident type 2 diabetes

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Abstract

Background and Aim: Non-alcoholic fatty liver disease (NAFLD) is associated with incident type 2 diabetes; however, the extent to which NAFLD may confer its risk remains uncertain, especially in Europeans. Emerging evidence suggests that sleep behaviors are linked to NAFLD and diabetes. We aimed to measure whether sleep behaviors modified the association between NAFLD and incident type 2 diabetes.

Methods: This prospective cohort study included 365 339 participants without type 2 diabetes at baseline in UK Biobank data. Five sleep behaviors, including sleep duration, insomnia, snoring, chronotype, and daytime sleepiness, were collected from the questionnaire. Overall sleep patterns were created by summing the five scores. Liver steatosis was based on the fatty liver index.

Results: During a median follow up of 11.0 years, we documented 8774 patients with incident type 2 diabetes. NAFLD was significantly associated with increased diabetes risk. Sleeping 7–8 h/day, no insomnia, no self-reported snoring, and no frequent daytime sleepiness were independently associated with incident type 2 diabetes, with a 20%, 18%, 16%, and 31% lower risk, respectively. About 33.8% and 33.5% of type 2 diabetes events in this cohort could be attributed to NAFLD and poor sleep pattern, respectively. Participants with NAFLD and poor sleep pattern showed the highest risk of type 2 diabetes (relative risk 3.17, 95% confidence interval 2.80, 3.59). Sleep pattern (healthy, intermediate, and poor) did not significantly modify the association between NAFLD and type 2 diabetes. However, when studying separately, we found a significant interaction between NAFLD and insomnia on the risk of incident type 2 diabetes (P for interaction = 0.003).

Conclusion: In this large prospective study, both NAFLD and some sleep behaviors were risk factors for type 2 diabetes. Although overall sleep pattern did not modify the association between NAFLD and type 2 diabetes, certain sleep behavior, especially insomnia, showed the modification effect.
Introduction

Non-alcoholic fatty liver disease (NAFLD) has become and is becoming the most common liver disease in developed and developing countries, affecting approximately one quarter of the world’s adult population, and its prevalence is expected to rise further in the near future. It has been realized that NAFLD is not just the simple “hepatic manifestation” of metabolic diseases, and it shares cardiometabolic risk factors and pathophysiological mechanisms with type 2 diabetes. Recent epidemiological studies have indicated that NAFLD may be a risk factor for the development of diabetes. A recent meta-analysis including approximately 300,000 individuals found that NAFLD is significantly associated with a twofold increased risk of incident diabetes. However, high heterogeneity in these studies was observed. The inconsistent associations or varying association strength might be partly due to the modification effects of varying lifestyle metrics related to NAFLD across the studies.

Emerging evidence has indicated that different sleep behaviors are associated with NAFLD. Among participants who had insomnia or excessive daytime sleepiness, an increased risk of NAFLD was also observed. Obstructive sleep apnea with snoring as a main symptom is associated with the development and evolution of NAFLD, possibly due to intermittent hypoxia causing oxidative stress, inflammation, and insulin resistance, a key dysfunction step in hepatic steatosis. Moreover, unhealthy sleep habits have also been linked to the development of type 2 diabetes. Thus, a hypothesis was formed that sleep behaviors might modify the association between NAFLD and incident type 2 diabetes.

In this prospective cohort of 365,339 participants from the UK Biobank, we measured the association between NAFLD and incident type 2 diabetes. To the best of our knowledge, this is the first large prospective study in individuals of European descent measuring such an association with a long follow-up time. We further examined the modification effect of sleep behaviors, including sleep duration, chronotype, insomnia, snoring, and excessive daytime sleepiness, in this association.

Materials and methods

Study design and sample. The UKB is a prospective cohort study that included more than 500,000 community-dwelling adults aged 40–69 years across the United Kingdom between 2006 and 2010 (https://www.ukbiobank.ac.uk/). Detailed information has been described in a previous study. We declare that all data are publicly available in the UKB repository. The North West Multicenter Research Ethics Committee Study approved the UKB study, and all participants provided written informed consent.

A total of 502,505 participants were recruited. We excluded those with missing values for any component of the fatty liver index (FLI) (body mass index [BMI], waist circumference, triglycerides, and gamma-glutamyl transferase) (n = 33,237), those with diabetes at baseline (n = 27,397), and those with missing sleep variables (n = 76,523) at baseline. The final sample was 365,339.

Exposure, moderator, and outcome. Non-alcoholic fatty liver disease was based on FLI evidence of fatty liver (defined by an FLI ≥ 60) and the exclusion of viral hepatitis (B or C), excessive alcohol consumption (alcohol consumption ≥ 30 g/day for male participants and 20 g/day for female participants) or aspartate transaminase or alanine aminotransferase > 500 U/L. The FLI is a non-invasive algorithm for identifying liver steatosis using BMI, waist circumference, triglycerides, and gamma-glutamyl transferase. The formula of FLI was as follows:

$$FLI = \frac{e^{0.953 \log_1 \text{triglycerides} + 0.139 \log_1 (\text{gamma-glutamyl transferase})} + 0.053 \times \text{waist circumference} - 15.745}{1 + e^{0.953 \log_1 \text{triglycerides} + 0.139 \log_1 (\text{gamma-glutamyl transferase})} + 0.053 \times \text{waist circumference} - 15.745} \times 100\%$$

Fatty liver index was expressed as a value ranging from 0 to 100. According to the original study from the Italian population, an FLI ≥ 60 indicates fatty liver with a sensitivity and specificity of 87% and 86%, respectively. It has been validated in European descendants in whom it accurately matched the observed percentages of patients with hepatic steatosis.

The outcome, type 2 diabetes, was extracted from “first occurrence of health outcomes defined by a 3-character International Statistical Classification of Diseases and Related Health Problems 10th Revision code” (category ID in UKB 1712). The diagnosis of incident type 2 diabetes was obtained by using linkage with death register, primary care, and hospital inpatient records. Detailed information regarding the linkage procedure is available online (https://biobank.ctsu.ox.ac.uk/crystal/exinfo.cgi?src=diag_xtabs_HES).

Self-reported information on the moderator sleep behaviors was collected at baseline recruitment. Detailed questions about sleep behaviors are described in Table S1. Five sleep behavior components were used to define sleep patterns, including sleep duration, chronotype, insomnia, snoring, and excessive daytime sleepiness. Based on previous studies, “sleep behaviors with low risk were defined as follows: sleeping 7–8 h/day, early chronotype (“morning” or “morning than evening”), reported never having or rarely having insomnia symptoms, no self-reported snoring, and no excessive daytime sleepiness (“never/rarely” or “sometimes”). Moreover, a previously validated sleep pattern was used, which has been explored in the association with coronary heart disease, stroke, and heart failure. In this pattern, sleep behaviors were coded as low or high risk as 1 or 0 points, respectively. Then, all
components were added to represent the overall sleep pattern (0–5 points), with a higher score indicating a healthier sleep pattern, which is feasible and practical in daily clinical work.

**Covariates.** The following potential confounders were included in the analysis: participants’ age, sex, ethnicity (White/others), education (university or college degree/others), Townsend index reflecting socioeconomic status (continuous), family history of diabetes (yes/no), smoking status (current, ever, or never), drinking status (drinks, continuous variable), physical activity (metabolic equivalent for task [MET] minutes per week, continuous), the MET is a unit that estimates the amount of energy used by the body during physical activity, as compared with resting metabolism, dietary score ≥ 4 (vegetable intake ≥ 4 table spoons each day [median], fresh fruit intake ≥ 2 pieces each day [median], oily and nonoily fish intake at least twice each week [median], urinary sodium ≥ 68.45 mmol/L [median], and processed meat intake no more than twice each week [median]; each favorable diet factor received one point, with a total score ranging from 0 to 5 [18]), overweight and obesity (BMI ≥ 25 kg/m²), hemoglobin A1c (HbA1c), systolic blood pressure, total cholesterol, use of blood pressure-lowering medications (yes/no), and use of cholesterol-lowering medications (yes/no). If the covariate information was missing, we imputed mean values for continuous variables or used a missing-indicator approach for categorical variables.

**Statistical analyses.** Data analyses were performed using IBM SPSS Statistics, Version 25 (IBM Corporation, Armonk, NY, USA) and SAS 9.2 (SAS Institute, Cary, NC). A *P* value < 0.05 indicated statistical significance (two-sided). However, to account for multiple testing in sleep behaviors, we used a Bonferroni-corrected *P* value threshold of 0.01 (0.05/5 outcomes). *P* values < 0.01 suggested significant associations, and *P* values between 0.01 and 0.05 suggested evidence of marginal associations needing further validation.19 Baseline characteristics of the study population are reported as the means or percentages according to participants with and without NAFLD. Cumulative cases of type 2 diabetes were calculated during follow-up visits. The follow-up time was determined from the baseline date (date of attending assessment center) to the diagnosis of type 2 diabetes, death, or censoring date (August 31, 2019), whichever came first.

A logistic regression model was used to estimate the relative risk (RR) and 95% confidence interval (CI). Model 1 was adjusted for age, sex, ethnicity (White/others), education (university or college degree/others), family history of diabetes (yes/no), and the Townsend index. Model 2 was further adjusted for smoking status (current, ever, or never), drinking status (drinks, continuous variable), physical activity (MET minutes per week, continuous), and dietary score ≥ 4. Model 3 was adjusted for the terms in Model 2 and overweight and obesity (BMI ≥ 25 kg/m²), HbA1c, systolic blood pressure, total cholesterol, triglyceride, use of blood pressure-lowering medications (yes/no), and use of cholesterol-lowering medications (yes/no).

We first measured the association of NAFLD and sleep behaviors with incident type 2 diabetes. To estimate the population-level risk attributable to NAFLD and sleep behaviors, the hypothetical population attributable risk (PAR%) was calculated. It is an estimate of the proportion of incident type 2 diabetes in the study population during follow up that theoretically would be prevented if all people were in the non-NAFLD group and low-risk sleep behavior groups, assuming a causal relationship.20

The interaction analysis between NAFLD and each sleep behavior was performed by using the likelihood ratio test comparing models with and without a cross-product term. Moreover, stratified analyses were performed a priori according to each sleep behavior.

We classified participants according to the joint categories of NAFLD (yes or no) and overall sleep patterns (healthy sleep pattern 4–5 points, intermediate sleep pattern 2–3 points, and poor sleep pattern 0–1 point). Using participants without NAFLD and healthy sleep patterns as the reference, multivariate RRs of type 2 diabetes were obtained in the left joint categories.

Finally, the incident time of type 2 diabetes used in the current analysis may be later than the actual onset time; thus, our main results were analyzed by logistic regression. We conducted sensitivity analyses on restricted subjects with incident type 2 diabetes to > 1 year from baseline and provided results from the Cox model in the supporting information. Additionally, we also performed the interaction analysis between NAFLD and different sleep pattern categories.

**Results**

Table 1 presents the baseline characteristics of participants with and without NAFLD. Of 365 339 participants, 95.5% were White, 1.6% were a mixed population, 1.3% were Asian, and 1.6% were Black. A total of 24.8% had NAFLD. Compared with those without NAFLD, participants with NAFLD were more likely to be men, older, and take antihypertension or cholesterol-lowering medications; less likely to be physically active and have a healthy diet; and had higher measurements of BMI and systolic blood pressure. They were also less likely to have healthy sleep behaviors, including sleeping 7–8 h/day, never/rarely having insomnia, not self-reporting snoring, and not having frequent daytime sleepiness.

During the median follow-up time of 11.0 years (3 974 523 person-years), we documented 8774 patients with incident type 2 diabetes. Tables 2 and S2 show the association of NAFLD and each sleep behavior with incident type 2 diabetes in different models. In the demographic and lifestyle-adjusted model, the RR of diabetes was approximately four times higher in participants with NAFLD than in those without NAFLD (RR 4.04, 95% CI 3.85, 4.25). This association was still significant after further adjustment for metabolic factors (Model 3). Moreover, in the final model, short (< 7 h) or long sleep duration (> 8 h), insomnia, snoring, and excessive daytime sleepiness were each associated with an increased risk of type 2 diabetes (Table S2). When sleep factors were categorized into high and low risks, low-risk sleep behaviors, including sleeping 7–8 h/day, free of insomnia, no self-reported snoring, and no frequent daytime sleepiness, were independently associated with incident type 2 diabetes, with a 20%, 18%, 16%, and 31% lower risk, respectively (all Bonferroni-corrected *P* for interaction < 0.001).

We also calculated the PAR% for NAFLD and sleep factors separately and combined (Table 2). Compared with non-NAFLD, NAFLD was estimated to explain 33.8% of the risk of the
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Table 1 Characteristics of participants with and without NAFLD

| Characteristics                  | NAFLD          | Non-NAFLD      | P     |
|----------------------------------|----------------|----------------|-------|
| N (%)                            | 90 748 (24.8)  | 274 591 (75.2) |       |
| Age at baseline (years)          | 57.0 ± 8.0     | 56.1 ± 8.1     | < 0.001 |
| Men (%)                          | 61.5           | 38.6           | < 0.001 |
| Body mass index (kg/m²)          | 31.5 ± 4.4     | 25.7 ± 3.7     | < 0.001 |
| Waist circumference (cm)         | 102.0 ± 9.6    | 85.3 ± 11.2    | < 0.001 |
| White (%)                        | 94.2           | 95.6           | < 0.001 |
| Family history of diabetes (%)   | 24.7           | 19.7           | < 0.001 |
| University or college degree (%) | 27.0           | 35.7           | < 0.001 |
| Townsend deprivation index       | −1.2 ± 3.1     | −1.6 ± 2.9     | < 0.001 |
| Smoker (current/ever %)          | 9.9/36.3       | 10.5/34.1      | < 0.001 |
| Drinks (per week)                | 4.0 ± 4.4      | 9.7 ± 10.9     | < 0.001 |
| MET (min/week)                   | 1478 ± 1829    | 1688 ± 1889    | < 0.001 |
| Healthy diet score (%)           | 31.7           | 42.8           | < 0.001 |
| HbA1c (mmol/mol)                 | 36.4 ± 5.4     | 34.7 ± 4.0     | < 0.001 |
| Systolic blood pressure (mmHg)   | 143 ± 18       | 138 ± 19       | < 0.001 |
| Total cholesterol (mmol/L)       | 5.79 ± 1.17    | 5.76 ± 1.09    | < 0.001 |
| Triglycerides (mmol/L)           | 2.4 ± 1.2      | 1.5 ± 0.8      | < 0.001 |
| Gamma glutamyltransferase (U/L)  | 49.0 ± 47.2    | 32.2 ± 36.1    | < 0.001 |
| Antihypertensive medications use (%) | 26.9           | 18.8           | < 0.001 |
| Cholesterol-lowering medications use (%) | 22.9           | 17.1           | < 0.001 |

Sleep behaviors (%)

- Sleep 7–8 h/day: 64.3 vs. 70.2, P < 0.001
- Early chronotype: 63.1 vs. 62.8, 0.150
- Never/rarely insomnia: 25.1 vs. 24.4, < 0.001
- No self-reported snoring: 51.1 vs. 67.3, < 0.001
- No frequent daytime sleepiness: 96.5 vs. 97.8, < 0.001

Mean ± SD for continuous variables and percentage for categorical variables. P values were calculated by Student’s t-test (continuous variables with normal distribution), Mann–Whitney U-test (continuous variables with skewed distribution), or χ² test (categorical variables).

Table 2 Multivariable-adjusted relative risks (95% confidence intervals) for type 2 diabetes by NAFLD and low-risk sleep factors

| % of 365 339 participants | Model 1          | Model 2          | Model 3          | Population attributable risk (%) |
|---------------------------|------------------|------------------|------------------|----------------------------------|
| NAFLD                     | 24.8             | 3.58 (3.42, 3.74) | 4.03 (3.85, 4.25) | 1.81 (1.71, 1.92) | 33.2 (30.4, 36.0) |
| Sleep 7–8 h/day           | 68.7             | 0.77 (0.74, 0.80) | 0.78 (0.75, 0.82) | 0.80 (0.77, 0.84) | 8.0 (6.1, 9.9) |
| Early chronotype          | 62.9             | 0.95 (0.91, 0.99) | 1.00 (0.96, 1.05) | 0.99 (0.94, 1.04) | 0.4 (−2.5, 3.4) |
| Never/rarely insomnia     | 24.6             | 0.79 (0.76, 0.83) | 0.81 (0.77, 0.85) | 0.82 (0.77, 0.87) | 15.6 (11.7, 19.5) |
| No self-reported snoring  | 63.3             | 0.71 (0.68, 0.74) | 0.74 (0.71, 0.77) | 0.84 (0.80, 0.88) | 7.3 (5.1, 9.5) |
| No frequent daytime sleepiness | 97.5             | 0.64 (0.58, 0.70) | 0.64 (0.58, 0.70) | 0.69 (0.62, 0.76) | 1.9 (1.2, 2.5) |
| NAFLD                     | 24.8             | 3.75 (3.59, 3.93) | 4.24 (4.04, 4.46) | 1.84 (1.74, 1.95) | 33.8 (31.0, 36.4) |
| Five healthy behaviors    | 7.2              | 0.60 (0.54, 0.67) | 0.65 (0.58, 0.72) | 0.68 (0.60, 0.76) | 33.5 (25.1, 41.3) |

Model 1 was adjusted for age, sex, ethnicity (White/others), education (university or college degree/others), family history of diabetes (yes/no) and the Townsend index (continuous). Model 2 was further adjusted for smoking status (current, ever, or never), drinking status (drinks, continuous variable), physical activity (MET minutes per week, continuous), and dietary score ≥ 4. Model 3 was adjusted for terms in Model 2 and overweight and obesity (BMI ≥ 25 kg/m²), HbA1c, systolic blood pressure, total cholesterol, triglyceride, use of blood pressure-lowering medications (yes/no), and cholesterol-lowering medications (yes/no).

Five separate sleep behaviors were included simultaneously in the model.

All Bonferroni-corrected P < 0.001 in all models.

NAFLD, non-alcoholic fatty liver disease.

population developing type 2 diabetes. For participants with low-risk sleep behavior, the PAR% ranged from 1.9% (excessive daytime sleepiness) to 15.6% (insomnia). When participants had an overall healthy sleep score of five, the PAR reached 33.5%.

These data indicated that if causal, 33.8% and 33.5% of type 2 diabetes events in our participants could have been prevented if all participants were in the group without NAFLD and with all five healthy sleep behaviors, respectively.
We conducted a stratified analysis according to each sleep behavior to evaluate whether high-risk or low-risk behaviors modified the association between NAFLD and the risk of type 2 diabetes (Table 3). We found a significant interaction effect between NAFLD and insomnia on the risk of incident type 2 diabetes ($P$ for interaction = 0.003). With insomnia as the strongest moderator, NAFLD presented more prominent associations with the risk of incident type 2 diabetes among participants with...
self-reported insomnia (RR 1.91, 95% CI 1.79, 2.04) than those without self-reported insomnia (RR 1.62, 95% CI 1.43, 1.84).

Due to the significant interaction between NAFLD and insomnia on the risk of diabetes, we further investigated the participants according to four groups in Table 4 (NAFLD and insomnia, NAFLD and non-insomnia, non-NAFLD and insomnia, and non-NAFLD and non-insomnia). After fully adjustment, compared with those with NAFLD and insomnia, participants with non-NAFLD and non-insomnia had a 55% lower risk for diabetes.

Participants were further divided into joint categories of NAFLD and sleep score groups. The non-NAFLD group with a healthy sleep pattern was set as the reference. As shown in Figure 1, participants with NAFLD and poor sleep pattern had the highest risk of developing type 2 diabetes (RR 3.17, 95% CI 2.80, 3.59), even though there was no statistically significant interaction between NAFLD and sleep pattern category for type 2 diabetes (P for interaction = 0.233).

In sensitivity analyses, the results were largely unchanged using the Cox regression model, but sleep duration was not a significant moderator in these models (Tables S3 and S4). The results also did not change appreciably when limiting participants with a follow-up time over 1 year (Tables S5 and S6).

**Discussion**

In this large-scale prospective cohort study with an 11-year follow-up time, we found that NAFLD and four sleep behaviors were significantly associated with incident type 2 diabetes. Participants with NAFLD and poor sleep pattern showed the highest risk of type 2 diabetes. NAFLD and a healthy sleep score of five may have a comparably important effect on the risk of incident type 2 diabetes (PAR% 33.8 vs 33.5). We also observed that the association between NAFLD and type 2 diabetes was modified by certain sleep behaviors, although overall sleep patterns did not show a significant interaction effect. The positive association between NAFLD and incident type 2 diabetes appeared to be strengthened among participants with insomnia.

Non-alcoholic fatty liver disease could impact the risk of type 2 diabetes. In our study, we found that the RR of diabetes was approximately three times higher in participants with NAFLD than in those without NAFLD in the demographic, lifestyle, and metabolic factor-adjusted model. This result is in accordance with a recent meta-analysis with a total of 19 observational studies and 296 439 adult individuals. Among them, 30.1% had NAFLD, and nearly 16 000 patients developed diabetes in the follow up over a median period of 5 years, with a hazard ratio of 2.22 compared with those without NAFLD. Compared with these studies, our study fills the gaps, as most of the previous studies were conducted in Asian populations, and very little is known about how long-term NAFLD may affect the risk of incident diabetes in such a large cohort.

Impaired sleep and disrupted circadian rhythms put a heavy toll on the metabolic health of humans. In this study, we found that low-risk sleep factors were independently associated with a lower risk of incident type 2 diabetes. Studies from other researchers support our findings. In overweight/obese adults with prediabetes/recently diagnosed, untreated type 2 diabetes, sleep duration was independently associated with HbA1c. Short and long sleep durations, obstructive sleep apnea, poor sleep quality, and circadian misalignment are associated with type 2 diabetes. Although sleep disturbances are often accompanied by depression or hypertension, sleep impairments could independently increase the risk of type 2 diabetes.

To elucidate the modification of sleep behaviors in the association between NAFLD and the risk of type 2 diabetes, the interaction between NAFLD and sleep should be considered. On the one hand, unhealthy sleep behaviors are strong risk factors for NAFLD development. Short sleep duration and insomnia were significantly associated with NAFLD risk. Severe obstructive sleep apnea is independently associated with increased liver inflammation and stiffness in patients with metabolic comorbidities. On the other hand, patients with NAFLD are prone to have worse sleep patterns than those without NAFLD. NAFLD is a metabolic disorder related to chronic low-grade inflammation. The inflammatory process may induce an increase in sleep duration and intensity and a disruption of sleep. Taken together, there is a vicious cycle between the progression of unhealthy sleep behaviors and NAFLD development. Therefore, the interaction between NAFLD and sleep behaviors on the development of type 2 diabetes should be further explored.

The interaction between NAFLD and sleep behaviors and its association with type 2 diabetes is biologically plausible. First, unhealthy sleep behaviors may lead to the development and progression of NAFLD through altered sympathetic nervous tone and hypoxia. Rhythmic variation in insulin sensitivity is in part due to autonomic rhythms generated by afferent input from the hypothalamus to the liver. Second, NAFLD may cause sleep disturbance through chronic low-grade inflammation. Proinflammatory cytokine administration could promote the amount and intensity of NREM sleep and suppress the amount of REM sleep. Third, sleep disturbance and NAFLD were both risk factors for type 2 diabetes. Rhythmic production of insulin is regulated by peripheral β-cell clocks, which have a 24-h rhythm. In genome-wide association studies, circadian-related variations in the melatonin 1b receptor and in cryptochrome 2 are both associated with blood glucose concentrations. Moreover, NAFLD and type 2 diabetes share multiple proinflammatory and profibrotic pathways, which have been well studied.

Unexpectedly, 33.5% of the new cases of type 2 diabetes could have potentially been prevented if people had all five healthy sleep behaviors. This PAR% was slightly lower than that of NAFLD (33.8%) and much higher for cardiovascular disease risk (11.5%) in another study using the same population data. Thus, adherence to a healthy sleep pattern may have an important role in diabetes prevention, especially in stratifying individuals with a high risk of diabetes. We also found that sleep behaviors, particularly insomnia, significantly modified the association between NAFLD and type 2 diabetes. This suggests that we should explore the role of sleep in NAFLD and chronic diseases in future studies.

To the best of our knowledge, this is the first study to measure the interaction between NAFLD and multiple sleep behaviors in incident type 2 diabetes. The strengths of our study included the large sample size and relatively long follow-up duration, which enabled adequate power to study the interaction in detail. We also collected a number of covariates, including demographic information, lifestyle, metabolic factors, and medications, which allowed for rigorous adjustment. Our study also has some limitations. First, this is an observational study, and the association between NAFLD...
and the risk of type 2 diabetes cannot be interpreted as a causal relationship. Randomized trials are further needed. Second, the application of the blood marker equation to define liver steatosis may not be accurate enough. However, liver biopsy, the current gold standard for diagnosing hepatic steatosis, was not feasible in such a large epidemiological study, and using blood markers to define steatosis has been used in many large epidemiological studies. Third, sleep behaviors were self-reported, and hence, recall bias and the possibility of classification errors could not be fully ruled out. However, as mentioned in previous studies, the design of the prospective study suggests that this bias may be random in terms of the outcome, leading to a lower effect estimate and thus an underestimation of the true association. Fourth, we carefully adjusted for various confounders; however, bias from residual and unmeasured confounding may still exist. Fifth, this cohort included people of European descent aged 40–69 years, who were mostly White British, which limits the generalizability to other ethnicities, such as Asians and Blacks. Sixth, although neck circumference, plasma insulin and systemic inflammatory markers other than C-reactive protein were potential confounders, they were not available in the database of the UK Biobank and could not be adjusted in the models. The UK Biobank aimed to be representative of the general population but is unrepresentative in terms of lifestyle because of a “healthy volunteer” selection bias. Therefore, caution is warranted when generalizing summary statistics to the general population.

Conclusion

In the present prospective population-based study of 365 339 individuals, both NAFLD and some sleep behaviors were risk factors for type 2 diabetes. Although overall sleep pattern did not modify the association between NAFLD and type 2 diabetes, certain sleep behaviors, especially insomnia, showed the modification effect. The findings highlight the need to consider sleep behaviors in investigations between NAFLD and human diseases. The clinical implications may be in the stratification of strategies of diabetes prevention, targeting improvement in NAFLD among people with unhealthy sleep behaviors.

Human and animal rights. This article does not contain any studies with human participants or animals performed by any of the authors.

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