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Sleep Duration, Sleep Quality, and the Development of Nonalcoholic Fatty Liver Disease

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1 **Sleep duration, sleep quality, and the development of non-alcoholic fatty liver disease: A**

2 **cohort study**

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Study Highlights

WHAT IS KNOWN

- Nonalcoholic fatty liver disease (NAFLD) is associated with the risk of cardio-metabolic disease.

- Inadequate sleep duration is related to obesity, metabolic syndrome, and cardiovascular disease.

- The cohort studies on the relationship of sleep duration and NAFLD show conflicting results.

WHAT IS NEW HERE

- Short sleep duration is a risk factor for developing NAFLD with or without fibrosis.

- BMI only partially mediated the association between sleep duration and NAFLD.

- Changes in sleep duration as a time-varying covariate produced similar results.

1 **Abstract**

2 **Objectives:** The longitudinal relationship between sleep duration, sleep quality, and the risk of

3 non-alcoholic fatty liver disease (NAFLD) is unknown. We aimed to examine the association

4 between sleep duration, sleep quality, and NAFLD development.

5 **Methods:** 143,306 NAFLD-free Korean adults with a mean age of 36.6 years were followed

6 for an average of 4.0 years. Sleep duration and quality were assessed using the Pittsburgh Sleep

7 Quality Index. Hepatic steatosis (HS) was assessed using ultrasonography and liver fibrosis by

8 the fibrosis-4 index (FIB-4) or the NAFLD fibrosis score (NFS). Flexible parametric

9 proportional hazard models were used to determine the hazard ratios (HRs) and 95% confidence

10 intervals (CIs).

11 **Results:** 21,817 subjects with incident HS were identified of whom 1471 had incident HS plus

12 intermediate/high FIB-4. Multivariable-adjusted HR (95% CIs) for incident HS comparing

13 sleep durations of ≤5, 6, 8, and ≥ 9 hours with 7 hours were 1.19 (1.14-1.23), 1.07 (1.04-

14 1.10), 0.98 (0.94-1.02), and 0.95 (0.87-1.03), respectively. The corresponding HRs for incident

15 HS plus intermediate/high FIB-4 were 1.30 (1.11-1.54), 1.14 (1.01-1.29), 1.11 (0.93-1.33) and

16 1.08 (0.71-1.63). The association between sleep duration and HS plus intermediate/high FIB-4

17 was inverse in individuals with good sleep quality but tended to be U-shaped in those with poor

18 sleep quality. The results were similar if FIB-4 was replaced by the NFS.

19 **Conclusions:** In young adults, short sleep duration was independently associated with an

20 increased risk of incident NAFLD with or without intermediate/high fibrosis score, suggesting

21 a role for inadequate sleep quantity in NAFLD risk and severity.

22 **Keywords:** Hepatic steatosis; Hepatic fibrosis; Sleep quality; Pittsburg sleep quality index;

23 Fibrosis-4 scores; NAFLD fibrosis score

24 **INTRODUCTION**

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent liver disorders worldwide,(1) with a global prevalence of approximately 25%.(2) NAFLD is now considered a multisystem disease that is associated with cardiometabolic disorders, all-cause mortality and cardiovascular disease (CVD) mortality.(3, 4) There are currently no approved medical therapies,(5) and the first-line treatment for NAFLD management is lifestyle modification.(6) Thus, it is important to identify all modifiable lifestyle factors, as it is plausible that improvements in each of these factors may help prevent the development of NAFLD.

We spend, on average, a one-third of our lifetime sleeping. Sleep has been reported to play a pivotal role in cardiovascular health, as well as the endocrine and immune systems.(7, 8) However, in recent decades, sleep duration has decreased, with a reported prevalence of short sleep duration (defined as <6 h) reaching over 20%.(9) A decrease in sleep duration may adversely affect insulin sensitivity and inflammatory activity,(8, 10) and may therefore contribute to the development of NAFLD. Epidemiological studies have also suggested that short sleep duration is closely associated with obesity, metabolic syndrome, and CVD,(11, 12) all of which are also commonly observed in patients with NAFLD.(13) Currently, the relationship between sleep duration and NAFLD is controversial. A meta-analysis reported a small but significant association between short sleep duration and increased risk of NAFLD,(14) whereas another meta-analysis showed no significant association between sleep duration and the risk of fatty liver disease.(15) However, the findings from both these meta-analyses were determined mostly based on results from cross-sectional studies. Currently, available cohort studies on this association have limitations, including small sample sizes, lack of consideration of sleep quality and changing status of sleep habits over time, and the inclusion of elderly adults who already had a high number of comorbidities, including sleep problems.(16-19) Furthermore, none of the cohort studies evaluated the impact of sleep duration on the

development of the more severe form of NAFLD, incident NAFLD with liver fibrosis, the most

important predictor of liver and non-liver mortality.(20, 21)

This study aimed to evaluate the relationship between sleep duration and sleep quality and

the development of incident hepatic steatosis (HS) with and without an intermediate/high

probability of liver fibrosis while accounting for time-dependent measures of change in sleep

duration, sleep quality, and potential confounders during the follow-up period.

MATERIALS AND METHODS

Study population

This cohort study is a part of the Kangbuk Samsung Health Study, a cohort study of Korean

adults who participated in a health examination annually or biennially at Kangbuk Samsung

Hospital Total Healthcare Centers in Seoul and Suwon, South Korea as previously

described.(22) The present study population was restricted to individuals who underwent a

health screening examination with information on sleep duration and sleep quality from

March 2011 to December 2017 and had at least one follow-up visit by December 31, 2019 (N

= 295,404). A total of 143,964 subjects met one or more of the exclusion criteria at baseline

(Figure 1). The final sample included 143,306 subjects in the analysis. This study was

approved by the Institutional Review Board of Kangbuk Samsung Hospital (IRB 2021-01-

024) and was conducted in accordance with the Declaration of Helsinki. The requirement for

informed consent was waived due to the use of a preexisting de-identified dataset that was

routinely collected during the health screening process.

Data collection

Data regarding the patient's demographic characteristics, behavioral factors, and medical

history were collected using a standardized, self-administered questionnaire, while

anthropometry, blood pressure, and serum biochemical parameters were measured by trained

staff during the health examinations.

Sleep duration and quality were assessed using the validated Pittsburgh Sleep Quality Index

(PSQI), 19-item self-administered questionnaire, at baseline and during the follow-up sessions

(23) (further details in **Supporting Documents).**

The diagnosis of HS was based on an abdominal ultrasound performed by an experienced

radiologist who was blinded to the aim of the present study. To assess severity of NAFLD,

two non-invasive indices of liver fibrosis were used: the fibrosis-4 index (FIB-4) and NAFLD

fibrosis score (NFS) (24, 25) (further details in **Supporting Documents).**

Statistical analysis

The primary endpoints were a) the development of incident HS (regardless of fibrosis score)

and b) the development of incident HS plus an intermediate/high probability of liver fibrosis.

Incident HS, and incident HS combined with an intermediate/high probability of liver fibrosis

based on the FIB-4 or NFS, were treated as separate endpoints in each model. The event

detection date was defined as the earliest date of identification of HS or HS with an

intermediate/high probability of liver fibrosis based on the FIB-4 score or NFS, which were

analyzed separately. The person-years were calculated as the sum of the follow-up duration

from baseline to the event detection date (HS or HS with fibrosis, separately) or until the final

examination (before December 31, 2019), whichever occurred first. Incidence rates were

calculated as the number of incident cases divided by the person-years of follow-up.

Therefore, as the primary endpoint occurred at an unknown time point between the event

1   detection date and the previous screening visit, a parametric proportional hazards model was

2   used to account for this type of interval censoring and to estimate the hazard ratios (HRs) and

3   95% confidence intervals (CIs). In these models, the baseline hazard function was

4   parameterized with restricted cubic splines in log time with four degrees of freedom. We

5   assessed the proportional hazards assumption by examining graphs of estimated log

6   ($-\log($survival$)$) versus the log of survival time graph. No violation of the assumption was

7   found.

8   The risk of incident HS and incident HS combined with an intermediate/high probability of

9   liver fibrosis were separately evaluated according to the sleep duration category (further

10   details in **Supporting Documents)**.

11   Statistical analyses were performed using STATA version 16.0 (StataCorp LP, College

12   Station, TX, USA). All reported *P-values* were two-tailed, and a *P*-value of < 0.05 was

13   considered statistically significant.

14

15   **RESULTS**

16   At baseline, the mean (SD) age and sleep duration of 143,306 subjects were 36.6 (6.6) years

17   and 7.0 (1.1) h, respectively. The prevalence of poor sleep quality was 20.1% and was

18   inversely associated with sleep duration, with the highest prevalence seen in those with a

19   short sleep duration of ≤5 h (45.8%). The sleep duration categories were positively

20   associated with being married but were inversely associated with age, male sex, current

21   smoking, alcohol drinking, depressive symptoms, and obesity as described in **Table 1**.

22   During 618,582.6 person-years of follow-up, 27,817 cases of incident HS were

23   identified (incidence rate 45.0 per 10^3 person-years). Median follow-up was 4.0 years

24   (interquartile range, 2.1-6.1). After adjustment for age, sex, the center, year of the screening

exam, season, alcohol consumption, smoking, physical activity, total energy intake, marital status, education level, depressive symptoms, history of diabetes, and history of hypertension (**Table 2**), multivariable-adjusted HR (95% CIs) for incident HS comparing sleep durations of ≤5, 6, 8, and ≥ 9 h with 7 h were 1.19 (1.14-1.23), 1.07 (1.04-1.10), 0.98 (0.94-1.02), and 0.95 (0.87-1.03), respectively. After further adjustment for BMI (**Model 3**), the association between short sleep duration and incident HS was attenuated but remained statistically significant. Results were similar if BMI was replaced by the waist circumference (Model 4). In time-dependent analyses where change in sleep duration, sleep quality and other covariates during follow-up were treated as a time-varying covariate, these results were similar. In the spline regression analyses, there was a dose-response relationship between sleep duration and the development of NAFLD (**Figure 2**).

During 680,986.1 person-years of follow-up, 1,471 cases of incident HS plus an intermediate/high FIB-4 were identified (incidence rate 2.2 per 10^3 person-years). After adjustment for potential confounders, the multivariable-adjusted HR (95% CI) for incident HS plus an intermediate/high FIB-4, comparing sleep durations of ≤5, 6, 8, and ≥ 9 h with 7 h (reference) were 1.30 (1.11-1.54), 1.14 (1.01-1.29), 1.11 (0.93-1.33), and 1.08 (0.71-1.63), respectively. Results were similar based on the NFS. After further adjustment for BMI (**Model 3**), the association between short sleep duration and incident HS plus intermediate/high fibrosis markers remained significant. In contrast, poor sleep quality was not significantly associated with the risk of either incident HS or HS plus intermediate/high fibrosis markers (**Tables 2 and 3**). All these associations were consistently observed in both males and females without significant interaction by sex.

The associations between sleep duration and risk of HS were similarly observed in those with or without poor sleep quality (P for interaction= 0.734), whereas the association

between sleep duration and HS plus intermediate/high fibrosis markers significantly differed

by sleep quality (**Table 4**). There was an inverse association between sleep duration and HS

plus an intermediate/high FIB-4 in individuals with good sleep quality but it tended to be U-

shaped in those with poor sleep quality. These associations were similarly observed in the

analysis using NFS instead of FIB-4.

Since obesity is closely associated with HS and sleep duration is also related to

obesity, we performed analyses among non-obese individuals to address residual confounding

factors due to obesity. The associations between sleep duration, HS, and HS plus an

intermediate/high FIB-4 were similar in non-obese individuals with a BMI of <25 kg/m^2.

Specifically, after adjustment for age, sex, center, year of screening exam, alcohol

consumption, smoking, physical activity, season, total energy intake, marital status, education

level, depression and history of hypertension, multivariable-adjusted HR (95% CIs) for

incident HS regardless of fibrosis score comparing sleep durations of ≤ 5, 6, 8, and ≥ 9 h with

7 h were 1.17 (1.12-1.22), 1.07 (1.04-1.11), 0.98 (0.93-1.02), and 0.88 (0.80-0.97),

respectively. The corresponding HRs (95% CIs) for HS plus an intermediate/high FIB-4 were

1.38 (1.05-1.79), 1.20 (0.98-1.47), 1.13 (0.86-1.49), and 1.20 (0.68-2.11), respectively.

DISCUSSION

In this large-scale prospective cohort study of relatively young adults with a median age

of 36.6 years, a median follow-up of over four years and the availability of repeated

measurements of sleep habits, NAFLD status, and other covariates, short sleep duration was

found to be independently associated with an increased risk of developing NAFLD both with

and without an intermediate/high fibrosis score. These associations between short sleep

duration and increased risk of developing NAFLD were attenuated after adjustment for either

11

BMI or waist circumference, but still remained significant. Additionally, the associations remained significant after adjustment for changes in sleep duration and other confounders over time, (as time-varying covariates in the time-dependent models). Interestingly, sleep quality was not significantly associated with the risk of NAFLD and the association between sleep duration and HS did not significantly differ by sleep quality. However, the association between sleep duration and HS plus intermediate/high FIB-4 significantly differed by sleep quality. In individuals with good sleep quality, sleep duration was inversely associated with HS plus an intermediate/high FIB-4 in a dose-response manner, while both short and long sleep durations were associated with an increased risk of HS plus an intermediate/high FIB-4, showing a U-shaped association in those with poor sleep quality. The reason for the increased risk of HS plus an intermediate/high FIB-4 level among individuals with long sleep duration in those with poor sleep quality, and the decreased risk in those with good sleep quality, is not fully understood. Compared with individuals with normal sleep duration, those with long sleep duration have been reported as having a higher risk of obstructive sleep apnea and insomnia symptoms, such as increased sleep fragmentation, wake after sleep onset, and sleep latency(26). Additionally, habitually long sleep duration has been reported to be associated with poor physical and mental health status(27, 28); thus, excessively long sleep duration may be an indicator of coping with and compensating for this poor sleep quality and other unmeasured features of poor health status(26-28).

A meta-analysis including five cross-sectional studies and one cohort study found a small but significantly increased risk of NAFLD among individuals with a short sleep duration compared to those with a longer sleep duration.(14) In contrast, another meta-analysis of six cross-sectional studies and two cohort studies found that neither short nor long sleep duration was related to NAFLD risk.(15) However, these meta-analyses were both limited in that they

1 included only a few cohort studies; the former only included one cohort study,(14) and the

2 latter two cohort studies.(15)

3 An earlier cohort study of 2133 middle-aged Japanese patients showed an association between

4 short sleep duration and reduced risk of NAFLD (17), whereas a recent cohort study of

5 12,306 Japanese adults reported a significant association between short sleep duration and

6 increased risk of NAFLD (19). A cohort study of 5427 Korean adults reported that long sleep

7 duration was associated with an increased incidence of NAFLD, based on the NAFLD scores

8 rather than on ultrasonography.(29) Finally, a different cohort study of 8965 Chinese subjects

9 with a mean age of 61.6 years demonstrated a positive association between long sleep

10 duration (8-9 h/day) and new-onset NAFLD. (16) However, this study was limited in that it

11 only included a very small number of subjects in the short sleep duration category (only 96

12 subjects with a sleep duration of <6 h).(16) Also, the prevalence of sleep disorders increases

13 with age, and approximately 50% of the elderly have sleep problems.(30) None of previous

14 studies evaluated the impact of sleep quality as either the main exposure or effect modifier on

15 the risk of incident NAFLD.

16   Several plausible mechanisms may explain the association between sleep and NAFLD. Sleep

17 deprivation may increase the ghrelin but decrease leptin levels, causing a rise in appetite,(31)

18 subsequently resulting in weight gain and obesity, which is a strong risk factor for

19 NAFLD.(1) In our study, adjustment for either BMI or waist circumference attenuated the

20 relationship between sleep duration and incident HS or HS plus an intermediate/high FIB-4,

21 but the results remained statistically significant. Furthermore, this association was observed in

22 non-obese individuals with a BMI < 25 kg/ m^2. Therefore, the association between sleep

23 duration and NAFLD appears to not be fully explained by obesity. However, given that the

24 association between sleep duration and NAFLD risk was attenuated by approximately 14%

1 after adjustment for BMI or waist circumference, the role of overall and abdominal obesity is

2 likely to contribute to the association between sleep duration and NAFLD risk. Studies

3 suggest that sleep deprivation and sleep disturbance can decrease insulin sensitivity,(10, 32) a

4 key pathogenic mechanism of NAFLD. Second, sleep deprivation provokes proinflammatory

5 activity (e.g., increased IL-6 or TNF-alpha(32, 33)),[39 41] which can induce inflammation,

6 another mechanism of NAFLD. Furthermore, melatonin is known to function as a strong

7 antioxidant, and low levels of melatonin may influence liver disease.(34) In support of the

8 beneficial effect of melatonin, a randomized controlled trial of 100 patients with

9 histologically proven NAFLD showed a beneficial effect of melatonin treatment on liver

10 enzyme levels.(35)

11   A major strength of our study is that we have shown the effect of sleep duration and sleep

12 quality on NAFLD and its severity using a large-scale cohort. Additionally, the availability of

13 repeated measurements of sleep habits, NAFLD status, and other covariates enabled us to take

14 into account the effects of changes in these variables as time-varying covariates. Furthermore,

15 our findings are derived from a relatively young population less likely to be affected by

16 survivor bias or bias related to comorbidities. However, age is an important risk factor for

17 NAFLD and its progression (36, 37). Therefore, our findings derived from young adults may

18 not be generalizable to older populations. However, recent studies suggest that the prevalence

19 of hepatic steatosis and fibrosis is increasing in younger populations(38, 39). The results of

20 our study emphasize the importance of starting lifestyle modifications at an early age to

21 prevent progression of the disease. Currently, the risk factors for lean NAFLD are not fully

22 understood,(40) despite an increase in its prevalence, especially in Asians.(41) Importantly,

23 our study findings suggest that short sleep duration could be a risk factor for lean NAFLD, as

24 we also know that short sleep duration is associated with an increased risk of NAFLD in non-

14

obese subjects. The effect size was comparably small. However, we emphasize that NAFLD is one of the most common liver diseases worldwide and sleep shortage is common, with an estimated prevalence of over 20% (9, 42). In the absence of approved medication for NAFLD, healthy lifestyle adoption, which also includes better quality and adequate sleep duration, continues to be at the center of primary and secondary prevention of this disease.

There were several limitations to our study. First, sleep duration was self-reported in the PSQI questionnaire, which has been reported to show a moderate correlation with objectively measured sleep duration(43). In a study of 112 volunteers, consisting of a group aged 18–32 years (n=59) and an older group aged 59–75 years (n=53), the global and component scores of the PSQI correlated well with sleep diary variables and CES-D scores(44). In contrast, the PSQI score did not correlate with sleep variables measured using Actigraph accelerometers in the whole group, while significant correlations were only observed between the PSQI sleep duration component and total sleep time in the younger group(44). Further studies with objective and subjective sleep measures are required to confirm the relationship between sleep quantity and quality and NAFLD risk. Second, a histologic assessment of the liver was not performed. However, abdominal ultrasonography is widely used in large cohort studies, as a measure to diagnose hepatic steatosis with acceptable diagnostic accuracy for the detection of fatty liver.(45) Although a high FIB-4 or NFS is a validated proxy measure of high probability of advanced liver fibrosis(24), it is possible that some subjects with intermediate FIB-4 or NFS scores do not have liver fibrosis. Finally, our study population comprised relatively young and middle-aged Koreans, possibly limiting the generalizability of our findings to other age groups, populations with a higher prevalence of comorbidities, or other ethnic groups.

In conclusion, our results show that short sleep duration was associated with an increased risk

of incident NAFLD, both with and without intermediate/high fibrosis scores at follow up. We suggest that interventional studies that modify sleep duration are necessary to test whether there is a beneficial effect of ameliorating sleep deprivation on the risk of NAFLD.

ACKNOWLEDGMENTS

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Table 1. Baseline characteristics of participants by sleep duration

Characteristics	Overall	Sleep duration (hours)				
		≤ 5	6	7	8	≥ 9
Number	143,306	19,003	48,163	49,589	21,766	4,785
Age (years)[a]	36.6 (6.6)	36.7 (7.0)	36.8 (6.8)	36.6 (6.5)	36.2 (6.3)	35.2 (6.1)
Men (%)	38.5	40.2	47.4	39.0	22.4	8.6
Obesity (%)	11.8	14.1	13.6	11.0	8.6	7.1
Current smoker (%)	13.3	15.8	15.8	12.9	8.0	3.8
Alcohol intake (%)[b]	25.0	27.4	29.2	24.6	17.1	12.4
Alcohol intake, gram/day	6.2 (6.5)	6.6 (6.8)	6.9 (6.9)	6.1 (6.5)	4.8 (5.5)	3.8 (4.6)
Men	9.9 (7.7)	10.2 (7.9)	10.1 (7.7)	9.8 (7.7)	9.4 (7.6)	9.2 (7.4)
Women	3.7 (3.9)	3.9 (4.2)	3.9 (4.0)	3.6 (3.9)	3.4 (3.7)	3.3 (3.8)
HEPA (%)	14.1	15.5	14.3	14.1	13.1	11.5
High education (%)[d]	87.9	86.8	88.9	88.6	86.0	82.7
Married (%)	78.4	72.1	74.9	79.8	86.0	90.7
Depression (%)	11.6	19.7	11.8	9.2	9.5	11.9
Hypertension (%)	4.4	4.9	4.9	4.3	3.2	2.3
Diabetes (%)	0.7	0.8	0.8	0.7	0.6	0.6
History of CVD (%)	0.8	1.0	0.9	0.7	0.4	0.8
BMI (kg/m^2)	21.9 (2.6)	22.1 (2.7)	22.1 (2.6)	21.8 (2.6)	21.4 (2.6)	21.0 (2.5)
Waist circumference (cm)	77.0 (7.2)	77.5 (8.1)	77.8 (8.1)	76.8 (7.9)	75.5 (7.6)	74.3 (7.2)
Systolic BP (mmHg)[a]	104.8 (11.7)	104.9 (11.7)	105.8 (11.8)	104.9 (11.8)	103.0 (11.3)	101.1 (10.5)
Diastolic BP (mmHg)[a]	66.9 (8.8)	66.9 (8.8)	67.5 (8.9)	67.0 (8.8)	65.8 (8.5)	64.7 (7.9)
Glucose (mg/dl)[a]	91.3 (9.2)	91.0 (9.7)	91.6 (9.4)	91.4 (9.2)	91.0 (8.7)	90.1 (8.7)
Total cholesterol (mg/dl)[a]	187.4 (31.6)	188.5 (31.8)	188.4 (31.5)	187.3 (31.4)	185.2 (31.6)	183.8 (32.1)
LDL-C (mg/dl)[a]	113.6 (29.4)	114.5 (29.7)	115.1 (29.6)	113.5 (29.2)	111.0 (28.8)	109.0 (28.6)
HDL-C (mg/dl)[a]	63.0 (14.9)	63.2 (15.2)	62.3 (14.9)	63.1 (14.8)	63.9 (14.8)	64.8 (14.4)

Triglycerides (mg/dl)[c]	75 (57-103)	75 (56-104)	76 (58-105)	75 (57-103)	72 (56-98)	71 (54-95)
ALT (U/l)[c]	15 (11-20)	15 (11-20)	15 (12-21)	15 (11-20)	13 (11-18)	12 (10-16)
GGT (U/l)[c]	15 (11-22)	15 (11-23)	16 (12-24)	15 (11-22)	13 (10-19)	12 (10-17)
HOMA-IR[c]	1.04 (0.71-1.48)	1.01 (0.68-1.44)	1.02 (0.69-1.46)	1.05 (0.71-1.49)	1.08 (0.73-1.53)	1.08 (0.73-1.53)
hsCRP (mg/l)[c]	0.3 (0.2-0.6)	0.3 (0.2-0.7)	0.3 (0.2-0.7)	0.3 (0.2-0.6)	0.3 (0.2-0.6)	0.3 (0.2-0.6)
Total energy intake[c,e]	1445.1 (1085.2-1833.5)	1451.5 (1072.1-1863.9)	1456.0 (1096.8-1851.7)	1444.8 (1094.1-1822.6)	1423.3 (1069.4-1801.3)	1397.0 (1017.5-1802.3)
Poor sleep quality (%)	20.1	45.8	21.8	13.2	10.8	13.4

Data are expressed as the [a] mean (standard deviation), [c] median (interquartile range), or percentage. [b] ≥ 10 g of ethanol per day; [d] ≥ college graduate; [e] among 143,306 subjects with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake)

Abbreviations: CVD, cardiovascular disease; ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physical activity; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 2. Hazard ratios [a] (95% CI) of incident hepatic steatosis (regardless of fibrosis score) by sleep duration and subjective sleep quality

	Sleep duration (hours)					P for trend	Subjective sleep quality	
	≤5	6	7	8	≥9		Good	Poor
Person-years (PY)	78,095	204,972	216,532	97,316	21,668		498,010	120,573
Incident cases	4,128	10,567	9,326	3,244	552		22,982	4,835
Incidence density (/10^3 PY)	52.9	51.6	43.1	33.3	25.5		46.1	40.1
Multivariable-adjusted HR								
Model 1	1.24 (1.19-1.28)	1.09 (1.06-1.12)	1.0	0.97(0.94 -1.01)	0.94 (0.86-1.03)	<0.001	1.0	1.07 (1.04-1.11)
Model 2	1.19 (1.14-1.23)	1.07 (1.04-1.10)	1.0	0.98(0.94 -1.02)	0.95 (0.87-1.03)	0.002	1.0	1.00 (0.97-1.04)
Model 3	1.07 (1.03-1.11)	1.02 (0.99-1.05)	1.0	0.99 (0.96-1.04)	1.00 (0.91-1.09)	0.001	1.0	1.05 (1.02-1.09)
Model 4	1.10 (1.05-1.14)	1.03 (1.00-1.06)	1.0	0.97 (0.93-1.01)	0.95 (0.87-1.04)	<0.001	1.0	1.03 (1.00-1.07)
Time dependent model 1 [b]	1.20 (1.15-1.25)	1.07 (1.04-1.10)	1.0	0.97 (0.93-1.01)	0.88 (0.80-0.97)	<0.001	1.0	0.97 (0.94-1.01)
Time dependent model 2 [b]	1.06 (1.02-1.10)	1.01 (0.99-1.04)	1.0	0.99 (0.95-1.03)	0.95 (0.86-1.04)	0.001	1.0	1.02 (0.99-1.06)
Time dependent model 3 [b]	1.16 (1.06-1.15)	1.03 (1.001-1.06)	1.0	0.98 (0.94-1.02)	0.91 (0.83-1.001)	<0.001	1.0	1.00 (0.96-1.03)

[a] Estimated from parametric proportional hazard models. Multivariable model 1 was adjusted for age and sex; model 2: model 1 plus adjustment for center, year of screening exam, season, alcohol consumption, smoking, physical activity, total energy intake, marital status, season, education level, depression, history of diabetes, and history of hypertension; model 3: model 2 plus adjustment for BMI; model 4: model 2 plus adjustment for waist circumference.

[b] Estimated from parametric proportional hazard models with sleep duration, smoking, alcohol consumption, physical activity, total energy intake, marital status, depression, history of diabetes, and history of hypertension as time-dependent categorical variables and baseline age, sex, center, year of screening exam, education level as time-fixed variables: Time dependent model 2; Time dependent model 1 plus adjustment for BMI as time-varying variable; Time dependent model 3; Time dependent model 1 plus adjustment for waist circumference as time-varying variable

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazards ratio.

Table 3. Hazard ratios [a] (95% CI) of incident hepatic steatosis (HS) plus intermediate/high probability of advanced fibrosis by sleep duration and subjective sleep quality

	Sleep duration (hours)					P for trend	Subjective sleep quality	
	≤5	6	7	8	≥9		Good	Poor
HS + Intermediate/high based on Fib4								
Person-years (PY)	87,425	229,519	237,443	103,907	22,692		550,419	130,567
Incident cases	232	591	461	163	24		1242	229
Incidence density (/10³ PY)	2.7	2.6	1.9	1.6	1.1		2.3	1.8
Multivariable-adjusted HR								
Model 1	1.37 (1.17-1.61)	1.16 (1.03-1.31)	1.0	1.11 (0.93-1.33)	1.06 (0.70-1.60)	0.002	1.0	1.08 (0.94-1.25)
Model 2	1.30 (1.11-1.54)	1.14 (1.01-1.29)	1.0	1.11 (0.93-1.33)	1.08 (0.71-1.63)	0.021	1.0	0.97 (0.84-1.13)
Model 3	1.19 (1.01-1.40)	1.08 (0.95-1.22)	1.0	1.14 (0.96-1.37)	1.14 (0.75-1.72)	0.392	1.0	1.02 (0.88-1.19)
Model 4	1.25 (1.05-1.49)	1.08 (0.94-1.24)	1.0	1.03 (0.84-1.27)	0.99 (0.62-1.57)	0.038	1.0	0.96 (0.81-1.13)
Time dependent model 1 [b]	1.21 (1.03-1.43)	1.03 (0.91-1.17)	1.0	0.86 (0.71-1.05)	1.03 (0.67-1.56)	0.006	1.0	1.03 (0.89-1.19)
Time dependent model 2 [b]	1.06 (0.91-1.25)	0.97 (0.86-1.10)	1.0	0.89 (0.73-1.08)	1.08 (0.71-1.64)	0.339	1.0	1.08 (0.93-1.25)
Time dependent model 3 [b]	1.09 (0.92-1.28)	0.99 (0.87-1.12)	1.0	0.86 (0.70-1.05)	1.03 (0.68-1.56)	0.139	1.0	1.05 (0.90-1.22)
HS + Intermediate/high based on NFS								
Person-years (PY)	87081	228,463	236,841	103,769	22,657		548,535	130,274
Incident cases	339	339	716	215	39		1911	353
Incidence density (/10³ PY)	3.9	4.2	3.0	2.1	1.7		3.5	2.7
Multivariable-adjusted HR								
Model 1	1.30 (1.14-1.48)	1.22 (1.11-1.35)	1.0	0.93 (0.80-1.09)	1.10 (0.80-1.53)	<0.001	1.0	1.07 (0.95-1.20)
Model 2	1.26 (1.10-1.44)	1.21 (1.10-1.33)	1.0	0.93 (0.80-1.09)	1.11 (0.80-1.53)	<0.001	1.0	1.01 (0.90-1.14)
Model 4	1.15 (1.00-1.34)	1.13 (1.01-1.26)	1.0	0.89 (0.74-1.06)	1.15 (0.80-1.63)	0.005	1.0	1.01 (0.88-1.15)
Time dependent model 1 [b]	1.20 (1.05-1.37)	1.16 (1.05-1.28)	1.0	0.86 (0.73-1.01)	0.95 (0.67-1.35)	<0.001	1.0	0.99 (0.87-1.12)
Time dependent model 3 [b]	1.01 (0.88-1.16)	1.07 (0.97-1.18)	1.0	0.86 (0.73-1.01)	0.97 (0.69-1.38)	0.065	1.0	1.02 (0.90-1.16)

[a] Estimated from parametric proportional hazard models. Multivariable model 1 was adjusted for age and sex; model 2: model 1 plus adjustment for center, year of screening exam, season, alcohol consumption, smoking, physical activity, total energy intake, marital status, season, education level, depression, history of diabetes (only for FIB4), and history of hypertension; model 3: model 2 plus adjustment for BMI; model 4: model 2 plus adjustment for waist circumference.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazards ratio.

Table 4. Hazard ratios [a] (95% CI) of incident hepatic steatosis (HS) without or with intermediate/high probability of advanced fibrosis by sleep duration among subjects with and without poor sleep quality

	Sleep duration (hours)					*P* for trend	*P for* interaction
	≤5	6	7	8	≥9		
HS regardless of fibrosis score							
Sleep quality							0.743
Good (N=114,577)	1.20 (1.15-1.25)	1.08 (1.04-1.11)	1.0	0.98 (0.94-1.03)	0.94 (0.86-1.03)	<0.001	
Poor (N=28,729)	1.13 (1.05-1.23)	1.05 (0.97-1.13)	1.0	0.94 (0.83-1.08)	0.99 (0.78-1.26)	<0.001	
HS+ Intermediate/high FIB-4							
Sleep quality							0.047
Good (N=114,577)	1.31 (1.08-1.58)	1.11 (0.97-1.26)	1.0	1.12 (0.93-1.35)	0.85 (0.52-1.38)	0.033	
Poor (N=28,729)	1.45 (0.97-2.15)	1.41 (0.96-2.08)	1.0	0.95 (0.46-1.98)	3.33 (1.48-7.51)	0.365	
HS+ Intermediate/high NFS							
Sleep quality							0.068
Good (N=114,577)	1.28 (1.10-1.49)	1.18 (1.07-1.31)	1.0	0.90 (0.77-1.06)	0.94 (0.65-1.36)	<0.001	
Poor (N=28,729)	1.36 (0.99-1.88)	1.44 (1.06-1.97)	1.0	1.34 (0.80-2.23)	2.72 (1.34-5.51)	0.684	

[a] Estimated from parametric proportional hazard models. Multivariable model was adjusted for age, sex, center, year of screening exam, season, alcohol consumption, smoking, physical activity, total energy intake, marital status, season, education level, depression, history of diabetes (not for **HS**+ Intermediate/high NFS) , and history of hypertension

P for quadratic term =0.001 for the association between sleep duration and incident HS; *P for quadratic term* =0.08 for the association between sleep duration and incident HS plus intermediate/high FIB-4; and *P for quadratic term* =0.192 for the association between sleep duration and incident HS plus intermediate/high NFS among participants with poor sleep quality

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazards ratio.

FIGURE LEGENDS

**Figure 1.** Flowchart of the included subjects.

Figure 2. Multivariable-adjusted HRs for NAFLD. The curves represent adjusted HRs for incident NAFLD based on restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of sleep duration distribution. The model was adjusted for age, sex, center, year of the screening exam, BMI, alcohol consumption, smoking, physical activity, total energy intake, marital status, education level, depression, history of diabetes, and history of hypertension.

Participants who underwent a comprehensive health examination with information on sleep duration and sleep quality at Kangbuk Samsung Hospital between 2011 and 2017 had at least one follow-up visit through December 31, 2019 (N=295,404)

Exclusions (n=143,964): some individuals met more than one exclusion criterion
- Missing information on liver ultrasound, body mass index or glucose (n=1,141)
- Night shift workers (n=22,277)
- History of sleep apnea based on self-report (n=1,535)
- History of narcolepsy (n=180)
- History of malignancy (n=6,439)
- Alcohol intake of ≥30 g/day for men and ≥20 g/day for women (n=44,984)
- Positive serologic markers for hepatitis B or C virus (n=9,496)
- Use of steatogenic medications within the past year (n=1,639)
- History of liver cirrhosis or findings of liver cirrhosis on ultrasound (n=91)
- History of hepatitis or use of medications for liver disease (n=10,454)
- Fatty liver based on ultrasound (n=82,433; 15,155 women and 67,278 men)
- Intermediate or high probability of advanced fibrosis based on either FIB-4 or NFS (n= 33,887)

Participants were included in the final analysis (n=143,306)

Sleeping duration

7 hr vs <5 hr

Normal Liver

1.19 fold

1.30 fold

Steatosis
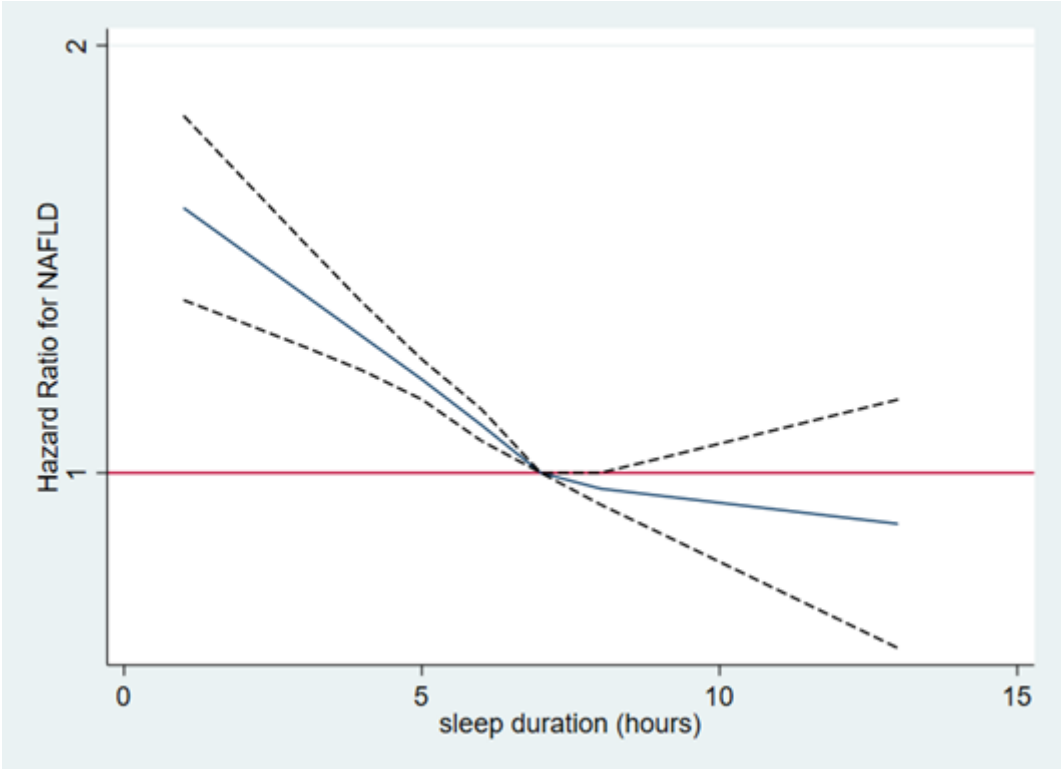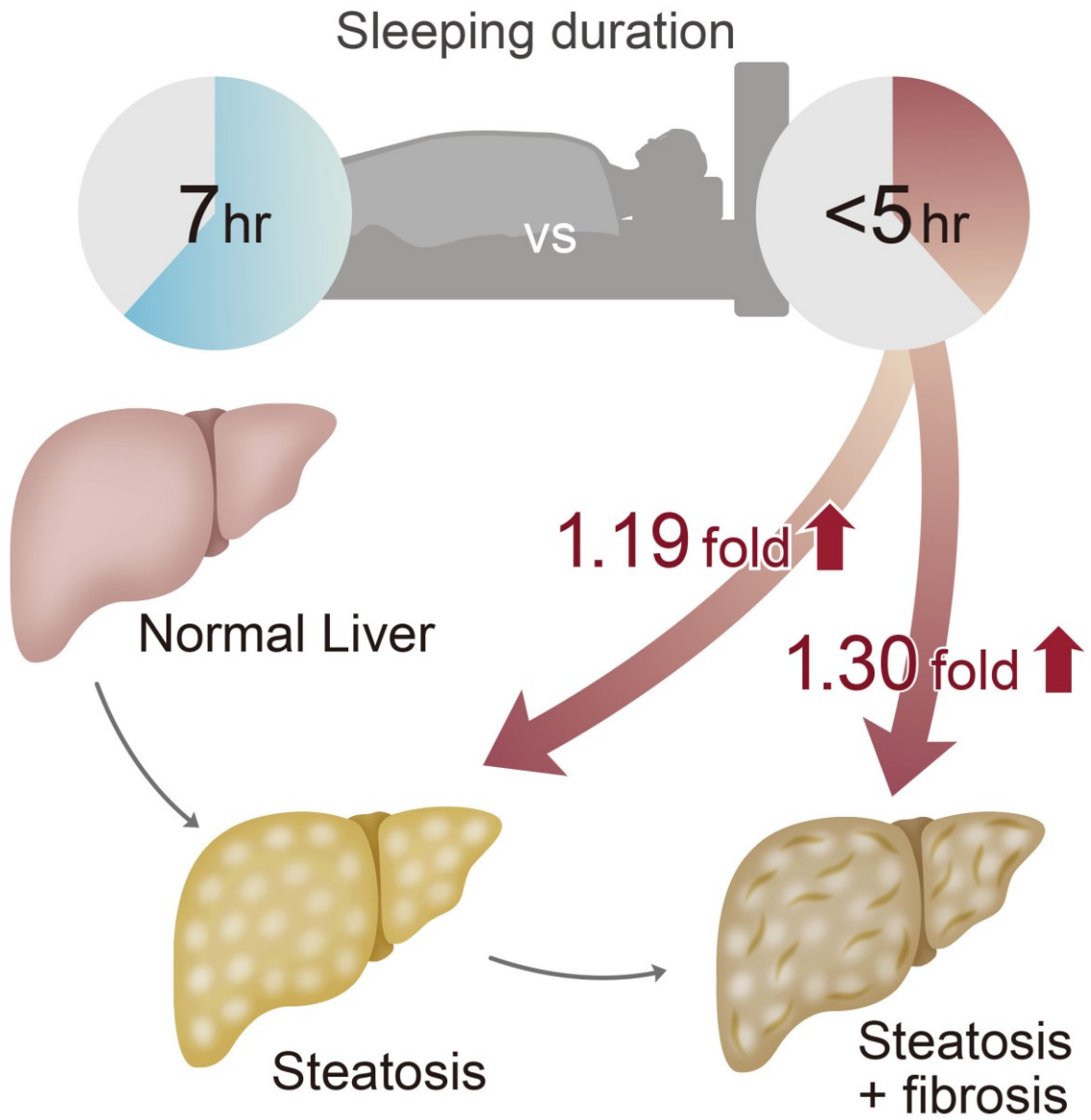
Steatosis + fibrosis

S1. Measurement

Pittsburgh Sleep Quality Index (PSQI), 19-item self-administered questionnaire, at baseline and during the follow-up sessions was used to assess sleep duration and quatliy.(1) It consists of seven components, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime function. Each component score ranges from 0 (best) to 3 (worst sleep properties), and the PSQI score is calculated as the sum of each component score to generate an overall score. In one of the PSQI items, the subjects were asked to report the hours of actual asleep at night in a typical 24 h period over the previous month. Sleep duration was obtained by rounding values of 30 min or more up to the nearest hour and rounding values less than 30 min down to the nearest hour. Sleep quality was categorized into two groups (good: PSQI score <6, poor: PSQI score ≥6) (1). Sleep duration were grouped into ≤5, 6, 7, 8, and ≥9 h. Since 7 hours per day or more for adults are considered appropriate to maintain ideal health,(2) 7 hours was chosen as the reference and shorter duration was defined as short sleep duration. Depressive symptoms were assessed using the Korean version of the Center for Epidemiologic Studies Depression (CES-D) scale and were categorized as a CES-D score of <16 and ≥16.(3, 4)

Physical activity levels were assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form.(5, 6) Health-enhancing physical activity (HEPA) was defined as follows: (1) vigorous activity ≥3 days/week with ≥1,500 accumulated metabolic equivalent (MET)-minutes/week, or (2) a combination of walking, moderate- or vigorous-intensity activities for 7 days accumulating to ≥3,000 MET-min/week.

Sitting blood pressure (BP), height, weight, and waist circumference were measured by trained nurses. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medication.

Blood and urine specimens were collected after at least 10 h of fasting. Fasting blood sample measurements included total cholesterol, low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides, AST, ALT, gamma-glutamyl transferase (GGT), glucose, uric acid, hsCRP, albumin, and platelet count. The homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated as follows: fasting blood insulin (mU/mL) × fasting blood glucose (mmol/L)/22.5.

S2. Assessment of hepatic steatosis and non-invasive fibrosis score

The diagnosis of hepatic steatosis was determined using standard criteria, including the presence of a diffuse increase in fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma, deep beam attenuation, and bright vessel walls.(7) Inter-observer and intra-observer reliability values for HS diagnoses were moderate to substantial (kappa statistic of 0.74) (8, 9) and excellent (kappa statistic of 0.94), respectively.(10)

The FIB-4 index was calculated using the following formula: FIB-4 = [age (years) × AST (U/L)] / [platelet count (×10^9/L) × ALT (U/L)$^{1/2}$]. The subjects were classified into three groups, reflecting the probability of advanced fibrosis based on the FIB-4 score: low (FIB-4 <1.30), intermediate (FIB-4 1.30-2.66), and high (FIB-4 ≥2.67).(11) NFS was calculated according to the following published formula: NFS = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glycemia or diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio - 0.013 × platelet (×10^9/L) - 0.66 × albumin (g/dL).(12) Subjects were also

categorized into three groups reflecting the probability of advanced fibrosis based on the NFS: high (NFS >0.676), intermediate (NFS: 0.676 to -1.455), and low (NFS < -1.455).(12)

S3. Statistical modeling for data analysis

The models were initially adjusted for age and sex and then adjusted for study center (Seoul, Suwon), year of the screening exam, season (spring, summer, fall, and winter), smoking (never, past, current, or unknown), alcohol intake (none, < 10, or ≥ 10 g/day, or unknown), physical activity (inactive, minimally active, health-enhancing physical activity (HEPA), or unknown), CES-D (<16, ≥ 16, or unknown), education level (< community college graduate, ≥ community college graduate, or unknown), total energy intake, history of diabetes, history of hypertension, and history of CVD (Model 2). Next, we sought to examine whether the relationship between sleep duration and development of the primary endpoints was mediated by body mass index (BMI) as a continuous variable (Model 3) on a priori grounds.

We evaluated the mediation effect of BMI on the association between sleep duration and risk of HS or HS plus an intermediate/high probability of liver fibrosis (Model 4) if the BMI met the three criteria for being a potential mediator as follows: 1) sleep duration was associated with BMI, 2) BMI was significantly associated with the incident endpoint when sleep duration was included in the model, and 3) the addition of BMI to the model attenuated the association between sleep duration and incident HS. To explore the role of central obesity, these analyses were repeated when BMI was replaced by waist circumference (Model 4).

To further explore the shape of the dose-response relationship of sleep duration with the development of NAFLD, restricted cubic splines with knots were used at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of sleep duration. We then evaluated whether the associations between sleep duration and the risk of NAFLD differed by sleep quality. The interactions

between sleep quality and sleep duration categories on the risk of NAFLD were tested using likelihood ratio tests. These tests were used to compare the models with and without multiplicative interaction terms.

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