

SCIENTIFIC REPORTS



OPEN

Sleep Duration and the Risk of Fatty Liver Disease: A Systematic Review and Meta-analysis

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Received: 12 January 2016

Accepted: 28 July 2016

Published: 23 August 2016

Recent studies have reported inconsistent results on the association between sleep duration and the risk of fatty liver disease (FLD). Thus, we quantitatively evaluated this association by performing a systematic review and meta-analysis, based on a comprehensive electronic search in databases of PubMed, Web of Science, EMBASE, ClinicalTrials.gov, Wanfangdata and Chinese National Knowledge Infrastructure (CNKI) (updated to April 2016). Multivariate adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were extracted and pooled by using a random-effects model. Eight eligible studies involving 97,371 participants were included. We found that neither short nor long sleep duration was significantly related with FLD risk. For short sleep duration, the pooled OR was 1.17 (95% CI = 0.98–1.38), and for long sleep duration, the pooled OR was 1.01 (95% CI = 0.72–1.41). Subgroup analyses by sex, outcome, and exposure reference also did not identify any effect of sleep duration on FLD onset. In summary, our findings suggested that short or long sleep duration was not significantly associated with FLD risk. Further cohort studies with refined designs are still warranted to validate our results.

Fatty liver disease (FLD) is a pathological condition in which excessive triglycerides accumulate in liver cells due to many different causes. In various countries, FLD prevalence ranges from 10% to 24% in general population¹. Nowadays, FLD, including non-alcoholic fatty liver disease (NAFLD), is becoming the most common chronic liver disease worldwide, resulting in an enormous clinical and economic burden for public health^{2,3}. Many efforts have been made to investigate FLD pathogenesis. Although mechanisms are still unclear, many lifestyle factors, including weight gain⁴, television viewing⁵ and sleep disorder⁶, are reportedly related to FLD risk.

Sleep patterns have changed with societal development, which may influence quality of life. Recent studies have suggested a link between sleep duration and long-term health status, including adult depression⁷, type 2 diabetes⁸ and cardiovascular outcomes⁹. However, the association between sleep duration and FLD risk was largely inconsistent. Kim *et al.* found that women with short sleep duration more frequently suffered from NAFLD¹⁰. Miyake *et al.* reported that less sleep was associated with reduced NAFLD risk in men¹¹. However, Hsieh *et al.* observed an insignificant association between short sleep duration and FLD risk in men¹², and Imaizumi *et al.* observed similar results in men and women¹³. Long sleep duration was reportedly protective against FLD¹², but this result was not supported by subsequent research¹³.

Insufficient power in individual studies may lead to these conflicting results. Thus, we systematically reviewed relevant literature and performed this meta-analysis to investigate the association of short and long sleep durations with FLD risk.

Results

Literature screening. As shown in Fig. 1, 701 relevant records were identified from databases of PubMed, Web of Science, EMBASE, ClinicalTrials.gov, Wanfangdata and Chinese National Knowledge Infrastructure (CNKI). After removing 118 duplicated records, 583 records underwent title and abstract screening. Then 559 records were excluded because they were experimental studies, review articles, comments, or irrelevant to sleep duration and outcome of interest. The remaining 24 studies were evaluated in detail for eligibility by full-text review. Of them, 16 studies were further excluded due to providing insufficient data about exposure/outcome

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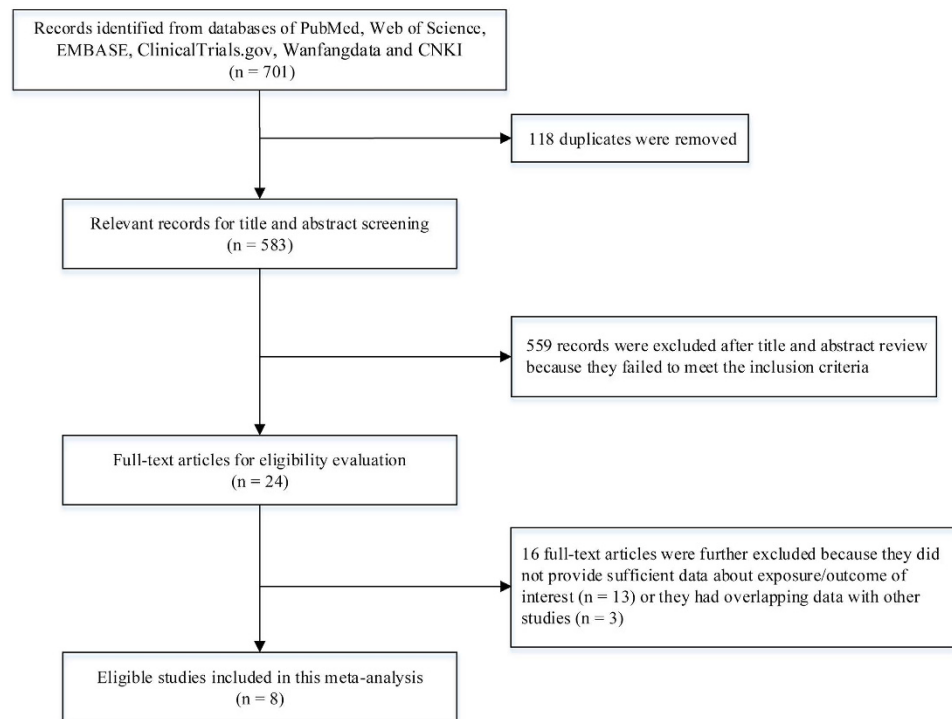


Figure 1. A flowchart of literature search and study selection. Abbreviations: CNKI, Chinese national knowledge infrastructure.

of interest or reporting overlapping data with other studies. Finally, we included eight eligible studies in this meta-analysis^{10–17}.

Characteristics of included studies. The characteristics of the included studies are presented in Table 1. All eligible studies were based on health check-up cohorts, six of which were conducted in Asia^{10–14,16} and two of which were conducted in Europe¹⁷ or America¹⁵. In total, 97,371 participants with a mean age range from 21.7 to 62.4 years were involved in our meta-analysis. Information on sleep duration was collected by self-administered questionnaire. The primary outcomes were fatty liver and NAFLD, which were determined by ultrasonography or liver enzymes tests. ORs and 95% CIs extracted from individual studies were adjusted by age and other covariates. Four studies^{10,11,13,14} reported results separately by sex and one¹⁶ reported by obstructive sleep apnea (OSA) status. Thus, we treated them as independent datasets.

Sleep duration and FLD risk. As a modifiable factor, sleep duration usually exhibits a U-shaped relationship with illness^{7–9}. Thus, we explored the effects of short and long sleep duration on the risk of FLD. By combining 13 independent datasets from the eight studies^{10–17} (involving 97,371 subjects), we identified that participants with the shortest sleep duration did not have significant risk for FLD, compared with those who slept longer (the pooled OR = 1.17, 95% CI = 0.98–1.38). Study heterogeneity was significant with high level ($P_{\text{heterogeneity}} < 0.001$, $I^2 = 66.3\%$) (Fig. 2A). We also investigated the effect of long sleep duration on FLD risk. By combining three independent datasets from the two studies^{12,13} (including 10,329 subjects), we showed that compared to normal sleep duration (5–7 hours), long sleep duration did not increase or decrease the risk of FLD (the pooled OR = 1.01, 95% CI = 0.72–1.41). The heterogeneity among studies was moderate ($P_{\text{heterogeneity}} = 0.110$, $I^2 = 54.7\%$) (Fig. 2B).

Meta-regression and subgroup analyses. Given the significant and high heterogeneity observed when pooling data about short sleep duration, we performed univariate meta-regression analysis to explore potential sources (Table 2) and made the scatter-plots to illustrate the relationships between short sleep duration and each potential moderator (Supplemental Figure S1). Publication year, mean age, sex, exposure reference (5–8 hours or not) and region (Asian or not) were considered influencing factors, but the results did not identify any significant factor (all P values > 0.05). We further investigated potential effect modification for short sleep duration according to sex, outcome and reference exposure. As shown in Table 3, less sleep, whether in males or females, did not modify FLD risk (Male: the pooled OR = 1.02, 95% CI = 0.81–1.29; Female: the pooled OR = 1.20, 95% CI = 0.89–1.62). Because seven of eight included studies focused on NAFLD^{10,11,13–17}, we examined the effect of short sleep duration on NAFLD risk and found no significant relationship (the pooled OR = 1.17, 95% CI = 0.95–1.43). In the reference exposure subgroup, we focused on studies that considered normal sleep duration (5–8 hours) as a reference, and also failed to observe any significant association (the pooled OR = 1.01, 95% CI = 0.76–1.35). Subgroup analysis was not conducted for long sleep duration because of the limited number of independent datasets. In addition, quality scores of Newcastle-Ottawa assessment indicated that all included studies were of high quality (all quality scores ≥ 5).

Study	Country	Sex, male (%)	Participants	Mean age (years)	Reference exposure	Exposure of interest	Outcome	Outcome assessment	Adjusted variables	Newcastle-Ottawa score
Hsieh <i>et al.</i> ¹²	Japan	M, 100	8157	51.6	5~<7 hours	<5 hours; ≥ 7 hours	Fatty liver	ultrasonography	age, poor sleep (defined as difficulty of getting to sleep or awakening easily)	5
Kim <i>et al.</i> ¹⁰	Korea	F/M, 57.6	45293	39.7	>7 hours	≤5 hours	NAFLD	ultrasonography	age, smoking, alcohol intake, physical activity, systolic blood pressure, education level, marital status, presence of job, sleep apnea, loud snoring, and BMI	7
Liu <i>et al.</i> ¹⁴	China	F/M, 39.8	20746	62.4	>8 hours	≤5 hours	NAFLD	ultrasonography	age, smoking, alcohol intake and BMI	7
Imazumi <i>et al.</i> ¹³	Japan	F/M, 33.7	2172	60.9	6~<7 hours	≤6 hours; > 8 hours	NAFLD	ultrasonography	age, smoking, no breakfast, snacking, regular exercise and BMI	6
Miyake <i>et al.</i> ¹¹	Japan	F/M, 27.5	2429	40.4	7~8 hours	≤6 hours	NAFLD	ultrasonography	age, BMI, SBP, TG, HDL-c, FPG, UA, ALT, Cre, snacking habit, and periodic exercise habit	6
Yu <i>et al.</i> ¹⁶	Korea	F/M, 57.2	621	56.6	≥5 hours	<5 hours	NAFLD	LAI value < 5 HU	age, sex, exercise, alcohol, smoking, DM, HTN, CVD, and BMI	7
Kim <i>et al.</i> ¹⁵	United States	F/M, 48.7	17245	46.0	≥9 hours	≤5 hours	NAFLD	ultrasonography	age, gender, ethnicity, BMI, waist circumference, educational level, marital status, economic status, smoking, diabetes and hypertension and sleep quality	6
Trovato <i>et al.</i> ¹⁷	Italy	F/M, 35.3	708	21.7	≥25 th lower percentile sleep hours	<25 th lower percentile sleep hours	NAFLD	ultrasonography	BMI, waist circumference, oversized clothes, sedentary lifestyle, cigarette smoking, coffee, daily frequency of eating	7

Table 1. Characteristics of included studies in this meta-analysis. Abbreviations: M, male; F, female; LAI, liver attenuation index; BMI, body mass index; SBP, systolic blood pressure; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; UA, uric acid; ALT, alanine aminotransferase; Cre, creatinine; DM, diabetes mellitus; HTN, hypertension; CVD, cardiovascular disease.

Factors ^a	Coefficient	Standard error	P
Publication year	-0.007	0.081	0.934
Mean age	0.001	0.010	0.921
Sex	-0.160	0.225	0.500
Reference exposure	0.244	0.211	0.271
Region	-0.264	0.287	0.379

Table 2. Univariate meta-regression analysis of the association between short sleep duration and FLD risk. ^aReference exposure referred to 5~8 hours or not; Region referred to Asian or non-Asian area.

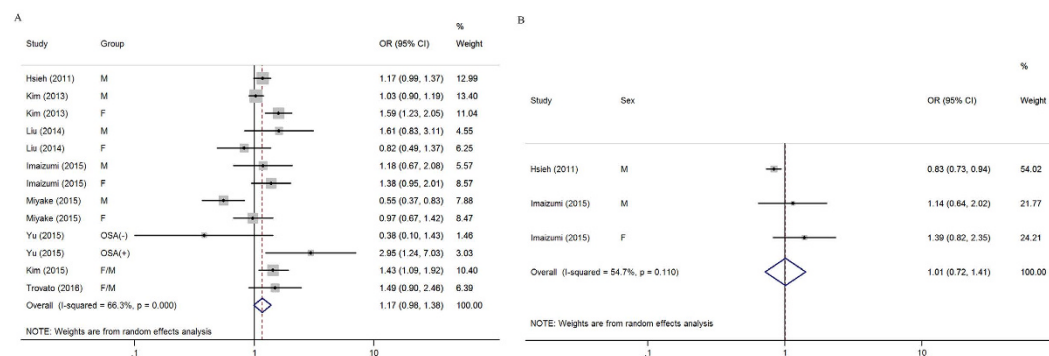


Figure 2. Overall forest plots. (A) Forest plot of the association between short sleep duration and FLD risk. **(B)** Forest plot of the association between long sleep duration and FLD risk. Abbreviations: M, male; F, female; OSA, obstructive sleep apnea.

	n ^a	OR (95% CI)	<i>P</i> _{heterogeneity}	<i>I</i> ² (%)
Sex				
Male	5	1.02 (0.81–1.29)	0.011	69.3
Female	4	1.20 (0.89–1.62)	0.050	61.7
Outcome				
NAFLD	12	1.17 (0.95–1.43)	<0.001	69.0
Reference exposure				
5~8 hours	5	1.01 (0.76–1.35)	0.010	69.7

Table 3. Subgroup analyses of the association between short sleep duration and FLD risk. Abbreviation: NAFLD, non-alcoholic fatty liver disease. ^an referred to individual datasets.

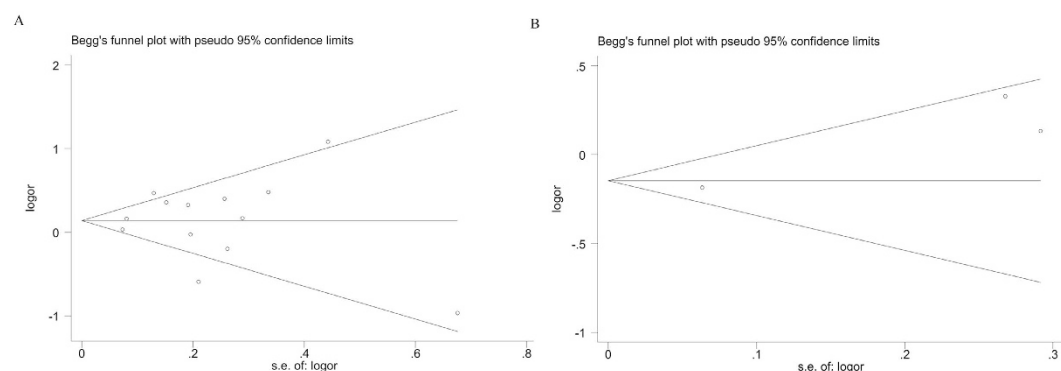


Figure 3. Funnel plots. (A) Funnel plot of the association between short sleep duration and FLD risk. (B) Funnel plot of the association between long sleep duration and FLD risk.

Sensitivity analyses and publication bias. Results for short or long sleep duration were not appreciably altered based on one-way sensitivity analyses (Supplemental Table S1). Although results changed somewhat by removing the male dataset from Miyake *et al.*¹¹, pooled ORs stratified by sex were still not significant, with low or moderate heterogeneity. That suggested that the results in this meta-analysis were relatively robust. For assessments of publication bias, we did not observe any asymmetry in funnel plots (Fig. 3A,B). Moreover, Begg's and Egger's tests did not provide any evidence of publication bias (For short sleep duration: $P_{\text{Egger's test}} = 0.870$, $P_{\text{Begg's test}} = 0.951$. For long sleep duration: $P_{\text{Egger's test}} = 0.189$, $P_{\text{Begg's test}} = 0.602$).

Discussion

In this present meta-analysis, we demonstrated that neither short nor long sleep duration was significantly associated with FLD risk. Further subgroup analyses showed that this lack of association was not appreciably modified by sex, outcome, or reference exposure.

Many studies on sleep duration and FLD risk focus on its association with obesity, a well-known pathogenic factor for FLD onset. A previous meta-analysis suggested that short sleep duration was related to obesity, whereas long sleep duration had no effect¹⁸. However, recent studies have shown that poor sleep quality may also play an important role in obesity^{19–21}. Moreover, Kim *et al.* found a significant relationship between poor sleep quality and NAFLD in both men and women¹⁰. In addition, sleep disorders, including obstructive sleep apnoea (OSA) have been revealed as risk factors for FLD^{6,22}. To date, several studies have investigated the effects of sleep duration on FLD risk^{10–17}, but many of them were not fully adjusted for confounders in design or analysis. This may explain why we found no association between sleep duration and FLD risk.

A major strength of our meta-analysis was its large overall sample size, including 97,371 participants. Besides, pooled data were extracted from multivariate adjusted models in original studies, which reduced confounding bias to some extent. In addition, our findings were strengthened by accordant results from subgroup analyses. These advantages made our pooled estimate more exact and credible.

However, several limitations should also be acknowledged in our meta-analysis. Firstly, the reference exposure of sleep duration were inconsistent among the included studies, which contributed to the significant heterogeneity during data integration. Therefore, we applied a random-effects model in all analyses in this meta-analysis. Secondly, the included studies measured sleep duration based on a self-reported questionnaire rather than actigraphy monitoring. Although a good correlation was shown between the two measurements²³, it is difficult to avoid non-robust estimations of the association between sleep duration and FLD risk because of subjective bias. Thirdly, the included studies were observational designs in which exposure misclassification possibly influenced the pooled results. Additionally, based on the different adjusted factors among studies, our pooled results may be biased by residual or unmeasured confounders in the original studies. Finally, only two studies comprising three datasets were included the evaluation of an association between long sleep duration and FLD risk. Although the

pooled results were stable according to sensitivity analysis and there was no evidence of publication bias, the results should be treated with caution, and further studies are needed to confirm them.

In summary, our meta-analysis suggested that there was no association between short or long sleep duration and FLD risk. Further subgroup analyses supported this conclusion. However, more cohort studies with large-scale and refined designs are still warranted to further validate our results.

Methods

Literature search and study selection. This current meta-analysis was performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement²⁴. We systematically searched the literature in databases of PubMed, Web of Science, EMBASE, ClinicalTrials.gov, Wanfangdata and Chinese National Knowledge Infrastructure (CNKI) through April 2016 to identify studies that examine the association between sleep duration and FLD risk, without any restriction. The search strategy included items of “sleep” and “fatty liver”, and it is described in Supplemental Table S2. To retrieve extra citations, we also manually checked the reference lists from relevant articles and reviews.

Studies were considered eligible if they (1) were cross-sectional, retrospective, or prospective designs and (2) reported odds ratios (ORs) and 95% confidence intervals (CIs) for the effects of sleep duration on FLD or sufficient data to extrapolate risk estimates. For studies involving data that overlapped with other studies, we selected the studies with newer results or larger sample sizes. Two authors independently conducted the literature searches and study selection, and any discrepancy was resolved by consensus.

Data extraction and quality assessment. Two independent authors extracted the following items from each eligible study: (1) general information, including first author’s name, publication year, and country; (2) study characteristics, including age, sex, and numbers of participants; (3) reference exposure and exposure of interest; (4) outcomes and outcome assessment; (5) covariates adjusted in the individual study; and (6) risk measures of association, including ORs and 95% CIs. Discrepancies were resolved by group discussion. We also evaluated the quality of each study using the Newcastle-Ottawa scale²⁵ (Supplemental Table S3).

Statistical Analysis. Multivariate adjusted ORs and 95% CIs were recorded from each eligible study to estimate the association between sleep duration and FLD risk. These ORs were pooled with a random-effects model based on the inverse of variance method²⁶. We used the Cochran’s Q test to examine between-study heterogeneity, which was also quantified by the I^2 index²⁷. Heterogeneity is considered significant if $P < 0.10$, and it is defined as low, moderate or high based on I^2 values of 25%, 50% and 75%, respectively²⁸. Meta-regression analysis was used to investigate potential sources of heterogeneity. To further explore potential effects of sleep duration on FLD risk, we conducted subgroup analyses and stratified data using modifiers that included sex, outcomes, and reference exposure. Publication bias was assessed by Egger’s regression test²⁹ and Begg’s rank correlation test³⁰. In addition, we performed sensitivity analyses to evaluate the robustness of the pooled results. Specifically, the pooled OR was estimated again by removing one included study at a time to check stability. All these analyses above were performed by using Stata 12.1 software (College Station, TX, USA), with a two-sided $P \leq 0.05$ as the significance level unless otherwise specified.

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Author Contributions

N.S. conceived and designed the study. P.W. and W.Y. performed literature search, study selection and data extraction. N.S. and P.W. conducted statistical analysis. P.W. and W.Y. prepared tables and figures. N.S. and P.W. drafted the manuscript. All these authors completely consented with all the data in the study and approved the final manuscript. N.S. had the primary responsibility for final manuscript.

Additional Information

Supplementary information accompanies this paper at <http://www.nature.com/srep>

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Shen, N. *et al.* Sleep Duration and the Risk of Fatty Liver Disease: A Systematic Review and Meta-analysis. *Sci. Rep.* **6**, 31956; doi: 10.1038/srep31956 (2016).



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