Research Article

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Sleep duration and quality in relation to non-alcoholic fatty liver disease in middle-aged workers and their spouses

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Background & Aims: Although accumulated evidence implies that short sleep duration and poor sleep quality may lead to an altered metabolic milieu, potentially triggering the development of non-alcoholic fatty liver disease (NAFLD), no studies have explored this association. This study sought to examine whether short sleep duration or poor sleep quality is associated with NAFLD in the general population.

Methods: We assessed sleep duration and quality using the Pittsburgh Sleep Quality Index in 69,463 middle-aged workers and their spouses and carried out biochemical and anthropometric measurements. The presence of fatty liver was determined using ultrasonographic findings. Logistic regression models were used to evaluate the association of sleep duration and quality with NAFLD, after adjusting for potential confounders.

Results: After controlling for the relevant confounding factors (age, alcohol intake, smoking, physical activity, systolic blood pressure, education level, marital status, presence of job, sleep apnea, and loud snoring), the adjusted odds ratio (95% confidence interval) for NAFLD comparing sleep duration ⩽5 h to the reference (>7 h) was 1.28 (1.13–1.44) in men and 1.71 (1.38–2.13) in women. After further adjustments for BMI, this association was not significant in men (OR: 1.03, 95% CI: 0.90–1.19) but remained significant in women (OR: 1.59, 95% CI: 1.23–2.05). The multivariate-adjusted odds ratio comparing participants with poor sleep quality *vs.* participants with good sleep quality was 1.10 (95% CI 1.02–1.19) and 1.36 (95% CI 1.17–1.59) in men and women, respectively.

Conclusions: In the middle-aged, general population, short sleep duration, and poor sleep quality were significantly associated with an increased risk of NAFLD. Prospective studies are required to confirm this association.

Introduction

Sleep disturbance and deprivation are common health problems in a modern society. Although the restorative function of sleep is essential for energy homeostasis, the duration of time devoted to sleep in working-aged populations has declined during the past few decades [1]. A national survey estimated that approximately 20% of the general population suffered from sleep disturbances, which affected their daily lives [2]. Mounting evidence indicates that short sleep duration or poor sleep quality is associated with adverse health outcomes [3,4]. Quantitatively and qualitatively disturbed sleep predisposes individuals to type 2 diabetes mellitus and cardiovascular disease. A recent meta-analysis demonstrated that sleep disturbance consistently predicted the future development of diabetes [5]. One prospective study showed that compared to normal sleepers (7 h), short sleepers (⩽6 h) had a 23% higher risk of coronary heart disease over a 12-year follow-up period [6]. Recent data from a large nationally representative sample demonstrated that poor sleep quality is an independent contributor to myocardial infarction, stroke and coronary artery disease [7]. Emerging work suggests that multiple biologic markers, such as increased body mass index (BMI), reduced insulin sensitivity, and inflammatory markers, may mediate the impact of decreased duration or quality of sleep on the adverse health outcomes mentioned above [8].

Keywords: Sleep duration; Sleep quality; Non-alcoholic fatty liver disease; Obesity.

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Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein-cholesterol; hsCRP, high sensitivity-C reactive protein; IR, insulin resistance; LDL-C, low-density lipoprotein-cholesterol; NAFLD, non-alcoholic fatty liver disease.

Non-alcoholic fatty liver disease (NAFLD) is becoming the most prevalent chronic liver disease worldwide [9]. NAFLD encompasses a broad spectrum of clinical and pathologic manifestations from simple steatosis to non-alcoholic steatohepatitis (NASH) [10,11]. It has been shown that NASH can progress to liver cirrhosis and its accompanying complications [12]. Moreover, recent evidence from epidemiological studies linked NAFLD to a substantial increase in risk for metabolic complications, such as type 2 diabetes mellitus and cardiovascular disease [13–16]. These associations are supported by studies displaying a close link between NAFLD and metabolic derangements, such as obesity, the metabolic syndrome and insulin resistance [17,18], which individuals with sleep disturbance are likely to develop. Therefore, it can be speculated that the metabolic milieu in individuals who experience sleep disturbance may trigger several pathophysiologic processes associated with NAFLD. Since the proportion of sleep disturbance and NAFLD continues to increase, an association between them would have significant implications for public health and clinical research. To our knowledge, no study has examined the relationship between sleep duration and quality and NAFLD.

Therefore, we sought to explore whether sleep duration and quality would be associated with NAFLD, as determined by ultrasonography, which is a practical and reliable diagnostic tool for detecting fatty liver, among the middle-aged population. In addition, we examined the role of biological mediators in sleep disturbance and its effects on the risk of NAFLD and gender differences in the association between sleep duration and quality and NAFLD.

Materials and methods

Subjects

The study population comprised workers and their spouses from one of the largest companies in Korea and its 26 affiliates. In Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. These companies supported the health screening program of the workers' spouses according to their welfare policies. Study subjects included all workers and their spouses from the above mentioned semiconductor companies who participated in comprehensive health examinations at Kangbuk Samsung Hospital in Seoul, Korea in 2011 (n = 69,463), including an ultrasound examination of the liver. For this analysis, we excluded participants with evidence of liver disease or with major risk factors for liver disease. Thus, we excluded 1168 subjects with a history of malignancy; 149 subjects with a history of liver cirrhosis; 44 subjects with a reported history of known liver disease (including genetic, autoimmune, and drug-induced liver disease), abnormal liver ultrasound findings (indicating, liver transplantation, liver cirrhosis, intrahepatic or extrahepatic cholelithiasis, or abnormal dilatation of the biliary tree); 2570 subjects with positive serologic markers for hepatitis B or C virus or who were taking medications for hepatitis; 153 subjects taking sleeping pills, 1189 subjects who had taken medications within the past year that could affect the development of hepatic steatosis (such as steroids, immune suppressants, anticonvulsants, etc.); 16,275 subjects reporting an alcohol intake $\geqslant$20 g/day [19]; 3939 night-shift workers; 2102 subjects with missing baseline data on their medical histories; and 13 subjects who did not participate in the liver ultrasonography. Because some individuals met more than one criterion for exclusion, the total number of eligible subjects for the study was 45,293. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted the requirement for informed consent as we retrospectively accessed data that were de-identified.

Measurements

We used the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality. The PSQI is a validated, self-administered questionnaire used to generate seven component scores calculated by 19 items which reflect subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime function [20]. Participants with poor sleep quality are defined as those with a sum of the scores greater than 5 for these seven components. Component 3, which asked the number of hours of actual night-time sleep during the past month, was used to assess sleep duration. Data on medical history, medication use, health-related behaviors, physical measurements, and serum biochemical measurements were collected during health examinations. Questions regarding alcohol intake included weekly frequency of alcohol consumption and the usual daily amount of consumption. Questionnaire data were also used to collect information on smoking history (duration and daily consumption of cigarettes). Pack-years were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person had smoked.

Physical activity of the subjects was evaluated using the Korean version of the International Physical Activity Questionnaire (IPAQ) short form, which has shown good reliability and adequate validity. The number of days per week and time spent walking per day, as well as moderate and vigorous activities were recorded. The IPAQ data were converted to metabolic equivalent scores (MET-min-week^{-1}) for each type of activity, by multiplying the number of minutes dedicated to each activity class by the specific MET score for that activity. Physical activity levels were also classified into three categories: inactive, minimally active, and health-enhancing physically active, according to the scoring system provided by the IPAQ.

Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment panel III as the presence of three or more than the following risk factors: (1) abdominal obesity as defined as waist circumference $\geqslant$90 cm in men and $\geqslant$85 cm in women [21], (2) impaired fasting glucose as defined by fasting blood glucose $\geqslant$100 mg/dl, (3) high triglycerides as defined by triglycerides $\geqslant$150 mg/dl (to convert to mmol/L, multiply by 0.01129); (4) low HDL-C as defined by HDL-C <40 mg/dl (to convert to mmol/L, multiply by 0.02586), and (5) blood pressure $\geqslant$130/85 mmHg. To define obesity in this study, we used a BMI of 25 kg/m^2 which was proposed as the appropriate threshold of obesity for Asian populations [22]. Anthropometric measurements and procedures for obtaining the blood samples were described in detail elsewhere [23].

Abdominal ultrasounds were performed using a 3.5-MHz transducer (Logiq 9; GE, Madison, WI, USA) by the eleven experienced radiologists who were unaware of the aims of the study and blinded to the laboratory values. Images were captured in a standard fashion with the subject in the supine position and with the right arm raised above the head. An ultrasonographic diagnosis of fatty liver was defined as the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma [24].

To assess the intra- and inter-observer reliability of the ultrasound diagnosis of fatty liver, a random sample of 200 stored ultrasonographic images was re-read at least two weeks apart by the eleven radiologists. All radiologists were blinded to clinical information. The inter-observer reliability and intra-observer reliability for fatty liver diagnosis were substantial (kappa statistic of 0.74) and excellent (kappa statistic of 0.94), respectively.

Statistical analysis

One-way ANOVA and χ^2-tests were used to compare the characteristics of participants according to sleep duration. Sleep duration was categorized into the following groups: >7, >6–7, >5–6, and $\leqslant$5 h.

The distribution of continuous variables was evaluated and appropriate transformations were performed during analysis, as needed. Odds ratios were used to measure the association of the risk of NAFLD with sleep duration categories. Logistic regression models were used to estimate odds ratios and 95% confidence intervals (CI), after adjusting for potential confounders.

The models were initially adjusted for age, then for smoking, alcohol intake, physical activity, educational level, marital status, and presence of job (yes or no). To determine linear trends of risk, the number of categories or quartiles was used as a continuous variable and tested on each model.

We calculated the mediation effect of BMI on the association between sleep duration and risk of NAFLD if BMI met the following 3 criteria for being a potential mediator: (1) sleep duration was associated with BMI, (2) BMI was significantly associated with the risk of NAFLD controlling for sleep duration, and (3) the addition of BMI to the model both attenuated the coefficient of sleep duration and had a statistically significant mediation effect.

We also examined the association of sleep duration and sleep quality with the fatty liver index as a surrogate marker of fatty liver in a sensitivity analysis. The fatty liver index was calculated according to the published formula: Fatty liver index (FLI) = $(e^{0.953 * \log_e(\text{triglycerides}) + 0.139 * \text{BMI} + 0.718 * \log_e(\text{ggt}) + 0.053 * \text{waist circumference} - 15.745})/(1 + e^{0.953 * \log_e(\text{triglycerides}) + 0.139 * \text{BMI} + 0.718 * \log_e(\text{ggt}) + 0.053 * \text{waist circumference} - 15.745}) * 100$ [25]. Subjects were divided into three groups: FLI <30, 30 $\leqslant$FLI <60, and FLI $\geqslant$60 [25]. The statistical analysis of the data was