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Insomnia, narcolepsy, sleep apnea syndromes and risk of nonalcoholic fatty liver disease: A systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 July 2024 and was last updated on 03 July 2024.

INTRODUCTION

Review question / Objective To conduct a systematic review of the existing risk between three relevant adverse sleep characteristics, including insomnia, narcolepsy、sleep apnea syndromes , and NAFLD.

Condition being studied NAFLD is a systemic disease characterized by steatosis and abnormal accumulation of fat in liver parenchymal cells. The pathogenesis of this condition, which is closely associated with insulin resistance (IR), creating metabolic stress liver injury, and is influenced by certain genetic factors, is complex and clinically diverse.

There are many categories of sleep disorders, the main ones of which include: Insomnia - where people have difficulty falling asleep or maintaining a sleep state, often leading to daytime fatigue, depressed or irritable mood, and problems with concentration; Narcolepsy - where the typical symptom is uncontrollable daytime sleepiness or sudden lapses into sleep; and sleep apnea. or sudden lapses into sleep; Sleep apnea syndrome - characterized by a narrowing of the upper airway during sleep that interferes with normal ventilation, with common symptoms including excessive daytime sleepiness, sleep fragmentation, snoring, fatigue, and decreased cognitive function.

In recent years, studies have found that sleep disorders may promote the development of NAFLD and are associated with problems such as obesity, inflammation, insulin resistance, and disorders of glucose and lipid metabolism. In particular, patients with sleep apnea syndromes are often accompanied by risk factors such as obesity and cardiovascular disease, all of which may be strongly associated with the onset and development of NAFLD. In addition, sleep apnea syndromes may reduce sleep quality, which in turn may have adverse effects on the metabolic and endocrine systems, indirectly increasing the risk of NAFLD. Notably, NAFLD appears to be strongly associated with obstructive sleep apnea (OSA) even in the absence of comorbidities such as obesity or metabolic syndrome (MetS). Hypoxia plays a key role in the pathogenesis of NAFLD, and

the underlying mechanism may be related to the activation of the hypothalamic-pituitary-adrenal axis, which in turn increases the secretion of stress hormones (e.g., cortisol and catecholamines), thereby increasing the risk of metabolic syndrome.
Given the lack of systematic and comprehensive studies on the relationship between insomnia, narcolepsy, sleep apnea syndromes and NAFLD, the present study aimed to investigate in depth the potential link between these sleep disorders and NAFLD by summarizing the existing epidemiological literature.

METHODS

Participant or population Adults older than 18 years with information on one of the sleep disorders (insomnia, narcolepsy, and sleep apnea syndromes) and a documented diagnosis of NAFLD.

Intervention In both cohort study and cross-sectional study, we select population with insomnia, sleep apnea syndrome, and narcolepsy as the case/exposure group; In case-control study, we select population with NAFLD as the case group.

Comparator In both cohort study and cross-sectional study, we select population who did not suffer from insomnia, narcolepsy, or sleep apnea syndrome as a control group; In case-control study, we select population who did not have NAFLD as a control group.

Study designs to be included Cross-sectional study, cohort study or case-control study.

Eligibility criteria (1) Participants with well-defined NAFLD; (2) Studies with methods clearly identify and validate insomnia, narcolepsy, sleep apnea syndromes; (3) Studies have adequate data on the association between insomnia, narcolepsy, sleep apnea syndromes; and NAFLD (including odds ratio(OR), relative risk (RR) or standardised incidence rate and 95% confidence intervals); (4) Studies type: include cross-sectional study, cohort study, case-control study.

Information sources Three researchers (LY, MY, and HB) searched the PubMed, Web of Science and Embase databases from their respective inception dates to 07/03/2024 using the following search terms:(“Sleep Initiation and Maintenance Disorders[Mesh]” OR “difficulty falling asleep” OR “short sleep duration” OR “chronic insomnia” OR “primary insomnia”) AND (“Narcolepsy[Mesh]” OR “excessive daytime sleepiness” OR “EDS” OR “hypersomnia” OR “type 1 narcolepsy ,NT1” OR “type 2 narcolepsy ,NT2” OR “idiopathic hypersomnia” OR “narcolepsy with cataplexy”) AND (“ Sleep Apnea Syndromes"[Mesh]” OR “SAS” OR “obstructive sleep apnea hypopnea syndrome” OR “obstructive sleep apnea” OR “OSAHS” OR “OSA” OR “OSAS” OR “SA”) AND (“Non-alcoholic Fatty Liver Disease[Mesh]” OR “NAFL” OR “NASH”).

Main outcome(s) In cohort studies, the main outcome was the difference in the incidence rate of NAFLD in people with or without sleep disorders (RR); In cross-sectional studies, the main outcome was the difference in the prevalence of NAFLD among people with or without sleep disorders (OR); In case-control studies, the main outcome was the difference in the prevalence of sleep disorders among those with or without NAFLD (OR).

Quality assessment / Risk of bias analysis The Newcastle-Ottawa Scale (NOS) was used to assess the quality of cohort and case-control studies. The NOS assigns a maximum of nine points to eight items in three categories. The scoring parameters were as follows: selection of study population (maximum 4 points), comparability between groups (maximum 2 points), and outcome measures (maximum 3 points). Studies that scored above average were considered high quality.
The evaluation criteria for an observational study of the Agency for Healthcare Research and Quality (AHRQ) were adapted to evaluate the quality of cross-sectional studies. Agency for Healthcare Research and Quality evaluation criteria for an observational study consists of 11 items. Every item of AHRQ criteria was answered as yes, no, or not reported. The items with “yes” scored one, and the items with “no” and “not reported” scored zero. The scores between 8 and 11 were regarded as high quality, 4 and 6 as moderate quality, and 0 and 3 as low quality.

Strategy of data synthesis Data were extracted from studies that met our inclusion criteria, and risk estimates (RR, HR and OR) and 95% CI for the association between Insomnia, Narcolepsy, and Sleep Apnea Syndromes and the risk of NAFLD were extracted for each study. A random-effects model was used to compute the pooled RR and 95% CI for all articles. The significance of the pooled RR will be determined by a z-test, with a p-value of 75% representing non-significant, low, moderate and high heterogeneity, respectively. The robustness of the meta-analysis results was judged by sensitivity analysis (exclusion of

literature on a case-by-case basis). Data were analyzed using RevMan and R software.

Subgroup analysis Considering the heterogeneity of study populations and different study designs, the following subgroup can be formed:
1. Study design: cross-sectional study, case-control study, cohort study;
2. Country and region where the study was conducted;
3. Subtypes and comorbidities of NAFLD studied;
4. Age of study population: adults (≧18 years), elderly (>65 years); Sex of study population: Male and Female, etc. of the study subjects.

Sensitivity analysis Sensitivity analyses for missing binary outcome data and potential selection bias are conducted with R package metasens.

Country(ies) involved China.

Keywords Sleep initiation and maintenance disorders, Sleep apnea syndromes, Narcolepsy, Non-alcoholic fatty liver disease, Meta-analysis.

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