

Excessive Daytime Napping Increases the Risk of Non-Alcoholic Fatty Liver Disease: A Meta-Analysis and a Mendelian Randomization Study

Xiuqi Qiao^{1,2}, Xiaoxia Wang¹, Lixin Guo^{1,2}, Qi Pan^{1,2}

¹Department of Endocrinology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, 100730, People's Republic of China; ²Graduate School of Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, 100730, People's Republic of China

Correspondence: Lixin Guo; Qi Pan, Email glx1218@163.com; panqi621@126.com

Background: Prior research based on observations has furnished evidence that supports a connection between daytime napping and the prevalence of non-alcoholic fatty liver disease (NAFLD). Nevertheless, the question of whether this correlation is indicative of a causal link has not been definitively answered.

Methods: We used meta-analysis and Mendelian randomization (MR) to synthesize genetic and observational data. A two-sample MR analysis was conducted, leveraging 105 single-nucleotide polymorphisms (SNPs) known to be associated with daytime napping patterns. Additionally, summary-level data pertaining to NAFLD outcomes were acquired from the comprehensive UK Biobank study. Network meta-analyses were employed to investigate the relationship between excessive daytime napping and NAFLD, while subgroup was also performed.

Results: Significant associations were observed between daytime napping and NAFLD. The systematic review/meta-analysis uncovered a heightened risk of NAFLD development among individuals who engaged in daytime naps exceeding 30 minutes, when compared to those who did not nap (odds ratio [OR] = 1.32, 95% confidence interval [CI]: 1.05 to 1.66). Furthermore, MR analysis indicated that a genetic propensity towards longer daytime napping was significantly linked to an increased likelihood of NAFLD (OR = 2.26, 95% CI: 1.38 to 3.73).

Conclusion: Daytime napping has been found to be causally related to a higher risk of NAFLD. Furthermore, across all participants, napping for an average duration over 30 minutes was linked to an elevated likelihood of NAFLD.

Keywords: daytime napping, non-alcoholic fatty liver disease, genetic variants, Mendelian randomization, network meta-analysis

Introduction

The worldwide occurrence of non-alcoholic fatty liver disease (NAFLD) stands at roughly 25% and is estimated to reach 56% by 2030.¹ The expanding scale of NAFLD, along with its array of complications, has emerged as a significant public health challenge, largely due to shifts in lifestyle and dietary patterns. The spectrum of NAFLD-related liver damage is broad, encompassing conditions from simple fatty liver (hepatic steatosis) to more severe inflammation (steatohepatitis), advanced fibrosis, cirrhosis, and even hepatocellular carcinoma.² Often asymptomatic, individuals with NAFLD can progress to terminal liver disease or liver cancer. In China, it is approximated that 20% of the population is affected by NAFLD, while in the United States, the prevalence soars to 35%.^{3,4} Urgent focus is thus required to mitigate the risks of NAFLD and its potential complications and mortality.

Daytime napping is a widely-accepted habit in numerous nations around the globe, particularly in China.⁵ In Chinese cultural traditions, the practice of afternoon napping has long been hailed as a beneficial habit for overall health.⁶ Contradictorily, research indications point to the potential adverse health effects of daytime napping under specific circumstances. Empirical studies have validated a positive association between daytime napping and the likelihood of NAFLD.^{7,8} Data from a recent study showed NAFLD was significantly related to usually nap during day.¹

To date, the existence of a causal link between napping and the incidence of NAFLD remains to be definitively established. Despite this, traditional observational studies, including well-constructed prospective studies with substantial

sample sizes, remain vulnerable to lingering confounding factors and the possibility of reverse causality. In contrast, instrumental variables (IVs) are randomly allocated at conception, making the Mendelian randomization (MR) method a type of “natural randomized control trial”.⁹ MR is a widely employed analytical approach for elucidating causal connections between clinical outcomes and exposure variables, utilizing genetic variations as instrumental variables. The inherent nature of the genotype, being innate and predating the occurrence of the outcome, coupled with its insulation from a host of confounding elements such as environmental factors, positions it as a potent instrument in the study of causal links between exposures and outcomes.^{9,10} Utilizing publicly accessible genome-wide association study (GWAS) data from a substantial cohort, we conducted a two-sample MR approach to assess the effect of daytime napping on the risk of NAFLD, thereby providing further clarity on the causal connection to better understand the risk factors for NAFLD and provide new insights for its prevention.

Methods

Systematic Review and Meta-Analysis

This network meta-analysis (NMA) was performed adhering to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.¹¹

Search Strategy

Utilizing the Population, Intervention, Comparator, Outcomes, and Study (PICOS) framework as our guiding principle, we conducted a comprehensive search across the PubMed, Embase, and Cochrane Library databases from inception to December 7, 2023 to determine how daytime napping impacts NAFLD risk. Our search strategy employed a combination of targeted keywords, truncation symbols, relevant Medical Subject Headings (MeSH) terms, and Boolean operators (AND/OR) to ensure a thorough and precise retrieval of relevant literature, which included the following terms related to NAFLD and daytime napping: (NAFLD[Title/Abstract]) OR (MAFLD[Title/Abstract]) OR (Nonalcoholic Fatty Liver Disease[Title/Abstract]) OR (Fatty Liver, Nonalcoholic[Title/Abstract]) OR (Liver, Nonalcoholic Fatty[Title/Abstract]) OR (Nonalcoholic Fatty Liver[Title/Abstract]) OR (Nonalcoholic Steatohepatitis[Title/Abstract]) OR (Nonalcoholic Steatohepatitides[Title/Abstract]) OR (Non-alcoholic Fatty Liver Disease[Title/Abstract]) combined with daytime napping (daytime napping[Title/Abstract]) OR (nap[Title/Abstract]) OR (doze[Title/Abstract]) OR (snooze[Title/Abstract]) OR (siesta[Title/Abstract]) OR (napping duration[Title/Abstract]).

Inclusion Criteria

For the purposes of this systematic review, we assessed the likelihood of NAFLD in both adolescent and adult populations with and without a habit of daytime napping. We included studies that consecutively enrolled participants diagnosed with NAFLD to ensure a comprehensive analysis of the available data. For study inclusion, NAFLD was diagnosed based on ultrasonography, which has been used in different populations.^{12,13} The following trials were excluded: i) animal experiments; ii) editorials, letters, reviews, commentaries, conference abstracts, or interviews; and iii) those with incomplete NAFLD data. Duplicate records were removed using EndNote X9. Teams of paired reviewers independently used EndNote X9 to first screen titles and abstracts, followed by full-text manuscripts. Then, data on sample size, napping duration, odds ratio (OR) (95% confidence interval [CI]), NAFLD events, and diagnostic method were extracted. Differences were resolved through discussion or, if necessary by third-party adjudication.

Data Collection and Registered Protocols

Articles that met the criteria for potential eligibility were gathered in accordance with the predefined inclusion and exclusion criteria. The following information was extracted from the articles selected for inclusion: basic study attributes (including author, year of publication, geographical location, participant age, study design, and sample size), exposure groups (napping duration), NAFLD events, and the definition of NAFLD.

The systematic review and meta-analysis protocols were registered on PROSPERO (CRD42023485932).

Statistical Analysis

The primary endpoints were the odds of NAFLD in people with/without daytime napping. This study was conducted within a frequentist random-effect NMA to assess the associations of the likelihood of developing NAFLD in relation to particular lengths of daytime napping. We calculated the OR to estimate the pooled prevalence. Sensitivity analysis was performed to assess the impact of country (China versus Iran) and napping duration (no naps, 0–30 min, 30–60 min, > 60 min). STATA 14 and R software was used for data analysis.

Risk of Bias Assessment

The Newcastle-Ottawa Scale (NOS) was employed in this NMA to assess the quality of observational studies.¹⁴ Scores of 7–9, 4–6, and 4 were classified as having a low, moderate, or high risk of bias, respectively.¹⁴

Mendelian Randomization (MR)

Two-Sample MR

Single-nucleotide polymorphisms (SNPs) are randomly assigned at the moment of conception, signifying that they are not influenced by environmental factors that occur after birth.⁹ The expanding availability of open databases has greatly aided in conducting two-sample MR studies. Employing this methodology, we utilized a two-sample MR analysis to evaluate the causal association between daytime napping and the risk of NAFLD. Initially, we identified IVs for MR analysis by treating napping-related traits as the “exposures” and NAFLD, along with associated liver parameters, as the “outcomes”. We then evaluated heterogeneity through Cochran’s Q -test. To further ensure the robustness of the causal inferences, we conducted sensitivity analyses to validate the reliability of the obtained causal estimates.

Data Sources

We accessed summary-level data from a GWAS on self-reported daytime napping within the UK Biobank, which included individuals of European descent ($n = 452,633$).¹⁵ In parallel, we retrieved NAFLD-related data from the Open GWAS database, specifically the GWAS catalog ($n = 377,998$).¹⁶

Selection of Instrumental Variables

A rigorous selection process was employed to identify suitable IVs. Initially, 107 SNPs with a strong association with daytime napping in individuals of European ancestry were identified as potential IVs, meeting a stringent significance threshold ($P < 5.00E-08$). SNPs were then excluded if they exhibited linkage disequilibrium ($r^2 < 0.001$) or were palindromic with intermediate allele frequencies. We searched for IVs using PhenoScanner (<http://www.phenoscaner.medschl.cam.ac.uk/>) to identify any previous associations with potential confounders. Additionally, SNPs that were not available in the outcome GWAS or their proxy SNPs were not utilized in the analysis. The selection of qualified IVs was based exclusively on summary-level GWAS data from European descent populations. The strength of the association between the IVs and daytime napping was quantified using F statistics, with only SNPs having an F statistic greater than 10 considered robust and valid for use as IVs in relation to daytime napping.¹⁷ Ultimately, the selected SNPs were incorporated as IVs for the MR analysis. Detailed information on these IVs is shown in [Supplementary Table 1](#).

Statistical Analysis

In applying the MR methodology, adherence to three fundamental premises is imperative: (1) the chosen IVs must exhibit a robust correlation with the exposure; (2) these IVs ought to remain uncorrelated with any potential confounding factors; and (3) the IVs’ impact on the outcomes is solely mediated by the exposure pathway, excluding alternative routes. The primary investigation employed the conventional random effects inverse variance weighting approach (IVW) to ascertain the causal relationship between napping and the incidence of NAFLD. Complementing this, four additional analytical techniques were utilized: the weighted median, weighted mode, simple mode methodologies, and the MR-Egger method. Sensitivity assessments were conducted utilizing Cochran’s Q -test and a leave-one-out strategy, deeming P -values below

0.05 statistically meaningful. The entirety of the analyses was executed within a two-sample MR framework, facilitated by the MR PRESSO package in R software, version 4.3.1.

Results

NMA of Daytime Napping Duration and NAFLD Incidence

The NMA of napping duration and the risk of incident NAFLD encompassed a total of 35,928 participants from six studies (Supplementary Table 2). Supplementary Figure 1 depicts a flowchart of the study selection procedure. Studies selected via systematic review suggested an association between excessive daytime napping and the odds of NAFLD (Figure 1). For all studies,^{8,18–22} subjects with more than 30 min of napping duration were found to have an elevated risk of incident NAFLD compared to the “no naps” group (OR_{30–60 min, > 60 min} and 95% [CI]: 1.40, 1.03 to 1.89; 1.78, 1.30 to 2.43). Additionally, a significant discrepancy was noted between the groups designated as “> 30 min” and “0–30 min” in terms of napping duration. A subsequent analysis involving five studies indicated that daily napping exceeding 30 minutes was associated with a greater likelihood of developing NAFLD compared to shorter daytime naps (OR = 1.41, 95% CI: 1.06 to 1.86) (Figure 2).

In the sensitivity analyses, after excluding studies individually, we observed findings similar to those of our primary analyses (Figure 3), with no evidence of small study effects on the analysis of funnel plot symmetry (Supplementary Figure 2). An evaluation of the risk of bias using NOS indicated that none of the studies fall into the high-risk category. (Supplementary Table 3).

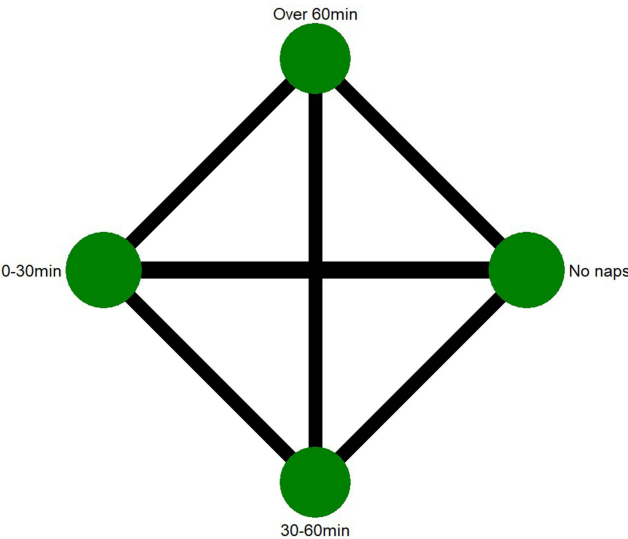


Figure 1 In the network plot, participants with varying lengths of napping were categorized into four distinct time-based groups: “no naps”, “0–30 min”, “30–60 min”, and “> 60 min.” The size of each node represented the number of subjects within each napping duration category, with the edges between nodes visually weighted to reflect the frequency of comparisons across different exposure groups, facilitating a comparative analysis among all groups.

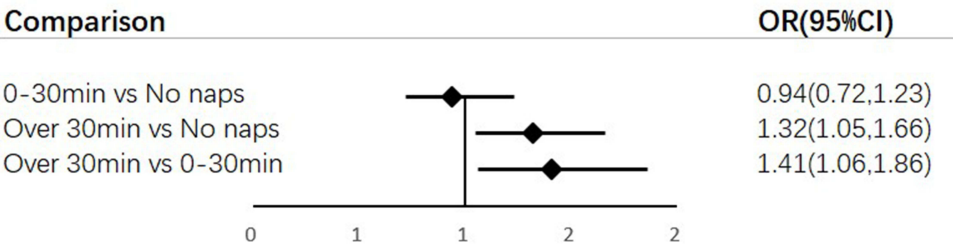


Figure 2 Forest plot for the odds ratio of Non-alcoholic fatty liver disease (NAFLD) in different comparisons. Abbreviations: OR, odds ratio; CI, confidence interval.

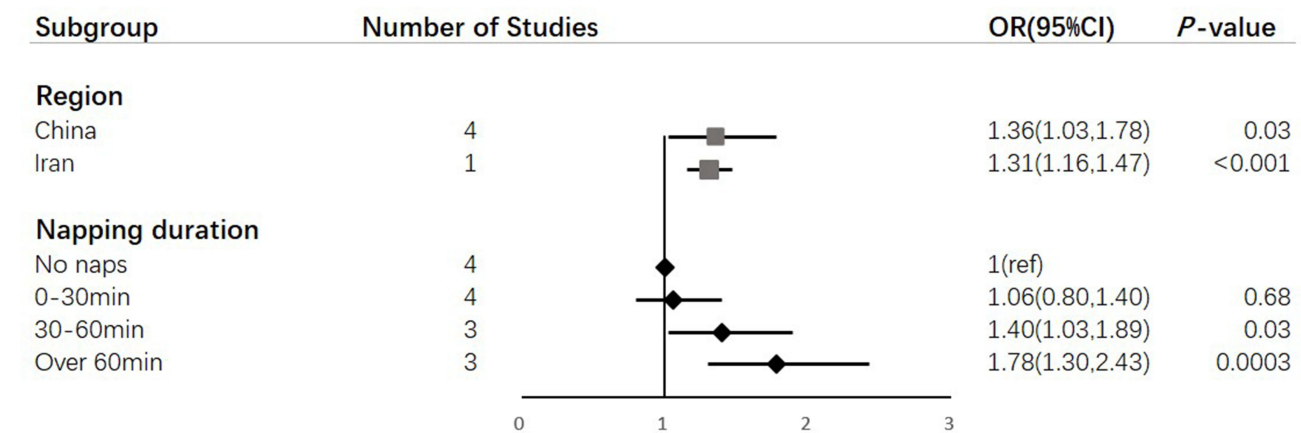


Figure 3 Subgroup analysis plot. The forest plot depicts a subgroup analysis examining the relationship between daytime napping and the incidence of NAFLD among individuals who nap, as compared to those who do not, within subgroups defined by geographical region and napping duration.

Abbreviations: OR, odds ratio; CI, confidence interval.

Cause-and-Effect Relationship Between Daytime Napping and NAFLD

The causal link between daytime napping and NAFLD was supported by the finding that a genetic inclination toward more regular daytime napping was robustly correlated with an elevated likelihood of NAFLD development in the IVW model (OR = 2.26, 95% CI: 1.38 to 3.73, $P = 0.0008$) (Figure 4). As shown in the scatter plots, the risk of NAFLD increased with excessive daytime napping (Figure 5). The MR estimates for NAFLD did not alter the inference of the results after removing two palindromic SNPs (rs10772659, rs285815). The analysis of NAFLD did not reveal any appreciable heterogeneity or pleiotropic influences (Supplementary Table 4). Additionally, the leave-one-out sensitivity analysis did not pinpoint any SNPs that had a substantial impact on the causal estimates (Supplementary Figure 3). As depicted in the plot, where all lines are clustered on one side of the y-axis and remain in close proximity, even extending beyond the axis, this convergence signifies the robustness of the results under investigation. All sensitivity analyses yielded results similar to those of the main analyses. Forest maps of the results are shown in Supplementary Figure 4.

Discussion

As far as we know, this study represents the first effort to comprehensively evaluate the causal relationships between self-reported daytime napping and NAFLD using a MR framework. By employing a dual approach that combines systematic review/meta-analysis and MR, we have compiled robust evidence to suggest a significant causal link between napping duration and NAFLD risk. In our two-sample MR analysis involving 830,631 participants, we uncovered compelling evidence indicating that genetically predisposed self-reported daytime napping is positively linked to the risk of NAFLD. Furthermore, the NMA corroborated this finding, indicating that individuals with a daytime napping duration of more than 30 minutes have a higher risk of NAFLD compared to those with a duration of less than 30 minutes or no napping at all. Our findings regarding the effect of daytime napping are consistent with those from a previous MR study in which NAFLD was

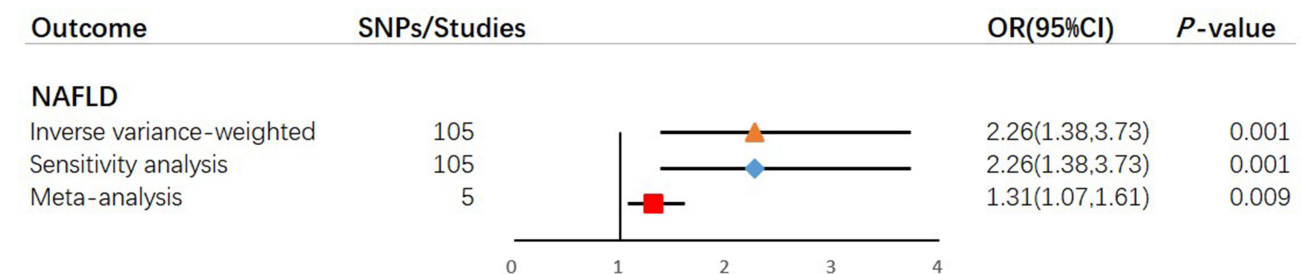


Figure 4 Findings from a two-sample Mendelian Randomization analysis examining the association between daytime napping and the risk of NAFLD.

Abbreviations: NAFLD, Non-alcoholic fatty liver disease; SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

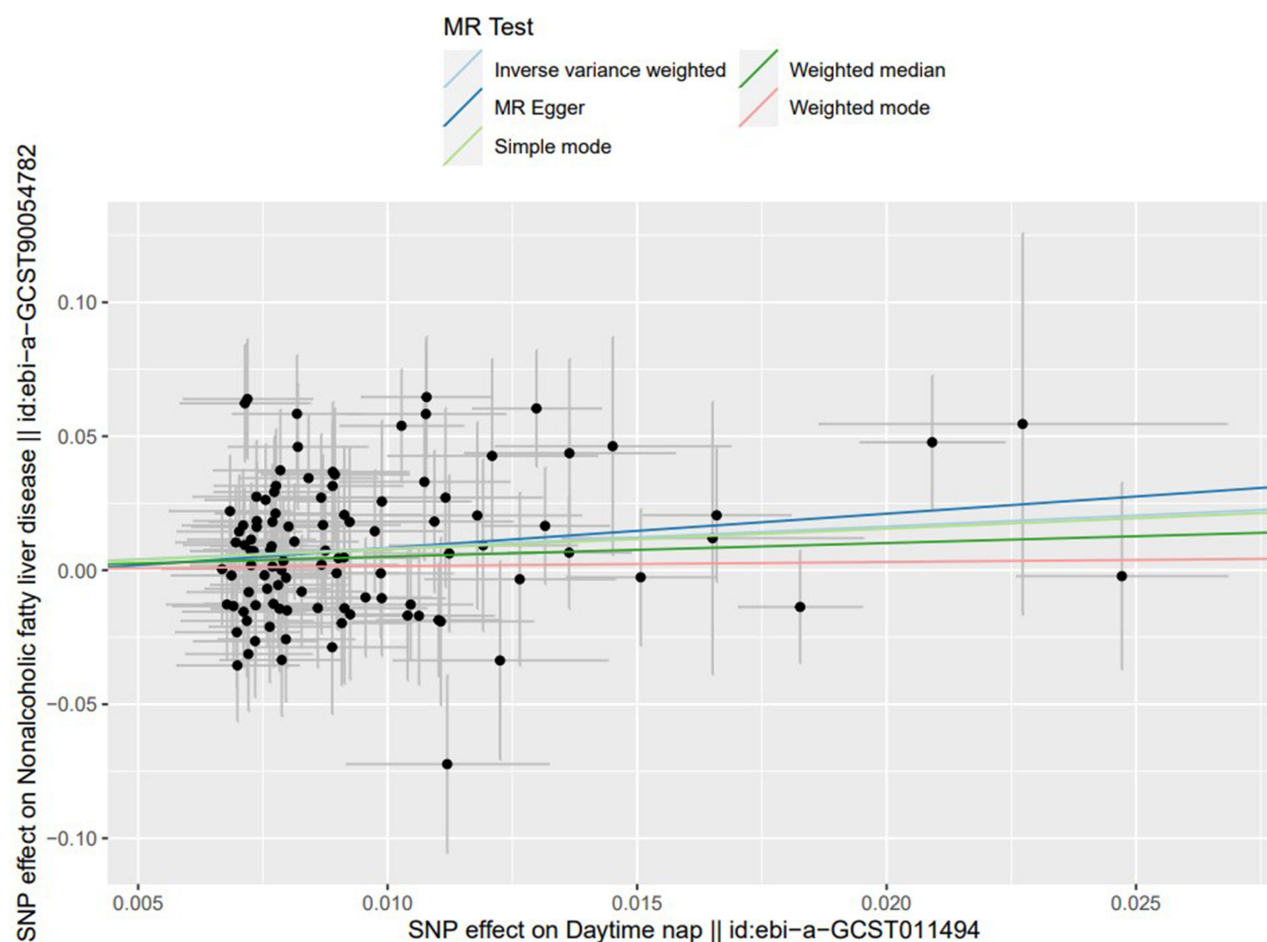


Figure 5 Scatter plots illustrating the impact of daytime napping on NAFLD risk are presented. Each black dot represents a genetic instrumental variable incorporated into the Mendelian Randomization analysis. The corresponding grey error bars indicate the 95% confidence intervals for the coefficients of these genetic instrumental variables.

found to be significantly associated with usual naps during the day (hazard ratio [HR]: 1.28; 95% CI: 1.02 to 1.61) compared to never or rarely nap.¹ The findings of this previous study corroborated that daytime napping was associated with NAFLD risk. However, due to the unavailability of daytime nap duration data in the UK Biobank using only MR, their analyses did not reveal a dose-dependent relationship. Furthermore, the results of our subgroup analyses revealed that the positive correlation between napping and the incidence of NAFLD was notable across all subgroups, encompassing geographical distribution and the duration of follow-up.

Our study revealed a dose-response association between the duration of daytime napping and the occurrence of NAFLD. Although the precise mechanism linking napping duration to NAFLD risk remains elusive, several hypotheses have been proposed to explain this relationship. Epidemiological research has demonstrated a correlation between extended daytime napping and disrupted glucose metabolism, which is significantly associated with NAFLD.^{5,19} Research has compellingly shown that the sleep homeostatic and circadian systems, with the sleep-wake cycle as their principal manifest rhythm, exert profound influences on a variety of physiological processes.^{19,23} These include the secretion of adrenal corticosterone and pituitary hormones, as well as energy metabolism regulation, encompassing lipolysis, insulin sensitivity, and basal metabolic rate. Further, the awakening response after prolonged daytime naps may elevate cortisol levels in the blood,^{24,25} potentially leading to insulin resistance and disordered glucose and lipid metabolism.²⁶ Cortisol is known to promote the accumulation of lipids and visceral fat, including in the liver.²⁷ Lastly, frequent daytime nap duration has been linked to increased levels of proinflammatory cytokines in the body, such as C-reactive protein,²⁸ which are known to be risk factors for NAFLD development. This observation underscores the significance of prolonged napping as an unhealthy lifestyle practice that

could potentially compromise an individual's health and hinder efforts to prevent disease. NAFLD is swiftly emerging as the predominant cause of hepatocellular carcinoma.²⁹ Critically, numerous risk factors for the onset of NAFLD also contribute to the development of hepatocellular carcinoma. Consequently, risk-stratified interventions could diminish the incidence of NAFLD and, subsequently, mitigate the associated mortality. Our research indicates that extended napping duration elevates the likelihood of NAFLD, underscoring the potential efficacy of lifestyle interventions targeting increased physical activity and improved dietary choices.

Our study boasts several strengths and also acknowledges certain limitations. Firstly, a notable strength of our research lies in the integration of NMA and MR to delve into the causal link between napping and NAFLD. NMA has traditionally been employed to synthesize findings from disparate epidemiological studies, while MR leverages genetic variants as IVs to ascertain whether a risk factor has a causal impact on a health outcome. Secondly, none of our IVs exhibited weak instrument bias, as evidenced by their F statistics exceeding 10. Moreover, we conducted a range of methods to assess pleiotropy and heterogeneity, thereby ensuring that the IVs conformed to the fundamental assumptions. Thirdly, we conducted a multitude of sensitivity analyses to minimize potential biases. We used the strict criteria of SNP selection and found no SNPs associated with potential confounders via online Phenoscanner. In terms of limitations, the evidence for the NMA is derived from Asian populations, while the MR evidence comes from European populations. Differences in ethnicity, lifestyle and age may affect the generalizability of results. As the age of the study population included in our meta-analysis fluctuated little, we did not incorporate subgroup analyses for elderly and younger adults in the NMA. Further, NAFLD was measured by ultrasonography in the meta-analysis, which is an imperfect indicator of NAFLD; therefore, the findings should be approached with circumspection. Leveraging IVW methods, we found that excessive daytime napping was significantly associated with NAFLD. However, further research is necessary to elucidate the underlying biological mechanisms linking these factors.

Conclusion

MR analysis indicates a causal relationship between daytime napping and an augmented risk of incident NAFLD. Similarly, in NMA, participants with an average napping duration exceeding 30 minutes were found to have a heightened risk of NAFLD compared to those with shorter or no naps.

Ethics Approval and Consent to Participate

This study utilizes aggregated data rather than individual-level data. The data involved all originate from publicly published GWAS summary databases, which complies with the conditions for exemption from review as stated in the “Ethical Review Measures for Life Sciences and Medical Research Involving Humans”.

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Disclosure

The authors affirm that the research was carried out free from any commercial or financial ties that could be interpreted as a potential conflict of interest.

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