Sleep Disturbances and Heart Failure: Observational Study and Mendelian Randomization Study

Keywords
Insomnia, Heart Failure, Observational Study, Sleep Disturbances, Mendelian Randomization Study

Abstract

Introduction
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Material and methods
Observational Study: NHANES data (2005-2008) involving 10,432 participants. Sleep disturbances defined as insomnia, sleep disorders, difficulty falling asleep, trouble sleeping, and waking up during the night. Mendelian randomization (MR) Study: Genetic variants linked to sleeplessness were obtained from GWAS datasets. MR Two-sample analysis was conducted using summary statistics from sleeplessness and HF GWASs.

Results
After full adjustment, the association between insomnia and HF remained significant, with an OR of 5.10 (1.81–14.33, P = 0.003). After full adjustment, the association between sleep disorder and HF remained significant, with an OR of 3.51 (1.67–7.39; P = 0.002). The IVW method provided evidence supporting a causal association between sleeplessness and HF (OR = 1.535, SE = 0.177, P = 0.016).MR-Egger analysis demonstrated a causal association between sleeplessness and HF (OR = 3.333, SE = 0.493, p =0.023). Our observational study may be influenced by unaddressed confounding factors; however, Mendelian randomization helps mitigate the bias and confounding commonly found in non-genetic observational research.

Conclusions
Our study identified a correlation between sleep disturbances and HF, potentially suggesting a causal relationship. Addressing sleep disturbances may be a key strategy in reducing the risk of HF.

Sleep Disturbances and Heart Failure: Observational Study and Mendelian Randomization Study

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Introduction

Heart failure (HF) occurs when the heart is unable to pump blood effectively due to structural or functional abnormalities, leading to a set of symptoms and signs that define the condition[1]. Globally, there are approximately 26 million HF patients, posing a serious threat to life and health[2]. In the United States and Europe, about one million new cases of HF are reported annually[2]. HF represents the end stage of many cardiovascular diseases, with high mortality and prevalence rates. Overall, the prevalence of HF ranges from 6.3% to 13.3%, with a five-year mortality rate as high as 75.4%[3]. Common causes of HF encompass a spectrum of conditions, including obesity, diabetes, myocardial ischemia, myocarditis, coronary artery disease, and arrhythmias[4, 5]. Sleep disturbances frequently serve as a common triggering factor for acute exacerbations of HF in patients during the stable phase of the condition[6]. Additionally, sleep disturbances are commonly present in patients with HF[7].

Sleep disorders manifest in various forms, including insomnia, difficulty falling asleep, trouble sleeping, and waking up during the night. About 10-15% of the population is affected by sleep disorders, especially common among middle-aged and elderly individuals[8]. Sleep disorders can compromise health, not only reducing quality of life but also leading to mental disorders and cardiovascular diseases such as hypertension[9,

10]. Sleep disorders contribute to endothelial dysfunction, systemic inflammation, oxidative stress, and neurohormonal imbalance, which can lead to myocardial remodeling, ventricular dysfunction, and the progression of HF[11]. Previous studies suggest a correlation between sleep disorders and HF[12]. A cohort study with over 10 years of follow-up demonstrated that insomnia is associated with the onset of heart failure, exhibiting a dose-response relationship[13].Another study confirmed that insomnia symptoms, both individually and cumulatively, are associated with incident HF in middle-aged and older adults[14]. However, residual confounding and reverse causality present alternative explanations for the observed strong correlation between sleep disorders and HF, both of which are difficult to disentangle in traditional observational studies[15]. While studies have shown a link between sleep disturbances and HF, they are limited to establishing correlation rather than causality. Mendelian randomization (MR), by leveraging genetic properties, provides a methodological approach to facilitate causal inference[15]. A recent trend in MR studies involves utilizing genetic variants as instrumental variables to simulate a randomized controlled trial design[16, 17]. In this approach, genotypes are assigned randomly to individuals before birth, allowing for causal inferences to be drawn[16, 17]. Several pioneering MR studies have investigated the causal relationship between sleep and cardiovascular disease[18-20]. However, research on the association

between sleep disturbances and HF is lacking. Therefore, further MR studies are needed to clarify the causal association between sleep disturbances and HF.

This study initially examines the association between sleep disturbances and HF through an observational study. Subsequently, it delves deeper into the causal relationship between insomnia and HF using MR studies. Our study synthesizes observational research and Mendelian randomization to examine the association between insomnia and heart failure. By harnessing the extensive data available from observational studies alongside the causal inference strengths of Mendelian randomization, we seek to deliver robust and comprehensive insights into this relationship.

Methods

Observational study

Study Population

The National Health and Nutrition Examination Survey (NHANES) is a comprehensive cross-sectional survey conducted by the National Center for Health Statistics to gather data on the noninstitutionalized U.S. civilian population. Our study utilizes NHANES survey data collected from 2005 to 2008, which included 10,432 participants. Flowchart of the inclusion procedure of patients in the present study. All participants provided informed consent after the study protocols received approval from the Institutional Review Board (IRB) of the National Center for Health Statistics.

Definition of Sleep Disturbances

Sleep disturbances in this study encompassed insomnia, sleep disorders, difficulty falling asleep, trouble sleeping, and waking up during the night. Participants were queried regarding the frequency of experiencing trouble falling asleep and waking up during the night, with response options including "Always", "Most of the time", "Sometimes", "Rarely", and "Never". In this study, "Always", "Most of the time", and "Sometimes" were categorized as "Yes", while "Rarely" and "Never" were categorized

as "No". Since "Rarely" occurs only once a month, it is reclassified as "No" to simplify categorization and maintain data consistency. Participants were asked if they had ever been informed by a doctor about trouble sleeping, sleep disorders, or insomnia, with response options including "Yes" or "No".

Other Data

Potential confounders were identified a priori based on a review of the existing literature. An in-home interview was conducted to collect comprehensive information regarding the patient's medical history and current pharmacological regimen, encompassing medications for hypertension, diabetes (both type 1 and type 2), hyperlipidemia, coronary heart disease, myocardial infarction, congestive heart failure, stroke, and angina. A physical examination included measurements of blood pressure, weight, and height, followed by calculation of body mass index (BMI) by dividing weight in kilograms by the square of height in meters.

Samples collected from the mobile examination center were stored at -20°C before being analyzed at central laboratories using standard methods for measuring high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, creatinine, and plasma glucose. LDL cholesterol and glucose levels were assessed only in a subset of survey participants who had fasted for at least eight hours prior to the survey.

Statistical analysis

Following NHANES analytic guidelines, our analyses incorporated sample weights, clustering, and stratification to ensure the findings' generalizability to the entire U.S. population. To address NHANES's complex sampling design, we applied suitable weights to achieve a representative sample of the U.S. national population. Weighted multivariate *Logistic regression* analyses were performed, with insomnia, sleep disorders, difficulty falling asleep, trouble sleeping, or waking up during the night as the independent variable and HF as the dependent variable. The objective of these analyses was to evaluate whether sleep disturbances is independently associated with HF. Patients with incomplete primary variable data were excluded from the analysis. For categorical covariates with missing data, a distinct category was created, whereas missing continuous variables were addressed through multiple imputation techniques. The R programming language was employed to address missing data through the utilization of the Mice package, which implements Multiple Imputation techniques.

In our study, we utilized three predefined models for adjustment: Model 1: This model was unadjusted to provide a baseline estimate of the association between sleep disturbances and heart failure. Model 2: We adjusted for demographic variables, including age, sex, ethnicity/race, marital status, poverty income ratio level, and education[21]. These

factors are essential as they can influence both the prevalence of sleep disturbances and heart failure risk[21]. Model 3: This model included additional clinical variables—hypertension, diabetes mellitus, coronary heart disease, heart attack, stroke, smoking, angina, alcohol consumption, systolic blood pressure, HbA1c, creatinine, LDL cholesterol, uric acid, and fasting triglyceride levels[22]. These adjustments are critical because they represent established cardiovascular risk factors and can significantly impact heart failure outcomes[22].

Analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p-value less than 0.05 was considered statistically significant.

MR study

Data sources and selection of genetic variants

We conducted a search on the IEU (https://gwas.mrcieu.ac.uk/), a comprehensive catalog containing reported associations from published GWAS studies. For exposure, we utilized publicly available summary statistical datasets of GWAS on sleeplessness from https://gwas.mrcieu.ac.uk/datasets/ukb-a-13/ (n = 336,965). As an outcome, we employed summary statistics from a GWAS involving 47,309 patients with HF of European descent[23]. A two-sample MR study employs genetic variants associated with gout as instrumental

variables (IVs) to enhance inference. We acquired summary statistics (beta coefficients and standard errors [SE]) for single-nucleotide polymorphisms (SNPs) associated with sleeplessness as instrumental variables (IVs) from GWASs.

Statistical analysis for Mendelian randomization

MR analysis necessitates genetic variants to be associated with, but not act as potential confounders of, an exposure[24]. Firstly, we evaluated the independent association of SNPs with sleeplessness. Secondly, we investigated the association between each SNP and the risk of HF. Thirdly, we integrated these findings to estimate the unconfounded causal association between sleeplessness and the risk of HF using MR analysis. We conducted a two-sample MR analysis, a method utilized to estimate the causal effect of an exposure (sleeplessness) on outcomes (HF), using summary statistics from GWASs[25]. This enabled us to evaluate the causal relationships between sleeplessness and HF risk, employing summary data from sleeplessness and HF GWASs with SNPs as IVs. To identify genetic loci associated with sleep disturbances, we utilized single nucleotide polymorphisms (SNPs) with P-values less than 5 × 10-8 as instrumental variables, thereby excluding weak associations. The strength of each independent variable was assessed using the F statistic (β^2 / SE^2), with a threshold of over 10 to ensure sufficient strength.

The IVW method employs a meta-analysis approach to integrate the Wald

ratio estimates of the causal effect derived from various SNPs. It yields a consistent estimate of the causal effect of the exposure on the outcome, provided that each genetic variant meets the assumptions of an IV[26]. To explore and address pleiotropy, we employed the weighted median estimator and *MR-Egger* regression methods. *MR-Egger* regression analysis examines and corrects for potential unbalanced pleiotropy by introducing a parameter for this bias, incorporating summary data estimates of causal effects from multiple individual variants. This method is robust for invalid IVs[27]. *MR-Egger* conducts a weighted linear regression of the gene-outcome coefficients on the gene-exposure coefficients[27]. The slope of this regression represents the estimate of the causal effect, and the intercept can be interpreted as an estimate of the average horizontal pleiotropic effect across the genetic variants[28]. The weighted median estimator yields a consistent estimate of the causal effect, even when up to 50% of the information contributing to the analysis is derived from genetic variants that are invalid IVs[29]. The weighted median estimator offers the advantage of maintaining greater precision in the estimates compared to *MR-Egger* analysis[29].

We evaluated heterogeneities between SNPs using *Cochran's Q statistics* and funnel plots[26]. Additionally, we conducted a "leave one out" analysis to explore whether the causal association was influenced by a single SNP. The analyses were conducted using the *TwoSampleMR*

package (version 0.4.25) and *MRPRESSO* (version 1.0) in R (version 4.1.3). The significance threshold was set at 0.05, with $p < 0.05$ considered statistically significant.

Results

Results of observational study

Our study comprised 10,432 individuals (Table 1 and eFigure1), with 2,394 experiencing troubles sleeping and 8,038 without (Table 1). The average age of the group without trouble sleeping was 46.63 years, significantly lower than that of the trouble sleeping group, which had an average age of 49.91 years ($P < 0.001$) (Table 1). The group without trouble sleeping had a higher proportion of male individuals (50.94%) compared to the trouble sleeping group (39.28%) (Table 1). The average blood glucose level in the group without trouble sleeping (5.83 mmol/L) was slightly lower than that in the trouble sleeping group (5.94 mmol/L, $P = 0.36$). Similarly, there were no significant differences between the groups without trouble sleeping and with trouble sleeping in terms of high-density lipoprotein cholesterol (1.38 mmol/L vs. 1.38 mmol/L, $P = 0.44$) and low-density lipoprotein cholesterol (2.98 mmol/L vs. 3.00 mmol/L, $P = 0.74$) (Table 1).

The odds ratios (OR) for HF were 2.91 (95% CI 1.58–5.38; $P = 0.001$) in the group with insomnia compared to the group without insomnia (eTable 1 and Figure 1). After full adjustment (model 3), the association between insomnia and HF remained significant, with an OR of 5.10 (1.81–14.33, $P = 0.003$) (eTable 1 and Figure 1). The odds ratio (OR) for HF was 3.81 (95% CI 2.96–4.90; $P < 0.001$) in the group with sleep disorder compared

to the group without sleep disorder (eTable 1 and Figure 1). After full adjustment (model 3), the association between sleep disorder and HF remained significant, with an OR of 3.51 (1.67–7.39; P = 0.002) (eTable 1 and Figure 1). The odds ratio for HF was 1.51 (95% CI 1.18–1.93; P = 0.002) in the group with trouble falling asleep compared to the group without trouble falling asleep (eTable 1 and Figure 1). After full adjustment (model 3), the association between trouble falling asleep and HF remained significant, with an OR of 1.55 (1.01–2.36; P = 0.04) (eTable 1 and Figure 1). The OR for HF was 2.21 (95% CI 1.77–2.76; P < 0.001) in the group with trouble sleeping compared to the group without Trouble sleeping (eTable 1 and Figure 1). After full adjustment (model 3), the association between trouble sleeping and HF remained significant, with an OR of 2.22 (1.49–3.30; P < 0.001) (eTable 1 and Figure 1). The odds ratio (OR) for HF was 1.49 (95% CI 1.14–1.95; P = 0.005) in the group with wakeup during night compared to the group without Wakeup during night (eTable 1 and Figure 1). However, after full adjustment (model 3), the association between wakeup during night and HF remained significant, with an OR of 1.47 (0.99–2.20; P = 0.06) (eTable 1 and Figure 1).

Result of Mendelian randomization study

25 SNPs identified in sleeplessness GWASs were chosen as instrumental variables (IVs). These SNPs are listed in eTable 2 and Figure 2. They

exhibit genome-wide significant associations with sleeplessness (eTable 2). All of these SNPs showed positive associations with HF (eTable 2).

The IVW method provided evidence supporting a causal association between sleeplessness and HF (OR = 1.535, SE = 0.177, P = 0.016) (Table 2 and Figure 2, 3). The intercept represents the average pleiotropic effect across the genetic variants, indicating the average direct effect of a variant on the outcome. If the intercept differs significantly from zero (as determined by the MR-Egger test), it suggests evidence of directional pleiotropy. MR-Egger regression analysis indicated that directional pleiotropy was unlikely to bias the results (intercept = -0.01; P = 0.107). MR-Egger analysis demonstrated a causal association between sleeplessness and HF (OR = 3.333, SE = 0.493, P = 0.023) (Table 2 and Figure 2, 3). Similarly, the weighted median approach provided evidence of a causal association between sleeplessness and HF (OR = 2.102, SE = 0.231, P = 0.001) (Table 2 and Figure 3). The association between sleeplessness and HF was consistent across the IVW, weighted median, weighted mode, and MR-Egger methods. The results of the MR analysis suggest a potential causal association between sleeplessness and an increased risk of HF.

The Cochran Q-test derived P-values for MR-Egger methods indicated no heterogeneity (Q = 32.63; P = 0.087), and in the absence of a significant intercept, no directional pleiotropy was observed (eFigure 2). Results

from a leave-one-out analysis demonstrated that only one single SNP (rs113851554) did not strongly violate the overall effect of sleeplessness on HF, while other single SNPs strongly violated the overall effect of sleeplessness on HF (Figure 4).

Key Findings

The OR for HF were as follows: 5.10 for insomnia, 3.51 for sleep disorder, 2.22 for trouble falling asleep, 2.22 for trouble sleeping, and 1.47 for waking up during the night. MR analysis using the IVW method provided evidence supporting a causal association between sleeplessness and HF, with an OR of 1.535.

Discussion

Our cross-sectional study found an association between sleep disturbances, including insomnia, sleep disorders, difficulty falling asleep, trouble sleeping, and waking up during the night and HF. Furthermore, MR studies have confirmed a causal relationship between insomnia and HF. Improving sleep disturbances may potentially reduce the risk of HF.

Sleep disturbances, characterized by difficulties initiating or maintaining sleep, non-restorative sleep, and early morning awakening, is a prevalent sleep disorder with significant implications for cardiovascular health. Previous research has indeed established a correlation between sleep disturbances and HF, which aligns with the conclusions of our study[30]. Epidemiological evidence indicates a reciprocal relationship between insomnia and HF, wherein each condition increases the risk of developing the other[31]. Sleep disturbance is a common comorbidity among individuals with HF, with prevalence rates reported to range from 30% to 70%[32, 33]. Individuals suffering from chronic insomnia are at an increased risk of developing HF, underscoring the bidirectional nature of this association[34]. Our study found a significant correlation between various sleep disorders, such as insomnia, difficulty falling asleep, trouble sleeping, waking up during the night, and HF. However, these findings cannot prove a causal relationship between insomnia and HF. We

conducted further research to investigate the causal relationship between insomnia and HF.

Our study, employing MR analysis, confirmed the causal relationship between insomnia and HF. One potential explanation for the observed phenomena is that disruptions in sleep patterns lead to changes in the growth hormone/insulin-like growth factor-1 (GH/IGF-1) pathway[14]. In the experimental environment, rats deprived of sleep exhibit decreased serum levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1)[35]. In humans, obstructive sleep apnea syndrome is correlated with diminished secretion of GH and insulin-like IGF-1[36]. Prior research has indicated that decreased serum concentrations of IGF-1 serve as a prognostic indicator for the likelihood of developing HF in the future[37]. Moreover, the occurrence of sleep disturbances may serve as a potential marker for depression, a known independent risk factor for HF in elderly individuals with hypertension[38].

An alternative explanation is that disruptions in sleep patterns may be associated with heightened inflammatory responses. Recent research has demonstrated elevated levels of C-reactive protein in individuals experiencing sleep deprivation[39]. Therefore, it is plausible that inflammation serves as a potential pathway through which sleep disruptions contribute to the development of HF, as elevated levels of

inflammatory markers have been shown to be predictive of the onset of HF[40, 41]. The complex pathophysiological mechanisms that connect insomnia and HF are diverse[42]. Sleep disturbances have been shown to disrupt the function of the autonomic nervous system, resulting in increased sympathetic activity, decreased parasympathetic activity, and changes in heart rate variability[43]. The aforementioned physiological alterations play a role in the development of endothelial dysfunction, systemic inflammation, oxidative stress, and neurohormonal dysregulation, ultimately leading to myocardial remodeling, ventricular dysfunction, and the advancement of HF[11]. These studies might elucidate the mechanisms underlying the causal association between insomnia and HF.

Our study confirms an association between sleep disorders and heart failure, with Mendelian randomization analysis establishing a causal relationship. Sleep disturbances may contribute to HF development through several pathophysiological mechanisms[31]: Dysregulation of the hypothalamic-pituitary-adrenal axis, leading to insulin resistance and diabetes onset[44]; Activation of the sympathetic nervous system, driven by increased cortisol and norepinephrine, leading to elevated resting heart rate, increased blood pressure, and altered heart rate variability[45]; Elevated secretion of pro-inflammatory cytokines, including C-reactive protein, tumor necrosis factor-α, and interleukin-6, which promote

atherosclerosis[11, 39, 46]; Impaired glucose tolerance and dyslipidemia. These mechanisms may account for our findings; however, further research is required to fully elucidate these mechanisms and their interconnections.

Our research indicates a significant association between sleep disturbances and heart failure, establishing a causal relationship between these conditions. Consequently, addressing sleep disturbances could be a crucial strategy in mitigating the incidence of heart failure. Evidence-based interventions, such as cognitive behavioral therapy for insomnia (CBT-I), pharmacological treatments like melatonin, and lifestyle modifications, may substantially reduce the risk of heart failure by targeting sleep disturbances[47-50]. When judiciously administered, pharmacological treatments can further facilitate sleep restoration while minimizing adverse effects[47]. Integrating sleep management into cardiovascular care, particularly for high-risk populations, is crucial for comprehensive disease prevention strategies[51]. The treatment of sleep disorders generally involves a comprehensive approach, with lifestyle interventions as the primary strategy, supported by medication when necessary[52].

Our findings suggest that sleep disturbances may significantly contribute to the development and progression of HF. We agree that it is crucial to focus on patients at risk of HF, particularly those with a history of acute

coronary syndromes or myocardial infarctions[53]. Excessive exercise is not recommended for these patients, as the anxiety caused by their condition may exacerbate sleep disturbances. In such cases, stronger interventions, such as medications, might be effective. We also recognize the importance of addressing sleep disturbances in individuals undergoing primary prevention. Early identification and management of sleep disturbances in these patients may help reduce the risk of developing HF later in life[54]. The prevention of atherosclerotic cardiovascular disease (ASCVD) primarily focuses on lifestyle modifications (e.g., exercise, smoking cessation) and managing risk factors (hypertension, diabetes, dyslipidemia)[55]. Incorporating sleep health into the primary prevention paradigm may offer a more comprehensive approach to cardiovascular health. Overall, for patients already at risk of HF, medications may be more effective for prevention[56]. In contrast, lifestyle interventions may be more effective for primary prevention of ASCVD[57].

Personalized management and intervention for sleep disorders could be an effective strategy to reduce the burden of heart failure. Incorporate sleep assessment and management into the prevention and treatment protocols for heart failure and other cardiovascular diseases. It is important to emphasize that excessive sleep duration may be harmful, as prolonged sleep may increase the risk of kidney damage, which in turn could elevate the risk of heart failure[58, 59]. Healthcare providers should

be encouraged to systematically evaluate and address patients' sleep health as an integral component of cardiovascular care.

Limitation

This study also encountered certain limitations. First, our observational study investigated the association between sleep disturbances, such as insomnia, and HF. The MR analysis primarily employed GWAS data on insomnia to examine the causal association between sleep disturbances and HF. However, these findings alone are adequate to establish both the correlation and potential causal link between sleep disturbances and HF. Second, the observational study primarily depended on self-reported data regarding sleep disturbances, potentially introducing reporting bias. Moreover, the observational study was confined to a single baseline evaluation of serum electrolytes. To mitigate these limitations, MR analysis was performed to supplement the findings of the observational study. Third, limitations of the observational study encompass residual confounding, time-varying confounding, unmeasured confounding, and potential selection bias. In the observational study, we adjusted for a comprehensive range of heart failure risk factors. Additionally, the MR study employed a randomization method that helped mitigate other potential confounding factors. Future experimental studies and cohort investigations are needed to enhance our understanding of the underlying

relationship between sleep disturbances and HF.

Conclusion

Our study identified an association between sleep disturbances, such as insomnia, sleep disorders, difficulty falling asleep, trouble sleeping, and nocturnal awakenings, and HF.

Additionally, MR studies have verified a causal link between insomnia and HF.

Addressing sleep disturbances could potentially lower the risk of developing HF.

Future longitudinal, randomized controlled, and interventional studies are necessary to validate the present findings.

Legend

Table 1 participants baseline information

Table 2 MR estimates from each method of the causal effect of sleeplessness on heart failure risk

Figure 1 OR (95% CI) of heart failure risk according to sleep disturbance status

Figure 2 Forest plot of the causal effects of sleeplessness associated SNPs on heart failure

Figure 3 Scatter plots of genetic associations comparing sleeplessness to the genetic associations with heart failure.

Figure 4 Leave-one-out analysis to investigate the possibility that the causal association was driven by a unique single-nucleotide polymorphism (SNP)

Supplementary appendix

eFigure 1 Flowchart of the inclusion procedure of patients

eTable1 OR (95% CI) of heart failure risk according to sleep disturbance status.

eTable 2 Instrumental SNPs from sleeplessness and GWAS of heart failure

eFigure 2 Funnel plot to assess heterogeneity

Author Contributions

Junwen Wang, Ziyi SUN and Yong PENG had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Junwen Wang, Ziyi Sun, Yi ZHONG, Yuyang YE, Xuefeng CHEN, Xinru HU and Yong Peng. Acquisition, analysis, or interpretation of data: Junwen Wan, Ziyi SUN, Xinru HU and Yong Peng. Rafting of the manuscript: Junwen Wang,Yi ZHONG and Yuyang YE. Critical revision of the manuscript for important: Yong Peng. Intellectual content: All authors. Administrative, technical, or material support: Junwen Wang, Ziyi SUN and Yong Peng.

Conflict of Interest Disclosures

No Potential Conflicts of Interest.

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Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics Approval

The Institutional Review Board of the National Center for Health Statistics approved this study.

Consent to Participate

Study protocols were ethically approved by the Institutional Review Board of the National Center for Health Statistics, and all participants provided written informed consent.

References

[1] G. Hao, X. Wang, Z. Chen, L. Zhang, Y. Zhang, B. Wei, C. Zheng, Y. Kang, L. Jiang, Z. Zhu, J. Zhang, Z. Wang, R. Gao, Prevalence of heart failure and left ventricular dysfunction in China: the China Hypertension Survey, 2012-2015, European journal of heart failure 21(11) (2019) 1329-1337.

[2] P. Ponikowski, S.D. Anker, K.F. AlHabib, M.R. Cowie, T.L. Force, S. Hu, T. Jaarsma, H. Krum, V. Rastogi, L.E. Rohde, U.C. Samal, H. Shimokawa, B. Budi Siswanto, K. Sliwa, G. Filippatos, Heart failure: preventing disease and death worldwide, ESC heart failure 1(1) (2014) 4-25.

[3] K.S. Shah, H. Xu, R.A. Matsouaka, D.L. Bhatt, P.A. Heidenreich, A.F. Hernandez, A.D. Devore, C.W. Yancy, G.C. Fonarow, Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes, Journal of the American College of Cardiology 70(20) (2017) 2476-2486.

[4] T.E. Owan, M.M. Redfield, Epidemiology of diastolic heart failure, Progress in cardiovascular diseases 47(5) (2005) 320-32.

[5] Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet (London, England) 392(10159) (2018) 1789-1858.

[6] P. van der Meer, H.K. Gaggin, G.W. Dec, ACC/AHA Versus ESC Guidelines on Heart Failure: JACC Guideline Comparison, Journal of the American College of Cardiology 73(21) (2019) 2756-2768.

[7] D. Hayes, Jr., M.I. Anstead, J. Ho, B.A. Phillips, Insomnia and chronic heart failure, Heart Fail Rev 14(3) (2009) 171-82.

[8] D. Riemann, C. Baglioni, C. Bassetti, B. Bjorvatn, L. Dolenc Groselj, J.G. Ellis, C.A. Espie, D. Garcia-Borreguero, M. Gjerstad, M. Goncalves, E. Hertenstein, M. Jansson-Frojmark, P.J. Jennum, D. Leger, C. Nissen, L. Parrino, T. Paunio, D. Pevernagie, J. Verbraecken, H.G. Weess, A. Wichniak, I. Zavalko, E.S. Arnardottir, O.C. Deleanu, B. Strazisar, M. Zoetmulder, K. Spiegelhalder, European guideline for the diagnosis and treatment of insomnia, J Sleep Res 26(6) (2017) 675-700.

[9] E. Hertenstein, B. Feige, T. Gmeiner, C. Kienzler, K. Spiegelhalder, A. Johann, M. Jansson-Frojmark, L. Palagini, G. Rucker, D. Riemann, C. Baglioni, Insomnia as a predictor of mental disorders: A systematic review and meta-analysis, Sleep Med Rev 43 (2019) 96-105.

[10] J. Fernandez-Mendoza, A.N. Vgontzas, D. Liao, M.L. Shaffer, A. Vela-Bueno, M. Basta, E.O. Bixler, Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort, Hypertension 60(4) (2012) 929-35.

[11] M.R. Costanzo, R. Khayat, P. Ponikowski, R. Augostini, C. Stellbrink, M. Mianulli, W.T. Abraham, Mechanisms and clinical consequences of untreated central sleep apnea in heart failure, Journal of the American College of Cardiology 65(1) (2015) 72-84.

[12] M. Berger, G. Solelhac, F. Roche, R. Heinzer, Insomnia, a new modifiable risk

factor for heart failure?, European heart journal 42(40) (2021) 4177-4179.
[13] L.E. Laugsand, L.B. Strand, C. Platou, L.J. Vatten, I. Janszky, Insomnia and the risk of incident heart failure: a population study, European heart journal 35(21) (2014) 1382-93.
[14] A. Mahmood, M. Ray, A. Dobalian, K.D. Ward, S. Ahn, Insomnia symptoms and incident heart failure: a population-based cohort study, European heart journal 42(40) (2021) 4169-4176.
[15] G.D. Smith, S. Ebrahim, 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease?, International journal of epidemiology 32(1) (2003) 1-22.
[16] G. Hemani, J. Zheng, B. Elsworth, K.H. Wade, V. Haberland, D. Baird, C. Laurin, S. Burgess, J. Bowden, R. Langdon, V.Y. Tan, J. Yarmolinsky, H.A. Shihab, N.J. Timpson, D.M. Evans, C. Relton, R.M. Martin, G. Davey Smith, T.R. Gaunt, P.C. Haycock, The MR-Base platform supports systematic causal inference across the human phenome, eLife 7 (2018).
[17] V.W. Skrivankova, R.C. Richmond, B.A.R. Woolf, N.M. Davies, S.A. Swanson, T.J. VanderWeele, N.J. Timpson, J.P.T. Higgins, N. Dimou, C. Langenberg, E.W. Loder, R.M. Golub, M. Egger, G. Davey Smith, J.B. Richards, Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): explanation and elaboration, BMJ (Clinical research ed.) 375 (2021) n2233.
[18] S. Ai, J. Zhang, G. Zhao, N. Wang, G. Li, H.C. So, Y. Liu, S.W. Chau, J. Chen, X. Tan, F. Jia, X. Tang, J. Shi, L. Lu, Y.K. Wing, Causal associations of short and long sleep durations with 12 cardiovascular diseases: linear and nonlinear Mendelian randomization analyses in UK Biobank, European heart journal 42(34) (2021) 3349-3357.
[19] I. Daghlas, H.S. Dashti, J. Lane, K.G. Aragam, M.K. Rutter, R. Saxena, C. Vetter, Sleep Duration and Myocardial Infarction, Journal of the American College of Cardiology 74(10) (2019) 1304-1314.
[20] L.Z. Liao, W.D. Li, Y. Liu, J.P. Li, X.D. Zhuang, X.X. Liao, Causal assessment of sleep on coronary heart disease, Sleep medicine 67 (2020) 232-236.
[21] W.M. Schultz, H.M. Kelli, J.C. Lisko, T. Varghese, J. Shen, P. Sandesara, A.A. Quyyumi, H.A. Taylor, M. Gulati, J.G. Harold, J.H. Mieres, K.C. Ferdinand, G.A. Mensah, L.S. Sperling, Socioeconomic Status and Cardiovascular Outcomes: Challenges and Interventions, Circulation 137(20) (2018) 2166-2178.
[22] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey, Jr., M.M. Colvin, M.H. Drazner, G. Filippatos, G.C. Fonarow, M.M. Givertz, S.M. Hollenberg, J. Lindenfeld, F.A. Masoudi, P.E. McBride, P.N. Peterson, L.W. Stevenson, C. Westlake, 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, Journal of the American College of Cardiology 68(13) (2016) 1476-1488.
[23] S. Shah, A. Henry, C. Roselli, H. Lin, G. Sveinbjörnsson, G. Fatemifar, K. Hedman Å, J.B. Wilk, M.P. Morley, M.D. Chaffin, A. Helgadottir, N. Verweij, A.

Dehghan, P. Almgren, C. Andersson, K.G. Aragam, J. Ärnlöv, J.D. Backman, M.L. Biggs, H.L. Bloom, J. Brandimarto, M.R. Brown, L. Buckbinder, D.J. Carey, D.I. Chasman, X. Chen, X. Chen, J. Chung, W. Chutkow, J.P. Cook, G.E. Delgado, S. Denaxas, A.S. Doney, M. Dörr, S.C. Dudley, M.E. Dunn, G. Engström, T. Esko, S.B. Felix, C. Finan, I. Ford, M. Ghanbari, S. Ghasemi, V. Giedraitis, F. Giulianini, J.S. Gottdiener, S. Gross, D.F. Guðbjartsson, R. Gutmann, C.M. Haggerty, P. van der Harst, C.L. Hyde, E. Ingelsson, J.W. Jukema, M. Kavousi, K.T. Khaw, M.E. Kleber, L. Køber, A. Koekemoer, C. Langenberg, L. Lind, C.M. Lindgren, B. London, L.A. Lotta, R.C. Lovering, J. Luan, P. Magnusson, A. Mahajan, K.B. Margulies, W. März, O. Melander, I.R. Mordi, T. Morgan, A.D. Morris, A.P. Morris, A.C. Morrison, M.W. Nagle, C.P. Nelson, A. Niessner, T. Niiranen, M.L. O'Donoghue, A.T. Owens, C.N.A. Palmer, H.M. Parry, M. Perola, E. Portilla-Fernandez, B.M. Psaty, K.M. Rice, P.M. Ridker, S.P.R. Romaine, J.I. Rotter, P. Salo, V. Salomaa, J. van Setten, A.A. Shalaby, D.T. Smelser, N.L. Smith, S. Stender, D.J. Stott, P. Svensson, M.L. Tammesoo, K.D. Taylor, M. Teder-Laving, A. Teumer, G. Thorgeirsson, U. Thorsteinsdottir, C. Torp-Pedersen, S. Trompet, B. Tyl, A.G. Uitterlinden, A. Veluchamy, U. Völker, A.A. Voors, X. Wang, N.J. Wareham, D. Waterworth, P.E. Weeke, R. Weiss, K.L. Wiggins, H. Xing, L.M. Yerges-Armstrong, B. Yu, F. Zannad, J.H. Zhao, H. Hemingway, N.J. Samani, J.J.V. McMurray, J. Yang, P.M. Visscher, C. Newton-Cheh, A. Malarstig, H. Holm, S.A. Lubitz, N. Sattar, M.V. Holmes, T.P. Cappola, F.W. Asselbergs, A.D. Hingorani, K. Kuchenbaecker, P.T. Ellinor, C.C. Lang, K. Stefansson, J.G. Smith, R.S. Vasan, D.I. Swerdlow, R.T. Lumbers, Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure, Nature communications 11(1) (2020) 163.

[24] S. Burgess, A. Butterworth, S.G. Thompson, Mendelian randomization analysis with multiple genetic variants using summarized data, Genetic epidemiology 37(7) (2013) 658-65.

[25] F.P. Hartwig, N.M. Davies, G. Hemani, G. Davey Smith, Two-sample Mendelian randomization: avoiding the downsides of a powerful, widely applicable but potentially fallible technique, International journal of epidemiology 45(6) (2016) 1717-1726.

[26] M. Egger, G.D. Smith, A.N. Phillips, Meta-analysis: principles and procedures, BMJ (Clinical research ed.) 315(7121) (1997) 1533-7.

[27] J. Bowden, G. Davey Smith, S. Burgess, Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression, International journal of epidemiology 44(2) (2015) 512-25.

[28] S. Burgess, S.G. Thompson, Erratum to: Interpreting findings from Mendelian randomization using the MR-Egger method, European journal of epidemiology 32(5) (2017) 391-392.

[29] J. Bowden, G. Davey Smith, P.C. Haycock, S. Burgess, Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator, Genetic epidemiology 40(4) (2016) 304-14.

[30] E. Ingelsson, L. Lind, J. Arnlöv, J. Sundström, Sleep disturbances independently predict heart failure in overweight middle-aged men, European journal

of heart failure 9(2) (2007) 184-90.
[31] S. Javaheri, S. Redline, Insomnia and Risk of Cardiovascular Disease, Chest 152(2) (2017) 435-444.
[32] F. Sofi, F. Cesari, A. Casini, C. Macchi, R. Abbate, G.F. Gensini, Insomnia and risk of cardiovascular disease: a meta-analysis, European journal of preventive cardiology 21(1) (2014) 57-64.
[33] L. Mallon, J.E. Broman, J. Hetta, High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population, Diabetes care 28(11) (2005) 2762-7.
[34] L. Mallon, J.E. Broman, J. Hetta, Sleep complaints predict coronary artery disease mortality in males: a 12-year follow-up study of a middle-aged Swedish population, Journal of internal medicine 251(3) (2002) 207-16.
[35] C.A. Everson, W.R. Crowley, Reductions in circulating anabolic hormones induced by sustained sleep deprivation in rats, American journal of physiology. Endocrinology and metabolism 286(6) (2004) E1060-70.
[36] L. Gianotti, S. Pivetti, F. Lanfranco, F. Tassone, F. Navone, E. Vittori, R. Rossetto, C. Gauna, S. Destefanis, S. Grottoli, R. De Giorgi, V. Gai, E. Ghigo, M. Maccario, Concomitant impairment of growth hormone secretion and peripheral sensitivity in obese patients with obstructive sleep apnea syndrome, The Journal of clinical endocrinology and metabolism 87(11) (2002) 5052-7.
[37] R.S. Vasan, L.M. Sullivan, R.B. D'Agostino, R. Roubenoff, T. Harris, D.B. Sawyer, D. Levy, P.W. Wilson, Serum insulin-like growth factor I and risk for heart failure in elderly individuals without a previous myocardial infarction: the Framingham Heart Study, Annals of internal medicine 139(8) (2003) 642-8.
[38] J. Abramson, A. Berger, H.M. Krumholz, V. Vaccarino, Depression and risk of heart failure among older persons with isolated systolic hypertension, Archives of internal medicine 161(14) (2001) 1725-30.
[39] H.K. Meier-Ewert, P.M. Ridker, N. Rifai, M.M. Regan, N.J. Price, D.F. Dinges, J.M. Mullington, Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk, Journal of the American College of Cardiology 43(4) (2004) 678-83.
[40] R.S. Vasan, L.M. Sullivan, R. Roubenoff, C.A. Dinarello, T. Harris, E.J. Benjamin, D.B. Sawyer, D. Levy, P.W. Wilson, R.B. D'Agostino, Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study, Circulation 107(11) (2003) 1486-91.
[41] M. Cesari, B.W. Penninx, A.B. Newman, S.B. Kritchevsky, B.J. Nicklas, K. Sutton-Tyrrell, S.M. Rubin, J. Ding, E.M. Simonsick, T.B. Harris, M. Pahor, Inflammatory markers and onset of cardiovascular events: results from the Health ABC study, Circulation 108(19) (2003) 2317-22.
[42] L.E. Laugsand, L.J. Vatten, C. Platou, I. Janszky, Insomnia and the risk of acute myocardial infarction: a population study, Circulation 124(19) (2011) 2073-81.
[43] N. Makarem, C. Alcántara, N. Williams, N.A. Bello, M. Abdalla, Effect of Sleep Disturbances on Blood Pressure, Hypertension (Dallas, Tex. : 1979) 77(4) (2021) 1036-1046.

[44] A.N. Vgontzas, D. Liao, S. Pejovic, S. Calhoun, M. Karataraki, E.O. Bixler, Insomnia with objective short sleep duration is associated with type 2 diabetes: A population-based study, Diabetes care 32(11) (2009) 1980-5.
[45] J.K. Johansson, E. Kronholm, A.M. Jula, Variability in home-measured blood pressure and heart rate: associations with self-reported insomnia and sleep duration, Journal of hypertension 29(10) (2011) 1897-905.
[46] S.R. Patel, X. Zhu, A. Storfer-Isser, R. Mehra, N.S. Jenny, R. Tracy, S. Redline, Sleep duration and biomarkers of inflammation, Sleep 32(2) (2009) 200-4.
[47] C.A. Espie, S.D. Kyle, P. Hames, E. Cyhlarova, M. Benzeval, The daytime impact of DSM-5 insomnia disorder: comparative analysis of insomnia subtypes from the Great British Sleep Survey, The Journal of clinical psychiatry 73(12) (2012) e1478-84.
[48] M.J. Sateia, D.J. Buysse, A.D. Krystal, D.N. Neubauer, J.L. Heald, Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline, Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 13(2) (2017) 307-349.
[49] E. Ferracioli-Oda, A. Qawasmi, M.H. Bloch, Meta-analysis: melatonin for the treatment of primary sleep disorders, PloS one 8(5) (2013) e63773.
[50] L. Shilo, Y. Dagan, Y. Smorjik, U. Weinberg, S. Dolev, B. Komptel, H. Balaum, L. Shenkman, Patients in the Intensive Care Unit Suffer from Severe Lack of Sleep A ssociated with Loss of Normal Melatonin Secretion Pattern, The American Journal of the Medical Sciences 317(5) 278.
[51] J.D. Edinger, J. Grubber, C. Ulmer, J. Zervakis, M. Olsen, A Collaborative Paradigm for Improving Management of Sleep Disorders in Primary Care: A Randomized Clinical Trial, Sleep 39(1) (2016) 237-47.
[52] M. Firmann, V. Mayor, P.M. Vidal, M. Bochud, A. Pécoud, D. Hayoz, F. Paccaud, M. Preisig, K.S. Song, X. Yuan, T.M. Danoff, H.A. Stirnadel, D. Waterworth, V. Mooser, G. Waeber, P. Vollenweider, The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome, BMC cardiovascular disorders 8 (2008) 6.
[53] M.T. Madsen, C. Huang, G. Zangger, A.D.O. Zwisler, I. Gögenur, Sleep Disturbances in Patients With Coronary Heart Disease: A Systematic Review, Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 15(3) (2019) 489-504.
[54] M.S. Khan, R. Aouad, The Effects of Insomnia and Sleep Loss on Cardiovascular Disease, Sleep medicine clinics 17(2) (2022) 193-203.
[55] J. Jeras, S. Ugovšek, A. Rehberger Likozar, M. Šebeštjen, Atherosclerotic Cardiovascular Disease: Risk Assessment, Prevention and Treatment Strategies, Journal of cardiovascular development and disease 9(12) (2022).
[56] F.D. Martinez, M. Kraft, AJRCCM: 100-Year Anniversary. Focus on Asthma in Children and Adults, American journal of respiratory and critical care medicine 195(9) (2017) 1085-1088.
[57] M. Endres, P.U. Heuschmann, U. Laufs, A.M. Hakim, Primary prevention of stroke:

blood pressure, lipids, and heart failure, European heart journal 32(5) (2011) 545-52.
[58] M. Mazidi, N. Shekoohi, N. Katsiki, M. Banach, Longer sleep duration may negatively affect renal function, International urology and nephrology 53(2) (2021) 325-332.
[59] Y. Qin, R. Liu, Y. Wang, J. Tang, L. Cong, J. Ren, S. Tang, Y. Du, Self-Reported Sleep Characteristics Associated with Cardiovascular Disease Among Older Adults Living in Rural Eastern China: A Population-Based Study, Clinical interventions in aging 17 (2022) 811-824.

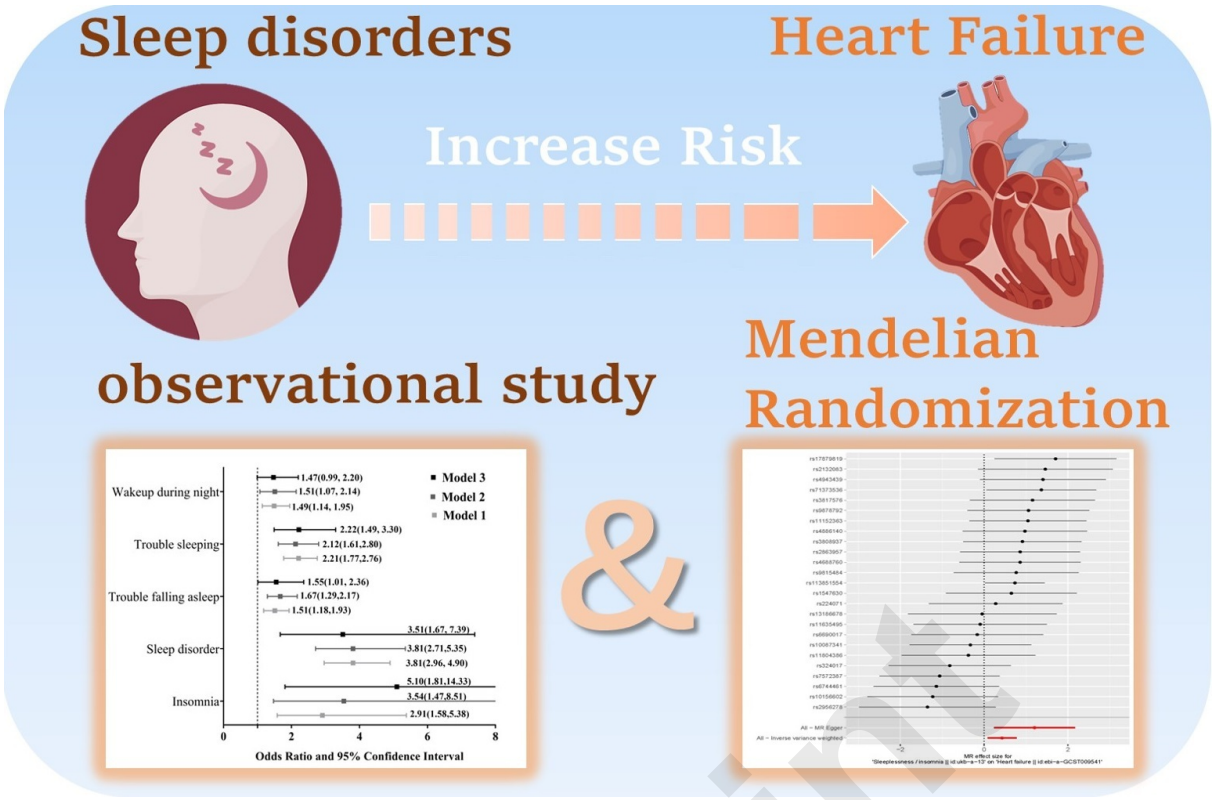
Sleep disorders
Heart Failure
Increase Risk
observational study
Mendelian Randomization
Wakeup during night
Trouble sleeping
Trouble falling asleep
Sleep disorder
Insomnia
1.47(0.99, 2.20)
1.51(1.07, 2.14)
1.49(1.14, 1.95)
2.22(1.49, 3.30)
2.12(1.61,2.80)
2.21(1.77,2.76)
1.55(1.01, 2.36)
1.67(1.29,2.17)
1.51(1.18,1.93)
3.51(1.67, 7.39)
3.81(2.71,5.35)
3.81(2.96, 4.90)
5.10(1.81,14.33)
3.54(1.47,8.51)
2.91(1.58,5.38)
Model 3
Model 2
Model 1
0
2
4
6
8
Odds Ratio and 95% Confidence Interval
&

Table 1 participants baseline information

Variable	Total (N=10432)	Non trouble sleeping (N=8038)	Trouble sleeping (N=2394)	P value
Age, years	46.63(0.42)	45.58(0.46)	49.91(0.45)	< 0.001
Poverty income ratio	3.06(0.06)	3.06(0.06)	3.08(0.07)	0.6
Fast Glucose, mmol/L	5.86(0.04)	5.83(0.04)	5.94(0.05)	0.04
HbA1c	5.52(0.02)	5.49(0.02)	5.61(0.03)	< 0.001
Creatinine, umol/L	79.59(0.45)	79.59(0.52)	79.58(0.59)	1
Uric acid, umol/L	322.93(1.36)	322.50(1.39)	324.25(2.84)	0.56
Iron, umol/L	15.61(0.13)	15.73(0.13)	15.22(0.23)	0.02
HDL cholesterol, mmol/L	1.38(0.01)	1.38(0.01)	1.38(0.01)	0.44
LDL cholesterol, mmol/L	2.99(0.02)	2.98(0.02)	3.00(0.05)	0.74
BMI, kg/m^2	28.55(0.14)	28.22(0.16)	29.57(0.16)	< 0.001
SBP, mmHg	121.65(0.29)	121.37(0.30)	122.52(0.37)	0.001
DBP, mmHg	70.58(0.24)	70.26(0.26)	71.58(0.37)	0.001
Sex				< 0.001
Female	5383(51.90)	3957(49.06)	1426(60.72)	
Male	5049(48.10)	4081(50.94)	968(39.28)	
Heart attack				< 0.001
no	9934(96.39)	7729(97.17)	2205(94.36)	
yes	486(3.51)	301(2.83)	185(5.64)	
Smoke				< 0.001
former	2614(24.42)	1924(23.32)	690(27.88)	
never	5502(52.15)	4420(54.16)	1082(46.05)	
now	2308(23.37)	1686(22.52)	622(26.07)	
DM				< 0.001
no	8270(86.11)	6476(88.79)	1794(83.31)	
yes	1778(12.37)	1232(11.21)	546(16.69)	
Stroke				< 0.001
no	9971(96.70)	7761(97.56)	2210(94.71)	
yes	441(3.13)	267(2.44)	174(5.29)	
Angina				< 0.001
no	10107(97.53)	7850(98.28)	2257(96.00)	
yes	301(2.27)	173(1.72)	128(4.00)	
Hyperlipidemia				< 0.001
no	3149(30.88)	2518(32.19)	631(26.85)	
yes	7281(69.10)	5518(67.81)	1763(73.15)	

HbA1C, Glycated Hemoglobin; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus

Table 2 MR estimates from each method of the causal effect of sleeplessness on heart failure risk

MR Method	Number of SNPs	OR	SE	Association P value
MR Egger	25	3.333	0.493	0.023
Weighted median	25	2.102	0.231	0.001
Inverse variance weighted	25	1.535	0.177	0.016
Weighted mode	25	2.458	0.301	0.006

MR Mendelian randomization, SNP single-nucleotide polymorphism, OR, odds ratio, SE standard error

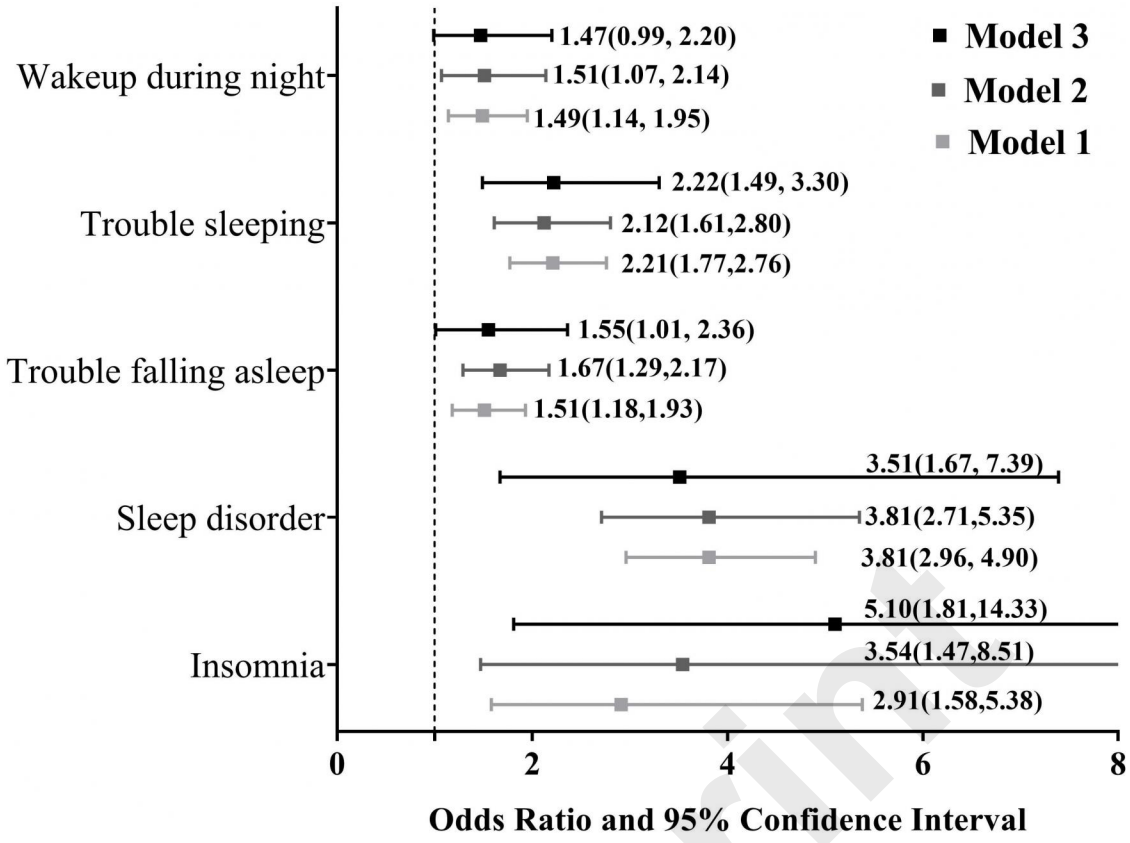

Figure 1 OR (95% CI) of heart failure risk according to sleep disturbance status

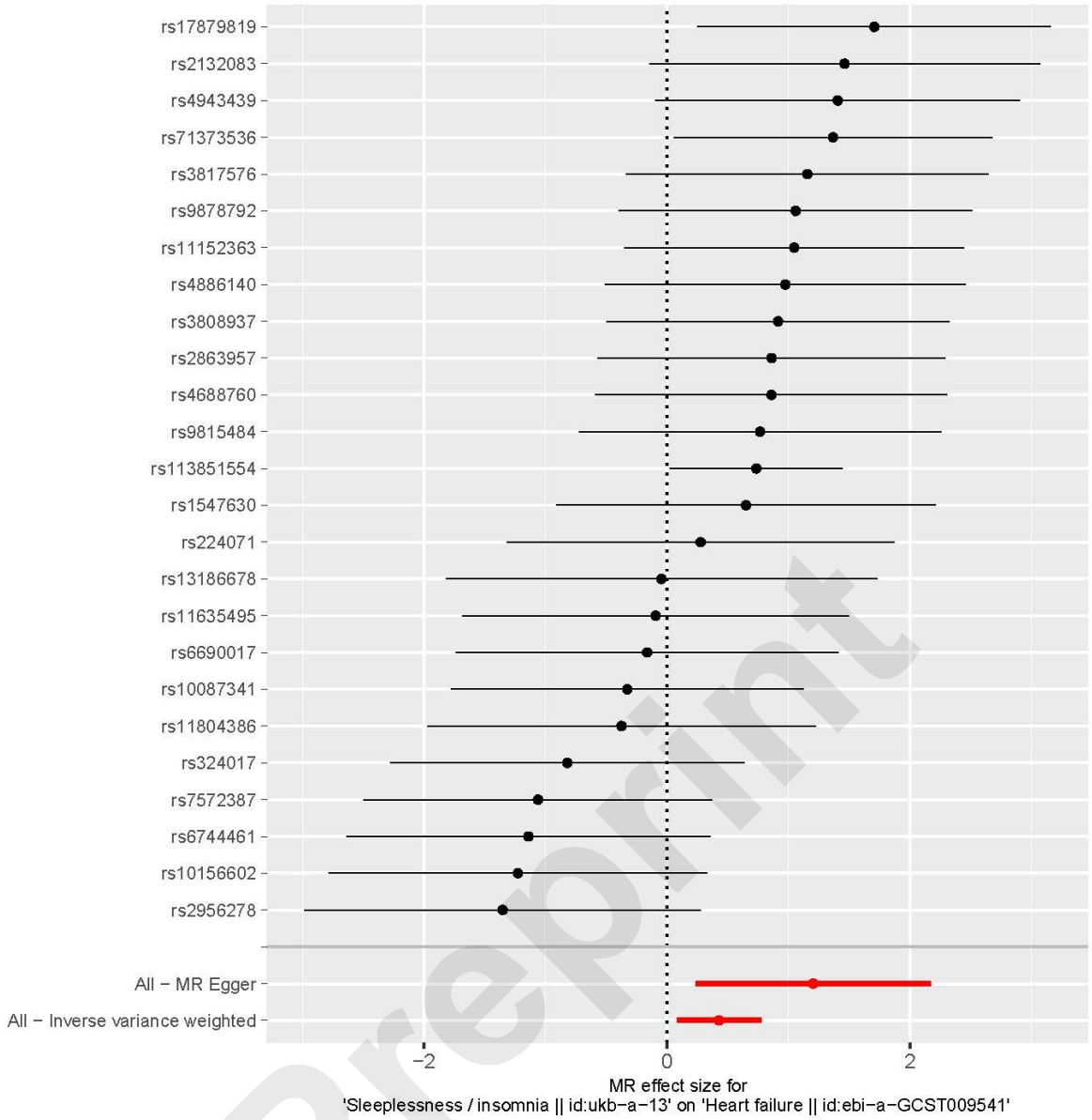

Figure 2 Forest plot of the causal effects of sleeplessness associated SNPs on heart failure

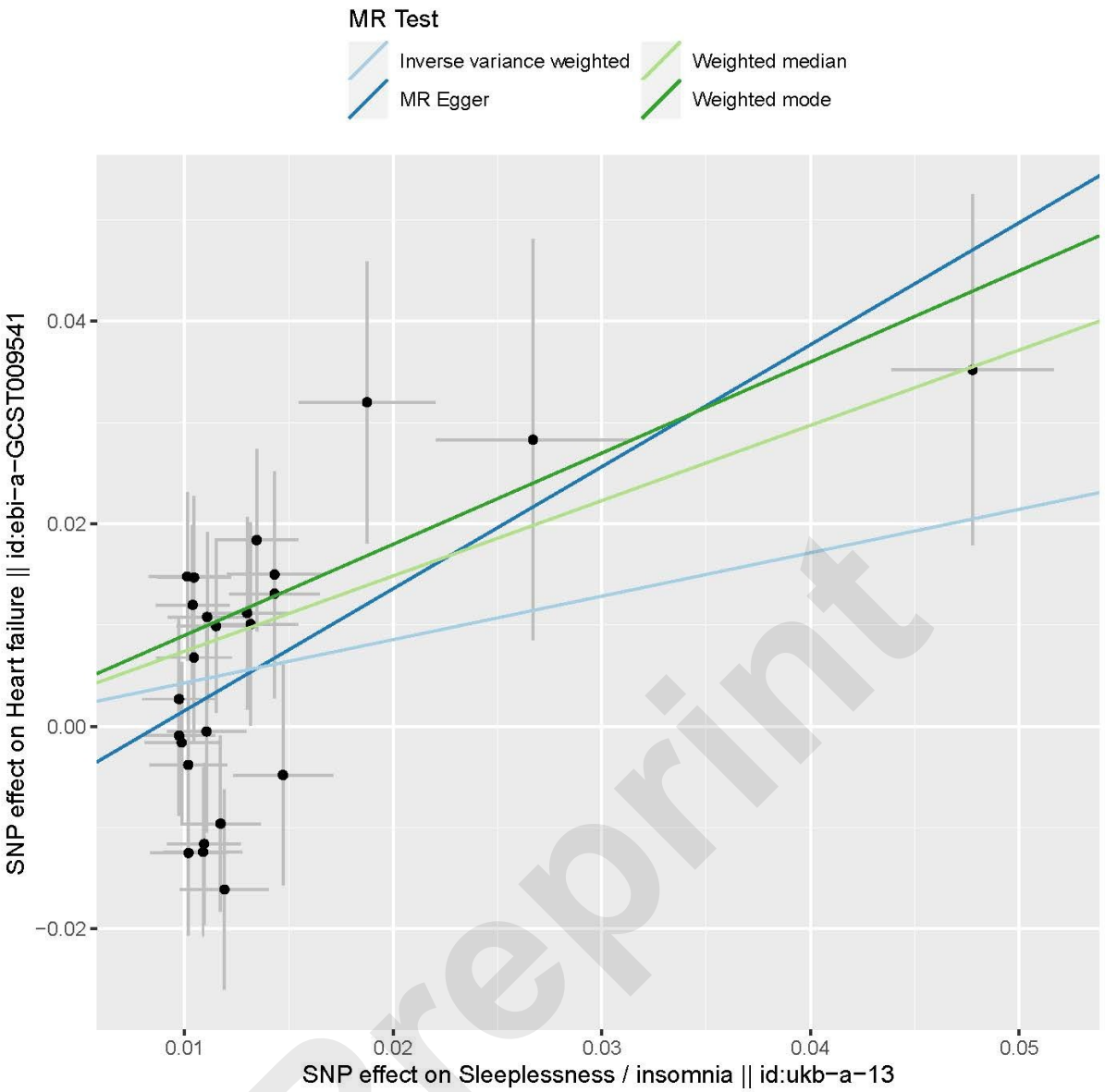

Figure 3 Scatter plots of genetic associations comparing sleeplessness to the genetic associations with heart failure.

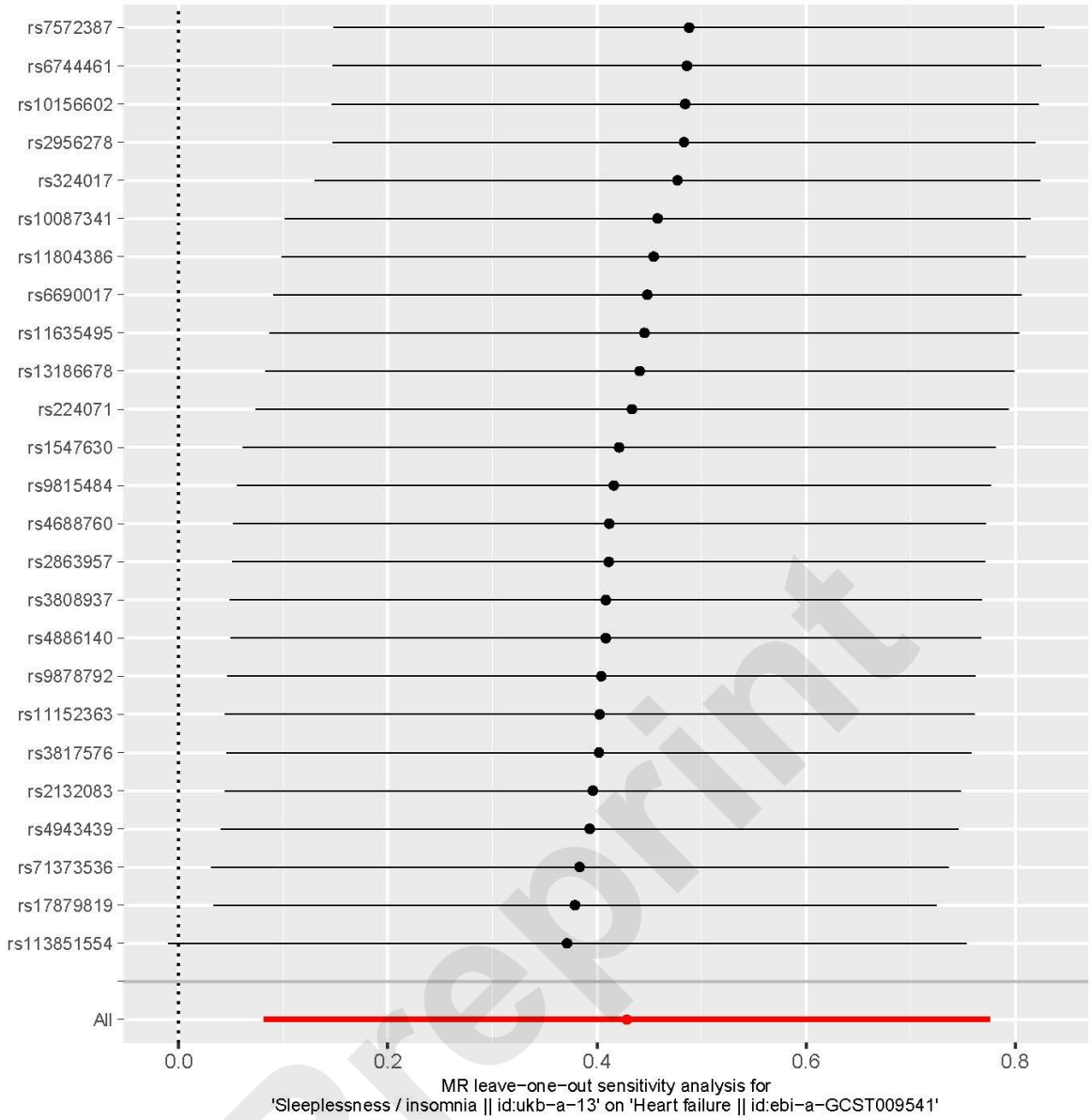

Figure 4 Leave-one-out analysis to investigate the possibility that the causal association was driven by a unique single-nucleotide polymorphism (SNP)