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ORIGINAL RESEARCH

Causal Effects of Sleep Traits on Angina Pectoris: Mediation by Cardiovascular Risk Factors

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Purpose: Angina pectoris (AP) is a major factor in heightened risk of cardiac arrest and has been previously linked to sleep patterns. It remains unclear if sleep traits play a role in the onset of AP. Our study aims to declare the causality of sleep traits on AP by Mendelian randomization (MR) analyses.

Methods: Genome-wide association study (GWAS) data of sleep traits (sleep duration, insomnia, nap during day, chronotype, getting up in morning, narcolepsy, snoring) were obtained from the UK Biobank. The AP datasets came from an analysis containing samples from the UK biobank, FinnGen, and BioBank Japan. The GWAS data of cardiovascular risk factors (hypertension, smoking, hyperlipidemia, type 2 diabetes mellitus (T2DM)) came from the FinnGen. Two-sample MR analyses were carried out to gain a general map of sleep traits, risk factors and AP, then a multivariable MR was performed and the effect of each factor was calculated.

Results: We discovered a positive association between nap, narcolepsy, insomnia and stable angina pectoris (SAP), while getting up in morning associated with SAP negatively. Adequate sleep duration related to a reduced risk of SAP and unstable angina pectoris (UAP). Hypertension and T2DM acted as complete mediators in the relationship of nap and SAP, with an effect value of 1.267 (95% CI = 1.178–1.363, $P < 0.01$) and 1.059 (95% CI = 1.000–1.120, $P < 0.05$), and the mediating proportion was 27.7% ($P < 0.05$) and 7.70% ($P = 0.102$).

Conclusion: Our study found that nap, narcolepsy, and insomnia increased the risk of SAP, with hypertension and T2DM mediating the causal relationship between nap and SAP. Getting up in the morning reduced the risk of SAP, while longer sleep duration lowered the risk of SAP and UAP. More evidences are required to clarify the roles of sleep traits and risk factors in AP.

Keywords: sleep traits, angina pectoris, hypertension, Mendelian randomization, mediation

Introduction

Angina pectoris (AP) is a clinical syndrome caused by transient myocardial hypoxia and ischemia resulting from inadequate blood supply in the coronary arteries. It impacts millions of individuals each year and represents a major issue for global health organizations.[1] In addition to causing direct pain and discomfort, AP often indicates a notable risk of cardiovascular disease (CVD).[2] There are many risk factors for the development of angina, including inflammation related factors, hypertension, diabetes, high cholesterol and family history of heart disease, and sleep is also one of the important factors.[3–5] In addition, individuals with conditions such as high blood pressure, diabetes, high cholesterol, and a family history of heart disease are at a greater risk of developing AP.[4,6] A survey of 30,397 participants showed a 2.59-fold increased risk of angina in those who slept ≤5 hours and an 1.13-fold increased risk of angina in those who slept ≥9 hours compared to 7 hours of sleep.[7] Another research study demonstrated a 96% higher risk of AP associated with sleep problems and a 53% higher risk linked to daytime sleepiness.[8] Furthermore, Li B et al discovered a significant connection between later bedtimes on both weekdays and weekends and a higher prevalence of AP.[9] Decreased or fragmented sleep activates sympathetic nerves and increases cardiac oxygen consumption, while snoring also causes lack of oxygen.[10,11] Irregular sleep duration is associated with higher risk of hypertension.[12] Sleep duration, sleep quality and sleep disorders are closely related to arteriosclerosis and autonomic nervous dysfunction, therefore they also interact with hypertension and other risk factors.[13] However, it was noted that in hypertensive populations, sleep duration and efficiency may not have an impact on AP attacks.[14] In summary, better sleep quality has been associated with

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a reduced risk of myocardial infarction, angina pectoris, stroke, heart failure, and ventricular fibrillation.[15] Recent research suggested that monocytes were recruited to the brain after myocardial infarction to augment sleep, which limits inflammation and promoted healing by suppressing sympathetic outflow to the heart.[16]

Recently, Mendelian randomization (MR) has emerged as a powerful tool in epidemiology and human biology, utilizing genetic variation as an instrumental variant (IV) to determine causal relationships between risk factors and health outcomes.[17,18] Furthermore, various MR analyses have demonstrated causal relationships between different sleep traits and the development of cardiometabolic diseases, autoimmune disorders, psychiatric disorders, and tumors.[19–23] However, current studies did not examine the causal relationship between sleep traits and AP in regard of inaccurate measurement of sleep, complexity of sleep disorders and sleep patterns, difference of research results, and insufficient evidences, while our study aims to fill this gap. Utilizing data from large cohorts of European and Asian populations, we investigate the process and mechanism through which sleep traits influence AP, including the analysis of multivariate mediating cardiovascular risk factors.

Methods

Data Sources

All of the data were from public datasets. The detail of GWAS data was listed in Table 1.

Data Sources for Traits of Sleep

The genome-wide association study (GWAS) summary data for traits of sleep were obtained from meta-analyses conducted by MRC-IEU and Neale Lab for European participants, and Pan-UKB team for East Asian participants (https://gwas.mrcieu.ac.uk/). All of the GWAS information came from the UK biobank touch-screen questionnaire

Table 1 Characters of Sleep Traits and Angina Pectoris

Traits	ID	Consortium	Sample size	n case	n control	Population	Year
Exposure							
Sleep duration	ukb-b-4424	MRC-IEU	460,099			European	2018
Sleeplessness/Insomnia	ukb-b-3957	MRC-IEU	462,341			European	2018
Nap during day	ukb-a-12	Neale Lab	337,074			European	2017
Morning/evening person (chronotype)	ukb-b-4956	MRC-IEU	413,343			European	2018
Getting up in morning	ukb-b-2772	MRC-IEU	461,658			European	2018
Daytime dozing/sleeping (narcolepsy)	ukb-a-15	Neale Lab	336,082			European	2017
Snoring	ukb-b-17400	MRC-IEU	430,438			European	2018
Sleep duration	ukb-e-1160_EAS	NA	2,631			East Asian	2020
Sleeplessness/Insomnia	ukb-e-1200_EAS	NA	2,654			East Asian	2020
Nap during day	ukb-e-1190_EAS	NA	2,606			East Asian	2020
Morning/evening person (chronotype)	ukb-e-1180_EAS	NA	2,343			East Asian	2020
Getting up in morning	ukb-e-1170_EAS	NA	2,640			East Asian	2020
Daytime dozing/sleeping (narcolepsy)	ukb-e-1220_EAS	NA	2,582			East Asian	2020
Snoring	ukb-e-1210_EAS	NA	2,348			East Asian	2020
Outcome							
Unstable angina pectoris	ebi-a-GCST90018932	NA	456,468	9,481	446,987	European	2021
Stable angina pectoris	ebi-a-GCST90018915	NA	343,026	17,894	325,132	European	2021
Unstable angina pectoris	ebi-a-GCST90018712	NA	152,105	5,891	146,214	East Asian	2021
Stable angina pectoris	ebi-a-GCST90018695	NA	165,047	18,833	146,214	East Asian	2021
Mediator							
Hypertension	finn-b-I9_HYPTENS	NA	218754	55,917	162,837	European	2021
Smoking	finn-b-SMOKING	NA	138088	1,321	136,767	European	2021
Mixed hyperlipidemia	finn-b-E4_HYPERLIPMIX	NA	197772	513	197,259	European	2021
Type 2 diabetes mellitus	finn-b-T2D	NA	211766	29,193	182,573	European	2021

completed at the Assessment Center on lifestyle and personal exposures. In the category of sleep, all participants were asked to answer questions about their duration of sleep, ease of getting up in morning, and associated information of napping, dozing, snoring, sleeplessness, and chronotype. The assessment of sleep characteristics was based on the participants' general habits. If these vary a lot, they were told to answer questions in relation to the last 4 weeks. The detailed description of these traits can be found at the website (https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100057).

Data Sources for Traits of Angina Pectoris

The stable angina pectoris (SAP) and unstable angina pectoris (UAP) datasets were obtained from a GWAS analysis of 220 human phenotypes,[24] containing samples from UK biobank, FinnGen, and BioBank Japan. The diagnoses of SAP and UAP were based on ICD-10. The Europe population consist of 17894 cases and 325132 controls for SAP, and 9481 cases and 446987 controls for UAP. The East Asia cohort consists of 18833 cases and 146214 controls for SAP and 5891 cases and 146214 controls for UAP (https://humandbs.dbcls.jp/en/hum0197-v3-220).

Data Sources for Traits of Cardiovascular Risk Factors

To reveal the effect of confounders on AP, MR analysis was performed to estimate the association between sleep traits and some well-accepted cardiovascular risk factors, including hypertension, diabetes, hyperlipidemia, and smoking.[25] The GWAS data of these risk factors came from the FinnGen (https://r10.finngen.fi/).

Statistical Analysis

We conducted MR analysis with TwoSample MR package (version 0.5.10), ieugwasr package (version 0.1.8), MendelianRadomization package (version 0.9.0), and a two-step multivariable Mendelian randomization (MVMR) package (version 0.4). The workflow was shown in Figure 1A.

Two Sample MR Analysis

Exposure related single-nucleotide polymorphisms (SNPs) were used as instrumental variants in MR study. We selected IVs by setting p-value of SNPs, then clumped the SNPs in linkage disequilibrium (LD). By calculating F-statistics, strong IVs were reserved. We harmonized SNPs of exposure and outcome. For these IVs, we firstly conducted MR PRESSO analysis to exclude significant outliers, then the rest IVs were used for MR analysis with methods of Inversed variance weighted (IVW), MR Egger regression, weighted median, weighted mode, and simple mode. Then sensitivity analysis was performed, including heterogeneity test by Cochrane's Q test, horizontal pleiotropy test, and leave one out test. For the result with heterogeneity, we chose the random-effect model IVW for MR analysis. MR PRESSO is a widely accepted method to test the horizontal pleiotropy. MR-PRESSO global test detects the existence of horizontal pleiotropy,

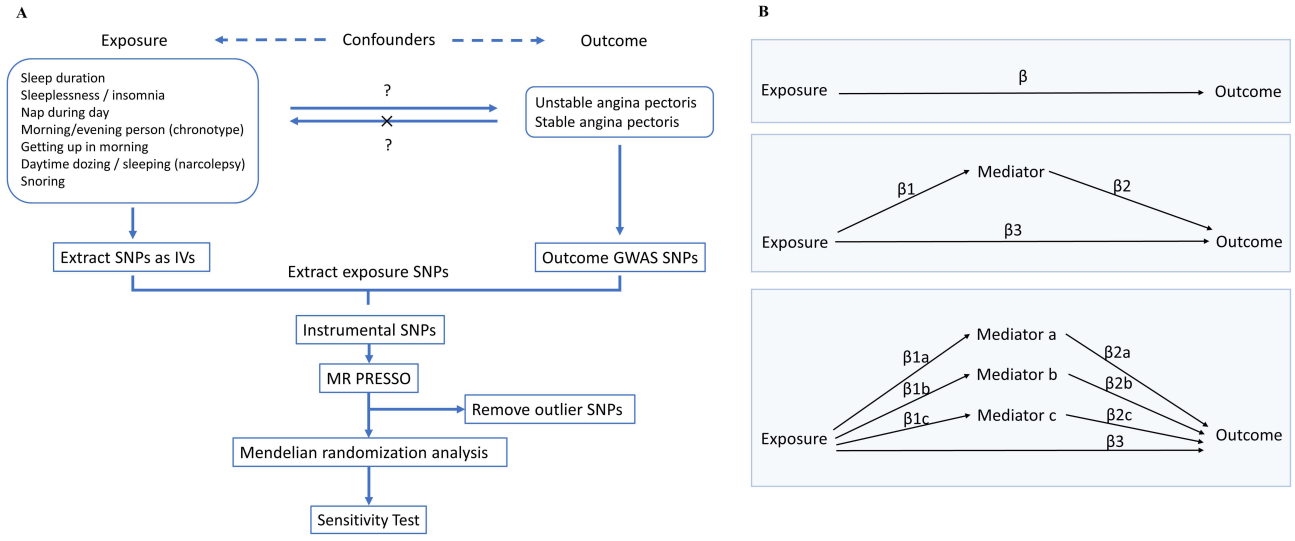

Figure 1 Flow chart of the study design for the Mendelian randomization study. (**A**) Flow chart of Mendelian randomization, (**B**) Calculation of intermediate effect values.

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MR-PRESSO outlier test removes abnormal SNPs (ie outliers) and estimates the result after correction, which removes horizontal pleiotropy. MR-PRESSO distortion test is used to verify if there is a difference between the result before and after correction.

In addition, we analyzed the statistical power of SNPs (https://shiny.cnsgenomics.com/mRnd/). We also performed reverse MR analysis by extracting SNPs of SAP and UAP and chose sleep traits as outcome to exclude reverse causality.

Multivariable Mendelian Randomization

We considered risk factors of AP as exposure to explore the confounding effect of them in the causal relationship between sleep characteristics and AP. After determining the causal relationship between risk factors and AP, we treated risk factors as mediators and performed a two-step MVMR analysis. First, we performed a two-sample MR of exposure to the mediators. Then we chose exposures and mediators with significant outcome to conduct an MVMR using MVMR package. Variables were adjusted to obtain a separate effect of one exposure/mediator on the outcome. Random effect Multivariable IVW, Multivariable MR-Egger, and Multivariable median were chosen as MR methods. In addition, we used LASSO regression to remove factors with high collinearity. Finally, heterogeneity test, and Cochrane's Q test were used for pleiotropy analysis.

Parameter Setting and Calculation

Instrument Variants Selection Criteria

To perform MR analysis, exposure and SNPs must have a strong association. In European population, we chose the P-value as 5×10^{-8}, while in East Asian population and mediators such as smoking and hyperlipidemia, the P-value was 1×10^{-5} as lower P-value may lead to fewer SNPs, which may lead to lower statistical power. As for LD, we chose kb = 10000, $r^2 = 0.001$ as the threshold. As number of SNPs were all over 10, F-value was calculated as $F = \left(\frac{N-K-1}{K}\right) * \left(\frac{R^2}{1-R^2}\right)$, while $R^2 = \frac{2*eaf*(1-eaf)*\beta^2}{2*eaf*(1-eaf)*\beta^2+2*eaf*(1-eaf)*se^2*N}$, to screen out strongly related IVs. Eaf, beta, and se are corresponding values of each SNP of exposure. N represents the sample size of exposure, while the K means the number of SNPs, and for each SNP, K equals 1. The SNPs with F-value over 10 were regarded as strong IVs.

The second assumption was there should be no association between SNPs and outcome except for through the exposure. After harmonized the IVs and outcome GWAS, we screened the p-value of SNPs in the outcome GWAS and excluded SNPs associated with outcome.

The third assumption was that SNPs should not be associated with confounding factors. In this study, we performed multivariable MR to analyze the influence of confounders on exposure to outcomes.

Calculation of Statistical Power

The statistical power of SNPs was evaluated by power and sample size. The power was calculated using the sample size of outcome, the proportion of case, the odds ratio of IVW method, and the sum of R^2 for each SNP. If the power is greater than 0.8, the significance of the results is considered acceptable. The statistical power can also be evaluated by sample size. Setting the power at 0.8, if the calculated needed sample size is smaller than the actual sample size, the result is acceptable.

Calculation of Intermediate Effect Values

In the two-sample MR, β means the total effect value of exposure on outcome, while β1 is the effect of exposure on mediators, S1 is the standard error of exposure on mediators. In the MVMR analysis, the effect of mediators to the outcome is β2, their standard error is S2, and the effect of exposure factors to the outcome, the direct effect, is β3 (Figure 1B). The effect of all mediators, including those which were not considered, was calculated as (β-β3). The effect of each mediator, ie the indirect effect, was calculated as β1*β2, with the proportion of a mediator's effect calculated as β1*β2/β. The standard error of indirect effect was calculated as $S = \sqrt{\beta 1^2 S2^2 + \beta 2^2 S1^2}$. We used the product test of coefficients method to test the indirect effect by calculating Z as Z = β1*β2/S.

Results

Total Effect of Sleep Traits on Angina Pectoris

The study examined the causal relationship between seven sleep characteristics and AP in European ancestry. SNPs with an F-value exceeding 10 were extracted as strong IVs for each sleep characteristic (Supplementary Table 1). After outlier removal, remained SNPs were used to analyze the causal links between sleep traits and SAP and UAP. Our findings revealed that daytime napping, narcolepsy, and insomnia were associated with an increased risk of SAP (OR = 1.367, 95% CI = 1.010–1.848, P = 0.043; OR = 1.780, 95% CI = 1.022–3.099, P = 0.042; OR = 1.745, 95% CI = 1.244–2.449, P = 0.001), while waking up in the morning and longer sleep duration were linked to a decreased risk of SAP (OR = 0.791, 95% CI = 0.637–0.982, P = 0.034; OR = 0.746, 95% CI = 0.585–0.951, P = 0.018). Moreover, adequate sleep duration was also associated with a reduced risk of UAP (OR = 0.619, 95% CI = 0.434–0.883, P = 0.008). Notably, only the relationship between sleep duration and SAP exhibited heterogeneity and horizontal pleiotropy in this study (Figure 2, Table 2, Supplementary Table 2). However, consistent causality direction was observed across different MR methods and random-effect model IVW estimation, indicating robust results (Table 2, Figure 3). The leave-one-out sensitivity test further validated the reliability of all outcomes (Figure 4). Importantly, no evidence of reverse causality was found between any sleep characteristic and SAP or UAP (Supplementary Table 3).

Two-Step MR Revealed Cardiovascular Risk Factors' Mediator Effect on the Casual Relationship of Sleep Traits and Angina Pectoris

To reveal the roles of confounder factors in the effect of sleep traits on AP, we used two-step MR method to uncover the casual relationship chain of exposure, mediator and outcome.

Casual Effect of Cardiovascular Risk Factors on Angina Pectoris

Commonly accepted cardiovascular risk factors, including hypertension, hyperlipidemia, smoking, and type 2 diabetes mellitus (T2DM), were chosen as exposures for two-sample MR analyses (Supplementary Table 4). Estimate of log odds of SAP for per standard deviation (SD) increase in hypertension, and T2DM were 1.298 (95% CI: 1.223–1.377, P < 0.001), and 1.126 (95% CI: 1.084–1.169, P < 0.001), respectively. While one-unit higher log odds of UAP for SD increase of hypertension, and T2DM was 1.320 (95% CI:1.239–1.407, P < 0.001), and 1.130 (95% CI: 1.073–1.190, P < 0.001), respectively. Other risk factors were not significantly associated with SAP or UAP (Table 3, Supplementary Table 5).

Casual Effect of Sleep Traits on Cardiovascular Risk Factors

We then analyzed the casual relationship of sleep traits on hypertension and T2DM. It showed that one-unit higher log odds of nap during day was associated with increased SD of hypertension (β = 0.513, 95% CI: 0.214–0.811, P < 0.001), and T2DM (β= 0.593, 95% CI: 0.195–0.991, P = 0.003). One-unit higher log odds of narcolepsy were associated with increased SD of hypertension (β = 0.744, 95% CI: 0.076–1.411, P = 0.029), and T2DM (β = 0.439, 95% CI: −0.36–1.24, P = 0.284). Other sleep traits did not have significant causal relationship with these risk factors (Table 3, Supplementary Table 6).

Reverse MR analysis suggested that one unit higher log odds of hypertension lead to one SD increase of nap during day (β = 0.01, 95% CI: 0.003–0.02, P = 0.006), and narcolepsy (β = 0.004, 95% CI: −0.003–0.01, P = 0.257). Estimated log odds of T2DM was associated with one SD increase of nap during day (β = 0.01, 95% CI: 0.003–0.02, P = 0.005) and narcolepsy (β = 0.006, 95% CI: 0.0009–0.01, P = 0.021) (Table 3, Supplementary Table 7).

Effect of Different Mediators by Multivariable MR

We chose hypertension and T2DM as mediators to explore their effect in the relationship of nap during day and SAP by MVMR. A total of 117 SNPs were extracted as IVs (Supplementary Table 8). It can be seen that after adjusting other factors, both hypertension and T2DM play a role in the causal relationship between nap during day and SAP (P < 0.001; P = 0.049), while the direct effect of nap during day was attenuated to OR 1.179 (95% CI: 0.717–1.937) with a p-value of 0.516, which means that hypertension and T2DM are complete mediators. No variable was removed by LASSO

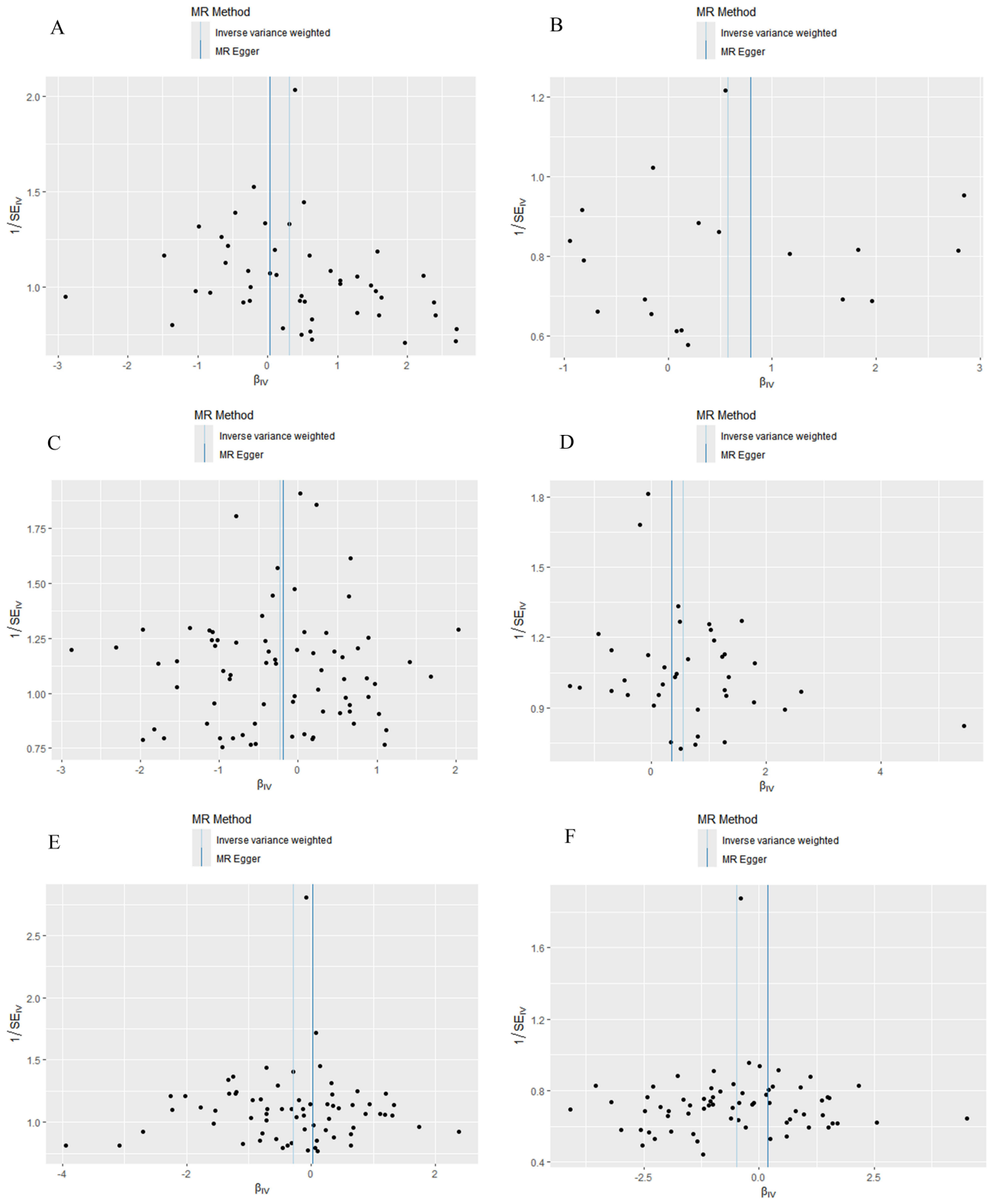

Figure 2 Funnel plot of causality. (**A**) Nap during day and SAP, (**B**) Daytime dozing/sleeping (narcolepsy) and SAP, (**C**) Getting up in morning and SAP, (**D**) Insomnia and SAP, (**E**) Sleep duration and SAP, (**F**) sleep duration and UAP.

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Table 2 MR Results of Sleep Traits on Angina Pectoris

Exposure	Outcome	Method	nsnp	Outlier	P-val	OR	95% CI	Heterogeneity		IVW_MRE		Horizontal Pleiotropy		MR-PRESSO
								Q	Q_P-val	OR	P-val	Egger intercept	Pleiotropy_P-val	P-val
Nap during day	Stable angina pectoris	Inverse variance weighted	47	rs2250377	0.043	1.367	1.010–1.848	58.856	0.097	-	-	0.003	0.631	0.094
Narcolepsy	Stable angina pectoris	Inverse variance weighted	19	-	0.042	1.780	1.022–3.099	17.242	0.507	-	-	−0.002	0.883	0.512
Getting up in morning	Stable angina pectoris	Inverse variance weighted	75	-	0.034	0.791	0.637–0.982	86.809	0.146	-	-	−0.001	0.904	0.157
Insomnia	Stable angina pectoris	Inverse variance weighted	39	-	0.001	1.745	1.244–2.449	51.498	0.071	-	-	0.002	0.740	0.087
Sleep duration	Stable angina pectoris	Inverse variance weighted	68	-	0.018	0.746	0.585–0.951	89.581	0.034	0.746	0.018	−0.004	0.499	0.033
Sleep duration	Unstable angina pectoris	Inverse variance weighted	67	rs2683630	0.008	0.619	0.434–0.883	80.463	0.109	-	-	−0.008	0.338	0.118

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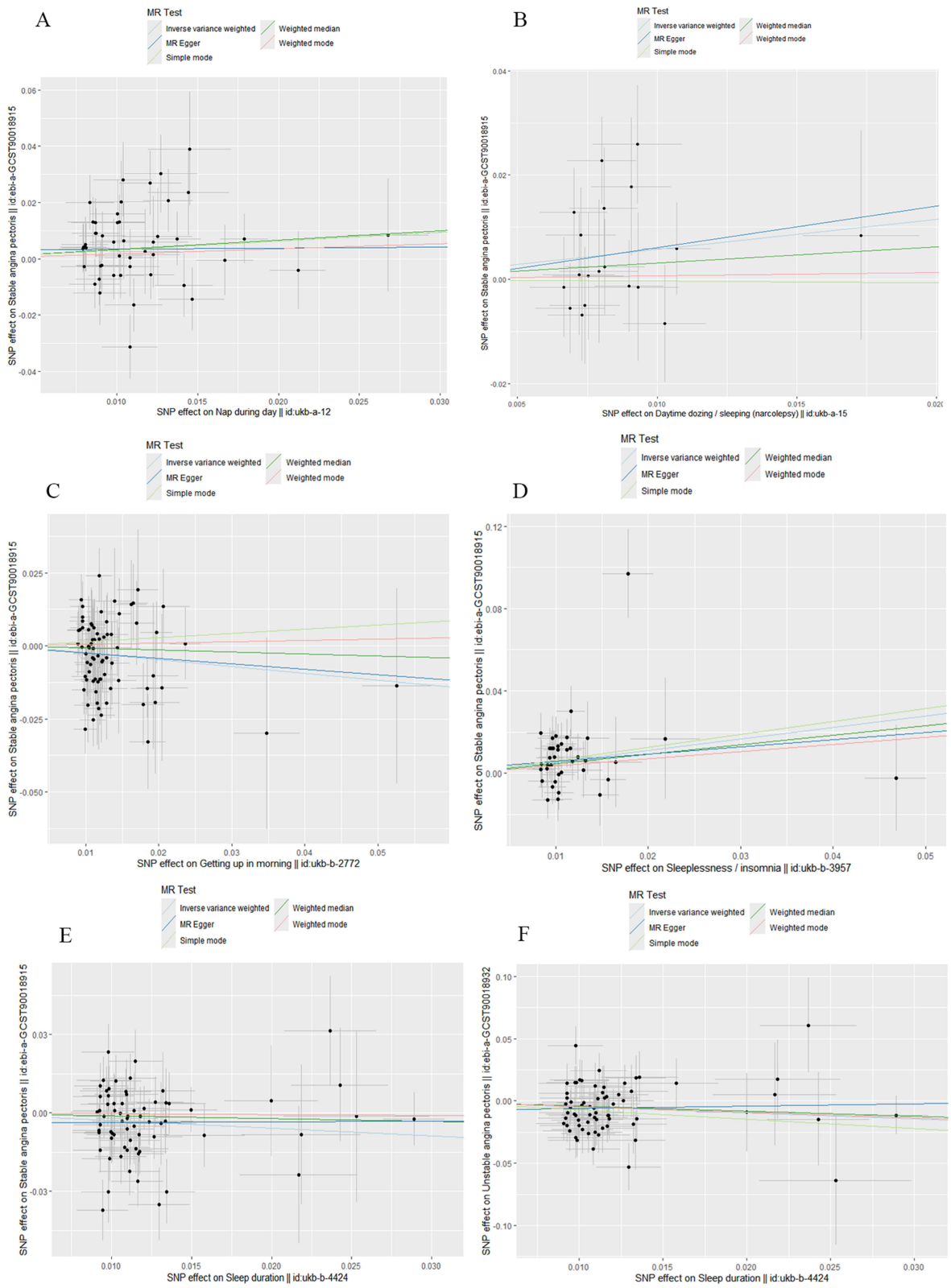

Figure 3 Scatterplot of the effect size for each SNP on sleep traits and the risk of AP. (**A**) Nap during day and SAP, (**B**) Daytime dozing/sleeping (narcolepsy) and SAP, (**C**) Getting up in morning and SAP, (**D**) Insomnia and SAP, (**E**) Sleep duration and SAP, (**F**) sleep duration and UAP.

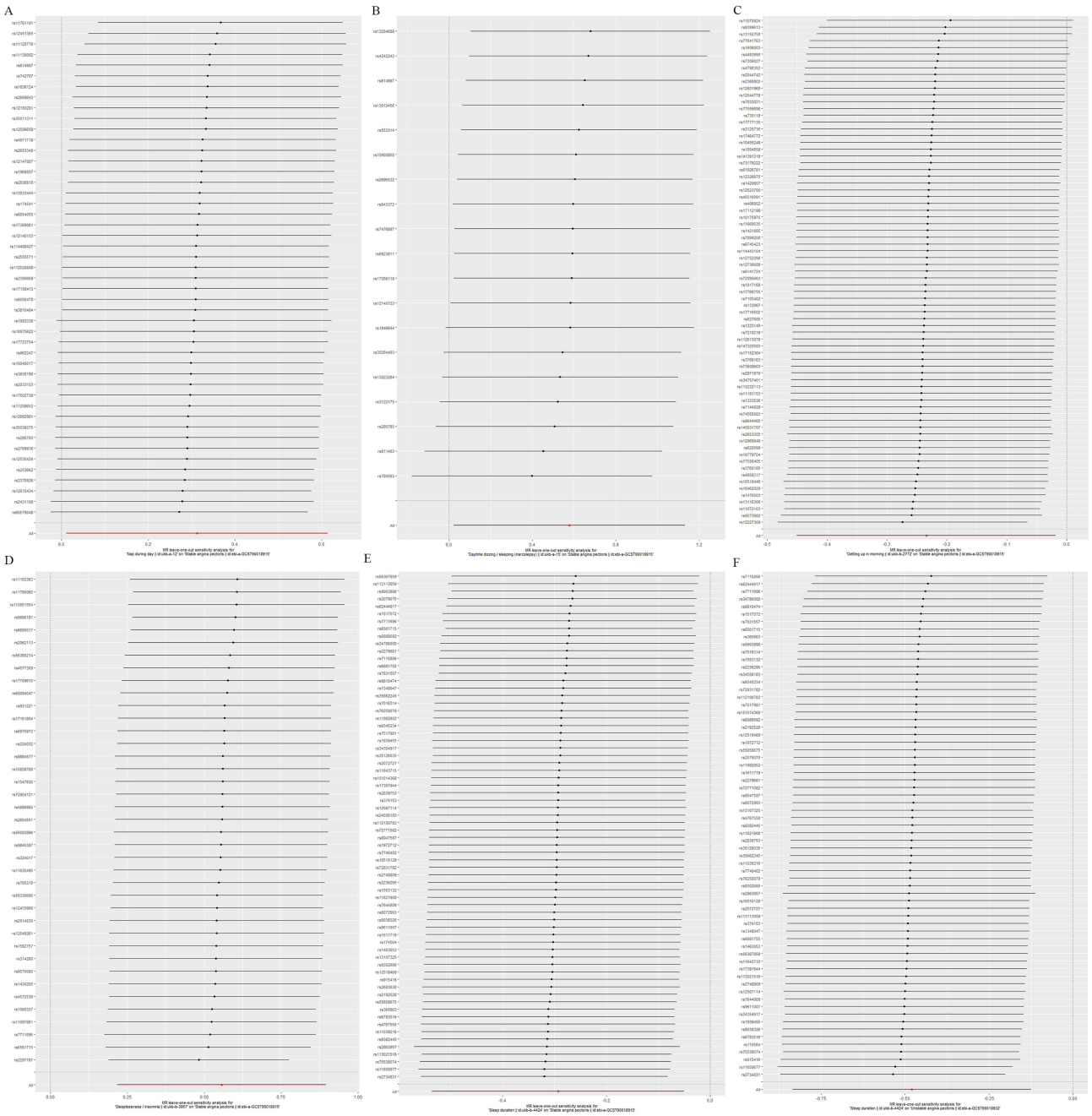

Figure 4 Leave-one-out analysis for the impact of individual SNPs on the association between sleep traits and the risk of AP. (**A**) Nap during day and SAP, (**B**) Daytime dozing/sleeping (narcolepsy) and SAP, (**C**) Getting up in morning and SAP, (**D**) Insomnia and SAP, (**E**) Sleep duration and SAP, (**F**) sleep duration and UAP.

regression screening. Although heterogeneity was suggested (P < 0.001), other MR methods, such as MR Egger and weighted median, showed the same trend, which firmed the MVMR result of IVW method (Supplementary Table 9). The effect of hypertension was OR 1.129 (95% CI: 1.042–1.223, P = 0.003) with an effect ratio of 27.7%, while the effect of T2DM was OR 1.034 (95% CI: 0.993–1.077, P = 0.102) with an effect ratio of 7.7% (Table 4, Supplementary Tables 9 and 10).

In narcolepsy-hypertension-SAP MVMR, the direct effect of narcolepsy was OR 1.235 (95% CI: 0.233–6.532, P = 0.804), and hypertension plays a role as a complete mediator (OR = 1.354, 95% CI: 1.219–1.503, P < 0.001). However, after LASSO regression, narcolepsy was removed, which means that narcolepsy had little effect on SAP, while hypertension may serve as a main factor (Table 5, Supplementary Table 11).

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Table 3 Results of IVW for Mediators on Outcome, Exposure on Mediators, and Mediators on Exposure

Results of Mediators on Outcome				
Exposure	**Outcome**	**Number of SNPs**	**OR (95% CI)**	**P-value**
Hypertension	SAP	50	1.298(1.223–1.377)	5.00E-18
Hypertension	UAP	55	1.320(1.239–1.407)	8.19E-18
T2DM	SAP	52	1.126(1.084–1.169)	8.99E-10
T2DM	UAP	54	1.130(1.073–1.190)	3.75E-06
Hyperlipidemia	SAP	19	1.003(0.994–1.013)	0.498
Hyperlipidemia	UAP	19	1.005(0.991–1.020)	0.480
Smoking	SAP	25	1.002(0.985–1.020)	0.788
Smoking	UAP	26	1.002(0.973–1.031)	0.915
Results of Exposure on Mediators				
Exposure	**Outcome**	**Number of SNPs**	**β (95% CI)**	**P-value**
Nap during day	Hypertension	48	0.513(0.214–0.811)	0.0008
Nap during day	T2DM	48	0.593(0.195–0.991)	0.003
Narcolepsy	Hypertension	19	0.744(0.076–1.411)	0.029
Narcolepsy	T2DM	17	0.439(−0.365–1.243)	0.284
Results of Mediators on Exposure				
Exposure	**Outcome**	**Number of SNPs**	**β (95% CI)**	**P-value**
Hypertension	Nap during day	55	0.012(0.003–0.020)	0.006
Hypertension	Narcolepsy	56	0.004(−0.003–0.012)	0.257
T2DM	Nap during day	49	0.010(0.003–0.017)	0.005
T2DM	Narcolepsy	52	0.006(0.001–0.011)	0.021

Table 4 MVMR of Nap, Hypertension, T2D and SAP

Exposure	**Outcome**	**Adjusted Factors**	**Number of SNPs**	**OR (95% CI)**	**P-value**	**Effect (95% CI) (P-value)**	**Mediation Ratio**
Hypertension	SAP	T2D, Nap during day	117	1.267 (1.178–1.363)	2.19E-10	0.121(0.041–0.201) (0.003)	0.277
T2D	SAP	Hypertension, Nap during day	117	1.059 (1.000–1.120)	0.049	0.034(−0.007–0.074) (0.102)	0.077
Nap during day	SAP	Hypertension, T2D	117	1.179 (0.717–1.937)	0.516	0.165(−0.332–0.661) (0.516)	-

Table 5 MVMR of Narcolepsy, Hypertension and SAP

Exposure	**Outcome**	**Adjusted Factors**	**Number of SNPs**	**OR (95% CI)**	**P-value**
Hypertension	SAP	Narcolepsy	67	1.35(1.219–1.503)	1.39E-08
Narcolepsy	SAP	Hypertension	67	1.235(0.233–6.532)	0.804
LASSO Regression					
Hypertension	SAP	-	54	1.357(1.211–1.520)	1.43E-07

Effect of Sleep Traits on Angina Pectoris in Asian Ancestry

MR analysis in Asian ancestry did not show similar results to those in European ancestry (Supplementary Table 12). The results showed that insomnia lead to a decreased risk of SAP (OR = 0.919, 95% CI = 0.850–0.993, P = 0.032), while chronotype lead to increased risk of UAP (OR = 1.125, 95% CI = 1.028–1.232, P = 0.010) (Supplementary Table 13). Reverse MR showed that UAP and SAP were protective factors of narcolepsy (β = −0.106, 95% CI = −0.196–-0.016, P = 0.021; β = −0.106, 95% CI = −0.201–-0.010, P = 0.011), while SAP lead to higher risk of chronotype (β = 0.250, 95% CI = 0.058–0.442, P = 0.030) (Supplementary Table 14).

Discussion

Our study is the first Mendelian randomization analysis to reveal a causal relationship between sleep characteristics and angina pectoris, and also considered the mediating effect of some cardiovascular risk factors. The results showed that in European population, day time napping, narcolepsy, and insomnia were positively related to SAP, while more easily waking up in the morning, and longer sleep duration showed a negative association with SAP. Adequate sleep duration was associated with a reduced risk of UAP. Moreover, our research also identified hypertension and T2DM as complete mediating factors in the causal connection between nap during day and SAP, although the effect value of T2DM was not significant. Additionally, we found that longer periods of sleepiness increase the risk of SAP, but this effect might be dimmed by hypertension. However, MR results in Asian ancestry were at variance with those in European ancestry, which may due to low statistic power caused by small sample size or racial difference.

AP is a kind of clinical syndrome caused by transient myocardial ischemia leading to discomfort or pressure in the precardiac area.[26] SAP has stable plaque, which usually leads to severe coronary artery obstruction and hypoxia during physical activity, and is not easy to progress to myocardial infarction. UAP may progress to myocardial infarction due to an unstable plaque, which will cause chest pain attack when it ruptures and leads to blood clot formation. In the United States, approximately 10 million adults with SAP face a 3 to 4% annual risk of myocardial infarction or death, whereas patients with UAP have a 5.7% incidence of sudden cardiac arrest.[27,28] Recent research has underscored the significant impact of sleep disorders on cardiovascular health, revealing that sleep issues are linked to a heightened risk of cardiovascular diseases like heart failure, coronary artery disease, AP, heart attack, and stroke.[8] Wang C et al conducted a study with 116,632 participants, revealing that daytime naps exceeding 6 hours were linked to a higher risk of major cardiovascular events and mortality.[29] Conversely, naps lasting less than 30 minutes were found to enhance alertness, performance, and learning. However, frequent and prolonged napping behaviors, particularly among the elderly, were associated with increased morbidity and mortality.[30] Our research not only established a causal connection between nap during day and SAP, but also identified hypertension as a mediating factor. Longer nap time might be due to shortened sleep time during night. Notably, individuals sleeping less than 5 hours or more than 9 hours per night were at a higher risk of developing hypertension compared to those sleeping 7–8 hours. Sleep less than 7 hours or more than 10 hours also increase the risk of cardiovascular diseases, including AP.[31] An evidence from a Chinese middle-aged population also recommended a sleep duration of 7–8 hours.[32] Sleep deprivation impacts metabolism, leading to reduced daily energy expenditure and increased sedentary behavior. Furthermore, it elevates sympathetic tone, cortisol levels, and activates inflammatory pathways, disrupting glucose metabolism and contributing to weight gain and excess visceral fat, thereby elevating the risk of myocardial infarction and AP.[33] Long sleep duration is linked to arterial stiffness and blood pressure variability.[34] Similarly, our investigation demonstrated a direct association between sleep duration and both SAP and UAP. Insomnia has emerged as a significant public health concern, posing a threat to overall well-being. The co-occurrence of insomnia and AP creates a complex interplay, with AP potentially triggering insomnia, which can negatively impact mood regulation, cognitive function, memory, systemic immunity, and result in multiorgan damage, including cardiovascular complications.[35,36] In a longitudinal study spanning 11 years, Sivertsen et al identified insomnia as a key contributor to the risk of AP, stroke, and hypertension.[37] Our findings further confirmed a substantial causal link between insomnia and SAP. In addition, the nocturnal sleep disturbances and excessive daytime sleepiness seen in narcolepsy can heighten cardiovascular risk and are often linked to other health conditions such as obesity, diabetes, depression, and other sleep disorders. These comorbidities can further elevate the risk of cardiovascular issues. Research

has established a causal connection between narcolepsy and conditions like coronary heart disease and heart failure.[38,39] Additionally, we found that longer periods of sleepiness increase the risk of SAP, providing compelling evidence for a deeper understanding of the implications and consequences of narcolepsy. Finally, it was observed that waking up early was associated with a lower incidence of SAP. However, it is important to note that a causal relationship between all sleep characteristics and AP would require further validation through clinical evidence.

Hypertension significantly contributes to various sleep disturbances, which in turn can exacerbate blood pressure issues, creating a vicious cycle.[40] While adults with T2DM or lower income seem to have poorer sleep quality.[41] Sleep duration, particularly short sleep, may influence blood pressure through elevated sympathetic activity, hormonal imbalances, and disrupted circadian rhythms.[42] Sleeping lower than 7 hours at night with napping over 30 minutes at daytime has the highest risk of cardiovascular disease (HR = 1.47, 95% CI: 1.14–1.89).[31] Napping over 1 hour may be a potential risk factor for decreased insulin sensitivity (QUICKI: β =- 0.135, P<0.01; Matsuda index: $\beta = -0.119$, $P < 0.05$), especially with a short nighttime sleep time ($\beta = -0.137$, $P < 0.05$).[43] Adjusting for BMI and waist circumference attenuated the risk associated with long naps in some studies.[44,45] However, effect of napping has regional variations, suggesting that social, behavior or environment factors may have some effect.[46] Socioeconomic status (SES) may be the most important factor in sleep quality, with longer and better sleep among higher SES groups. The reasons may be related to better education, healthier lifestyle and stronger social support networks.[47] All in all, people with unhealthy sleep pattern may also have worse life habits, which might induce metabolic dysfunction and cardiovascular diseases. It is crucial to address these social problems to improve the quality of life and CVD management.

Our research also had some limitations. First, the GWAS data of angina pectoris we selected combined the data from the UK Biobank and the FinnGen database, while the exposure GWAS data was based on the UK Biobank and the mediator GWAS data came from FinnGen. Since we cannot get the proportion of the population from both databases in the outcome data, the sample overlap rate cannot be calculated. For this reason, our analysis may not rule out the possibility of sample overlap bias, which may cause false positive results. Second, by calculating the statistical efficiency, it was found that our results did not have high statistical efficiency, which may be due to the insufficient sample size or the influence of relevant risk factors.[48] The Asian data of sleep traits had low sample sizes as about 2500, which may provide an explanation of these confusing results. Therefore, our multivariate MR analysis only included the causal relationship in the European population. Further research on different ancestry is needed. Sensitivity analysis showed that there was heterogeneity in some MR results, but we used the random-effect model IVW to obtain significant results. In addition, other MR methods were used to analyze, and the trend was consistent with the IVW method, which increased the robustness of the results. A plausible explanation of pleiotropy is that these traits with pleiotropy might affect AP through other factors that were not included in our analysis. We have not analyzed other cardiovascular risk factors, which may act as exposure or mediators that affect AP. In addition, for each mediator, we only selected one GWAS dataset for analysis, but there may be different types of diseases such as hypertension and diabetes. The mediating role of these subtypes still needs to be further explored.

Conclusions

Our study demonstrated that nap during day, narcolepsy, and insomnia led to an increased risk of SAP and revealed the mediating role of hypertension and T2DM in the causal relationship between nap during day and SAP. Getting up in the morning and sleep duration led to a reduced risk of SAP, and sleep duration also led to a reduced risk of UAP. We did not find similar trends in the Asian population, which may be related to the small sample size.

Data Sharing Statement

The data used in this study are derived from the GWAS databases. Detailed information regarding the data sources and the methodology for data retrieval can be found in the Methods section of this manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Renmin Hospital of Wuhan University. The ethical approval number is WDRY2024-K280. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki and relevant national guidelines.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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