Original Article

Associations between daytime napping, sleep duration, and depression and 15 cardiovascular diseases: a Mendelian randomization study

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Background: Numerous studies have documented the effects of daytime napping, sleep duration, and depression on cardiovascular diseases (CVDs). However, the evidence has been gleaned from observational studies that might be riddled with confounding variables and the possibility of reverse causation bias. Therefore, the present study employed a Mendelian randomization (MR) methodology to meticulously explore the relationships between daytime napping, sleep duration, and depression, and the risk profiles of CVDs.

Methods: Genome-wide significant genetic variants associated with daytime napping, sleep duration, and depression were used as the instrumental variables (IVs). Data on the genetic correlations between these IVs and 15 CVDs were derived from the United Kingdom (UK) Biobank, Finnish Genome Studies, and other large-scale collaborations. We conducted both univariate and multivariate MR analyses to assess the overall effects and mediated relationships after adjusting for potential confounders, including body mass index (BMI), smoking status, and type 2 diabetes. The effect sizes were estimated using inverse variance-weighted (IVW) regression.

Results: The MR analysis revealed that an increased risk of heart failure (HF) [odds ratio (OR): 1.366; 95% confidence interval (CI): 1.013–1.842; P=0.04], coronary atherosclerosis (OR: 1.918; 95% CI: 1.257–2.927; P=0.003), myocardial infarction (MI) (OR: 1.505; 95% CI: 1.025–2.211; P=0.04), and coronary artery disease (CAD) (OR: 1.519; 95% CI: 1.130–2.043; P=0.006) was significantly associated with genetically predicted daytime napping. Prolonged sleep duration was found to be related to a reduced risk of HF (OR: 0.995; 95% CI: 0.993–0.998; P=2.69E–04), peripheral vascular disease (PVD) (OR: 0.984; 95% CI: 0.971–0.997; P=0.02), and CAD (OR: 0.997; 95% CI: 0.994–0.999; P=0.006). Additionally, a statistically significant positive relationship was observed between depressive disorders and the occurrence of atrial fibrillation (AF) (OR: 1.298, 95% CI: 1.065–1.583, P=0.01), indicating a heightened susceptibility. The multivariable MR analyses substantiated the reliability of the observed associations between daytime napping and the incidence of HF and CAD, following adjustments for genetically predicted BMI and smoking. The sensitivity analysis did not reveal any evidence of horizontal pleiotropy or heterogeneity, thus supporting the validity of the study's results.

Conclusions: This MR investigation posits a potential causal nexus between daytime napping, sleep duration, and depression, and the genesis of CVDs, offering new perspectives on the prevention and management of CVDs.

Keywords: Daytime napping; sleep duration; depression; cardiovascular diseases (CVDs); Mendelian randomization (MR)

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Introduction

Cardiovascular disease (CVD) represents the predominant contributor to global morbidity and mortality (1,2). In 2020, CVDs were responsible for an estimated 19 million fatalities worldwide, representing a substantial increase of 18.7% from the figures documented in 2010 (3). Despite significant advancements in preventive strategies, the etiological factors underlying CVD remain incompletely understood (2,4). Consequently, elucidating the risk factors associated with CVD development is essential for the refinement of preventive practices and strategies.

Numerous studies have documented the effects of sleep characteristics, including daytime napping and sleep duration on CVDs (5-7). Nonetheless, the correlation between daytime napping or sleep duration and the onset of CVDs remains equivocal. Various investigations have suggested that daytime napping may be a contributory factor to the development of hypertension (8-10), stroke (11), coronary artery disease (CAD) (12-14), and heart failure (HF) (15). Conversely, some studies have posited that napping during the daytime could potentially provide a protective benefit against the development of hypertension (10,16,17), CAD (18,19), and HF (19). In addition, it has been suggested that prolonged sleep duration may elevate the risk of atrial fibrillation (AF) development (20-23). Additionally, several studies have uncovered a link between short sleep duration and extended daytime napping, exceeding one hour, and an increased risk of depression (24,25). Notably, there is evidence of a link between depression and sleep quality (24,26,27), which in turn could heighten the risk of CVDs (28-36). Nonetheless, the causal nature of these associations remains uncertain, as a considerable amount of the evidence has been gleaned from observational studies that might be riddled with confounding variables and the possibility of reverse causation bias.

With the advent of genome-wide association studies (GWASs), the technique of Mendelian randomization (MR) analysis has seen a surge in usage (37). MR is a method that employs genetic variations as instrumental variables (IVs) to evaluate the causal effects of associations between an exposure and an outcome (38). Relative to observational studies, genetic variants are randomly allocated at the time of conception, which diminishes the probability of confounding influences (39). Additionally, this strategy significantly reduces the risk of reverse causation, as it operates on the principle that germline phenotypes are intrinsic and cannot be altered by subsequent disease states (40,41). In this article, we present a MR study that sought to assess the causal relationship between daytime napping, sleep duration, and depression, and 15 CVDs. To elucidate the potential mechanisms, we proceeded to perform a multivariate MR analysis to scrutinize the mediating roles of body mass index (BMI), smoking, and type 2 diabetes. We present this article in accordance with the STROBE-MR reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-313/rc).

Highlight box

Key findings

- Daytime napping, sleep duration, and depression are strongly associated with the development of cardiovascular diseases (CVDs), providing new perspectives on CVDs prevention and management.

What is known and what is new?

- Numerous studies have documented the effects of daytime napping, sleep duration or depression on CVDs.
- This two-sample Mendelian randomization (MR) analysis revealed that daytime napping and depression were positively associated with several CVDs. Conversely, a genetic predisposition to a longer sleep duration was linked to reduced risks of several CVDs.

What is the implication, and what should change now?

- The management of daytime napping, adequate sleep duration, and depression have the potential to prevent CVDs, among which body mass index, smoking and type 2 diabetes play an intermediary role.

Methods

Study design and data sources

We conducted a two-sample MR analysis to determine the causal effects of three exposures (i.e., daytime napping, sleep duration, and depression) on the following 15 CVDs: HF, hypertension, stroke, AF, arrhythmia, conduction disorders, coronary atherosclerosis, myocardial infarction

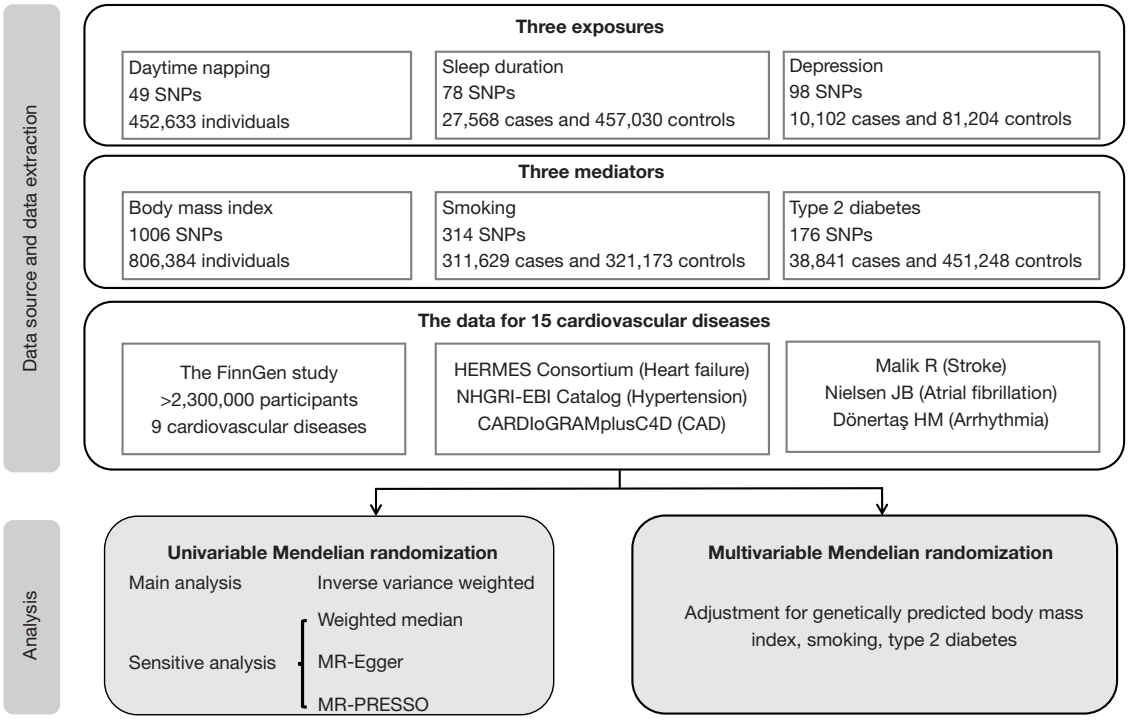

Figure 1 Study design. SNPs, single nucleotide polymorphisms; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; CAD, coronary artery disease.

(MI), non-ischemic cardiomyopathy, non-rheumatic valve diseases, pulmonary embolism, aortic aneurysm, dissection of aorta, peripheral vascular disease (PVD), and CAD. *Figure 1* provides a comprehensive overview of the study design. Our MR method is based on the following three basic assumptions: (I) the genetic variants are closely related to daytime napping, sleep duration, and depression (Assumption 1); (II) the genetic variants are not related to other confounders (Assumption 2); and (III) the genetic variants are only related to the clinical outcome through daytime napping, sleep duration, and depression (Assumption 3) (*Figure 2*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The specific studies and data sets used for the MR analyses are detailed in *Table 1*.

IV selection

To select the IVs, the following rigorous three-step methodology was adopted: (I) the single nucleotide polymorphisms (SNPs) that met the genome-wide significance threshold of $P<5\times10^{-8}$ were selected; (II) corresponding linkage disequilibrium (LD) was used to identify the SNPs in a LD state. We ensured the independence of the SNPs by excluding those within a 10,000-kb window by applying a r^2 threshold of <0.001; (III) the efficacy of the individual SNPs was affirmed by a F-statistic evaluation. The SNPs with F-statistics >10 were considered robust and credible IVs, which protected the MR outcomes against the potential skewing effects of weak instrument bias (42,43). Comprehensive details regarding the SNPs employed are provided in Tables S1-S3.

Data sources for three exposures

GWAS summary statistics for daytime napping, sleep duration, and depression were obtained from the United Kingdom (UK) Biobank (44). The daytime napping GWAS data comprised a substantial cohort of 452,633 individuals of European descent (45). The sleep duration GWAS data comprised 10,102 cases and 81,204 controls (46). Genetic variants exhibiting LD (as characterized by a r^2 value >0.01 or clump distance <10,000 kilobases) and those demonstrating a less significant correlation to the exposure

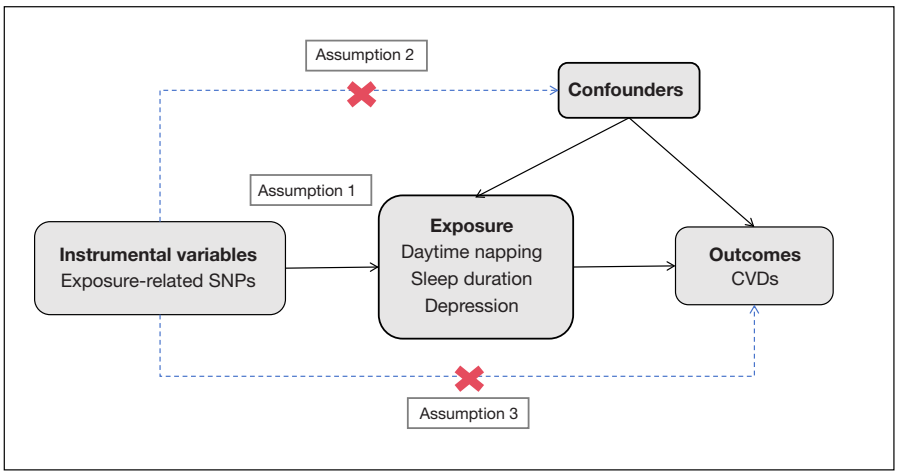

Figure 2 An illustrative diagram of the Mendelian randomization assumptions. SNPs, single nucleotide polymorphisms; CVDs, cardiovascular diseases.

of interest were systematically excluded. Following this filtration process, 49 independent SNPs were retained as IVs for the analysis of daytime napping, 78 for sleep duration, and 98 for depressive symptoms. The summary data set for depression comprised 27,568 cases and 457,030 controls (*Table 1*).

Data sources for CVD diseases

For the dependent variables under investigation, the aggregated data for HF (comprising 47,309 affected individuals and 930,014 unaffected controls), hypertension (comprising 11,863 affected individuals and 8,663 controls), conduction disorders (comprising 4,416 affected individuals and 156,711 controls), coronary atherosclerosis (comprising 23,363 affected individuals and 187,840 controls), MI (comprising 20,917 affected individuals and 440,906 controls), non-ischemic cardiomyopathy (comprising 11,400 affected individuals and 175,752 controls), non-rheumatic valve diseases (comprising 10,235 affected individuals and 156,711 controls), pulmonary embolism (comprising 4,185 affected individuals and 214,228 controls), aortic aneurysm (comprising 3,230 affected individuals and 475,964 controls), aortic dissection (comprising 470 affected individuals and 206,541 controls), PVD (comprising 1,037 affected individuals and 206,541 controls), and CAD (comprising 122,733 affected individuals and 424,528 controls) were systematically obtained from respective large-scale GWASs (see *Table 1*) (47-51). The definition of each outcome has been listed in the Appendix 1. Summary statistics representing the data sets for stroke (comprising 40,585 affected individuals and 406,111 unaffected controls), AF (comprising 60,620 affected individuals and 970,216 controls), and arrhythmia (comprising 7,207 affected individuals and 477,391 controls) were derived from GWASs conducted by Malik *et al.* (52), Nielsen *et al.* (53), and Dönertaş *et al.* (54), respectively. CVD existed concomitantly at baseline.

Data sources for possible mediators

A multivariable MR (MVMR) analysis was conducted to account for the putative confounding factors, including BMI, smoking status, and type 2 diabetes mellitus. These three variables were chosen for inclusion in the analysis, as they have previously been identified as factors significantly correlated with an extensive array of cardiovascular pathologies in prior MR investigations (55-57). At the same time, it is also related to sleep duration, daytime napping, and depression (49,58). Consequently, these factors were considered candidates for mediation. The genetic IVs for BMI, smoking behavior, and type 2 diabetes mellitus were sourced individually from the UK Biobank (for further details and information, see *Table 1*).

Statistical analysis

The initial analysis incorporated both random-effect and fixed-effect inverse variance-weighted (IVW) MR

Table 1 Information of included studies and consortia

Exposure/mediator/outcome	Consortium/first author	Population	Participants	Web source/PubMed ID
Exposure				
Daytime napping	UK Biobank	European	452,633 individuals	https://www.ukbiobank.ac.uk/
Sleep duration	UK Biobank	European	10,102 cases and 81,204 controls	https://www.ukbiobank.ac.uk/
Depression	UK Biobank	European	27,568 cases and 457,030 controls	https://www.ukbiobank.ac.uk/
Mediator				
Body mass index	UK Biobank	European	806,384 individuals	https://www.ukbiobank.ac.uk/
Smoking	UK Biobank	European	311,629 cases and 321,173 controls	https://www.ukbiobank.ac.uk/
Type 2 diabetes	UK Biobank	European	38,841 cases and 451,248 controls	https://www.ukbiobank.ac.uk/
Outcome				
Heart failure	HERMES Consortium	European	47,309 cases and 930,014 controls	https://www.hermesconsortium.org/
Hypertension	NHGRI-EBI Catalog	Hispanic or Latin American	11,863 cases and 8,663 controls	https://www.ebi.ac.uk/gwas/
Stroke	Malik R	European	40,585 cases and 406,111 controls	29531354
Atrial fibrillation	Nielsen JB	European	60,620 cases and 970,216 controls	30061737
Arrhythmia	Dönertaş HM	European	7,207 cases and 477,391 controls	33959723
Conduction disorders	The FinnGen study	European	4,416 cases and 156,711 controls	https://www.finngen.fi/fi
Coronary atherosclerosis	The FinnGen study	European	23,363 cases and 187,840 controls	https://www.finngen.fi/fi
Myocardial infarction	The FinnGen study	European	20,917 cases and 440,906 controls	https://www.finngen.fi/fi
Non-ischemic cardiomyopathy	The FinnGen study	European	11,400 cases and 175,752 controls	https://www.finngen.fi/fi
Non-rheumatic valve diseases	The FinnGen study	European	10,235 cases and 156,711 controls	https://www.finngen.fi/fi
Pulmonary embolism	The FinnGen study	European	4,185 cases and 214,228 controls	https://www.finngen.fi/fi
Aortic aneurysm	The FinnGen study	European	3,230 cases and 475,964 controls	https://www.finngen.fi/fi
Dissection of aorta	The FinnGen study	European	470 cases and 206,541 controls	https://www.finngen.fi/fi
Peripheral vascular disease	The FinnGen study	European	1,037 cases and 206,541 controls	https://www.finngen.fi/fi
Coronary artery disease	CARDIoGRAMplusC4D	European	122,733 cases and 424,528 controls	http://www.cardiogramplusc4d.org/

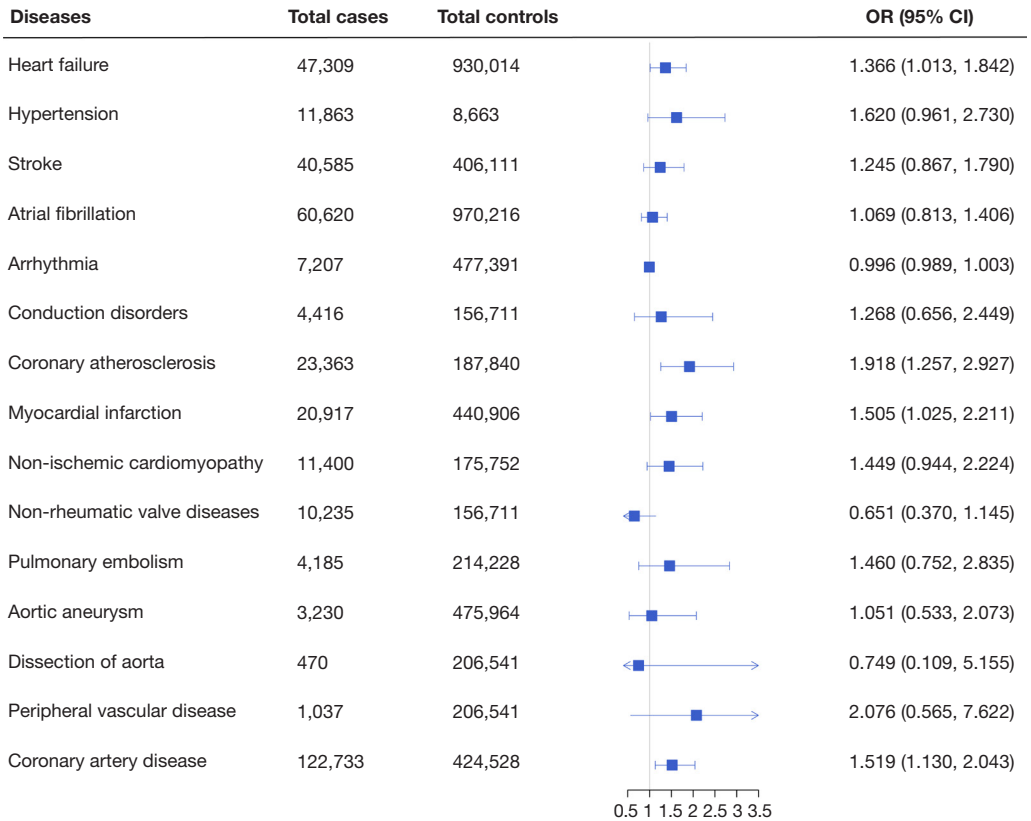

Figure 3 Associations between a genetic predisposition to daytime napping, and cardiovascular diseases. OR, odds ratio; CI, confidence interval.

techniques to estimate the causal effects. The horizontal pleiotropy of the selected SNPs was appraised using the MR-Egger method and the weight median approach. The Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) technique was used to identify outliers exhibiting horizontal pleiotropy and compensate for their influence. The variability in the estimates derived from the SNPs was assessed using Cochran's Q statistic. Additionally, a leave-one-out sensitivity analysis was conducted to ascertain if any individual SNP significantly affected the findings. The effects of daytime napping, sleep duration, and depression on the occurrence of CVDs were quantified as the odds ratio (OR) accompanied by the corresponding 95% confidence interval (CI). The robustness of the IVs was evaluated by calculating the F-statistic, with a value >10 indicating sufficient strength. Further, to detect any false positive findings due to multiple comparisons, the Bonferroni correction technique was applied. Power analysis was performed using an online tool (59). In this study, a relationship was considered to have a suggestive level of statistical significance if it had a nominal P value <0.05, and an adjusted P value >0.05 following the Benjamini-Hochberg procedure. All the statistical analyses conducted in this study were performed using the TwoSampleMR and MR-PRESSO packages within R software (version 4.3.1).

Results

Both random and fixed-effects IVW models were used, and through two-sample MR analyses employing these SNPs as IVs, we revealed the causal associations between daytime napping, sleep duration, and depression with the genetically predicted risk of CVDs (*Figures 2-4* and Table S4). The results of the MVMR analyses, which took into account various mediators by way of adjustments, are presented in Tables S5-S7. Most associations were well powered (Table S4). For daytime napping, sleep duration, and depression, there was 80% power to detect the smallest OR ranging from 0.651 to 2.076, 0.984 to 1.012, and 0.573 to 1.976 for included outcomes. Although power was lower for sleep duration, it was adequate to detect a moderate effect

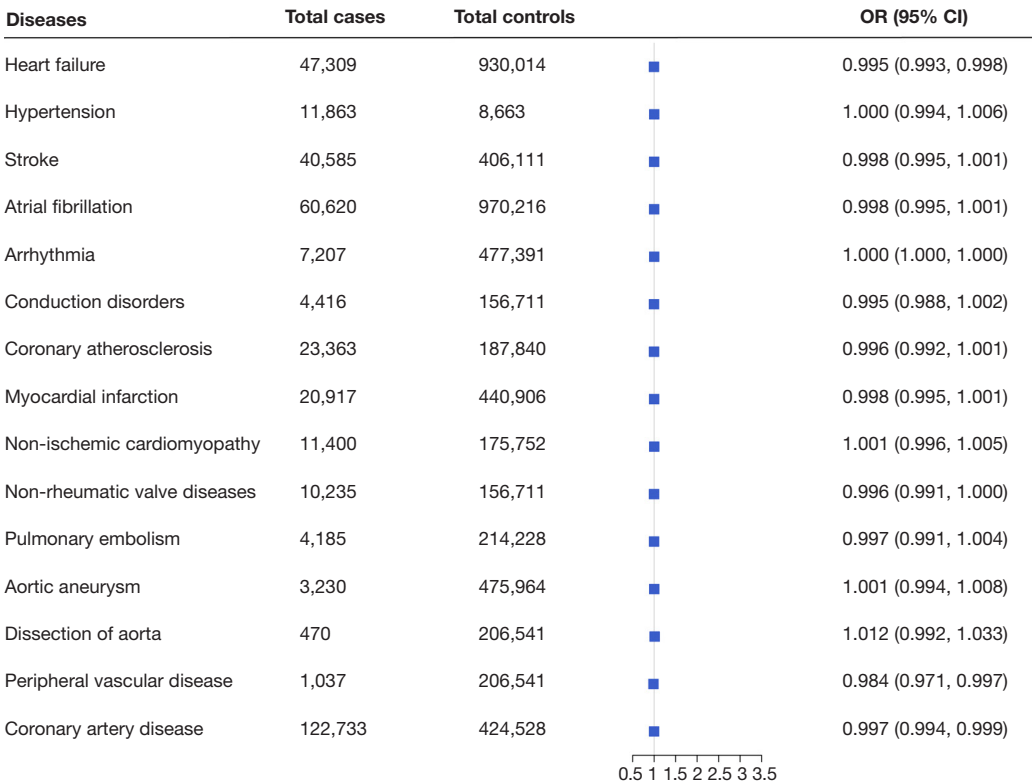

Figure 4 Associations between a genetic predisposition to sleep duration and cardiovascular diseases. OR, odds ratio; CI, confidence interval.

size for most common CVD.

Daytime napping and CVD

The genetic predisposition to daytime napping was found to be significantly associated with an increased likelihood of HF (OR: 1.366; 95% CI: 1.013–1.842; P=0.04), coronary atherosclerosis (OR: 1.918; 95% CI: 1.257–2.927; P=0.003), MI (OR: 1.505; 95% CI: 1.025–2.211; P=0.04), and CAD (OR: 1.519; 95% CI: 1.130–2.043; P=0.006) (*Figure 3*). After adjusting for BMI, the causal effect of daytime napping demonstrated continued significance in relation to HF (OR: 1.379; 95% CI: 1.026–1.853; P=0.04) and CAD (OR: 1.676; 95% CI: 1.256–2.237; P=4.52E-04) (Table S5). In the MVMR analysis, which accounted for the genetically predicted effects of smoking, an association was found between a genetic propensity for daytime napping and a heightened risk of HF (OR: 1.353; 95% CI: 1.038–1.763; P=0.03) and CAD (OR: 1.381; 95% CI: 1.058–1.801; P=0.02). After adjusting for the three aforementioned mediating factors, the causal association between the practice of daytime napping and the risk of CAD (OR: 1.466; 95% CI: 1.083–1.986; P=0.01) remained statistically significant. After adjusting for smoking, there was a negative correlation between daytime napping and non-rheumatic valvular diseases (OR: 0.592; 95% CI: 0.363–0.965; P=0.04).

Sleep duration and CVD

The MR analysis showed that a longer sleep duration was associated with a decreased risk of developing HF (OR: 0.995; 95% CI: 0.993–0.998, P=2.69E-04), PVD (OR: 0.984; 95% CI: 0.971–0.997, P=0.02), and CAD (OR: 0.997; 95% CI: 0.994–0.999, P=0.006) (*Figure 4*). After adjusting for genetically predicted BMI (OR: 2.474; 95% CI: 1.219–5.021; P=0.01) and considering the combined effect of the three mediators (OR: 2.325; 95% CI: 1.157–4.675; P=0.02), the genetic predisposition to a longer sleep duration showed a more pronounced positive association with the risk of HF (Table S6). After adjusting for smoking, sleep duration was associated with a increased risk of developing stroke (OR: 6.526; 95% CI: 1.768–24.086; P=0.005). After adjusting for type 2 diabetes, sleep duration still had a protective effect on the causal influence of PVDs (OR: 0.011; 95% CI:

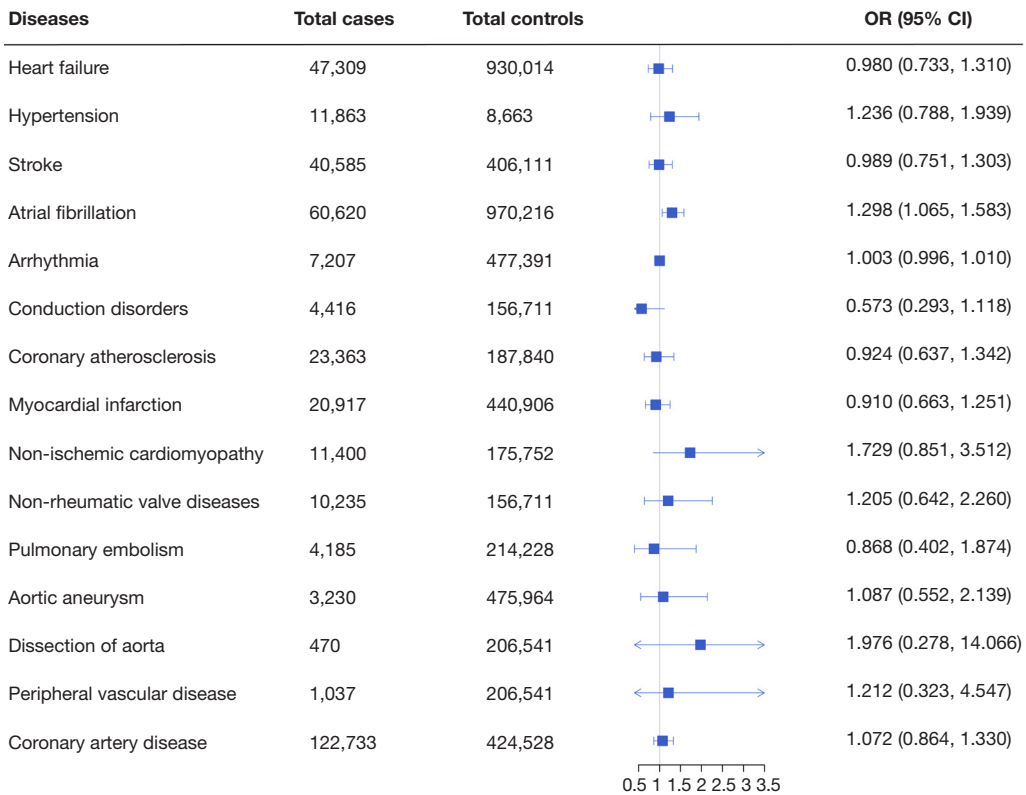

Figure 5 Associations between a genetic predisposition to depression and cardiovascular diseases.

0.000–0.467; P=0.02). However, after adjusting for smoking, sleep duration became a risk factor for PVD (OR: 191.403; 95% CI: 1.561–23,472.847; P=0.03).

Depression and CVD

Depression was positively related to AF (OR: 1.298; 95% CI: 1.065–1.583, P=0.01) (*Figure 5*). However, the causal association between depression and AF attenuated to null after adjusting for BMI, smoking, and type 2 diabetes. In this study, when the causal effect of depression on HF was assessed, the association was weakened but remained positive after adjusting for BMI (OR: 6.727; 95% CI: 1.010–44.820; P=0.05) and a combination of the three mediators (OR: 6.991; 95% CI: 1.040–47.010; P=0.05). However, after accounting for the effect of smoking, the association was weakened and became negative (OR: 0.023; 95% CI: 0.001–0.655; P=0.03) (Table S7). After adjusting for the three mediators, the study found that depression was significantly associated with a heightened risk of conduction disorders (OR: 95.880; 95% CI: 1.478–6,218.371; P=0.03), coronary atherosclerosis (OR: 20.179; 95% CI: 1.512–269.360; P=0.02), and CAD (OR: 1.185; 95% CI: 1.055–1.332; P=0.004). According to the MVMR analysis, after adjusting for type 2 diabetes, depression was significantly associated with an elevated risk of both arrhythmia (OR: 1.097; 95% CI: 1.017–1.183; P=0.02) and MI (OR: 95.233; 95% CI: 1.548–5,858.572; P=0.03).

Sensitivity analysis

The outcomes of the sensitivity analyses were consistent (Table S4). Figures S1-S3 display scatter diagrams illustrating the associations between daytime napping, sleep duration, depression, and the incidence of CVDs, revealing analogous patterns in the data. The leave-one-out sensitivity analysis suggested that the association between daytime napping, sleep duration, depression, and CVDs were robust and not reliant on any individual SNP (Figures S4-S6). The relationships between individual genetic variants and their associations with daytime napping, sleep duration, depression, and CVD risk are delineated in Figures S7-S9. The MR-PRESSO detection identified one to four outliers in the analysis. The findings following the exclusion of

these outliers were found to be in alignment with the initial findings in all instances with significant results (Table S4).

The predisposition to daytime napping, as influenced by genetics, was significantly correlated with increased BMI levels (Table S8). The data did not reveal any association between BMI, smoking, type 2 diabetes, and sleep duration (Table S9). However, there was a significant genetic propensity to depression that was correlated with an increased risk of smoking (Table S10).

Discussion

This study undertook a thorough examination of the causal effects of daytime napping, sleep duration, and depression on an array of CVDs. We used a two-sample MR analysis, leveraging extensive GWAS data to draw our conclusions. Our findings indicate that daytime napping was correlated with an increased risk of HF, coronary atherosclerosis, MI, and CAD. Conversely, sleep duration was found to be linked to a reduced risk of HF, PVD, and CAD. Additionally, depression was positively correlated with AF.

Consistent with previous findings, the MR analysis showed that the genetic prediction of daytime napping was related to an increased risk of HF (15,19,57,60,61). However, others find that taking a nap during the day is beneficial (61-63). Failure to take into account the frequency of daytime napping could explain these inconsistent results (61). Unfortunately, most of these previous studies are based on self-reports, which may be unreliable, especially among the elderly, who may not have an accurate description of their nap habits due to cognitive disabilities (64,65). Studies have shown that waking up from a daytime napping leads to excessive sympathetic activation, which can result in an escalated heart rate and elevated blood pressure levels (66-68). The physiological response of a heightened heart rate and elevated blood pressure on waking could inflict additional strain on blood vessels and amplify the demand for oxygen by the heart muscle. Such changes are of particular concern, as they can significantly contribute to the development or exacerbation of HF (15,60,69-76). Our MR analysis results provided evidence that daytime napping has a causal link to a heightened risk of developing coronary atherosclerosis. These findings are in alignment with those of previous research studies (15,57,77). Daytime napping can disturb the sleep cycle, lead to an imbalance in hormone secretion related to the sleep-wake cycle disorder, induce the increase of inflammatory factors in the blood, and thus increase the risk of coronary atherosclerosis (15,74,78,79). A study has shown that health screenings of people at risk for daytime napping habits could be improved to help in the diagnosis and treatment of coronary atherosclerosis (57). The MR analyses shows that daytime napping did not show significant associations with non-rheumatic valvular disease. However, daytime napping plays a significant protective role in preventing the development of non-rheumatic valvular disease when adjusting for smoking. To our best knowledge, the present study may be the first time to assess daytime napping as a causal risk factor for non-rheumatic valvular disease. Therefore, further large intervention trial is needed to explore the effect of daytime napping on non-rheumatic valvular disease.

Consistent with the results of our study, a number of studies have revealed that sleep duration plays a significant protective role in preventing the development of HF (57,60,80,81). Additionally, findings from various studies have reported a correlation between genetically predicted shorter sleep durations and an elevated risk of HF (45,60,82-87). There are several mechanisms to explain the relationship between sleep duration and HF. Sleep restriction can increase sympathetic nerve activity, which in turn can lead to CAD and hypertension, all of which are important risk factors for HF (88). In addition, research has shown that short sleep duration may lead to hypoxia and more severe cardiac dysfunction (72,89). While the association between sleep duration and HF reached statistical significance, it is not quite evident whether it reaches clinical significance given the ORs presented. The OR value of sleep duration to HF is relatively small, which shows that it has little protection for him. The results of this OR value are similar to the original research papers, both of which show that the OR value is small (90). It may be due to the limitations of sample size or statistical methods. Therefore, further large intervention trial is needed to explore the effect of sleep duration on HF. The MR analyses conducted substantiated an inverse relationship between sleep duration and the prevalence of PVD. These findings are consistent with a previous study (91). Further, research has indicated a significant connection between short durations of sleep and the likelihood of developing PVD (91). Short sleep duration may lead to hyperactivity of the sympathetic nerve, an increased inflammatory reaction and oxidative stress, and damage the activity of the coagulation system, thus increasing the risk of PVD (92-94). Short sleep time may also change the circulating levels of leptin and ghrelin (95,96), thus increasing the risk of obesity (96,97) by increasing appetite and calorie

intake and reducing energy consumption (97,98), leading to hypertension (99), impaired glycemic control (100), and endothelial dysfunction (101), and thus increasing the risk of PVD. Moreover, results from various meta-analyses have indicated a link between a shorter sleep duration and an increased risk of several health conditions, such as obesity, hypertension, and type 2 diabetes. These conditions are recognized as significant risk factors for PVD (91,102). However, a massive OR is reported for the relationship between prolonged sleep duration and PVD when adjusting for smoking. Numerous studies show that there is a correlation between smoking and PVD (103,104). Some studies have shown that there is a dose correlation between smoking and PVD (105,106). It has been suggested that smoking causes PVD in association with leukocyte and platelet activation, increased inflammatory molecules, vasodilatory dysfunction, smooth muscle proliferation, and increased prothrombotic factors (107,108). In line with our observations, one study has shown that sleep duration exerts a significant protective effect on CAD (82). Previous studies have shown that the genetic prediction of short sleep duration increases the risk of CAD (5,19,82,109-113). Short sleep duration promotes the secretion of inflammatory mediators (93,114) and impels cortisol secretion (115), which activate chronic inflammation (116) and lead to endothelial dysfunction (117,118), increasing the risk of vascular damage (118) and atherosclerosis (119-121). The MR analyses shows that sleep duration did not show significant associations with stroke, which was similar to a previous study (90). However, the relationship between a longer sleep duration and increased stroke risk when adjusting for smoking status appears to be greater in magnitude of effect. Previous MR analyses provided genetic support for a causal relationship between smoking and stroke (122,123). Evidence from observational studies shows that smoking increases the risk of stroke (124). Smoking may increase the risk of stroke through platelet activation, endothelial dysfunction, inflammation, thrombosis and increased coagulation (125). In addition, nicotine may decrease cerebral blood flow (125). The MR analysis showed that a longer sleep duration was associated with a decreased risk of developing HF, PVD, and CAD. However, the impact of sleep duration may not necessarily be linear. Too long sleep duration may rather be harmful. For older adults with HF, previous study revealed that longer sleep durations of ≥8 hours indicates an increase in the risk of cognitive frailty (126,127). For patients with CAD, longer sleep duration is independently related to higher all-cause mortality (128). Moreover, a large amount of evidence from observational studies supports the link between long sleep duration and the risk of CAD (129-131). A number of confounding factors may influence the association between sleep duration and CVDs (132-135). Thus, the significant correlation between long sleep duration and CVD observed in many observational studies may be confounded by these unmeasured factors, and reflect a potential reverse causality. Therefore, further large-scale intervention experiments are needed to explore the influence of sleep duration and CVD, and subgroups of different sleep duration groups should be analyzed in the future.

The MR analysis suggested that depression was positively related to AF. The presence of depression or depressive symptoms has been shown to be associated with an elevated relative risk for AF (10,26,136,137). Similarly, patients with depression are at risk of new-onset AF, and the risk of AF increases further after repeated episodes of depression (137,138). It has been hypothesized that increased levels of acute phase reactants, including pro-inflammatory cytokines, and C-reactive protein, in individuals with depression (139), and heightened angiotensin II through the activation of the renin-angiotensin-aldosterone system, contribute to atrial fibrosis and heightened intra-cardiac pressure. These factors may exacerbate susceptibility to AF (140). In addition, increased sympathetic nerve activity and its arrhythmogenic effects can lead to AF (140). It should be noted that patients with depression exhibited a reduction in cerebral blood flow compared to individuals in a healthy control group (141). This finding suggests that the hemodynamic alterations experienced during AF could be a contributing factor to the observed connection between AF and depression, which offers insight into the underlying mechanism linking the two conditions (137). Indeed, it has been observed that patients with persistent or permanent AF may experience more significant cerebral perfusion deficits than those with paroxysmal AF alone (137). The MR analyses shows that depression did not show significant associations with HF. However, the relationship between depression and HF reverse when adjusting for smoking. This MR analyses did not support previous finds from some observational studies, which showed that smoking has been associated with a higher risk of HF (142-145). In addition, due to reverse causality and confounding, observational studies are prone to bias and may lead to unreliable causal effects. Therefore, further large-scale intervention experiments are needed to explore the influence of depression and smoking on HF. Moreover, in the previous literature, the presence

of depression had a negative impact on a variety of CVD, instead of AF alone. Gloria Hoi-Yee Li *et al.* revealed that depression was associated with increased risk of incident stroke and MI (26). This is inconsistent with our findings. It may be related to inconsistencies in sample size and research methods. Further research is needed to clarify the potential link between depression and CVD.

Our study is distinguished by several methodological strengths. Paramount among these is the use of a MR study design, which markedly reduced the likelihood of biases typically associated with observational research, thereby bolstering the credibility of our results. Additionally, our study probed potential mediating pathways through the application of multivariate MR analyses. This approach not only elucidates the mechanistic links but also serves to inform and guide future clinical interventions and preventive strategies. Further, the robustness of our investigation is underscored by the substantial sample sizes employed in each MR analysis, coupled with the reliable estimation of the effect exerted by each IV, as evidenced by the F-statistics surpassing the threshold of 10. Ultimately, after employing MR-PRESSO to rule out pleiotropy, we further ensured the consistency of our causal estimates by conducting sensitivity analyses using the MR-Egger approach, leave-one-out analysis, and the weighted median method. This demonstrates the robustness of our research outcomes.

However, some limitations of the study should be noted in interpreting our findings. Firstly, sleep traits may differ between age groups, and subgroup analyses of different age groups should be performed in the future. Second, this study population was limited to a European population, which may limit the extrapolation of our results. Third, the reliance on questionnaires for assessing sleep duration in the primary research might have resulted in biases related to measurement inaccuracies. Fourth, daytime napping, sleep duration, and depression may have associations among themselves. The current MR analysis has not been able to verify the association between daytime napping, sleep duration and depression. It is hoped that some subsequent observational studies will explore this further. Fifth, considering that disease states may impact sleep characteristics, there may be a bidirectional relationship. This study did not carry out a two-sample MR study, and future studies could go deep into the effects of CVDs on sleep duration, daytime naps and depression. Fifth, considering that disease states may impact sleep characteristics, there may be a bidirectional relationship. This study did not carry out a two-sample MR study, and future studies could go deep into the effects of CVDs on sleep duration, daytime napping and depression. Finally, despite employing a range of methods to analyze pleiotropic effects, the possibility of directed pleiotropy's influence cannot be entirely discounted. Fortunately, the use of multiple methods has yielded consistent findings, with no indications of heterogeneity or horizontal pleiotropy detected. Future studies need to be conducted to confirm causality and investigate underlying mechanisms.

Conclusions

This two-sample MR analysis revealed a causal positive association between daytime napping and the risk of several CVDs, including HF, coronary atherosclerosis, MI, and CAD. Conversely, a genetic predisposition to a longer sleep duration was linked to reduced risks of HF, PVD, and CAD. Additionally, depression was positively related to AF. These discoveries offer genetic proof to support the prevention of CVDs, with a particular focus on the significance of daytime naps, adequate sleep duration, and depression management.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-313/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-313/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as

revised in 2013).

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