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Causal roles of daytime sleepiness in cardiometabolic diseases and osteoporosis

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Abstract. – OBJECTIVE: Daytime sleepiness has some association with cardiometabolic diseases and osteoporosis, but it is unknown whether their relationship is causal. This two-sample Mendelian randomization (MR) study aims to explore their causal relationship.

MATERIALS AND METHODS: We included the largest genome-wide association studies (GWASs) associated with daytime sleepiness, cardiometabolic diseases and osteoporosis. 34 single nucleotide polymorphisms (SNPs) were used as the instrumental variables of daytime sleepiness.

RESULTS: Genetic predisposition to excessive daytime sleepiness was strongly associated with increased risk of coronary artery disease (beta-estimate: 0.610, 95% confidence interval [CI]: 0.128 to 1.093, standard error [SE]: 0.246, *p*-value=0.013) and may increase the incidence of type 2 diabetes (beta-estimate: 0.614, 95% CI: 0.009 to 1.219, SE: 0.309, *p*-value=0.047). We found no causal influence of daytime sleepiness on heart failure, atrial fibrillation, cerebral ischemia, intracerebral hemorrhage, forearm bone mineral density (FA-BMD), femoral neck BMD (FN-BMD), and lumbar spine BMD (LS-BMD).

CONCLUSIONS: This study suggested that excessive daytime sleepiness was causally associated with increased risk of coronary artery disease, which may benefit to prevent this disease.

Key Words:
Daytime sleepiness, Cardiometabolic diseases, Osteoporosis, Mendelian randomization study.

Introduction

Excessive daytime sleepiness has the typical feature of chronic insufficient sleep and can cause several sleep disorders, including sleep apnea, narcolepsy and circadian rhythm disorders[1,2]. Its occurrence also results from the progression and treatment of some diseases[3,4]. Excessive daytime sleepiness has become the risk factor of motor vehicle crashes, work-related accidents and loss of productivity[5,6]. In addition, these patients also commonly suffer from poor cognition, behavior and quality of life[7].

Previous observational studies[8-10] documented that excessive daytime sleepiness may be associated with the incidence of cardiometabolic disorders, stroke and osteoporosis, but these connections may be affected by potential confounding factors and reverse causality. Genetic factors contribute to the variation in daytime sleepiness because the heritability of daytime sleepiness is approximately between 0.37 and 0.48 in twin studies[11,12]. Genome-wide association studies (GWASs) find that daytime sleepiness, cardiometabolic disorders and osteoporosis are highly polygenic traits[13-20].

In order to explore the causal roles of daytime sleepiness in cardiometabolic diseases and osteoporosis, Mendelian randomization (MR) study has been designed and conducted to establish the causal relationship between exposure phenotype and outcome phenotype[19-23]. This two-sample MR study can increase the scope and statistical power of MR by using instrumental variables of daytime sleepiness[20,24,25], and aim to explore the causal effect of daytime sleepiness on the incidence of cardiometabolic diseases and osteoporosis.

Materials and Methods

Genetic Instrument for Daytime Sleepiness

The largest available GWAS reported the frequency of daytime sleepiness among 452,071 par-

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Table I. Details of studies and datasets used for analyses.

	Traits	Samples size	Population	Consortium or cohort study (Link URL)
Exposure	Daytime sleepiness	452,071	European	UK Biobank
Cardiometabolic diseases	Coronary artery disease	547,261	European	UK Biobank and CARDIoGRAMplusC4D (https://cvd.hugeamp.org/)
	Heart failure	977,323	European	UK Biobank (http://www.broadcvdi.org/)
	Atrial fibrillation	587,446	Predominant European (Mixed)	Meta-analysis of more than 50 studies (http://www.broadcvdi.org/)
	Type 2 diabetes	898,130	European	DIAGRAM (http://diagram-consortium.org)
Stroke	Cerebral ischemia	401,937	European	UK Biobank (https://www.leelabsg.org/resources)
	Intracerebral hemorrhage	399,717	European	
Osteoporosis	forearm BMD	53236	European	GEFOS (http://www.gefos.org)
	femoral neck BMD	53236	European	
	lumbar spine BMD	53236	European	

ticipants of European genetic ancestry (Table I). Daytime sleepiness was determined by the question: "How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g.: when working, reading or driving)", and answer categories included "never" (n=347,285), "sometimes" (n=92,794), "often" (n=11,963) and "all of the time" (n=29). Four categories were analyzed as a continuous variable using a linear mixed regression model adjusted for age, sex, genotyping array, ten principal components (PCs) of ancestry and genetic relatedness matrix[26].

Initially, 37 SNPs were thought to have robust association with daytime sleepiness ($p<5\times10^{-8}$, **Supplementary Table I**). Linkage disequilibrium (LD) between selected SNPs was calculated using European samples from the 1000 Genomes project, and three SNPs (rs34478464, rs7162082, rs189568347) were excluded due to high LD ($r^2\geq0.001$). Finally, 34 SNPs were used as instrumental variables of daytime sleepiness (**Supplementary Table II**).

Outcome Data Sources

Table I demonstrated the summary-level data for the genetic associations with the outcomes. Briefly, we used the GWAS summary data of cardiometabolic diseases including coronary artery disease (547,261 individuals) from UK Biobank and CARDIoGRAMplusC4D[27], heart failure (977,323 individuals) from UK Biobank[28], atrial fibrillation (587,446 individuals) from one large meta-analysis[29] and type 2 diabetes (898,130 individuals) from DIAGRAM[30]. For the association with stroke, GWAS summary data reported cerebral ischemia (401,937 individuals) and intracerebral hemorrhage (399,717 individuals) from UK Biobank[16]. Another large meta-analysis[31] reported the genetic variants associated with FN-BMD, FA-BMD and LS-BMD among 53,236 individuals of European ancestry. BMD was measured at the trabecular structure of forearm (distal 1/3 of radius), femoral neck and lumbar spine (L1-4). BMD was measured by dual X-ray absorptiometry.

Most GWASs were adjusted for sex, BMI and genetic principal components. All participants were all from European descent except those with atrial fibrillation from predominantly European descent (mixed descents). Summary statistics for SNPs related to daytime sleepiness and corresponding statistics of outcomes were presented in **Supplementary Table II**.

Statistical Analysis

To determine MR estimates of daytime sleepiness on each outcome, we conducted the inverse variance weighted (IVW), weighted median and MR-Egger regression methods[32,33]. MR-PRESSO was used to assess the presence of pleiotropy and the effect estimates were recalculated after excluding SNP outliers[34]. The ethical approval for each study included in this investigation can be found in the original publications (including informed consent from each participant). The differences with $p<0.05$ were considered statistically significant. All these analyses were conducted in R V.4.0.4 by using the R packages of 'MendelianRandomization'[35], 'TwoSampleMR'[36] and 'MR-PRESSO'[37].

Results

Cardiometabolic Diseases

We evaluated the causal effect of daytime sleepiness on coronary artery disease, heart failure, atrial fibrillation and type 2 diabetes in this MR

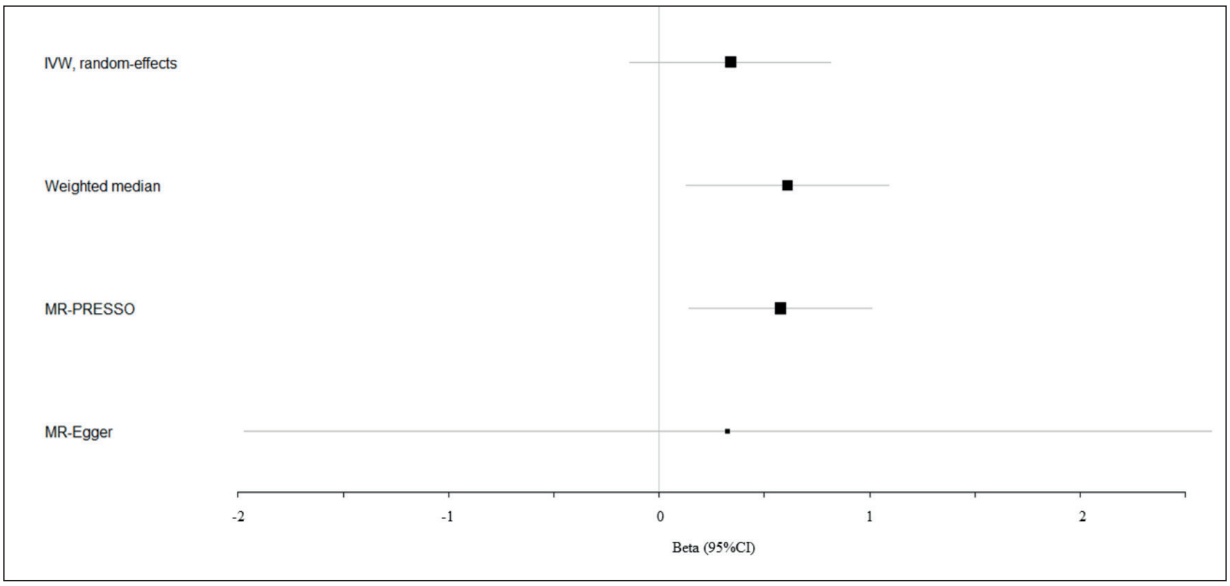

Figure 1. Beta (95% CIs) for causal association between daytime sleepiness and coronary artery disease through multiple analyses.

study (Table II). According to the weighted-median analysis, genetically excessive daytime sleepiness played a significant causal role in increased the risk of coronary artery disease (beta-estimate: 0.610, 95% CI: 0.128 to 1.093, SE: 0.246, *p*-value=0.013), but it was not supported by IVW analysis (beta-estimate: 0.339, 95% CI: -0.137 to 0.816, SE: 0.243, *p*-value=0.163, Figure 1).

In addition, the weighted-median analysis suggested some evidence to support the causal effect of excessive daytime sleepiness on increased risk of type 2 diabetes (beta-estimate: 0.614, 95% CI: 0.009 to 1.219, SE: 0.309, *p*-value=0.047), which was not confirmed by the IVW analysis (beta-estimate: 0, 95% CI: -0.794 to 0.794, SE: 0.405, *p*-value=1, Figure 2). IVW analyses showed that

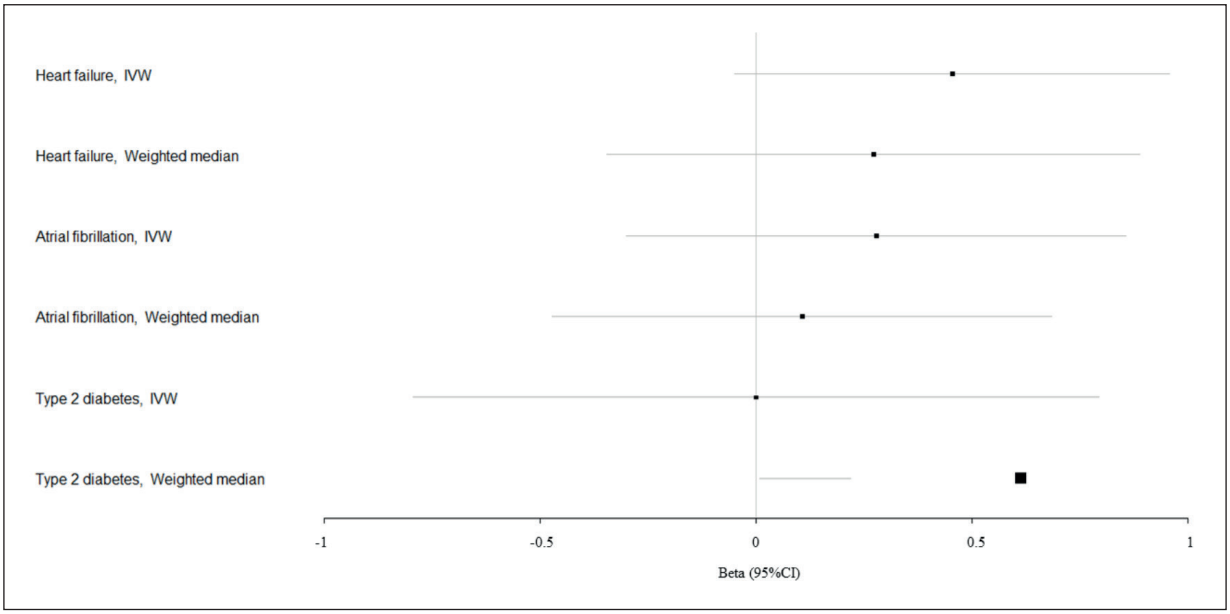

Figure 2. Beta (95% CIs) for causal influence of daytime sleepiness on heart failure, atrial fibrillation and type 2 diabetes through multiple analyses.

daytime sleepiness demonstrated no significantly causal impact on heart failure (beta-estimate: 0.455, 95% CI: -0.049 to 0.958, SE: 0.257, *p*-value=0.077) or atrial fibrillation (beta-estimate: 0.279, 95% CI: -0.301 to 0.858, SE: 0.296, *p*-value=0.439), which were both confirmed by the weighted-median analyses (Figure 2).

Stroke

Excessive daytime sleepiness was often reported in patients who experienced stroke[38]. Our IVW analyses found no causal roles of daytime sleepiness in cerebral ischemia (beta-estimate: -0.241, 95% CI: -1.587 to 1.105, SE: 0.687, *p*-value=0.726) or intracerebral hemorrhage (beta-estimate: 1.988, 95% CI: -4.727 to 0.751, SE: 1.397, *p*-value=0.115, Figure 2), which were both confirmed by the weighted-median and MR-Egger analyses (Table II).

Osteoporosis

Previous studies[39] demonstrated that daytime sleepiness was a risk factor of low BMD. Here, we explored the causal effect of daytime sleepiness on FA-BMD, FN-BMD and LS-BMD (Table II). According to IVW analysis, daytime sleepiness showed no causal influence on FA-BMD (beta-estimate: 0.058, 95% CI: -0.824 to 0.939, SE:0.450, *p*-value=0.898), FN-BMD (beta-estimate: 0.238, 95% CI: -0.145 to 0.621, SE: 0.195, *p*-value=0.173) or LS-BMD (beta-estimate: -0.222, 95% CI: -0.835 to 0.390, SE:0.312, *p*-value=0.173, Figure 3). These results were confirmed by the weighted-median and MR-Egger analyses (Table II).

Evaluation of Assumptions and Sensitivity Analyses

We found little evidence of directional pleiotropy for all models (MR-Egger intercept *p*-value>0.05, Table II). Significant heterogeneity remained for coronary artery disease, atrial fibrillation, and type 2 diabetes. Thus, MR-PRESSO method was conducted to identify 2 outliers (rs1846644, rs11078398) for coronary artery disease, 2 outliers (rs7607363, rs843372) for atrial fibrillation, 3 outliers (rs12140153, rs4665972, rs11078398) for type 2 diabetes and 1 outlier (rs11078398) for LS-BMD (Table III).

After excluding these SNP outliers, genetically excessive daytime sleepiness was confirmed to have a causal effect on increased risk of coronary artery disease (beta-estimate: 0.576, 95% CI: 0.140 to 1.011, SE: 0.222, *p*-value=0.010, Figure 1 and Table III). In addition, the MR association between daytime sleepiness with other outcomes were not changed after excluding the SNP outlier variants (Table III).

Discussion

Overall, our two-sample MR study confirms that excessive daytime sleepiness is strongly and causally associated with increased risk of coronary artery disease and may result in the increased risk of type 2 diabetes. However, we found no causal effect of daytime sleepiness on heart failure, atrial fibrillation, cerebral ischemia, intracerebral hemorrhage and three sites of BMD (i.e., FA-BMD, FN-BMD and LS-BMD).

Many studies[8,40,41] reported the associations between daytime sleepiness and cardiovascular diseases, such as coronary heart disease and stroke, but yielded conflicting results. Effective treatment of daytime sleepiness significantly improves the sleepiness symptoms and the quality of life[42-44]. If there are causal relationships between daytime sleepiness and cardiovascular diseases, the assessment, diagnosis, and treatment of excessive daytime sleepiness is of critical significance for the primary prevention of cardiovascular diseases.

These inconsistent results may be subject to potential confounding factors and reverse causality, which can be effectively prevented in this two-sample MR study[19,32]. Large-scale patient population were involved in our study, including the GWAS meta-analyses of daytime sleepiness (n=452,071) and coronary artery disease (n=547,261 individuals). Our research results revealed excessive daytime sleepiness displayed a robustly causal role in the increased risk of coronary artery disease, which was further confirmed by the PRESSO test (beta-estimate: 0.576, 95% CI: 0.140 to 1.011, SE: 0.222, *p*-value=0.010).

The positive MR association between daytime sleepiness and coronary artery disease is revealed in this study, and its mechanisms are attributed to systemic inflammation and metabolic syndrome[45]. Inflammatory cytokines contribute to sleepiness and fatigue, and they are presumed to be protective responses and promote recovery from illness[46]. During the process of atherosclerosis in patients with coronary artery disease, multiple mediators of inflammation induce immune cells to infiltrate the arterial intima[47,48]. The systemic inflammation in patients with daytime sleepiness participates in the pathogenesis of metabolic disorders, such as obe-

Table II. Mendelian randomization estimates of daytime sleepiness on outcomes.

Variables	IVW							Weighted median				MR-Egger							
	Estimate	SE	95% CI	*p*-value	Q value	I^2	Heterogeneity p-value	Estimate	SE	95% CI	*p*-value	Estimate	SE	95% CI	*p*-value	Intercept	SE	95% CI	Pleiotropy *p* value
Cardiometabolic disease																			
Coronary artery disease	0.339	0.243	-0.137,0.816	0.163	86.326	62.90%	0.000	0.610	0.246	0.128,1.093	0.013	0.326	1.171	-1.970,2.622	0.781	0.000	0.009	-0.017,0.017	0.991
Heart failure	0.455	0.257	-0.049,0.958	0.077	52.484	37.10%	0.017	0.273	0.315	-0.345,0.890	0.387	1.892	1.192	-0.443,4.228	0.112	-0.011	0.009	-0.028,0.006	0.217
Atrial fibrillation	0.279	0.296	-0.301,0.858	0.346	78.777	59.40%	0.000	0.107	0.296	-0.473,0.686	0.718	0.308	1.418	-2.472,3.088	0.828	0.000	0.010	-0.021,0.020	0.983
Type 2 diabetes	0.000	0.405	-0.794,0.794	1.000	142.509	77.50%	0.000	0.614	0.309	0.009,1.219	0.047	2.067	1.885	-1.629,5.762	0.273	-0.015	0.014	-0.043,0.012	0.262
Stroke																			
Cerebral ischemia	-0.241	0.687	-1.587,1.105	0.726	30.963	0.00%	0.519	-1.230	0.975	-3.140,0.680	0.207	-5.113	3.202	-11.389,1.163	0.110	0.037	0.024	-0.009,0.083	0.119
Intracerebral hemorrhage	-1.988	1.397	-4.727,0.751	0.115	30.548	0.00%	0.540	-2.996	2.017	-6.950,0.958	0.137	2.082	6.511	-10.680,14.845	0.749	-0.031	0.048	-0.125,0.063	0.522
Osteoporosis																			
FA-BMD	0.058	0.450	-0.824,0.939	0.898	40.536	18.60%	0.172	0.620	0.592	-0.540,1.780	0.295	2.941	2.060	-1.096,6.978	0.153	-0.022	0.015	-0.052,0.008	0.152
FN-BMD	0.238	0.195	-0.145,0.621	0.223	33.198	0.60%	0.458	0.330	0.287	-0.232,0.892	0.250	-0.082	0.920	-1.885,1.722	0.929	0.002	0.007	-0.011,0.016	0.722
LS-BMD	-0.222	0.312	-0.835,0.390	0.477	62.324	47.10%	0.002	-0.101	0.356	-0.798,0.596	0.777	0.133	1.470	-2.749,3.014	0.928	-0.003	0.011	-0.024,0.019	0.805

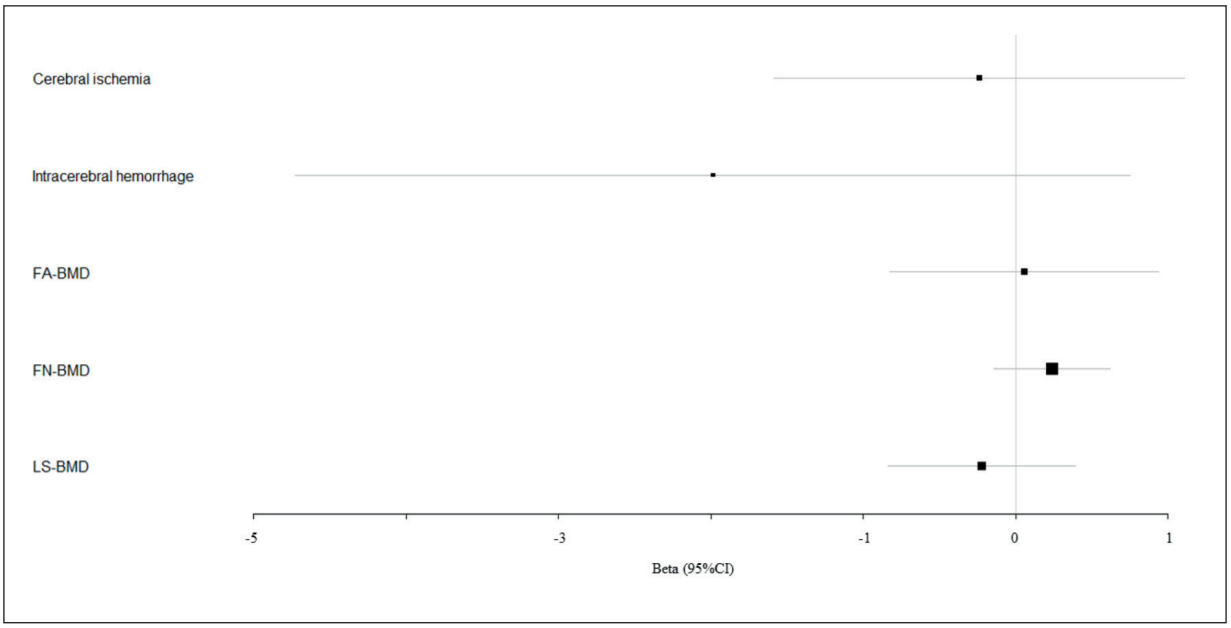

Figure 3. Beta (95% CIs) for causal influence of daytime sleepiness on cerebral ischemia, intracerebral hemorrhage, FA-BMD, FN-BMD and LS-BMD through the IVW analyses.

sity and diabetes[49]. Metabolic syndrome is associated with compromised insulin sensitivity, raised blood pressure and increased low-density lipoprotein cholesterol levels, which are widely accepted as the risk factors of coronary artery disease[50-53]. In addition, we also find the potential causal association between excessive daytime sleepiness and increased risk of type 2 diabetes, which is regulated by reduced insulin sensitivity[51].

Osteoporosis leads to low bone mass and microstructure deterioration. These patients have increased risk of fracture[54-57]. Excessive daytime sleepiness is common in the elderly, which suggests some association between daytime sleepiness and BMD[9,58]. In one observational study, daytime napping duration ≥30 min in postmenopausal women (n=4,962) and ≥60 min in premenopausal women (n=1,548) were found to increase the risk of osteopenia and osteoporosis[9]. However, our MR study found no causal association between daytime sleepiness and three sites of BMD (i.e., FA-BMD, FN-BMD and LS-BMD), which was confirmed by multiple MR analyses and sensitivity analyses. The positive association found in observational studies may result from confounding factors and reverse causality. In addition, we find limited evidence of associations between daytime sleepiness and heart failure, atrial fibrillation, cerebral ischemia and intracerebral hemorrhage.

Limitations

We should consider several limitations. Firstly, all included participants are of predominantly European people, and we do not know whether our findings are applicable to other populations. Secondly, excessive daytime sleepiness shows the MR association with increased risk of coronary artery disease, but the related mechanisms

Table III. Mendelian randomization estimates between daytime sleepiness and outcomes after excluding outliers detected by MR-PRESSO.

Outcomes	Estimate	SE	95% CI	*p*-value
Coronary artery disease excluding 2 outliers (rs1846644, rs11078398)	0.576	0.222	0.140,1.011	0.010
Atrial fibrillation excluding 2 outliers (rs7607363, rs843372)	0.261	0.247	-0.224,0.746	0.291
Type 2 diabetes excluding 3 outliers (rs12140153, rs4665972, rs11078398)	0.297	0.254	-0.199,0.794	0.241

are not clear. Thirdly, MR association between daytime sleepiness and type 2 diabetes is not robust, and more populations should be included to confirm it.

Conclusions

This two-sample MR study supports that excessive daytime sleepiness causally results in increased risk of coronary artery disease, which may help prevent it.

Conflict of Interest

The authors declare that they have no conflict of interest.

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None.

Data Availability

Data supporting the findings of this study were available within the paper.

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