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ORIGINAL RESEARCH

Genetically Predicted Insomnia in Relation to 14 Cardiovascular Conditions and 17 Cardiometabolic Risk Factors: A Mendelian Randomization Study

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BACKGROUND: This Mendelian randomization study aims to investigate causal associations between genetically predicted insomnia and 14 cardiovascular diseases (CVDs) as well as the potential mediator role of 17 cardiometabolic risk factors.

METHODS AND RESULTS: Using genetic association estimates from large genome-wide association studies and UK Biobank, we performed a 2-sample Mendelian randomization analysis to estimate the associations of insomnia with 14 CVD conditions in the primary analysis. Then mediation analysis was conducted to explore the potential mediator role of 17 cardiometabolic risk factors using a network Mendelian randomization design. After correcting for multiple testing, genetically predicted insomnia was consistent significantly positively associated with 9 of 14 CVDs, those odds ratios ranged from 1.13 (95% CI, 1.08–1.18) for atrial fibrillation to 1.24 (95% CI, 1.16–1.32) for heart failure. Moreover, genetically predicted insomnia was consistently associated with higher body mass index, triglycerides, and lower high-density lipoprotein cholesterol, each of which may act as a mediator in the causal pathway from insomnia to several CVD outcomes. Additionally, we found very little evidence to support a causal link between insomnia with abdominal aortic aneurysm, thoracic aortic aneurysm, total cholesterol, low-density lipoprotein cholesterol, glycemic traits, renal function, and heart rate increase during exercise. Finally, we found no evidence of causal associations of genetically predicted body mass index, high-density lipoprotein cholesterol, or triglycerides on insomnia.

CONCLUSIONS: This study provides evidence that insomnia is associated with 9 of 14 CVD outcomes, some of which may be partially mediated by 1 or more of higher body mass index, triglycerides, and lower high-density lipoprotein cholesterol.

Key Words: cardiometabolic risk factors ■ cardiovascular disease ■ insomnia ■ mediator ■ Mendelian randomization

Insomnia is the second most prevalent mental disorder with an annual incidence of approximately 35% to 50% in the general population.[1,2] In the past decade, there has been increasing evidence suggesting insomnia as an important risk factor of cardiovascular disease (CVD),[3–6] but evidence originating from observational studies (eg, the association between insomnia and hypertension[7–12]) can sometimes be inconsistent, which may, at least in part, be explained by confounding or bias due to reverse causation. The American Heart Association published a scientific statement asking health organizations to develop

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CLINICAL PERSPECTIVE

What Is New?

- Insomnia is the second most prevalent mental disorder.
- Except for some major cardiovascular diseases (CVDs), the causal relationships between insomnia and the development of other CVDs such as arterial hypertension are still unclear, and the potential pathways involved in the association from insomnia to CVDs have not been studied.
- This study performed Mendelian randomization analysis to investigate the causal associations between genetically predicted insomnia and 14 CVDs as well as the potential mediator role of 17 cardiometabolic risk factors.

What Are the Clinical Implications?

- Insomnia was found to increase the risk of 9 of 14 CVD outcomes, including ischemic stroke, transient ischemic attack, thrombotic diseases, and 5 other CVDs (eg, coronary artery disease, heart failure, arterial hypertension).
- Genetic predicted insomnia was associated with higher body mass index and triglycerides as well as lower high-density lipoprotein cholesterol (without bidirectional causality), each of which may act as a mediator in the causal pathway from insomnia to several CVD outcomes.
- These results are consistent with previous studies that suggest insomnia as an important causal risk factor for some major CVDs.

Nonstandard Abbreviations and Acronyms

IS	ischemic stroke
IVW	inverse variance weighted
MR	Mendelian randomization
WC	waist circumference
WHR	waist-hip ratio

evidence-based sleep recommendations for a number of sleep disorders, including insomnia.[13] Therefore, it is an urgent need to address the causal evidence to determine whether insomnia is in fact on the causal pathway for each CVD outcome. Although several Mendelian randomization (MR) studies have investigated that insomnia may be a causal risk factor for some major CVDs, including coronary artery disease (CAD), heart failure (HF), and ischemic stroke (IS),[14–16] uncertainty persists about the causal role of insomnia for the development of other CVDs, such as arterial hypertension. Moreover, the potential pathways involved in the association from insomnia to CVDs have not been studied. Previous studies presented evidence that insomnia is associated with impaired glucose metabolism[17] and several risk factors for CVD, such as body mass index (BMI) and waist-hip ratio (WHR),[14,15] so cardiometabolic risk factors may act as potential mediators that lie in the pathway from insomnia to the risk of specific CVD outcome.

MR is a powerful approach to estimate the causal effect of an exposure on an outcome in observational data.[18,19] The analytical method is less susceptible to bias due to confounders and evades potential bias by reverse causation through the use of genetic variants randomly allocated during conception, generally single-nucleotide polymorphisms (SNPs), as instrumental variables for exposure.[18,19] The following 3 key assumptions guarantee the altered genetic variants to be valid instrumental variables: (1) (Relevance) genetic variants are associated with the exposure; (2) (Independence) genetic variants are not associated with any confounder of the exposure-outcome association; and (3) (Exclusion restriction) genetic variants are not associated with outcome conditional on exposure and confounders.[20,21] Well-powered genome-wide association studies (GWAS) have identified hundreds of SNPs associated with insomnia[14]; additionally, several consortia with large numbers of participants have made summarized data publicly available for many risk factors. These create the opportunity to conduct MR analysis in a 2-sample strategy using summarized data to obtain more precise estimates of the causal effects. Moreover, compared with standard MR, the network MR method[22] is increasingly being used to answer causal mediation questions within the MR framework. It calculated the causal effects of the exposure on a mediator and the mediator on the outcome; these 2 estimates can then be multiplied together to estimate the indirect effect.[22–24] The proportion mediated is calculated by dividing the indirect effect by the total effect; therefore, the network MR method can be used to investigate the effect of an exposure on the outcome operating through each mediator (indirect effect).

In this study, based on summary data obtained from large consortia and calculated based on individuals from UK Biobank, we performed a series of 2-sample MR analyses to establish whether insomnia has a causal effect on the risks of 14 CVD outcomes. Then we conducted a mediation analysis to examine each of 17 cardiometabolic risk factors as a possible mediator in the causal relationship between genetically determined insomnia and each CVD outcome using a network MR design. A flow chart of our study design was provided in Figure 1.

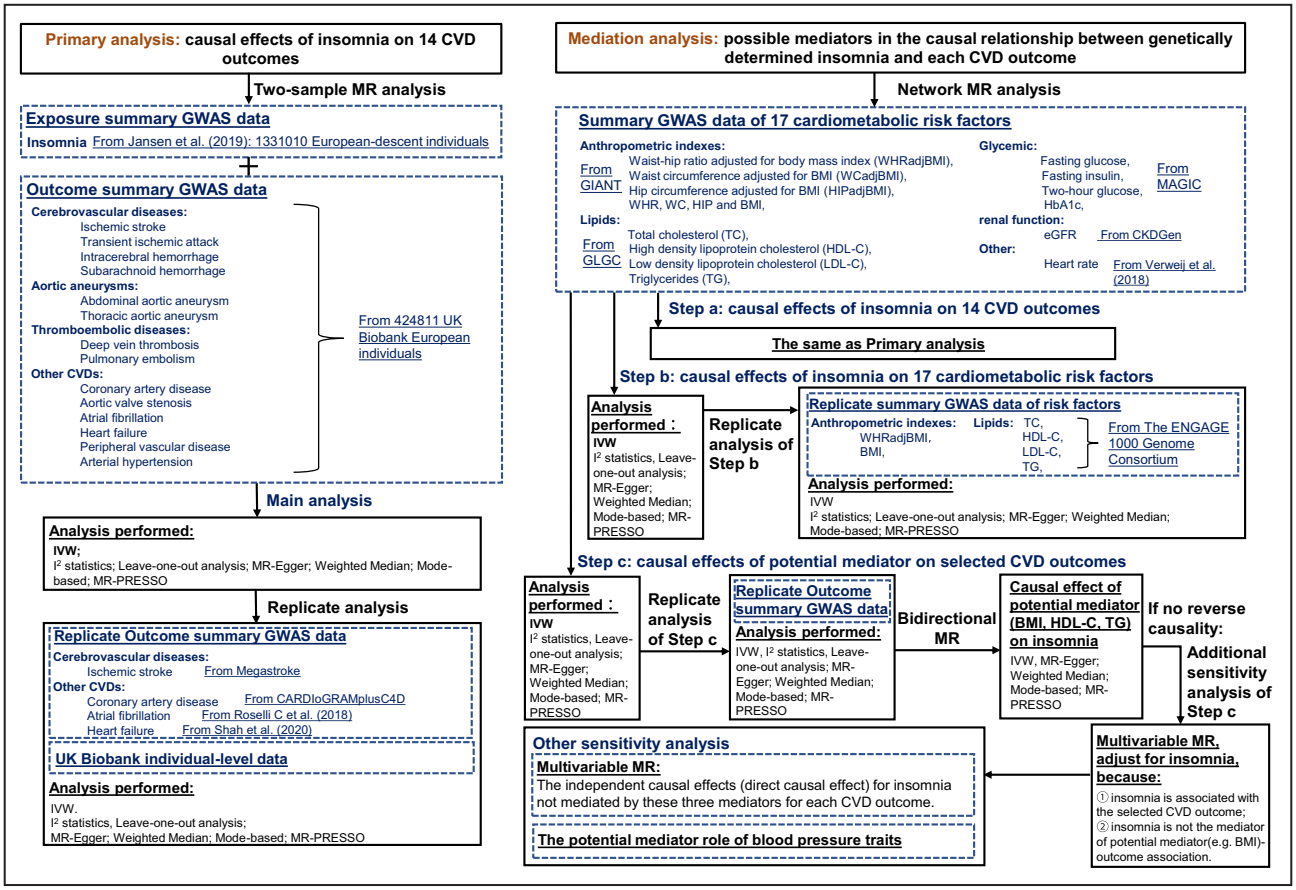

Figure 1. The flow chart of study design and data sources for each analysis performed.
CKDGen indicates the Kidney Disease Genetics consortium; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ENGAGE, European Network for Genetic and Genomic Epidemiology; GIANT, the Genetic Investigation of Anthropometric Traits consortium; GWAS, genome-wide association study; HbA1c, hemoglobin A1c; IVW, inverse variance weighted; MAGIC, the Meta-Analyses of Glucose and Insulin-Related Traits consortium; MR, Mendelian randomization; and MR-PRESSO, Mendelian randomization-pleiotropy residual sum and outlier.

METHODS

The data used in these analyses are publicly available. The UK Biobank study was approved by the North West Multi-centre Research Ethics Committee, and all its participants provided informed consent. The UK Biobank data were accessed through application 51470. The analyses of other publicly available data or summary statistics do not require additional ethical approval. All generated results were presented in the article and its supplement.

Genetic Instruments

Instrumental variables for insomnia were obtained from a GWAS meta-analysis of 1 331 010 European-descent individuals,[14] the insomnia complaints were measured using questionnaire data, and the specific definition was provided in Table S1. This study identified 248 independent lead SNPs (r^2<0.1) located in 202 genomic risk loci (distinct genomic loci are >250kb apart) associated with insomnia at genome-wide significance (2-sided *P* value from the meta-analysis of the GWAS results of insomnia: $P<5\times10^{-8}$), explaining 2.6% of the variance in insomnia (corresponding to an *F* statistic of 143.24).[14] This means that assumption (1) is satisfied and avoids the bias caused by weak instrument in terms of the rule of thumb[25]; see Data S1 for the details. The effect estimates (in units of log odds ratios [ORs]) and corresponding standard errors of these SNPs were extracted from Table S6 in Jansen et al[14] (the details of those SNPs were provided in the Table S2). For all analyses in this study, SNPs were aligned to the same effect allele across the data sources before analyses, and we checked the effect allele frequencies for concordance.

Data Sources

Data Sources of CVD Outcomes

The summary statistics of genetic associations with the outcomes were derived based on the imputed genotype data of the UK Biobank, an ongoing large

prospective cohort study. The UK Biobank recruited over 500 000 people aged 40 to 69 years, mean age 56.5 years, from Great Britain between 2006 and 2010, with 94% self-reported European ancestry, 45.6% men, and median follow-up time currently 11.1 years (https://www.ukbiobank.ac.uk/).[26] In this study, we considered outcomes including the following 14 subtypes of CVD as Larsson et al[27] did: cerebrovascular diseases (IS, transient ischemic attack, intracerebral hemorrhage, and subarachnoid hemorrhage), aortic aneurysms (abdominal and thoracic aortic aneurysm), thrombotic diseases (deep vein thrombosis and pulmonary embolism), and other CVDs (CAD, aortic valve stenosis, atrial fibrillation [AF], HF, peripheral vascular disease as well as arterial hypertension). The outcomes were defined based on electronic health records, hospital procedure codes, and self-reported information confirmed by interview with a nurse. The specific definitions and sources of information can be found in Table S3. For quality control, we excluded participants with (1) non-White British ancestry, (2) mismatch between genetic sex and self-reported sex, (3) excess relatedness with kinship more than 10 putative third-degree relatives, (4) poor-quality genotyping with heterozygosity and missing rates > 1.5%, or (5) outliers with high heterozygosity and high missing rate (see Figure S1 for the flow chart of individual selection). Finally, a total of 424 811 UK Biobank participants who satisfied the inclusion criteria were included in this study. The mean age was 57.37 years (5th to 95th percentile: 43 to 69 years), and 45.65% of the population were men (descriptive statistics were reported in Table S4). For each CVD outcome, individuals suffering from any other 13 CVD outcomes or without genetic data were further excluded from the analysis's data set (Figure S1). Then the genetic associations with each CVD outcome (on a log OR scale) were obtained from the identified White British individuals in UK Biobank using logistic regression controlling for 10 principal components, which can further control for population stratification.

Data Sources of Cardiometabolic Risk Factors

The genetic association estimates with 17 cardiometabolic risk factors, including anthropometric indexes (WHR adjusted for BMI, waist circumference [WC] adjusted for BMI, hip circumference adjusted for BMI, WHR, WC, hip circumference, and BMI), lipids (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglycerides [TG]), glycemic traits (fasting glucose, fasting insulin, 2-hour glucose, hemoglobin A1c), renal function (estimated glomerular filtration rate), and heart rate increase during exercise were taken from the GIANT (Genetic Investigation of Anthropometric Traits) consortium,[28,29] the GLGC (Global Lipids Genetic Consortium),[30] the MAGIC (Meta-Analyses of Glucose and Insulin-related Traits Consortium),[31–33] the CKDGen (Kidney Disease Genetics) consortium,[34] and published GWAS study in Verweij et al,[35] respectively. We constrained the population of these GWAS summary statistics data mainly from European ancestry to minimize the bias caused by population stratification. The basic characteristics of these consortia and the genetic association estimates were presented in Table S5.

Statistical Analysis

Primary analysis

Our primary analysis aimed to explore the causal associations of insomnia with 14 CVD outcomes. Because 1 of 248 SNPs (rs77641763 in chr9) was unavailable in the outcome data set (UK Biobank), 247 SNPs were used as genetic instrumental variables for insomnia.

For each CVD outcome, the overall causal estimate of insomnia on this CVD outcome was obtained using an inverse variance weighted (IVW) method[36] (under a multiplicative random-effects model), combining the variant-specific Wald (ratio) estimators[37,38] estimated for each SNP through the SNP-CVD association divided by the SNP-insomnia association. This method provides the highest precision and retains maximal power under the assumption that all SNPs are valid instrumental variables,[39] that is, the pleiotropic effects of the genetic variants (genetic variant affects the outcome via a different biological pathway from the exposure under investigation) are all zero.[40] Moreover, it accounts for heterogeneity in the variant-specific causal estimates.[41] The results were converted to ORs expressed per genetically predicted 1-unit-higher log-odds of liability to insomnia, corresponding to per 2.72-fold increase in the prevalence of insomnia according to Burgess et al.[42] As many MR analyses with multi-outcomes[43] did, to account for multiple testing and to preserve the type I error of the global null hypothesis of all tested associations being in fact null,[44] we used a Bonferroni-corrected threshold of $P<3.6\times10^{-3}$ ($\alpha=0.05/14$ outcomes) at the outcome level in our primary analysis. We note that these outcomes are related to each other; therefore, the tests are not completely independent of each other and the Bonferroni correction may be conservative. We reported the actual P values of each effect; the association between our threshold and 0.05 was considered suggestive evidence of association, requiring confirmation.[43]

Mediation Analysis

We further conducted a mediation analysis to explore whether the chosen cardiometabolic risk factors

mediate the causal pathway from insomnia to CVD outcome that insomnia is significantly associated with, using a network MR design. For each CVD outcome, this design consists of 3 different steps (Steps a-c):[22]

Step a: We estimated the causal effect of genetically determined insomnia on this CVD outcome, this step was in accordance with our primary analysis.

Step b: Up to 248 independent SNPs associated with insomnia at genome-wide significance from Jansen et al[14] were used to estimate the causal effect of genetically determined insomnia on each potential cardiometabolic risk factor, using the respective GWAS summary statistics described previously,[28–35] using the IVW approach (under a multiplicative random-effects model). The estimated effects were SD or per unit change in risk factors expressed per genetically predicted 1-unit-higher log-odds of liability to insomnia (per 2.72-fold increase in the prevalence of insomnia). There was no sample overlap between insomnia GWAS study and consortia of all risk factors except for heart rate (~4%). The Bonferroni-corrected threshold of $P<3\times10^{-3}$ (α=0.05/17 mediators) was used in this step.

Step c: For possible mediators that causal association was observed in Step b (BMI, HDL-C, and TG), we estimated the causal effect of each mediator on this CVD outcome, respectively, using the IVW approach (under a multiplicative random-effects model). The details of instrumental SNPs and the summary statistics we used for each mediator in Step c were shown in Data S2 and Table S6–S8, and SNP-CVD outcome coefficients were calculated from the identified White British individuals in UK Biobank using logistic regression controlling for 10 principal components. There was no sample overlap between each mediator GWAS study and UK Biobank. The results were converted to ORs expressed per genetically predicted 1 SD increased of the mediator, and Bonferroni-corrected threshold of $P<5.6\times10^{-3}$ (α=0.05/9 outcomes that insomnia significantly associated with) was used in this step.

If causal associations were observed in all 3 steps, the conclusion can be drawn that the specific cardiometabolic risk factor is a mediator in the pathway linking insomnia to this CVD outcome. The indirect effect of insomnia on this CVD outcome mediated through each mediator was estimated by multiplying the results from Step b and Step c. We finally divided the mediated effect by the total effect to estimate the proportion mediated by each mediator (see Data S3 for the calculation of proportions and Data S4 for the calculation of their 95% CIs).

Sensitivity Analysis

A series of sensitivity analyses were performed to examine the robustness of the results in the primary analysis and each step for mediation analysis. First, the presence of substantial heterogeneity among Wald estimates based on individual SNPs would indicate the presence of invalid instruments.[45] In this study, the magnitude of heterogeneity among variant-specific Wald estimates was evaluated using the I^2 statistic, which is defined as the percentage of the total variation in the estimates explained by heterogeneity rather than sampling error if all genetic variants are valid instruments and relationships between all variables (genetic variants, exposure, and outcome) are linear and homogeneous for all individuals in the population, independent of the number of estimates.[46,47] Moreover, leave-one-out sensitivity analysis was also performed to assess the reliance of the MR results on each particular variant.

Second, we performed a range of robust methods making different consistency assumptions. We examined the potential bias from invalid instruments when using multiple genetic variants through weighted median and mode-based estimation, which rely on weaker assumptions about the invalid instruments and are more robust to outliers. The former method will provide a consistent estimate if at least 50% of the weights come from valid instrumental variables,[48] and the latter assumes more variants estimate the true causal effect than estimating any other quantity,[49] but have been shown to have low precision in some studies and simulations.[50] In addition, we applied the MR-Egger regression method, which can obtain a valid estimate of the causal effect even if all the genetic instruments are invalid under the Instrument Strength Independent of Direct Effect assumption, but with low power.[40] Moreover, the non-zero intercept indicates the existence of directional pleiotropy; therefore, MR-Egger intercept test can help to assess the validity of instrumental variable assumption (3).[40] MR pleiotropy residual sum and outlier method was also used to detect and correct for horizontal pleiotropic through the removal of SNPs that are most likely to display horizontal pleiotropic effects (outliers).[51] As suggested by Slob and Burgess[50], these 4 methods can adequately assess the evidence of the causal effects of each exposure on the outcome and detect the sensitivity of the results to different patterns of violations of instrumental variable assumptions; consistency of results across methods strengthens an inference of causality.

Additionally, we performed a bidirectional MR analysis to examine whether each selected mediator can casually affect insomnia (bidirectional causality) by using mediator-associated independent SNPs as instrumental variables (Data S2 and Table S6–S8), the summary statistics of insomnia were obtained from Jansen et al.[14] If there was no evidence that one genetically predicted mediator causally affects insomnia, then we applied regression-based multivariable MR as an additional sensitivity analysis of Step c for

mediation analysis. We estimated the causal effect of this mediator on each CVD outcome, respectively, adjusting for the genetic effects of the instruments on insomnia obtained from Jansen et al,[14] as suggestive by Carter et al.[52,53] We additionally performed multivariable MR to consider the role of multiple mediators simultaneously and to investigate the direct causal effect of insomnia on each CVD outcome not mediated by these 3 mediators; see Data S5 for the details.

In our analyses, we considered arterial hypertension as a CVD outcome. As blood pressure traits (including systolic blood pressure, diastolic blood pressure [DBP]) are also important cardiometabolic risk factors, we additionally performed analyses to explore whether systolic blood pressure and DBP mediate the causal pathway from insomnia to the other 8 insomnia-associated CVD outcomes using a network MR design. The details were provided in Data S6.

Replication Analysis

We conducted replication analysis by varying different data sets to further assess the robustness of our results. For the primary analysis, we estimated that approximately 30% of individuals from GWAS on insomnia were also included in the UK Biobank.[54] Thus, we further performed a replication analysis using summary data of 4 CVD outcomes, including IS, CAD, AF, and HF, from previously published GWAS studies[55–58] that have no or limited sample overlap with the GWAS of insomnia. Full details of each GWAS can be found in Table S9. We also validated these results with UK Biobank individual-level data in a 2-sample setting (see Data S7). For mediation analysis, we performed replication analysis using a most recent data (the ENGAGE (European Network for Genetic and Genomic Epidemiology) 1000 Genome Consortium, http://diagram-consortium.org/2015_ENGAGE_1KG/,[59,60] see Table S10 for the details) as the replication data set for 6 anthropometric and lipid traits in Step b. For Step c, we also performed replication analysis using summary statistics of 4 CVD outcomes from published GWAS studies (Table S9). All replication analysis were conducted using IVW in addition to similar heterogeneity assessment approaches and 4 robust methods for sensitivity analysis.

All statistical tests were 2 sided. Analyses in this study were performed using PLINK2 and R version 4.0.2 together with the R package *MendelianRandomization*,[61] *MRPRESSO*.[51]

RESULTS

Causal Association Between Genetically Predicted Insomnia and CVD Outcomes

We found that genetically predicted insomnia was significantly positively associated with 10 of the 14 outcomes using the IVW method; the ORs ranged from 1.13 (95% CI, 1.08–1.18) for AF to 1.24 (95% CI, 1.16–1.32) for HF (Figure 2). Additionally, there was suggestive evidence of positive associations between genetically predicted insomnia and intracerebral hemorrhage (OR, 1.18; 95% CI, 1.02–1.37; *P*=0.03) and subarachnoid hemorrhage (OR, 1.23; 95% CI, 1.06–1.43; *P*=0.005), whereas statistically nonsignificant positively associations were observed between insomnia and abdominal aortic aneurysm (OR, 1.14; 95% CI, 1–1.30; *P*=0.06) or thoracic aortic aneurysm (OR, 1.02; 95% CI, 0.79–1.31; *P*=0.9) (Figure 2).

There was no evidence of SNP that has a strong influence on the estimations of causal association (Table S11). Although we noted that MR-Egger and mode-based estimates were sometimes different from the other MR methods, for example, pulmonary embolism and aortic valve stenosis, most OR estimates were consistent using different MR approaches (Table S12). The intercept of MR-Egger regression for 247 SNPs in each CVD outcome was not statistically significant except for intracerebral hemorrhage (Intercept=−0.03; 95% CI, −0.06 to −0.01; *P*=0.01). After excluding SNPs because of their pleiotropic effects, the analyses of the remaining SNPs did not materially change the OR of insomnia on intracerebral hemorrhage (OR, 1.15; 95% CI, 1–1.34; *P*=0.057). However, results of replication analysis showed that genetically predicted insomnia was still significantly positively associated with 9 of the 10 outcomes identified, except for aortic valve stenosis (OR, 1.25; 95% CI, 0.93–1.68; *P*=0.14) (Table S13–S16).

Causal Association Between Genetically Predicted Insomnia and Cardiometabolic Risk Factors

The causal estimates between genetically predicted insomnia and 17 cardiometabolic risk factors using the IVW method were displayed in Figure 3. Genetically predicted insomnia was significantly positively associated with 4 risk factors, including BMI (0.07; 95% CI, 0.04–0.10), TG (0.06; 95% CI, 0.04–0.09), WC (0.06; 95% CI, 0.03–0.09), and WHR (0.05; 95% CI, 0.03–0.07). However, no association was observed with insomnia for the latter 2 indexes after the adjustment for BMI (WC adjusted for BMI [0; 95% CI, −0.03 to 0.02] and WHR adjusted for BMI [0.02; 95% CI, −0.01 to 0.04]). Moreover, genetically predicted insomnia was significantly negatively associated with HDL-C (−0.06; 95% CI, −0.09 to −0.03).

There was no evidence of SNP that has a strong influence on the estimations of causal associations (Table S17). Associations estimated by the weighted median, mode-based, MR-Egger, and MR-PRESSO method were broadly similar to our main results for BMI, TG, and HDL-C, with little evidence for the presence of pleiotropy

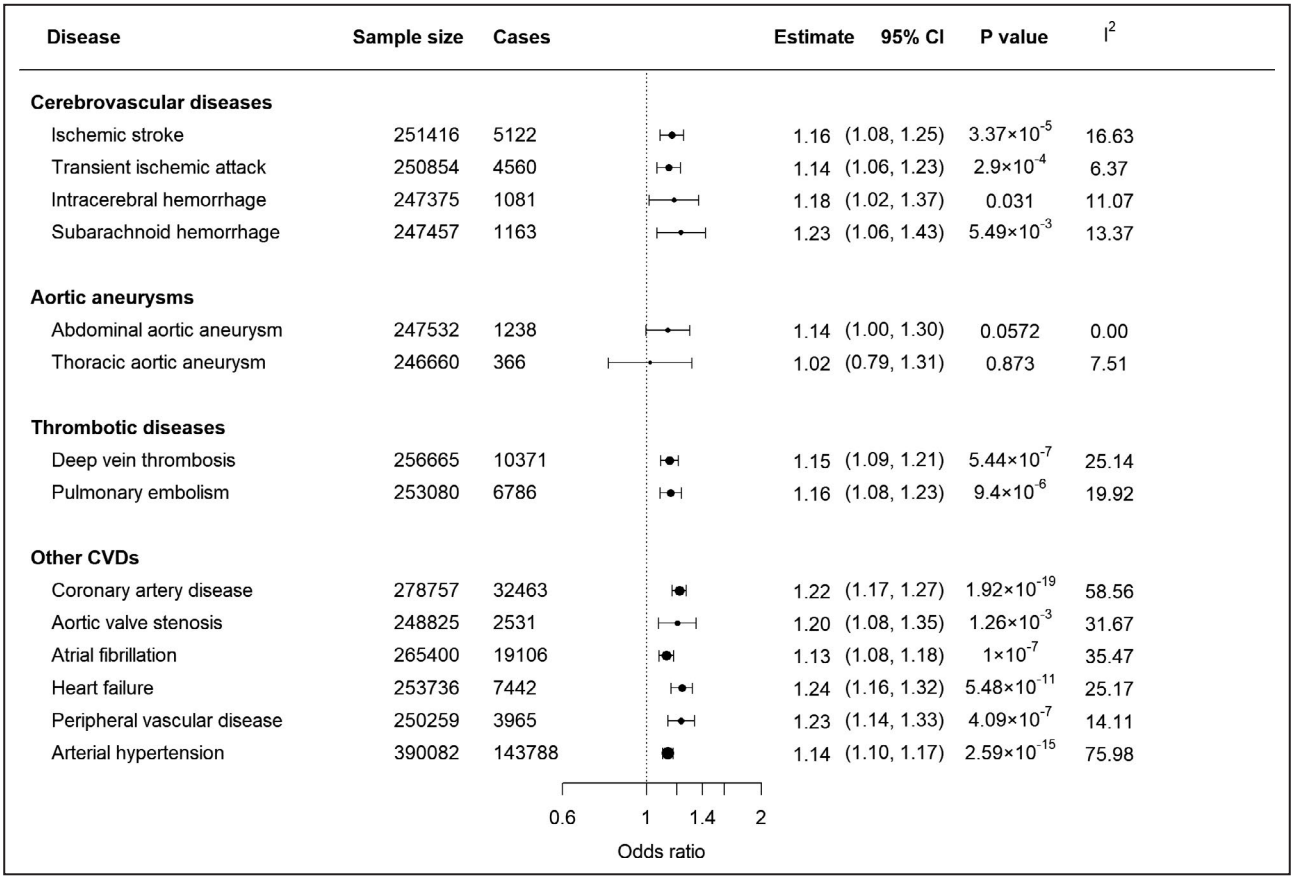

Figure 2. Associations between genetically predicted insomnia and 14 cardiovascular diseases (CVDs).
Results were obtained from the multiplicative random-effects inverse-variance weighted method. Sample size denotes the total number of individuals in the analysis data set for each CVD outcome (see Figure S1 for flow chart of individual selection). Estimates represent odds ratios (OR) expressed per genetically predicted 1-unit-higher log-odds of liability to insomnia (per 2.72-fold increase in the prevalence of insomnia); I^2 statistic quantifies the amount of heterogeneity among estimates based on individual single-nucleotide polymorphisms. Circles show the estimated ORs, and the sizes of these circles represent the precision of these estimates.

(Table S18). However, the association estimated by mode-based and MR-Egger method was generally underpowered with wide CIs. Our replication studies for BMI, TG, and HDL using the ENGAGE 1000 Genome data also provided consistent results (Tables S19–S20). There was consistently no statistically significant association between genetically predicted insomnia with TC, LDL-C, glycemic traits, renal function as well as heart rate increase during exercise. Finally, 3 of 17 cardiometabolic risk factors including BMI, TG, and HDL-C were suggested to be possible mediators from insomnia to CVD outcomes and were chosen to conduct further analyses.

Causal Association Between Genetically Predicted BMI, TG, HDL, and CVD Outcomes

We evaluated further whether each of BMI, TG, and HDL causally associated with each of 9 selected CVD outcomes. To begin with, we used 74 of 78 independent SNPs (R^2=2.2%) associated with BMI ($P<5\times10^{-8}$)[29] as instrumental variables. Under a Bonferroni-corrected threshold of $P<0.0056$, a genetically predicted 5 kg/m^2 (1 SD) increase of BMI was significantly associated with 7 of 9 CVD outcomes using the IVW method, with ORs ranging from 1.52 (95% CI, 1.37–1.67) for arterial hypertension to 2.14 (95% CI, 1.78–2.58) for HF (Figure S2). There was no evidence of SNP that has a strong influence on the estimations of causal associations and presents of pleiotropy (Tables S21–S22), except for the analyses of BMI on CAD. After excluding SNPs due to the potential pleiotropic effects, analyses of the remaining SNPs yielded a similar OR of 1.57 (95% CI, 1.37–1.79; $P=2.89\times10^{-11}$). The results of sensitivity analysis and replication analysis (Tables S23–S24) were broadly similar to our main results for BMI.

Then 85 of 86 independent SNPs (R^2=5.9%) as well as 51 independent SNPs (R^2=4.6%)[30] associated with HDL-C and TG, respectively, were used as instrumental variables. According to the results of IVW method, a genetically predicted 1 SD increase of HDL-C was negatively associated with higher risk of CAD (OR, 0.82;

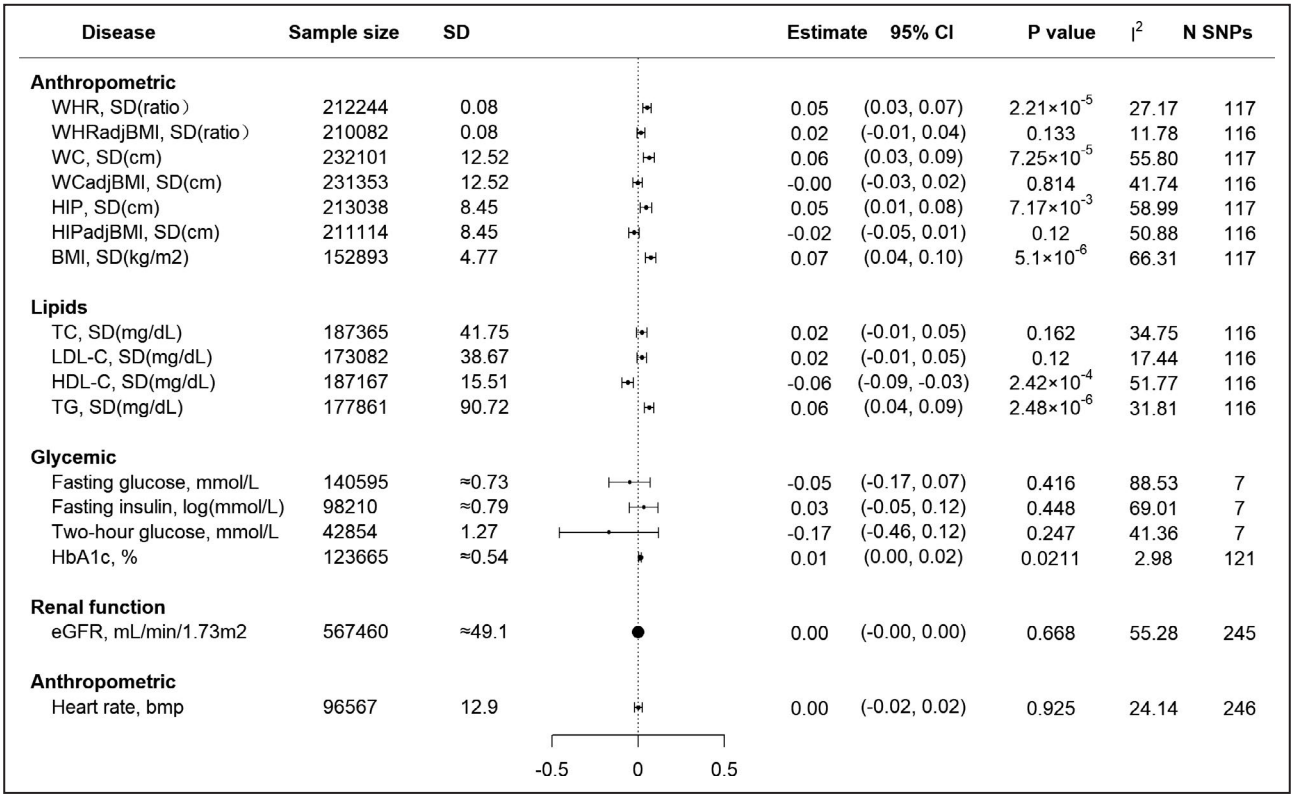

Figure 3. Associations between genetically predicted insomnia and 17 cardiometabolic risk factors.
Results were obtained from the multiplicative random-effects inverse-variance weighted method. Estimated effects were SD or per unit change in risk factor expressed per genetically predicted 1-unit-higher log-odds of liability to insomnia (per 2.72-fold increase in the prevalence of insomnia). I^2 statistic quantifies the amount of heterogeneity among estimates based on individual SNPs. N SNPs was the number of instrument SNPs we used for Mendelian randomization analysis of the association of genetically predicted insomnia on each risk factor. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HIP, hip circumference; HIPadjBMI, HIP adjusted for BMI; LDL-C, low-density lipoprotein cholesterol; SNP, single-nucleotide polymorphism; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WCadjBMI, WC adjusted for BMI; WHR, waist-hip ratio; and WHRadjBMI, WHR adjusted for BMI.

95% CI, 0.73–0.91), peripheral vascular disease (OR, 0.80; 95% CI, 0.69–0.94) and arterial hypertension (OR, 0.86; 95% CI, 0.80–0.93) (Figure S3). A genetically predicted 1 SD increase of TG was positively associated with higher risk of CAD (OR, 1.44; 95% CI, 1.29–1.61), HF (OR, 1.33; 95% CI, 1.17–1.51), and arterial hypertension (OR, 1.18; 95% CI, 1.09–1.27) (Figure S4). There was no evidence of SNPs that have a strong influence on the estimations of causal associations (Table S25–S26). After excluding SNPs suggested to have potential pleiotropic effects (Table S27–S28), analyses of the remaining SNPs did not materially change the ORs of HDL-C on CAD (OR, 0.68; 95% CI, 0.6–0.79; $P=2.52\times10^{-8}$), HDL-C on arterial hypertension (OR, 0.78; 95% CI, 0.72–0.84; $P=3.48\times10^{-10}$), TG on CAD (OR, 1.39; 95% CI, 1.25–1.54; $P=3.88\times10^{-10}$), and TG on arterial hypertension (OR, 1.16; 95% CI, 1.08–1.24; $P=2.88\times10^{-5}$). However, results of replication analysis did not support that a genetically predicted 1 SD increase of HDL-C was significantly associated with a higher risk of CAD (OR, 0.88; 95% CI, 0.8–0.98; $P=0.015$) under a Bonferroni-corrected threshold of $P<0.0125$; other replication analysis results were accordant with our main results (Table S29–S32).

The results of bidirectional MR showed no evidence of causal association of genetically predicted BMI, HDL-C, or TG on insomnia (Table S33). Thus, insomnia does not tend to lie on the causal pathway from each mediator to each CVD outcome (ie, insomnia is not the mediator of risk factor-CVD association). Therefore, for all 3 mediators, regression-based multivariable MR was conducted as an additional sensitivity analysis to estimate the causal effect of the mediator on each CVD outcome, respectively, adjusting for the genetic effect of the instruments on insomnia. The results of multivariable MR shown in Figure S5–S7 were highly accordant to our main results.

According to the results of network MR analysis, we found that some or all of BMI, TG, and HDL might act as mediators in the causal pathway from insomnia

to deep vein thrombosis, pulmonary embolism, CAD, AF, HF, peripheral vascular disease, and arterial hypertension. The proportion of the total effect of insomnia on each CVD outcome that each mediator accounts for was provided in the Table. The results of the direct causal effect of insomnia on each CVD outcome not mediated by these 3 mediators were shown in Data S5 and Table S34.

The Potential Mediator Role of Blood Pressure Traits

Finally, when we consider blood pressure traits (Table S35) as cardiometabolic risk factors rather than consider arterial hypertension as a CVD outcome, our results showed that genetically predicted insomnia was significantly positively associated with DBP (0.41; 95% CI, 0.24–0.58; P=1.75×10^{-6}); nevertheless, no association was observed with insomnia and DBP after adjustment for BMI (0.11; 95% CI, −0.05 to 0.27) (Table S36). In addition, a genetically predicted 1 mm Hg increase of DBP was positively associated with a higher risk of IS (OR, 1.09; 95% CI, 1.06–1.13), CAD (OR, 1.08; 95% CI, 1.06–1.09), AF (OR, 1.04; 95% CI, 1.02–1.06), and HF (OR, 1.07; 95% CI, 1.04–1.09) (Table S37) after Bonferroni correction, and the results of bidirectional MR showed no evidence of causal association of genetically predicted DBP on insomnia (Table S38). The sensitivity analysis yielded a similar pattern of effects; there was no evidence of the presence of pleiotropic effect (Table S36 and Table S38). In addition, we found that no SNP had an influential effect on the results for each blood pressure trait (Table S39). Therefore, DBP might act as a mediator in the causal pathway from insomnia to IS, CAD, AF, and HF. The proportion of the total effect of insomnia on each CVD outcome that DBP accounts for was provided in Table S40.

DISCUSSION

Principal Findings

In this study, using publicly available summary statistics from large consortia and data from UK Biobank, we performed a series of 2-sample MR analyses to systematically assess the causal roles of genetically predicted insomnia for a wide range of cardiovascular conditions. We further explored 17 cardiometabolic risk factors as possible mediators in the causal relationship between genetically determined insomnia and each CVD outcome. Our results provided consistent evidence that genetically determined insomnia was causally associated with increased risk of IS, transient

Table. The Proportion of the Total Effect of Insomnia on Each Cardiovascular Disease That Each Mediator Accounts For

Exposure (*X*)	Mediator (*M*)	Outcome (*Y*)	TE_{XY}	β_{XM}	OR_{MY}	NIE_{XY} (95% CI)	Proportion (95% CI)
Insomnia	BMI	Deep vein thrombosis	1.15	0.07	1.79	0.041 (0.02– 0.061)	29.16% (14%–44.32%)
Insomnia	BMI	Pulmonary embolism	1.16	0.07	1.66	0.035 (0.014–0.057)	23.9% (8.53%–39.27%)
Insomnia	BMI	Coronary artery disease	1.22	0.07	1.53	0.03 (0.014–0.046)	14.97% (7.44%–22.5%)
Insomnia	triglycerides	Coronary artery disease	1.22	0.06	1.44	0.022 (0.01–0.034)	11% (5.03%–16.98%)
Insomnia	BMI	Atrial fibrillation	1.13	0.07	1.56	0.031 (0.015–0.048)	25.47% (11.67%–39.27%)
Insomnia	BMI	Heart failure	1.24	0.07	2.14	0.053 (0.026–0.081)	24.76% (12.93%–36.59%)
Insomnia	triglycerides	Heart failure	1.24	0.06	1.33	0.017 (0.006, 0.028)	7.95% (2.5%–13.41%)
Insomnia	BMI	Peripheral vascular disease	1.23	0.07	1.73	0.038 (0.013–0.063)	18.53% (6.5%–30.57%)
Insomnia	HDL-C	Peripheral vascular disease	1.23	−0.06	0.8	0.013 (0.001–0.025)	6.47% (0.53%–12.4%)
Insomnia	BMI	Arterial hypertension	1.14	0.07	1.52	0.029 (0.014–0.044)	22.37% (12.07%–32.67%)
Insomnia	HDL-C	Arterial hypertension	1.14	−0.06	0.86	0.009 (0.002–0.016)	6.91% (1.75%–12.06%)
Insomnia	triglycerides	Arterial hypertension	1.14	0.06	1.18	0.01 (0.003–0.017)	7.58% (2.42%–12.74%)

BMI indicates body mass index; β_{XM}, effect of the exposure on the mediator; HDL-C, high-density lipoprotein cholesterol; TE_{XY}, total effect of the exposure on the outcome expressed in odds ratios (OR) scale; NIE_{XY}, natural indirect effect of exposure on the outcome in log OR scale; and Proportion, the proportion of the total effect of exposure on outcome that mediator accounts for.

ischemic attack, thrombotic diseases, and 5 other CVDs (CAD, HF, AF, peripheral vascular disease, arterial hypertension). Additionally, we concluded that genetically predicted insomnia was associated with higher BMI and TG as well as lower HDL-C, each of which may act as a mediator in the causal pathway from insomnia to several CVD outcomes. In addition, we found very little evidence to support a causal link between genetically predicted insomnia with abdominal aortic aneurysm, thoracic aortic aneurysm, TC, LDL-C, glycemic traits, renal function as well as heart rate increase during exercise. Finally, we found no evidence of a causal association of genetically predicted BMI, HDL-C, or TG on insomnia.

Comparisons With Other Studies

Although caution should be taken when comparing our results with other observational studies, because of the variations in measurement and definition of insomnia, nonetheless, our findings for CVDs from the primary analysis are generally consistent with those based on observational studies, which suggested that insomnia is an important risk factor for CVDs including hypertension,[9,10] CAD, AF,[62–64] and HF[5,65]. The null results for genetically predicted insomnia and abdominal aortic aneurysm are consistent with findings from a cohort study of 22 444 men and 10 982 women showing no association between insomnia and later development of abdominal aortic aneurysm,[66] but we cannot rule out the possibility that our analyses were underpowered to detect such a relatively modest association. Our results are also similar to previously reported MR studies of insomnia and risk of CAD,[14–16,67] HF,[15] and IS.[15] For AF, the OR of our analyses was similar to the result of Larsson et al[15] (1.04; 95% CI, 1.01–1.07; P=7.28×10^{-3}), but they did not conduct a significant conclusion under a stricter Bonferroni-corrected threshold ($\alpha = 0.05/7$). We are not aware of any observational or MR study of insomnia in relation to other cardiovascular conditions. In this study, we found genetically predicted insomnia was associated with an increased risk of transient ischemic attack, deep vein thrombosis, pulmonary embolism, and peripheral vascular disease.

Associations between insomnia and lipid markers (TC, TG, LDL-C, and HDL-C) reported by observational studies have been inconsistent.[68–73] In addition, a previous observational study has shown that insomnia is not associated with a higher BMI,[74] insomnia symptoms were found to have a close association with high hemoglobin A1c in Japanese men,[75] insomnia scores were found to have a strong negative correlation with estimated glomerular filtration rate.[76] Our findings for cardiometabolic risk factors are generally contradictory to those based on observational studies but similar to previously reported MR studies on insomnia and BMI[14] as well as WHR.[14] In this study, we found strong and consistent evidence that genetically predicted insomnia was associated with higher BMI, WHR, WC, and TG as well as lower HDL-C. Moreover, there was consistent no statistically significant association between genetically predicted insomnia with TC, LDL-C, glycemic traits, estimated glomerular filtration rate as well as heart rate increase during exercise. The contradiction may reflect reverse causation or confounding effects of previous observational studies.

In addition, our results that genetically predicted BMI was significantly associated with 7 of 9 CVD outcomes were consistent with those results from MR analysis in Larsson et al[27] previously. Several MR studies have investigated the associations between genetically predicted lipid traits and the risk of some major CVDs. For instance, Hindy et al[77] reported that genetically elevated TG did not associate with IS or any of its subtypes; for HDL-C, only weak evidence of association with 1 subtype of IS (small artery occlusion stroke) was found.[77] A higher genetically predicted TG was observed to be causally associated with a higher risk of hypertension[78] and CAD,[79] and lower genetically predicted HDL-C was observed to be causally associated with a higher risk of hypertension[78] and no significant association with CAD.[79] Our finding was consistent with previous MR studies, which showed that a genetically predicted 1 SD increase of HDL-C was negatively associated with a higher risk of peripheral vascular disease and arterial hypertension. A genetically predicted 1 SD increase of TG was positively associated with a higher risk of CAD, HF, and arterial hypertension.

Potential Mechanisms

The mechanisms underpinning the association are unclear but may involve that insomnia increases the activity of hypothalamic-pituitary-adrenal axis[80–83] and increases the systemic inflammation[84,85]; these provide a biologic rationale for insomnia to possibly lead to increased risk of CVD. In addition, studies also demonstrated that subjects with insomnia had increased sympathetic nervous system activity, which is an integral part of cardiovascular homeostasis and plays a critical role in the pathogenesis of hypertension, CAD, and HF.[86] Moreover, there might be potential mechanisms to explain the link between insomnia and dyslipidemia as well as the increase of BMI. Genetically determined insomnia usually contributes to reduced sleep duration. People with reduced sleep duration tend to show a preference for high energy-density fatty food[87] and have a higher BMI via reducing leptin and elevating ghrelin.[88,89] Moreover, higher BMI and intake of fat rich food are able to increase the risk of dyslipidemia,[90] which may further lead to the increased risk of CVD.

Strengths and Limitations

In this study, we performed a series of 2-sample MR analyses, which reduced the possibility that the observed associations were biased by unmeasured confounding, reverse causation, and measurement error.[18] We conducted mediation analysis using a network MR design, which can be used to decompose the direct and indirect effects[22,24] and can overcome some of the strong assumptions required for traditional causal mediation methods (eg, no unmeasured confounding and no measurement error in the exposure or mediator,[53] which are unlikely to be met in many scenarios[23,91,92]) to interpret the results as causal. Moreover, most of these analyses were performed using summarized data, which considerably increases the power to detect a causal effect. We used multiple independent genetic instruments that explained a large variance of exposure, further validated the relevance assumption by the rule of thumb,[25] and tested the exclusion assumption by MR-Egger intercept test and the MR-PRESSO test. Although we cannot entirely rule out the possibility of the violations of MR assumptions (eg, the independence assumption), most of our results were corroborated by both sensitivity analysis that makes allowance for violation of MR assumptions and the replication analysis, which further strengthens the inference of causality. In addition, we have made sure that most of our summary data estimates of SNP-exposure and SNP-outcome associations were gleaned from 2 independent but large homogeneous (European descent) study populations, which minimized the bias from population stratification.

Our study has several limitations. First, insomnia was determined based on self-reported questionnaires, which may not be completely accurate. In addition, it should be cautious when considering our results, which may vary when using different definitions of insomnia. Insomnia we used is a binary exposure. Some studies have pointed that an MR estimate with a binary exposure and binary outcome is difficult to interpret as a specific causal effect.[93,94] Second, in our primary analysis, the number of cases was few for some CVD outcomes, such as intracerebral hemorrhage, subarachnoid hemorrhage, and abdominal aortic aneurysm. We thus cannot rule out that we may have overlooked weak associations due to insufficient power. Third, the reason SNP-outcome estimates were obtained from UK Biobank is the availability of adequate outcome variables, such as arterial hypertension, aortic valve stenosis, which lacks published GWAS study. Nevertheless, there is around 30% sample overlap between UK Biobank and insomnia GWAS study, which may have introduced some bias in the MR estimates of primary analysis. However, we used a strict Bonferroni-corrected threshold to control the possible increase of type I error rate caused by sample overlap.[54] In addition, we conducted replication studies using summary data from previously published GWAS studies that have no or limited sample overlap with the GWAS of insomnia and UK Biobank individual-level data as sensitivity analysis, the same way as Siedlinski et al[95] did, to validate our results. To be noted, our genetic instruments were strongly related to the exposures (F statistic≈143.24), implying that bias from participant overlap is relatively small according to Burgess et al.[54] Fourth, this study evaluated only whether the liability to insomnia is associated with CVD, so we cannot rule out that there are other causal pathways leading to insomnia that causes CVD.[15]

CONCLUSIONS

This MR study provides evidence that genetically predicted insomnia is associated with increased risks of 9 CVD outcomes, some of them may be partially mediated by one or more of higher BMI, TG, and lower HDL-C.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Data S1: The selection criteria of genetic instruments

In two-sample MR analysis, although the bias due to weak instruments (i.e., instruments do not explain much variation in the exposure) will not lead to inflated Type I error rates and false-positive findings, it will bias the effect in the direction of the null. [54] In addition, this bias may lead to lower power to detect a causal effect and increase the probability of a Type II error, although the standard errors typically also attenuate, mitigating this somewhat. [54]

In the pre-processing step of primary analysis, the independent instrument SNPs of insomnia were identified using a common statistical approach: i) associated with insomnia at genome-wide significance (two-sided *P*-value from the meta-analysis of the GWAS results of insomnia: $P<5\times10^{-8}$), ii) r^2 between SNPs <0.1 and distinct genomic loci are >250kb apart. [14] As indicated by *Swerdlow et al. (2016)* [96], in a MR study with a fixed sample size, the *P*-value for the SNP-biomarker association provides an indirect measure of the effect size, and these specific metrics of effect size can be used to inform the selection of SNPs as instruments in an MR analysis. Statistical analyses in GWAS set stringent significance thresholds (typically *P*-value < 5×10^{-8}) in order to reduce the number of false-positive associations arising from the vast number of statistical tests performed. [96] Provided an association is identified robustly ($P<5\times10^{-8}$), the size of the genetic effect gains importance when prioritizing SNPs for use as MR instruments, with SNPs of larger effect preferred because they increase statistical power provided the minor allele frequency is sufficiently high. [20]

In addition, we reported the R^2 statistic and the related *F* statistic. The R^2 statistic measures the variance in the exposure explained by those selected SNPs. Using SNPs with a large R^2 can avoid that the instrument is weak and weak instrument bias. The *F* statistic is a measure of instrument strength and can be used to judge the extent of weak instrument bias. [97] In this study, we calculated *F* statistics through the formula

$$F=\left(\frac{N-k-1}{k}\right)\left(\frac{R^2}{1-R^2}\right),$$ [98]

where N denotes the sample size and *k* denotes the number of instruments. In terms of the rule of

thumb [25], *F* statistic greater than 10 means that assumption (a) is satisfied and avoids the bias caused by weak instrument. [97,98]

Data S2: Genetic variant instruments for mediators in step c

Genetic variant instruments for BMI

The summary data of genetic associations with BMI were obtained from large GWAS of BMI [29] (after imputation, 2 554 637 variants in 339 224 individuals of European descent) in GIANT (Genetic Investigation of Anthropometric Traits) consortium (http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium). Totally 78 independent SNPs that were associated with BMI at genome-wide significance ($P<5\times10^{-8}$) were clumped by *Noyce et al.* [99], and together this explained 2.2% of the variance in BMI (*F statistics* = 97.81). Since four of 78 SNPs (rs16951275 in chr2, rs29941 in chr14, rs1528435 in chr15, and rs7141420 in chr19) were unavailable in UK Biobank, the leaving 74 SNPs were utilized as genetic instrumental variables for BMI in mediation analysis. Data on major and minor alleles for each instrument SNP, along with allele frequencies, beta coefficients for allele dose and 5-kg/m^2 change in BMI (i.e., the change in BMI on a 5-kg/m^2 scale per effect allele), *P*-values, and standard errors (SEs) were extracted. SNPs were aligned to the same effect allele across the data sources before analysis, and we checked the effect allele frequencies for concordance (The details of those SNPs were provided in Table S6).

Genetic variant instruments for HDL-C and TG

The summary data of genetic associations with HDL-C and TG were obtained from publicly available data through the Global Lipids Genetics Consortium, which included 188 577 individuals of primarily European ancestry. [30] Totally 86 independent SNPs that were associated with HDL-C at genome-wide significance ($P<5\times10^{-8}$) and a total of 51 independent SNPs that were associated with TG at genome-wide significance ($P<5\times10^{-8}$) were clumped by *Hindy et al. (2018)*[77], these SNPs explained 5.9% and 4.6% of the variance in HDL-C and TG, respectively (*F statistics* = 137.42 and 178.24, respectively). Since one of 86 SNPs of HDL-C (rs7422339 in chr2) was unavailable in UK Biobank, the leaving 85 SNPs were utilized as genetic instrumental variables for HDL-C in mediation analysis. Besides, all 51 SNPs of TG were available in UK Biobank and were utilized as

genetic instrumental variables for TG in mediation analysis. Data on major and minor alleles for each instrument SNP, along with allele frequencies, beta coefficients for allele dose and 1 SD change in each lipid trait (i.e., the change in HDL-C or TG on a 1 SD scale per effect allele), P-values, and standard errors (SEs) were extracted. SNPs were aligned to the same effect allele across the data sources before analysis, and we checked the effect allele frequencies for concordance (The details of those SNPs were provided in Table S7 and S8).

Data S3: Estimate the proportion mediated by each mediator

The extent to which the association of insomnia with each CVD outcome selected in Step a of mediation analysis was mediated by BMI, TC, or HDL-C was tested in a post hoc analysis after BMI, TC, and HDL-C were identified as the potential mediators, using a similar approach as *Zhan et al. (2017)* [100] did.

Taking insomnia as exposure, BMI as a mediator, CAD as an outcome as an example, the total effect (odds ratio: *OR*) per genetically predicted 1-unit-higher log-odds of liability to insomnia on CAD was 1.22 [log(*OR*)= 0.199]. The effect of genetically determined insomnia on BMI was 0.07, and 1 SD increase in BMI was associated with CAD [log(*OR*)=log(1.53)=0.425]. Thus, the mediated effect of BMI was 0.07×0.425=0.030. The mediated proportion was (0.07× log(1.53))/log(1.22) = 14.97%.

Data S4: Confidence interval of the proportion mediated by mediator

Under the assumption of homogeneity of causal effects across individuals in the population and that all effects are linear without interaction terms, the indirect effect of an exposure *X* on an outcome *Y* mediated by a mediator *M* (denoted as $IE_{X\to Y}$) can be obtained as the product of the effects of *X* on *M* (β_{MX}) and *M* on *Y* (β_{YM}) [22]:

$$IE_{X\to Y} = \beta_{MX}\beta_{YM}.$$

We first consider the variance of indirect effect $IE_{X\to Y}$, i.e., the variance of product $\beta_{MX}\beta_{YM}$. According to *Kendall and Stuart (1977, page 85)* [101], if β_{MX} and β_{YM} are bivariate normally

distributed, then we have

$$\sigma^2\left(\beta_{MX}\beta_{YM}\right)=\mu^2_{\beta_{YM}}\sigma^2\left(\beta_{MX}\right)+\mu^2_{\beta_{MX}}\sigma^2\left(\beta_{YM}\right)+\left[\sigma\left(\beta_{MX},\beta_{YM}\right)\right]^2 +2\mu_{\beta_{MX}}\mu_{\beta_{YM}}\sigma\left(\beta_{MX},\beta_{YM}\right)+\sigma^2\left(\beta_{MX}\right)\sigma^2\left(\beta_{YM}\right).$$

where $\sigma^2(\cdot)$ denotes the variance, $\mu_{\cdot}$ denotes the expectation, and $\sigma(\cdot,\cdot)$ denotes the covariance. Since β_{MX} and β_{YM} are estimated from independent studies of large sample size using different instrument SNPs, β_{MX} and β_{YM} can be assume to be independent, then $\sigma\left(\beta_{MX},\beta_{YM}\right)=0$. We have

$$\sigma^2\left(IE_{X\to Y}\right)=\sigma^2\left(\beta_{MX}\beta_{YM}\right)=\mu^2_{\beta_{YM}}\sigma^2\left(\beta_{MX}\right)+\mu^2_{\beta_{MX}}\sigma^2\left(\beta_{YM}\right)+\sigma^2\left(\beta_{MX}\right)\sigma^2\left(\beta_{YM}\right). \quad (1)$$

Let β_{YX} denotes the total effect of *X* on *Y*, and $DE_{X\to Y}$ denotes the direct effect of an exposure *X* on an outcome *Y*. The variance of the proportion mediated by mediator *M* (*P*):

$$P=\frac{IE_{X\to Y}}{\beta_{YX}}$$

can be derived according to the Delta method [102]:

$$\begin{aligned}\sigma^2\left(P\right)&\approx\left(\frac{\mu_{IE_{X\to Y}}}{\mu_{\beta_{YX}}}\right)^2\left[\frac{\sigma^2\left(IE_{X\to Y}\right)}{\mu^2_{IE_{X\to Y}}}+\frac{\sigma^2\left(\beta_{YX}\right)}{\mu^2_{\beta_{YX}}}-\frac{2\sigma\left(IE_{X\to Y},\beta_{YX}\right)}{\mu_{IE_{X\to Y}}\mu_{\beta_{YX}}}\right]\\&=\left(\frac{\mu_{IE_{X\to Y}}}{\mu_{\beta_{YX}}}\right)^2\left[\frac{\sigma^2\left(IE_{X\to Y}\right)}{\mu^2_{IE_{X\to Y}}}+\frac{\sigma^2\left(\beta_{YX}\right)}{\mu^2_{\beta_{YX}}}-\frac{2\sigma\left(IE_{X\to Y},IE_{X\to Y}+DE_{X\to Y}\right)}{\mu_{IE_{X\to Y}}\mu_{\beta_{YX}}}\right], \quad (2)\\&=\left(\frac{\mu_{IE_{X\to Y}}}{\mu_{\beta_{YX}}}\right)^2\left[\frac{\sigma^2\left(IE_{X\to Y}\right)}{\mu^2_{IE_{X\to Y}}}+\frac{\sigma^2\left(\beta_{YX}\right)}{\mu^2_{\beta_{YX}}}-\frac{2\sigma^2\left(IE_{X\to Y}\right)}{\mu_{IE_{X\to Y}}\mu_{\beta_{YX}}}\right]\end{aligned}$$

Where the second equation is due to $\beta_{YX}=IE_{X\to Y}+DE_{X\to Y}$, and the third equation is due to $\sigma\left(IE_{X\to Y},DE_{X\to Y}\right)=0$. In equation (1) and (2), the expected values of β_{MX}, β_{YM}, $IE_{X\to Y}$ and β_{YX} are unknown. In practice, we can replace them by their estimates $\hat{\beta}_{MX}$, $\hat{\beta}_{YM}$, $\hat{IE}_{X\to Y}$ and $\hat{\beta}_{YX}$, i.e.,

$$\hat{\sigma}^2\left(\hat{IE}_{X\to Y}\right)=\hat{\beta}^2_{YM}\hat{\sigma}^2\left(\hat{\beta}_{MX}\right)+\hat{\beta}^2_{MX}\hat{\sigma}^2\left(\hat{\beta}_{YM}\right)+\hat{\sigma}^2\left(\hat{\beta}_{MX}\right)\hat{\sigma}^2\left(\hat{\beta}_{YM}\right),$$

$$\hat{\sigma}^2\left(\hat{P}\right)\approx\left(\frac{\hat{IE}_{X\to Y}}{\hat{\beta}_{YX}}\right)^2\left[\frac{\hat{\sigma}^2\left(\hat{IE}_{X\to Y}\right)}{\hat{IE}^2_{X\to Y}}+\frac{\hat{\sigma}^2\left(\hat{\beta}_{YX}\right)}{\hat{\beta}^2_{YX}}-\frac{2\hat{\sigma}^2\left(\hat{IE}_{X\to Y}\right)}{\hat{IE}_{X\to Y}\hat{\beta}_{YX}}\right].$$

The variance can be utilized to calculate normal 95% confidence intervals of the proportion mediated by mediator M ($\hat{P}$): $\left(\hat{P} \pm 1.96\sqrt{\hat{\sigma}^2\left(\hat{P}\right)}\right)$.

Data S5: Multivariable mendelian randomization (MVMR)

To consider the role of multiple mediators (BMI, TG, and HDL-C) simultaneously and to investigate the independent causal effects (direct causal effect) for insomnia not mediated by these three mediators for each CVD outcome, we additionally performed MVMR using summary data estimates of the association between SNP-exposure, SNP-mediators and SNP-outcome. To be noted, we also included LDL-C in the MVMR analysis to adjusts for potential pleiotropic effects, since relevant genetic variants are likely to be associated with multiple lipid traits.

To minimize the sample-overlap between the samples used to estimate the SNP-exposure associations and SNP-outcome associations, we used summary statistics for the SNPs-insomnia associations from GWAS meta-analysis in both UK Biobank and 23andMe, but this data was only available for 248 independent SNPs (see Table S1 and S2) associated with insomnia at genome-wide significance ($P<5\times10^{-8}$). [14] In addition, since much more summary statistics for the associations between these SNPs and risk factors are available in ENGAGE 1000 Genome Consortium[59,60] (Table S10) than the GIANT [29] and GLGC consortium [30], we used summary statistics of BMI, TG, HDL-C, and LDL-C obtained from the ENGAGE 1000 Genome Consortium in this study. Summary statistics for the associations between these SNPs and CVD outcomes were calculated from the identified white British individuals in UK Biobank. We excluded SNPs whose associations with any of BMI, TG, HDL-C, LDL-C, and CVD outcomes was unavailable from their respective publicly available data. Totally 239 independent SNPs were finally included as instrumental variables in MVMR analysis. We also performed replication analysis using summary data of IS, CAD, AF, and HF from previous published GWAS studies (Table S9). [55-58] The multivariable inverse-variance weighted (MVMR-IVW) method was applied to the data to investigate the direct causal effect of insomnia, BMI, TG, and HDL-C on each CVD outcome, respectively. We evaluated instrument strength using two sample conditional *F*-statistic and tests for horizontal pleiotropy using R package *MVMR*. [103]

The results of MVMR analysis were shown in Table S34. After adjusting for BMI,

HDL-C, TG, and LDL-C, the main analysis of MVMR-IVW suggested that insomnia was independent causally associated with a higher risk of all 9 CVD outcomes selected in the primary analysis, the *OR*s ranged from 1.11 (95% *CI*: 1.06-1.16) for atrial fibrillation (AF) to 1.22 (95% *CI*: 1.14-1.3) for heart failure (HF). Except for ischemic stroke (IS), the estimated direct effects of insomnia on the other 8 CVD outcomes were all attenuated compared to the total effects (primary analysis). The replication analysis showed similar results, except for AF. The results of replication analysis did not support that a genetically predicted insomnia was significant directly associated with a higher risk of AF (*OR* = 1.03, 95% *CI*: 1-1.06, *P* = 0.045) under a Bonferroni-corrected threshold of $P < 0.0125$ ($\alpha = 0.05/4$ outcomes). Theoretically speaking, this MVMR analysis was unable to calculate conditional *F*-statistics to assess the strength of our multi-variable instruments: the pairwise covariance between a SNP estimated association with any two exposures will equal to zero only when the effects of the SNPs on each exposure were estimated from separate samples; when the samples are overlapping, the requisite pairwise covariance are determinable only using individual-level data. [103] If we directly assumed that the pairwise covariances between SNP associations are zero, the conditional *F*-statistics for insomnia, BMI, HDL-C, TG, and LDL-C equals 11.01, 1.65, 0.94, 0.75, and 2.19, respectively. This suggested that conditional *F*-statistics for BMI, HDL-C, TG, and LDL-C were likely to be small, and the effect estimates were likely to subject to weak instrument bias. The horizontal pleiotropy statistic for this model is 262.76, the critical value at a 5% level of significance for a chi-squared distribution with 233 degrees of freedom is 269.61 ($P = 0.09$), which indicates no potential pleiotropy. [103]

Data S6: The potential mediator role of blood pressure traits

In our main study, arterial hypertension was considered as a CVD outcome. Since blood pressure traits (including systolic blood pressure (SBP), diastolic blood pressure (DBP)) are also important cardiometabolic risk factors, we additionally explored whether SBP and DBP mediate the causal pathway from insomnia to other 13 CVD outcomes using a network MR design.

Data sources

The genetic association estimates with 2 blood pressure traits were taken from *Evangelou et al.* [104], however, this GWAS analysis was adjusted for body mass index [denoted these two traits as Systolic blood pressure adjusted body mass index (SBPadjBMI) and diastolic blood pressure

adjusted body mass index (DBPadjBMI), respectively]. [104] In addition, we used genetic association estimates with SBP and DBP calculated from 424 811 white British participants in the UK Biobank (see Figure S1 for the flow chart of individual selection). The blood pressure traits were recorded automatically at the baseline assessment center for all participants, we used the second reading of the automated blood pressure, where missing data were replaced with the first measure, as did by *Carter et al. (2019)* [52]. For each blood pressure trait, we additional excluded individuals with this trait missing or individuals without genetic data from our total analysis dataset (N=424 811) that passed our quality control, then the genetic associations with each blood pressure trait were obtained from the individuals in UK Biobank using linear regression controlling for 10 principal components, which can further control for population stratification. The basic characters of these summary data were presented in the Table S35.

Methods

Then we explored whether SBPadjBMI, DBPadjBMI, SBP and DBP mediate the causal pathway from insomnia to CVD outcome using a network MR design. For each CVD outcome, this design consists of 3 different MR analyses (Step a-c) [22]

Step a: the estimation of causal effect of genetically determined insomnia on this CVD outcome was obtained, which was in accordant with our primary analysis;

Step b: 248 independent SNPs associated with insomnia at genome-wide significance from *Jansen et al. (2019)* [14] were utilized as instrumental variables to estimate the causal effects of genetically determined insomnia on each blood pressure traits, using the respective GWAS summary statistics described in Supplemental Section 6.1 and Table S35. This step was conducted using IVW method, in addition, complementary approaches including weighted median method, mode-based estimate, MR-Egger regression method, MR-PRESSO method were used to examine causal effect. Moreover, leave-one-out sensitivity analysis was also performed to assessing the reliance of the MR results on a particular variant. All the estimated effects were unit change in a blood pressure trait expressed per genetically predicted 1-unit-higher log-odds of liability to insomnia (per 2.72-fold multiplicative increase in the odds of insomnia). The Bonferroni-corrected threshold $P \le 0.0125(0.05/4)$ was used in this step, $P \le 0.05$ but above the Bonferroni corrected significance threshold was considered as suggestive association. The sample overlap between

insomnia GWAS study and two consortia of blood pressure traits (ICBP and UK Biobank) are 31% and 29%, respectively.

Step c: for blood pressure traits that causal association is observed in Step b (DBP), we estimated the causal effect of each mediator on this CVD outcomes, respectively, using conventional one-sample MR analysis using individual data from UK Biobank. Totally 98 independent SNPs that were associated with DBP at genome-wide significance ($P<5\times10^{-8}$) were clumped by *Sun et al.* [105] (*F statistics* = 32.8). Since 1 of 98 SNPs (rs687621 in chr5) was unavailable in UK Biobank, the leaving 97 SNPs were utilized as genetic instrumental variables for DBP in mediation analysis. The causal effect estimate of DBP on this CVD outcome was obtained using the two-stage least-squares (2SLS) method: in the first stage, the exposure is regressed on the genetic variants and 10 principal components in a multivariate linear regression; in the second stage the outcome is regressed on the predicted values of the exposure from the first regression and 10 principal components in a logistic regression. The results were converted to *ORs* expressed per genetically predicted 1 mm Hg increased of the blood pressure trait, and the Bonferroni-corrected threshold $P \le 0.0063(0.05/8)$ was used in this step.

If causal associations were observed in all three steps, the conclusion can be drawn that the specific blood pressure traits are mediators in the pathway of insomnia to this CVD outcome. The indirect effect of insomnia on this CVD outcome mediated through each mediator and the proportion mediated by each mediator were calculated (see Data S3 for details of mediation analysis and Data S4 for the calculation of 95% confidence intervals).

Finally, to examine the existence of bidirectional causality between selected mediator and insomnia, we performed a bidirectional MR analysis to examine whether the selected mediator can casually affect insomnia by using mediator-associated independent SNPs as IV (97 independent SNPs selected by *Sun et al.* [105]), the summary statistics of DBP and insomnia were obtained from UK Biobank (Table S35) and *Jansen et al. (2019)* [14], respectively.

Data S7: Replication analysis using UK Biobank individual-level data

Insomnia complaints in UK Biobank were defined according to Table S1. Insomnia was available in 424516 individuals of 424811 identified white British individuals, with the prevalence equals to

28.63% [N cases/(cases+controls) = 121526/424516]. We randomly divided this sample into two equally sized groups. For each of 247 SNPs, we calculated its effect on insomnia (on a log *OR* scale) using the first sample using logistic regression, adjusted for age, sex, and 10 genetic principal components. And for each CVD outcome, individuals suffering from any other 13 CVD outcomes were further excluded from the analysis's dataset from the second sample (as the primary analysis did). Then the genetic associations with each CVD outcome (on a log *OR* scale) were obtained using the same way as the primary analysis. Finally, the overall causal estimate of insomnia on each CVD outcome was obtained using an inverse variance weighted (IVW) method performed using a multiplicative random-effects model.

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Table S1. The definition of insomnia complaints in GWAS meta-analysis of Jansen et al. (2019).

Study	**Sample size**	**Definition of insomnia [14]**
UK Biobank version 2	386533	Insomnia was collected in the UK Biobank Study via a touchscreen device once during the first research visit (2006-2010). Insomnia complaints were assessed by asking: “Do you have trouble falling asleep at night or do you wake up in the middle of the night?” Participants were instructed to answer this question in relation to the previous four weeks when in doubt. The participants were able to choose one of the following four answers: “never/rarely”, “sometimes”, “usually”, or “prefer not to answer”. Insomnia cases were defined as participants who answered this question with “usually”, while participants answering “never/rarely” or “sometimes” were defined as controls.
23andMe	944477	Participants completed one or more questions related to seven phenotypic concepts concerning sleep. Insomnia cases affirmed at least one of the following questions: "Have you ever been diagnosed with, or treated for: Insomnia?"; “Have you ever been diagnosed with, or treated for, any of the following conditions: Insomnia but not Narcolepsy, Sleep apnea or Restless leg syndrome”; "Has a doctor ever told you that you have any of 242 these conditions: Insomnia (difficulty getting to sleep or staying asleep)?"; "Have you ever been diagnosed by a doctor with any of the following neurological conditions: Sleep disturbance"; "Do you routinely have trouble getting to sleep at night?"; "What sleep disorders have you been diagnosed with? Please select all that apply: Insomnia, trouble falling or staying asleep"; "Have you ever taken these medications? Prescription sleep aids"; "In the last 2 years, have you taken any of these medications? Prescription sleep aids". Participants were classified as controls if they did not provide a positive or uncertain ("I don't know": "I am not sure") to any of the questions listed above, nor to any of the following questions: "Have you ever been diagnosed with, or treated for Insomnia, Narcolepsy, Sleep apnea, Restless leg syndrome?", "Have you ever been diagnosed with or treated for any of the following conditions? Post-traumatic stress disorder (PTSD); Autism; Asperger's; Sleep disorder", "Have you ever been diagnosed with or treated for a sleep disorder?".

Table S2. Single-nucleotide polymorphisms used as instrumental variables in the Mendelian randomization analysis of insomnia in primary analysis.

SNP	Chr	EA	NEA	BETA (logOR)	SE	P value
rs10800992	1	T	C	0.04210118	0.006	3.84E-12
rs11119409	1	C	C	0.03459145	0.006	1.19E-08
rs11588755	1	G	G	0.03459145	0.006	5.14E-09
rs11803128	1	G	G	0.040822	0.006	6.85E-11
rs12030482	1	A	T	0.04114194	0.007	8.16E-09
rs1289939	1	C	C	0.040822	0.007	6.00E-09
rs1620977	1	A	G	0.05164323	0.007	2.27E-14
rs1937447	1	G	G	0.03874083	0.007	2.08E-08
rs2089358	1	C	C	0.040822	0.007	2.75E-10
rs2815757	1	T	C	0.05543471	0.008	2.24E-13
rs5877	1	T	C	0.03633193	0.006	1.23E-08
rs61765555	1	C	C	0.04499737	0.007	4.00E-11
rs623025	1	C	C	0.03770187	0.007	3.16E-08
rs6702604	1	G	G	0.03666398	0.006	1.30E-09
rs699844	1	A	G	0.06015392	0.011	4.11E-08
rs1064213	2	G	G	0.03666398	0.006	6.41E-10
rs10928256	2	T	C	0.03440143	0.006	1.61E-08
rs11126082	2	G	G	0.0429075	0.006	8.26E-13
rs113851554	2	T	G	0.20620083	0.014	1.56E-51
rs116466468	2	T	C	0.04401689	0.007	2.11E-10
rs11679943	2	A	G	0.03729579	0.006	3.16E-09
rs12614369	2	A	G	0.04401689	0.008	7.21E-09
rs12991815	2	C	G	0.04018179	0.006	3.02E-11
rs13010288	2	G	G	0.05975	0.009	9.26E-12
rs1519102	2	G	G	0.03666398	0.006	1.90E-08
rs1530938	2	A	G	0.03633193	0.006	8.82E-10
rs1861412	2	A	G	0.03825871	0.006	1.67E-10
rs34036083	2	C	C	0.03562718	0.006	2.07E-08
rs34967082	2	A	G	0.03536714	0.006	4.34E-09
rs4664299	2	C	C	0.040822	0.007	4.95E-09
rs55772859	2	A	C	0.04210118	0.006	4.82E-11
rs56097173	2	T	C	0.04018179	0.006	2.69E-10

rs62149809	2	A	G	0.14755756	0.025	5.71E-09
rs62158170	2	A	G	0.06578774	0.007	1.20E-19
rs62194948	2	C	G	0.03922071	0.007	4.64E-09
rs62213452	2	T	G	0.03729579	0.007	2.39E-08
rs6545798	2	T	T	0.040822	0.006	1.19E-11
rs6734957	2	G	G	0.0418642	0.007	1.82E-09
rs6756610	2	C	G	0.03729579	0.006	1.14E-09
rs72820274	2	A	G	0.03440143	0.006	1.28E-08
rs75452188	2	A	G	0.05164323	0.009	1.58E-08
rs7566062	2	T	C	0.05921186	0.007	1.37E-16
rs7571486	2	G	G	0.03874083	0.007	1.40E-08
rs7599697	2	C	C	0.03666398	0.006	5.00E-09
rs78206187	2	G	G	0.09431068	0.013	2.96E-13
rs823247	2	C	C	0.03666398	0.006	5.25E-10
rs984306	2	C	C	0.0429075	0.007	7.94E-10
rs10865954	3	T	C	0.04210118	0.006	1.92E-11
rs138014720	3	A	T	0.06952606	0.013	3.46E-08
rs1567084	3	A	G	0.03343478	0.006	2.14E-08
rs1580173	3	A	G	0.03343478	0.006	2.28E-08
rs17025198	3	A	G	0.04114194	0.007	2.19E-08
rs2216427	3	C	G	0.03536714	0.006	1.60E-08
rs2364921	3	C	C	0.03355678	0.006	2.13E-08
rs35110063	3	A	G	0.03922071	0.006	8.82E-11
rs3774751	3	G	G	0.040822	0.006	7.32E-12
rs4260410	3	T	C	0.03440143	0.006	4.87E-08
rs4858708	3	T	T	0.03355678	0.006	1.23E-08
rs492858	3	C	C	0.0661398	0.011	3.46E-09
rs62264767	3	A	C	0.06485097	0.008	1.63E-14
rs6808140	3	T	C	0.03922071	0.006	5.35E-11
rs694786	3	C	C	0.04395189	0.006	1.97E-13
rs73079014	3	C	C	0.04919024	0.009	3.65E-08
rs73163783	3	C	C	0.03770187	0.007	1.39E-08
rs7432782	3	C	C	0.08338161	0.014	7.42E-09
rs7615602	3	G	G	0.03978087	0.007	2.59E-09
rs7625896	3	A	G	0.03633193	0.006	5.28E-09
rs11722569	4	T	C	0.03440143	0.006	2.91E-08

rs13135092	4	G	G	0.08883121	0.011	2.53E-16
rs13138995	4	A	G	0.03440143	0.006	1.97E-08
rs16990210	4	C	C	0.04604394	0.008	1.97E-08
rs17005118	4	A	G	0.04210118	0.007	6.13E-10
rs2903385	4	A	G	0.04305949	0.006	4.53E-13
rs4699157	4	C	C	0.08121006	0.015	3.98E-08
rs62301574	4	G	G	0.0418642	0.007	1.37E-08
rs72657797	4	C	C	0.05551271	0.008	1.52E-12
rs12187443	5	T	C	0.04018179	0.006	1.64E-10
rs12520974	5	C	C	0.03562718	0.006	1.69E-09
rs152555	5	G	G	0.05234648	0.008	4.83E-10
rs16903122	5	T	C	0.05543471	0.007	9.04E-16
rs17083297	5	C	C	0.04395189	0.008	1.60E-08
rs17223714	5	A	G	0.04592893	0.007	2.44E-10
rs17367725	5	C	C	0.03562718	0.006	9.29E-09
rs2431108	5	C	C	0.05340078	0.006	7.83E-17
rs35539975	5	A	G	0.04210118	0.007	4.49E-09
rs37445	5	G	G	0.03562718	0.006	4.88E-09
rs4502882	5	C	C	0.03874083	0.006	7.96E-10
rs55972276	5	A	C	0.07325046	0.009	4.19E-17
rs62383308	5	G	G	0.05975	0.011	3.98E-08
rs6601080	5	A	G	0.03536714	0.006	2.21E-08
rs6888135	5	A	C	0.03825871	0.006	1.21E-10
rs701394	5	G	G	0.03562718	0.006	6.83E-09
rs71575448	5	A	G	0.05069311	0.009	3.38E-09
rs8180457	5	C	C	0.05551271	0.008	1.12E-11
rs10944696	6	G	G	0.03770187	0.007	7.99E-09
rs10947428	6	C	C	0.06827884	0.007	9.06E-21
rs10947690	6	G	G	0.04709161	0.007	4.04E-12
rs10947987	6	C	C	0.03252319	0.006	4.08E-08
rs1147852	6	A	G	0.03922071	0.006	9.94E-10
rs11756035	6	C	G	0.05069311	0.009	1.29E-08
rs1264419	6	C	G	0.03633193	0.006	8.91E-10
rs138678612	6	G	G	0.11653382	0.02	1.41E-08
rs238869	6	C	C	0.03355678	0.006	3.36E-08
rs2388840	6	G	G	0.03666398	0.006	1.37E-09

rs3131638	6	G	G	0.04395189	0.007	7.88E-10
rs314281	6	C	C	0.0429075	0.006	6.03E-13
rs4709655	6	C	C	0.05445619	0.009	3.09E-09
rs62429521	6	A	C	0.05069311	0.008	1.78E-09
rs6457796	6	C	C	0.03874083	0.007	1.12E-08
rs728017	6	G	G	0.03459145	0.006	9.51E-09
rs9373590	6	A	T	0.04018179	0.006	2.18E-11
rs9394502	6	C	C	0.05445619	0.006	7.76E-18
rs9469434	6	G	G	0.03562718	0.007	4.41E-08
rs12540241	7	T	T	0.04604394	0.008	1.58E-09
rs12666306	7	A	G	0.04210118	0.006	2.24E-12
rs1357685	7	T	C	0.03343478	0.006	1.39E-08
rs1731951	7	T	T	0.03459145	0.006	1.36E-08
rs17520265	7	G	G	0.0910194	0.016	2.87E-08
rs190073	7	G	G	0.03355678	0.006	2.86E-08
rs2030672	7	C	G	0.03440143	0.006	1.10E-08
rs2598293	7	T	C	0.03536714	0.006	2.48E-09
rs521484	7	G	G	0.03978087	0.007	1.53E-08
rs6465151	7	T	C	0.05638033	0.009	1.90E-09
rs670501	7	T	C	0.05259245	0.007	7.40E-13
rs6967168	7	G	G	0.04395189	0.007	1.39E-10
rs6973090	7	G	G	0.03770187	0.007	4.31E-08
rs6978112	7	T	C	0.03440143	0.006	2.11E-08
rs73671843	7	G	G	0.05551271	0.009	5.49E-10
rs75932578	7	C	C	0.03978087	0.007	4.15E-08
rs8180817	7	G	G	0.04919024	0.006	1.83E-16
rs940780	7	T	C	0.03825871	0.006	8.50E-10
rs10955647	8	T	G	0.03343478	0.006	1.84E-08
rs17643634	8	C	C	0.05975	0.008	1.34E-13
rs2737240	8	A	G	0.03633193	0.007	3.37E-08
rs28552587	8	A	G	0.03343478	0.006	3.30E-08
rs28611339	8	T	G	0.05826891	0.009	8.46E-11
rs4588900	8	A	G	0.03343478	0.006	1.57E-08
rs671985	8	G	G	0.03770187	0.006	2.79E-10
rs871994	8	A	C	0.03536714	0.006	5.50E-09
rs874168	8	T	C	0.03440143	0.006	7.95E-09

rs10756571	9	T	C	0.03633193	0.006	1.80E-08
rs10758593	9	G	G	0.03562718	0.006	4.90E-09
rs10761240	9	G	G	0.0429075	0.006	2.12E-12
rs118166957	9	T	C	0.06765865	0.008	1.95E-16
rs1927902	9	T	C	0.05259245	0.007	1.15E-14
rs2792990	9	C	G	0.05448819	0.008	1.15E-10
rs4090240	9	C	C	0.03874083	0.007	8.46E-09
rs6597649	9	T	C	0.03343478	0.006	3.05E-08
rs7040224	9	A	G	0.03729579	0.006	4.24E-09
rs7044885	9	G	G	0.040822	0.006	5.67E-12
rs72773790	9	T	C	0.03729579	0.006	3.71E-09
rs10825503	10	T	G	0.03343478	0.006	1.43E-08
rs11001276	10	T	T	0.03770187	0.007	2.52E-08
rs12251016	10	T	T	0.03874083	0.006	3.89E-10
rs224029	10	C	C	0.03874083	0.006	2.51E-10
rs7475916	10	G	G	0.03666398	0.006	6.70E-09
rs1064939	11	A	T	0.13015068	0.02	2.16E-10
rs10898940	11	A	C	0.03440143	0.006	8.09E-09
rs11605348	11	G	G	0.04499737	0.006	7.01E-13
rs12790660	11	C	C	0.03978087	0.006	4.49E-10
rs214934	11	T	T	0.03770187	0.006	3.16E-09
rs2221119	11	C	G	0.03633193	0.006	2.00E-09
rs4592425	11	T	G	0.04018179	0.006	4.31E-10
rs524859	11	G	G	0.04395189	0.006	1.48E-12
rs56133505	11	A	G	0.04114194	0.006	5.59E-12
rs566673	11	G	G	0.03874083	0.006	1.18E-10
rs647905	11	T	C	0.03343478	0.006	2.87E-08
rs6589988	11	G	G	0.03770187	0.006	4.70E-09
rs667730	11	T	C	0.03343478	0.006	2.26E-08
rs72899452	11	T	C	0.0741794	0.012	1.00E-09
rs79693059	11	G	G	0.07257069	0.011	1.61E-11
rs1167132	12	T	C	0.03536714	0.006	8.73E-09
rs12310246	12	A	G	0.04497337	0.007	4.74E-11
rs2286729	12	A	G	0.06952606	0.011	5.37E-11
rs28582096	12	G	G	0.05445619	0.007	1.74E-13
rs324017	12	A	C	0.03922071	0.007	1.61E-09

rs4767645	12	G	G	0.03666398	0.006	6.47E-10
rs61921611	12	C	C	0.04395189	0.006	7.84E-12
rs6606731	12	A	T	0.04305949	0.008	1.51E-08
rs7486418	12	T	G	0.04114194	0.006	6.84E-11
rs1031654	13	C	C	0.05129329	0.007	3.88E-12
rs11149313	13	A	G	0.04018179	0.007	2.38E-09
rs117630493	13	G	G	0.10092592	0.018	3.61E-08
rs11838830	13	G	G	0.08012604	0.013	5.20E-10
rs1536053	13	C	C	0.03770187	0.006	6.04E-09
rs2389631	13	C	C	0.03978087	0.006	2.03E-10
rs2491124	13	T	C	0.04879016	0.006	8.81E-16
rs6562066	13	T	C	0.03922071	0.006	1.38E-10
rs79204944	13	A	G	0.07881118	0.014	4.24E-08
rs7992992	13	A	G	0.05069311	0.009	1.15E-08
rs8181889	13	G	G	0.03770187	0.006	8.90E-10
rs9316619	13	T	C	0.04592893	0.008	5.50E-09
rs9527083	13	G	G	0.07580171	0.006	1.61E-32
rs9540729	13	A	T	0.03633193	0.006	1.40E-09
rs9563886	13	C	C	0.03355678	0.006	3.08E-08
rs4981170	14	G	G	0.05445619	0.008	7.33E-13
rs1038093	15	T	C	0.03922071	0.006	2.47E-10
rs12912299	15	C	C	0.0429075	0.006	4.42E-13
rs12917449	15	C	C	0.0418642	0.008	2.97E-08
rs176644	15	T	G	0.03536714	0.006	9.49E-09
rs4702	15	G	G	0.04814038	0.006	6.78E-16
rs715338	15	A	G	0.04114194	0.006	7.85E-12
rs7168238	15	C	G	0.06391333	0.011	1.80E-08
rs7402939	15	C	C	0.03562718	0.006	5.19E-09
rs1015438	16	A	G	0.05826891	0.008	2.51E-14
rs12924275	16	T	C	0.03825871	0.007	1.93E-08
rs2398144	16	A	C	0.03825871	0.006	5.09E-10
rs3184470	16	G	G	0.03770187	0.006	9.73E-10
rs34214423	16	A	C	0.04497337	0.008	3.18E-09
rs35322724	16	A	C	0.04879016	0.006	3.75E-16
rs3902952	16	T	C	0.04783733	0.008	2.55E-10
rs4238755	16	C	C	0.0429075	0.007	2.30E-10

rs45453598	16	A	T	0.04688359	0.008	4.42E-09
rs4788203	16	G	G	0.03459145	0.006	6.32E-09
rs66674044	16	T	T	0.05975	0.009	2.18E-12
rs67501351	16	C	G	0.04497337	0.007	5.36E-11
rs830716	16	C	G	0.04497337	0.007	8.68E-12
rs9931543	16	T	C	0.04783733	0.007	1.11E-12
rs11650304	17	C	G	0.06672363	0.012	1.23E-08
rs1553754	17	G	G	0.03355678	0.006	3.51E-08
rs2447094	17	C	C	0.03355678	0.006	2.50E-08
rs34490907	17	C	G	0.05354077	0.009	1.76E-08
rs4643373	17	T	C	0.04114194	0.007	1.58E-10
rs4790076	17	T	C	0.04783733	0.008	1.76E-09
rs62068188	17	T	C	0.04879016	0.008	1.18E-09
rs7214267	17	G	G	0.04395189	0.006	5.09E-13
rs8076183	17	C	C	0.03770187	0.006	2.75E-10
rs9889282	17	C	C	0.0418642	0.006	4.70E-12
rs10502966	18	G	G	0.03874083	0.006	8.54E-11
rs12454003	18	G	G	0.03459145	0.006	4.94E-09
rs12605642	18	T	G	0.03536714	0.006	2.13E-09
rs60565673	18	G	G	0.0429075	0.006	1.59E-12
rs9964420	18	A	C	0.03536714	0.007	4.54E-08
rs12983032	19	G	G	0.0429075	0.006	1.07E-11
rs429358	19	T	C	0.04592893	0.008	2.13E-08
rs6510033	19	G	G	0.03666398	0.007	4.66E-08
rs908668	19	T	C	0.04974209	0.007	1.41E-11
rs2867690	20	T	C	0.04210118	0.008	3.70E-08
rs6019663	20	T	C	0.04018179	0.007	6.47E-10
rs6119267	20	G	G	0.05975	0.006	2.32E-20
rs742760	20	A	T	0.04305949	0.008	2.48E-08
rs76145129	20	G	G	0.05024122	0.009	2.73E-08
rs910187	20	G	G	0.03459145	0.006	1.63E-08
rs2838787	21	G	G	0.03562718	0.006	7.65E-09
rs11090039	22	A	G	0.03922071	0.007	1.82E-09
rs17324524	23	C	C	0.05762911	0.009	5.01E-10
rs62590551	23	A	G	0.05448819	0.01	4.61E-09
rs77641763	9	T	C	0.07139	0.009	6.53E-15

SNP: single-nucleotide polymorphisms; EA: effect allele; SE: standard error.

Table S3. Definitions and sources of information for 14 cardiovascular disease in UK Biobank

Disease	ICD-9 diagnosis [27]	ICD-10 diagnosis [27]	OPCS procedure [27]	Self-report [27]
Cerebrovascular diseases				
Ischemic stroke	434.X, 436.X	I63.X, I64.X		20002
Transient ischemic attack	435.X	G45.X		20002
Intracerebral hemorrhage	431.X	I61.X		20002
Subarachnoid hemorrhage	430.X	I60.X		20002
Aortic aneurysms				
Abdominal aortic aneurysm	441.3, 441.4	I71.3, I71.4	L19.4, L19.5	
Thoracic aortic aneurysm	441.1, 441.2	I71.1, I71.2		
Thrombotic diseases				
Deep vein thrombosis	451.1	I80.2	L90.2	20002
Pulmonary embolism	415.1	I26.X		20002
Other CVDs				
Coronary artery disease	410.X, 411.X, 412.X, 414.0, 414.8, 414.9	I21.X, I22.X, I23.X, I24.X, I25.1, I25.2, I25.5, I25.6, I25.8, I25.9	K40.X, K41.X, K42.X, K43.X, K44.X, K45.X, K46.X, K49.X, K50.1, K50.2, K50.4, K75.X	20002, 6150
Aortic valve stenosis		I35.0, I35.2		20002
Atrial fibrillation	427.3	I48		20002
Heart failure	428.X	I11.0, I13.0, I13.2, I50.X		20002
Peripheral vascular disease	443.8, 443.9	I73.8, I73.9		20002
Arterial hypertension	401.X	I10		6150, 6177

CVDs: cardiovascular diseases; ICD: international classification of disease; OPCS: office of population censuses and surveys classification of surgical operations and procedures; 6150: data code used in UK Biobank represents health condition diagnosed by doctor (self-reported from touchscreen); 6177: data code used in UK Biobank represents medication for health condition (self-reported from touchscreen); 20002: data code used in UK Biobank represents non-cancer illness code (self-reported from interview with nurse).

Table S4. Baseline characteristics of participants from UK Biobank used in the analysis.

Variable	**Participants (*n* = 424811)**
Age, mean (SD)	57.37 (8.01)
Male, No. (%)	193927 (45.65%)
Disease prevalence rates, No. (%)	
Ischemic stroke	5279 (1.24%)
Transient ischemic attack	4674 (1.10%)
Intracerebral hemorrhage	1110 (0.26%)
Subarachnoid hemorrhage	1205 (0.28%)
Abdominal aortic aneurysm	1279 (0.30%)
Thoracic aortic aneurysm	377 (0.089%)
Deep vein thrombosis	10719 (2.52%)
Pulmonary embolism	7015 (1.65%)
Coronary artery disease	33459 (7.88%)
Aortic valve stenosis	2623 (0.62%)
Atrial fibrillation	19686 (4.63%)
Heart failure	7730 (1.82%)
Peripheral vascular disease	4107 (0.97%)
Arterial hypertension	148031 (34.85%)
Assessed blood pressure traits, mean (SD)	
Systolic blood pressure, mmHg	137.40 (19.37)
Diastolic blood pressure, mmHg	83.36 (10.99)
Receiving BP-related medication, No. (%)	47771 (11.25%)

Table S5. The basic characters of summary data of 17 cardiometabolic risk factors

Trait	Total sample size	SD	Units	Pop.	First author or consortia	Web site	Study
Anthropometric							
Waist-to-hip ratio (WHR)	212244	0.08	SD (ratio)	European	GIANT [28]	https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	BLSA, COROGENE, DESIR (GWAS), EGCUT-370, EGCUT-OMNI, ERF, FamHS, GOOD, HBCS, Health ABC, HERITAGE, HYPERGENES, InCHIANTI, LifeLines, LLS, LOLIPOP_EW610, LOLIPOP_EWA, LOLIPOP_EWP, PREVEND, PROCARDIS, QFS, RISC, RS-II, RSIII, SHIP-TREND, Sorbs, TRAILS, TWINGENE, TwinsUK, WGHS, YFS, AGES Reykjavik~, Amish, ARIC, B58C (T1DGC), B58C (WTCCC), BRIGHT, CHS, CoLaus, deCODE, DGI, EGCUT, EPIC-Obesity Study, Fenland, FRAM, FTC, FUSION, GENMETS, KORA3, KORA4 NFBC-1966, NHS, NTR & NESDA, ORCADES, PROCARDIS, RS-I, SHIP, T2D_WTCCC, VIS, MICROS, ADVANCE-CAD controls, ARIC Metabochip, B1958C, BHS, CLHNS, D2D 2007, DESIR (Metabochip), DIAGEN, DILGOM, DPS, DR'S EXTRA, DUNDEE cases, DUNDEE controls, EGCUT, Ely Study, EMIL, EPIC-Norfolk Cohort, EPIC-Norfolk T2D cases, FBPP, Fenland, FUSION stage 2, GLACIER, GXE, HNR, HUNT 2, IMPROVE, KORA S3, KORA S4, Leipzig Adults, LURIC, METSIM, MORGAM, NSHD, PIVUS, PROMIS, SardiNIA, SCARFSHEEP, SPT, STR, TANDEM, THISEAS, Tromsø, ULSAM, WHI Metabochip, Whitehall, WTCCC-T2D
Waist-to-hip ratio adjust BMI (WHRadjBMI)	210082	0.08	SD (ratio)	European	GIANT [28]		
Waist circumference (WC)	232101	12.52	SD (cm)	European	GIANT [28]		
Waist circumference adjust BMI (WCadjBMI)	231353	12.52	SD (cm)	European	GIANT [28]		
Hip circumference (HIP)	213038	8.45	SD (cm)	European	GIANT [28]		
Hip circumference adjust BMI (HIPadjBMI)	211114	8.45	SD (cm)	European	GIANT [28]		
Body mass index (BMI)	152893	4.77	SD (kg/m2)	European	GIANT [29]		AGES, Amish HAPI Heart Study, ARIC, B58C (T1DGC), B58C (WTCCC), BRIGHT, CAD_WTCCC, "CAPS1Cases", "CAPS1 Controls", "CAPS2 Cases", "CAPS2 Controls", CHS, CoLaus, CROATIA, deCODE, DGI (cases), DGI (controls), EGCUT, EPIC-Obesity Study, Fenland, FRAM, FTC, FUSION cases, FUSION controls, GENMETS cases, GENMETS controls,

							GerMiFSI, GerMiFSII, KORA3, KORA4, MICROS, Migen (cases), Migen (controls), NBS_WTCCC, NFBC-1966, NHS, NSPHS, NTRNESDA cases, NTRNESDA controls, ORCADES, PLCO, RS-I, RUNMC, "SASBAC Cases", "SASBAC Controls", SEARCH/UKOPS, SHIP T2D_WTCCC, AE, ASCOT, BLSA, BSN (BHS), COROGENE, DESIR, DNBC, EGCUT-370, EGCUT-OMNI, Erasmus Ruchphen Family Study (ERF), FamHS FinGesture cases, GOOD, Health ABC, HBCS, HERITAGE Family Study, InCHIANTI, IPM (Mount Sinai BioMe), LifeLines, LLS, LOLIPOP_EW610, LOLIPOP_EWA, LOLIPOP_EWP, MGS, NELSON, PLCO2, PROCARDIS, PROSPER/PHASE, QFS, QIMR, RISC, RSIII, SHIP-TREND, Sorbs, TRAILS, TWINGENE, TwinsUK, WGHS, YFS, ADVANCE-CAD, AMC-PAS, ARIC Metabochip, B1958C, BHS, CARDIOGENICS, CLHNS, D2D 2007, DESIR, DIAGEN, DILGOM, DPS, DR'S EXTRA, DUNDEE, EAS, EGCUT, Ely Study, EMIL (SWABIA), EPIC-Norfolk T2D, FBPP, Fenland, FUSION stage 2, GLACIER, GXE, HNR, HUNT 2, IMPROVE, KORA S3, KORA S4, Leipzig Adults, LURIC , MEC Metabochip, METSIM, MORGAM, MRC NSHD, PIVUS, PROMIS, SardiNIA, SCARFSHEEP, SPT, STR TANDEM, THISEAS, Tromsø, ULSAM, WHI Metabochip, Whitehall, WTCCC-T2D, HRS
Lipids							
Total cholesterol (TC)	187365	41.75	SD (mg/dl)	Mixed	GLGC [30]	http://csg.sph.umich.edu/willer/public/lipids2013/	ADVANCE, AMC-PAS, AMISH, BC58, D2D 2007 (T2D), D2D 2007 (controls), deCODE, DIAGEN (T2D), DIAGEN (controls), DILGOM, DPS (T2D), DPS (controls), DR'S EXTRA (T2D), DR'S EXTRA (controls), EAS, EGCUT, Ely, EPIC-CAD cases (EPIC-Norfolk CAD set), EPIC-T2D cases (EPIC-Norfolk T2D set), EPIC-T2D controls, Fenland, FINCAVAS, FRISCII, FUSION2 (T2D), FUSION2 (controls), GLACIER, Go-DARTs, HUNT (T2D), HUNT (controls), IMPROVE, KORA F3, KORA F4, LURIC (cases), LURIC (controls), MDC, METSIM (T2D), METSIM (controls),
Low-density lipoprotein cholesterol (LDL-C)	173082	38.67	SD (mg/dl)	Mixed	GLGC [30]		
High-density lipoprotein cholesterol (HDL-C)	187167	15.51	SD (mg/dl)	Mixed	GLGC [30]		
Triglycerides (TG)	177861	90.72	SD (mg/dl)	Mixed	GLGC [30]		

							NFBC86, NSHD, PIVUS, SardiNIA, SCARFSHEEP, STR, THISEAS, TROMSO (T2D), TROMSO (controls), ULSAM, WHII
Glycemic							
Fasting glucose	140595	≈0.73	mmol/L	European	MAGIC [31]	https://www.magicinvestigators.org/downloads/	
Fasting insulin	98210	≈0.79	log(mmol/L)	European	MAGIC [31]		
Two-hour glucose	42854	1.27	mmol/L	European	MAGIC [33]		Fenland, Ely, ULSAM, GLACIER, AMC-PAS, KORA F4, Whitehall, FIN-D2D 2007, DPS, DR's EXTRA, FUSION stage 2, METSIM, DIAGEN, EAS, DILGOM/ Finrisk07, LEIPZIG_ADULT_IFB, LEIPZIG_CHILDHOOD_IFB, LURIC
Hemoglobin A1c (HbA1c)	123665	≈0.54	%	European	MAGIC [32]		ARIC, B58C-T1DGC, 58C, BLSA, Croatia_Vis, deCODE EPIC_GWA cases, EPIC_GWA cohort, DESIR, DGI, Fenland, FHS, GenomeEUtwin, HEALTH2000 InterAct (GWASsubcohort), KORA F3, KORA S4, Lifelines, LOLIPOP_EW610 (updated), LOLIPOP_EW_A, LOLIPOP_EW_P, LURIC, NTR, ORCADES, PROCARDIS, SHIP, Sorbs, Swedish Twins , TRAILS - Population cohort, WGHS (HbA1c ≥ 6.5% excluded), METSIM, NHANES, Roche, Segovia, AMCPAS, FIN-D2D 2007, DPS, METSIM, DIAGEN, GoDARTS, Ely, EPIC Metabo-CHD, EPIC Metabo T2D Controls, InterAct Metabo Sub-cohort, Fenland, KORAF3 KORAF4 LEIPZIG_ADULT_IFB, LEIPZIG_CHILDHOOD_IFB, NSHD, ORCADES, DESIR (Replication), SardiNIA, STR TROMSØ, Whitehall
Renal function							
Estimated glomerular filtration rate (eGFR) [106]	567,460	≈49.1[a]	mL/min/1.73 m2	European	CKDGen [34]	https://ckdgen.imbi.uni-freiburg.de/	AA-DHS, ADVANCE, AFTER EU, AGES, Airwave, Amish, ARIC, ASPS, ASPS-Fam, BES, Biobank Japan, BioMe, CHNS, CHRIS, CHS, Cilento, CoLaus, CROATIA-Korcula, CROATIA-Split, CROATIA-Vis, Czech post-MONICA, DECODE, DIACORE, EGCUT, ERF, ESTHER, FamHS, FHS, FINCAVAS, Finrisk, GCKD, Generation R, GS:SFHS, GSK, HANDLS, HYPERGENES, INGI-CARL, INGI-FVG, INGI-VBI, INTERVAL, Jackson Heart Study (JHS), JUPITER, KORA, LIFE-Adult, LIFE-Child, LIFE-Heart, Lifelines,

							Living-Biobank, LLFS, LOLIPOP, LURIC, MDC-CC, MESA, METSIM, MICROS, MyCode (Geisinger Research), NEO, NESDA, OGP, ORCADES, PIVUS, POPGEN, PREVEND, QIMR adolescent, QIMR adult, RS, SCES, SCHS - CHD cases and controls, DC, SHIP, SHIP-Trend, SiMES, SINDI, SKIPOGH, SOLID-TIMI 52, Sorbs, SP2, STABILITY, TRAILS, TwinGene, ULSAM, Vanderbilt, VIKING, WGHS, YFS
Other							
Heart rate *	58818	12.9	bmp	European	Verweij et al. [35]	https://data.mendeley.com/datasets/tg5tvgm436/1	UK Biobank

* HR increase was determined as the difference between peak HR during exercise and resting HR;SD: standard deviation; Pop.: population.

Table S6. Single-nucleotide polymorphisms used as instrumental variables in the mendelian randomization study of body mass index in step c of mediation analysis

SNP	EA	NEA	BETA	SE
rs1000940	G	A	0.0192	0.0034
rs10132280	A	C	-0.023	0.0034
rs1016287	T	C	0.0229	0.0034
rs10182181	A	G	-0.0307	0.0031
rs10733682	A	G	0.0174	0.0031
rs10938397	A	G	-0.0402	0.0031
rs10968576	G	A	0.0249	0.0033
rs11030104	A	G	0.0414	0.0038
rs11057405	A	G	-0.0307	0.0055
rs11165643	C	T	-0.0218	0.0031
rs1167827	A	G	-0.0202	0.0033
rs11727676	C	T	-0.0358	0.0064
rs12286929	G	A	0.0217	0.0031
rs12401738	A	G	0.0211	0.0033
rs12429545	G	A	-0.0334	0.0047
rs12940622	A	G	-0.0182	0.0031
rs13021737	A	G	-0.0601	0.004
rs13078960	T	G	-0.0297	0.0039
rs13107325	C	T	-0.0477	0.0068
rs13191362	A	G	0.0277	0.0048
rs13201877	A	G	-0.0233	0.0045
rs1441264	A	G	0.0175	0.0032
rs1460676	T	C	-0.0197	0.004
rs1516725	T	C	-0.0451	0.0046
rs1558902	A	T	0.0818	0.0031
rs16851483	G	T	-0.0483	0.0077
rs17001654	C	G	-0.0306	0.0053
rs17024393	C	T	0.0658	0.0088
rs17094222	C	T	0.0249	0.0038
rs17203016	G	A	0.021	0.0039
rs17405819	C	T	-0.0224	0.0033
rs17724992	A	G	0.0194	0.0035

rs1808579	T	C	-0.0167	0.0031
rs1928295	C	T	-0.0188	0.0031
rs2033529	G	A	0.019	0.0033
rs2033732	C	T	0.0192	0.0035
rs205262	A	G	-0.0221	0.0035
rs2112347	G	T	-0.0261	0.0031
rs2121279	T	C	0.0245	0.0044
rs2176040	G	A	-0.0141	0.0031
rs2176598	T	C	0.0198	0.0036
rs2207139	G	A	0.0447	0.004
rs2245368	T	C	-0.0317	0.0057
rs2287019	C	T	0.036	0.0042
rs2365389	C	T	0.02	0.0031
rs2820292	A	C	-0.0195	0.0031
rs2836754	C	T	0.0164	0.0032
rs3101336	T	C	-0.0334	0.0031
rs3736485	A	G	0.0176	0.0031
rs3817334	C	T	-0.0262	0.0031
rs3849570	A	C	0.0188	0.0034
rs3888190	A	C	0.0309	0.0031
rs4256980	G	C	0.0209	0.0031
rs4740619	T	C	0.0179	0.0031
rs4787491	A	G	-0.0159	0.0034
rs492400	T	C	-0.0158	0.0031
rs543874	G	A	0.0482	0.0039
rs6091540	C	T	0.0188	0.0035
rs6465468	G	T	-0.0166	0.0035
rs6477694	C	T	0.0174	0.0031
rs6567160	C	T	0.0556	0.0036
rs657452	A	G	0.0227	0.0031
rs6804842	A	G	-0.0185	0.0031
rs7138803	G	A	-0.0315	0.0031
rs7239883	G	A	0.0164	0.0031
rs758747	C	T	-0.0225	0.0037
rs7599312	G	A	0.022	0.0034
rs7715256	G	T	0.0163	0.0031

rs7899106	A	G	-0.0395	0.0071
rs7903146	T	C	-0.0234	0.0034
rs9374842	T	C	0.0187	0.0035
rs9400239	C	T	0.0188	0.0033
rs9540493	G	A	-0.0172	0.0033
rs977747	T	G	0.0167	0.0031

SNP: single-nucleotide polymorphisms; EA: effect allele; SE: standard error.

Table S7. Single-nucleotide polymorphisms used as instrumental variables in the mendelian randomization study of high-density lipoprotein cholesterol in step c of mediation analysis

SNP	EF	NEF	BETA	SE
rs10019888	G	A	-0.027	0.005
rs10282707	C	T	0.025	0.004
rs103294	T	C	0.052	0.004
rs10773105	T	C	-0.036	0.004
rs10790162	A	G	-0.095	0.007
rs11045163	A	G	-0.022	0.004
rs11246602	C	T	0.034	0.005
rs11660468	T	C	0.039	0.003
rs12133576	A	G	0.024	0.004
rs12145743	T	G	-0.02	0.004
rs12226802	G	A	0.033	0.005
rs12678919	A	G	-0.155	0.006
rs12801636	A	G	0.024	0.004
rs13107325	C	T	0.071	0.008
rs13326165	G	A	-0.029	0.004
rs1367117	A	G	-0.022	0.004
rs1515110	T	G	-0.032	0.004
rs1532085	A	G	0.107	0.004
rs1535	A	G	0.039	0.004
rs1689797	A	C	-0.036	0.004
rs16942887	A	G	0.083	0.005
rs17145738	T	C	0.041	0.005
rs17173637	C	T	-0.036	0.006
rs17695224	G	A	0.029	0.004
rs17788930	A	G	0.036	0.004
rs1800961	C	T	0.127	0.01
rs181362	C	T	0.038	0.004
rs1883025	C	T	0.07	0.004
rs205262	A	G	0.028	0.004
rs2240327	G	A	0.024	0.003
rs2241210	G	A	0.033	0.004
rs2255141	A	G	0.034	0.004

rs2278236	A	G	0.033	0.004
rs2290547	A	G	-0.03	0.005
rs2293889	T	G	-0.031	0.004
rs2412710	G	A	0.084	0.014
rs2472509	G	T	0.023	0.004
rs2602836	G	A	-0.019	0.003
rs261342	C	G	-0.107	0.006
rs2642438	G	A	0.03	0.004
rs2652834	A	G	-0.029	0.004
rs2925979	C	T	0.035	0.004
rs2954022	C	A	-0.04	0.003
rs2980885	G	A	-0.035	0.004
rs326214	A	G	-0.061	0.005
rs3741414	C	T	-0.03	0.004
rs3822072	A	G	-0.025	0.003
rs3996352	A	G	-0.03	0.003
rs4075205	C	T	-0.022	0.004
rs4148005	G	T	-0.028	0.004
rs4240624	A	G	0.082	0.006
rs4332136	C	G	0.48	0.065
rs442177	T	G	-0.022	0.003
rs4465830	G	A	-0.06	0.004
rs4650994	A	G	-0.021	0.003
rs4660293	G	A	-0.035	0.004
rs4846914	G	A	-0.048	0.003
rs4917014	G	T	0.022	0.004
rs492571	T	C	0.066	0.009
rs4939883	C	T	0.08	0.005
rs4969178	G	A	0.026	0.004
rs4983559	G	A	0.02	0.004
rs499974	A	C	-0.026	0.004
rs5880	C	G	-0.307	0.009
rs634869	T	C	-0.023	0.003
rs6450176	A	G	-0.025	0.004
rs646776	T	C	-0.034	0.004
rs653178	T	C	0.026	0.004

rs6805251	T	C	0.02	0.004
rs686030	A	C	0.055	0.005
rs687339	T	C	-0.032	0.004
rs702485	G	A	0.024	0.003
rs7117842	C	T	0.027	0.004
rs731839	A	G	0.022	0.004
rs7607980	T	C	-0.045	0.005
rs7897379	C	T	0.019	0.003
rs838876	G	A	-0.049	0.004
rs894210	G	A	-0.069	0.003
rs9491696	G	C	-0.02	0.003
rs952044	C	T	0.023	0.004
rs9686661	T	C	-0.028	0.004
rs970548	C	A	0.026	0.004
rs9930333	T	G	0.02	0.004
rs998584	A	C	-0.026	0.004
rs9989419	A	G	-0.147	0.004

SNP: single-nucleotide polymorphisms; EA: effect allele; SE: standard error.

Table S8. Single-nucleotide polymorphisms used as instrumental variables in the mendelian randomization study of triglycerides in step c of mediation analysis

SNP	EF	NEF	BETA	SE
rs10029254	T	C	0.027	0.004
rs10401969	T	C	0.121	0.007
rs10493326	A	G	0.031	0.004
rs10790162	A	G	0.231	0.007
rs1260326	T	C	0.115	0.003
rs12678919	A	G	0.17	0.006
rs1367117	A	G	0.025	0.004
rs1515110	T	G	0.027	0.003
rs1532085	A	G	0.031	0.003
rs1535	A	G	-0.046	0.004
rs17145738	T	C	-0.115	0.005
rs1781930	G	A	0.031	0.004
rs2068888	G	A	0.024	0.003
rs2247056	C	T	0.038	0.004
rs2255141	A	G	-0.021	0.004
rs2412710	G	A	-0.099	0.013
rs261342	C	G	-0.045	0.006
rs2652834	A	G	0.025	0.004
rs2954022	C	A	0.078	0.003
rs2980885	G	A	0.058	0.004
rs3198697	T	C	-0.02	0.003
rs3741414	C	T	0.028	0.004
rs3761445	A	G	0.023	0.003
rs3817588	T	C	0.067	0.004
rs38855	A	G	0.019	0.003
rs442177	T	G	0.031	0.003
rs4465830	G	A	0.053	0.004
rs4587594	G	A	0.069	0.004
rs4722551	C	T	-0.027	0.004
rs4846914	G	A	0.04	0.003
rs4921914	C	T	0.035	0.004
rs492571	T	C	-0.08	0.009

rs5880	C	G	0.048	0.009
rs603446	C	T	0.05	0.003
rs634869	T	C	0.027	0.003
rs6831256	G	A	0.026	0.004
rs687339	T	C	0.029	0.004
rs6882076	C	T	0.029	0.004
rs7254892	G	A	-0.124	0.011
rs731839	A	G	-0.022	0.004
rs749671	G	A	0.021	0.003
rs7607980	T	C	0.036	0.005
rs7897379	C	T	-0.027	0.003
rs799160	T	C	0.04	0.004
rs8077889	C	A	0.025	0.004
rs894210	G	A	0.067	0.003
rs9686661	T	C	0.038	0.004
rs9693857	C	T	-0.02	0.003
rs9930333	T	G	-0.021	0.004
rs998584	A	C	0.029	0.004
rs9989419	A	G	0.024	0.004

SNP: single-nucleotide polymorphisms; EA: effect allele; SE: standard error.

Table S9. The details of genome-wide association studies of 4 cardiovascular diseases in replicate study of primary analysis

CVD outcomes	Total sample size	Population	Consortia	Web site	Studies	Overlap[a]
Ischemic stroke	40,585 cases; 406,111 controls	European	Megastroke [55]	(https://www.megastroke.org/download.html)	CHARGE, METASTROKE, SIGN, DECODE, EPIC-CVD, Young Lacunar DNA, SIFAP, INTERSTROKE EUR, HVH1, Glasgow, CADISP, Barcelona, FINLAND, SAHLSIS, MDC, HVH2 ICH.	0%
Coronary artery disease	60,801 cases and 123,504 controls	Mainly European, South Asian, and East Asian	CARDIoGRAMplusC4D [56]	(http://www.cardiogramplusc4d.org/data-downloads/)	PROCARDIS, HSDS, ADVANCE, BEIJING (BAS), CARDIOGENICS, CHINA (CAS), CCGB_2, COROGENE, DUKE_2, EGCUT, FGENTCARD, GENRIC, GERMIFS I, GERMIFS II, GERMIFS III (KORA), GERMIFS_IV, GODARTS, HPS, IPM_AA, IPM_EA, IPM_HA, LOLIPOP, LURIC, MEDSTAR, MIGen, OHGS_A2, OHGS_B2, OHGS_C2, PENNCATH, PIVUS, PREDICTCVD, SDS/AIDHS, THISEAS, TWINGENE, ULSAM, WTCCC, PROMIS1, PROMIS2, LIFE-HEART, WGHS, ITH_2,MAYO-VDB, AGES, RS, FHS, FamHS, PROSPER, ARIC	0%
Atrial fibrillation	65446 cases and 522744 controls	Mainly European, Japanese, African American, Brazilian and Hispanic	Roselli C et al. (2018) [57]	(ftp://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/RoselliC_29892015_GCST006061/)	The Age, Gene/Environment Susceptibility Study (AGES) Reykjavik study, the Atrial Fibrillation Biobank LMU (AFLMU) in the context of the Arrhythmia-Biobank-LMU, ANGES1, the Atherosclerosis Risk in Communities (ARIC) study, BEAT-AF, Biobank Japan (BBJ), BioMe1, Cleveland Clinic Lone Atrial Fibrillation GeneBank Study (CCAF), the Cardiovascular Health Study (CHS), Corogene, Framingham Heart Study (FHS), FINCAVAS, GS:SFHS, LURIC, MDCS, MESA, Massachusetts General Hospital (MGH) AF study, MGH CAMP, PIVUS , PREVEND, the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), the Rotterdam Study (RS), SiGN, the Study of Health in Pomerania (SHIP), SPHFC, TWINGENE, UK Biobank, ULSAM1, the Women's Genome Health Study (WGHS) and WTCCC2-Munich, Australian Familial AF Study, Danish AF Study, Duke Biobank, EAST - AFNET 4 biomarker substudy (EAST), EGCUT, Genetics in AF (GENAF), German MI Family Study (GerMIFS) 6, Groningen Genetics of Atrial Fibrillation (GGAF), Genetic Risk Assessment of Defibrillator Events (GRADE), Hopkins, Heart and Vascular Health Study (HVH), Incor Warfarin Study, Intermountain, Maastricht AFCT, MGH – DOFEGEN, MGH Stroke Study, MPP, Myocardial Applied Genomics Network (MAGNet) repository, Partners HealthCare Biobank (PHB), Penn Medicine Biobank (Penn), Texas Cardiac Arrhythmia Institute (TCAI), UCSF, UMass, Vanderbilt Atrial Fibrillation Registry, Vanderbilt AF Ablation Registry (VAFAR), Vanderbilt BioVU	26%

Heart failure	977323 (47,309 cases and 930,014 controls)	European	Shah et al. (2020)[58]	(https://www.ebi.ac.uk/gwas/publications/31919418#study_panel)	ARIC, BIOSTAT-CHF (Validation), CHS, COGEN, deCODE, DiscovEHR, EPHESUS, EPIC-Norfolk, EGCUT 370, EGCUT Exome, GCUT Omni, FHS, FINRISK, GoDARTS (Affymetrix), GoDARTS (Illumina), GRADE, LURIC, MDCS, PHFS, PIVUS, PREVEND, PROSPER, Rotterdam 1, SHIP, SOLID, TwinGene, UK Biobank, ULSAM, WGHS	29.6%

[a] The estimated overlap of insomnia GWAS with each CVD GWAS. The percentages represent the part of the CVD GWAS that had overlap with insomnia GWAS.
CVD: cardiovascular disease

Table S10. The basic characters of included genome-wide association studies of replication analyses in step b of mediation analysis.

Trait	Total sample size	SD	Units	Pop.	First author or consortia	Web site
Anthropometric						
Waist-to-hip ratio adjust BMI (WHRadjBMI)	54572	0.08	SD (ratio)	European	Horikoshi et al. [59]	http://diagram-consortium.org/2015_ENGAGE_1KG/
Body mass index (BMI)	87048	4.77	SD (kg/m2)	European		
Lipids						
Total cholesterol (TC)	62166	41.75	SD (mg/dl)	European	Surakka I et al. [60]	
Low density lipoprotein cholesterol (LDL-C)	62166	38.67	SD (mg/dl)	European		
High density lipoprotein cholesterol (HDL-C)	62166	15.51	SD (mg/dl)	European		
Triglycerides (TG)	62166	90.72	SD (mg/dl)	European		

Table S11. Leave-one-out analysis of association between genetically predicted insomnia and the risk of cardiovascular disease in primary analysis.

Outcome	IVW Estimate [Min, Max] [a]	P value [Min, Max] [b]
Cerebrovascular diseases		
Ischemic stroke	[1.16,1.17]	[0.00000748369931013361,0.0000636400747879641]
Transient ischemic attack	[1.14,1.16]	[0.00007985831995362 2,0.00050928078772593]
Intracerebral hemorrhage	[1.16,1.2]	[0.0150707747197087,0.0532830564685888]
Subarachnoid hemorrhage	[1.21,1.25]	[0.0029884924600 4255,0.0100260051662759]
Aortic aneurysms		
Abdominal aortic aneurysm	[1.12,1.15]	[0.0379139705781785,0.0976436702464448]
Thoracic aortic aneurysm	[1,1.04]	[0.741660459459183,0.989625293441805]
Thrombotic diseases		
Deep vein thrombosis	[1.14,1.16]	[0.000000100113043531601,0.00000134547550287536]
Pulmonary embolism	[1.15,1.16]	[0.000003702031817579 18,0.0000212175559301195]
Other CVDs		
Coronary artery disease	[1.21,1.23]	[0.000000000000000000000004691231713292 05,0.00000000000000000000620091219092247]
Aortic valve stenosis	[1.19,1.22]	[0.00059927295737908 8,0.00240005141062859]
Atrial fibrillation	[1.12,1.13]	[0.000000019750571865 9678,0.000000217128104309981]
Heart failure	[1.23,1.25]	[0.000000000009089394380 50027,0.0000000001370987794 46152]
Peripheral vascular disease	[1.22,1.24]	[0.000000125008699928124,0.00000089431057307921]
Arterial hypertension	[1.13,1.14]	[0.000000000000000001325970752511 79,0.00000000000000 998106683415205]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value;

IVW: inverse variance weighted; CVDs: cardiovascular diseases.

Table S12. Associations between genetically predicted insomnia and 14 cardiovascular diseases in sensitivity analysis.

Outcome	Weighted median		Mode-based		MR-Egger				MRPRESSO		
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	Intercept	P value	OR	P value	No. of outliers
Cerebrovascular diseases											
Ischemic stroke	1.2(1.09,1.33)	0.00031	1.38(0.99,1.92)	0.057825	0.97(0.73,1.3)	0.857983	0.01(0,0.02)	0.21253	1.17	1.15E-05	0
Transient ischemic attack	1.16(1.04,1.29)	0.005396	1.37(0.89,2.11)	0.153299	0.89(0.67,1.19)	0.447825	0.01(0,0.02)	0.087282	1.14	0.000353	0
Intracerebral hemorrhage	1.19(0.97,1.47)	0.102951	0.95(0.52,1.74)	0.864987	2.49(1.38,4.48)	0.002406	-0.03(-0.06,-0.01)	0.01022	1.18	0.032004	0
Subarachnoid hemorrhage	1.26(1.02,1.56)	0.032373	1.98(1.05,3.72)	0.034597	1.73(0.96,3.11)	0.068066	-0.02(-0.04,0.01)	0.242887	1.23	0.005917	0
Aortic aneurysms											
Abdominal aortic aneurysm	1.17(0.96,1.42)	0.112196	1.31(0.75,2.27)	0.339659	1.04(0.61,1.78)	0.875731	0(-0.02,0.03)	0.746492	1.14	0.056903	0
Thoracic aortic aneurysm	0.97(0.67,1.4)	0.865331	0.84(0.29,2.43)	0.744793	1.69(0.62,4.62)	0.307995	-0.02(-0.07,0.02)	0.311718	1.02	0.872938	0
Thrombotic diseases											
Deep vein thrombosis	1.13(1.05,1.21)	0.00085	1.12(0.86,1.44)	0.397167	1.05(0.85,1.31)	0.651064	0(-0.01,0.01)	0.417335	1.15	1.04E-06	1
Pulmonary embolism	1.1(1.01,1.2)	0.024066	0.99(0.75,1.3)	0.939084	0.95(0.73,1.23)	0.687487	0.01(0,0.02)	0.121749	1.16	1.42E-05	1
Other CVDs											
Coronary artery disease	1.24(1.18,1.29)	2.04E-21	1.16(0.99,1.36)	0.068586	1.13(0.95,1.34)	0.164563	0(0,0.01)	0.382699	1.23	1.38E-22	6
Aortic valve stenosis	1.1(0.95,1.27)	0.18423	0.9(0.6,1.35)	0.608073	0.96(0.61,1.52)	0.859994	0.01(-0.01,0.03)	0.316769	1.2	0.001428	1
Atrial fibrillation	1.13(1.07,1.2)	5.06E-06	1.21(0.99,1.48)	0.06557	1.05(0.88,1.25)	0.58585	0(0,0.01)	0.424777	1.13	1.26E-08	2
Heart failure	1.26(1.15,1.37)	1.09E-07	1.32(0.96,1.82)	0.087946	1.26(0.97,1.63)	0.078988	0(-0.01,0.01)	0.888837	1.24	3.2E-10	1
Peripheral vascular disease	1.22(1.09,1.37)	0.000449	1.16(0.83,1.63)	0.383837	1.08(0.78,1.49)	0.651828	0.01(-0.01,0.02)	0.406422	1.23	8.04E-07	1
Arterial hypertension	1.14(1.11,1.17)	1.85E-20	1.07(0.97,1.18)	0.160416	1.06(0.93,1.2)	0.38005	0(0,0.01)	0.263218	1.16	1.77E-24	19

MR: mendelian randomization; MRPRESSO: MR pleiotropy residual sum and outlier; OR: odd ratio; CI: confidence interval; No.: number; CVDs: cardiovascular diseases.

Table S13. Associations between genetically predicted insomnia and 4 cardiovascular diseases in replication analysis using previously published GWAS studies.

Exposure	Outcome	Method	OR	LB	UB	P value	Egger P value	No. of outliers	Sample size	Cases
Insomnia	Ischemic stroke	IVW	1.08	1.04	1.11	6.74×10^{-5}	-	-	446696	40585
Insomnia	Ischemic stroke	Weighted median	1.08	1.03	1.14	0.0027	-	-	446696	40585
Insomnia	Ischemic stroke	Mode-based	1.05	0.92	1.21	0.47	-	-	446696	40585
Insomnia	Ischemic stroke	MR-Egger	0.99	0.86	1.14	0.88	0.24	-	446696	40585
Insomnia	Ischemic stroke	MR-PRESSO	1.08			8.92×10^{-5}	-	0	446696	40585
Insomnia	Coronary artery disease	IVW	1.13	1.08	1.18	2.02×10^{-8}	-	-	184305	60801
Insomnia	Coronary artery disease	Weighted median	1.12	1.07	1.18	4.96×10^{-6}	-	-	184305	60801
Insomnia	Coronary artery disease	Mode-based	1.14	1	1.3	0.044	-	-	184305	60801
Insomnia	Coronary artery disease	MR-Egger	1.15	0.96	1.37	0.13	0.84	-	184305	60801
Insomnia	Coronary artery disease	MR-PRESSO	1.13			6.42×10^{-10}	-	5	184305	60801
Insomnia	Atrial fibrillation	IVW	1.04	1.01	1.07	7.28×10^{-3}	-	-	588190	-
Insomnia	Atrial fibrillation	Weighted median	1.05	1.01	1.09	0.009	-	-	588190	-
Insomnia	Atrial fibrillation	Mode-based	1.07	0.95	1.22	0.27	-	-	588190	-
Insomnia	Atrial fibrillation	MR-Egger	0.99	0.88	1.11	0.83	0.37	-	588190	-
Insomnia	Atrial fibrillation	MR-PRESSO	1.04			0.006	-	2	588190	-
Insomnia	Heart failure	IVW	1.10	1.07	1.14	1.8×10^{-11}	-	-	977323	-
Insomnia	Heart failure	Weighted median	1.12	1.07	1.16	6.2×10^{-8}	-	-	977323	-
Insomnia	Heart failure	Mode-based	1.15	1.04	1.28	0.007	-	-	977323	-
Insomnia	Heart failure	MR-Egger	1.21	1.08	1.37	0.001	0.1	-	977323	-
Insomnia	Heart failure	MR-PRESSO	1.1			2.9×10^{-10}	-	1	977323	-

OR: odd ratio; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; No.: number; MR: mendelian randomization; IVW: inverse variance weighted; MR-PRESSO: MR pleiotropy residual sum and outlier.

Table S14. Leave-one-out analysis of association between genetically predicted insomnia and the risk of 4 cardiovascular diseases in replication analysis using previously published GWAS studies.

Outcome	Estimate [Min, Max] [a]	P value [Min, Max] [b]
Ischemic stroke	[1.07,1.08]	[0.0000268453009723746,0.000120058579533057]
Coronary artery disease	[1.12,1.13]	[0.000000000819083524801232,0.0000000480897072408428]
Atrial fibrillation	[1.04,1.04]	[0.00356769100034803,0.0116350521246951]
Heart failure	[1.1,1.11]	[0.000000000007317088116960 7,0.000000000193609760454 61]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value.

Table S15. Associations between genetically predicted insomnia and 14 cardiovascular diseases in replication analysis using UK Biobank individual data.

Outcome	Sample size [a]	Cases	OR [b]	95% CI	P-value	I^2 [c]
Cerebrovascular diseases						
Ischemic stroke	128799	2714	1.33	[1.09,1.62]	0.004456	0.289527
Transient ischemic attack	128478	2393	1.25	[1.01,1.54]	0.038139	0
Intracerebral hemorrhage	126681	596	2.01	[1.32,3.06]	0.001131	2.126243
Subarachnoid hemorrhage	126658	573	1.73	[1.12,2.67]	0.01311	3.713564
Aortic aneurysms						
Abdominal aortic aneurysm	126718	633	1.09	[0.72,1.63]	0.69163	0
Thoracic aortic aneurysm	126280	195	1.29	[0.6,2.77]	0.512824	10.76701
Thrombotic diseases						
Deep vein thrombosis	131482	5397	1.40	[1.21,1.62]	9.54×10^{-6}	9.001975
Pulmonary embolism	129598	3513	1.39	[1.16,1.66]	0.000375	6.097343
Other CVDs						
Coronary artery disease	142768	16683	1.58	[1.42,1.75]	1.05×10^{-17}	35.54868
Aortic valve stenosis	127416	1331	1.25	[0.93,1.68]	0.142407	10.84998
Atrial fibrillation	135939	9854	1.32	[1.18,1.48]	2.10×10^{-6}	15.07042
Heart failure	129924	3839	1.67	[1.4,2.01]	$2.38E\times10^{-8}$	14.91265
Peripheral vascular disease	128150	2065	1.45	[1.15,1.84]	0.001844	8.444229
Arterial hypertension	200385	74300	1.33	[1.23,1.43]	9.43×10^{-14}	60.57762

Results were obtained from multiplicative random-effects inverse-variance weighted method.

[a] The sample size denotes the total number of individuals (case + control) in the second sample for each CVD outcome (for each CVD outcome, individuals suffering from any other 13 CVD outcomes were further excluded from the control group).

[b] Estimate represent odds ratios (*OR*) expressed per genetically predicted 1-unit-higher log-odds of liability to insomnia (per 2.72-fold increase in the prevalence of the insomnia);

[c] I^2 statistic quantifies the amount of heterogeneity among estimates based on individual SNPs.

Table S16. Associations between genetically predicted insomnia and 14 cardiovascular diseases in sensitivity analysis of replication analysis using UK Biobank individual data.

Outcome	Weighted median		Mode-based		MR-Egger				MRPRESSO		
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	Intercept	P value	OR	P value	No. of outliers
Cerebrovascular diseases											
Ischemic stroke	1.36(1,1.84)	0.05069	1.45(0.43,4.9)	0.553289	1.08(0.71,1.64)	0.70946	0(0,0.01)	0.263095	1.33	0.004831	0
Transient ischemic attack	1.19(0.86,1.64)	0.287488	1.1(0.25,4.79)	0.894128	0.85(0.55,1.32)	0.465768	0.01(0,0.02)	0.051516	1.25	0.035284	0
Intracerebral hemorrhage	2.2(1.15,4.22)	0.017524	2.54(0.1,66.02)	0.57418	3.16(1.32,7.58)	0.009766	-0.01(-0.03,0.01)	0.245429	2.01	0.001291	0
Subarachnoid hemorrhage	1.31(0.67,2.56)	0.425288	1.74(0,775.3)	0.85918	1.35(0.54,3.36)	0.518847	0.01(-0.01,0.02)	0.543049	1.73	0.013779	0
Aortic aneurysms											
Abdominal aortic aneurysm	1.04(0.55,1.95)	0.904579	0.85(0.1,6.91)	0.875951	0.99(0.42,2.33)	0.982602	0(-0.02,0.02)	0.811516	1.09	0.688684	0
Thoracic aortic aneurysm	0.98(0.32,3.07)	0.97694	1.09(0,831.51)	0.980775	2.88(0.6,13.85)	0.186389	-0.02(-0.05,0.01)	0.251076	1.29	0.513435	0
Thrombotic diseases											
Deep vein thrombosis	1.44(1.15,1.79)	0.001284	1.07(0.45,2.57)	0.875078	1.16(0.85,1.58)	0.347212	0(0,0.01)	0.182534	1.4	1.44E-05	0
Pulmonary embolism	1.22(0.93,1.59)	0.149856	1.09(0.59,2)	0.780765	1.06(0.73,1.54)	0.764693	0.01(0,0.01)	0.11115	1.39	0.000449	0
Other CVDs											
Coronary artery disease	1.47(1.29,1.68)	1.63E-08	1.34(0.95,1.89)	0.095718	1.2(0.97,1.49)	0.09804	0.01(0,0.01)	0.004729	1.59	1.16E-18	3
Aortic valve stenosis	1.03(0.66,1.6)	0.901872	0.64(0.01,33.36)	0.825286	0.85(0.45,1.58)	0.598214	0.01(0,0.02)	0.163477	1.25	0.143684	0
Atrial fibrillation	1.3(1.1,1.53)	0.002331	0.91(0.32,2.61)	0.868086	1.18(0.93,1.51)	0.173968	0(0,0.01)	0.305178	1.35	5.71E-07	1
Heart failure	1.63(1.25,2.13)	0.000367	1.58(0.42,5.99)	0.503372	1.33(0.91,1.95)	0.138908	0.01(0,0.01)	0.179871	1.67	6.27E-08	0
Peripheral vascular disease	1.71(1.2,2.45)	0.003022	1.68(0.38,7.46)	0.497716	1.07(0.66,1.76)	0.774147	0.01(0,0.02)	0.171459	1.45	0.002063	0
Arterial hypertension	1.24(1.15,1.35)	1.25E-07	1.15(0.79,1.67)	0.46176	1.11(0.95,1.3)	0.181581	0(0,0.01)	0.010414	1.34	5.94E-16	9

MR: mendelian randomization; MRPRESSO: MR pleiotropy residual sum and outlier; OR: odd ratio; CI: confidence interval; No.: number; CVDs: cardiovascular diseases.

Table S17. Leave-one-out analysis of association between genetically predicted insomnia and 17 cardiometabolic risk factors in step b of mediation analysis.

Outcome	Estimate [Min, Max] [a]	P value [Min, Max] [b]
Anthropometric		
WHR, SD (ratio)	[0.05,0.05]	[0.0000044074495162145,0.0000955072065612272]
WHRadjBMI, SD (ratio)	[0.01,0.02]	[0.0666985586582434,0.298626831744182]
WC, SD (cm)	[0.06,0.07]	[0.000011474457411313,0.00027153121612l882]
WCadjBMI, SD (cm)	[-0.01,0]	[0.357219321161669,0.993436794871279]
HIP, SD (cm)	[0.04,0.05]	[0.00212081286585905,0.016590823509128]
HIPadjBMI, SD (cm)	[-0.03,-0.02]	[0.0253044628516898,0.19409129810722]
BMI, SD (kg/m2)	[0.06,0.08]	[0.000000287555435685851,0.0000205938559705472]
Lipids		
TC, SD (mg/dL)	[0.02,0.03]	[0.0524568403969068,0.256497366815301]
LDL-C, SD (mg/dL)	[0.02,0.03]	[0.057799426928969,0.20824777920477]
HDL-C, SD (mg/dL)	[-0.07,-0.05]	[0.00003468990607l6208,0.000631131156786682]
TG, SD (mg/dL)	[0.06,0.07]	[0.000001758808341315l5,0.0000087946162664l192]
Glycemic		
Fasting glucose, mmol/L	[-0.08,0]	[0.293251287768197,0.982671572871615]
Fasting insulin, log(mmol/L)	[0,0.05]	[0.267271766744033,0.987832172990524]
Two-hour glucose, mmol/L	[-0.33,-0.1]	[0.0305746515343448,0.48973182482394]
HbA1c, %	[0.01,0.01]	[0.00596736341191292,0.0444372014979117]
Renal function		
eGFR, mL/min/1.73m2	[0,0]	[0.500785470165884,0.775721580164342]
Other		
Heart rate	[0,0]	[0.778187134683311,0.998706350145354]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value.

WHR: waist-hip ratio; WHRadjBMI: waist-hip ratio adjusted for body mass index (BMI); WC: waist circumference; WCadjBMI: waist circumference adjusted for BMI; HIP: hip circumference; HIPadjBMI: hip circumference adjusted for BMI; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglycerides; SD: standard deviation;

Table S18. Sensitivity analysis of association between genetically predicted insomnia and 17 cardiometabolic risk factors in step b of mediation analysis.

Outcome	Weighted median		Mode-based		MR-Egger				MRPRESSO		
	Beta (95% CI)	P value	Beta (95% CI)	P value	Beta (95% CI)	P value	Intercept	P value	Beta (95% CI)	P value	No. of outliers
WHR, SD(ratio)	0.05(0.02,0.08)	0.001055	0.02(-0.06,0.1)	0.594317	0.12(0,0.24)	0.049583	0(-0.01,0)	0.245998	0.05	4.47E-05	1
WHRadjBMI, SD(ratio)	0.02(-0.01,0.05)	0.225307	0.03(-0.05,0.11)	0.486937	0.04(-0.07,0.15)	0.470193	0(-0.01,0)	0.660034	0.02	0.135643	0
WC, SD(cm)	0.06(0.02,0.09)	0.000876	0.04(-0.03,0.12)	0.227796	0.19(0.03,0.34)	0.020908	-0.01(-0.01,0)	0.118062	0.06	6.86E-05	6
WCadjBMI, SD(cm)	0(-0.03,0.03)	0.883556	0.04(-0.05,0.13)	0.410405	0.07(-0.06,0.21)	0.284709	0(-0.01,0)	0.255373	-0.01	0.514761	2
HIP, SD(cm)	0.03(0,0.07)	0.064058	-0.01(-0.09,0.06)	0.775762	0.15(-0.02,0.32)	0.081979	0(-0.01,0)	0.215517	0.05	0.002038	5
HIPadjBMI, SD(cm)	-0.04(-0.07,0)	0.035052	-0.04(-0.11,0.04)	0.308672	0.05(-0.11,0.2)	0.53865	0(-0.01,0)	0.349829	-0.04	0.005367	3
BMI, SD(kg/m2)	0.07(0.04,0.1)	6.06E-06	0.06(0,0.13)	0.070235	0.14(-0.02,0.3)	0.077826	0(-0.01,0)	0.369075	0.07	2.09E-09	8
TC, SD(mg/dL)	0.04(0,0.07)	0.056682	0.06(-0.03,0.14)	0.1985	0.02(-0.13,0.17)	0.779325	0(-0.01,0.01)	0.996661	0.03	0.021157	2
LDL-C, SD(mg/dL)	0.02(-0.02,0.06)	0.293272	0.01(-0.08,0.09)	0.899871	-0.03(-0.17,0.1)	0.644699	0(0,0.01)	0.433083	0.02	0.122918	0
HDL-C, SD(mg/dL)	-0.06(-0.1,-0.02)	0.000972	-0.07(-0.17,0.03)	0.160605	0.06(-0.1,0.22)	0.454293	-0.01(-0.01,0)	0.131129	-0.06	1.68E-05	3
TG, SD(mg/dL)	0.05(0.02,0.09)	0.003712	0.02(-0.07,0.11)	0.67521	0.11(-0.03,0.24)	0.11374	0(-0.01,0)	0.506018	0.07	8.01E-07	1
Fasting glucose, mmol/L	0.01(-0.04,0.07)	0.702227	0.02(-0.04,0.08)	0.49077	0.18(-0.27,0.64)	0.434114	-0.01(-0.03,0.01)	0.302816	0	0.983512	1
Fasting insulin, log(mmol/L)	0.01(-0.05,0.08)	0.659476	0.02(-0.05,0.09)	0.56861	-0.04(-0.39,0.31)	0.832681	0(-0.01,0.02)	0.683154	0	0.985805	1
Two-hour glucose, mmol/L	-0.23(-0.55,0.1)	0.171779	0.1(-0.3,0.49)	0.631316	0.3(-0.84,1.45)	0.600739	-0.02(-0.07,0.03)	0.398483	-0.17	0.290979	0
HbA1c, %	0.01(0,0.03)	0.02478	0.03(0,0.06)	0.082255	0.02(-0.03,0.06)	0.454955	0(0,0)	0.76129	0.01	0.022864	0
eGFR, mL/min/1.73m2	0(0,0)	0.432535	0(0,0.01)	0.691012	0(-0.01,0)	0.300632	0(0,0)	0.23925	0	0.532634	6
Heart rate	-0.01(-0.04,0.02)	0.686824	-0.01(-0.08,0.07)	0.848805	0(-0.09,0.08)	0.950197	0(0,0)	0.929231	0	0.924897	1

MR: mendelian randomization; MRPRESSO: MR pleiotropy residual sum and outlier; OR: odd ratio; CI: confidence interval; No.: number; WHR: waist-hip ratio; WHRadjBMI: waist-hip ratio adjusted for body mass index (BMI); WC: waist circumference; WCadjBMI: waist circumference adjusted for BMI; HIP: hip circumference; HIPadjBMI: hip circumference adjusted for BMI; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglycerides; SD: standard deviation;

Table S19. Association between genetically predicted insomnia and 6 cardiometabolic risk factors in replication analysis of step b of mediation analysis.

Exposure	Outcome	Method	Beta	LB	UB	P value	Egger P value	No. of outliers	No. of SNP	Sample size	SD
Insomnia	WHRadjBMI	IVW	0.04	0.01	0.06	1.48×10^{-3}	-	-	241	54572	0.08
Insomnia	WHRadjBMI	Weighted median	0.04	0.01	0.07	0.02	-	-	241	54572	0.08
Insomnia	WHRadjBMI	Mode-based	0.01	-0.08	0.1	0.77	-	-	241	54572	0.08
Insomnia	WHRadjBMI	MR-Egger	0.08	-0.01	0.17	0.08	0.32	-	241	54572	0.08
Insomnia	WHRadjBMI	MR-PRESSO	0.04			0.002	-	0	241	54572	0.08
Insomnia	BMI	IVW	0.05	0.03	0.08	4.34×10^{-5}	-	-	241	87048	4.77
Insomnia	BMI	Weighted median	0.06	0.04	0.09	8.56×10^{-6}	-	-	241	87048	4.77
Insomnia	BMI	Mode-based	0.08	0	0.15	0.05	-	-	241	87048	4.77
Insomnia	BMI	MR-Egger	0.1	-0.01	0.21	0.06	0.37	-	241	87048	4.77
Insomnia	BMI	MR-PRESSO	0.06			2.55×10^{-8}	-	0	241	87048	4.77
Insomnia	TC	IVW	0.02	-0.01	0.05	0.162	-	-	241	62166	41.75
Insomnia	TC	Weighted median	0.01	-0.02	0.04	0.42	-	-	241	62166	41.75
Insomnia	TC	Mode-based	0.04	-0.05	0.13	0.4	-	-	241	62166	41.75
Insomnia	TC	MR-Egger	0.06	-0.11	0.23	0.48	0.42	-	241	62166	41.75
Insomnia	TC	MR-PRESSO	0			0.80	-	0	241	62166	41.75
Insomnia	LDL-C	IVW	0	-0.04	0.04	0.995	-	-	241	62166	38.67
Insomnia	LDL-C	Weighted median	0.02	-0.02	0.05	0.24	-	-	241	62166	38.67
Insomnia	LDL-C	Mode-based	0.04	-0.05	0.14	0.35	-	-	241	62166	38.67
Insomnia	LDL-C	MR-Egger	0.05	-0.14	0.23	0.63	0.61	-	241	62166	38.67
Insomnia	LDL-C	MR-PRESSO	0.02			0.19	-	0	241	62166	38.67
Insomnia	HDL-C	IVW	-0.04	-0.07	-0.01	7.12×10^{-3}	-	-	241	62166	15.51
Insomnia	HDL-C	Weighted median	-0.05	-0.08	-0.02	0.002	-	-	241	62166	15.51
Insomnia	HDL-C	Mode-based	-0.07	-0.15	0.02	0.14	-	-	241	62166	15.51
Insomnia	HDL-C	MR-Egger	0.02	-0.11	0.15	0.81	0.36	-	241	62166	15.51
Insomnia	HDL-C	MR-PRESSO	-0.04			0.004	-	0	241	62166	15.51
Insomnia	TG	IVW	0.05	0.02	0.07	1.27×10^{-4}	-	-	241	62166	90.72
Insomnia	TG	Weighted median	0.06	0.03	0.09	0.0002	-	-	241	62166	90.72
Insomnia	TG	Mode-based	0.07	-0.02	0.16	0.11	-	-	241	62166	90.72
Insomnia	TG	MR-Egger	0.06	-0.05	0.16	0.28	0.87	-	241	62166	90.72
Insomnia	TG	MR-PRESSO	0.05			1.13×10^{-5}	-	0	241	62166	90.72

OR: odd ratio; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; No.: number; MR: mendelian randomization; IVW: inverse variance weighted; MR-PRESSO: MR pleiotropy residual sum and outlier. TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglycerides.

Table S20. Leave-one-out analysis of association between genetically predicted insomnia and 6 cardiometabolic risk factors in replication analysis of step b of mediation analysis.

Outcome	**Estimate [Min, Max] [a]**	**P value [Min, Max] [b]**
WHRadjBMI, SD (ratio)	[0.03,0.04]	[0.000704554697255648,0.00281415967551047]
BMI, SD (kg/m2)	[0.05,0.06]	[0.000003199597047307 88,0.0000900335583009329]
TC, SD (mg/dl)	[-0.01,0.01]	[0.516540259928238,0.856786557960117]
LDL-C, SD (mg/dl)	[0,0.02]	[0.188223217376048,0.999536661057882]
HDL-C, SD (mg/dl)	[-0.05,-0.04]	[0.00159739285038294,0.0115165343420197]
TG, SD (mg/dl)	[0.05,0.05]	[0.000007254024375701 28,0.000212009729329835]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value;

WHRadjBMI: waist-hip ratio adjusted for body mass index (BMI); TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglycerides

Table S21. Leave-one-out analysis of the associations between genetically predicted body mass index and 9 cardiovascular diseases in step c of mediation analysis.

Outcome	Estimate [Min, Max] [a]	P value [Min, Max] [b]
Ischemic stroke	[1.16,1.26]	[0.0208938013377172,0.168614544585888]
Transient ischemic attack	[1.23,1.34]	[0.00489839578517984,0.0552958170604236]
Deep vein thrombosis	[1.74,1.81]	[1.90396657795132e-17,1.70718307444615e-14]
Pulmonary embolism	[1.6,1.72]	[1.8321564471447e-07,5.27205862687396e-06]
Coronary artery disease	[1.51,1.56]	[1.94868440759027e-14,9.53147122238278e-11]
Atrial fibrillation	[1.53,1.59]	[1.44615843927846e-13,2.19948606826492e-11]
Heart failure	[2.08,2.22]	[1.88201156658876e-18,1.6573281459026e-13]
Peripheral vascular disease	[1.65,1.8]	[1.486890821036e-06,0.00029543062372266]
Arterial hypertension	[1.5,1.55]	[2.83451668772078e-20,2.59107359599498e-13]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value.

Table S22. Sensitivity analysis of the associations between genetically predicted body mass index and 9 cardiovascular diseases in step c of mediation analysis.

Outcome	Weighted median		Mode-based		MR-Egger				MRPRESSO		
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	Intercept	P value	OR (95% CI)	P value	No. of outliers
Ischemic stroke	1.35(1,1.82)	0.051835	1.43(0.93,2.18)	0.102521	1.16(0.74,1.81)	0.528728	0(-0.01,0.01)	0.806112	1.22	0.049292	0
Transient ischemic attack	1.53(1.08,2.17)	0.017943	1.56(0.97,2.49)	0.06453	1.56(0.98,2.47)	0.061196	-0.01(-0.02,0.01)	0.360317	1.28	0.012568	0
Deep vein thrombosis	1.66(1.32,2.09)	1.67E-05	1.61(1.21,2.16)	0.00131	2.09(1.51,2.89)	8.06E-06	0(-0.01,0)	0.292047	1.79	6.78E-12	0
Pulmonary embolism	1.48(1.12,1.96)	0.006284	1.48(1.07,2.05)	0.017823	1.66(1.02,2.68)	0.039394	0(-0.01,0.01)	0.99716	1.66	7.53E-06	1
Coronary artery disease	1.41(1.24,1.6)	1.58E-07	1.43(1.24,1.64)	1.04E-06	1.16(0.88,1.54)	0.293591	0.01(0,0.02)	0.034827	1.51	4.59E-11	3
Atrial fibrillation	1.47(1.23,1.75)	2.51E-05	1.44(1.19,1.76)	0.000222	1.24(0.93,1.64)	0.143104	0.01(0,0.02)	0.072585	1.56	7.29E-10	1
Heart failure	2.09(1.6,2.73)	5.07E-08	1.99(1.48,2.69)	6.77E-06	1.72(1.12,2.63)	0.013384	0.01(-0.01,0.02)	0.259598	2.14	8.68E-12	1
Peripheral vascular disease	2.3(1.62,3.25)	2.72E-06	2.16(1.43,3.26)	0.000263	2.28(1.27,4.08)	0.00555	-0.01(-0.02,0.01)	0.307878	1.73	4.98E-05	1
Arterial hypertension	1.61(1.47,1.75)	4.71E-26	1.59(1.45,1.74)	1.12E-23	1.43(1.13,1.8)	0.002878	0(0,0.01)	0.572754	1.53	9.23E-16	7

MR: mendelian randomization; MRPRESSO: MR pleiotropy residual sum and outlier; OR: odd ratio; CI: confidence interval; No.: number; CVDs: cardiovascular diseases.

Table S23. Associations between genetically predicted body mass index and 4 cardiovascular diseases in replication analysis of Step c of mediation analysis.

Exposure	Outcome	Method	Beta	LB	UB	P value	Egger P value	No. of outliers	Sample size	Cases
BMI	Ischemic stroke	IVW	1.13	1	1.27	0.043	-	-	446696	40585
BMI	Ischemic stroke	Weighted median	1.1	0.94	1.29	0.23	-	-	446696	40585
BMI	Ischemic stroke	Mode-based	1.11	0.93	1.32	0.26	-	-	446696	40585
BMI	Ischemic stroke	MR-Egger	1.05	1.8	1.37	0.75	0.55	-	446696	40585
BMI	Ischemic stroke	MR-PRESSO	1.11			0.07	-	1	446696	40585
BMI	Coronary artery disease	IVW	1.5	1.33	1.69	1×10^{-11}	-	-	184305	60801
BMI	Coronary artery disease	Weighted median	1.44	1.24	1.68	2.7×10^{-6}	-	-	184305	60801
BMI	Coronary artery disease	Mode-based	1.41	1.17	1.71	0.00033	-	-	184305	60801
BMI	Coronary artery disease	MR-Egger	1.72	1.31	2.25	8.6×10^{-5}	0.27	-	184305	60801
BMI	Coronary artery disease	MR-PRESSO	1.49			2.87×10^{-11}	-	3	184305	60801
BMI	Atrial fibrillation	IVW	1.4	1.29	1.53	1.48×10^{-14}	-	-	588190	-
BMI	Atrial fibrillation	Weighted median	1.39	1.24	1.55	2.5×10^{-8}	-	-	588190	-
BMI	Atrial fibrillation	Mode-based	1.4	1.23	1.6	4.03×10^{-7}	-	-	588190	-
BMI	Atrial fibrillation	MR-Egger	1.22	1	1.48	0.05	0.12	-	588190	-
BMI	Atrial fibrillation	MR-PRESSO	1.39			3.6×10^{-11}	-	1	588190	-
BMI	Heart failure	IVW	1.64	1.47	1.84	7.1×10^{-18}	-	-	977323	-
BMI	Heart failure	Weighted median	1.69	1.47	1.94	1.41×10^{-13}	-	-	977323	-
BMI	Heart failure	Mode-based	1.63	1.39	1.93	4.73×10^{-9}	-	-	977323	-
BMI	Heart failure	MR-Egger	1.58	1.21	2.06	0.0007	0.74	-	977323	-
BMI	Heart failure	MR-PRESSO	1.66			1.33×10^{-13}	-	1	977323	-

OR: odd ratio; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; No.: number; MR: mendelian randomization; IVW: inverse variance weighted; MR-PRESSO: MR pleiotropy residual sum and outlier; BMI: body mass index.

Table S24. Leave-one-out study of the associations between genetically predicted body mass index and 4 cardiovascular diseases in replication analysis of Step c of mediation analysis.

Outcome	Estimate [Min, Max] [a]	P value [Min, Max] [b]
Ischemic stroke	[1.11,1.14]	[0.0210179446998324,0.0747850379309697]
Coronary artery disease	[1.44,1.53]	[4.26024284769228e-14,4.00512670283135e-10]
Atrial fibrillation	[1.39,1.42]	[3.20767936509516e-16,5.61342592525009e-13]
Heart failure	[1.62,1.68]	[8.53390783989489e-20,5.3906134693216e-15]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value.

Table S25. Leave-one-out analysis of the associations between genetically predicted high-density lipoprotein cholesterol and 9 cardiovascular diseases in Step c of mediation analysis.

Outcome	Estimate [Min, Max] [a]	P value [Min, Max] [b]
Ischemic stroke	[0.84,0.91]	[0.0126066313079608,0.1693632019069]
Transient ischemic attack	[0.9,0.93]	[0.0920844378383305,0.284177128359895]
Deep vein thrombosis	[0.92,0.95]	[0.149099801277927,0.377699417426023]
Pulmonary embolism	[0.97,1.03]	[0.668888811283748,0.9994523844723]
Coronary artery disease	[0.78,0.83]	[3.52097236597681e-05,0.00154603784519906]
Atrial fibrillation	[0.92,0.94]	[0.0318960837809394,0.146762598813867]
Heart failure	[0.87,0.91]	[0.0423597071243165,0.173163928920795]
Peripheral vascular disease	[0.77,0.82]	[0.00197327933943299,0.0152890690730209]
Arterial hypertension	[0.84,0.87]	[1.57189139683656e-05,0.000182478892586666]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value.

Table S26. Leave-one-out analysis of associations between genetically predicted triglycerides and 9 cardiovascular diseases of Step c of mediation analysis.

Outcome	Estimate [Min, Max] [a]	P value [Min, Max] [b]
Ischemic stroke	[1.16,1.25]	[0.0143880245946882,0.107684167726366]
Transient ischemic attack	[1.06,1.14]	[0.135873356643229,0.47724803861545]
Deep vein thrombosis	[0.83,0.87]	[0.0181667164155343,0.0824794940987828]
Pulmonary embolism	[0.83,0.88]	[0.0157498347567607,0.10290988959661]
Coronary artery disease	[1.41,1.47]	[0.000000000000062771276585441 8,0.0000000031086529845111]
Atrial fibrillation	[1.03,1.06]	[0.182224545732321,0.630916519312097]
Heart failure	[1.28,1.37]	[0.0000046149877913583 4,0.000140212542090974]
Peripheral vascular disease	[1.21,1.3]	[0.00496771215383943,0.0429594493545899]
Arterial hypertension	[1.17,1.19]	[0.0000041795968959957 5,0.000140564076388081]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value.

Table S27. Sensitivity analysis of the associations between genetically predicted high-density lipoprotein cholesterol and 9 cardiovascular diseases in Step c of mediation analysis

Outcome	Weighted median		Mode-based		MR-Egger				MRPRESSO		
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	Intercept	P value	OR (95% CI)	P value	No. of outliers
Ischemic stroke	0.92(0.77,1.1)	0.342824	0.96(0.79,1.17)	0.681077	1.11(0.91,1.35)	0.313728	-0.01(-0.02,0)	0.006608	0.9	0.110661	1
Transient ischemic attack	0.93(0.78,1.1)	0.4033	0.98(0.83,1.15)	0.773338	1.04(0.85,1.27)	0.734119	-0.01(-0.02,0)	0.121503	0.91	0.17599	1
Deep vein thrombosis	0.97(0.87,1.09)	0.652463	0.98(0.88,1.09)	0.658896	0.98(0.81,1.19)	0.861748	0(-0.01,0.01)	0.484925	0.94	0.173106	5
Pulmonary embolism	1.04(0.9,1.19)	0.593897	1.03(0.9,1.19)	0.670696	1.12(0.91,1.36)	0.28295	-0.01(-0.02,0)	0.162954	1.01	0.842248	1
Coronary artery disease	0.86(0.79,0.93)	0.000263	0.92(0.84,1.01)	0.071417	1.05(0.88,1.24)	0.584776	-0.02(-0.02,-0.01)	0.00021	0.8	7.65E-07	12
Atrial fibrillation	0.99(0.91,1.07)	0.754674	0.99(0.91,1.07)	0.722785	1(0.89,1.13)	0.973059	0(-0.01,0)	0.145613	0.94	0.052031	2
Heart failure	1.04(0.89,1.2)	0.633788	1.06(0.92,1.21)	0.42148	1.09(0.89,1.33)	0.389353	-0.01(-0.02,0)	0.014593	0.95	0.306119	4
Peripheral vascular disease	0.88(0.73,1.06)	0.174831	0.92(0.77,1.09)	0.329675	0.97(0.76,1.24)	0.810767	-0.01(-0.02,0)	0.053422	0.82	0.008365	1
Arterial hypertension	0.95(0.9,0.99)	0.020224	0.97(0.94,1)	0.073594	1.04(0.93,1.15)	0.496088	-0.01(-0.02,-0.01)	1.11E-05	0.88	5.62E-06	18

MR: mendelian randomization; MRPRESSO: MR pleiotropy residual sum and outlier; OR: odd ratio; CI: confidence interval; No.: number.

Table S28. Sensitivity analysis of associations between genetically predicted triglycerides and 9 cardiovascular diseases of Step c of mediation analysis

Outcome	Weighted median		Mode-based		MR-Egger				MRPRESSO		
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	Intercept	P value	OR (95% CI)	P value	No. of outliers
Ischemic stroke	1.19(0.97,1.45)	0.094563	1.19(0.99,1.44)	0.067569	1.09(0.82,1.45)	0.551374	0.01(-0.01,0.02)	0.418855	1.2	0.041579	1
Transient ischemic attack	1.18(0.95,1.47)	0.136753	1.21(0.97,1.52)	0.092447	1.04(0.78,1.38)	0.786194	0(-0.01,0.02)	0.624262	1.1	0.264545	1
Deep vein thrombosis	0.9(0.78,1.05)	0.170635	0.92(0.81,1.05)	0.198874	0.98(0.77,1.26)	0.887544	-0.01(-0.02,0)	0.170583	0.88	0.088 05	2
Pulmonary embolism	0.9(0.76,1.06)	0.203165	0.92(0.78,1.08)	0.293458	0.89(0.7,1.15)	0.383 96	0(-0.02,0.01)	0.659056	0.86	0.043077	1
Coronary artery disease	1.3(1.18,1.43)	4.91E-08	1.3(1.19,1.42)	2.52E-09	1.18(0.99,1.41)	0.061963	0.01(0,0.02)	0.006527	1.46	2.82E-11	5
Atrial fibrillation	1.03(0.92,1.15)	0.580697	1.06(0.95,1.18)	0.292 06	1.04(0.88,1.23)	0.639087	0(-0.01,0.01)	0.941684	1.06	0.188392	1
Heart failure	1.35(1.15,1.58)	0.000207	1.27(1.08,1.49)	0.003433	1.28(1.03,1.6)	0.023605	0(-0.01,0.01)	0.723391	1.31	5.33E-05	1
Peripheral vascular disease	1.13(0.9,1.41)	0.294564	1.2(0.97,1.49)	0.093 91	1.15(0.83,1.58)	0.396 03	0.01(-0.01,0.02)	0.495 11	1.25	0.022008	1
Arterial hypertension	1.17(1.11,1.23)	2.27E-10	1.14(1.1,1.19)	6.58E-11	1.03(0.92,1.17)	0.593 17	0.01(0,0.01)	0.009745	1.16	1.12E-07	11

MR: mendelian randomization; MRPRESSO: MR pleiotropy residual sum and outlier; OR: odd ratio; CI: confidence interval; No.: number.

Table S29. Associations between genetically predicted high-density lipoprotein cholesterol and 4 cardiovascular diseases in replication analysis of Step c of mediation analysis.

Exposure	Outcome	Method	OR	LB	UB	P value	Egger P value	No. of outliers	Sample size	Cases
HDL-C	Ischemic stroke	IVW	0.92	0.85	0.99	0.021	-	-	446696	40585
HDL-C	Ischemic stroke	Weighted median	0.95	0.88	1.04	0.26	-	-	446696	40585
HDL-C	Ischemic stroke	Mode-based	0.96	0.88	1.03	0.25	-	-	446696	40585
HDL-C	Ischemic stroke	MR-Egger	1.06	0.94	1.19	0.35	0.003	-	446696	40585
HDL-C	Ischemic stroke	MR-PRESSO	0.93			0.02	-	1	446696	40585
HDL-C	Coronary artery disease	IVW	0.88	0.8	0.98	0.015	-	-	184305	60801
HDL-C	Coronary artery disease	Weighted median	0.99	0.91	1.07	0.74	-	-	184305	60801
HDL-C	Coronary artery disease	Mode-based	1.02	0.96	1.1	0.49	-	-	184305	60801
HDL-C	Coronary artery disease	MR-Egger	1.1	0.96	1.26	0.17	2.45×10^{-5}	-	184305	60801
HDL-C	Coronary artery disease	MR-PRESSO	0.91			0.02	-	8	184305	60801
HDL-C	Atrial fibrillation	IVW	0.98	0.93	1.04	0.52	-	-	588190	-
HDL-C	Atrial fibrillation	Weighted median	0.98	0.93	1.04	0.55	-	-	588190	-
HDL-C	Atrial fibrillation	Mode-based	0.99	0.94	1.05	0.79	-	-	588190	-
HDL-C	Atrial fibrillation	MR-Egger	0.98	00.9	1.07	0.63	0.92	-	588190	-
HDL-C	Atrial fibrillation	MR-PRESSO	0.98			0.31	-	1	588190	-
HDL-C	Heart failure	IVW	0.90	0.84	0.97	0.0063	-	-	977323	-
HDL-C	Heart failure	Weighted median	0.94	0.88	1	0.06	-	-	977323	-
HDL-C	Heart failure	Mode-based	0.95	0.89	1.01	0.13	-	-	977323	-
HDL-C	Heart failure	MR-Egger	0.97	0.86	1.09	0.56	0.18	-	977323	-
HDL-C	Heart failure	MR-PRESSO	0.94			0.02	-	5	977323	-

OR: odd ratio; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; No.: number; MR: mendelian randomization; IVW: inverse variance weighted; MR-PRESSO: MR pleiotropy residual sum and outlier; HDL-C: high-density lipoprotein cholesterol.

Table S30. Leave-one-out analysis of the associations between genetically predicted high-density lipoprotein cholesterol and 4 cardiovascular diseases in replication analysis of Step c of mediation analysis.

Outcome	Estimate [Min, Max] [a]	P value [Mix, Max] [b]
Ischemic stroke	[0.9,0.93]	[0.00866033594102891,0.0401643065497412]
Coronary artery disease	[0.85,0.89]	[0.00407595308759956,0.0295407431055493]
Atrial fibrillation	[0.97,0.99]	[0.305500332589488,0.741111768821401]
Heart failure	[0.89,0.91]	[0.0024120993143106,0.0143112747474303]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value.

Table S31. Associations between genetically predicted triglycerides and 4 cardiovascular diseases in replication analysis of Step c of mediation analysis.

Exposure	Outcome	Method	OR	LB	UB	P value	Egger P value	No. of outliers	Sample size	Cases
TG	Ischemic stroke	IVW	1.2	1.01	1.42	0.037	-	-	446696	40585
TG	Ischemic stroke	Weighted median	1	0.91	1.1	0.95	-	-	446696	40585
TG	Ischemic stroke	Mode-based	0.99	0.91	1.09	0.90	-	-	446696	40585
TG	Ischemic stroke	MR-Egger	0.97	0.85	1.11	0.64	0.33	-	446696	40585
TG	Ischemic stroke	MR-PRESSO	1.02			0.60	-	1	446696	40585
TG	Coronary artery disease	IVW	1.44	1.29	1.61	1.55×10^{-10}	-	-	184305	60801
TG	Coronary artery disease	Weighted median	1.24	1.12	1.38	6.69×10^{-5}	-	-	184305	60801
TG	Coronary artery disease	Mode-based	1.25	1.12	1.38	2.14×10^{-5}	-	-	184305	60801
TG	Coronary artery disease	MR-Egger	1.09	0.93	1.29	0.29	0.01	-	184305	60801
TG	Coronary artery disease	MR-PRESSO	1.37			1.62×10^{-7}	-	5	184305	60801
TG	Atrial fibrillation	IVW	1.05	0.95	1.16	0.37	-	-	588190	-
TG	Atrial fibrillation	Weighted median	1	0.93	1.07	0.94	-	-	588190	-
TG	Atrial fibrillation	Mode-based	1	0.94	1.07	0.90	-	-	588190	-
TG	Atrial fibrillation	MR-Egger	1.02	0.89	1.17	0.76	0.40	-	588190	-
TG	Atrial fibrillation	MR-PRESSO	0.99			0.75	-	1	588190	-
TG	Heart failure	IVW	1.33	1.17	1.51	1.58×10^{-5}	-	-	977323	-
TG	Heart failure	Weighted median	1.17	1.09	1.27	4.8×10^{-5}	-	-	977323	-
TG	Heart failure	Mode-based	1.17	1.08	1.26	4.61×10^{-5}	-	-	977323	-
TG	Heart failure	MR-Egger	1.18	1.05	1.33	0.004	0.96	-	977323	-
TG	Heart failure	MR-PRESSO	1.17			6.09×10^{-6}	-	1	977323	-

OR: odd ratio; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; No.: number; MR: mendelian randomization; IVW: inverse variance weighted; MR-PRESSO: MR pleiotropy residual sum and outlier; TG: triglycerides.

Table S32. Leave-one-out analysis of the associations between genetically predicted triglycerides and 4 cardiovascular diseases in replication analysis of Step c of mediation analysis.

Outcome	Estimate [Min, Max] [a]	P value [Min, Max] [b]
Ischemic stroke	[1.01,1.03]	[0.383762940650492,0.776469734303151]
Coronary artery disease	[1.27,1.35]	[0.00000016227301775 9942,0.0000195233479628422]
Atrial fibrillation	[0.96,0.99]	[0.294623128451253,0.793134017725766]
Heart failure	[1.17,1.19]	[0.00000012045194257,0.0000144655051569308]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value.

Table S33. Association of genetic predicted BMI, HDL-C, and TG on insomnia in bidirectional MR analysis.

Exposure	Outcome	Method	OR	LB	UB	P value	SNPs	Egger P value	No. of outliers
BMI	Insomnia	IVW	1.06	0.98	1.14	0.14	72	-	-
BMI	Insomnia	Weighted median	1.03	0.94	1.12	0.58	72	-	-
BMI	Insomnia	Mode-based	1.02	0.93	1.11	0.67	72	-	-
BMI	Insomnia	MR-Egger	0.87	0.73	1.03	0.10	72	0.01	-
BMI	Insomnia	MR-PRESSO	1.07	1.00	1.15	0.05	72	-	3
HDL-C	Insomnia	IVW	1.00	0.96	1.03	0.87	85	-	-
HDL-C	Insomnia	Weighted median	0.98	0.94	1.02	0.37	85	-	-
HDL-C	Insomnia	Mode-based	0.99	0.95	1.03	0.67	85	-	-
HDL-C	Insomnia	MR-Egger	1.02	0.97	1.08	0.44	85	0.25	-
HDL-C	Insomnia	MR-PRESSO	1	0.97	1.03	0.77	85	-	2
TG	Insomnia	IVW	1.02	0.98	1.06	0.41	51		
TG	Insomnia	Weighted median	1	0.96	1.05	0.92	51		
TG	Insomnia	Mode-based	0.99	0.95	1.04	0.72	51		
TG	Insomnia	MR-Egger	0.95	0.9	1.01	0.11	51	0.008	
TG	Insomnia	MR-PRESSO	1.02	0.42	0.98	1.06	51		0

BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; OR: odd ratio; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; No.: number; MR: mendelian randomization; IVW: inverse variance weighted; MR-PRESSO: MR pleiotropy residual sum and outlier.

Table S34. The direct effect of insomnia on 14 CVD outcomes adjusts for body mass index, high-density lipoprotein cholesterol, triglycerides, and low-density lipoprotein cholesterol using multivariable inverse-variance weighted method.

Outcome	***OR***	**95% CI**	**P-value**
Cerebrovascular diseases			
Ischemic stroke	1.17	[1.08,1.26]	6.67E-05
Transient ischemic attack	1.13	[1.05,1.22]	0.001777
Intracerebral hemorrhage	1.18	[1.01,1.39]	0.036206
Subarachnoid hemorrhage	1.2	[1.02,1.41]	0.023548
Aortic aneurysms			
Abdominal aortic aneurysm	1.1	[0.96,1.27]	0.178032
Thoracic aortic aneurysm	1.02	[0.78,1.34]	0.887476
Thrombotic diseases			
Deep vein thrombosis	1.14	[1.08,1.21]	5.91E-06
Pulmonary embolism	1.14	[1.07,1.23]	0.000126
Other CVDs			
Coronary artery disease	1.19	[1.14,1.24]	1.34E-15
Aortic valve stenosis	1.18	[1.05,1.33]	0.005945
Atrial fibrillation	1.11	[1.06,1.16]	9.08E-06
Heart failure	1.22	[1.14,1.3]	8.40E-09
Peripheral vascular disease	1.21	[1.12,1.32]	6.85E-06
Arterial hypertension	1.12	[1.08,1.16]	3.34E-11
Replication analysis*			
Ischemic stroke*	1.07	[1.03,1.11]	0.00062
Coronary artery disease*	1.11	[1.07,1.16]	5.57E-07
Atrial fibrillation*	1.03	[1,1.06]	0.044907
Heart failure*	1.08	[1.05,1.11]	1.94E-07

* Replication analysis using summary data of IS, CAD, AF, and HF from previous published GWAS studies (Table S9). [48-51]

Table S35. The basic characters of summary data of blood pressure traits.

Trait	Total sample size	SD	Units	Pop.	First author or consortia	Web site	Study
Systolic blood pressure adjusted body mass index (SBPadjBMI)	458575	20.7	mm Hg	European	Evangelou et al. [104]	https://grasp.nhlbi.nih.gov/FullResults.aspx	AGES, ARIC, ASPS, B58C, BHS, CHS, COLAUS, CORO ALL, CROATIA-Korcula, CROATIA-Split, CROATIA-Vis, EGCUT, EGCUT2, EPIC, ERF, Fenland, FHS, FINNRISK CASE ALL, FINRISK CTRL ALL, FUSION, GRAPHIC, H2000 ALL, Health ABC, HTO, INGI_VB, INGI-CARL, Cilento study, INGI-FVG, IPM, KORAS3, KORAS4, LBC1921, LBC1936, LOLIPOP_EW610, MESA, MICROS, MIGen, NESDA, NSPHS, NTR, ORCADES, PROSPER, PIVUS, PROCARDIS, RSI, RSII, RSIII, SHIP, STR, TRAILS, TRAILS-CC, ULSAM, WGHS, YFS, ASCOT-SC, ASCOT-UK, BRIGHT, 3C-DIJON, EPIC-CVD, GWAS-Fenland, OMICS-Fenland, EPIC-InterAct, EPIC-Norfolk, GAPP, GoDARTS, GS:SFHS, HCS, JUPITER, Lifelines, MDC, METSIM, NEO, PREVEND, SardiNIA, TWINSUK, UKHLS, UK Biobank
Diastolic blood pressure adjusted body mass index (DBPadjBMI)	458577	11.3	mm Hg	European			
Systolic blood pressure (SBP)	389351	19.4	mm Hg	European	UK Biobank [26]	https://www.ukbiobank.ac.uk/	UK Biobank
Diastolic blood pressure (DBP)	389354	11	mm Hg	European			

Table S36. Associations between genetically predicted insomnia and 4 blood pressure traits.

Exposure	Outcome	Method	Beta	LB	UB	P value	Egger P value	No. of outliers	No. of SNPs used
Insomnia	SBP, mm Hg	IVW	0.28	-0.01	0.57	0.06	-	-	247
Insomnia	SBP, mm Hg	Weighted median	0.23	-0.02	0.48	0.08	-	-	247
Insomnia	SBP, mm Hg	Mode-based	0.13	-0.2	0.47	0.43	-	-	247
Insomnia	SBP, mm Hg	MR-Egger	-0.16	-1.33	1.02	0.79	0.45	-	247
Insomnia	SBP, mm Hg	MR-PRESSO	0.29			0.01	-	17	247
Insomnia	SBPadjBMI, mm Hg	IVW	0.08	-0.2	0.37	0.58	-	-	243
Insomnia	SBPadjBMI, mm Hg	Weighted median	0	-0.18	0.19	0.98	-	-	243
Insomnia	SBPadjBMI, mm Hg	Mode-based	-0.12	-0.34	0.11	0.30	-	-	243
Insomnia	SBPadjBMI, mm Hg	MR-Egger	-0.78	-1.95	0.38	0.19	0.13	-	243
Insomnia	SBPadjBMI, mm Hg	MR-PRESSO	0.11			0.24	-	33	243
Insomnia	DBP, mm Hg	IVW	0.41	0.24	0.58	1.75×10^{-6}	-	-	247
Insomnia	DBP, mm Hg	Weighted median	0.39	0.25	0.54	1.2×10^{-7}	-	-	247
Insomnia	DBP, mm Hg	Mode-based	0.33	0.14	0.52	5.3×10^{-4}	-	-	247
Insomnia	DBP mm Hg	MR-Egger	0.16	-0.53	0.84	0.65	0.45	-	247
Insomnia	DBP, mm Hg	MR-PRESSO	0.39			3.5×10^{-9}	-	21	247
Insomnia	DBPadjBMI, mm Hg	IVW	0.11	-0.05	0.27	0.18	-	-	244
Insomnia	DBPadjBMI, mm Hg	Weighted median	0.07	-0.04	0.17	0.21	-	-	244
Insomnia	DBPadjBMI, mm Hg	Mode-based	0	-0.13	0.14	0.94	-	-	244
Insomnia	DBPadjBMI, mm Hg	MR-Egger	-0.22	-0.86	0.42	0.50	0.30	-	244
Insomnia	DBPadjBMI, mm Hg	MR-PRESSO	0.1			0.05	-	27	244

SBP: systolic blood pressure; DBP: diastolic blood pressure; SBPadjBMI: systolic blood pressure adjusted body mass index; DBPadjBMI: diastolic blood pressure adjusted body mass index; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; No.: number; MR: mendelian randomization; IVW: inverse variance weighted; MR-PRESSO: MR pleiotropy residual sum and outlier.

Table S37. Association between genetically predicted diastolic blood pressure and 8 cardiovascular diseases selected in primary study.

Disease	***OR***	**95% CI**	**P value**
Cerebrovascular diseases			
Ischemic stroke	1.09	(1.06 ,1.13)	1.34E-09
Transient ischemic attack	1.04	(1.01 ,1.07)	0.010297
Thrombotic diseases			
Deep vein thrombosis	1	(0.98 ,1.02)	0.804438
Pulmonary embolism	1.01	(0.98 ,1.03)	0.532069
Other CVDs			
Coronary artery disease	1.08	(1.06 ,1.09)	2.42E-35
Atrial fibrillation	1.04	(1.02 ,1.06)	3.86E-07
Heart failure	1.07	(1.04 ,1.09)	1.90E-07
Peripheral vascular disease	1.03	(1 ,1.07)	0.056221

OR: odd ratio; CI: confidence interval; CVDs: cardiovascular diseases.

Table S38. Associations between genetically predicted diastolic blood pressure and insomnia.

Exposure	**Outcome**	**Method**	**OR**	**LB**	**UB**	**P value**	**Egger P value**	**No. of outliers**	**No. of SNPs used**
DBP, mm Hg	Insomnia	IVW	1.00	0.99	1.01	0.58	-	-	247
DBP, mm Hg	Insomnia	Weighted median	1	0.99	1.01	0.40	-	-	247
DBP, mm Hg	Insomnia	Mode-based	1	0.98	1.02	0.86	-	-	247
DBP, mm Hg	Insomnia	MR-Egger	1	0.98	1.01	0.58	0.75	-	247
DBP, mm Hg	Insomnia	MR-PRESSO	1			0.29	-	1	247

DBP: diastolic blood pressure; LB: lower bound of 95% confidence interval; UB: upper bound of 95% confidence interval; No.: number; MR: mendelian randomization; IVW: inverse variance weighted; MR-PRESSO: MR pleiotropy residual sum and outlier.

Table S39. Leave-one-out analysis of association between genetically predicted insomnia and 4 blood pressure traits.

Outcome	IVW Estimate [Min, Max] [a]	P value [Min, Max] [b]
SBP	[0.24,0.34]	[0.0186049858690466,0.100537941458835]
SBPadjBMI	[0.04,0.14]	[0.304494868109331,0.795806711330309]
DBP	[0.39,0.45]	[0.000000115628218417038,0.00000428086654195319]
DBPadjBMI	[0.09,0.15]	[0.03674968466824,0.273221141001499]

[a] the minimum value and maximum value of inverse variance weighted estimate;

[b] the minimum value and maximum value of P value;

SBP: systolic blood pressure; DBP: diastolic blood pressure; SBPadjBMI: systolic blood pressure adjusted body mass index; DBPadjBMI: diastolic blood pressure adjusted body mass index; IVW: inverse variance weighted.

Table S40. The proportion of the total effect of insomnia on each cardiovascular disease that diastolic blood pressure accounts for.

Exposure (*X*)	Mediator (*M*)	Outcome (*Y*)	TE_{XY}	β_{XM}	OR_{MY}	NIE_{XY} (95% *CI*)	Proportion (95% *CI*)
Insomnia	DBP	Ischemic stroke	1.16	0.41	1.09	0.035 (0.016,0.055)	23.81% (9.1% ,38.51%)
Insomnia	DBP	Coronary artery disease	1.22	0.41	1.08	0.032 (0.018,0.045)	15.87% (9.22% ,22.51%)
Insomnia	DBP	Atrial fibrillation	1.13	0.41	1.04	0.016 (0.007,0.025)	13.16% (4.85% ,21.46%)
Insomnia	DBP	Heart failure	1.24	0.41	1.07	0.028 (0.013,0.042)	12.9% (5.82% ,19.97%)

TE_{XY}: total effect of the exposure on the outcome expressed in odds ratios (*OR*) scale; NIE_{XY}: natural indirect effect of exposure on the outcome in log *OR* scale; Proportion: the proportion of the total effect of exposure on outcome that mediator accounts for; *CI*: confidence interval; DBP: diastolic blood pressure.

Figure S1. Flowchart of UK Biobank individual selection.

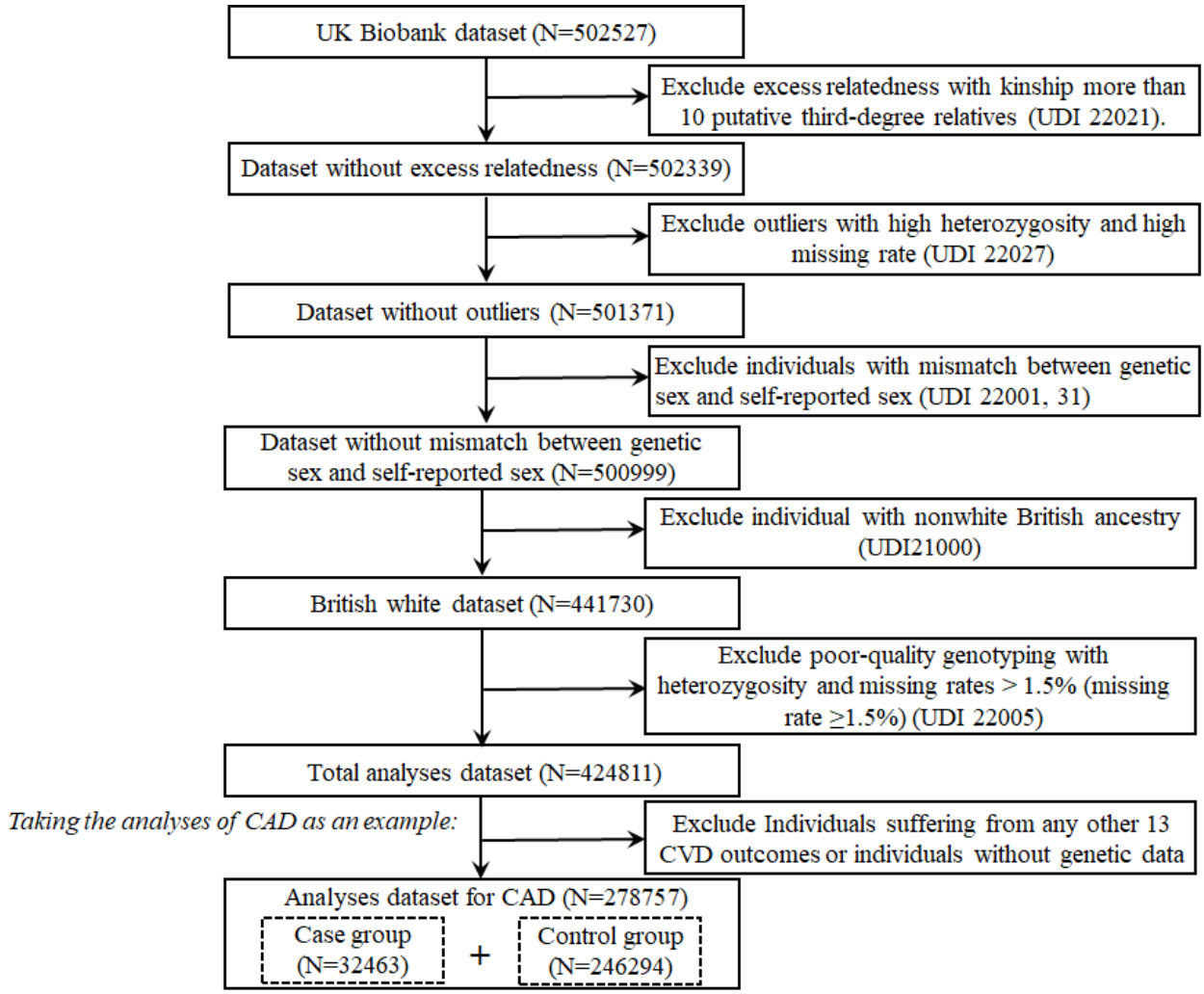
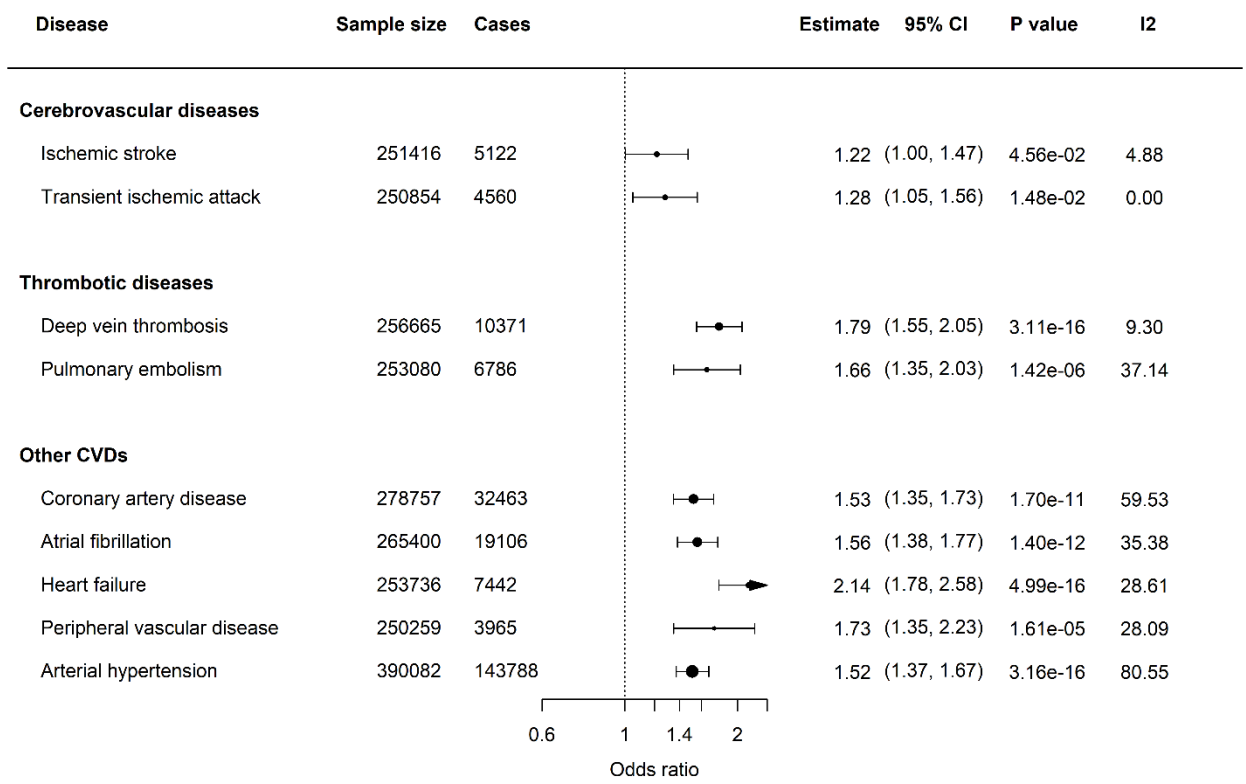
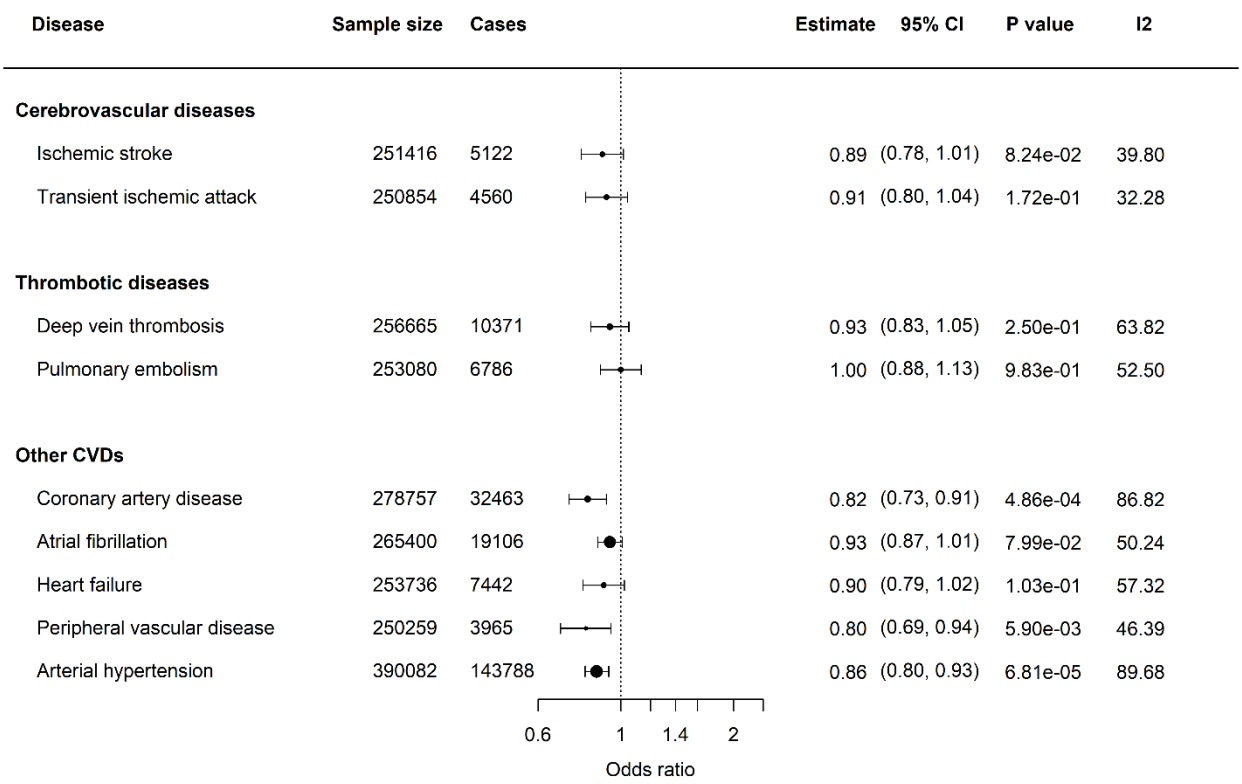


Figure S2. Associations between genetically predicted body mass index and 9 cardiovascular diseases selected in primary study.



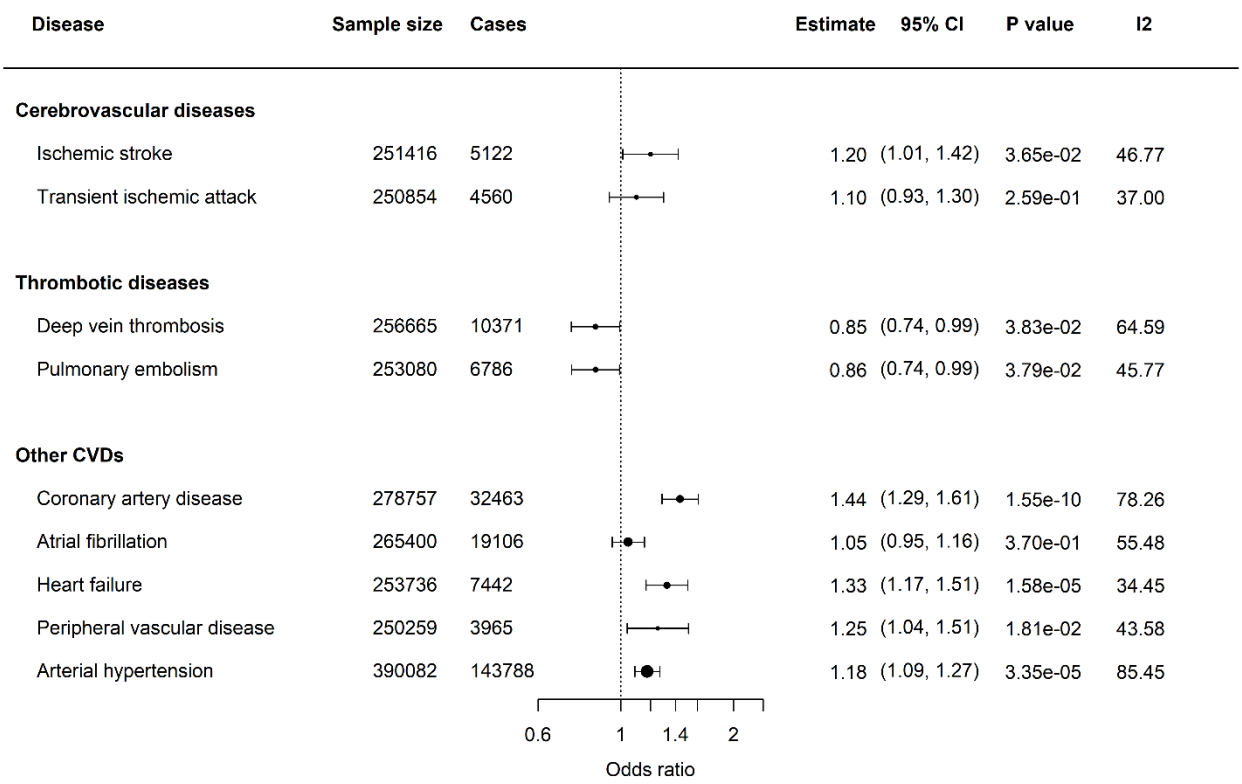
Results were obtained from multiplicative random-effects inverse-variance weighted method. For each CVD outcome, the individuals suffer from any other CVD outcomes were excluded from the control group, the sample size denotes the total number of case and control. Estimate represent odds ratios (*OR*) expressed per genetically predicted 1 SD increased of body mass index; I^2 statistic quantifies the amount of heterogeneity among estimates based on individual SNPs.

Figure S3. Associations between genetically predicted high-density lipoprotein cholesterol and 9 cardiovascular diseases selected in primary study.



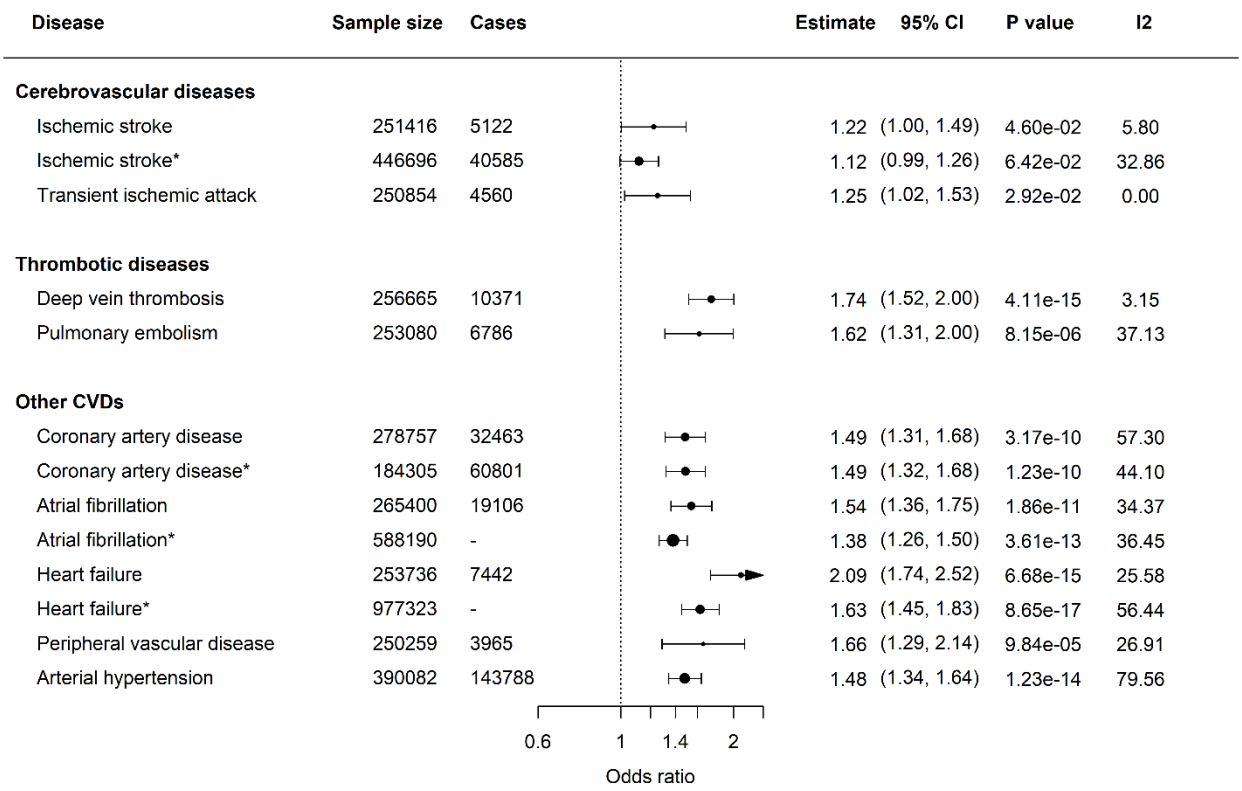
Results were obtained from multiplicative random-effects inverse-variance weighted method. For each CVD outcome, the individuals suffer from any other CVD outcomes were excluded from the control group, the sample size denotes the total number of case and control. Estimate represent odds ratios (*OR*) expressed per genetically predicted 1 SD increased of high-density lipoprotein cholesterol; I^2 statistic quantifies the amount of heterogeneity among estimates based on individual SNPs.

Figure S4. Associations between genetically predicted triglycerides and 9 cardiovascular diseases selected in primary study.



Results were obtained from multiplicative random-effects inverse-variance weighted method. For each CVD outcome, the individuals suffer from any other CVD outcomes were excluded from the control group, the sample size denotes the total number of case and control. Estimate represent odds ratios (*OR*) expressed per genetically predicted 1 SD increased of triglycerides; I^2 statistic quantifies the amount of heterogeneity among estimates based on individual SNPs.

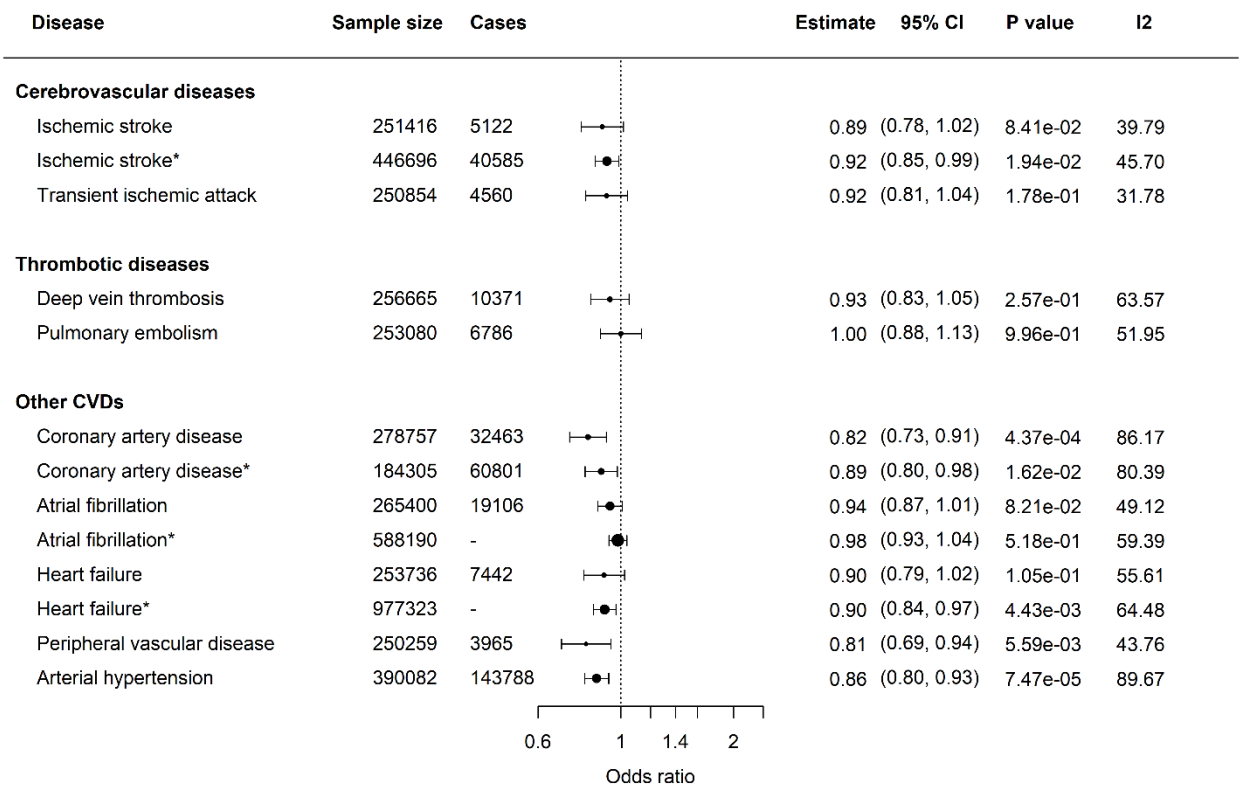
Figure S5. Results of associations between genetically predicted body mass index and 9 cardiovascular diseases outcomes using multivariable mendelian randomization analysis adjust for insomnia.



Results were obtained from regression-based multivariable MR adjusting for the genetic effect of the instruments on insomnia. For each CVD outcome, the individuals suffer from any other CVD outcomes were excluded from the control group, the sample size denotes the total number of case and control. Estimate represent odds ratios (*OR*) expressed per genetically predicted 1 SD increased of body mass index; I^2 statistic quantifies the amount of heterogeneity among estimates based on individual SNPs.

*: replication analysis.

Figure S6. Associations between genetically predicted high-density lipoprotein cholesterol and 9 cardiovascular diseases using multivariable MR analysis adjust for insomnia.



Results were obtained from regression-based multivariable MR adjusting for the genetic effect of the instruments on insomnia. For each CVD outcome, the individuals suffer from any other CVD outcomes were excluded from the control group, the sample size denotes the total number of case and control. Estimate represent odds ratios (*OR*) expressed per genetically predicted 1 SD increased of high-density lipoprotein cholesterol; I^2 statistic quantifies the amount of heterogeneity among estimates based on individual SNPs.

*: replication analysis.

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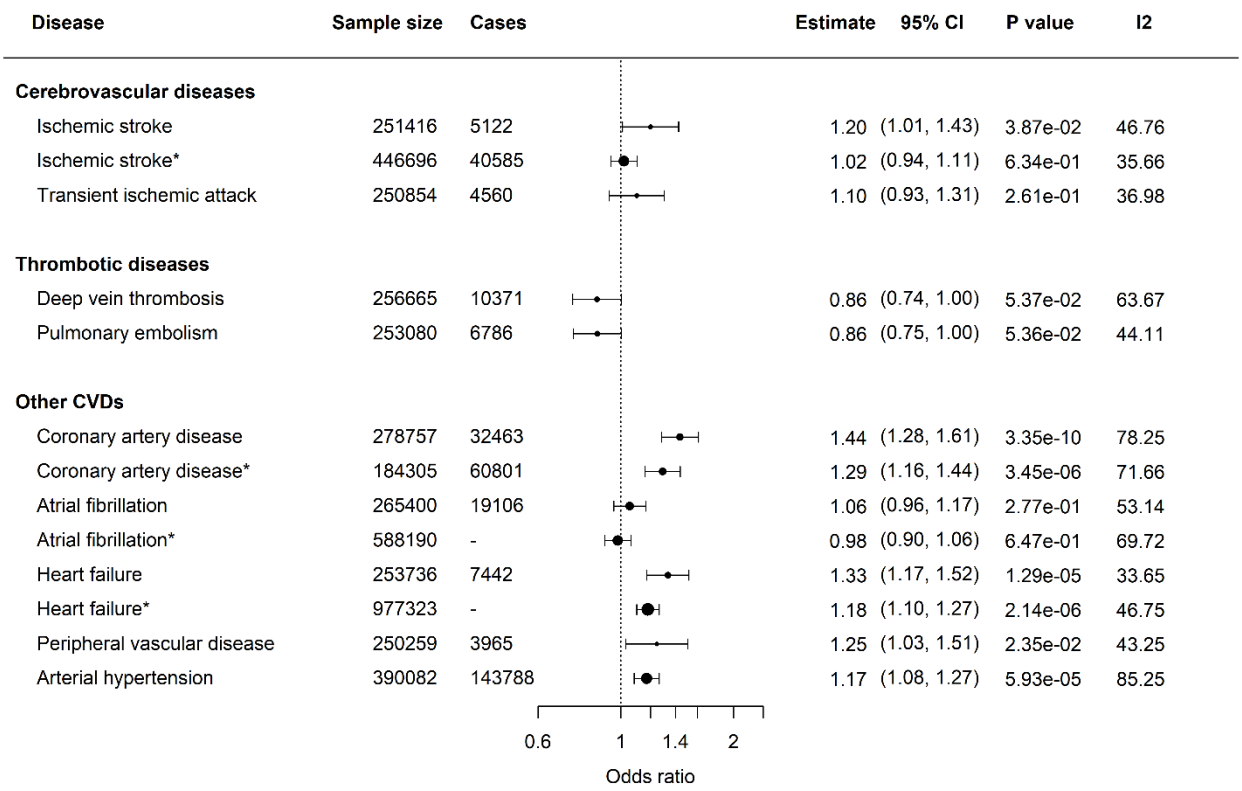
Figure S7. Results of associations between genetically predicted triglycerides and 9 cardiovascular diseases using multivariable MR analysis adjust for insomnia.



Results were obtained from regression-based multivariable MR adjusting for the genetic effect of the instruments on insomnia. For each CVD outcome, the individuals suffer from any other CVD outcomes were excluded from the control group, the sample size denotes the total number of case and control. Estimate represent odds ratios (*OR*) expressed per genetically predicted 1 SD increased of triglycerides; I^2 statistic quantifies the amount of heterogeneity among estimates based on individual SNPs.

*: replication analysis.

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