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. 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.

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) $\text{r}^2$ between SNPs $<0.1$ and distinct genomic loci are $>250$kb apart. As indicated by Swerdlow et al. (2016), 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 $< 5\times10^{-8}$) in order to reduce the number of false-positive associations arising from the vast number of statistical tests performed. 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.

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. In this study, we calculated $F$ statistics through the formula

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

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

\[ \text{F statistic greater than 10 means that assumption (a) is satisfied and avoids the bias caused by weak instrument.}^{97,98} \]

**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 \((P<5 \times 10^{-8})\) were clumped by Noyce et al.\(^{99}\), and together this explained 2.2% of the variance in BMI \((F \text{ statistics} = 97.81)\). 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 \((P<5 \times 10^{-8})\) and a total of 51 independent SNPs that were associated with TG at genome-wide significance \((P<5 \times 10^{-8})\) 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 \((F \text{ statistics} = 137.42 \text{ and } 178.24, \text{ respectively})\). 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) 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 \(IE_{X \rightarrow Y}\)) can be obtained as the product of the effects of X on M (\(\beta_{MX}\)) and M on Y (\(\beta_{YM}\)):

\[
IE_{X \rightarrow Y} = \beta_{MX} \beta_{YM}.
\]

We first consider the variance of indirect effect \(IE_{X \rightarrow Y}\), i.e., the variance of product \(\beta_{MX} \beta_{YM}\). According to Kendall and Stuart (1977, page 85), if \(\beta_{MX}\) and \(\beta_{YM}\) are bivariate normally
distributed, then we have

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

where \( \sigma^2(\cdot) \) denotes the variance, \( \mu \) denotes the expectation, and \( \sigma(\cdot, \cdot) \) denotes the covariance. Since \( \beta_{\text{MX}} \) and \( \beta_{\text{YM}} \) are estimated from independent studies of large sample size using different instrument SNPs, \( \beta_{\text{MX}} \) and \( \beta_{\text{YM}} \) can be assumed to be independent, then

\[ \sigma(\beta_{\text{MX}}, \beta_{\text{YM}}) = 0. \]

We have

\[ \sigma^2(IE_{X \rightarrow Y}) = \sigma^2(\beta_{\text{MX}} \beta_{\text{YM}}) = \mu_{\beta_{\text{XM}}}^2 \sigma^2(\beta_{\text{MX}}) + \mu_{\beta_{\text{YM}}}^2 \sigma^2(\beta_{\text{YM}}) + \sigma^2(\beta_{\text{MX}}) \sigma^2(\beta_{\text{YM}}). \tag{1} \]

Let \( \beta_{XY} \) denote the total effect of \( X \) on \( Y \), and \( DE_{X \rightarrow Y} \) denotes the direct effect of an exposure \( X \) on an outcome \( Y \). The variance of the proportion mediated by mediator \( M \) (\( P \)):

\[ P = \frac{IE_{X \rightarrow Y}}{\beta_{XY}} \]

can be derived according to the Delta method: 102.

\[
\sigma^2(P) \approx \left( \frac{\mu_{IE_{X \rightarrow Y}}}{\mu_{\beta_{XY}}} \right)^2 \left[ \frac{\sigma^2(IE_{X \rightarrow Y}) + \sigma^2(\beta_{XY})}{\mu_{\beta_{XY}}} \right]^2 + \frac{2\sigma(IE_{X \rightarrow Y}, \beta_{XY})}{\mu_{\beta_{XY}}} + \frac{\sigma^2(\beta_{XY})}{\mu_{\beta_{XY}}}.
\]

Where the second equation is due to \( \beta_{XY} = IE_{X \rightarrow Y} + DE_{X \rightarrow Y} \), and the third equation is due to

\[ \sigma(IE_{X \rightarrow Y}, DE_{X \rightarrow Y}) = 0. \]

In equation (1) and (2), the expected values of \( \beta_{\text{MX}} \), \( \beta_{\text{YM}} \), \( IE_{X \rightarrow Y} \) and \( \beta_{XY} \) are unknown. In practice, we can replace them by their estimates \( \hat{\beta}_{MX} \), \( \hat{\beta}_{YM} \), \( \hat{IE}_{X \rightarrow Y} \) and \( \hat{\beta}_{XY} \), i.e.,

\[ \hat{\sigma}^2(\hat{IE}_{X \rightarrow Y}) = \hat{\beta}_{YM}^2 \hat{\sigma}^2(\hat{\beta}_{MX}) + \hat{\beta}_{MX}^2 \hat{\sigma}^2(\hat{\beta}_{YM}) + \hat{\sigma}^2(\hat{\beta}_{MX}) \hat{\sigma}^2(\hat{\beta}_{YM}), \]

\[ \hat{\sigma}^2(\hat{P}) \approx \left( \frac{\hat{IE}_{X \rightarrow Y}}{\hat{\beta}_{XY}} \right)^2 \left[ \frac{\hat{\sigma}^2(\hat{IE}_{X \rightarrow Y})}{\hat{IE}_{X \rightarrow Y}^2} + \frac{\hat{\sigma}^2(\hat{\beta}_{XY})}{\hat{\beta}_{XY}^2} \right] - \frac{2\hat{\sigma}^2(\hat{IE}_{X \rightarrow Y})}{\hat{IE}_{X \rightarrow Y} \hat{\beta}_{XY}}. \]
The variance can be utilized to calculate normal 95% confidence intervals of the proportion mediated by mediator $M(\hat{p})$:

$$\hat{p} \pm 1.96\sqrt{\hat{p}(1-\hat{p})}.$$ 

**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 ($P<5 \times 10^{-8}$). 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 ORs 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: 1.0-1.06, P = 0.045) under a Bonferroni-corrected threshold of P < 0.0125 (α = 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]. 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). 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.

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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) 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 $P \leq 0.0125(0.05/4)$ was used in this step, $P \leq 0.05$ 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 \( P<5 \times 10^{-8} \) were clumped by Sun et al.\(^{105}\) \( (F \text{ statistics } = 32.8) \). 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 \( \text{ORs} \) expressed per genetically predicted 1 mm Hg increased of the blood pressure trait, and the Bonferroni-corrected threshold \( P \leq 0.0063 \left( 0.05/8 \right) \) 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)\(^1^{14}\), 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.
MEGASTROKE Authors

The full author list of the MEGASTROKE Consortium is as follows:

Rainer Malik, Ganesh Chauhan, Matthew Traylor, Muralidharan Sargurupremraj, Yukinori Okada, Aniket Mishra, Loes Rutten-Jacobs, Anne-Katrin Giese, Sander W van der Laan, Solveig Grettarsdottir, Christopher D Anderson, Michael Chong, Heib HH Adams, Tetsuro Ago, Peter Almgren, Philippe Amouyel, Hakan Ay, Traci M Bartz, Oscar R Benavente, Steve Bevan, Giorgio B Boncoraglio, Robert D Brown, Jr., Adam S Butterworth, Caty Carrera, Sara L Carty, Daniel I Chasman, Wei-Min Chen, John W Cole, Adolfo Correa, Ioana Cotlarciuc, Carlos Cruchaga, John Danesh, Paul IW de Bakker, Anita L DeStefano, Marcel den Hoed, Qing Duan, Stefan T Engelert, Guido J Falcone, Rebeca F Gottesman, Raji P Grewal, Vilmundur Guðnason, Stefan Gustafsson, Jeffrey Haessler, Tamara B Harris, Ahamad Hassan, Akhila S Havulinna, Susan R Heckbert, Elizabeth G Holliday, George Howard, Fang-Chi Hsu, Hyacinth I Hyacinth, M Arfan Ikram, Erik Ingelsson, Marguerite R Irvin, Xueqiu Jiu, Jordi Jiménez-Conde, Julie A Johnson, J Wouter Jukema, Masahiro Kanai, Keith L Keene, Brett M Kissela, Dawn O Kleindorfer, Charles Kooperberg, Miichaki Kubo, Leslie A Lange, Carl D Langefeld, Claudia Langenberg, Lenore J Launer, Jin-Moo Lee, Robin Lemmens, Didier Leys, Cathryn M Lewis, Wei-Yu Lin, Arne G Lindgren, Erik Lorentzen, Patrik K Magnusson, Jane Maguire, Ani Manichaikul, Patrick F Mcardle, James F Meschia, Braxton D Mitchell, Thomas H Mosley, Michael A Nalls, Toshiharu Ninomiya, Martin J O’Donnell, Bruce M Psaty, Sara L Pulit, Kristiina Rannikmäe, Alexander P Reiner, Kathryn M Rexrode, Kenneth Rice, Stephen S Rich, Paul M Ridker, Natalia S Rost, Peter M Rothwell, Jerome I Rotter, Tatjana Runde, Ralph L Sacco, Saori Sakaue, Michele M Sale, Veikko Salomaa, Bishwa R Sapkota, Reinhold Schmidt, Carsten O Schmidt, Ulf Schminke, Pankaj Sharma, Agnieszka Slowik, Cathie LM Sudlow, Christian Tanislav, Turgut Tatlisumak, Kent D Taylor, Vincent NS Thijs, Guðmar Thorleifsson, Unnur Thorsteinsdottir, Steffen Tiedt, Stella Trompet, Christophe Tzourio, Cornelia M van Duijn, Matthew Walters, Nicholas J Wareham, Sylvia Wassertheil-Smoller, James G Wilson, Kerri L Wiggins, Qiong Yang, Salim Yusuf, Najaf Amin, Hugo S Aparicio, Donna K Arnett, John Attia, Alexandra S Beiser, Claudine Berr, Julie E Buring, Mariana Bustamante, Valeria Caso, Yu-Ching Cheng, Seung Hoan Choi, Ayesha Chowhan, Natalia Cullell, Jean-François Dartigues, Hossein Delavaran, Pilar Delgado, Marcus Dör, Gunnar Engström, Ian Ford, Wander S Gurpreet, Anders Hamsten, Laura Heitsch, Atsushi Hozawa, Laura Ibanez, Andreea Ilinca, Martin Ingelsson, Motoki Iwasaki, Rebecca D Jackson, Katarina Jood, Pekka Jousilahti, Sara Kaffashian, Lalit Kalra, Masahiro Kamouchi, Takanari Kitazono, Olafur Kjartansson, Manja Kloss, Peter J Koudstaal, Jerzy Kupinski, Daniel L Labovitz, Cathy C Laurie, Christopher R Levi, Linxin Li, Lars Lind, Cecilia M Lindgren, Vasileios Lioutas, Yong Mei Liu, Oscar L Lopez, Hirata Makoto, Nicolas Martinez-Majander, Koichi Matsuda, Naoko Minegishi, Joan Montaner, Andrew P Morris, Elena Muñó, Martina Müller-Nurasyid, Bo Norrving, Soichi Ogishima, Eugenio A Parati,
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1 Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany
2 Centre for Brain Research, Indian Institute of Science, Bangalore, India
3 Stroke Research Group, Division of Clinical Neurosciences, University of Cambridge, UK
4 INSERM U1219 Bordeaux Population Health Research Center, Bordeaux, France
5 University of Bordeaux, Bordeaux, France
6 Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan
7 Department of Statistical Genetics, Osaka University Graduate School of Medicine, Osaka, Japan
8 Laboratory of Statistical Immunology, Immunology Frontier Research Center (WPI-IFReC), Osaka University, Suita, Japan.
9 Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
10 Laboratory of Experimental Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, University of Utrecht, Utrecht,Netherlands
11 deCODE genetics/AMGEN inc, Reykjavik, Iceland
12 Center for Genomic Medicine, Massachusetts General Hospital (MGH), Boston, MA, USA
13 J. Philip Kistler Stroke Research Center, Department of Neurology, MGH, Boston, MA, USA
14 Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA
15 Population Health Research Institute, McMaster University, Hamilton, Canada
16 Department of Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands
17 Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, Netherlands
18 Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
19 Department of Clinical Sciences, Lund University, Malmö, Sweden
20 Univ. Lille, Inserm, Institut Pasteur de Lille, LabEx DISTALZ-UMR1167, Risk factors and molecular determinants of aging-related diseases, F-59000 Lille, France
21 Centre Hosp. Univ Lille, Epidemiology and Public Health Department, F-59000 Lille, France
22 AA Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
23 Cardiovascular Health Research Unit, Departments of Biostatistics and Medicine, University of Washington, Seattle, WA, USA
24 Division of Neurology, Faculty of Medicine, Brain Research Center, University of British Columbia, Vancouver, Canada
25 School of Life Science, University of Lincoln, Lincoln, UK
26 Department of Cerebrovascular Diseases, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano, Italy
27 Department of Neurology, Mayo Clinic Rochester, Rochester, MN, USA
28 MRC/BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
29 The National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics, University of Cambridge, UK
30 Neurovascular Research Laboratory, Vall d'Hebron Institut of Research, Neurology and Medicine Departments-Universitat Autònoma de Barcelona, Vall d’Hebrón Hospital, Barcelona, Spain
31 Stroke Pharmacogenomics and Genetics, Fundacio Docència i Recerca MutuaTerrassa, Terrassa, Spain
32 Children's Research Institute, Children's National Medical Center, Washington, DC, USA
33 Center for Translational Science, George Washington University, Washington, DC, USA
34 Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA
35 Harvard Medical School, Boston, MA, USA
36 Center for Public Health Genomics, Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA
37 Department of Neurology, University of Maryland School of Medicine and Baltimore VAMC, Baltimore, MD, USA
38 Departments of Medicine, Pediatrics and Population Health Science, University of Mississippi Medical Center, Jackson, MS, USA
39 Institute of Cardiovascular Research, Royal Holloway University of London, UK & Ashford and St Peters Hospital, Surrey UK
40 Department of Psychiatry, The Hope Center Program on Protein Aggregation and Neurodegeneration (HPAN), Washington University, School of Medicine, St. Louis, MO, USA
41 Department of Developmental Biology, Washington University School of Medicine, St. Louis, MO, USA
42 NIHR Blood and Transplant Research Unit in Donor Health and Genomics, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
43 Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK
44 British Heart Foundation, Cambridge Centre of Excellence, Department of Medicine, University of Cambridge, Cambridge, UK
45 Department of Medical Genetics, University Medical Center Utrecht, Utrecht, Netherlands
46 Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands
47 Boston University School of Public Health, Boston, MA, USA
48 Framingham Heart Study, Framingham, MA, USA
49 Department of Immunology, Genetics and Pathology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden
50 Department of Genetics, University of North Carolina, Chapel Hill, NC, USA
51 Department of Neurology and Stroke Center, Basel University Hospital, Switzerland
52 Neurorehabilitation Unit, University and University Center for Medicine of Aging and Rehabilitation Basel, Felix Platter Hospital, Basel, Switzerland
53 Department of Neurology, Yale University School of Medicine, New Haven, CT, USA
54 Program in Medical and Population Genetics, The Broad Institute of Harvard and MIT, Cambridge, MA, USA
55 Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
56 Neuroscience Institute, SF Medical Center, Trenton, NJ, USA
57 Icelandic Heart Association Research Institute, Kopavogur, Iceland
58 University of Iceland, Faculty of Medicine, Reykjavik, Iceland
59 Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden
60 Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
61 Laboratory of Epidemiology and Population Science, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA
62 Department of Neurology, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Leeds, UK
63 National Institute for Health and Welfare, Helsinki, Finland
64 FIMM - Institute for Molecular Medicine Finland, Helsinki, Finland
65 Department of Epidemiology, University of Washington, Seattle, WA, USA
66 Public Health Stream, Hunter Medical Research Institute, New Lambton, Australia
67 Faculty of Health and Medicine, University of Newcastle, Newcastle, Australia
68 School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA
69 Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA
70 Aflac Cancer and Blood Disorder Center, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA
71 Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, CA, USA
72 Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden
73 Epidemiology, School of Public Health, University of Alabama at Birmingham, USA
74 Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA
75 Neurovascular Research Group (NEUVAS), Neurology Department, Institut Hospital del Mar d'Investigació Médica, Universitat Autònoma de Barcelona, Barcelona, Spain
107 Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
108 Clinical Research Facility, Department of Medicine, NUI Galway, Galway, Ireland
109 Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA
110 Department of Epidemiology, University of Washington, Seattle, WA
111 Department of Health Services, University of Washington, Seattle, WA, USA
112 Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA
113 Brain Center Rudolf Magnus, Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands
114 Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK
115 Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
116 Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA
117 Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
118 Department of Biostatistics, University of Washington, Seattle, WA, USA
119 Nuffield Department of Clinical Neurosciences, University of Oxford, UK
120 Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA
121 Division of Genomic Outcomes, Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA
122 Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA
123 Department of Allergy and Rheumatology, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan
124 Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA
125 Department of Pediatrics, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
126 Department of Neurology, Medical University of Graz, Graz, Austria
127 University Medicine Greifswald, Institute for Community Medicine, SHIP-KEF, Greifswald, Germany
128 University Medicine Greifswald, Department of Neurology, Greifswald, Germany
129 Department of Neurology, Jagiellonian University, Krakow, Poland
130 Department of Neurology, Justus Liebig University, Giessen, Germany
131 Department of Clinical Neurosciences/Neurology, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden
132 Sahlgrenska University Hospital, Gothenburg, Sweden
133 Stroke Division, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Heidelberg, Australia
134 Austin Health, Department of Neurology, Heidelberg, Australia
135 Department of Internal Medicine, Section Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands
136 INSERM U1219, Bordeaux, France
165 Department of Epidemiology and Biostatistics, Imperial College London, London, UK
166 Department of Cardiology, Ealing Hospital NHS Trust, Southall, UK
167 National Heart, Lung and Blood Research Institute, Division of Intramural Research, Population Sciences Branch, Framingham, MA, USA
168 A full list of members and affiliations appears at the end of the manuscript
169 Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
170 Oklahoma Center for Neuroscience, Oklahoma City, OK, USA
171 Department of Pathology and Genetics, Institute of Biomedicine, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden
172 Department of Neurology, Helsinki University Hospital, Helsinki, Finland
173 Clinical Neurosciences, Neurology, University of Helsinki, Helsinki, Finland
174 Department of Neurology, University of Washington, Seattle, WA, USA
175 Albrecht Kossel Institute, University Clinic of Rostock, Rostock, Germany
176 Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
177 Department of Genetics, Perelman School of Medicine, University of Pennsylvania, PA, USA
178 Faculty of Medicine, University of Iceland, Reykjavik, Iceland
179 Departments of Neurology and Public Health Sciences, University of Virginia School of Medicine, Charlottesville, VA, USA
180 Department of Neurology, Boston University School of Medicine, Boston, MA, USA
181 Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX, USA
182 Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
183 Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
184 German Center for Neurodegenerative Diseases (DZNE), Munich, Germany
185 Boston University School of Medicine, Boston, MA, USA
186 University of Kentucky College of Public Health, Lexington, KY, USA
187 University of Newcastle and Hunter Medical Research Institute, New Lambton, Australia
188 Univ. Montpellier, Inserm, U1061, Montpellier, France
189 Centre for Research in Environmental Epidemiology, Barcelona, Spain
190 Department of Neurology, Università degli Studi di Perugia, Umbria, Italy
191 Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA
192 Broad Institute, Cambridge, MA, USA
193 Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, UMR 1219, Bordeaux, France
194 Bordeaux University Hospital, Department of Neurology, Memory Clinic, Bordeaux, France
195 Neurovascular Research Laboratory. Vall d'Hebrón Institut of Research, Neurology and Medicine Departments-Universitat Autònoma de Barcelona. Vall d’Hebrón Hospital, Barcelona, Spain
196 University Medicine Greifswald, Department of Internal Medicine B, Greifswald, Germany
197 DZHK, Greifswald, Germany
258 Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, Netherlands
259 Landspitali University Hospital, Reykjavik, Iceland
260 Survey Research Center, University of Michigan, Ann Arbor, MI, USA
261 University of Virginia Department of Neurology, Charlottesville, VA, USA
Table S1. The definition of insomnia complaints in GWAS meta-analysis of Jansen et al. (2019).

| Study              | Sample size | Definition of insomnia |
|--------------------|-------------|------------------------|
| 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 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    |
| SNP          | N | Ref Allele | Var Allele | Minor Allele Frequency | Major Allele Frequency | p-Value |
|--------------|---|------------|------------|------------------------|------------------------|---------|
| 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             | 0.007                  | 8.82E-11 |
| 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          | 0.0421018              | 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 |
| rs         | MAF1 | MAF2 | p-value | p-value_corrected |
|------------|------|------|---------|-----------------|
| 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       | 0.0551271       | 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 |
| SNP        | Chromosome | Allele 1 | Allele 2 | Minor Allele Frequency | P-value |
|------------|------------|----------|----------|------------------------|---------|
| rs3131638  | 6          | G        | G        | 0.04395189             | 7.88E-10|
| rs314281   | 6          | C        | C        | 0.0429075              | 6.03E-13|
| rs4709655  | 6          | C        | C        | 0.05445619             | 3.09E-09|
| rs62429521 | 6          | A        | C        | 0.05069311             | 1.78E-09|
| rs6457796  | 6          | C        | C        | 0.03874083             | 1.12E-08|
| rs728017   | 6          | G        | G        | 0.03459145             | 9.51E-09|
| rs9373590  | 6          | A        | T        | 0.04018179             | 2.18E-11|
| rs9394502  | 6          | C        | C        | 0.05445619             | 7.76E-18|
| rs9469434  | 6          | G        | G        | 0.03562718             | 4.41E-08|
| rs12540241 | 7          | T        | T        | 0.04604394             | 1.58E-09|
| rs12666306 | 7          | A        | G        | 0.04210118             | 2.24E-12|
| rs1357685  | 7          | T        | C        | 0.03343478             | 1.39E-08|
| rs1731951  | 7          | T        | T        | 0.03459145             | 1.36E-08|
| rs17520265 | 7          | G        | G        | 0.0910194              | 2.78E-08|
| rs190073   | 7          | G        | G        | 0.0335678              | 2.86E-08|
| rs2030672  | 7          | C        | G        | 0.0440143              | 1.10E-08|
| rs2598293  | 7          | T        | C        | 0.03536714             | 2.48E-09|
| rs521484   | 7          | G        | G        | 0.03978087             | 1.53E-08|
| rs6465151  | 7          | T        | C        | 0.05638033             | 1.90E-09|
| rs670501   | 7          | T        | C        | 0.05259245             | 7.40E-13|
| rs6967168  | 7          | G        | G        | 0.04395189             | 1.39E-10|
| rs6973090  | 7          | G        | G        | 0.03770187             | 4.31E-08|
| rs6978112  | 7          | T        | C        | 0.03440143             | 2.11E-08|
| rs73671843 | 7          | G        | G        | 0.05551271             | 5.49E-10|
| rs75932578 | 7          | C        | C        | 0.03978087             | 4.15E-08|
| rs8180817  | 7          | G        | G        | 0.04919024             | 1.83E-16|
| rs940780   | 7          | T        | C        | 0.03825871             | 8.50E-10|
| rs10955647 | 8          | T        | G        | 0.03343478             | 1.84E-08|
| rs17643634 | 8          | C        | C        | 0.05975               | 1.34E-13|
| rs2737240  | 8          | A        | G        | 0.03633193             | 3.37E-08|
| rs28552587 | 8          | A        | G        | 0.03343478             | 3.30E-08|
| rs28611339 | 8          | T        | G        | 0.05826891             | 8.46E-11|
| rs4588900  | 8          | A        | G        | 0.03343478             | 1.57E-08|
| rs671985   | 8          | G        | G        | 0.03770187             | 2.79E-10|
| rs871994   | 8          | A        | C        | 0.03536714             | 5.50E-09|
| rs874168   | 8          | T        | C        | 0.03440143             | 7.95E-09|
| rs              | Chr | SNP    | Genotype | Minor allele freq | Major allele freq | p-value |
|-----------------|-----|--------|----------|------------------|------------------|---------|
| 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-08|
| 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|
| SNP         | Chromosome | Allele 1 | Allele 2 | p-value  | LOD-score |
|------------|------------|----------|----------|----------|-----------|
| rs4767645  | 12         | G        | G        | 0.03666398 | 6.47E-10 |
| rs61921611 | 12         | C        | C        | 0.04395189 | 7.84E-12 |
| rs6606731  | 12         | A        | T        | 0.04305949 | 1.51E-08 |
| rs7486418  | 12         | T        | G        | 0.04114194 | 6.84E-11 |
| rs1031654  | 13         | C        | C        | 0.05129329 | 3.88E-12 |
| rs11149313 | 13         | A        | G        | 0.04018179 | 2.38E-09 |
| rs117630493| 13         | G        | G        | 0.04395189 | 3.61E-08 |
| rs11838830 | 13         | C        | G        | 0.04305949 | 7.84E-12 |
| rs1389631  | 13         | C        | C        | 0.03978087 | 2.03E-10 |
| rs2491124  | 13         | T        | C        | 0.04879016 | 8.81E-16 |
| rs6562066  | 13         | T        | C        | 0.03770187 | 6.04E-09 |
| rs79204944 | 13         | A        | G        | 0.04395189 | 4.24E-08 |
| rs9316619  | 13         | T        | C        | 0.04592893 | 5.50E-09 |
| rs9527083  | 13         | G        | G        | 0.07580171 | 1.61E-32 |
| rs9540729  | 13         | A        | G        | 0.05069311 | 1.15E-08 |
| rs9563886  | 13         | C        | C        | 0.03770187 | 8.90E-10 |
| rs9563886  | 13         | C        | C        | 0.03355678 | 3.08E-08 |
| rs9563886  | 13         | C        | C        | 0.05445619 | 7.33E-13 |
| rs1038093  | 15         | T        | C        | 0.03922071 | 4.24E-08 |
| rs12912299 | 15         | C        | C        | 0.0429075  | 4.42E-13 |
| rs12917449 | 15         | C        | C        | 0.0418642  | 2.97E-08 |
| rs176644   | 15         | T        | G        | 0.03536714 | 9.49E-09 |
| rs4702     | 15         | G        | G        | 0.04814038 | 6.78E-16 |
| rs715338   | 15         | A        | G        | 0.04114194 | 7.85E-12 |
| rs7168238  | 15         | C        | G        | 0.06391333 | 1.80E-08 |
| rs7402939  | 15         | C        | C        | 0.03562718 | 5.19E-09 |
| rs1015438  | 16         | A        | G        | 0.05826891 | 2.51E-14 |
| rs12924275 | 16         | T        | C        | 0.03825871 | 1.93E-08 |
| rs2398144  | 16         | A        | C        | 0.03825871 | 5.09E-10 |
| rs3184470  | 16         | G        | G        | 0.03770187 | 9.73E-10 |
| rs34214423 | 16         | A        | C        | 0.04497337 | 3.18E-09 |
| rs35322724 | 16         | A        | C        | 0.04879016 | 3.75E-16 |
| rs3902952  | 16         | T        | C        | 0.04783733 | 2.55E-10 |
| rs4238755  | 16         | C        | C        | 0.0429075  | 2.30E-10 |
| SNP             | Chromosome | Allele 1 | Allele 2 | Effect Size | Standard Error | p-Value       |
|-----------------|------------|----------|----------|-------------|----------------|---------------|
| 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      |
| rs908666        | 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 | ICD-10 diagnosis | OPCS procedure | Self-report |
|--------------------------------|-----------------|------------------|----------------|-------------|
| **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,   | I21.X, I22.X,    | K40.X, K41.X,  | 20002, 6150 |
|                               | 412.X, 414.0,   | I23.X, I24.X,    | K42.X, K43.X,  |             |
|                               | 414.8, 414.9    | I25.1, I25.2,    | K44.X, K45.X,  |             |
|                               |                 | I25.5, I25.6,    | K46.X, K49.X,  |             |
|                               |                 | I25.8, I25.9     | K50.1, K50.2,  |             |
|                               |                 |                  | K50.4, K75.X   |             |
| Aortic valve stenosis          | I35.0, I35.2    |                  |                | 20002       |
| Atrial fibrillation            | 427.3           | I48              |                | 20002       |
| Heart failure                  | 428.X           | I11.0, I13.0,    |                | 20002       |
|                               |                 | I13.2, I50.X     |                |             |
| 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                  |                                                                            |                                                                        |
| Lipids                      | Sample Size | Mean (SD) | Sample Type | Processing | Genotyping | Additional Information |
|----------------------------|-------------|-----------|-------------|------------|------------|------------------------|
| Total cholesterol (TC)     | 187365      | 41.75     | SD (mg/dl)  | Mixed      | GLGC 30    | [Link to dataset]       |
| 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    |                        |

Additional information: GerMiFSI, GerMiFSII, KORA3, KORA4, MICROS, Migen (cases), Migen (controls), NBS_WTCCC, NFBC-1966, NHS, NSPHS, NTRNESDA cases, NTRNESDA controls, ORCADES, PLCO, RS-I, RUMP, "SASBAC Cases", "SASBAC Controls", SEARCH/UKOPS, SHIP T2D_WTCCC, AE, ASCOT, BLSA, BSN (BHS), COROGENE, DESIR, DNBC, EGCU-370, EGCU-OMNI, Erasmus Ruchphen Family Study (ERF), FamHS FinGesture cases, GOOD, Health ABC, HBCS, HERITAGE Family Study, InCHIANTI, IPM (Mount Sinai BioMe), LifeLines, LLS, LOLIPOP_EWA, LOLIPOP_EWP, MGS, NELSON, PLCO2, PROCARDIS, PROSPER/PHASE, QFS, QIMR, RISC, RSII, SHIP-TREND, Sorbs, TRAILS, TWINGENE, TwinsUK, WGHS, YFS, ADVANCE-CAD, AMC-PAS, ARIC Metabochip, B1958C, BHS, CARDIOGENICS, CHNS, D2D 2007, DESIR, DIAGEN, DILGOM, DPP, DR'S EXTRA, DUNDEE, EAS, EGCU, 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 ADVANCE, AMC-PAS, AMISH, BC58, D2D 2007 (T2D), D2D 2007 (controls), deCODE, DIAGEN (T2D), DIAGEN (controls), DILGOM, DPP (T2D), DPP (controls), DR'S EXTRA (T2D), DR'S EXTRA (controls), EAS, EGCU, Ely, EPIC-CAD cases (EPIC-Norfolk CAD set), EPIC-T2D cases (EPIC-Norfolk T2D set), EPIC-T2D controls, Finland, FINCAVAS, FRISCII, FUSION2 (T2D), FUSION2 (controls), GLACIER, GODARTs, HUNT (T2D), HUNT (controls), IMPROVE, KORA F3, KORA F4, LURIC (cases), LURIC (controls), MDC, METSIM (T2D), METSIM (controls).
### Glycemic

|                      | Value   | Unit   | Study Population | Source                                                                 |
|----------------------|---------|--------|-------------------|----------------------------------------------------------------------|
| Fasting glucose      | 140595  | mmol/L | European          | MAGIC 31, https://www.magicinvestigators.org/downloads/               |
| Fasting insulin      | 98210   | mmol/L | European          | MAGIC 31, https://www.magicinvestigators.org/downloads/               |
| Two-hour glucose     | 42854   | mmol/L | European          | MAGIC 33, https://www.magicinvestigators.org/downloads/               |
| Hemoglobin A1c (HbA1c) | 123665  | %      | European          | MAGIC 32, https://www.magicinvestigators.org/downloads/               |

### Renal function

|                      | Value   | Unit     | Study Population | Source                                                                 |
|----------------------|---------|----------|-------------------|----------------------------------------------------------------------|
| Estimated glomerular filtration rate (eGFR) | 567.460 | mL/min/1.73 m2 | European          | CKDGen 34, https://ckdgen.imbi.uni-freiburg.de/                     |

**Note:** Values are rounded to two decimal places. European studies include MAGIC, European CKDGen (CKDGen 31-34), and additional studies listed in the supplementary material.
| Other      |   |   |   |   | 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 |
| Heart rate* | 58818 | 12.9 | bmp | European | Verweij et al. 33 | https://data.mendeley.com/datasets/tg5tvmg436/1 | 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|
| Genotype | Frequency | p-value | q-value |
|----------|-----------|---------|---------|
| 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 |
| SNP          | Effect Allele | Reference Allele | EA  | SE   |
|--------------|---------------|------------------|-----|------|
| 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 |
| SNP        | Nucleotide 1 | Nucleotide 2 | p-value 1 | p-value 2 |
|------------|--------------|--------------|-----------|-----------|
| 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     |
| SNP          | Effect Allele | Control Allele | EA   | SE   |
|--------------|---------------|----------------|------|------|
| 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 |
| SNP     | EA | SE  |
|---------|----|-----|
| 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* |
|-----------------------|-------------------|------------------------------------------------------|----------------------------|----------------------------------------------------|------------------------------------------------------------------------|----------|
| 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, Glasow, CADISP, Barcelona, FINLAND, SAHLIS, 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, EGUCUT, F genetics CARD, 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, PENN CATH, PIVUS, PREDICTCVD, SADS/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 (AFMU) in the context of the Arrhythmia-Biobank-LMU, ANGES1, the Atherosclerosis Risk in Communities (ARIC) study, BEAT-AF, Biobank Japan (BBJ), BioMe@, 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), SGN, 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), EGUCUT, 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 AFCM, 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) [8] (https://www.ebi.ac.uk/gwas/publications/31919418#study_panel) | ARIC, BIOSTAT-CHF (Validation), CHS, COGEN, deCODE, DiscovEHR, EPHEUS, 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% |

* 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  | 54572             | 0.08 | SD (ratio)       | European | Horikoshi et al. 59      | http://diagram consortium.org/2015_EN/2/GAGE_1KG/1/ |
| 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      | GAGE_1KG/1/             |
| 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]                | [0.000079858319953622,0.00050928078772593] |
| Intracerebral hemorrhage       | [1.16,1.2]                 | [0.0150707747197087,0.0532830564685888] |
| Subarachnoid hemorrhage        | [1.21,1.25]                | [0.00298849246004255,0.0100260051662759] |
| **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]                | [0.00000370203181757918,0.0000212175559301195] |
| **Other CVDs**                 |                            |                     |
| Coronary artery disease        | [1.21,1.23]                | [0.00000000000000000469123171329205,0.0000000000000000000000000000062091219092247] |
| Aortic valve stenosis          | [1.19,1.22]                | [0.000599272957379088,0.00240005141062859] |
| Atrial fibrillation            | [1.12,1.13]                | [0.00000000197505718659678,0.000000021712810430981] |
| Heart failure                  | [1.23,1.25]                | [0.000000000000908939438050027,0.000000000000137098779446152] |
| Peripheral vascular disease    | [1.22,1.24]                | [0.0000000125008699928124,0.000000089431057307921] |
| Arterial hypertension          | [1.13,1.14]                | [0.00000000000000000132597075251179,0.00000000000000998106683415205] |

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 | 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(0.0,0.02) | 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(0.0,0.02) | 0.08782 | 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) | 0.24287 | 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(0.0,0.02) | 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(0.0,0.01) | 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(0.0,0.01) | 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(0.0,0.01) | 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 | 2.02×10⁻⁵   | -             | -              | 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 | 7.28×10⁻⁴   | -             | -              | 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 | 6.2×10⁻⁴   | -             | -              | 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]          | [0.0000000000819083524801232, 0.00000000480897072408428] |
| Atrial fibrillation          | [1.04, 1.04]          | [0.00356769100034803, 0.0116350521246951] |
| Heart failure                | [1.1, 1.11]           | [0.0000000000071370881169607, 0.0000000000019360976045461] |

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 trombosis           | 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×10⁻⁸ | 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 | No. of outliers |
|------------------------------|-----------------|------------|----------|----------|----------------|
|                              | OR (95% CI)     | P value    | OR (95% CI) | P value | Intercept | P value | OR | P value |
| **Cerebrovascular diseases** |                 |            |          |          |            |         |    |         |
| Ischemic stroke              | 1.36(1.18,1.84) | 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(0,0.02) | 0.051516 | 1.25 | 0.035284 | 0 |
| Intracerebral hemorrhage     | 2.2(1.15,4.22)  | 0.017524   | 2.54(0.166,0.02) | 0.57418 | 3.16(1,2,7.58) | 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(0,0.02) | 0.543049 | 1.73 | 0.013779 | 0 |
| **Aortic aneurysms**         |                 |            |          |          |            |         |    |         |
| Abdominal aortic aneurysm    | 1.04(0.55,1.95) | 0.904579   | 0.85(0.16,91) | 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(0.83,1.51) | 0.980775 | 2.88(0.61,3.85) | 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) | 0.764963 | 0(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(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(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(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(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] | P value [Min, Max] |
|--------------------------|---------------------|--------------------|
| **Anthropometric**       |                     |                    |
| WHR, SD (ratio)          | [0.05, 0.05]        | [0.000044074495162145, 0.0000955072065612272] |
| WHRadjBMI, SD (ratio)    | [0.01, 0.02]        | [0.0666985586582434, 0.298626831744182] |
| WC, SD (cm)              | [0.06, 0.07]        | [0.000011474457411313, 0.000271531216121882] |
| 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]        | [0.0000002875553568581, 0.00002593859705472] |
| **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]      | [0.0000346899060716208, 0.000631131156786682] |
| TG, SD (mg/dL)           | [0.06, 0.07]        | [0.000000175880534131525, 0.00000879461626441192] |
| **Glycemic**             |                     |                    |
| Fasting glucose, mmol/L  | [-0.08, 0]          | [0.293251287768197, 0.982671572871615] |
| Fasting insulin, log(mmol/L) | [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] |

* the minimum value and maximum value of inverse variance weighted estimate;

* 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 | No. of outliers |
|--------------------------------|-----------------|------------|----------|----------|----------------|
|                                | Beta (95% CI)   | P value    | Beta (95% CI) | P value | Intercept | P value | Beta (95% CI) | P value |               |
| WHR, SD(ratio)                 | 0.05(0.02,0.08) | 0.001055   | 0.02(-0.06,0.1) | 0.594317 | 0.12(0.0,0.24) | 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(0.0,0.07)  | 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(0.0,0.13) | 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(0.0,0.07)  | 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) | 0.506081 | 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   | 0.958505 | 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(0.0,0.03)  | 0.02478    | 0.03(0.0,0.06) | 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) | 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 | 4.34×10⁻³    | -             | -              | 241         | 87048       | 4.77  |
| Insomnia   | BMI      | Weighted median | 0.06  | 0.04| 0.09 | 8.56×10⁻⁹    | -             | -              | 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  |      |      | 2.55×10⁻³    | -             | 0              | 241         | 87048       | 4.77  |
| Insomnia   | TC       | IVW             | 0.02  | -0.01| 0.05 | 0.16         | -             | -              | 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     | 0.8 | 0.05 | -             | -             | 0              | 241         | 62166       | 41.75 |
| Insomnia   | LDL-C    | IVW             | 0.04  | -0.08| 0.03 | 0.72         | 0.33          | -              | 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      | 0.08  | -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  | -0.09| 0.05 | 0.37         | -             | 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  |      |      | 1.13×10⁻³    | -             | 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] | [0.00000319959704730788,0.000900335583009329] |
| TC, SD (mg/dl) | [-0.01,0.01] | [0.516540259928238,0.856786557960117] |
| LDL-C, SD (mg/dl) | [0.0,0.02] | [0.188223217376054,0.999536661057882] |
| HDL-C, SD (mg/dl) | [-0.05,0.04] | [0.00159739285038294,0.011516534320197] |
| TG, SD (mg/dl) | [0.05,0.05] | [0.00000725402437570128,0.000212009729329835] |

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] | P value [Min, Max] |
|----------------------------------|--------------------|--------------------|
| 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-17,1.7071830744615e-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-18,1.65732814595026e-13] |
| Peripheral vascular disease     | [1.65,1.8]         | [1.486890821036e-06,0.0002954306237266] |
| Arterial hypertension           | [1.5,1.55]         | [2.83451668772078e-20,2.59107359599498e-13] |

* 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 OR (95% CI) | P value | Mode-based OR (95% CI) | P value | MR-Egger OR (95% CI) | P value | Intercept | P value | MRPRESSO OR (95% CI) | P value | No. of outliers |
|----------------------------------|-----------------------------|---------|------------------------|---------|----------------------|---------|-----------|---------|---------------------|---------|-------------------|
| Ischemic stroke                  | 1.35(1.82)                  | 0.051835 | 1.43(0.3,2.18)         | 0.1025  | 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(0.90,7.249)       | 0.0645  | 1.56(0.98,2.47)      | 0.061196 | 0(-0.01,0.01) | 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)        | 0.0013  | 2.09(1.51,2.89)      | 8.06E-06 | 0(-0.01,0.01) | 0.292047 | 1.79                | 6.78E-12 | 0                 |
| Pulmonary embolism               | 1.48(1.12,1.96)             | 0.006284 | 1.48(1.07,2.05)        | 0.0178  | 1.66(1.22,2.68)      | 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(1.24,4.164)       | 1.04E-06 | 1.16(0.88,1.54)      | 0.293591 | 0(0,0.02)     | 0.034827 | 1.51                | 4.59E-11 | 3                 |
| Atrial fibrillation              | 1.47(1.23,1.75)             | 2.51E-05 | 1.44(1.12,4.176)       | 0.0002  | 1.24(0.93,1.64)      | 0.143104 | 0(0,0.02)     | 0.072585 | 1.56                | 7.29E-10 | 1                 |
| Heart failure                    | 2.09(1.62,2.73)             | 5.07E-08 | 1.99(1.4,8.269)        | 6.77E-06 | 1.72(1.12,2.63)      | 0.013384 | 0(-0.01,0.02) | 0.259598 | 2.14                | 8.68E-12 | 1                 |
| Peripheral vascular disease      | 2.31(1.62,3.25)             | 2.72E-06 | 2.16(1.4,3.326)        | 0.0002  | 2.28(1.74,6.08)      | 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(1.45,5.174)       | 1.12E-03 | 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   | 1.27   | 0.043  | -        | -             | -               | 446696     | 40585  |
| BMI        | Ischemic stroke            | Weighted median | 1.1    | 0.94   | 0.23   | -        | -             | -               | 446696     | 40585  |
| BMI        | Ischemic stroke            | Mode-based | 1.11   | 0.93   | 0.32   | 0.26     | -             | -               | 446696     | 40585  |
| BMI        | Ischemic stroke            | MR-Egger   | 1.05   | 1.37   | 0.75   | 0.55     | -             | -               | 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^{-4} | -             | -               | 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^{-3} | 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^{-4} | -             | -             | 588190     | -      |
| BMI        | Atrial fibrillation        | Weighted median | 1.39   | 1.24   | 1.55   | 2.5×10^{-3} | -             | -             | 588190     | -      |
| BMI        | Atrial fibrillation        | Mode-based | 1.4    | 1.23   | 1.6    | 4.03×10^{-3} | -             | -             | 588190     | -      |
| BMI        | Atrial fibrillation        | MR-Egger   | 1.22   | 1.48   | 0.05   | 0.12     | -             | -             | 588190     | -      |
| BMI        | Atrial fibrillation        | MR-PRESSO  | 1.39   |        |        | 3.6×10^{-31} | -             | 1             | 588190     | -      |
| BMI        | Heart failure              | IVW        | 1.64   | 1.47   | 1.84   | 7.1×10^{-14} | -             | -             | 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^{-4} | -             | -             | 977323     | -      |
| BMI        | Heart failure              | MR-Egger   | 1.58   | 1.21   | 2.06   | 0.00007  | 0.74         | -             | 977323     | -      |
| BMI        | Heart failure              | MR-PRESSO  | 1.66   |        |        | 1.33×10^{-31} | -             | 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   | [0.90, 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] |

* 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]          | [0.014388024594688, 0.107684167726366] |
| Transient ischemic attack           | [1.06, 1.14]          | [0.135873365643229, 0.47724803861545] |
| Deep vein thrombosis                | [0.83, 0.87]          | [0.0181667164155343, 0.08247949098728] |
| Pulmonary embolism                  | [0.83, 0.88]          | [0.0157498347567607, 0.10290988959661] |
| Coronary artery disease             | [1.41, 1.47]          | [0.0000000000000627712765854418, 0.0000000031086529845111] |
| Atrial fibrillation                 | [1.03, 1.06]          | [0.182224545732321, 0.630916519312097] |
| Heart failure                       | [1.28, 1.37]          | [0.000000461498779135834, 0.00014021254209974] |
| Peripheral vascular disease         | [1.21, 1.3]           | [0.00496771215383943, 0.042959493545899] |
| Arterial hypertension               | [1.17, 1.19]          | [0.000000417959689599575, 0.000140564076388081] |

* 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  | Intercept | P value | OR (95% CI) | P value    |
| Arterial stroke              | 0.92(0.77,1.2)  | 0.34282    | 0.96(0.7 9,1.17) | 0.6810   | 0.3137    | 0.00600 | 0.9   0.110661 | 1         |
| Transient ischemic attack    | 0.93(0.78,1.1)  | 0.40332    | 0.98(0.8 3,1.15) | 0.7733   | 0.104(0.8 5,1.27) | 0.7341 | 0.12150 | 0.91 0.17599 | 1         |
| Deep vein thrombosis         | 0.97(0.87,1.09) | 0.65246    | 0.98(0.8 8,1.09) | 0.6588   | 0.0867  | 0.148492 | 0.94 0.173106 | 5         |
| Pulmonary embolism           | 1.04(0.9,1.19)  | 0.59389    | 1.03(0.9 1,1.19) | 0.6706   | 0.129(0.9 1,1.36) | 0.2829 | 0.16295 | 1.01 0.842248 | 1         |
| Coronary artery disease      | 0.86(0.79,0.93) | 0.00026    | 0.97(0.8 4,1.01) | 0.0714   | 1.050(0.8 8,1.24) | 0.5847 | 0.00021 | 0.86 7.65E-07 | 12        |
| Atrial fibrillation          | 0.90(0.91,1.07) | 0.75467    | 0.90(0.9 1,1.07) | 0.7727   | 1.0(0.89,1 13) | 0.9730 | 0.01569 | 0.95 0.306119 | 4         |
| Heart failure                | 1.04(0.89,1.12) | 0.63378    | 1.06(0.9 2,1.21) | 0.4214   | 1.090(0.8 9,1.33) | 0.3893 | 0.01549 | 0.95 0.306119 | 4         |
| Peripheral vascular disease  | 0.88(0.73,1.06) | 0.17483    | 0.92(0.8 7,1.09) | 0.3296   | 0.97(0.8 7,1.24) | 0.8107 | 0.05342 | 0.82 0.0008365 | 1         |
| Arterial hypertension        | 0.95(0.9,0.99)  | 0.02022    | 0.97(0.9 4,1) | 0.0735   | 1.040(0.9 3,1.15) | 0.4960 | 0.115E-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  | Intercept | P value | OR (95% CI) | P value |
| Ischemic stroke              | 1.19(0.97,1.45) | 0.094563   | 1.19(0.99,1 44) | 0.067569 | 1.090(0.82,1 45) | 0.553374 | 0.01(-0.01,0.02) | 0.418855 | 1.2 0.041579 | 1         |
| Transient ischemic attack    | 1.18(0.95,1.04) | 0.136753   | 1.21(0.97,1.2) | 0.092447 | 1.040(0.78,1 38) | 0.786194 | 0(-0.01,0.02) | 0.624262 | 1.1 0.264545 | 1         |
| Deep vein thrombosis         | 0.90(0.78,1 05) | 0.170635   | 0.92(0.81,1 05) | 0.198874 | 0.887544 | 0.01(-0.01,0.02) | 0.170583 | 0.88 0.08505 | 2         |
| Pulmonary embolism           | 0.90(0.76,1 06) | 0.203165   | 0.92(0.78,1 06) | 0.293458 | 0.890(1.71,1 5) | 0.38396 | 0(-0.02,0.01) | 0.659056 | 0.86 0.043077 | 1         |
| Coronary artery disease      | 1.3(1.18,1.44) | 0.691697   | 1.19(1.19,1 49) | 2.32E-09 | 1.180(0.99,1 41) | 0.001963 | 0.01(0.00,0.09) | 0.006527 | 1.46 2.82E-05 | 5         |
| Atrial fibrillation          | 1.03(0.92,1 5) | 0.580697   | 1.060(1.05,1 8) | 0.29206 | 1.040(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(0.91,1 1) | 0.294564   | 1.29(0.97,1 49) | 0.09391 | 1.150(0.83,1 58) | 0.39603 | 0(-0.01,0.02) | 0.49511 | 1.25 0.022008 | 11        |
| Arterial hypertension        | 1.17(1.11,1 23) | 2.27E-10   | 1.14(1.11,1 9) | 6.58E-11 | 1.030(0.92,1 7) | 0.59317 | 0.01(0.00,0.01) | 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    | 2.45×10⁻³     | -             | 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 | 0.90  | 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: odds 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]           | [0.305500332589488,0.74111768821401]         |
| 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           | Coronary artery disease | MR-PRESSO                  | 1.02| 0.60 | -    | 1       | -             | -             | 184305     | 60801 |
| 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 | 6.69×10^4 | -             | -             | 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     | 6    |
| TG           | Atrial fibrillation | Weighted median              | 1   | 0.93 | 1.07 | 0.94    | -             | -             | 588190     | 6    |
| TG           | Atrial fibrillation | Mode-based                  | 1   | 0.94 | 1.07 | 0.90    | -             | -             | 588190     | 6    |
| TG           | Atrial fibrillation | MR-Egger                    | 1.02| 0.89 | 1.17 | 0.76    | 0.40          | -             | 588190     | 6    |
| TG           | Atrial fibrillation | MR-PRESSO                   | 0.99| 0.75 | -    | 1       | -             | -             | 588190     | 6    |
| TG           | Heart failure      | IVW                          | 1.33| 1.17 | 1.51 | 1.58×10^4 | -             | -             | 977323     | 6    |
| TG           | Heart failure      | Weighted median              | 1.17| 1.09 | 1.27 | 4.8×10^5 | -             | -             | 977323     | 6    |
| TG           | Heart failure      | Mode-based                  | 1.17| 1.08 | 1.26 | 4.61×10^5 | -             | -             | 977323     | 6    |
| TG           | Heart failure      | MR-Egger                    | 1.18| 1.05 | 1.33 | 0.004   | 0.96          | -             | 977323     | 6    |
| TG           | Heart failure      | MR-PRESSO                   | 1.17| 6.09×10^4 | -       | 1       | 977323      | -             | 977323     | 6    |

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]         | [0.0000000162273017759942,0.00000195233479628422] |
| Atrial fibrillation   | [0.96,0.99]           | [0.294623128451253,0.793134017725766] |
| Heart failure         | [1.17,1.19]           | [0.00000012045194257,0.00001465505169308] |

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   | 0.01          | -              |
| 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| [1.01,1.06]      | 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](https://grasp.nhlbi.nih.gov/FullResults.aspx) | AGES, ARIC, ASPS, B58C, BHS, CHS, COLAUS, CORO ALL, CROATIA-Korcula, CROATIA-Split, CROATIA-Vis, EGCU, EGCU2, EPIC, ERF, Fenland, FHS, FINNISK CASE ALL, FINNISK 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, GAP, GoDARTS, GS:SFHS, HCS, JUPITER, Lifelines, MDC, METSIM, NEO, PREVEND, SardiNIA, TWINSUK, UK Biobank                                                                 |
| Diastolic blood pressure adjusted body mass index (DBPadjBMI) | 458577            | 11.3 | mm Hg           | European      |                           |                                               | AGES, ARIC, ASPS, B58C, BHS, CHS, COLAUS, CORO ALL, CROATIA-Korcula, CROATIA-Split, CROATIA-Vis, EGCU, EGCU2, EPIC, ERF, Fenland, FHS, FINNISK CASE ALL, FINNISK 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, GAP, GoDARTS, GS:SFHS, HCS, JUPITER, Lifelines, MDC, METSIM, NEO, PREVEND, SardiNIA, TWINSUK, UK Biobank                                                                 |
| Systolic blood pressure (SBP)              | 389351            | 19.4 | mm Hg           | European      | UK Biobank 26             | [https://www.ukbiobank.ac.uk/](https://www.ukbiobank.ac.uk/) | AGES, ARIC, ASPS, B58C, BHS, CHS, COLAUS, CORO ALL, CROATIA-Korcula, CROATIA-Split, CROATIA-Vis, EGCU, EGCU2, EPIC, ERF, Fenland, FHS, FINNISK CASE ALL, FINNISK 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, GAP, GoDARTS, GS:SFHS, HCS, JUPITER, Lifelines, MDC, METSIM, NEO, PREVEND, SardiNIA, TWINSUK, UK Biobank                                                                 |
| Diastolic blood pressure (DBP)             | 389354            | 11   | mm Hg           | European      |                           |                                               | AGES, ARIC, ASPS, B58C, BHS, CHS, COLAUS, CORO ALL, CROATIA-Korcula, CROATIA-Split, CROATIA-Vis, EGCU, EGCU2, EPIC, ERF, Fenland, FHS, FINNISK CASE ALL, FINNISK 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, GAP, GoDARTS, GS:SFHS, HCS, JUPITER, Lifelines, MDC, METSIM, NEO, PREVEND, SardiNIA, TWINSUK, UK Biobank                                                                 |
**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   | 0.08   | -0.2  | 0.37  | 0.58    | -             | -               | 243             |
| Insomnia | SBPadjBMI, mm Hg | IVW | 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  | 0.07   | -0.04 | 0.17  | 0.21    | -             | -               | 244             |
| Insomnia | DBPadjBMI, mm Hg | IVW | 0.11   | -0.05 | 0.27  | 0.18    | -             | -               | 244             |
| Insomnia | DBPadjBMI, mm Hg | Mode-based | 0.22   | -0.86 | 0.42  | 0.50    | 0.30          | -               | 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             | 1.07  | (1.01, 1.07)| 0.010297|
| Pulmonary embolism               | 1.01  | (0.98, 1.03)| 0.532069|
| Other CVDs                       |       |             |         |
| Coronary artery disease          | 1.08  | (1.06, 1.10)| 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] | P value [Min, Max] |
|---------------|-------------------------|--------------------|
| 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] |

* the minimum value and maximum value of inverse variance weighted estimate;  
* 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\textsubscript{XY} | \( \beta_{XM} \) | \( OR_{MY} \) | NIE\textsubscript{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\textsubscript{XY}: total effect of the exposure on the outcome expressed in odds ratios (OR) scale; NIE\textsubscript{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.
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 S2. Associations between genetically predicted body mass index and 9 cardiovascular diseases selected in primary study.

| Disease                        | Sample size | Cases  | Estimate   | 95% CI     | P value | $I^2$ |
|-------------------------------|-------------|--------|------------|------------|---------|-------|
| Cerebrovascular diseases       |             |        |            |            |         |       |
| Ischemic stroke               | 251416      | 5122   | 1.22       | (1.00, 1.47)| 4.56e-02| 4.88  |
| Transient ischemic attack     | 250854      | 4560   | 1.28       | (1.05, 1.56)| 1.48e-02| 0.00  |
| Thrombotic diseases           |             |        |            |            |         |       |
| Deep vein thrombosis          | 256665      | 10371  | 1.79       | (1.55, 2.05)| 3.11e-16| 9.30  |
| Pulmonary embolism            | 253080      | 6786   | 1.66       | (1.35, 2.03)| 1.42e-06| 37.14 |
| Other CVDs                    |             |        |            |            |         |       |
| Coronary artery disease       | 278757      | 32463  | 1.53       | (1.35, 1.73)| 1.70e-11| 59.53 |
| Atrial fibrillation           | 265400      | 19106  | 1.56       | (1.38, 1.77)| 1.40e-12| 35.38 |
| Heart failure                 | 253736      | 7442   | 2.14       | (1.78, 2.58)| 4.99e-18| 28.61 |
| Peripheral vascular disease   | 250259      | 3965   | 1.73       | (1.35, 2.23)| 1.61e-05| 28.09 |
| Arterial hypertension         | 390082      | 143788 | 1.52       | (1.37, 1.67)| 3.16e-16| 80.55 |
**Figure S3.** Associations between genetically predicted high-density lipoprotein cholesterol and 9 cardiovascular diseases selected in primary study.

| Disease            | Sample size | Cases | Estimate | 95% CI       | P value | I² |
|--------------------|-------------|-------|----------|--------------|---------|----|
| **Cerebrovascular diseases** |             |       |          |              |         |    |
| Ischemic stroke    | 251416      | 5122  | 0.89     | (0.78, 1.01) | 8.24e-02| 39.80 |
| Transient ischemic attack | 250854      | 4560  | 0.91     | (0.80, 1.04) | 1.72e-01| 32.28 |
| **Thrombotic diseases** |             |       |          |              |         |    |
| Deep vein thrombosis | 256665      | 10371 | 0.93     | (0.83, 1.05) | 2.50e-01| 63.82 |
| Pulmonary embolism | 253080      | 6786  | 1.00     | (0.88, 1.13) | 9.83e-01| 52.50 |
| **Other CVDs**     |             |       |          |              |         |    |
| Coronary artery disease | 278757      | 32483 | 0.82     | (0.73, 0.91) | 4.86e-04| 86.82 |
| Atrial fibrillation | 265400      | 19106 | 0.93     | (0.87, 1.01) | 7.99e-02| 50.24 |
| Heart failure      | 253736      | 7442  | 0.90     | (0.79, 1.02) | 1.03e-01| 57.32 |
| Peripheral vascular disease | 250259      | 3965  | 0.80     | (0.69, 0.94) | 5.90e-03| 46.39 |
| Arterial hypertension | 390082      | 143788| 0.86     | (0.80, 0.93) | 6.81e-05| 89.68 |

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.

| Disease                        | Sample size | Cases | Estimate  | 95% CI      | p value  | I2  |
|--------------------------------|-------------|-------|-----------|-------------|----------|-----|
| Cerebrovascular diseases       |             |       |           |             |          |     |
| Ischemic stroke                | 251416      | 5122  | 1.20      | (1.01, 1.42)| 3.65e-02 | 48.77 |
| Transient ischemic attack      | 250854      | 4560  | 1.10      | (0.93, 1.30)| 2.59e-01 | 37.00 |
| Thrombotic diseases            |             |       |           |             |          |     |
| Deep vein thrombosis           | 256665      | 10371 | 0.85      | (0.74, 0.99)| 3.83e-02 | 64.59 |
| Pulmonary embolism             | 253080      | 6786  | 0.86      | (0.74, 0.99)| 3.79e-02 | 45.77 |
| Other CVDs                     |             |       |           |             |          |     |
| Coronary artery disease        | 278757      | 32483 | 1.44      | (1.29, 1.61)| 1.55e-01 | 78.26 |
| Atrial fibrillation            | 265400      | 19106 | 1.05      | (0.95, 1.16)| 3.70e-01 | 55.48 |
| Heart failure                  | 253736      | 7442  | 1.33      | (1.17, 1.51)| 1.58e-05 | 34.45 |
| Peripheral vascular disease    | 250259      | 3965  | 1.25      | (1.04, 1.51)| 1.81e-02 | 43.58 |
| Arterial hypertension          | 390082      | 143788| 1.18      | (1.09, 1.27)| 3.35e-05 | 85.45 |

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.

| Disease                        | Sample size | Cases   | Estimate | 95% CI     | P value | I²  |
|-------------------------------|-------------|---------|----------|------------|---------|-----|
| **Cerebrovascular diseases**  |             |         |          |            |         |     |
| Ischemic stroke               | 251416      | 5122    | 1.22     | (1.00, 1.49)| 4.80e-02| 5.80|
| Ischemic stroke*              | 446696      | 40585   | 1.12     | (0.99, 1.26)| 6.42e-02| 32.86|
| Transient ischemic attack     | 290854      | 4560    | 1.26     | (1.02, 1.53)| 2.92e-02| 0.00|
| **Thrombotic diseases**       |             |         |          |            |         |     |
| Deep vein thrombosis          | 256665      | 10371   | 1.74     | (1.52, 2.00)| 4.11e-15| 3.15|
| Pulmonary embolism            | 253080      | 6786    | 1.62     | (1.31, 2.00)| 8.15e-06| 37.13|
| **Other CVDs**                |             |         |          |            |         |     |
| Coronary artery disease       | 278757      | 32483   | 1.49     | (1.31, 1.68)| 3.17e-10| 57.30|
| Coronary artery disease*      | 184305      | 80801   | 1.49     | (1.32, 1.68)| 1.23e-10| 44.10|
| Atrial fibrillation           | 285400      | 19106   | 1.54     | (1.36, 1.75)| 1.86e-11| 34.37|
| Atrial fibrillation*          | 588190      | -       | 1.38     | (1.26, 1.50)| 3.61e-13| 36.45|
| Heart failure                 | 253736      | 7442    | 2.09     | (1.74, 2.52)| 6.68e-15| 25.58|
| Heart failure*                | 977323      | -       | 1.63     | (1.45, 1.83)| 8.65e-17| 56.44|
| Peripheral vascular disease   | 250259      | 3965    | 1.66     | (1.29, 2.14)| 9.84e-05| 28.91|
| Arterial hypertension         | 390082      | 143788  | 1.48     | (1.34, 1.64)| 1.23e-14| 79.56|

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.
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.

**Figure S6.** Associations between genetically predicted high-density lipoprotein cholesterol and 9 cardiovascular diseases using multivariable MR analysis adjust for insomnia.
**Figure S7.** Results of associations between genetically predicted triglycerides and 9 cardiovascular diseases using multivariable MR analysis adjusting for insomnia.

| Disease                        | Sample size | Cases     | Estimate   | 95% CI     | P value  | I2     |
|--------------------------------|-------------|-----------|------------|------------|----------|--------|
| **Cerebrovascular diseases**   |             |           |            |            |          |        |
| Ischemic stroke                | 251416      | 5122      | 1.20       | (1.01, 1.43)| 3.87e-02| 48.76  |
| Ischemic stroke*               | 446696      | 40585     | 1.02       | (0.94, 1.11)| 6.34e-01| 35.66  |
| Transient ischemic attack      | 290854      | 4560      | 1.10       | (0.93, 1.31)| 2.61e-01| 38.98  |
| **Thrombotic diseases**        |             |           |            |            |          |        |
| Deep vein thrombosis           | 256665      | 10371     | 0.86       | (0.74, 1.00)| 5.37e-02| 63.67  |
| Pulmonary embolism             | 253080      | 6786      | 0.86       | (0.75, 1.00)| 5.36e-02| 44.11  |
| **Other CVDs**                 |             |           |            |            |          |        |
| Coronary artery disease        | 278757      | 32483     | 1.44       | (1.28, 1.61)| 3.35e-10| 78.25  |
| Coronary artery disease*       | 184305      | 60801     | 1.29       | (1.16, 1.44)| 3.45e-06| 71.66  |
| Atrial fibrillation            | 285400      | 19106     | 1.06       | (0.96, 1.17)| 2.77e-01| 53.14  |
| Atrial fibrillation*           | 588190      | -         | 0.98       | (0.90, 1.06)| 6.47e-01| 69.72  |
| Heart failure                  | 253736      | 7442      | 1.33       | (1.17, 1.52)| 1.29e-05| 33.65  |
| Heart failure*                 | 977323      | -         | 1.18       | (1.10, 1.27)| 2.14e-06| 48.75  |
| Peripheral vascular disease    | 250259      | 3965      | 1.25       | (1.03, 1.51)| 2.35e-02| 43.25  |
| Arterial hypertension          | 390082      | 143788    | 1.17       | (1.08, 1.27)| 5.93e-05| 85.25  |

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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