SUPPLEMENTAL MATERIAL

Supplemental Methods

Data S1: The selection criteria of genetic instruments

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

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

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

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

where N denotes the sample size and k denotes the number of instruments. In terms of the rule of thumb [25], *F* statistic greater than 10 means that assumption (a) is satisfied and avoids the bias caused by weak instrument. [97,98]

Data S2: Genetic variant instruments for mediators in step c

Genetic variant instruments for BMI

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

Genetic variant instruments for HDL-C and TG

The summary data of genetic associations with HDL-C and TG were obtained from publicly available data through the Global Lipids Genetics Consortium, which included 188 577 individuals of primarily European ancestry. [30] Totally 86 independent SNPs that were associated with HDL-C at genome-wide significance ($P<5\times10^{-8}$) and a total of 51 independent SNPs that were associated with TG at genome-wide significance ($P<5\times10^{-8}$) were clumped by *Hindy et al. (2018)*[77], these SNPs explained 5.9% and 4.6% of the variance in HDL-C and TG, respectively (*F statistics* = 137.42 and 178.24, respectively). Since one of 86 SNPs of HDL-C (rs7422339 in chr2) was unavailable in UK Biobank, the leaving 85 SNPs were utilized as genetic instrumental variables for HDL-C in mediation analysis. Besides, all 51 SNPs of TG were available in UK Biobank and were utilized as genetic instrumental variables for TG in mediation analysis. Data on major and minor alleles for each instrument SNP, along with allele frequencies, beta coefficients for allele dose and 1 SD change in each lipid trait (i.e., the change in HDL-C or TG on a 1 SD scale per effect allele), P-values, and standard errors (SEs) were extracted. SNPs were aligned to the same effect allele across the data sources before analysis, and we checked the effect allele frequencies for concordance (The details of those SNPs were provided in Table S7 and S8).

Data S3: Estimate the proportion mediated by each mediator

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

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

Data S4: Confidence interval of the proportion mediated by mediator

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

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

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

$$\begin{aligned}\sigma^2(\beta_{MX}\beta_{YM}) = {} & \mu_{\beta_{YM}}^2\sigma^2(\beta_{MX}) + \mu_{\beta_{MX}}^2\sigma^2(\beta_{YM}) + \left[\sigma(\beta_{MX},\beta_{YM})\right]^2 \\ & + 2\mu_{\beta_{MX}}\mu_{\beta_{YM}}\sigma(\beta_{MX},\beta_{YM}) + \sigma^2(\beta_{MX})\sigma^2(\beta_{YM}).\end{aligned}$$

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

$$\sigma^2(IE_{X\to Y}) = \sigma^2(\beta_{MX}\beta_{YM}) = \mu_{\beta_{YM}}^2\sigma^2(\beta_{MX}) + \mu_{\beta_{MX}}^2\sigma^2(\beta_{YM}) + \sigma^2(\beta_{MX})\sigma^2(\beta_{YM}). \tag{1}$$

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

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

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

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

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

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

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

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

Data S5: Multivariable mendelian randomization (MVMR)

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

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

The results of MVMR analysis were shown in Table S34. After adjusting for BMI, HDL-C, TG, and LDL-C, the main analysis of MVMR-IVW suggested that insomnia was independent causally associated with a higher risk of all 9 CVD outcomes selected in the primary analysis, the *OR*s ranged from 1.11 (95% *CI*: 1.06-1.16) for atrial fibrillation (AF) to 1.22 (95% *CI*: 1.14-1.3) for heart failure (HF). Except for ischemic stroke (IS), the estimated direct effects of insomnia on the other 8 CVD outcomes were all attenuated compared to the total effects (primary analysis). The replication analysis showed similar results, except for AF. The results of replication analysis did not support that a genetically predicted insomnia was significant directly associated with a higher risk of AF ($OR = 1.03$, 95% *CI*: 1-1.06, $P = 0.045$) under a Bonferroni-corrected threshold of $P < 0.0125$ ($\alpha = 0.05/4$ outcomes). Theoretically speaking, this MVMR analysis was unable to calculate conditional F-statistics to assess the strength of our multi-variable instruments: the pairwise covariance between a SNP estimated association with any two exposures will equal to zero only when the effects of the SNPs on each exposure were estimated from separate samples; when the samples are overlapping, the requisite pairwise covariance are determinable only using individual-level data. [103] If we directly assumed that the pairwise covariances between SNP associations are zero, the conditional F-statistics for insomnia, BMI, HDL-C, TG, and LDL-C equals 11.01, 1.65, 0.94, 0.75, and 2.19, respectively. This suggested that conditional F-statistics for BMI, HDL-C, TG, and LDL-C were likely to be small, and the effect estimates were likely to subject to weak instrument bias. The horizontal pleiotropy statistic for this model is 262.76, the critical value at a 5% level of significance for a chi-squared distribution with 233 degrees of freedom is 269.61 ($P = 0.09$), which indicates no potential pleiotropy. [103]

Data S6: The potential mediator role of blood pressure traits

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

Data sources

The genetic association estimates with 2 blood pressure traits were taken from *Evangelou et al.* [104], however, this GWAS analysis was adjusted for body mass index [denoted these two traits as Systolic blood pressure adjusted body mass index (SBPadjBMI) and diastolic blood pressure adjusted body mass index (DBPadjBMI), respectively].[104] In addition, we used genetic association estimates with SBP and DBP calculated from 424 811 white British participants in the UK Biobank (see Figure S1 for the flow chart of individual selection). The blood pressure traits were recorded automatically at the baseline assessment center for all participants, we used the second reading of the automated blood pressure, where missing data were replaced with the first measure, as did by *Carter et al. (2019)*[52]. For each blood pressure trait, we additional excluded individuals with this trait missing or individuals without genetic data from our total analysis dataset (N=424 811) that passed our quality control, then the genetic associations with each blood pressure trait were obtained from the individuals in UK Biobank using linear regression controlling for 10 principal components, which can further control for population stratification. The basic characters of these summary data were presented in the Table S35.

Methods

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

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

Step b: 248 independent SNPs associated with insomnia at genome-wide significance from *Jansen et al. (2019)*[14] were utilized as instrumental variables to estimate the causal effects of genetically determined insomnia on each blood pressure traits, using the respective GWAS summary statistics described in Supplemental Section 6.1 and Table S35. This step was conducted using IVW method, in addition, complementary approaches including weighted median method, mode-based estimate, MR-Egger regression method, MR-PRESSO method were used to examine causal effect. Moreover, leave-one-out sensitivity analysis was also performed to assessing the reliance of the MR results on a particular variant. All the estimated effects were unit change in a blood pressure trait expressed per genetically predicted 1-unit-higher log-odds of liability to insomnia (per 2.72-fold multiplicative increase in the odds of insomnia). The Bonferroni-corrected threshold $P \le 0.0125(0.05/4)$ was used in this step, $P \le 0.05$ but above the Bonferroni corrected significance threshold was considered as suggestive association. The sample overlap between insomnia GWAS study and two consortia of blood pressure traits (ICBP and UK Biobank) are 31% and 29%, respectively.

Step c: for blood pressure traits that causal association is observed in Step b (DBP), we estimated the causal effect of each mediator on this CVD outcomes, respectively, using conventional one-sample MR analysis using individual data from UK Biobank. Totally 98 independent SNPs that were associated with DBP at genome-wide significance ($P<5\times10^{-8}$) were clumped by *Sun et al.* [105] (*F statistics* = 32.8). Since 1 of 98 SNPs (rs687621 in chr5) was unavailable in UK Biobank, the leaving 97 SNPs were utilized as genetic instrumental variables for DBP in mediation analysis. The causal effect estimate of DBP on this CVD outcome was obtained using the two-stage least-squares (2SLS) method: in the first stage, the exposure is regressed on the genetic variants and 10 principal components in a multivariate linear regression; in the second stage the outcome is regressed on the predicted values of the exposure from the first regression and 10 principal components in a logistic regression. The results were converted to *ORs* expressed per genetically predicted 1 mm Hg increased of the blood pressure trait, and the Bonferroni-corrected threshold $P \le 0.0063\left(0.05/8\right)$ 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)* [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[55] is as follows:

Rainer Malik [1], Ganesh Chauhan [2], Matthew Traylor [3], Muralidharan Sargurupremraj [4,5], Yukinori Okada [6,7,8], Aniket Mishra [4,5], Loes Rutten-Jacobs [3], Anne-Katrin Giese [9], Sander W van der Laan [10], Solveig Gretarsdottir [11], Christopher D Anderson [12,13,14,14], Michael Chong [15], Hieab HH Adams [16,17], Tetsuro Ago [18], Peter Almgren [19], Philippe Amouyel [20,21], Hakan Ay [22,13], Traci M Bartz [23], Oscar R Benavente [24], Steve Bevan [25], Giorgio B Boncoraglio [26], Robert D Brown, Jr. [27], Adam S Butterworth [28,29], Caty Carrera [30,31], Cara L Carty [32,33], Daniel I Chasman [34,35], Wei-Min Chen [36], John W Cole [37], Adolfo Correa [38], Ioana Cotlarciuc [39], Carlos Cruchaga [40,41], John Danesh [28,42,43,44], Paul IW de Bakker [45,46], Anita L DeStefano [47,48], Marcel den Hoed [49], Qing Duan [50], Stefan T Engelter [51,52], Guido J Falcone [53,54], Rebecca F Gottesman [55], Raji P Grewal [56], Vilmundur Gudnason [57,58], Stefan Gustafsson [59], Jeffrey Haessler [60], Tamara B Harris [61], Ahamad Hassan [62], Aki S Havulinna [63,64], Susan R Heckbert [65], Elizabeth G Holliday [66,67], George Howard [68], Fang-Chi Hsu [69], Hyacinth I Hyacinth [70], M Arfan Ikram [16], Erik Ingelsson [71,72], Marguerite R Irvin [73], Xueqiu Jian [74], Jordi Jiménez-Conde [75], Julie A Johnson [76,77], J Wouter Jukema [78], Masahiro Kanai [6,7,79], Keith L Keene [80,81], Brett M Kissela [82], Dawn O Kleindorfer [82], Charles Kooperberg [60], Michiaki Kubo [83], Leslie A Lange [84], Carl D Langefeld [85], Claudia Langenberg [86], Lenore J Launer [87], Jin-Moo Lee [88], Robin Lemmens [89,90], Didier Leys [91], Cathryn M Lewis [92,93], Wei-Yu Lin [28,94], Arne G Lindgren [95,96], Erik Lorentzen [97], Patrik K Magnusson [98], Jane Maguire [99], Ani Manichaikul [36], Patrick F McArdle [100], James F Meschia [101], Braxton D Mitchell [100,102], Thomas H Mosley [103,104], Michael A Nalls [105,106], Toshiharu Ninomiya [107], Martin J O'Donnell [15,108], Bruce M Psaty [109,110,111,112,] Sara L Pulit [113,45], Kristiina Rannikmäe [114,115], Alexander P Reiner [65,116], Kathryn M Rexrode [117], Kenneth Rice [118], Stephen S Rich [36], Paul M Ridker [34,35], Natalia S Rost [9,13], Peter M Rothwell [119], Jerome I Rotter [120,121], Tatjana Rundek [122], Ralph L Sacco [122], Saori Sakaue [7,123], Michele M Sale [124], Veikko Salomaa [63], Bishwa R Sapkota [125], Reinhold Schmidt [126], Carsten O Schmidt [127], Ulf Schminke [128], Pankaj Sharma [39], Agnieszka Slowik [129], Cathie LM Sudlow [114,115,] Christian Tanislav [130], Turgut Tatlisumak [131,132], Kent D Taylor [120,121], Vincent NS Thijs [133,134], Gudmar Thorleifsson [11], Unnur Thorsteinsdottir [11], Steffen Tiedt [1], Stella Trompet [135], Christophe Tzourio [5,136,137], Cornelia M van Duijn [138,139], Matthew Walters [140], Nicholas J Wareham [86], Sylvia Wassertheil-Smoller [141], James G Wilson [142], Kerri L Wiggins [109], Qiong Yang [47], Salim Yusuf [15], Najaf Amin [16], Hugo S Aparicio [185,48], Donna K Arnett [186], John Attia [187], Alexa S Beiser [47,48], Claudine Berr [188], Julie E Buring [34,35], Mariana Bustamante [189], Valeria Caso [190], Yu-Ching Cheng [191], Seung Hoan Choi [192,48], Ayesha Chowhan [185,48], Natalia Cullell [31], Jean-François Dartigues [193,194], Hossein Delavaran [95,96], Pilar Delgado [195], Marcus Dörr [196,197], Gunnar Engström [19], Ian Ford [198], Wander S Gurpreet [199], Anders Hamsten [200,201], Laura Heitsch [202], Atsushi Hozawa [203], Laura Ibanez [204], Andreea Ilinca [95,96], Martin Ingelsson [205], Motoki Iwasaki [206], Rebecca D Jackson [207], Katarina Jood [208], Pekka Jousilahti [63], Sara Kaffashian [4,5], Lalit Kalra [209], Masahiro Kamouchi [210], Takanari Kitazono [211], Olafur Kjartansson [212], Manja Kloss [213], Peter J Koudstaal [214], Jerzy Krupinski [215], Daniel L Labovitz [216], Cathy C Laurie [118], Christopher R Levi [217], Linxin Li [218], Lars Lind [219], Cecilia M Lindgren [220,221], Vasileios Lioutas [222,48], Yong Mei Liu [223], Oscar L Lopez [224], Hirata Makoto [225], Nicolas Martinez-Majander [172], Koichi Matsuda [225], Naoko Minegishi [203], Joan Montaner [226], Andrew P Morris [227,228], Elena Muiño [31], Martina Müller-Nurasyid [229,230,23]1, Bo Norrving [95,96], Soichi Ogishima [203], Eugenio A Parati [232], Leema Reddy Peddareddygari [56], Nancy L Pedersen [98,233], Joanna Pera [129], Markus Perola [63,234], Alessandro Pezzini [235], Silvana Pileggi [236], Raquel Rabionet [237], Iolanda Riba-Llena [30], Marta Ribasés [238], Jose R Romero [185,48], Jaume Roquer [239,240], Anthony G Rudd [241,242], Antti-Pekka Sarin [243,244], Ralhan Sarju [199], Chloe Sarnowski [47,48], Makoto Sasaki [245], Claudia L Satizabal [185,48], Mamoru Satoh [245], Naveed Sattar [246], Norie Sawada [206], Gerli Sibolt [172], Ásgeir Sigurdsson [247], Albert Smith [248], Kenji Sobue [245], Carolina Soriano-Tárraga [240], Tara Stanne [249], O Colin Stine [250], David J Stott [251], Konstantin Strauch [229,252], Takako Takai [203], Hideo Tanaka [253,254], Kozo Tanno [245], Alexander Teumer [255], Liisa Tomppo [172], Nuria P Torres-Aguila [31], Emmanuel Touze [256,257], Shoichiro Tsugane [206], Andre G Uitterlinden [258], Einar M Valdimarsson [259], Sven J van der Lee [16], Henry Völzke [255], Kenji Wakai [253], David Weir [260], Stephen R Williams [261], Charles DA Wolfe [241,242], Quenna Wong [118], Huichun Xu [191], Taiki Yamaji [206], Dharambir K Sanghera [125,169,170], Olle Melander [19], Christina Jern [171], Daniel Strbian [172,173], Israel Fernandez-Cadenas [31,30], W T Longstreth, Jr [174,65], Arndt Rolfs [175], Jun Hata [107], Daniel Woo [82], Jonathan Rosand [12,13,14], Guillaume Pare [15], Jemma C Hopewell [176], Danish Saleheen [177], Kari Stefansson [11,178], Bradford B Worrall [179], Steven J Kittner [37], Sudha Seshadri [180,48], Myriam Fornage [74,181], Hugh S Markus [3], Joanna MM Howson [28], Yoichiro Kamatani [6,182], Stephanie Debette [4,5], Martin Dichgans [1,183,184]

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 Mèdica, Universitat Autònoma de Barcelona, Barcelona, Spain

76 Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, University of Florida, College of Pharmacy, Gainesville, FL, USA
77 Division of Cardiovascular Medicine, College of Medicine, University of Florida, Gainesville, FL, USA
78 Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands
79 Program in Bioinformatics and Integrative Genomics, Harvard Medical School, Boston, MA, USA
80 Department of Biology, East Carolina University, Greenville, NC, USA
81 Center for Health Disparities, East Carolina University, Greenville, NC, USA
82 University of Cincinnati College of Medicine, Cincinnati, OH, USA
83 RIKEN Center for Integrative Medical Sciences, Yokohama, Japan
84 Department of Medicine, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA
85 Center for Public Health Genomics and Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA
86 MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK
87 Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA
88 Department of Neurology, Radiology, and Biomedical Engineering, Washington University School of Medicine, St. Louis, MO, USA
89 KU Leuven – University of Leuven, Department of Neurosciences, Experimental Neurology, Leuven, Belgium
90 VIB Center for Brain & Disease Research, University Hospitals Leuven, Department of Neurology, Leuven, Belgium
91 Univ.-Lille, INSERM U 1171. CHU Lille. Lille, France
92 Department of Medical and Molecular Genetics, King's College London, London, UK
93 SGDP Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
94 Northern Institute for Cancer Research, Paul O'Gorman Building, Newcastle University, Newcastle, UK
95 Department of Clinical Sciences Lund, Neurology, Lund University, Lund, Sweden
96 Department of Neurology and Rehabilitation Medicine, Skåne University Hospital, Lund, Sweden
97 Bioinformatics Core Facility, University of Gothenburg, Gothenburg, Sweden
98 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
99 University of Technology Sydney, Faculty of Health, Ultimo, Australia
100 Department of Medicine, University of Maryland School of Medicine, MD, USA
101 Department of Neurology, Mayo Clinic, Jacksonville, FL, USA
102 Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, MD, USA
103 Division of Geriatrics, School of Medicine, University of Mississippi Medical Center, Jackson, MS, USA
104 Memory Impairment and Neurodegenerative Dementia Center, University of Mississippi Medical Center, Jackson, MS, USA
105 Laboratory of Neurogenetics, National Institute on Aging, National institutes of Health, Bethesda, MD, USA
106 Data Tecnica International, Glen Echo MD, USA

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

137 Department of Public Health, Bordeaux University Hospital, Bordeaux, France
138 Genetic Epidemiology Unit, Department of Epidemiology, Erasmus University Medical Center Rotterdam, Netherlands
139 Center for Medical Systems Biology, Leiden, Netherlands
140 School of Medicine, Dentistry and Nursing at the University of Glasgow, Glasgow, UK
141 Department of Epidemiology and Population Health, Albert Einstein College of Medicine, NY, USA
142 Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA
143 A full list of members and affiliations appears in the Supplementary Note
144 Department of Human Genetics, McGill University, Montreal, Canada
145 Department of Pathophysiology, Institute of Biomedicine and Translation Medicine, University of Tartu, Tartu, Estonia
146 Department of Cardiac Surgery, Tartu University Hospital, Tartu, Estonia
147 Clinical Gene Networks AB,Stockholm, Sweden
148 Department of Genetics and Genomic Sciences, The Icahn Institute for Genomics and Multiscale Biology Icahn School of Medicine at Mount Sinai, New York, NY , USA
149 Department of Pathophysiology, Institute of Biomedicine and Translation Medicine, University of Tartu, Biomeedikum, Tartu, Estonia
150 Integrated Cardio Metabolic Centre, Department of Medicine, Karolinska Institutet, Karolinska Universitetssjukhuset, Huddinge, Sweden.
151 Clinical Gene Networks AB, Stockholm, Sweden
152 Sorbonne Universités, UPMC Univ. Paris 06, INSERM, UMR_S 1166, Team Genomics & Pathophysiology of Cardiovascular Diseases, Paris, France
153 ICAN Institute for Cardiometabolism and Nutrition, Paris, France
154 Department of Biomedical Engineering, University of Virginia, Charlottesville, VA, USA
155 Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA
156 Seattle Epidemiologic Research and Information Center, VA Office of Research and Development, Seattle, WA, USA
157 Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA
158 Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust, Gjettum, Norway
159 Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore
160 National Heart and Lung Institute, Imperial College London, London, UK
161 Department of Gene Diagnostics and Therapeutics, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan
162 Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA
163 Department of Cardiology,University Medical Center Groningen, University of Groningen, Netherlands
164 MRC-PHE Centre for Environment and Health, School of Public Health, Department of Epidemiology and Biostatistics, Imperial College London, London, UK

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 Phamaceutical Sciences, Collge 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'Hebron 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

198 Robertson Center for Biostatistics, University of Glasgow, Glasgow, UK
199 Hero DMC Heart Institute, Dayanand Medical College & Hospital, Ludhiana, India
200 Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
201 Karolinska Institutet, Stockholm, Sweden
202 Division of Emergency Medicine, and Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA
203 Tohoku Medical Megabank Organization, Sendai, Japan
204 Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA
205 Department of Public Health and Caring Sciences / Geriatrics, Uppsala University, Uppsala, Sweden
206 Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan
207 Department of Internal Medicine and the Center for Clinical and Translational Science, The Ohio State University, Columbus, OH, USA
208 Institute of Neuroscience and Physiology, the Sahlgrenska Academy at University of Gothenburg, Goteborg, Sweden
209 Department of Basic and Clinical Neurosciences, King's College London, London, UK
210 Department of Health Care Administration and Management, Graduate School of Medical Sciences, Kyushu University, Japan
211 Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Japan
212 Landspitali National University Hospital, Departments of Neurology & Radiology, Reykjavik, Iceland
213 Department of Neurology, Heidelberg University Hospital, Germany
214 Department of Neurology, Erasmus University Medical Center
215 Hospital Universitari Mutua Terrassa, Terrassa (Barcelona), Spain
216 Albert Einstein College of Medicine, Montefiore Medical Center, New York, NY, USA
217 John Hunter Hospital, Hunter Medical Research Institute and University of Newcastle, Newcastle, NSW, Australia
218 Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, UK
219 Department of Medical Sciences, Uppsala University, Uppsala, Sweden
220 Genetic and Genomic Epidemiology Unit, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK
221 The Wellcome Trust Centre for Human Genetics, Oxford, UK
222 Beth Israel Deaconess Medical Center, Boston, MA, USA
223 Wake Forest School of Medicine, Wake Forest, NC, USA
224 Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA
225 BioBank Japan, Laboratory of Clinical Sequencing, Department of Computational biology and medical Sciences, Graduate school of Frontier Sciences, The University of Tokyo, Tokyo, Japan

226 Neurovascular Research Laboratory, Vall d'Hebron Institut of Research, Neurology and Medicine Departments-Universitat Autònoma de Barcelona. Vall d’Hebrón Hospital, Barcelona, Spain
227 Department of Biostatistics, University of Liverpool, Liverpool, UK
228 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK
229 Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany
230 Department of Medicine I, Ludwig-Maximilians-Universität, Munich, Germany
231 DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany
232 Department of Cerebrovascular Diseases, Fondazione IRCCS Istituto Neurologico “Carlo Besta”, Milano, Italy
233 Karolinska Institutet, MEB, Stockholm, Sweden
234 University of Tartu, Estonian Genome Center, Tartu, Estonia, Tartu, Estonia
235 Department of Clinical and Experimental Sciences, Neurology Clinic, University of Brescia, Italy
236 Translational Genomics Unit, Department of Oncology, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy
237 Department of Genetics, Microbiology and Statistics, University of Barcelona, Barcelona, Spain
238 Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addictions, Vall d’Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Spain
239 Department of Neurology, IMIM-Hospital del Mar, and Universitat Autònoma de Barcelona, Spain
240 IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
241 National Institute for Health Research Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust and King's College London, London, UK
242 Division of Health and Social Care Research, King's College London, London, UK
243 FIMM-Institute for Molecular Medicine Finland, Helsinki, Finland
244 THL-National Institute for Health and Welfare, Helsinki, Finland
245 Iwate Tohoku Medical Megabank Organization, Iwate Medical University, Iwate, Japan
246 BHF Glasgow Cardiovascular Research Centre, Faculty of Medicine, Glasgow, UK
247 deCODE Genetics/Amgen, Inc., Reykjavik, Iceland
248 Icelandic Heart Association, Reykjavik, Iceland
249 Institute of Biomedicine, the Sahlgrenska Academy at University of Gothenburg, Goteborg, Sweden
250 Department of Epidemiology, University of Maryland School of Medicine, Baltimore, MD, USA
251 Institute of Cardiovascular and Medical Sciences, Faculty of Medicine, University of Glasgow, Glasgow, UK
252 Chair of Genetic Epidemiology, IBE, Faculty of Medicine, LMU Munich, Germany
253 Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan
254 Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
255 University Medicine Greifswald, Institute for Community Medicine, SHIP-KEF, Greifswald, Germany
256 Department of Neurology, Caen University Hospital, Caen, France
257 University of Caen Normandy, Caen, France

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CVD: cardiovascular disease

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

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

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

Outcome	**IVW Estimate [Min, Max]** [a]	**P value [Min, Max]** [b]
Cerebrovascular diseases		
Ischemic stroke	[1.16,1.17]	[0.00000748369931013361,0.0000636400747879641]
Transient ischemic attack	[1.14,1.16]	[0.000079858319953622,0.00050928078772593]
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]	[0.0000000000000000000000469123171329205,0.000000000000000000620091219092247]
Aortic valve stenosis	[1.19,1.22]	[0.000599272957379088,0.00240005141062859]
Atrial fibrillation	[1.12,1.13]	[0.0000000197505718659678,0.000000217128104309981]
Heart failure	[1.23,1.25]	[0.00000000000908939438050027,0.000000000137098779446152]
Peripheral vascular disease	[1.22,1.24]	[0.000000125008699928124,0.00000089431057307921]
Arterial hypertension	[1.13,1.14]	[0.0000000000000000132597075251179,0.00000000000000998106683415205]

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

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

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

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

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

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

Outcome	**Estimate [Min, Max]** [a]	**P value [Min, Max]** [b]
Ischemic stroke	[1.07,1.08]	[0.0000268453009723746,0.000120058579533057]
Coronary artery disease	[1.12,1.13]	[0.000000000819083524801232,0.0000000480897072408428]
Atrial fibrillation	[1.04,1.04]	[0.00356769100034803,0.0116350521246951]
Heart failure	[1.1,1.11]	[0.00000000000731708811169607,0.000000000193609760454461]

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

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

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

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

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

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

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

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

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

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

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

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

Outcome	**Estimate [Min, Max]** [a]	**P value [Min, Max]** [b]
Anthropometric		
WHR, SD (ratio）	[0.05,0.05]	[0.0000044074495162145,0.0000955072065612272]
WHRadjBMI, SD (ratio）	[0.01,0.02]	[0.0666985586582434,0.298626831744182]
WC, SD (cm)	[0.06,0.07]	[0.000011474457411313,0.000271531216121882]
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]	[0.00000028755543568585I,0.0000205938559705472]
Lipids		
TC, SD (mg/dL)	[0.02,0.03]	[0.0524568403969068,0.256497366815301]
LDL-C, SD (mg/dL)	[0.02,0.03]	[0.057799426928969,0.20824777920477]
HDL-C, SD (mg/dL)	[-0.07,-0.05]	[0.0000346899060716208,0.000631131156786682]
TG, SD (mg/dL)	[0.06,0.07]	[0.00000017588083413152 5,0.0000087946162664119 2]
Glycemic		
Fasting glucose, mmol/L	[-0.08,0]	[0.293251287768197,0.982671572871615]
Fasting insulin, log(mmol/L)	[0,0.05]	[0.267271766744033,0.987832172990524]
Two-hour glucose, mmol/L	[-0.33,-0.1]	[0.0305746515343448,0.48973182482394]
HbA1c, %	[0.01,0.01]	[0.00596736341191292,0.0444372014979117]
Renal function		
eGFR, mL/min/1.73m2	[0,0]	[0.500785470165884,0.775721580164342]
Other		
Heart rate	[0,0]	[0.778187134683311,0.998706350145354]

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

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

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

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

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

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

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

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

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

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

Outcome	**Estimate [Min, Max]** [a]	**P value [Min, Max]** [b]
WHRadjBMI, SD (ratio)	[0.03,0.04]	[0.000704554697255648,0.00281415967551047]
BMI, SD (kg/m2)	[0.05,0.06]	[0.0000031995970473078 8,0.0000900335583009329]
TC, SD (mg/dl)	[-0.01,0.01]	[0.516540259928238,0.856786557960117]
LDL-C, SD (mg/dl)	[0,0.02]	[0.188223217376048,0.999536661057882]
HDL-C, SD (mg/dl)	[-0.05,-0.04]	[0.00159739285038294,0.0115165343420197]
TG, SD (mg/dl)	[0.05,0.05]	[0.0000072540243757012 8,0.000212009729329835]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Outcome	**Estimate [Min, Max]** [a]	**P value [Min, Max]** [b]
Ischemic stroke	[1.16,1.25]	[0.0143880245946882,0.107684167726366]
Transient ischemic attack	[1.06,1.14]	[0.135873356643229,0.47724803861545]
Deep vein thrombosis	[0.83,0.87]	[0.0181667164155343,0.0824794940987828]
Pulmonary embolism	[0.83,0.88]	[0.0157498347567607,0.10290988959661]
Coronary artery disease	[1.41,1.47]	[0.0000000000000627712765854418,0.0000000031086529845111]
Atrial fibrillation	[1.03,1.06]	[0.182224545732321,0.630916519312097]
Heart failure	[1.28,1.37]	[0.00000461498779135834,0.000140212542090974]
Peripheral vascular disease	[1.21,1.3]	[0.00496771215383943,0.0429594493545899]
Arterial hypertension	[1.17,1.19]	[0.00000417959689599575,0.000140564076388081]

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

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

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

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

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

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

Outcome	**Weighted median**		**Mode-based**		**MR-Egger**				**MRPRESSO**		
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**Intercept**	**P value**	**OR (95% CI)**	**P value**	**No. of outliers**
Ischemic stroke	1.19(0.97,1.45)	0.094563	1.19(0.99,1.44)	0.067569	1.09(0.82,1.45)	0.551374	0.01(-0.01,0.02)	0.418855	1.2	0.041579	1
Transient ischemic attack	1.18(0.95,1.47)	0.136753	1.21(0.97,1.52)	0.092447	1.04(0.78,1.38)	0.786194	0(-0.01,0.02)	0.624262	1.1	0.264545	1
Deep vein thrombosis	0.9(0.78,1.05)	0.170635	0.92(0.81,1.05)	0.198874	0.98(0.77,1.26)	0.887544	-0.01(-0.02,0)	0.170583	0.88	0.08805	2
Pulmonary embolism	0.9(0.76,1.06)	0.203165	0.92(0.78,1.08)	0.293458	0.89(0.7,1.15)	0.38396	0(-0.02,0.01)	0.659056	0.86	0.043077	1
Coronary artery disease	1.3(1.18,1.43)	4.91E-08	1.3(1.19,1.42)	2.52E-09	1.18(0.99,1.41)	0.061963	0.01(0,0.02)	0.006527	1.46	2.82E-11	5
Atrial fibrillation	1.03(0.92,1.15)	0.580697	1.06(0.95,1.18)	0.29206	1.04(0.88,1.23)	0.639087	0(-0.01,0.01)	0.941684	1.06	0.188392	1
Heart failure	1.35(1.15,1.58)	0.000207	1.27(1.08,1.49)	0.003433	1.28(1.03,1.6)	0.023605	0(-0.01,0.01)	0.723391	1.31	5.33E-05	1
Peripheral vascular disease	1.13(0.9,1.41)	0.294564	1.2(0.97,1.49)	0.09391	1.15(0.83,1.58)	0.39603	0.01(-0.01,0.02)	0.49511	1.25	0.022008	1
Arterial hypertension	1.17(1.11,1.23)	2.27E-10	1.14(1.1,1.19)	6.58E-11	1.03(0.92,1.17)	0.59317	0.01(0,0.01)	0.009745	1.16	1.12E-07	11

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

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

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

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

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

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

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

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

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

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

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

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

Outcome	Estimate [Min, Max] [a]	P value [Min, Max] [b]
Ischemic stroke	[1.01,1.03]	[0.383762940650492,0.776469734303151]
Coronary artery disease	[1.27,1.35]	[0.000000162273017759942,0.0000195233479628422]
Atrial fibrillation	[0.96,0.99]	[0.294623128451253,0.793134017725766]
Heart failure	[1.17,1.19]	[0.00000012045194257,0.0000144655051569308]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Outcome	**IVW Estimate [Min, Max]** [a]	**P value [Min, Max]** [b]
SBP	[0.24,0.34]	[0.0186049858690466,0.100537941458835]
SBPadjBMI	[0.04,0.14]	[0.304494868109331,0.795806711330309]
DBP	[0.39,0.45]	[0.00000011562821841 7038,0.0000042808665419 5319]
DBPadjBMI	[0.09,0.15]	[0.03674968466824,0.273221141001499]

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

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

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

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

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

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

Figure S1. Flowchart of UK Biobank individual selection.

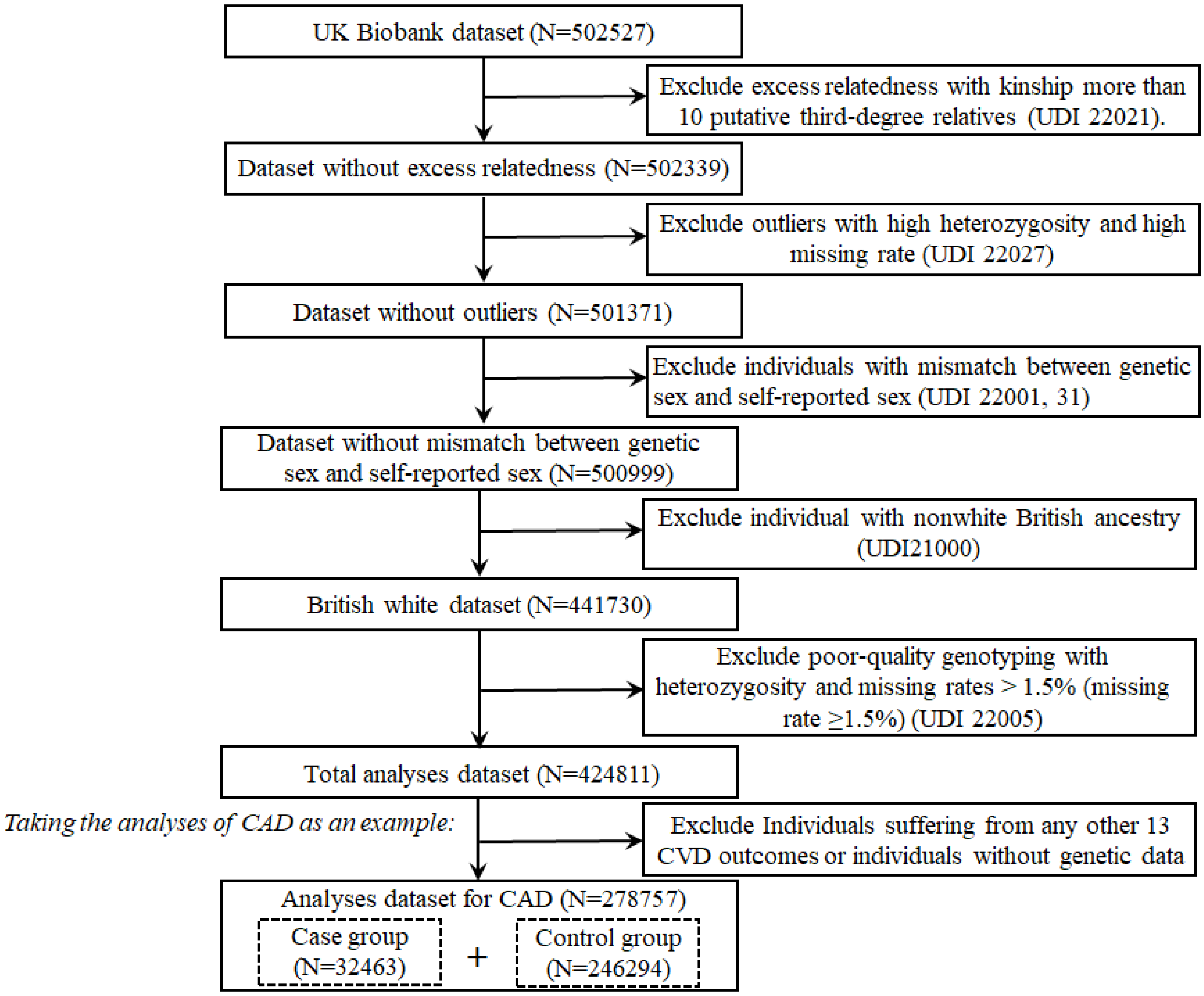
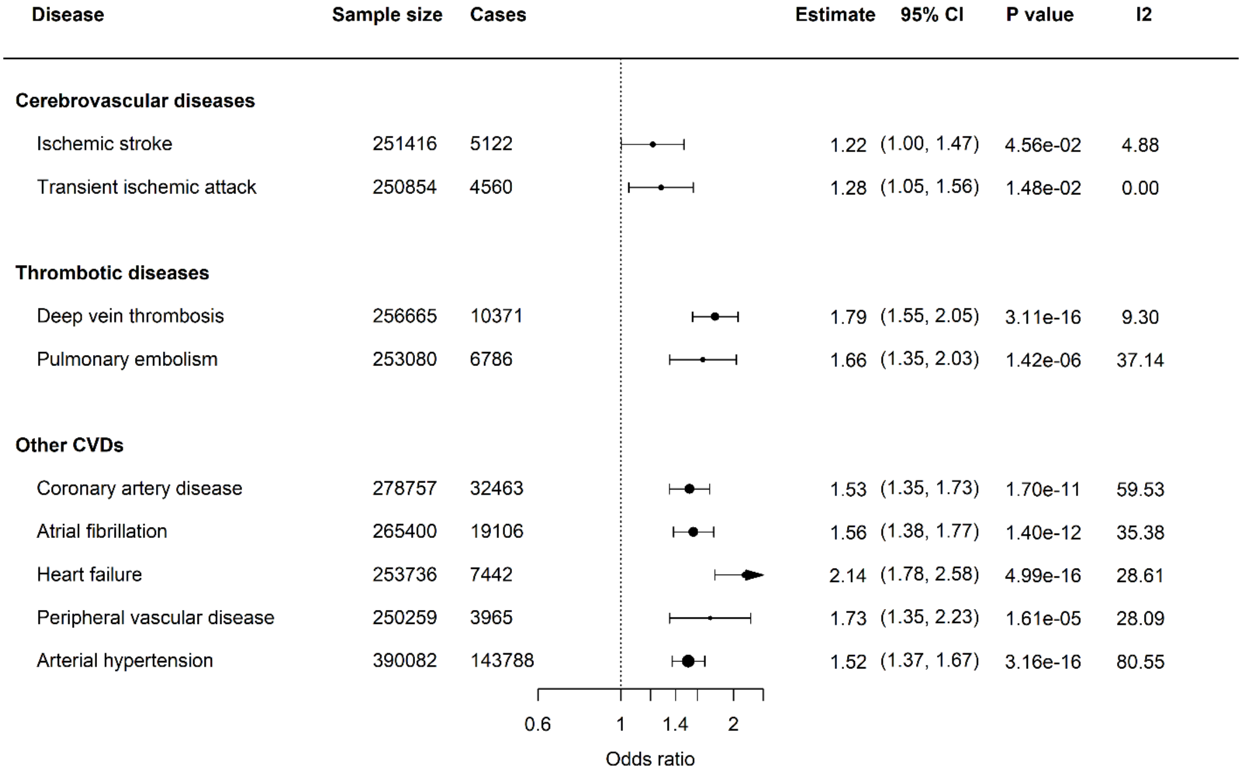


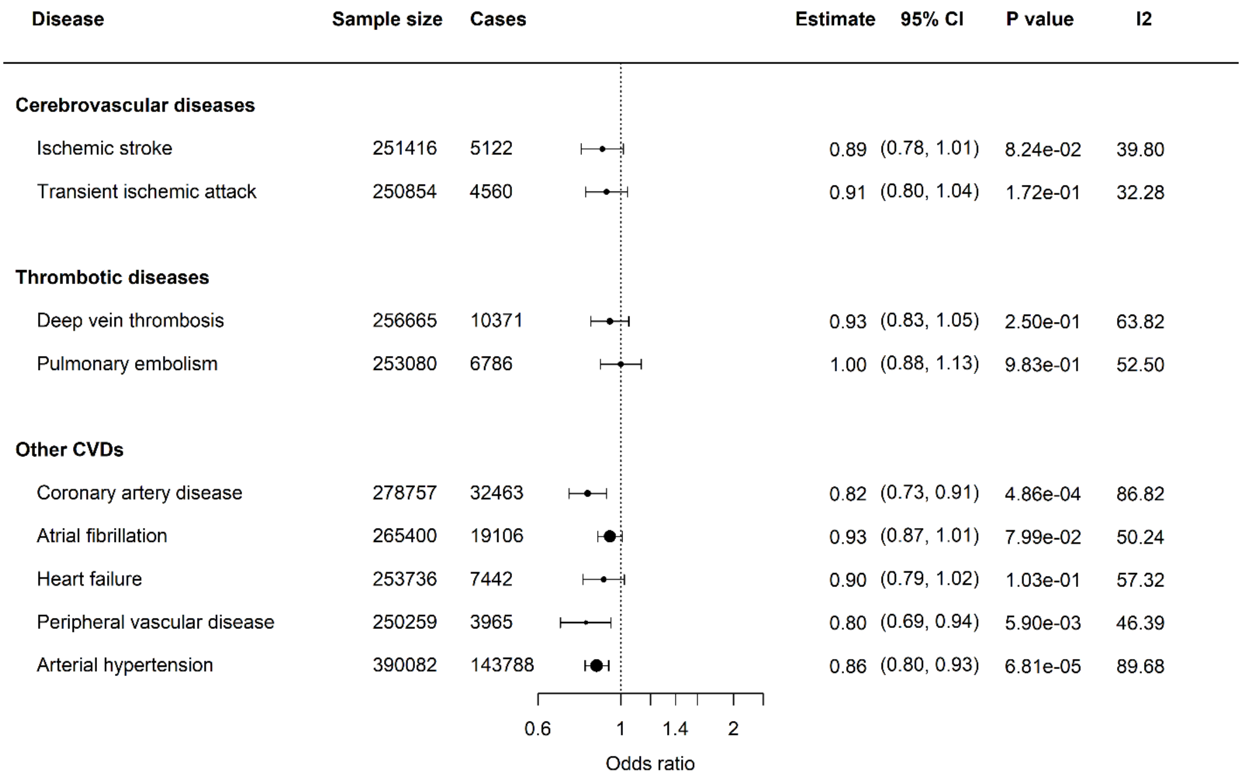
Figure S2. Associations between genetically predicted body mass index and 9 cardiovascular diseases selected in primary study.



Disease	Sample size	Cases	Estimate	95% CI	P value	I2
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-16	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

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

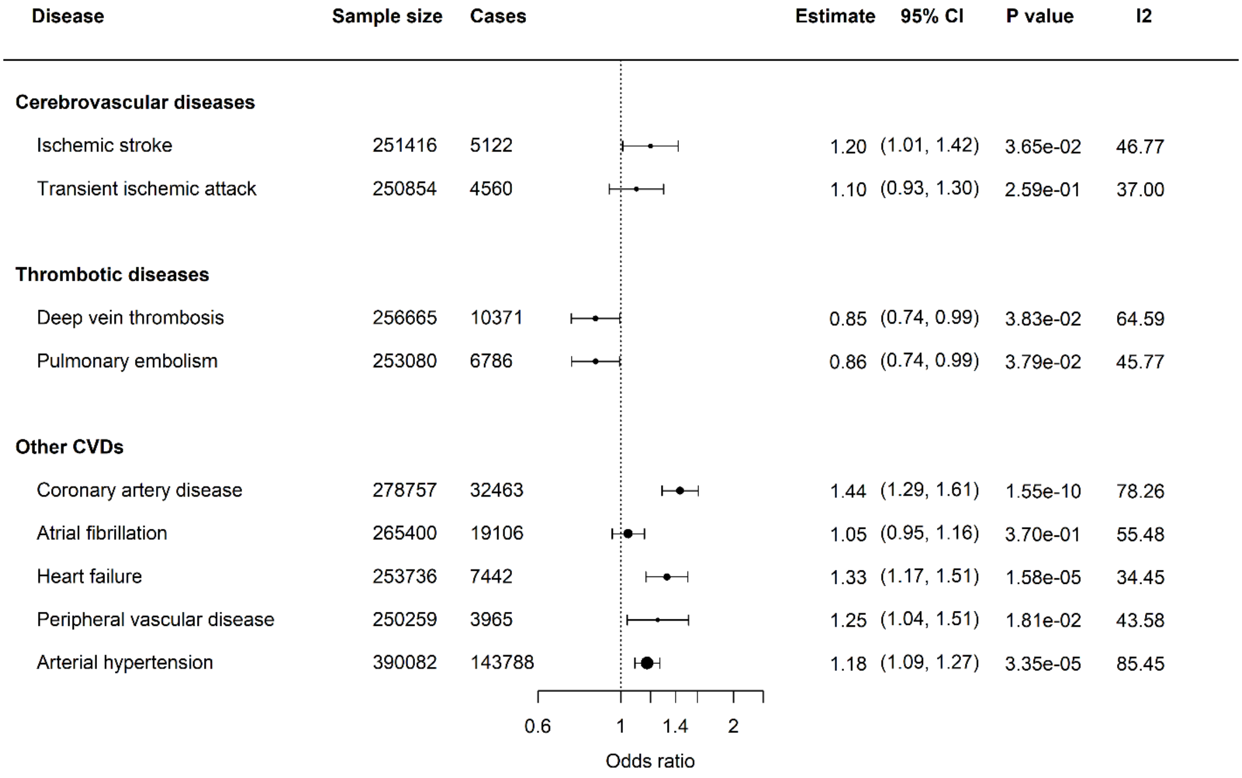
Figure S3. Associations between genetically predicted high-density lipoprotein cholesterol and 9 cardiovascular diseases selected in primary study.



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	32463	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.

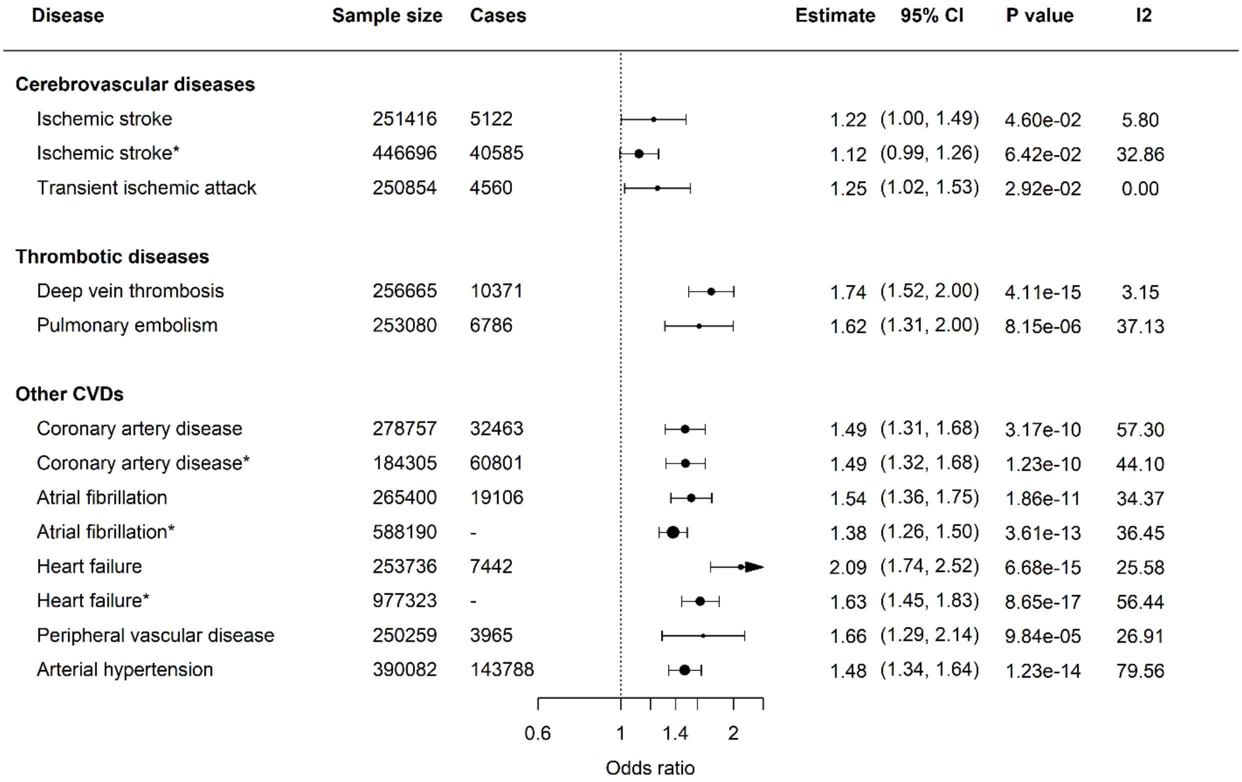
Figure S4. Associations between genetically predicted triglycerides and 9 cardiovascular diseases selected in primary study.



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	46.77
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	32463	1.44	(1.29, 1.61)	1.55e-10	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.



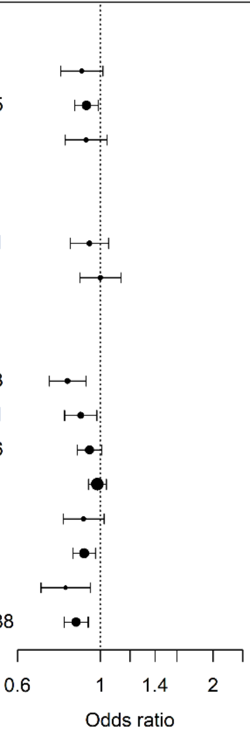
Disease	Sample size	Cases	Estimate	95% CI	P value	I2
Cerebrovascular diseases						
Ischemic stroke	251416	5122	1.22	(1.00, 1.49)	4.60e-02	5.80
Ischemic stroke*	446696	40585	1.12	(0.99, 1.26)	6.42e-02	32.86
Transient ischemic attack	250854	4560	1.25	(1.02, 1.53)	2.92e-02	0.00
Thrombotic diseases						
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	32463	1.49	(1.31, 1.68)	3.17e-10	57.30
Coronary artery disease*	184305	60801	1.49	(1.32, 1.68)	1.23e-10	44.10
Atrial fibrillation	265400	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	26.91
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.

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

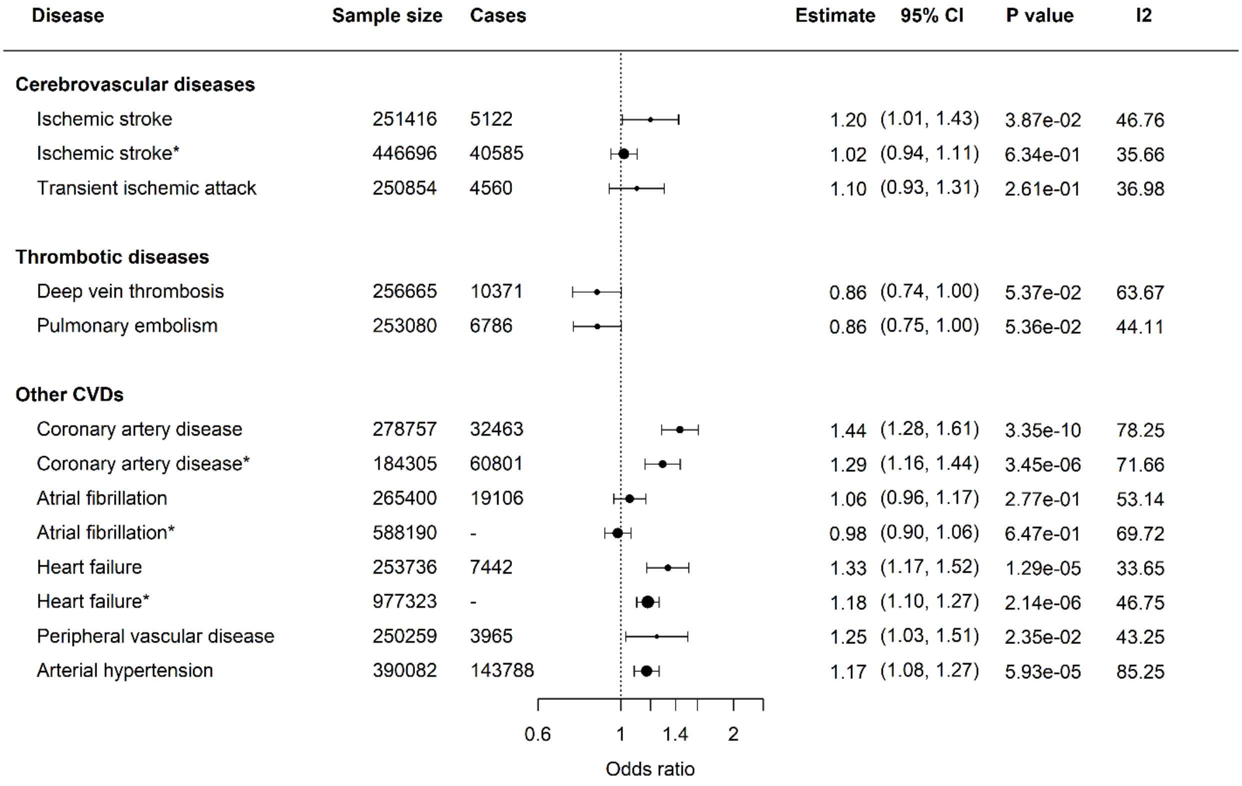
Disease	Sample size	Cases	Estimate	95% CI	P value	I2
Cerebrovascular diseases						
Ischemic stroke	251416	5122	0.89	(0.78, 1.02)	8.41e-02	39.79
Ischemic stroke*	446696	40585	0.92	(0.85, 0.99)	1.94e-02	45.70
Transient ischemic attack	250854	4560	0.92	(0.81, 1.04)	1.78e-01	31.78
Thrombotic diseases						
Deep vein thrombosis	256665	10371	0.93	(0.83, 1.05)	2.57e-01	63.57
Pulmonary embolism	253080	6786	1.00	(0.88, 1.13)	9.96e-01	51.95
Other CVDs						
Coronary artery disease	278757	32463	0.82	(0.73, 0.91)	4.37e-04	86.17
Coronary artery disease*	184305	60801	0.89	(0.80, 0.98)	1.62e-02	80.39
Atrial fibrillation	265400	19106	0.94	(0.87, 1.01)	8.21e-02	49.12
Atrial fibrillation*	588190	-	0.98	(0.93, 1.04)	5.18e-01	59.39
Heart failure	253736	7442	0.90	(0.79, 1.02)	1.05e-01	55.61
Heart failure*	977323	-	0.90	(0.84, 0.97)	4.43e-03	64.48
Peripheral vascular disease	250259	3965	0.81	(0.69, 0.94)	5.59e-03	43.76
Arterial hypertension	390082	143788	0.86	(0.80, 0.93)	7.47e-05	89.67



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 S7. Results of associations between genetically predicted triglycerides and 9 cardiovascular diseases using multivariable MR analysis adjust 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	46.76
Ischemic stroke*	446696	40585	1.02	(0.94, 1.11)	6.34e-01	35.66
Transient ischemic attack	250854	4560	1.10	(0.93, 1.31)	2.61e-01	36.98
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	32463	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	265400	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	46.75
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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