Online Supplement

Supplementary Table S11. Summary statistics of 25 genetic instruments included in the mendelian randomization analysis to examine the causal effects of myocardial infarction on broad depression.

Supplementary Table S12. Summary statistics of 11 genetic instruments included in the mendelian randomization analysis to examine the causal effects of broad depression on atrial fibrillation.

Supplementary Table S13. Summary statistics of 152 genetic instruments included in the mendelian randomization analysis to examine the causal effects of atrial fibrillation on broad depression.

Supplementary Table S14. Univariable Mendelian Randomization analysis in evaluating the causal association between various CVD and the two depression phenotypes.

Supplementary Figure S1. Power calculation of MR analyses.

(a) Power of MR analysis in evaluating the causal association between genetic predisposition to depression and CAD.
(b) Power of MR analysis in evaluating the causal association between genetic predisposition to depression and MI.
(c) Power of MR analysis in evaluating the causal association between genetic predisposition to depression and AF.
(d) Power of MR analysis in evaluating the causal association between genetic predisposition to CAD and depression.
(e) Power of MR analysis in evaluating the causal association between genetic predisposition to MI and depression.
(f) Power of MR analysis in evaluating the causal association between genetic predisposition to AF and depression.
(g) Power of MR analysis in evaluating the causal association between genetic predisposition to broad depression and CAD.
(h) Power of MR analysis in evaluating the causal association between genetic predisposition to broad depression and MI.
(i) Power of MR analysis in evaluating the causal association between genetic predisposition to broad depression and AF.
(j) Power of MR analysis in evaluating the causal association between genetic predisposition to CAD and broad depression.
(k) Power of MR analysis in evaluating the causal association between genetic predisposition to MI and broad depression.
(l) Power of MR analysis in evaluating the causal association between genetic predisposition to AF and broad depression.

Supplementary Figure S2. Scatter plot of potential effects of genetic instruments on depression versus their effects on coronary artery disease.

Supplementary Figure S3. Scatter plot of potential effects of genetic instruments on depression versus their effects on myocardial infarction.

Supplementary Figure S4. Scatter plot of potential effects of genetic instruments on depression versus their effects on atrial fibrillation.

Supplementary Figure S5. Scatter plot of potential effects of genetic instruments on CAD versus their effects on depression.

Supplementary Figure S6. Scatter plot of potential effects of genetic instruments on myocardial infarction versus their effects on depression.

Supplementary Figure S7. Scatter plot of potential effects of genetic instruments on atrial fibrillation versus their effects on depression.

Supplementary Figure S8. Result of Mendelian Randomization analysis in evaluating the causal association between broad depression and various cardiovascular diseases.

Supplementary Figure S9. Sensitivity analysis result in evaluating the causal association between broad depression and various cardiovascular diseases after excluding proxies which were not genome-wide significant.

Supplementary Figure S10. Scatter plot of potential effects of genetic instruments on broad depression versus their effects on coronary artery disease.

Supplementary Figure S11. Scatter plot of potential effects of genetic instruments on broad depression versus their effects on myocardial infarction.

Supplementary Figure S12. Scatter plot of potential effects of genetic instruments on broad depression versus their effects on atrial fibrillation.

Supplementary Figure S13. Scatter plot of potential effects of genetic instruments on CAD versus their effects on broad depression.

Supplementary Figure S14. Scatter plot of potential effects of genetic instruments on myocardial infarction versus their effects on broad depression.

Supplementary Figure S15. Scatter plot of potential effects of genetic instruments on atrial fibrillation versus their effects on broad depression.

Supplementary Methods 1. Selection of genetic instruments

To infer causality of depression on various CVD, 102 independent SNPs significantly associated with depression in the largest meta-analysis to date (Howard et al., 2019) were initially employed as genetic instruments. The meta-analysis included the three largest GWAS using different depression phenotypes in participants from 23andMe, Psychiatric Genomics Consortium (PGC) and UK Biobank. Notably, the summary statistics of all genetic variants in the study by Howard *et al* were only publicly available in the form of meta-analysis of PGC and UK Biobank studies without samples from 23andme, comprising of 170,756 cases and 329,443 controls. The smaller sample size lowered the power of the GWAS meta-analysis, and some of the 102 independent SNPs no longer reached genome-wide significance ($p<5x10^{-8}$) in the reduced sample. Given the same result pattern observed in the MR analyses performed by previous PGC study in evaluating the causal association between MDD and CAD with and without samples from 23andMe cohort (Wray et al., 2018), we kept all the 102 depression-associated independent SNPs as the initial genetic instruments in the main analysis such that they could explain a larger proportion of variance and hence maintain the power of the MR analyses. These 102 SNPs were then matched with the publicly available GWAS datasets of mediators and outcome. If the initial instruments were unavailable in any one dataset of mediators and outcome, proxies in linkage disequilibrium (LD) with the initial instruments ($r^2>0.8$) were selected as the instruments. To comply with the MR assumption that genetic instruments can only act on the outcome through the exposure (depression) or / and mediators, genetic instruments associated with the CVD outcome via other pathways (such as psychiatric disorders (Correll et al., 2017), height (Nelson et al., 2015, Nuesch et al., 2016) and education attainment (Tillmann et al., 2017)) were excluded. A total of 93 genetic instruments were adopted in evaluating the

causal association between depression and various CVD. Similarly, in evaluating the causality of various CVD on depression, independent SNPs significantly associated with the respective CVD traits were selected as the initial genetic instruments. As independent genome-wide significant SNPs were not identified by the original GWAS of CAD and MI (Nikpay et al., 2015), clump command in PLINK 1.9 (Chang et al., 2015) was adopted to select the independent SNPs: variants that were within 3Mb with the index variants ($p<5x10^{-8}$) and shared a LD with r^2 of greater than 0.1 were clumped together, and only the most significant variant was selected. Upon matching the SNPs in the mediator and outcome datasets, identifying the proxies, and removing the pleiotropic instruments (such as SNPs which were associated with allergy (Harter et al., 2019) and Alzheimer's disease (Saczynski et al., 2010), which may in turn affect the depression outcome), the remaining genetic instruments constituted the basis of the main MR analysis. The summary statistics of genetic instruments adopted in each main MR analysis were retrieved from the datasets of exposure, potential mediator and outcome, and they are listed out in Supplementary Tables S2-S7.

For depression, publicly available summary statistics were obtained from a reduced sample without participants of 23andMe cohort. The decreased sample size resulted in lower power of the GWAS meta-analysis that some of the 102 independent SNPs could no longer reach genome-wide significance in the depression dataset. Together with proxies which were not genome-wide significantly associated with depression, these instruments were excluded, and the MR analysis was repeated as a sensitivity analysis.

We also tested the bi-directional causal association between broad depression and various CVD as secondary analyses. The selection method of genetic instruments was the same as above. Fourteen independent SNPs with genome-wide significant association with broad depression (Howard et al., 2018) were initially employed as genetic instruments. Sensitivity analysis was also conducted after excluding proxies which were not genome-wide significantly associated with the broad depression dataset. The summary statistics of the selected genetic instruments for each MR analysis are listed in Supplementary Tables 8-13. The number of genetic instruments adopted in each MR analysis is listed out in Table 1.

Supplementary Methods 2. Mendelian randomization analyses

Univariable inverse-variance weighted (IVW) (Burgess et al., 2013) method was used for main MR analysis to assess the total effect of the exposure on the outcome (Burgess et al., 2017). Although inverse-variance weighted (IVW) is the conventional method of MR analysis, the major drawback is that it assumes all instrumental variables are valid. Weighted median method provides consistent estimates even when up to 50% of the information comes from invalid instrumental variables (Bowden et al., 2016) and it was used as a sensitivity analysis. MR-Egger (Bowden et al., 2015) and MR pleiotropy residual sum and outlier (MR-PRESSO) (Verbanck et al., 2018) were employed to test for the presence of directional pleiotropy. The intercept of MR-Egger regression represents the average pleiotropic effects across all SNPs, under the assumption that the magnitude of the pleiotropic effects are independent of the SNP-risk factor associations across all variants, also known as the INstrument Strength Independent of Direct Effect (INSIDE) assumption (Bowden *et al.*, 2015). Whereas, MR-PRESSO comprises of 3 components: (i) global test has adequate power to evaluate the overall horizontal pleiotropy among all instruments even if pleiotropy just occurs in less than half of the instruments; (ii) outlier test provides the causal estimate upon removal of pleiotropic genetic instruments; and (iii) distortion test determines if there is significant difference in the causal estimate before and after the removal of pleiotropic genetic instruments (Verbanck *et al.*, 2018). MR-PRESSO analysis was performed using "MRPRESSO" package in R (Verbanck *et al.*, 2018). In case univariable MR analysis revealed a causal association between the exposure and outcome, multivariable IVW analysis was also performed to dissect the mechanisms in the causal pathway from the risk factor to the outcome (Burgess *et al.*, 2017, Burgess et al., 2015). The direct causal effect of the risk factors on the outcome were evaluated by multivariable IVW by adjusting for the beta

estimates of potential mediators, including blood lipid levels, diabetes, BMI, blood pressure, IL-6 level, CRP level, physical activity, smoking status and insomnia. If the multivariable IVW analysis yielded an estimate which is deviated from the null, this implies the risk factor is independent that keeping the potential mediators unchanged would not affect the outcome (Burgess and Thompson, 2015). On the contrary, attenuation of causal estimates to null upon adjustment for beta estimates of potential mediators implies that the mediators play a role in the causal pathway that keeping them constant would affect the outcome. Multivariable MR-Egger intercept test was applied to detect for presence of residual pleiotropy via other unmeasured risk factors (Rees et al., 2017). Weighted median method, univariable and multivariable IVW and MR-Egger analyses were conducted with 'MendelianRandomization' package in R (Yavorska et al., 2017).

Supplementary Text 1. Secondary analysis in evaluating the causal association between broad depression and various CVD

Broad depression and CAD

With 10 genetic instruments in the main analysis, genetically doubling the odds of broad depression was associated with increased risk of CAD in the univariable IVW analysis (OR=2.067; 95% CI:1.141-3.742) (Supplementary Figures S8a and S10a). The result had a wide confidence interval and it was no longer significant after corrected for multiple testing. In multivariable MR analyses adjusted for beta estimates of blood lipid levels (OR=1.656; 95% CI: 0.880-3.117), type 2 diabetes (OR=1.599; 95% CI: 0.783-3.263), BMI (OR=1.744; 95% CI: 0.846-3.595), blood pressure (OR=1.843; 95% CI: 0.936-3.630) and smoking status (OR=1.470; 95% CI: 0.772-2.799), the causal association was attenuated but little change in causal estimates were observed after adjustment for other potential mediators (Supplementary Figure S8b). Similar causal estimates were yielded from the sensitivity analysis after excluding 1 genetic instrument which was not significantly associated with broad depression. With 9 genetic instruments, univariable IVW analysis showed that doubling the odds of broad depression was causally associated with increased risk of CAD (OR=2.136; 95% CI: 1.120-4.072) (Supplementary Figures S9a and S10b). Causal association was attenuated after adjusted for the same set of potential mediators in multivariable MR analysis (Supplementary Figure S9b). MR-PRESSO global test and MR-Egger intercept tests in both univariable and multivariable MR analyses were insignificant ($P>0.05$), indicating the absence of horizontal pleiotropy.

Broad depression and MI

In assessing the causal association between broad depression and MI, univariable IVW and weighted median methods of the main analysis suggested that genetically doubling the odds of broad depression was associated with increased risk of MI (IVW: OR=3.779; 95% CI:2.013-7.092; weighted median: OR=3.870; 95% CI: 1.604-9.335) (Supplementary Figures S8a and S11a). The association remained significant after multiple testing correction. There was little change in causal estimates in multivariable MR analysis adjusted for various potential mediators (Supplementary Figure S8b). Sensitivity analysis after excluding one genetic instrument insignificantly associated with broad depression yielded similar results. Both IVW and weighted median methods demonstrated that genetically doubling the odds of broad depression were associated with increased risk of MI (IVW: OR=3.868; 95% CI: .963-7.620; weighted median: OR=5.624; 95% CI: 2.232-14.172) (Supplementary Figures S9a and S11b). Similarly, little changes were observed in the causal estimates in multivariable IVW analysis after adjustment for each of the potential mediator (Supplementary Figure S9b). In both the main and sensitivity analyses, MR-PRESSO global test was insignificant ($P>0.05$), but univariable and multivariable MR-Egger intercept tests after adjustment for physical activity and insomnia were significant ($P<0.05$), indicating some evidence of pleiotropy.

Broad depression and AF

In both the main and sensitivity analyses, univariable IVW and weighted median methods demonstrated that genetic susceptibility to broad depression did not have causal association with AF (Supplementary Figures S8a, S9a, S12). No evidence of pleiotropy was shown by both MR-Egger intercept and MR-PRESSO global tests ($P>0.05$).

Various CVD and broad depression

We found no evidence of causal effects of any CVD on broad depression (Supplementary Table S14b, Supplementary Figures S13-S15). In all the MR analyses evaluating the causal effects of various CVD on broad depression, MR-PRESSO global tests, univariable and multivariable MR-Egger intercept tests suggested the absence of horizontal pleiotropy (Supplementary Table S14b).

Discussion

For broad depression, the causal association with CAD was attenuated after adjusting for blood lipid levels, type 2 diabetes, BMI, blood pressure and smoking status in multivariable MR analysis, indicating that causality might be partly mediated by these factors. How blood lipid levels and smoking status might mediate the causal pathway from broad depression and CVD were discussed in the main text. A meta-analysis demonstrated that patients with MDD had a higher risk of type 2 diabetes when compared to population controls (Vancampfort et al., 2015). Type 2 diabetes has been recognized as a major risk factor of CVD for a long time, with the incidence of CVD

among diabetic patients doubling and tripling in males and females, respectively, when compared with non-diabetic individuals (Kannel et al., 1979). This can be explained by the high blood glucose level in type 2 diabetes patients which cause damage to large blood vessels. Regarding BMI, a meta-analysis revealed that people with depression had an increased risk of obesity (defined as BMI≥30; pooled OR=1.58), which may be contributed by neuroendocrine disturbances (Luppino et al., 2010). Meanwhile, people with higher BMI had higher risk of experiencing a CVD event (Khan et al., 2018). We also found that broad depression had a significant genetic correlation with diastolic blood pressure (DBP) (r=0.0684; SE=0.0314; P=0.0294) but not systolic blood pressure (r=0.0292; SE=0.0323; P=0.3664) using LDSC. Broad depression might be a proxy phenotype for stress (Supplementary Text 2 on details of depression phenotypes), which is positively associated with hypertension (Sparrenberger et al., 2009), a known risk factor for CAD. This may explain how blood pressure mediates the causal effects of broad depression on CAD.

Supplementary Text 2. Discussion on depression phenotypes

Intrinsic heterogeneity may exist across different depression definitions, including but not limited to clinically diagnosed depression, self-declaration of clinically diagnosed depression and self-declared depressive symptoms (Zeng et al., 2016). MDD is a clinically diagnosed definition of depression but GWAS of MDD has been proved to be difficult in identifying genome-wide significant variants, mainly due to the large number of loci of small effect sizes that are associated with MDD (Wray *et al.*, 2018), moderate heritability, high prevalence, heterogeneity of genetic and non-genetic factors and misdiagnosis of MDD (Levinson et al., 2014). It was reported that even genetic correlation among MDD phenotypes in independent cohorts are relatively low (Gratten et al., 2014, Zeng *et al.*, 2016). Studies demonstrated that self-declared depression is a scalable alternative to MDD due to their high correlation (Fabbri, 2016, Howard *et al.*, 2018, Zeng *et al.*, 2016). Meanwhile, it is relatively easier to collect and hence increasing the sample size and power. The depression definition adopted in the primary analysis of the current study is indeed a combination of broad depression, structured diagnostic interviews, electronic medical records, traditional diagnosis methods and treatment registries. Among which, approximately 74.70% of the depression cases were participants with broad depression. The remaining 25.30% cases had clinical diagnosis of depression, which is considered a more homogeneous population Whereas, broad depression is defined as self-reported help-seeking behaviour from general practitioner or psychiatrist for problems with nerves, anxiety, tension or depression (Howard *et al.*, 2018). It may include participants with early depression or other mood disorder symptoms but not yet meeting the conventional diagnostic criteria of MDD (Howard *et al.*, 2018). Broad depression also implies self-awareness of potential depression and other mood problems like anxiety, nerves or tension. Such awareness to possible mood

problems might trigger or mark the presence of stress, turning broad depression a proxy phenotype of stress.

Supplementary Text 3. Discussion on different results observed for MR analyses of depression and broad depression on CAD/MI

The MR analyses of depression and broad depression on CAD and MI showed consistent causal direction but some differences were observed. Firstly, the magnitude of causal estimates and standard error of broad depression were higher than that of depression. Secondly, our multivariable analysis demonstrated that the causal association between broad depression and CAD may be partly mediated by BMI, blood pressure and CRP level, which was not observed for depression on CAD. Similarly, smoking was a mediator in the causal pathway for depression, but not broad depression to MI. Thirdly, there was some evidence of causal association between depression and AF, but null for broad depression and AF. The above discrepancies may be largely attributed to the different definition of depression and broad depression cases (Supplementary Text 2), with depression definition slightly more homogeneous than that of broad depression. Moreover, only 14 independent SNPs were found to reach genome-wide significance in the GWAS of broad depression (n=322,580) (Howard *et al.*, 2018). The small number of genetic instruments may lead to the higher standard error in MR analysis.

Supplementary Text 4. Comparison of present study with previous MR publications

By bi-directional MR approach, the PGC used the summary statistics derived from their GWAS meta-analysis of MDD to evaluate the causal relationship between MDD and CAD (Wray *et al.*, 2018). Their MR analyses suggested insignificant causality in both directions. Whereas, our study provides robust evidence inferring causality of both depression phenotypes on CAD using genetic instruments derived from GWAS with increased sample size and power. Similarly, Howard *et al* made use of the results of their GWAS meta-analysis to conduct two-sample MR analyses to examine causality of depression on 24 other traits, and nine other traits on depression (Howard *et al.*, 2019). Their findings were indeed supportive on the presence of causal effects of depression on CAD (IVW test: beta=0.158; SE=0.057; $P=5.44x10^{-3}$), but they concluded there was no evidence of causal relationship after correction for multiple testing. Notably, they only used 58 out of the 102 independent SNPs and employed summary statistics derived from the meta-analysis including 23andme and UK Biobank participants (Howard *et al.*, 2019). Meanwhile, we identified proxies for the genetic variants and utilized a total of 89 (out of 102) genetic instruments explaining higher proportion for phenotypic variance. Our study and Howard *et al* utilized summary statistics from different genetic instruments derived from different subsets of participants but we still yielded consistent evidence on the causal effects of depression on CAD, implying robustness of the causality. On the other hand, a recent one-sample MR study in 367,703 unrelated UK Biobank participants demonstrated that coronary heart disease is not causally associated with probable lifetime major depression (Khandaker et al., 2019), which is consistent with our findings. Nevertheless, the study has not investigated the reverse causation of depression on coronary heart disease. Thus,

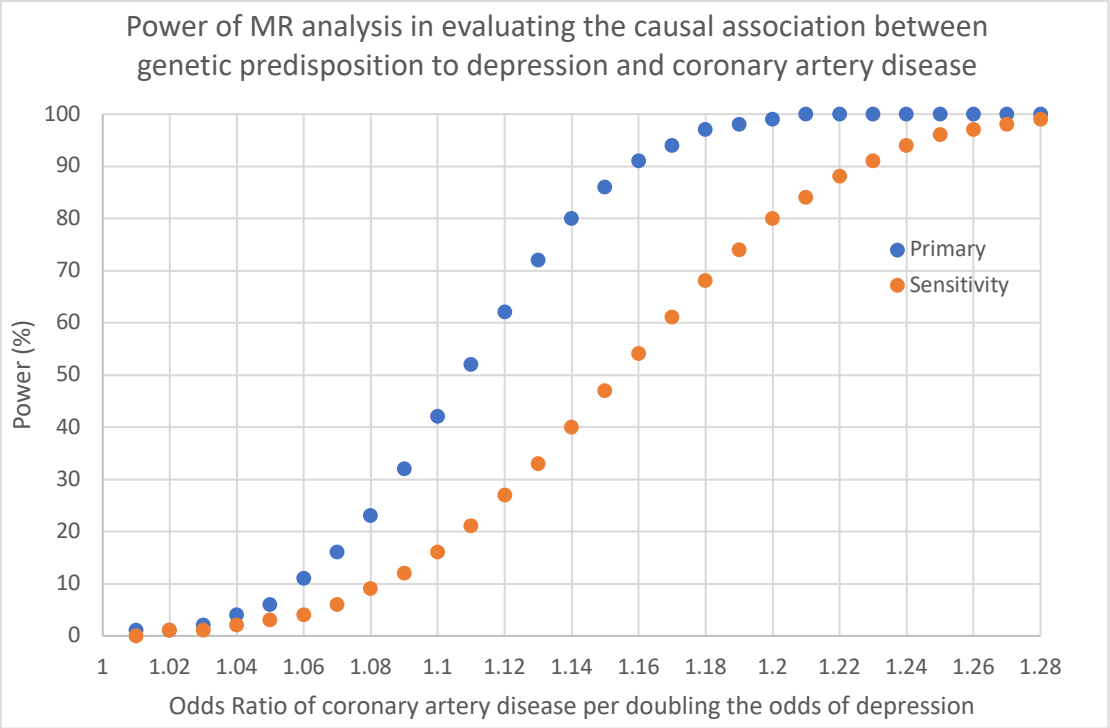
our study provides a complementary evidence that both depression phenotypes are causal factors of CAD and MI.

Supplementary Tables S1-S14. Large data files are uploaded to the following hyperlink for easy viewing:

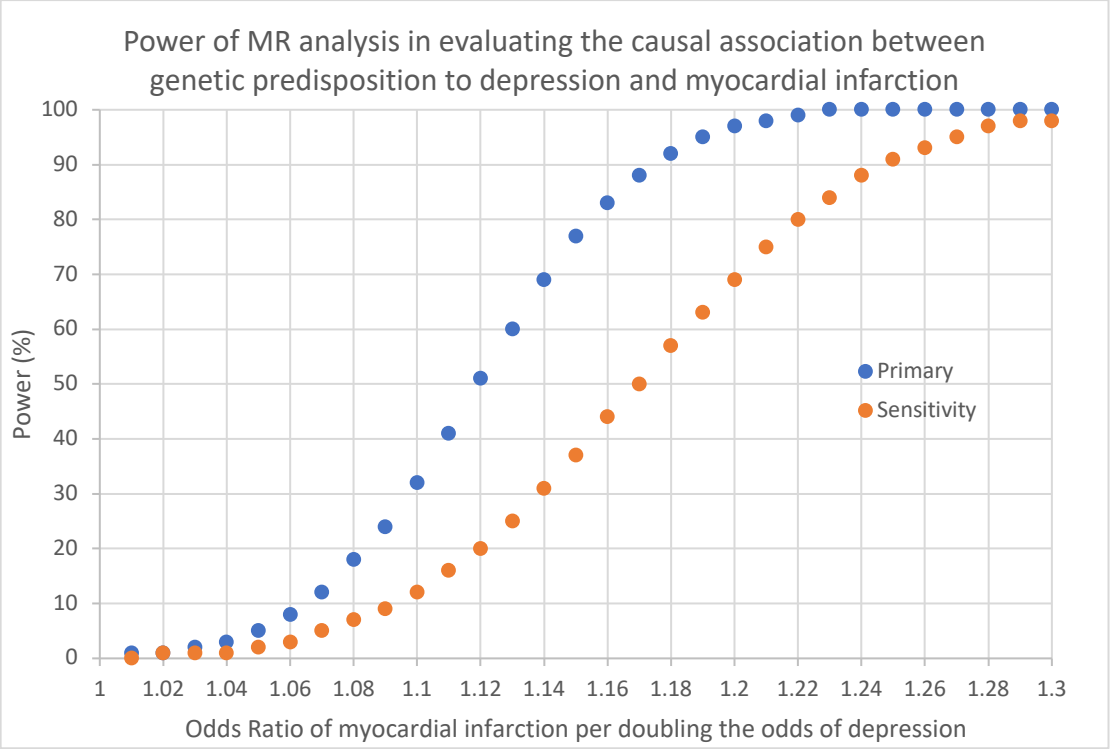
https://drive.google.com/file/d/1FMhKHW9ussaRahOAPK0NLvZHL3P10x4k/view?usp=sharing

Supplementary Figure S1. Power calculation of MR analyses.

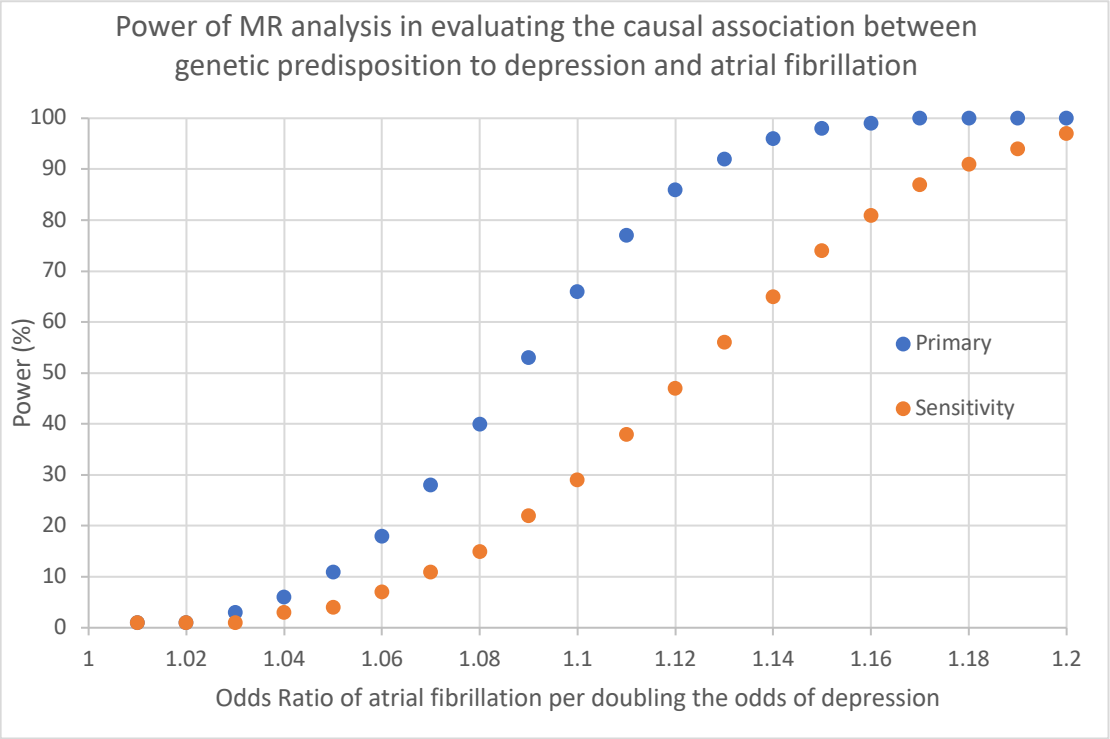
(a) Power of MR analysis in evaluating the causal association between genetic predisposition to depression and CAD.



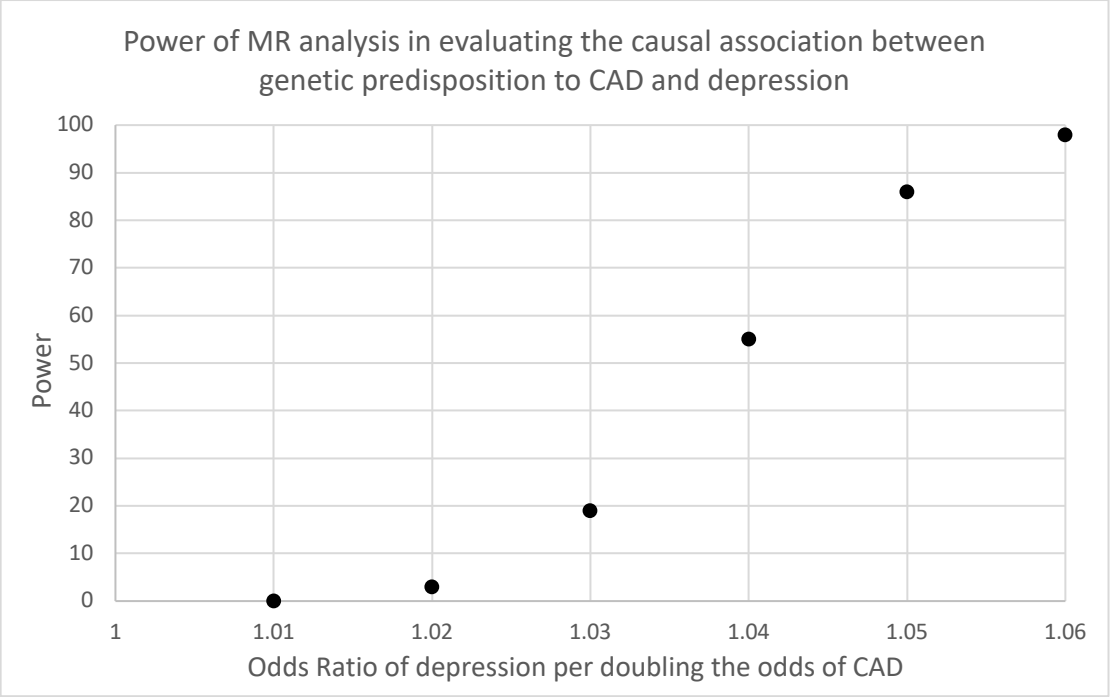
(b) Power of MR analysis in evaluating the causal association between genetic predisposition to depression and MI.



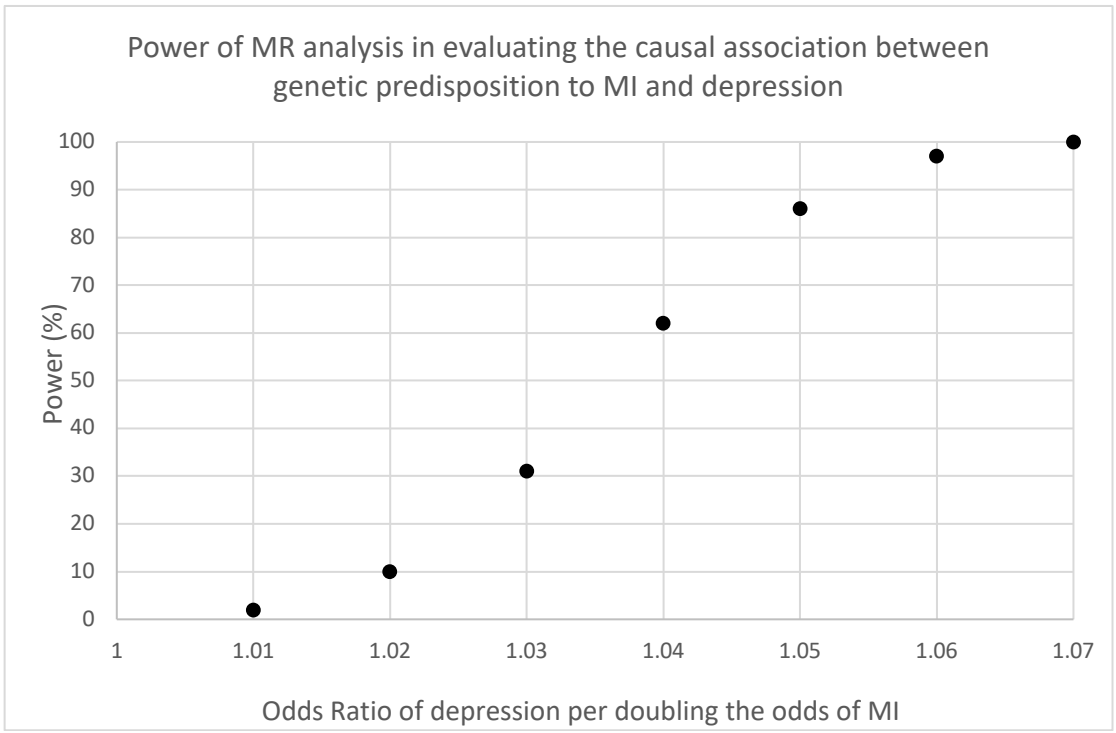
(c) Power of MR analysis in evaluating the causal association between genetic predisposition to depression and AF.



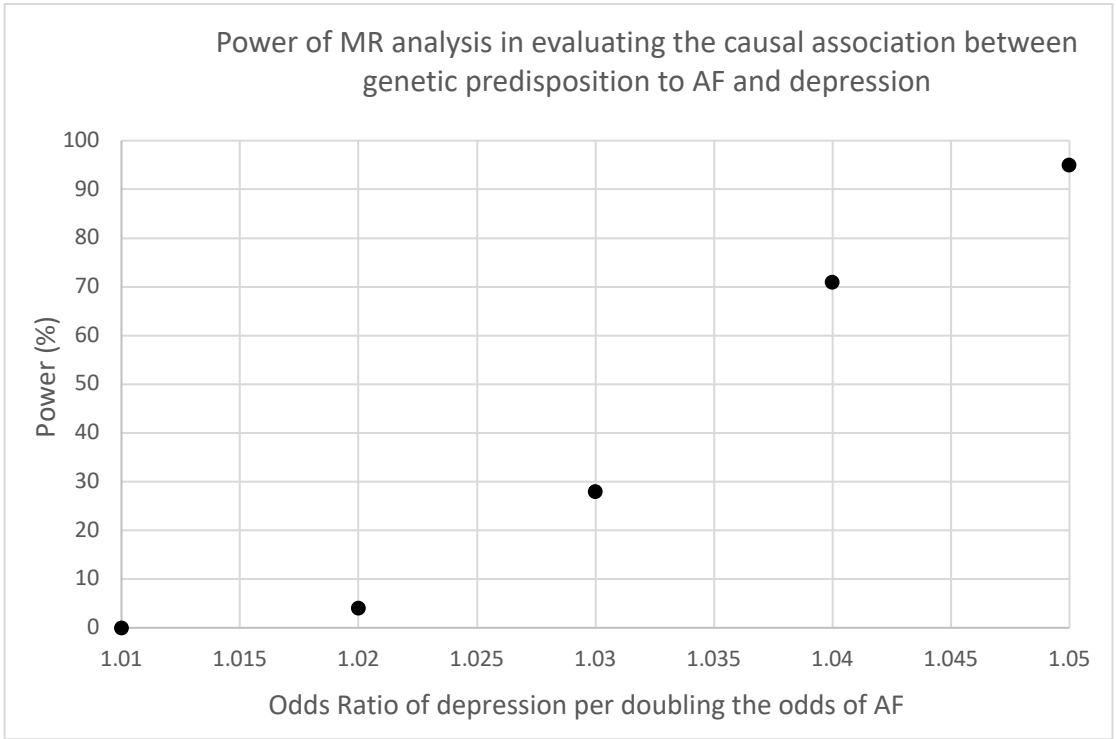
(d) Power of MR analysis in evaluating the causal association between genetic predisposition to CAD and depression.



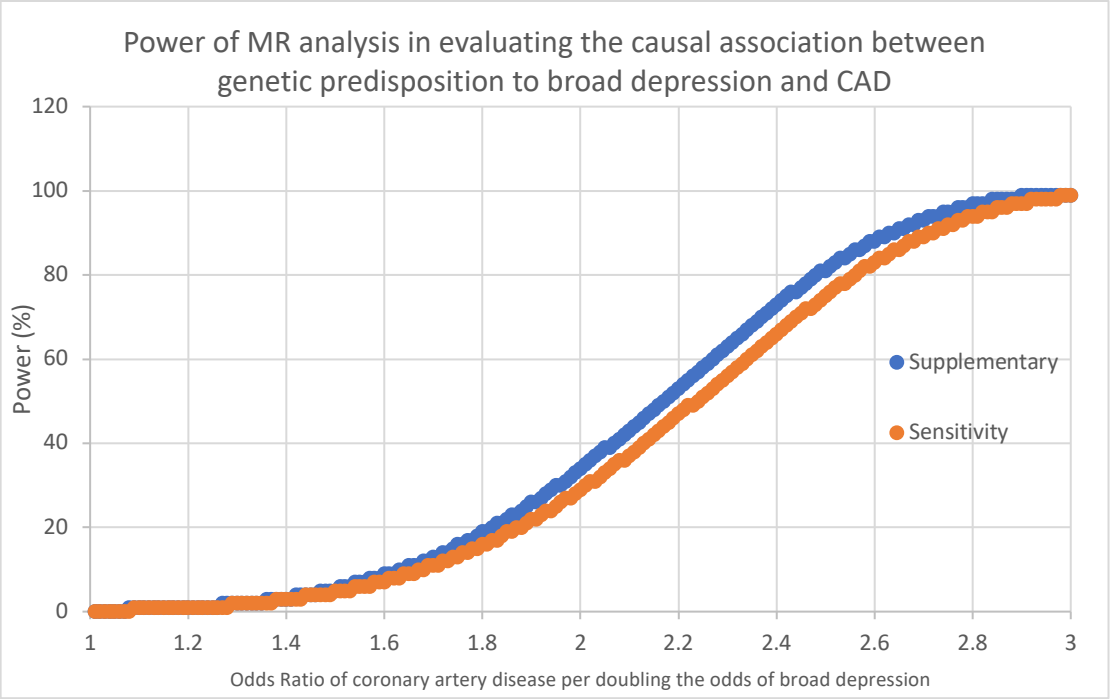
(e) Power of MR analysis in evaluating the causal association between genetic predisposition to MI and depression.



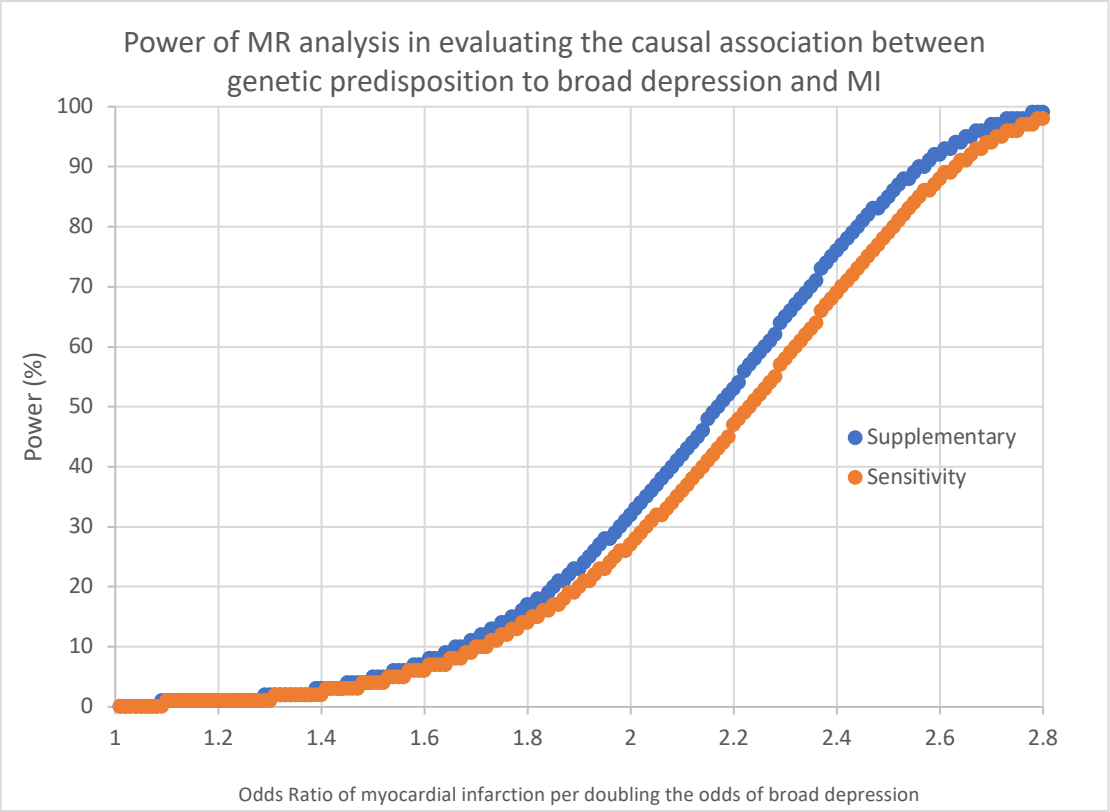
(f) Power of MR analysis in evaluating the causal association between genetic predisposition to AF and depression.



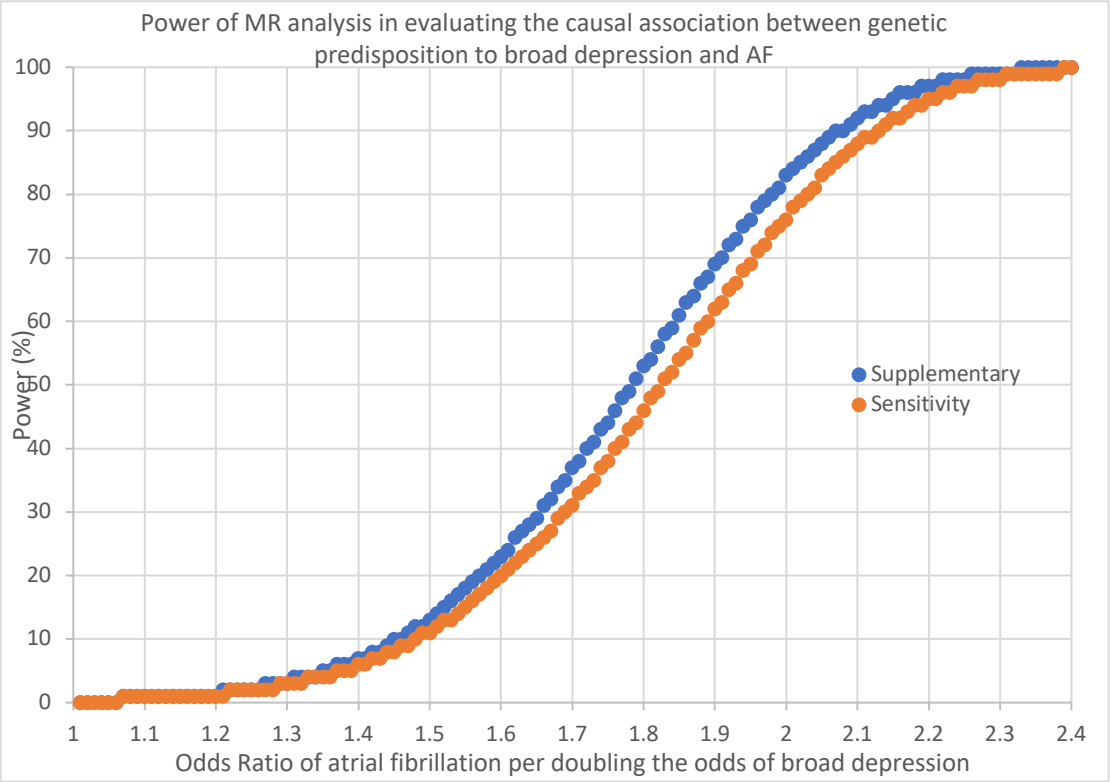
(g) Power of MR analysis in evaluating the causal association between genetic predisposition to broad depression and CAD.



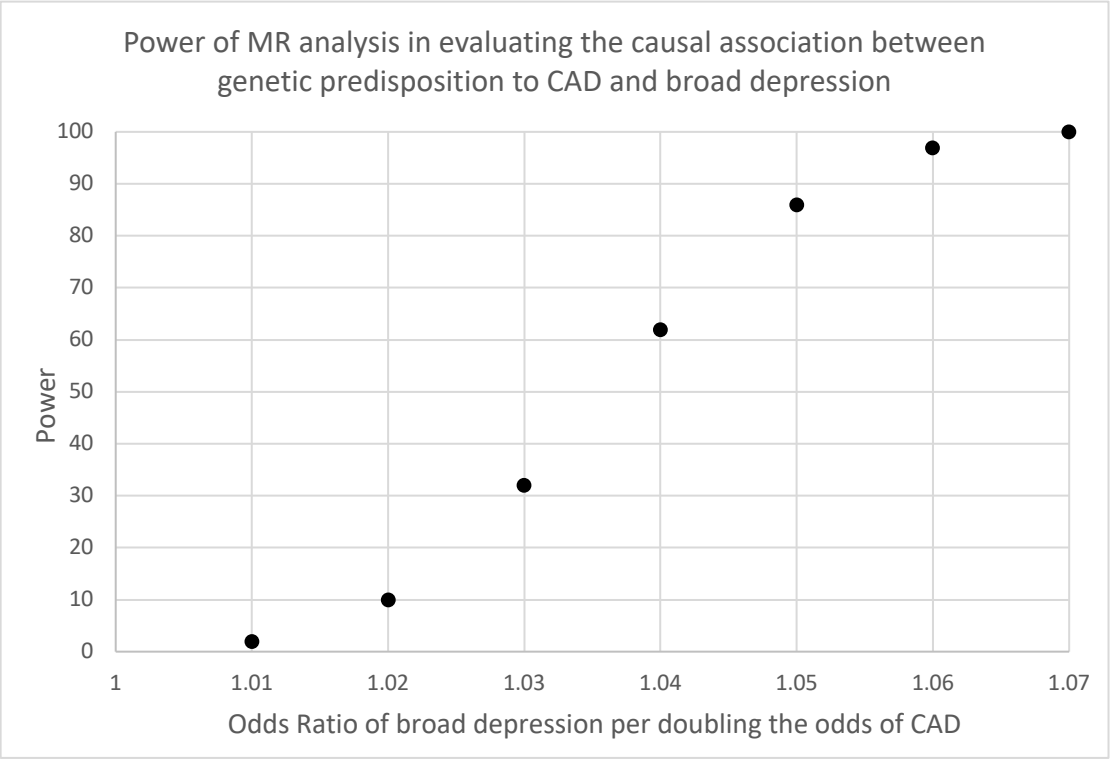
(h) Power of MR analysis in evaluating the causal association between genetic predisposition to broad depression and MI.



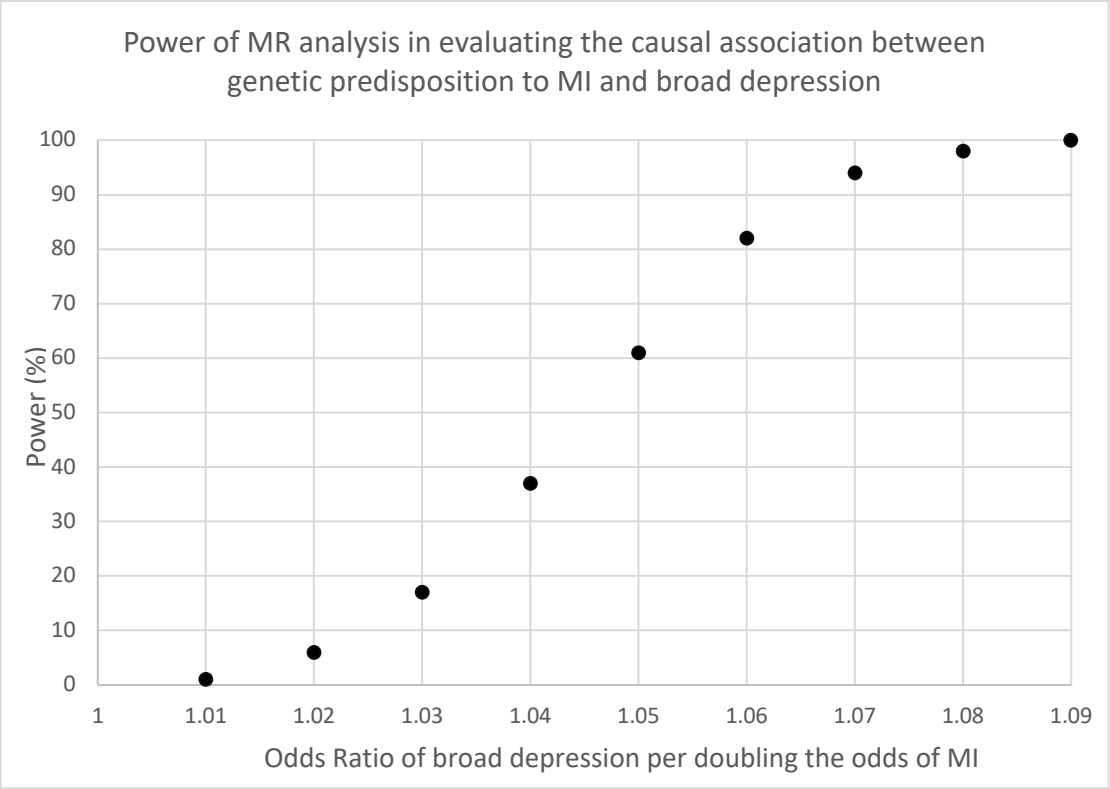
(i) Power of MR analysis in evaluating the causal association between genetic predisposition to broad depression and AF.



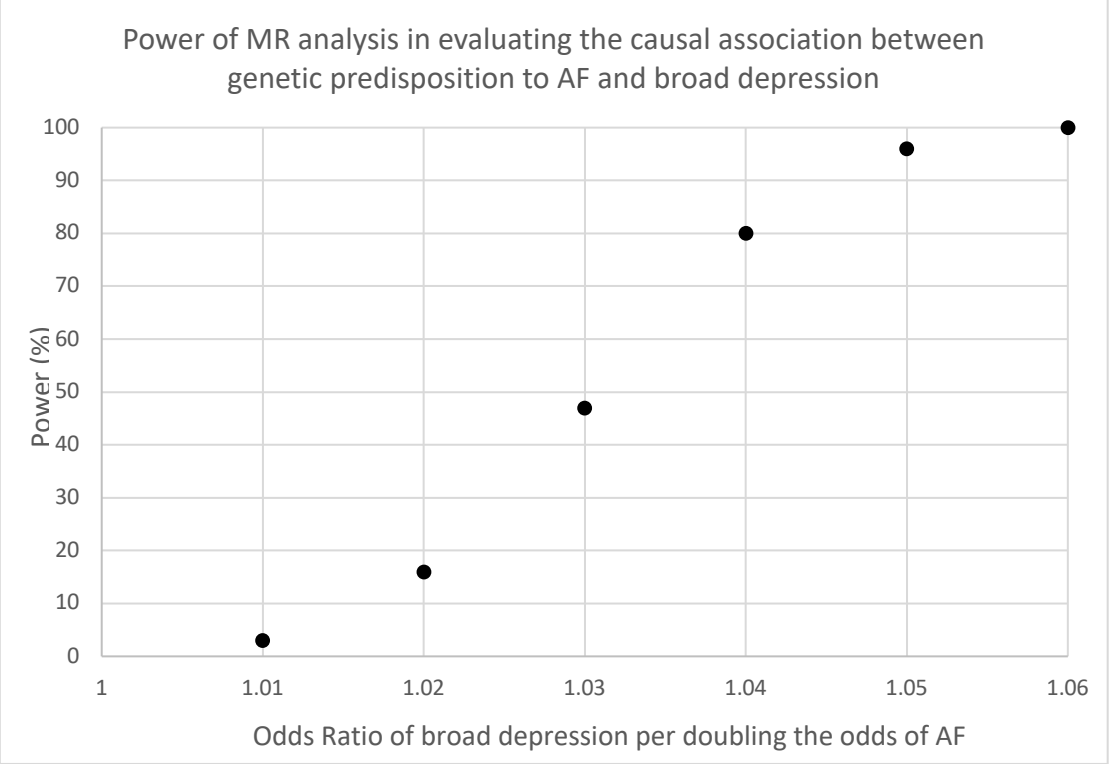
(j) Power of MR analysis in evaluating the causal association between genetic predisposition to CAD and broad depression.



(k) Power of MR analysis in evaluating the causal association between genetic predisposition to MI and broad depression.

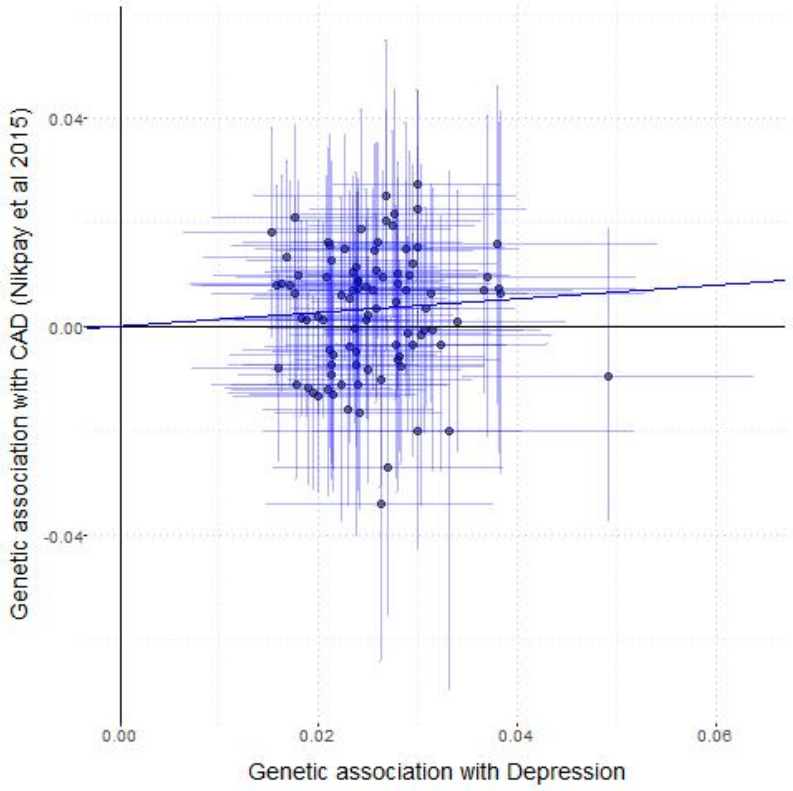


(l) Power of MR analysis in evaluating the causal association between genetic predisposition to AF and broad depression.

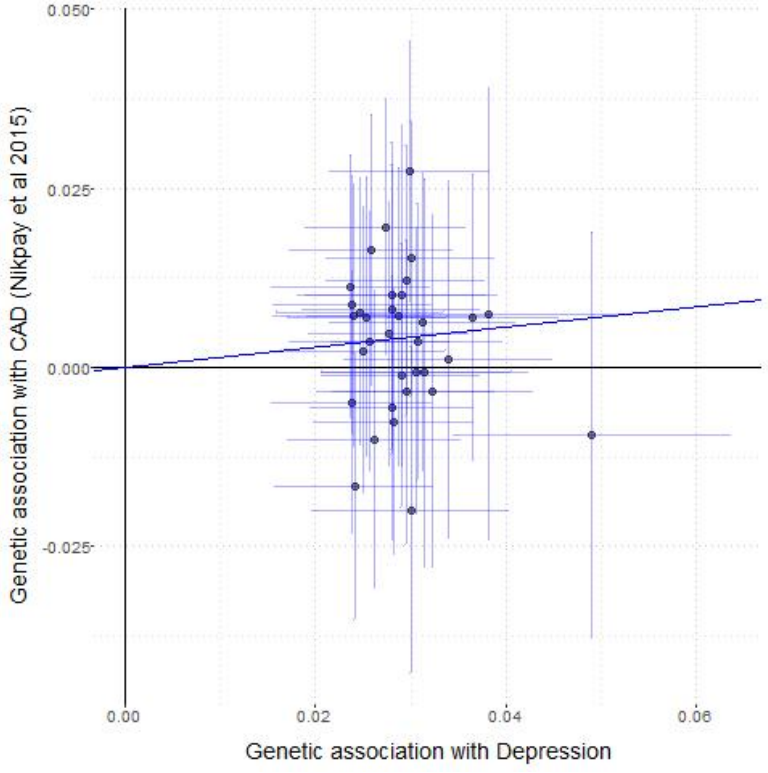


Supplementary Figure S2. Scatter plot of potential effects of genetic instruments on depression versus their effects on coronary artery disease.

(a) Primary analysis using all 93 genetic instruments

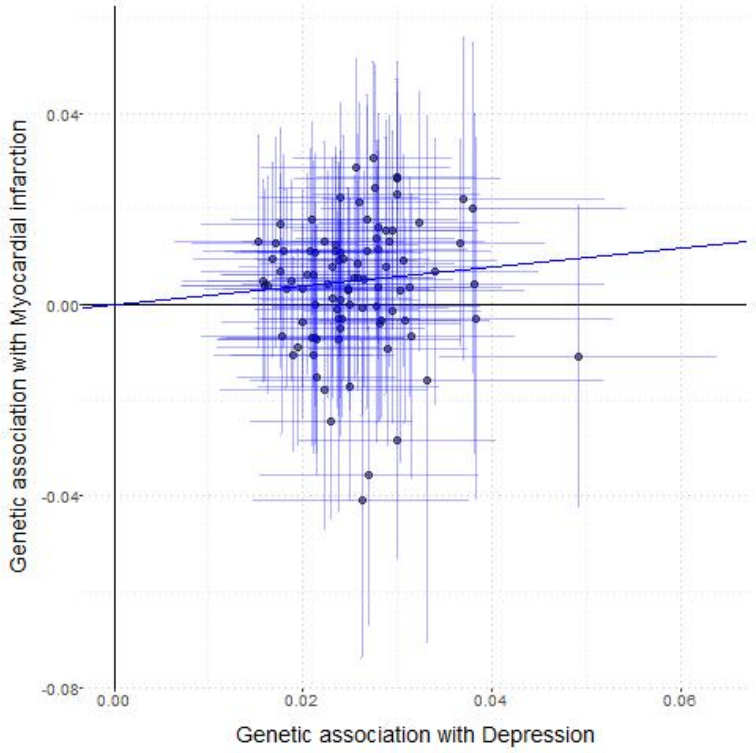


(b) Sensitivity analysis using 34 genetic instruments which remained genome-wide significant in the reduced sample after excluding samples from 23andme cohort

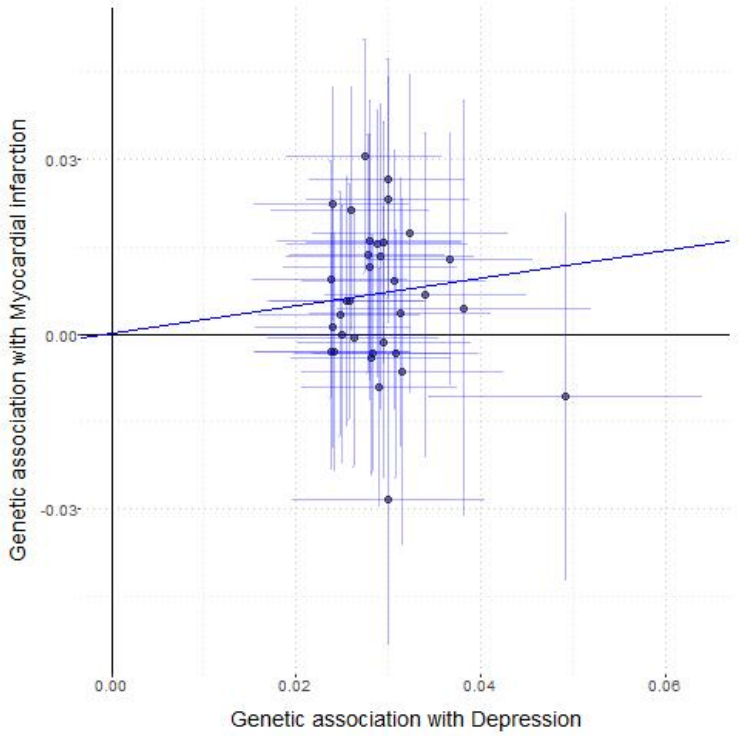


Supplementary Figure S3. Scatter plot of potential effects of genetic instruments on depression versus their effects on myocardial infarction.

(a) Primary analysis using all 93 genetic instruments

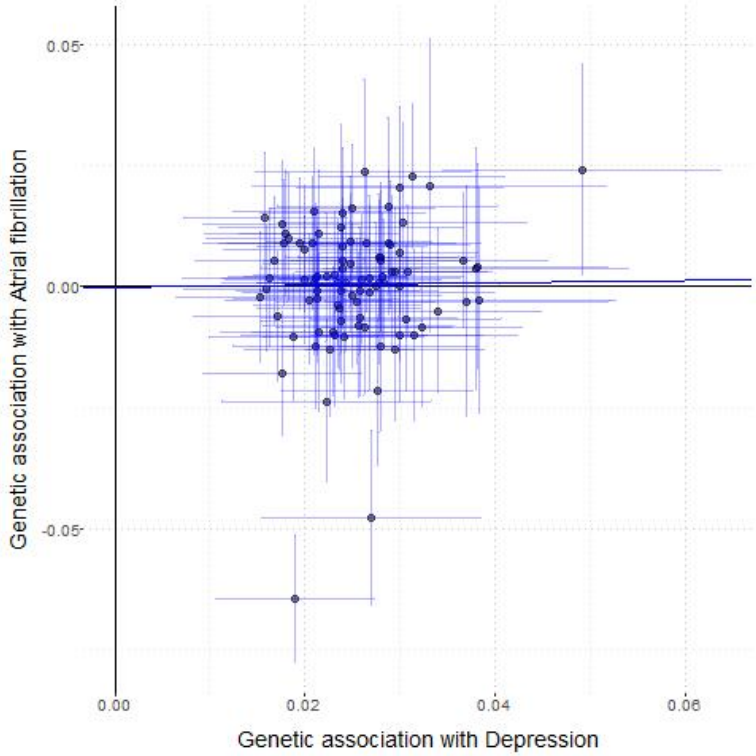


(b) Sensitivity analysis using 34 genetic instruments which remained genome-wide significant in the reduced sample after excluding samples from 23andme cohort

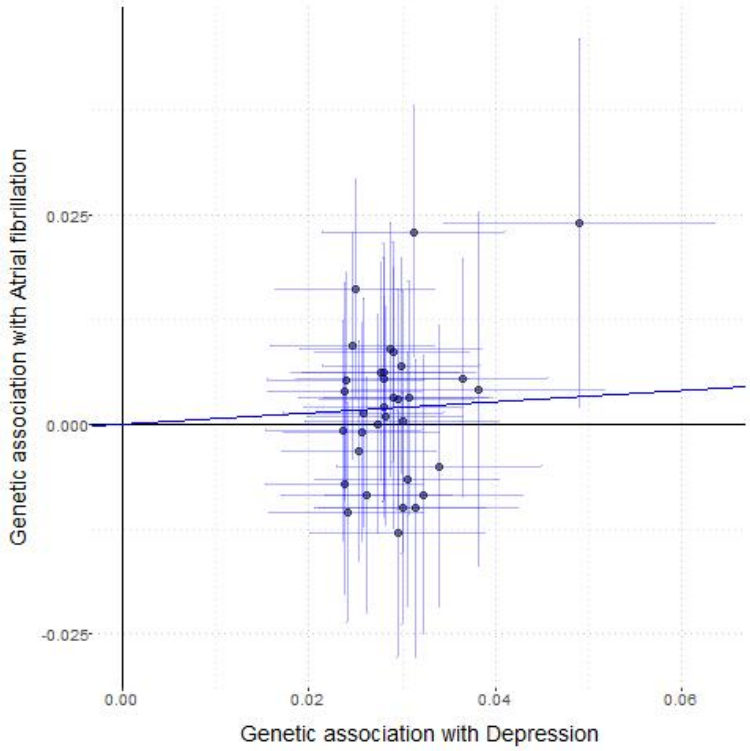


Supplementary Figure S4. Scatter plot of potential effects of genetic instruments on depression versus their effects on atrial fibrillation.

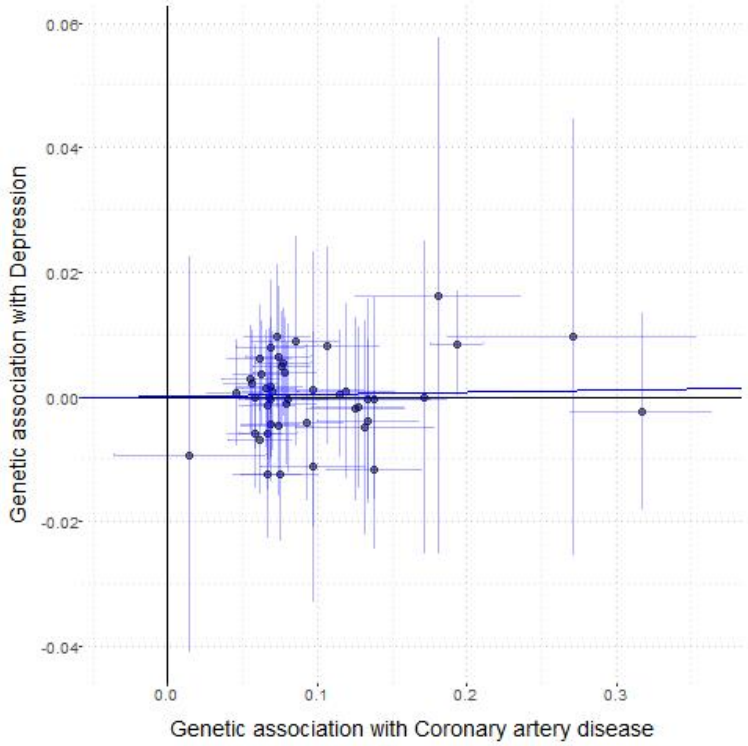
(a) Primary analysis using all 93 genetic instruments



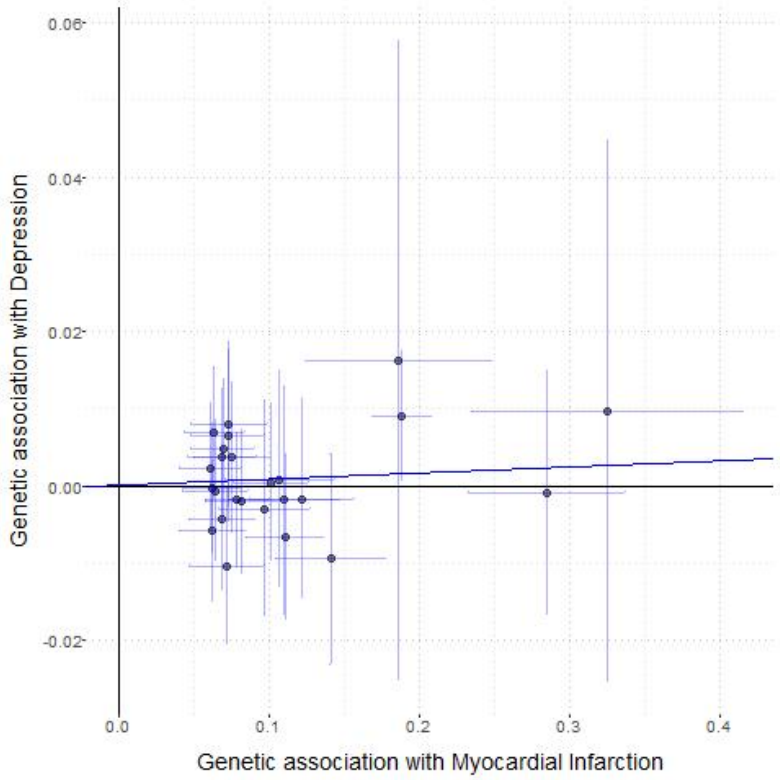
(b) Sensitivity analysis using 34 genetic instruments which remained genome-wide significant in the reduced sample after excluding samples from 23andme cohort



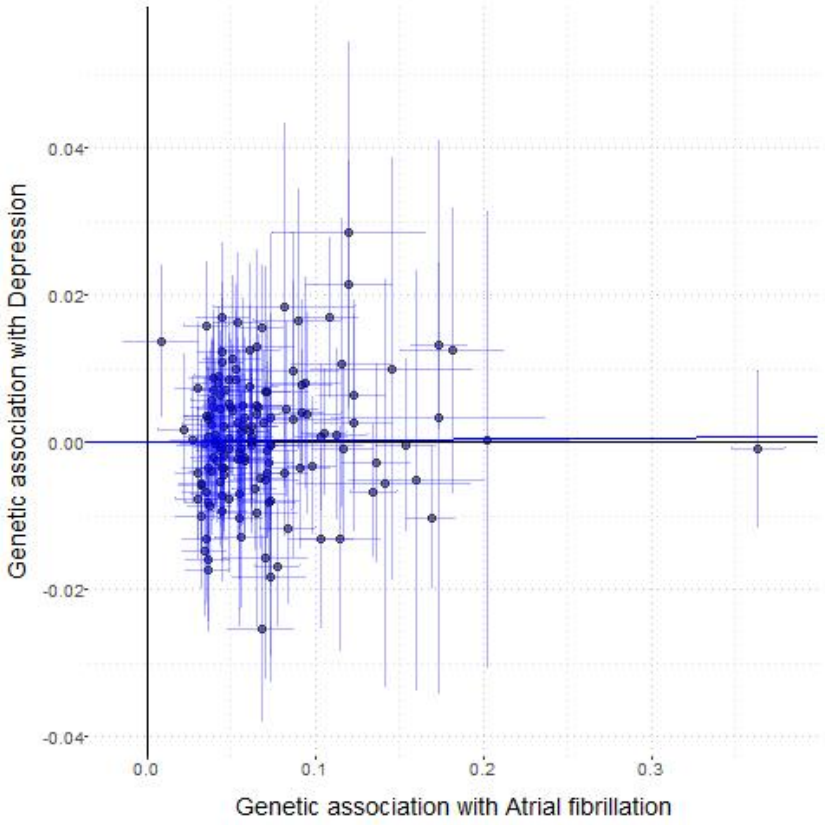
Supplementary Figure S5. Scatter plot of potential effects of genetic instruments on CAD versus their effects on depression.



Supplementary Figure S6. Scatter plot of potential effects of genetic instruments on myocardial infarction versus their effects on depression.

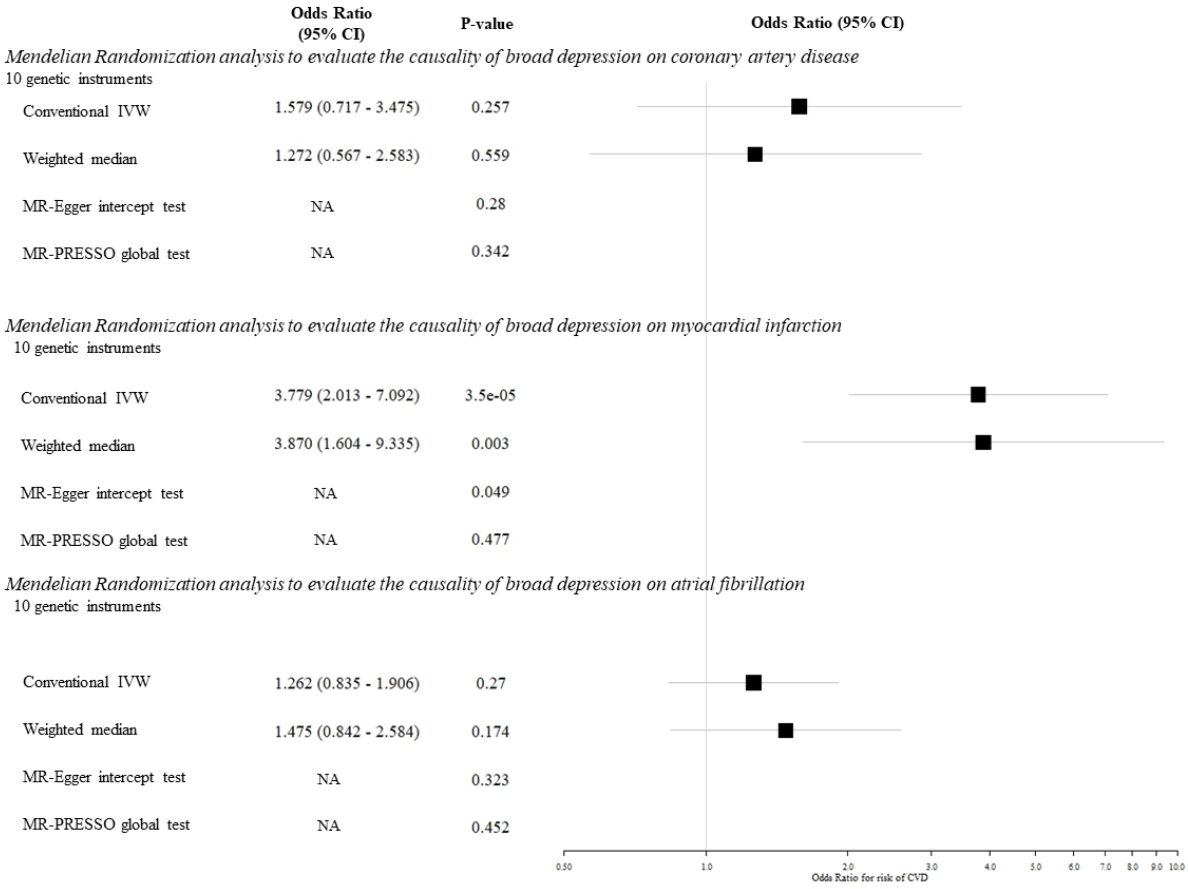


Supplementary Figure S7. Scatter plot of potential effects of genetic instruments on atrial fibrillation versus their effects on depression.

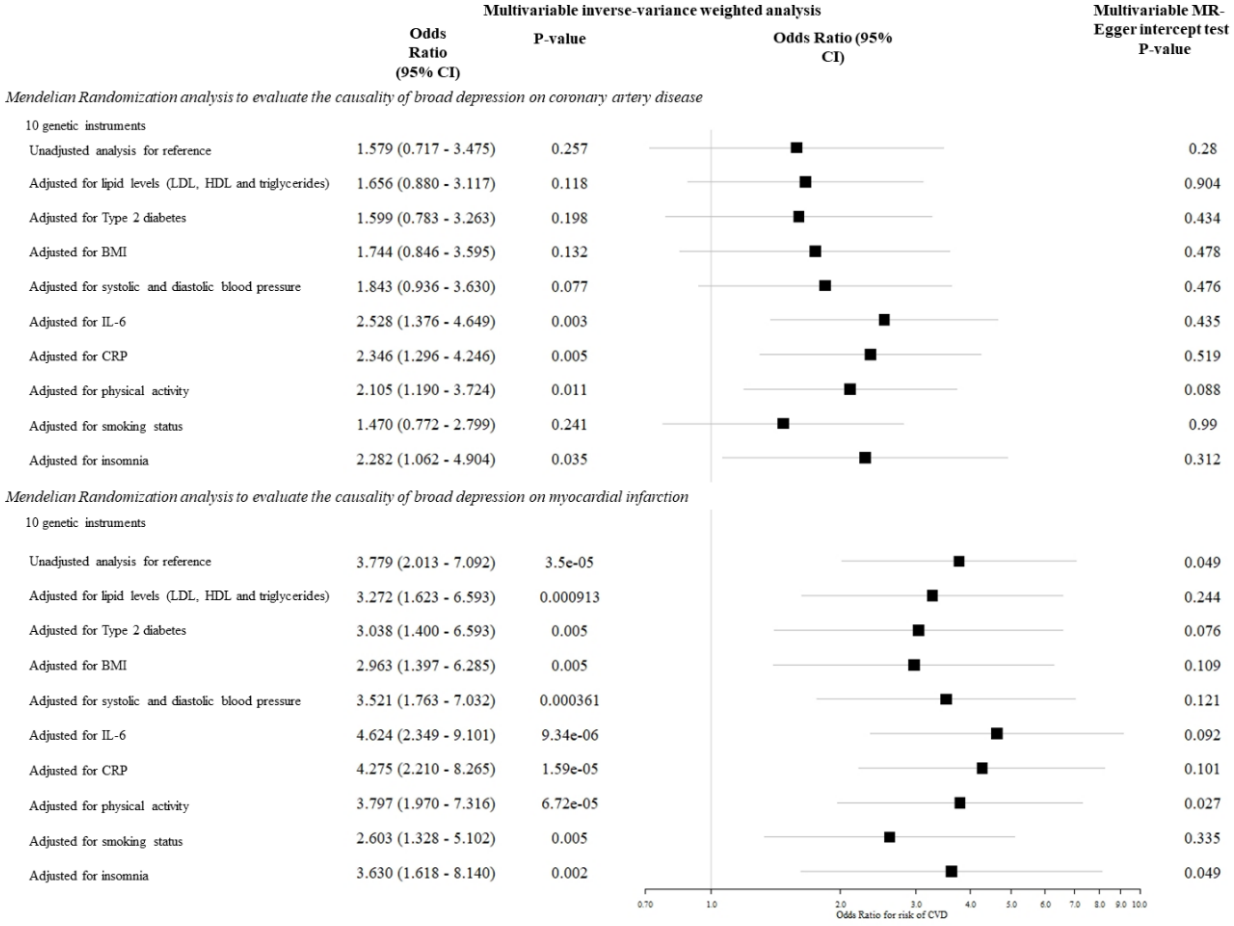


Supplementary Figure S8. Result of Mendelian Randomization analysis in evaluating the causal association between broad depression and various cardiovascular diseases.

(a) Causal estimates for various CVD (in odds ratio) per doubling of the odds of broad depression in univariable MR analysis.

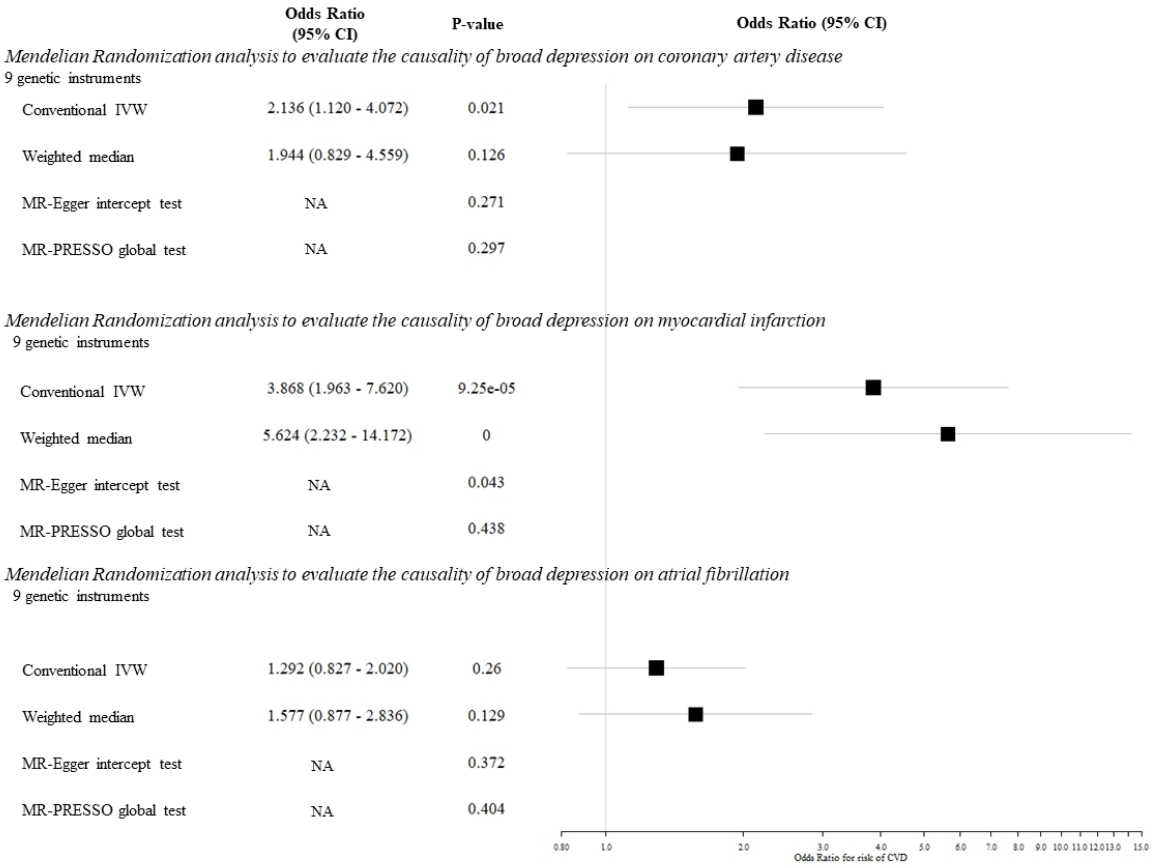


(b) Causal estimates for various CVD (in odds ratio) per doubling of the odds of broad depression in multivariable MR analysis

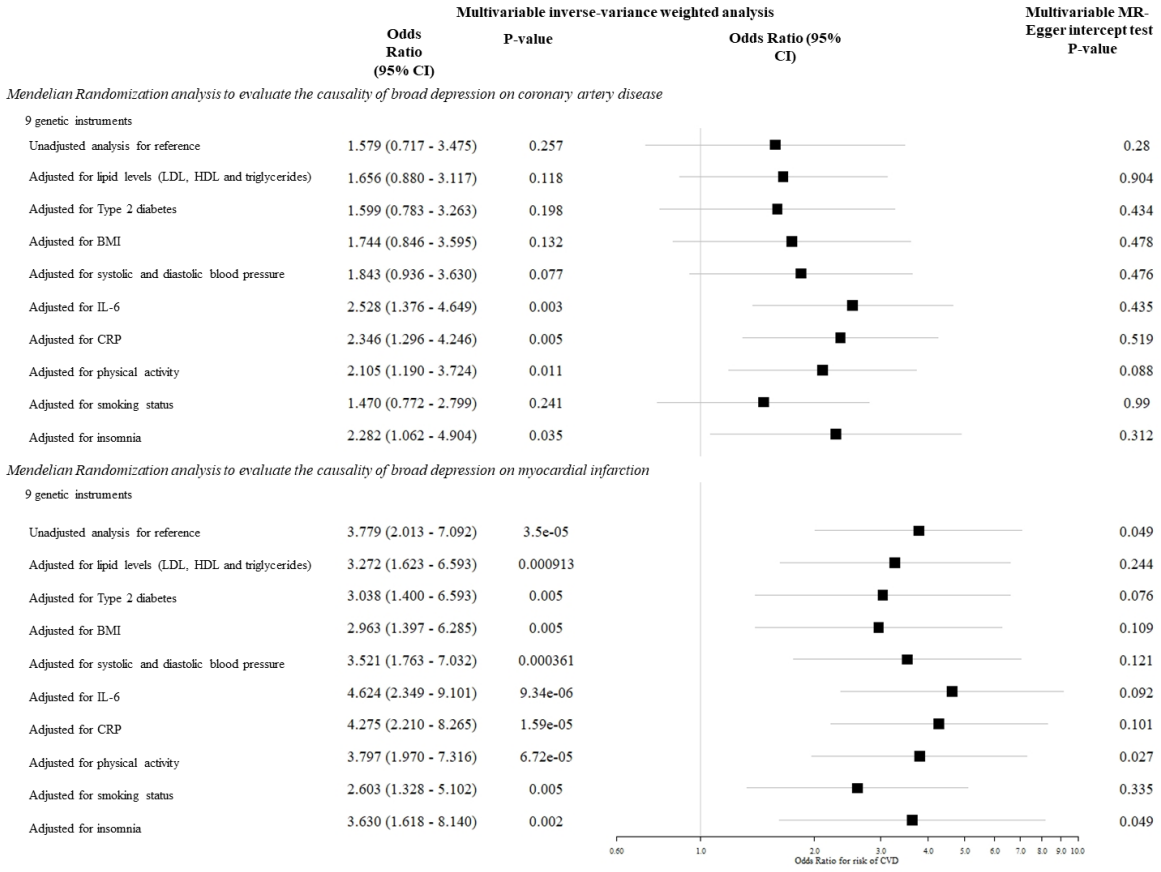


Supplementary Figure S9. Sensitivity analysis result in evaluating the causal association between broad depression and various CVD after excluding proxies which were not genome-wide significant.

(a) Causal estimates for various CVD (in odds ratio) per doubling of the odds of broad depression in univariable MR analysis.

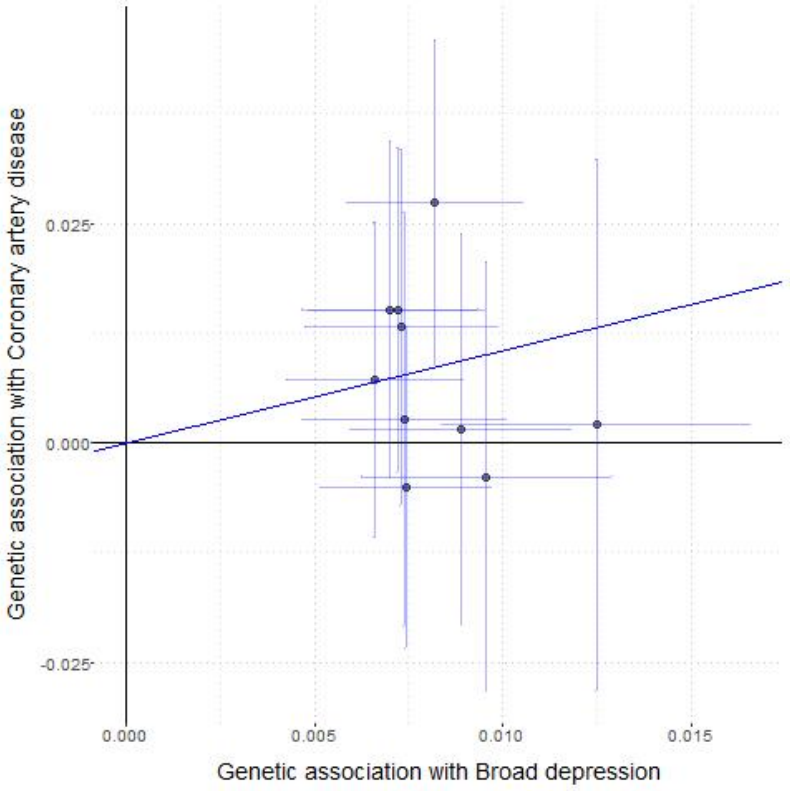


(b) Causal estimates for various CVD (in odds ratio) per doubling of the odds of broad depression in multivariable MR analysis.

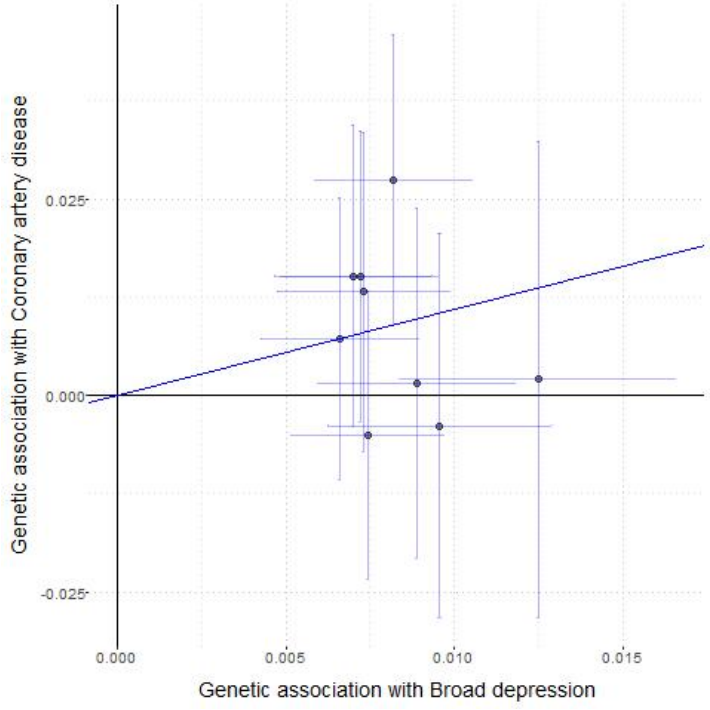


Supplementary Figure S10. Scatter plot of potential effects of genetic instruments on broad depression versus their effects on coronary artery disease.

(a) Analysis using 10 genetic instruments

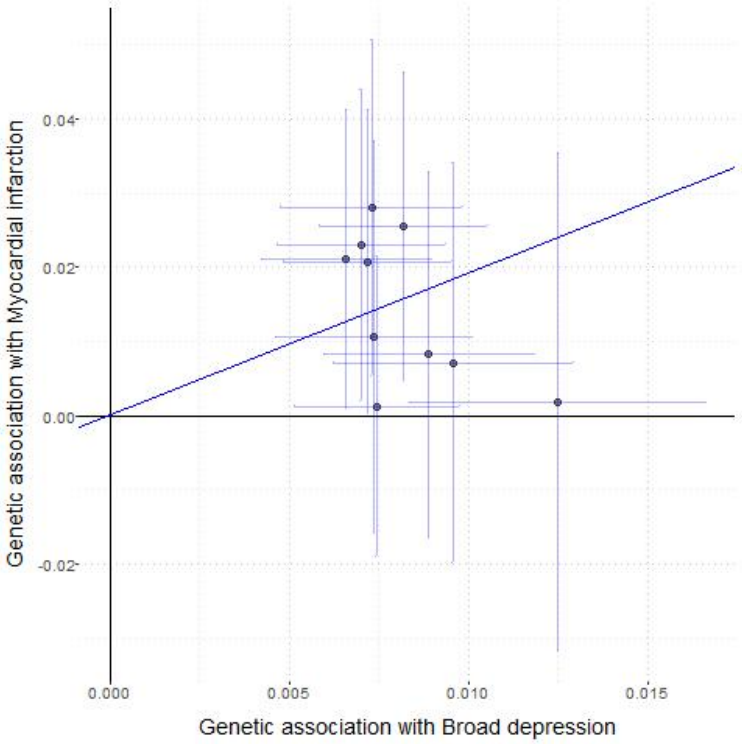


(b) Sensitivity analysis using 9 genetic instruments after excluding 1 proxy which did not reach genome-wide significance with broad depression

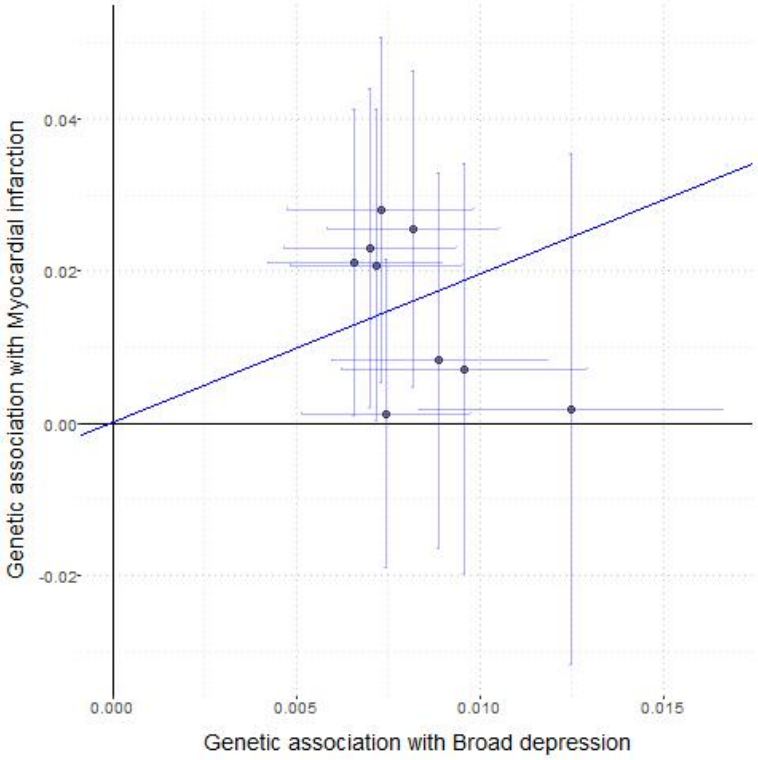


Supplementary Figure S11. Scatter plot of potential effects of genetic instruments on broad depression versus their effects on myocardial infarction.

(a) Analysis using 10 genetic instruments

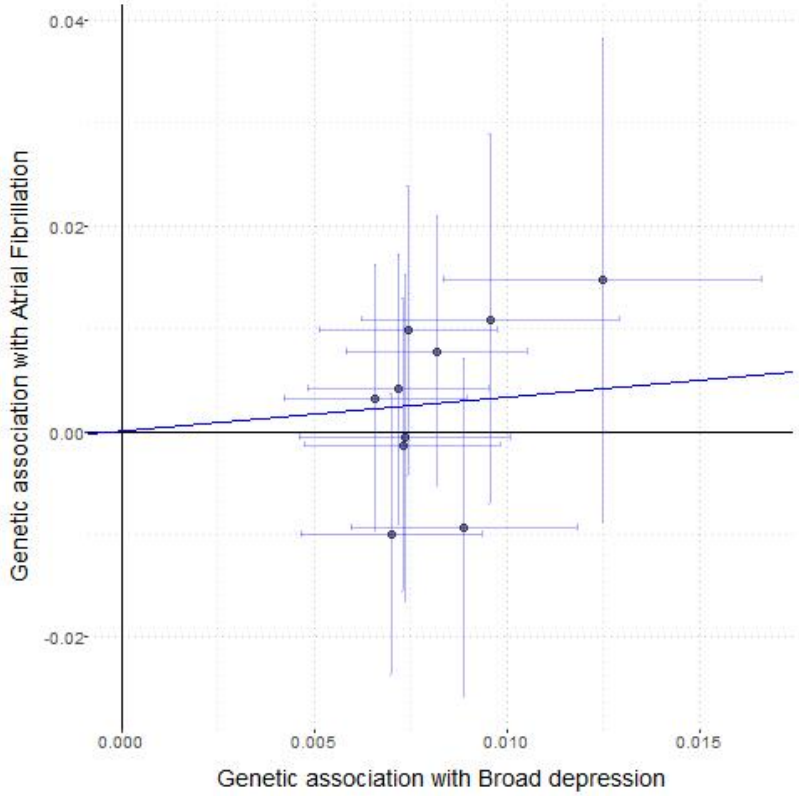


(b) Sensitivity analysis using 9 genetic instruments after excluding 1 proxy which did not reach genome-wide significance with broad depression

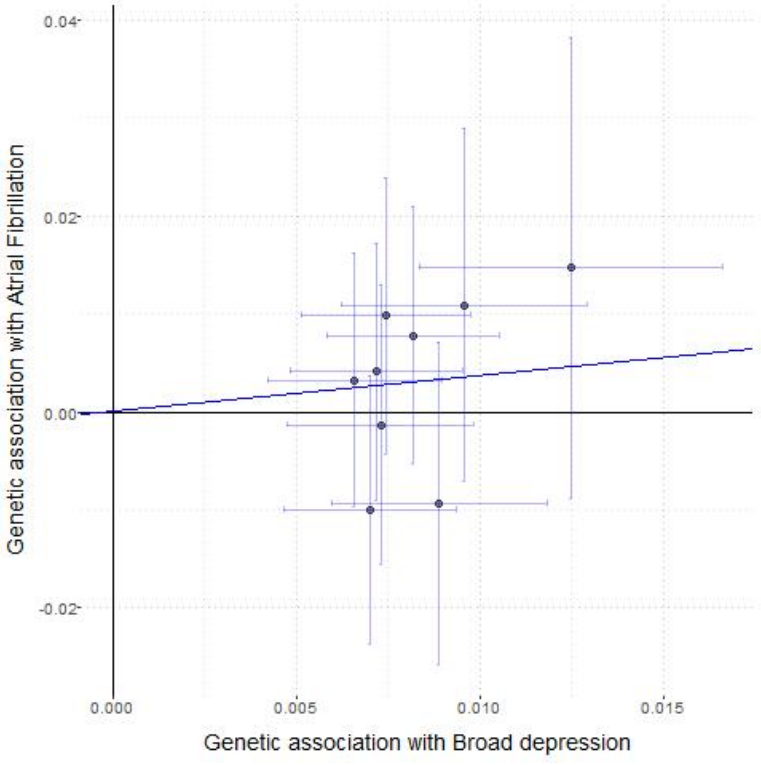


Supplementary Figure S12. Scatter plot of potential effects of genetic instruments on broad depression versus their effects on atrial fibrillation.

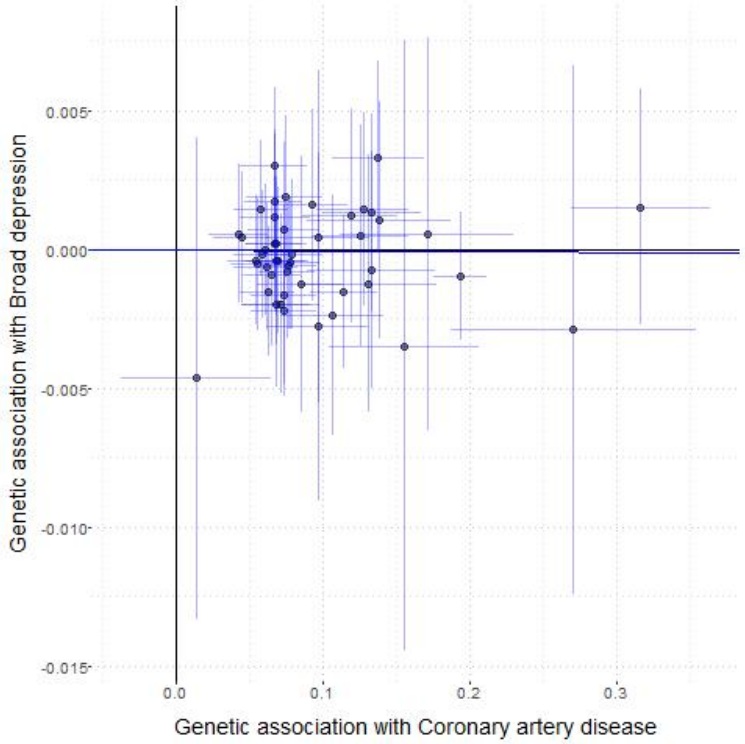
(a) Analysis using 10 genetic instruments



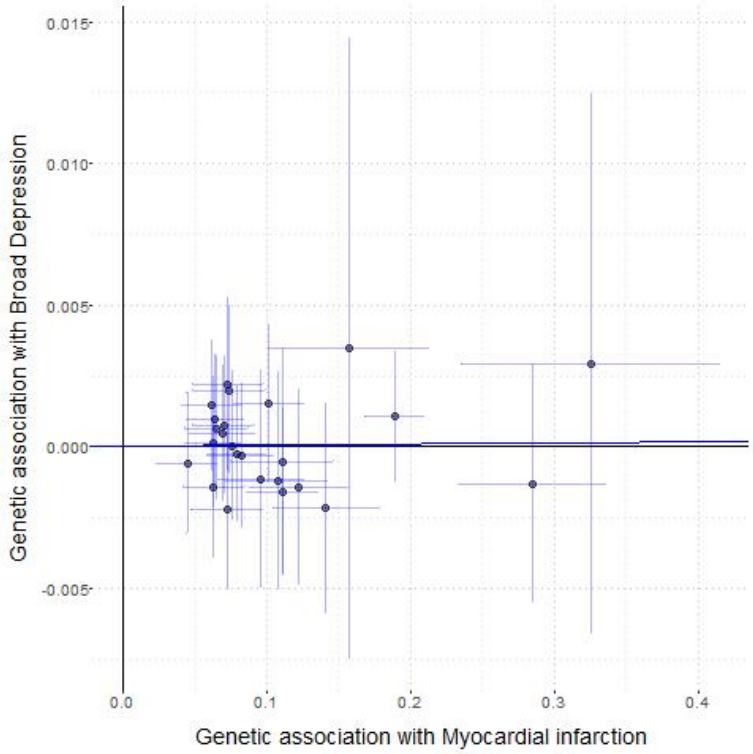
(b) Sensitivity analysis using 9 genetic instruments after excluding 1 proxy which did not reach genome-wide significance with broad depression



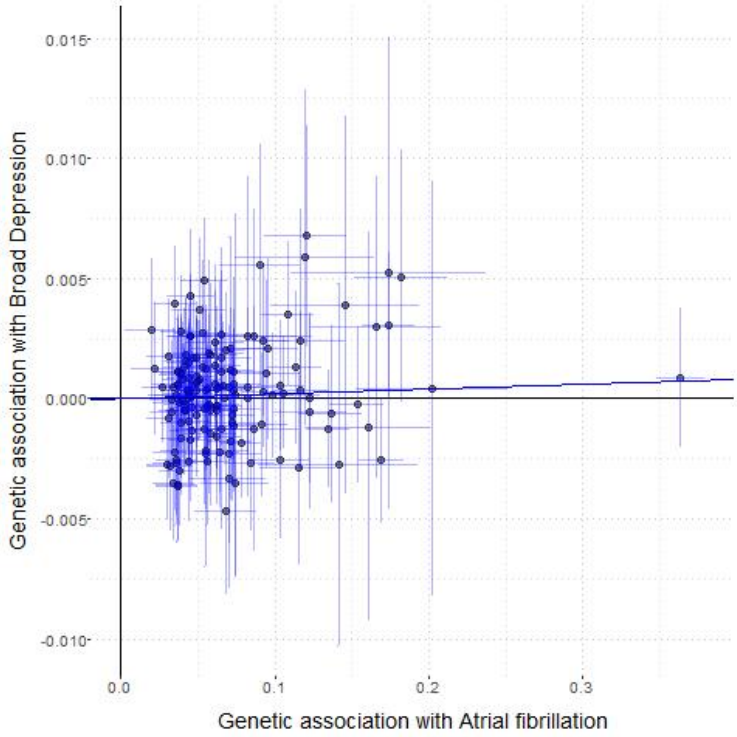
Supplementary Figure S13. Scatter plot of potential effects of genetic instruments on CAD versus their effects on broad depression.



Supplementary Figure S14. Scatter plot of potential effects of genetic instruments on myocardial infarction versus their effects on broad depression.



Supplementary Figure S15. Scatter plot of potential effects of genetic instruments on atrial fibrillation versus their effects on broad depression.



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