

Supplementary Table S1. Assessment of bias due to sample overlap

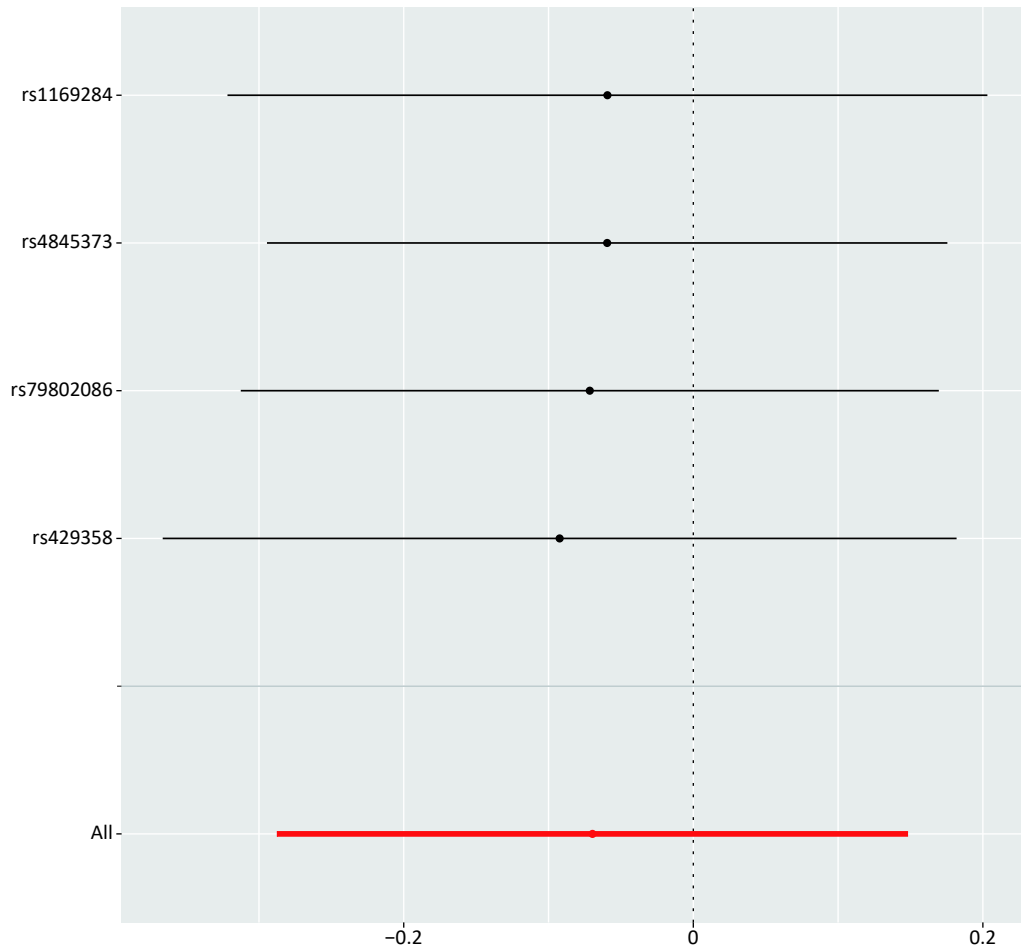
Outcome	Observational estimate	Sample size	Proportion of cases	Overlap proportion	Type 1 error rate	Bias
Ischemic stroke	1.46 ^a	210,054	0.084	0.5	0.050	0.011
Arrhythmia	2.02 ^b	212,453	0.084	0.5	0.050	0.015
Atrial fibrillation	2.02 ^b	36,792	0.222	0.5	0.050	0.015
Congestive heart failure	2.64 ^c	212,453	0.044	0.5	0.050	0.020

Note. ^aRefer to Zhou Y, Han W, Gong D, et al. Hs-CRP in stroke: A meta-analysis. *Clin Chim Acta*, 2016; 453, 21–7. ^bRefer to Kwon CH, Kang JG, Lee HJ, et al. C-reactive protein and risk of atrial fibrillation in East Asians. *Europace*, 2017; 19, 1643–9. ^cRefer to Kardys I, Knetsch AM, Bleumink GS, et al. C-reactive protein and risk of heart failure. The Rotterdam Study. *American Heart Journal*, 2006; 152, 514–20.

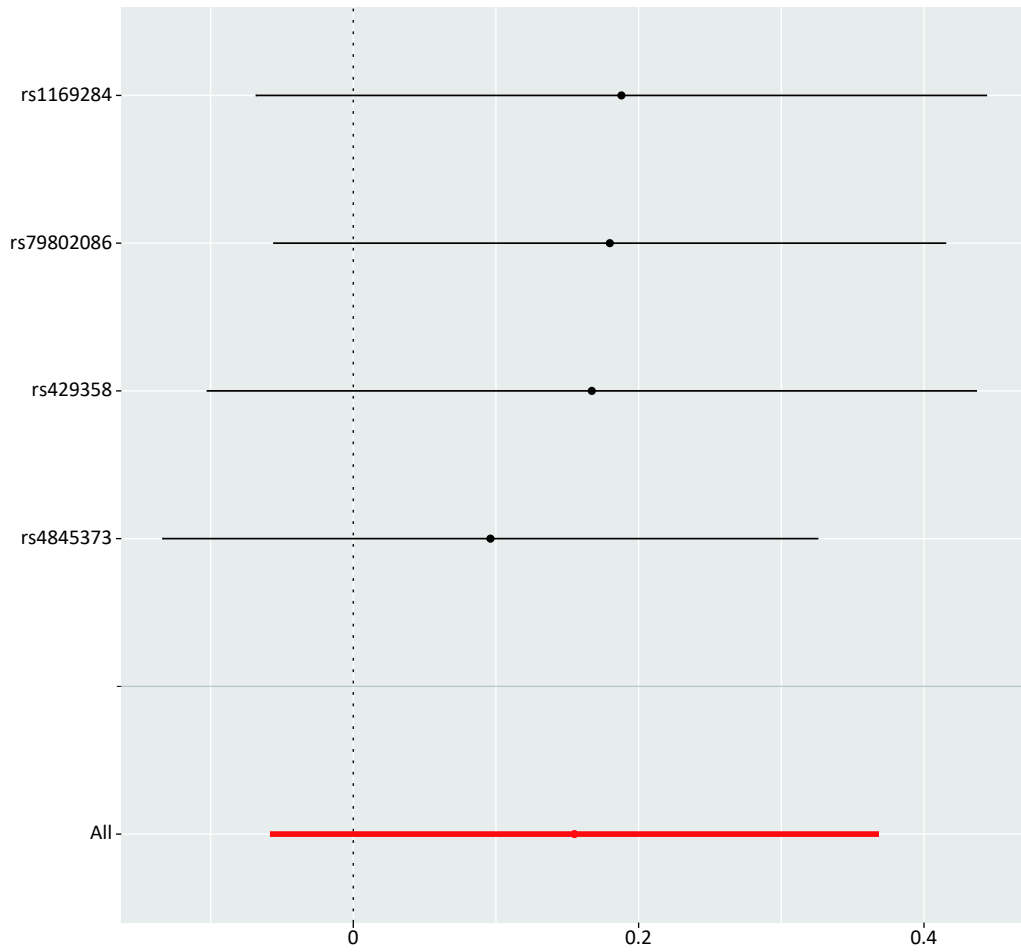
Supplementary Table S2. MR-Egger intercepts and heterogeneity tests of CRP causally linked to four cardiovascular outcomes

Outcome	SNP (N)	Intercept	P^a	Cochran's Q	Q_df	P^b
Ischemic stroke	4	-0.006	0.785	0.104	3	0.991
Atrial fibrillation	4	-0.044	0.532	6.064	3	0.109
Arrhythmia	4	0.016	0.505	1.924	3	0.588
Congestive heart failure	4	0.022	0.511	1.672	3	0.643

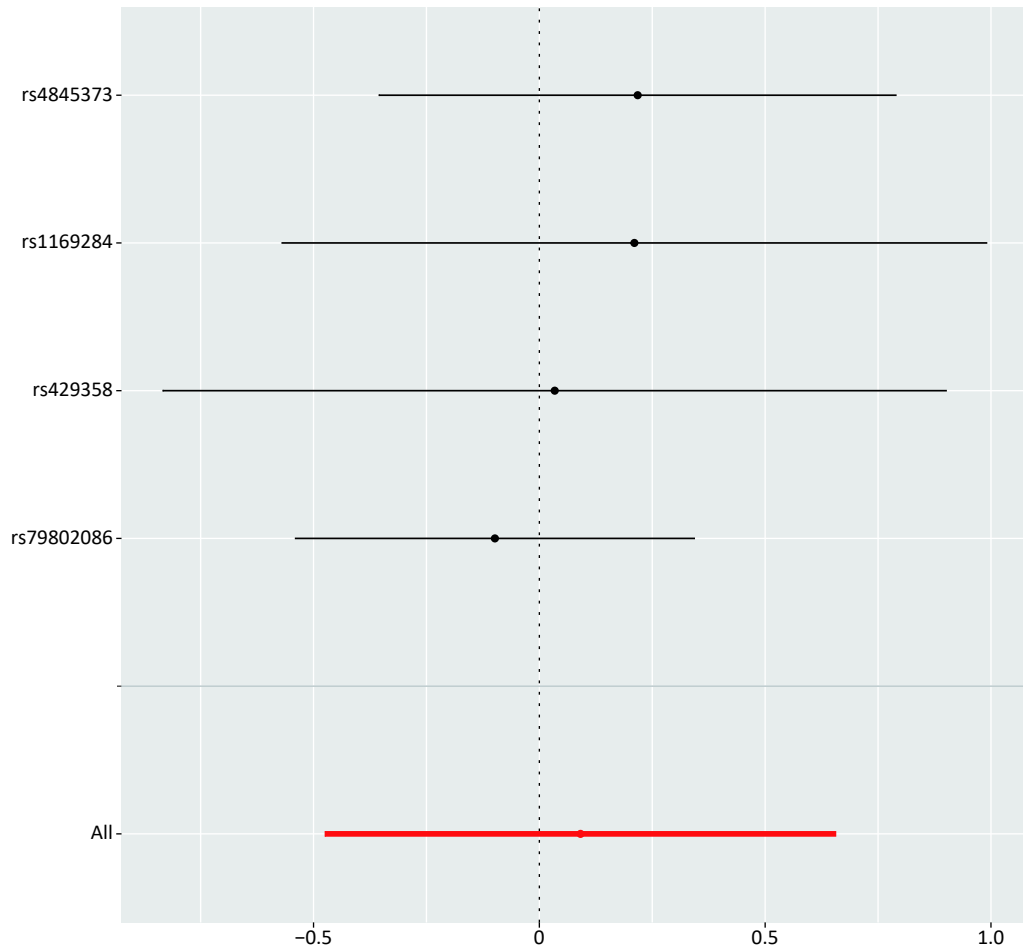
Note. P^a is the value of P for MR-Egger intercept. P^b is the value of P for heterogeneity tests by performing inverse-variance weighted method. CRP, C-reactive protein; CVDs, Cardiovascular diseases; SNP, single-nucleotide polymorphism; MR, Mendelian randomization.



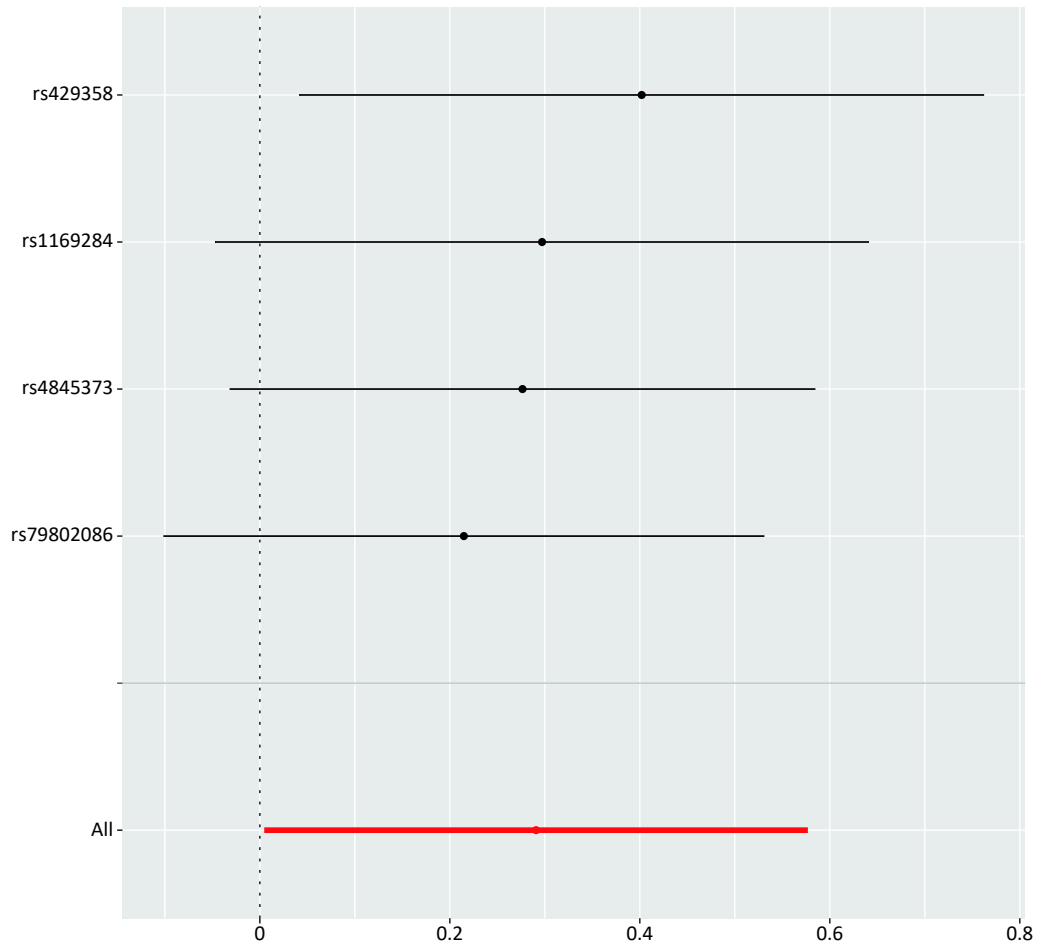
Supplementary Figure S1. MR leave-one-out sensitivity analysis of the effect of C-reactive protein on ischemic stroke. Leave-one-out analysis: each row represents an MR analysis of the effect of CRP on ischemic stroke, using all instruments except for the SNP associated with CRP listed on the y-axis. The point represents the beta with that SNP removed, and the line represents the 95% confidence interval.



Supplementary Figure S2. MR leave-one-out sensitivity analysis of the effect of C-reactive protein on arrhythmia. Leave-one-out analysis: each row represents an MR analysis of the effect of CRP on arrhythmia, using all instruments except for the SNP associated with CRP listed on the y-axis. The point represents the beta with that SNP removed, and the line represents the 95% confidence interval.



Supplementary Figure S3. MR leave-one-out sensitivity analysis of the effect of C-reactive protein on atrial fibrillation. Leave-one-out analysis: each row represents an MR analysis of the effect of CRP on atrial fibrillation, using all instruments except for the SNP associated with CRP listed on the y-axis. The point represents the beta with that SNP removed, and the line represents the 95% confidence interval.



Supplementary Figure S4. MR leave-one-out sensitivity analysis of the effect of C-reactive protein on congestive heart failure. Leave-one-out analysis: each row represents an MR analysis of the effect of CRP on congestive heart failure, using all instruments except for the SNP associated with CRP listed on the y-axis. The point represents the beta with that SNP removed, and the line represents the 95% confidence interval.