

# Supplementary Material

## Causal Relationship between PECAM-1 Level and Cardiovascular Diseases: A Mendelian Randomization Study

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**Supplemental Table 1.** Detailed characteristics of SNPs for PECAM-1 reached genome-wide significance

SNP	CHR	BP	EA	OA	EAF	BETA	SE	P-value	N	R2	F statistic
rs1354034	3	56849749	t	c	0.3911	-0.0513	0.0099	2.04E-07	21758	1.23E-03	27
rs138841709	9	136303891	c	g	0.0245	-0.3168	0.0386	2.28E-16	21758	3.09E-03	67
rs181224696	9	135611974	a	g	0.0479	0.1768	0.0349	3.07E-07	21758	1.20E-03	26
rs35434910	9	136042324	a	t	0.2247	-0.2023	0.0121	1.53E-62	21758	1.27E-02	279
rs615477	9	135987017	t	c	0.1656	-0.0736	0.0139	1.26E-07	21758	1.29E-03	28
rs77137587	11	126228258	a	t	0.9043	-0.0807	0.0146	3.63E-08	21758	1.40E-03	31

Abbreviations: CHR, chromosome. EA, effect allele. EAF, effect allele frequency. OA, other allele. R<sup>2</sup>, explained variation by SNPs. SE, standard error. SNPs, Single-nucleotide polymorphisms.

**Supplemental Table 2.** Evidence of association ( $p < 5 \times 10^{-6}$ ) of the SNPs used as genetic variants for Mendelian randomization analyses of PECAM-1 with confounders or CVDs in the PhenoScanner and the GWAS catalog.

SNP	CHR	Position	Disease and trait	Excluded from MR analysis
rs1354034	3	56849749	High light scatter percentage of red cells (PMID:27863252); High light scatter reticulocyte count (PMID:27863252); Lymphocyte count (PMID:27863252); Lymphocyte percentage of white cells (PMID:27863252); Mean platelet volume (PMID:2786352); Neutrophil percentage of white cells (PMID:27863252); Platelet count (PMID:27863252); Plateletcrit (PMID:27863252); Reticulocyte count (PMID:27863252); Reticulocyte fraction of red cells (PMID:27863252); Red blood cell count, Hemoglobin concentration, Mean corpuscular hemoglobin, Mean corpuscular volume, White blood cell count (PMID:23263863); Blood protein levels (PMID:28240269)	NO
rs138841709	9	136303891	Red blood cell count (PMID:27863252); Blood clot in the leg (UKBB); Bronchitis, emphysema, asthma, rhinitis, eczema or allergy diagnosed by doctor (UKBB); Self-reported deep venous thrombosis (UKBB)	NO
rs181224696	9	135611974	Zoster (UKBB); Red blood cell count (PMID:27863252); Red cell distribution width (PMID:27863252)	NO
rs35434910	9	136042324	Hematocrit (PMID:27863252); Hemoglobin concentration (PMID:27863252); Phlebitis and thrombophlebitis (UKBB)	NO
rs615477	9	135987017	High light scatter percentage of red cells (PMID:27863252)	NO
rs77137587	11	126228258	Mean Platelet volume (PMID:27863252)	NO

Abbreviations: CHR, chromosome. MR, mendelian randomization. SNP, Single-nucleotide polymorphisms. UKBB, UK biobank.

**Supplemental Table 3.** Directional Heterogeneity test for the Mendelian randomization analysis.

Exposure	Outcomes	SNP selection	Cochran's Q	Degrees of Freedom	P-value
PECAM-1	Coronary artery disease	All	4.551	5	0.4731
	Myocardial infarction	All	4.3538	5	0.4997
	Atrial fibrillation	All	2.7631	5	0.7365
	Heart failure	All	3.5143	5	0.6212
	Hypertension	All	2.0906	5	0.8365
	Ischemia stroke	All	6.1386	5	0.293

Cardioembolic stroke	All	5.7868	5	0.3275
Large artery stroke	All	3.4519	5	0.6307
Small vessel stroke	All	11.3487	5	0.0449

Abbreviations: CHR, chromosome. MR, mendelian randomization. SNPs, Single nucleotide polymorphisms frequency.

**Supplemental Table 4.** MR-Egger pleiotropy test for all SNPs included in Mendelian randomization.

outcomes	SNPs	MR-Egger		MR-Egger-intercept		I <sup>2</sup> <sub>CG</sub>
		OR (95% CI)	P-value	OR (95% CI)	P-value	
Coromary artery disease	6	0.741 (0.621-0.885)	0.0009	1.017 (0.996-1.039)	0.1168	0.9765
Myocardial infarction	6	0.685 (0.562-0.834)	0.0001	1.021 (0.997-1.046)	0.8817	0.9772
Atrial fibrillation	6	1.023 (0.908-1.152)	0.7092	1.007 (0.992-1.022)	0.3582	0.9801
Heart failure	6	0.854 (0.743-0.983)	0.0275	1.01 (0.992-1.028)	0.2638	0.9789
Hypertension	6	1.111 (0.809-1.526)	0.5143	0.985 (0.949-1.023)	0.4481	0.9783
Cardioembolic stroke	6	0.796 (0.662-0.957)	0.1502	1.021 (0.998-1.044)	0.7535	0.9786
Ischemia stroke	6	0.784 (0.546-1.124)	0.1859	1.036 (0.992-1.083)	0.1109	0.9793
Large artery stroke	6	0.691 (0.438-1.089)	0.1116	1.028 (0.971-1.087)	0.3456	0.9786
Small vessel stroke	6	0.833 (0.414-1.679)	0.6101	1.018 (0.933-1.111)	0.6839	0.9797

Abbreviations: SNPs, Single-nucleotide polymorphisms.

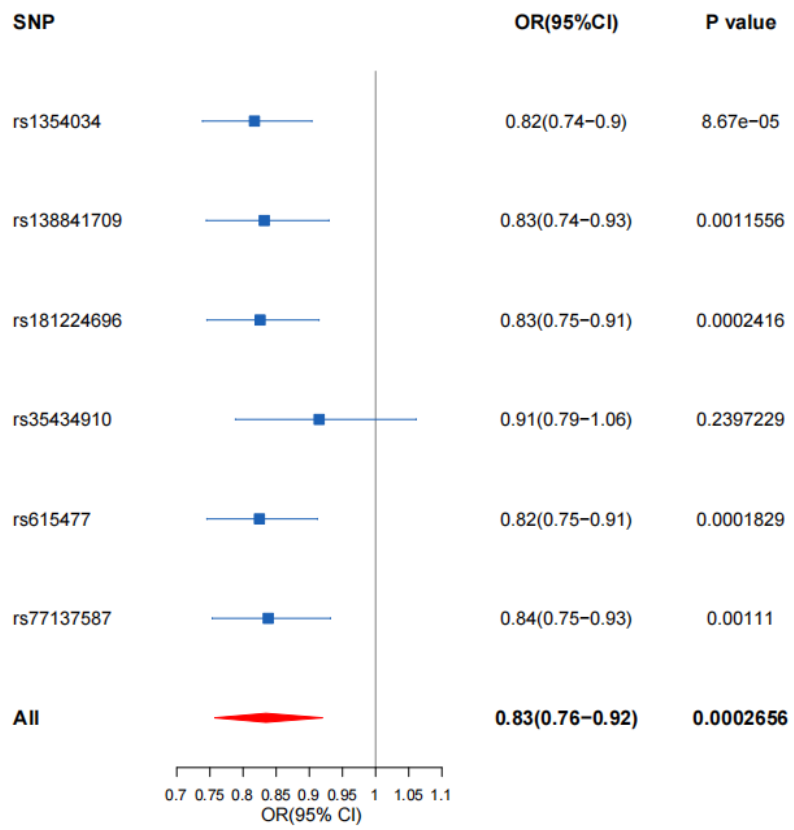
**Supplemental Table 5.** SE and beta value of SNPs for CVDs and confounding factors.

SNP	CAD BETA SE	MI BETA SE	AF BETA SE	HF BETA SE	hypertension BETA SE	IS BETA SE	CS BETA SE	LAS BETA SE	SVS BETA SE	TC BETA SE	TG BETA SE	LDL-C BETA SE	HDL-C BETA SE	Alcohol BETA SE	T2D BETA SE	Smoking BETA SE	BMI BETA SE	Depression BETA SE
rs1354034	-0.0040	0.0012	0.0012	-0.0107	0.0070	-0.0026	-0.0155	-0.0238	-0.0039	-0.0289	0.0012	0.0012	-0.0062	0.0012	-0.0429	-0.0846	-0.0050	-0.0513

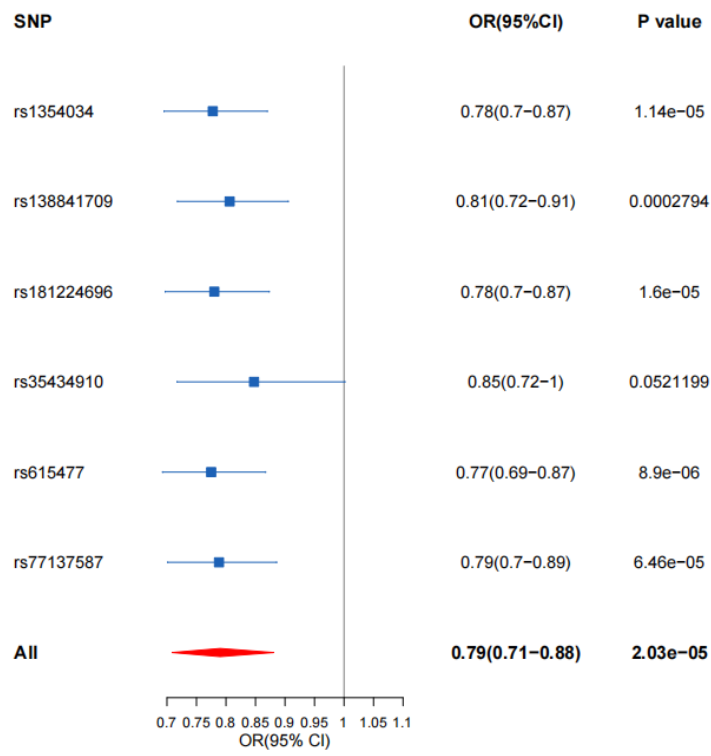
	0.0010	0.0117	0.0131	0.0068	0.0163	0.0082	0.0102	0.0195	0.0250	0.0232	0.0107	0.0107	0.0164	0.0107	0.0132	0.0235	0.0096	0.0099
rs138841709	0.0051	0.0016	0.0003	-0.0235	-0.0992	0.0530	0.0883	0.0240	0.2537	0.2272	0.1167	0.1167	0.0423	0.1167	-0.0064	-0.0326	0.0508	-0.3168
	0.0433	0.0483	0.0762	0.0298	0.0823	0.0343	0.0505	0.1062	0.1210	0.1087	0.0483	0.0483	0.0023	0.0483	0.0021	0.0446	0.0433	0.0386
rs181224696	-0.0118	-0.0149	0.0032	-0.0184	0.0075	0.0169	0.0019	0.0763	0.0144	0.1531	-0.0150	-0.0150	-0.0446	-0.0150	0.0026	0.0699	-0.0118	0.1786
	0.0303	0.0355	0.0443	0.0258	0.0599	0.0270	0.0351	0.0734	0.0875	0.0898	0.0355	0.0355	0.0037	0.0355	0.0368	0.0146	0.0304	0.0349
rs35434910	0.0055	0.0579	0.0176	-0.0134	0.0056	0.0234	0.0216	0.0241	0.0323	-0.0009	0.0580	0.0580	0.0012	0.0580	-0.0015	-0.1459	0.0505	-0.2023
	0.0132	0.0147	0.0172	0.0084	0.0235	0.0099	0.0129	0.0250	0.0323	0.0302	0.0147	0.0147	0.0037	0.0147	0.0024	0.0025	0.0133	0.0121
rs615477	0.0023	-0.0001	-0.0153	-0.0035	0.0127	0.0075	0.0137	0.0059	-0.0041	0.0296	-0.0009	-0.0009	0.0003	-0.0009	-0.0154	-0.0370	0.0023	-0.0736
	0.0134	0.0151	0.0179	0.0094	0.0229	0.0110	0.0141	0.0276	0.0357	0.0354	0.0151	0.0151	0.0006	0.0151	0.0257	0.0124	0.0134	0.0139
rs77137587	0.0120	0.0163	0.0129	0.0119	-0.0098	-0.0020	-0.0017	-0.0490	0.0152	0.0603	0.0163	0.0163	0.0237	0.0163	-0.2358	-0.0370	0.0191	-0.0807
	0.0105	0.0169	0.0229	-0.0109	0.0357	0.0137	0.0174	0.0331	0.0430	0.0418	0.0169	0.0169	0.0002	0.0169	0.0135	0.0013	0.0154	0.0146

Abbreviations: SE, standard error. SNPs, Single-nucleotide polymorphisms. CAD, coronary artery disease. MI, myocardial infarction. AF, atrial fibrillation. HF, heart failure. IS, ischemic stroke. CS, cardioembolic stroke. LAS, large artery stroke. SVS, small vessel stroke. TC, total cholesterol, TG, triglyceride, LDL-C, low-density-lipoprotein cholesterol, HDL-C, high-density-lipoprotein cholesterol, T2D, type 2 diabetes, BMI, body mass index

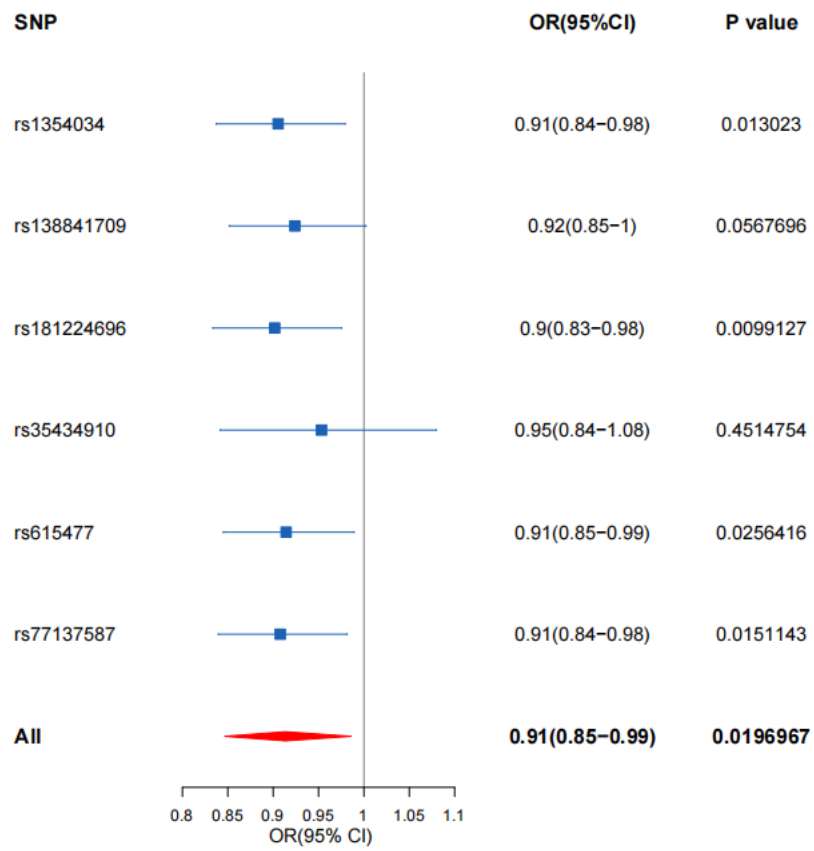
**Supplemental Figure 1.** MR Leave one out analyses for PECAM-1 on coronary artery disease.



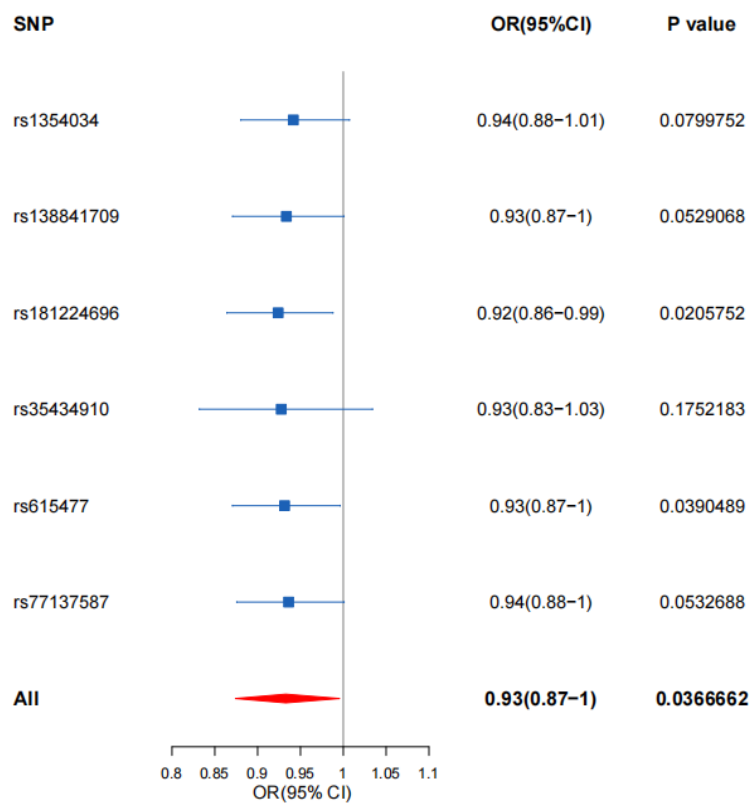
**Supplemental Figure 2.** MR Leave one out analyses for PECAM-1 on myocardial infarction.



**Supplemental Figure 3.** MR Leave one out analyses for PECAM-1 on heart failure.

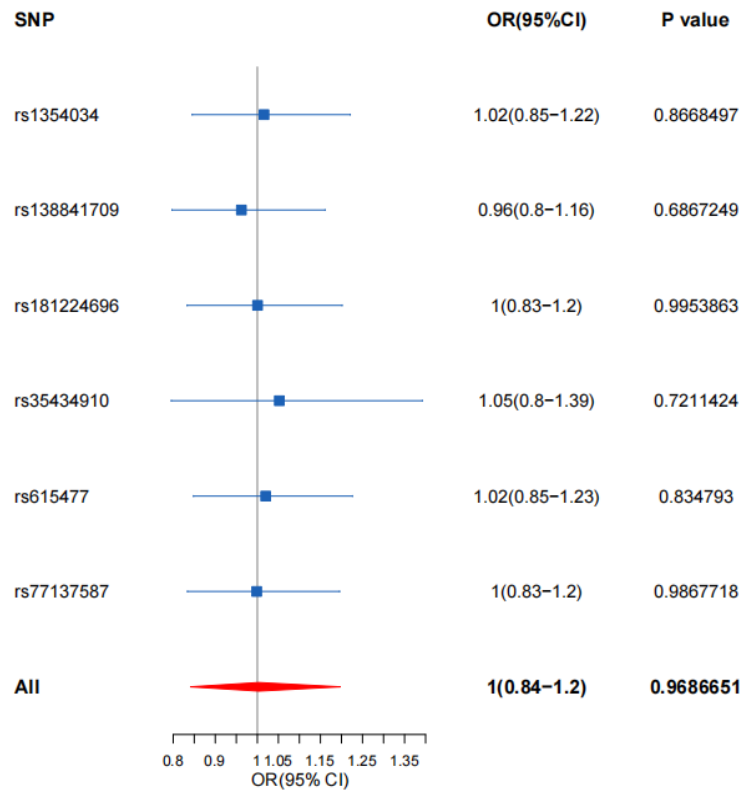


**Supplemental Figure 4.** MR Leave one out analyses for PECAM-1 on atrial fibrillation.

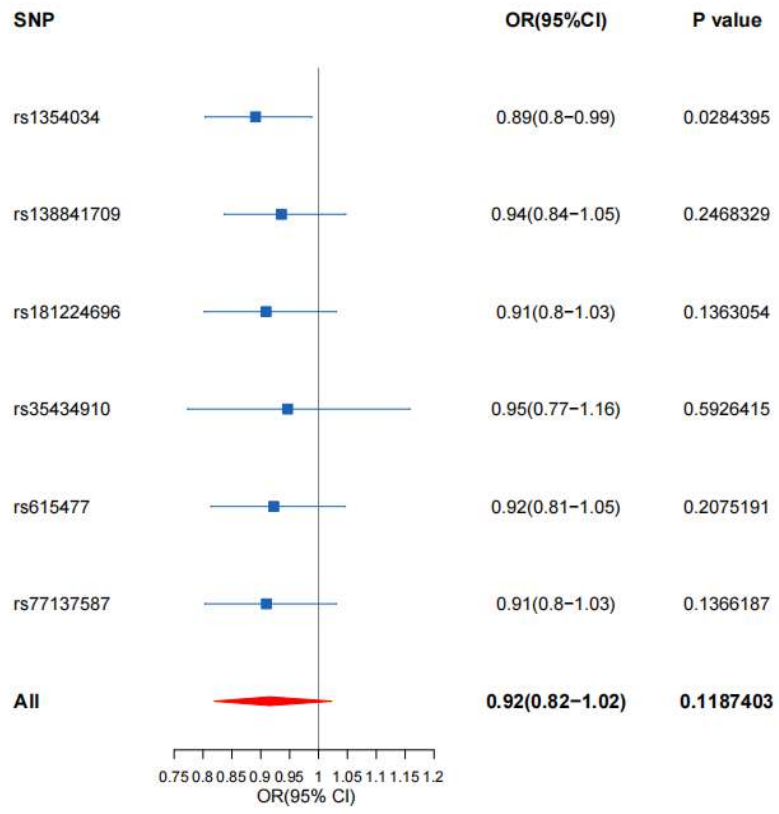


**Supplemental Figure 5.** MR Leave one out analyses for PECAM-1 on hypertension.

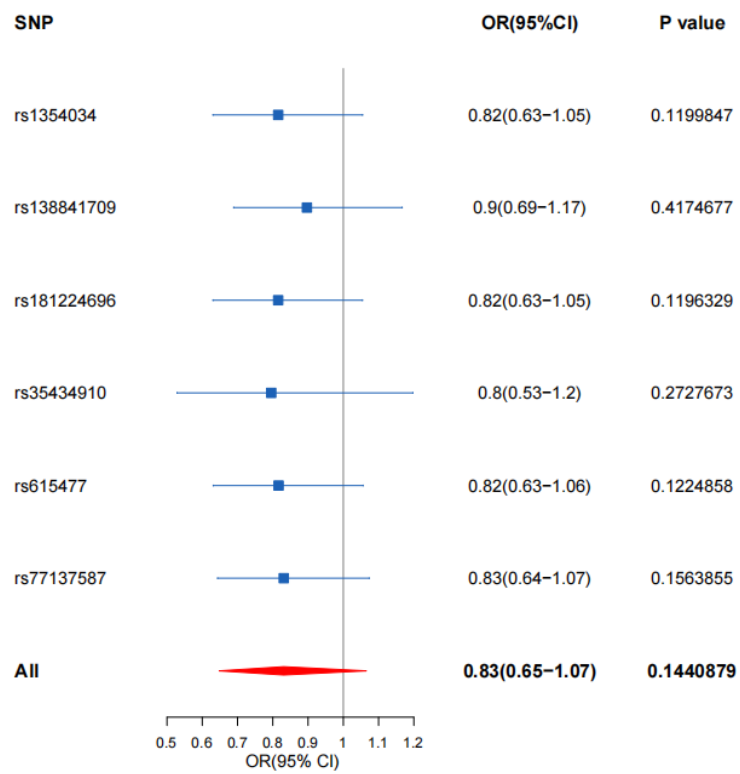




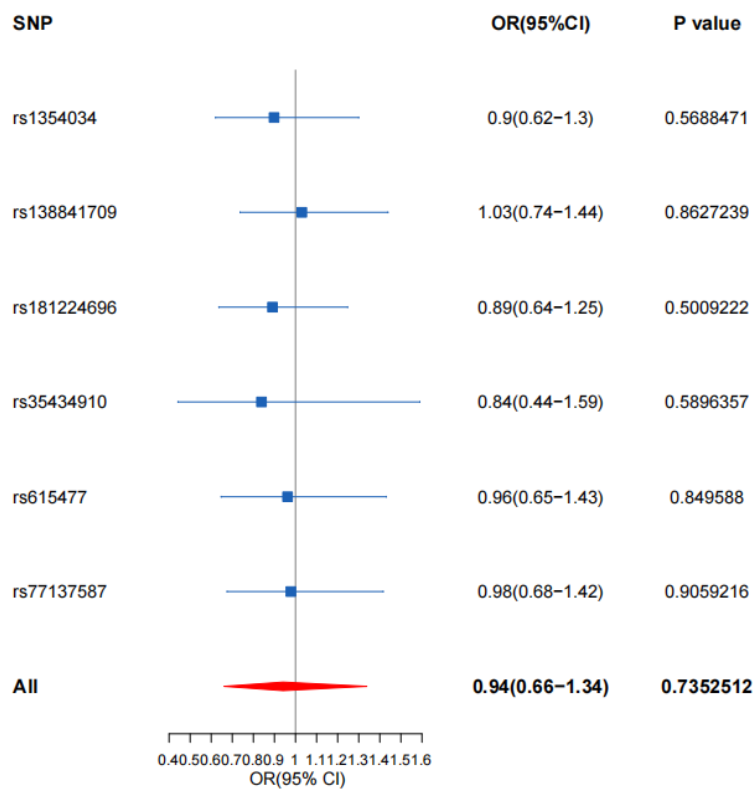
**Supplemental Figure 6.** MR Leave one out analyses for PECAM-1 on ischemia stroke.



**Supplemental Figure 7.** MR Leave one out analyses for PECAM-1 on large artery stroke.



**Supplemental Figure 8.** MR Leave one out analyses for PECAM-1 on small vessel stroke.



**Supplemental Figure 9.** MR Leave one out analyses for PECAM-1 on cardioembolic stroke.

