

PLASMA PROTEIN LEVEL RATIOS IDENTIFY NOVEL CIRCULATING TARGETS ASSOCIATED WITH STROKE RISK

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Abstract: Previous studies have nominated individual plasma proteins as therapeutic targets for stroke. Whether ratios of protein levels, which can capture relative pathway activity, are causally related to stroke remains unknown. We evaluated the potential causal associations between plasma protein level ratios and stroke risk. We conducted bidirectional, two-sample Mendelian randomization (MR) to estimate the associations between circulating protein level ratios and overall stroke and stroke subtypes. Pathway enrichment and protein–protein interaction (PPI) analyses were used to explore potential mechanisms. Forward MR indicated that a higher TGFBR2/THBD ratio was associated with increased risk of any ischemic stroke (AIS) (OR = 1.15; 95% CI, 1.09–1.21; $p = 4.07e-7$). A higher GP1BA/SDC4 ratio was associated with increased risk of small-vessel stroke (SVS) (OR = 1.25; 95% CI, 1.14–1.37; $p = 2.25e-6$), whereas a higher SDC4/SEMA4D ratio was associated with lower SVS risk (OR = 0.82; 95% CI, 0.76–0.89; $p = 1.18e-6$). Reverse MR found no evidence that AIS or SVS causally influenced these ratios, supporting the inferred direction of effect. Sensitivity analyses supported the robustness of the estimates. Pathway enrichment and PPI analyses implicated TGF- β signaling and coagulation in AIS pathobiology, and platelet activation, extracellular matrix organization, and axon guidance in SVS. Plasma protein level ratios may help identify biologically relevant pathways and therapeutic targets for stroke prevention and treatment.

Keywords: Stroke; Mendelian randomization; Plasma proteins; Protein level ratios

1 INTRODUCTION

Stroke is one of the leading causes of death and disability worldwide, accounting for 143 million disability-adjusted life-years (DALYs) and 6.55 million deaths in 2019[1]. Therefore, studies aimed at reducing stroke incidence are urgently needed. Advances in high-throughput sequencing technology have enabled numerous genome-wide association studies (GWASs) to identify genetic loci associated with stroke[2-5]. These studies have helped unravel the hereditary basis of stroke and identify potential therapeutic targets.

Circulating plasma proteins reflect physiological and pathological states. Compared with the genome and transcriptome, the proteome more directly reflects ongoing biological processes and disease states. Combined with GWAS, plasma proteomics has significantly contributed to understanding disease pathology, identifying targets, and drug development[6-8].

Mendelian randomization (MR) is an effective method for investigating causal relationships using genetic variants associated with exposures and outcomes. MR provides stronger evidence for causal inference than conventional observational studies because genetic variants are randomly allocated at conception, making MR less susceptible to confounding and reverse causality. In addition, MR studies are cost-effective because they can be conducted using publicly available GWAS summary statistics.

Previous stroke GWASs and circulating proteomic GWASs provided valuable genetic instruments for MR studies assessing the relationship between plasma proteins and stroke risk. Chen et al. tested 308 plasma proteins for causal relationships with stroke and found that TFPI, CD40, MMP12, and IL6RA were associated with a lower risk of stroke, whereas CD6 and TMPRSS5 were associated with a higher risk[9]. Zou et al. analyzed data from 734 plasma proteins and 151 cerebrospinal fluid (CSF) proteins to identify causal relationships with ischemic stroke[10]. Their results suggested that the CSF protein prekallikrein had a strongly protective effect on ischemic stroke (OR=0.41, 95% CI: 0.27-0.63). Additionally, the plasma proteins SWAP70 and MMP12 were associated with a reduced risk of ischemic stroke.

In March 2024, Suhre et al. reported a GWAS of 2821 plasma protein ratio quantitative trait loci (rQTLs), which increased the number of proteogenomic loci by 25%[11]. Compared with traditional protein quantitative trait loci (pQTLs), rQTLs are based on ratios between partially correlated proteins and may better capture biological interactions and relative pathway activity. However, the causal relationships between plasma protein level ratios and stroke risk remain unclear. Therefore, we conducted a bidirectional two-sample MR study to investigate the causal relationships between plasma protein level ratios and stroke risk and to identify novel circulating targets associated with stroke.

2 METHODS

2.1 Study Design and Ethical Statements

A bidirectional two-sample MR design was used to investigate the causal relationship between plasma protein level ratios and the risk of stroke as well as its subtypes. MR analysis relies on three core assumptions: (1) the genetic instrumental variables (IVs) are strongly associated with the exposure; (2) the IVs are independent of confounding factors; and (3) the IVs influence the outcome only through the exposure. We first performed the forward MR analysis using plasma protein level ratios as the exposure and stroke risk as the outcome. Reverse MR analysis was subsequently conducted to assess potential reverse causality.

The data used in this MR study were obtained entirely from public databases and published studies, all of which had received ethical approval and informed consent from participants.

2.2 Data Sources

2.2.1. Exposure data

For plasma protein level ratios, we used 2821 rQTLs identified by Suhre from the UK Biobank Pharma Proteomics Project (UKB PPP) consortium dataset[11]. The UKB PPP consists of a collaboration between the UK Biobank (UKB) and thirteen biopharmaceutical companies, aiming to elucidate the plasma proteomic profiles of 54219 UKB participants. Genetic associations for 2923 plasma proteins were mapped by the UKB PPP and published in 2023; the Olink proteomics data were also made publicly available. Recently, Suhre reported genetic associations for 2821 protein-protein ratios between 1473 proteins at 8461 rQTLs using a ratio GWAS strategy. Unlike pQTLs which use quantitative protein levels, the ratios between two proteins were used for association analysis, which facilitate the identification of novel pQTLs and biologically relevant links between proteins.

2.2.2 Outcome data

For stroke risk, we used genome-wide association meta-analysis data from the MEGASTROKE Consortium by Malik et al[12]. To maintain consistency between the exposure and outcome populations, we used the European GWAS data from their study, comprising 446696 participants (40585 cases and 406111 controls). Stroke and its subtypes included in the analysis were: any stroke (AS), any ischemic stroke (AIS), large-artery atherosclerotic stroke (LAS), cardioembolic stroke (CES), and small-vessel stroke (SVS). A summary of the GWAS datasets is presented in Table 1.

Table 1 Summary of Genome-Wide Association Studies (GWAS) Data Sources

Phenotype	Author, published year	Consortium	Population	Sample size	No. of cases	PMID
Plasma protein level ratios	Suhre et al, 2024	UKB PPP	European	54,219	/	38412862
Stroke	Malik et al, 2018	MEGASTROKE	European	446,696	40,585	29531354

2.3 Selection of Genetic Instrumental Variables

Single nucleotide polymorphisms (SNPs) from GWASs were used as genetic IVs. The selected IVs that were robustly associated with the exposure met the significance threshold of $p < 5e^{-8}$. If the number of selected SNPs was fewer than 5, a relaxed threshold of $p < 1e^{-5}$ was applied[13]. Linkage disequilibrium was avoided by clumping SNPs with $r^2 < 0.001$ and a distance of 10 Mb. Weak IVs were excluded if the F statistic was < 10 . The F statistic was calculated by the formula: $F = R^2(N-k-1)/k(1-R^2)$.

SNPs with palindromic sequences were excluded. Exposure and outcome datasets were harmonized to ensure consistent alignment of effect alleles.

2.4 Two-Sample Mendelian Randomization Analysis

Five methods were employed for MR analysis: inverse variance weighted (IVW), MR-Egger, weighted median (WM), simple mode, and weighted mode. The IVW method was considered the primary analysis approach according to the third version of the MR guidelines published in 2023[14]. MR-Egger regression can detect and adjust for directional pleiotropy, although it has lower statistical power. The weighted median method can provide consistent causal estimates when at least 50% of the instrumental variables are valid. Additionally, the simple mode and weighted mode were employed as complementary methods.

Associations with $p < 3.54e^{-6}$ ($0.05 / (2821 \text{ exposures} \times 5 \text{ outcomes})$) were deemed significant, while those with $3.54e^{-6} < p < 0.05$ were considered potentially significant. Causal estimates were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

2.5 Sensitivity Analysis

Sensitivity analysis was conducted to validate the robustness of the MR analysis. Cochran's Q test and the MR-Egger regression intercept were utilized to assess the heterogeneity of the IVs and potential horizontal pleiotropy, respectively. MR-PRESSO was employed to detect outliers and to calculate estimates after their removal. Leave-one-out analysis was performed to determine if any single SNP unduly influences the overall result. The funnel plot was employed to visually assess potential asymmetry.

2.6 Functional Analysis and Software

Functional analyses were performed on significant protein ratios, including pathway enrichment analysis and protein-protein interaction (PPI) analysis. Pathway enrichment analysis was achieved by Kyoto Encyclopedia of Genes and Genomes (KEGG) database (<https://www.kegg.jp/>) and Reactome database (<https://reactome.org/>). PPI analysis was performed using the STRING database (<https://string-db.org/>). Protein interaction networks were constructed using the default settings, and a combined score > 0.7 was considered indicative of high-confidence interactions. Cytoscape (v3.8.0) was used for PPI network visualization. The cytoNCA plugin was used to calculate betweenness centrality (BC), and the MCODE plugin was used for cluster analysis. Cluster annotation was further performed using the Metascape database (<https://metascape.org/>)[15]. MR analysis was performed using the TwoSampleMR package and MR-PRESSO package in R 4.4.0.

3 RESULTS

3.1. Selection of Instrumental Variables

For stroke risk, we first selected SNPs with a significance of $p < 5e^{-8}$. As the selected SNPs for the stroke subtypes were insufficient for analysis after the removal of dependent SNPs (4 SNPs for LAS and CES, 1 SNP for SVS), we then applied a significance of $p < 1e^{-5}$, under which 79 SNPs were selected for AS, 87 SNPs for AIS, 61 SNPs for LAS, 47 SNPs for CES, and 38 SNPs for SVS. All of the selected IVs met the threshold of F-statistics > 10 . More details of the IVs are listed in Table S1 - Table S5.

For plasma protein level ratios, we selected SNPs strongly associated with 2799 protein ratios ($p < 5e^{-8}$). For the remaining 22 protein ratios, the selected SNPs were fewer than 5 each, so we applied a relaxed criterion of $p < 1e^{-5}$. SNPs were clumped to ensure independence using an LD threshold of $r^2 < 0.001$, and palindromic SNPs were removed. All IVs had F-statistics > 10 , indicating sufficient instrument strength. Detailed information on IVs is provided in Supplementary Tables S6-S7 and Dataset S1.

3.2 Forward Mendelian Randomization Analysis

We performed forward MR analysis to investigate the causal associations between plasma protein ratios and stroke risk. The IVW and weighted median analysis showed that the ratio of TGFBR2/THBD was significantly associated with AIS (IVW: OR = 1.15, 95% CI: 1.09-1.21, $p = 4.07e^{-7}$; WM: OR = 1.17, 95% CI: 1.10-1.24, $p = 3.17e^{-7}$). Additionally, two protein ratios showed significant associations with SVS by the IVW method: GP1BA/SDC4 (OR = 1.25, 95% CI: 1.14-1.37, $p = 2.25e^{-6}$), SDC4/SEMA4D (OR = 0.82, 95% CI: 0.76-0.89, $p = 1.18e^{-6}$). No significant associations were identified for AS, LAS, or CES. The results are shown in Figure 1.

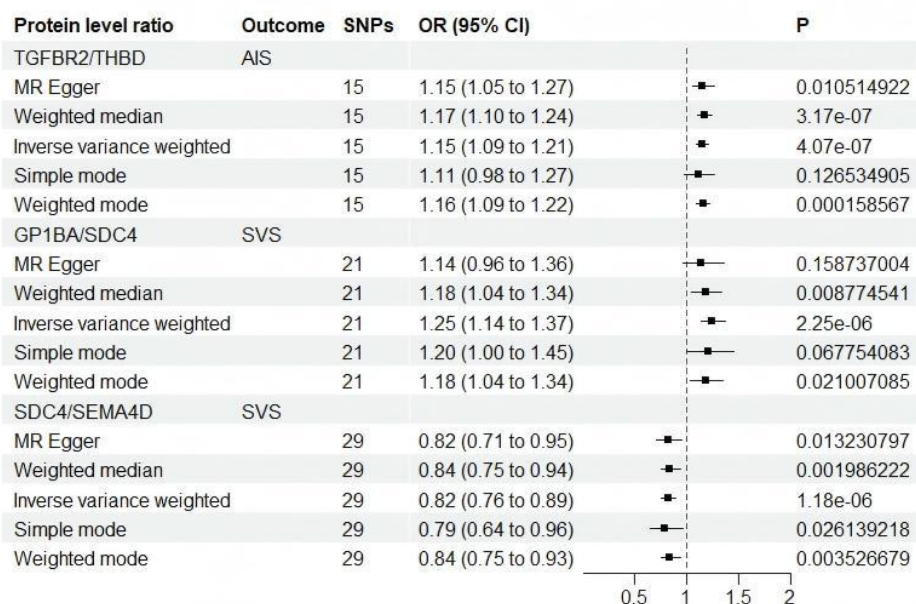


Figure 1 Mendelian Randomization Results for the Relationship between Plasma Protein Level Ratios and Stroke

No evidence of heterogeneity or horizontal pleiotropy was observed (Table 2 and Table 3, all $p > 0.05$). Leave-one-out analysis indicated that no single SNP disproportionately influenced the results. The forest plots, funnel plots, leave-one-out plots, and scatter plots are shown in Figure S1 to Figure S3.

Table 2 Heterogeneity Test and Pleiotropy Test for forward Mendelian Randomization Analysis

Exposure	Outcome	MR-Egger			MR-IVW			MR-Egger intercept		
		Q	Q df	Q pval	Q	Q df	Q pval	Intercept	SE	P value
TGFBR2/THBD protein level ratio	AIS ¹	16.06027	13	0.245891	16.10414	14	0.307056	-0.0012	0.006392	0.85344
GP1BA/SDC4 protein level ratio	SVS ²	11.55586	19	0.903723	13.00571	20	0.877139	0.01061	0.008812	0.24334
SDC4/SEMA4D protein level ratio	SVS	17.65543	27	0.913699	17.65679	28	0.934466	0.00026	0.00706	0.970884

Note: ¹ AIS, any ischemic stroke; ² SVS, small-vessel stroke.

Table 3 MR-PRESSO Analysis for forward Mendelian Randomization

Exposure	Outcome	MR-PRESSO						Global P value
		Outliers	Beta	SD	T-stat	P value		
TGFBR2/THBD protein level ratio	AIS	0	0.1362542	0.02689874	5.06545	1.723299e-04	0.387	
GP1BA/SDC4 protein level ratio	SVS	0	0.2208741	0.03766257	5.864552	9.762154e-06	0.858	
SDC4/SEMA4D protein level ratio	SVS	0	-0.1972432	0.03223894	-6.118167	1.332441e-06	0.947	

3.3 Reverse Mendelian Randomization Analysis

To determine whether stroke affects the plasma protein ratios, we conducted a reverse MR analysis. However, no significant association was observed in stroke or its subtypes (all $p > 3.54e^{-6}$). Sensitivity analyses supported the robustness of the findings.

3.4. Pathway enrichment and PPI analysis on protein ratios associated with stroke risk

To explore the potential biological mechanisms underlying the identified associations, we performed pathway enrichment analysis using KEGG and Reactome databases. Key pathways related to coagulation, vascular remodeling, and nervous system development were identified (Table 4). Notably, the TGFBR2/THBD ratio was enriched in the TGF- β signaling pathway (KEGG, map04350) and hemostasis-related pathways (Reactome, R-HSA-109582), suggesting potential involvement in fibrosis- and coagulation-related processes. The shared enrichment of TGFBR2 and THBD in the AGE-RAGE signaling pathway (KEGG, map04933) suggests that these proteins may participate in pathways related to diabetic vascular injury and coagulation regulation. Similarly, GP1BA/SDC4 ratio was linked to platelet activation (KEGG, map04611) and cell adhesion (KEGG, map04514). Additionally, they were both included in extracellular matrix (ECM)-receptor interactions (KEGG, map04512), indicating their potential contributions to small vessel pathology. However, no overlapping pathways were observed for SDC4/SEMA4D, implying their association with stroke risk may arise from independent biological processes, such as ECM remodeling (SDC4) and axonal repair (SEMA4D).

Table 4 KEGG and Reactome Pathways Enriched from Protein Ratios Associated with Stroke Risk

Protein ratio	Stroke subtype	KEGG pathway	Reactome pathway
TGFBR2		TGF- β signaling pathway	Signaling by TGF- β receptor complex
THBD	AIS	Complement and coagulation cascades	Formation of fibrin clot
Common pathway		AGE-RAGE signaling pathway in diabetic complications	None
GP1BA		Platelet activation	Formation of fibrin clot
SDC4	SVS	Cell adhesion molecules	Metabolism of carbohydrates: I. Glycosaminoglycan metabolism; II. Heparan sulfate/heparin (HS-GAG) metabolism
Common pathway		ECM ³ -receptor interaction	None
SDC4		Cell adhesion molecules	Metabolism of carbohydrates: I. Glycosaminoglycan metabolism; II. Heparan sulfate/heparin (HS-GAG) metabolism
SEMA4D	SVS	Axon guidance	Axon guidance
Common pathway		None	None

Note: ³ECM: extracellular matrix

To further explore potential functional relationships underlying the identified protein ratios, we constructed protein–protein interaction (PPI) networks using the STRING database. Although no direct interactions were observed between TGFBR2/THBD, GP1BA/SDC4, or SDC4/SEMA4D, extended networks revealed indirect connections through intermediary proteins (combined score > 0.7, Figure 2). For TGFBR2/THBD, NRP1 (Neuropilin-1) emerged as a potential bridging protein (NRP1-THBD: combined score=0.755; NRP1-TGFBR2: 0.782), suggesting potential links between coagulation-related processes and TGF- β signaling. The GP1BA/SDC4 network showed a more interconnected interaction pattern involving ITGB3 (Integrin beta-3) and TNC (Tenascin) (GP1BA-ITGB3: combined score=0.886; ITGB3-TNC: combined score=0.952; TNC-SDC4: combined score=0.953), suggesting potential platelet–matrix interactions involved in small vessel pathology. Similarly, SDC4/SEMA4D network required two intermediaries (GIPC1 and PLXND1 [Plexin D1]) to establish indirect network connections (SDC4-GIPC1, combined score=0.974; GIPC1-PLXND1, combined score=0.869; PLXND1-SEMA4D, combined score=0.816), suggesting potential crosstalk between axonal guidance and ECM organization in small vessel stroke pathology.

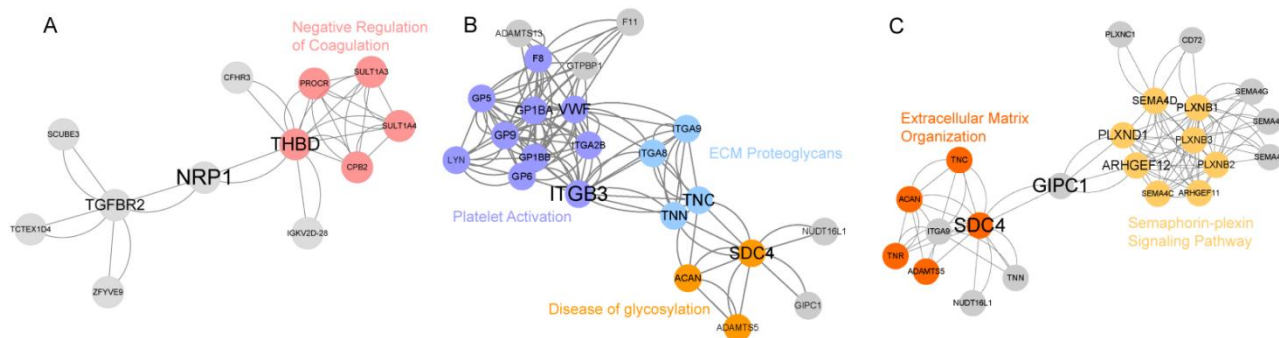


Figure 2 Extended PPI Networks of Protein Ratios

Note: Edges represent high-confidence interactions (combined score > 0.7). Panels A-C show the networks of TGFBR2/THBD, GP1BA/SDC4, and SDC4/SEMA4D, respectively. Clustered proteins are marked by different colors, and cluster annotations are shown in the corresponding colors.

4 DISCUSSION

In the present study, we used the bidirectional two-sample MR method to investigate the causal relationships between plasma protein level ratios and stroke. The forward MR analysis showed that the TGFBR2/THBD ratio was associated with a higher risk of AIS, while the GP1BA/SDC4 ratio and SDC4/SEMA4D ratio were associated with a higher and a lower risk of SVS, respectively. However, the reverse MR showed no significant effects of stroke on plasma protein level ratios. Our functional analysis on the protein ratios suggested the involvement of TGF- β signaling pathway and coagulation in AIS pathology, as well as the participation of platelet activation, ECM, and axon guidance in SVS pathology.

Transforming growth factor beta receptor 2 (TGFBR2) is a TGF- β receptor subunit that binds TGF- β to modulate cellular processes such as cell proliferation, wound healing, and immunosuppression. Hollander et al reported small-sized focal ischemia (resembling lacunar stroke), vascular inflammation, and neurological deficits in myeloid-specific TGFBR2 KO mice, suggesting an increased risk of ischemic stroke due to TGFBR2 loss[16]. Thrombomodulin (THBD) is an endothelial membrane receptor that binds thrombin, playing a role in anticoagulation and antithrombotic processes. Reports on the association between THBD and ischemic stroke have been inconsistent[17-19]. One study reported that polymorphisms in both TGFBR2 and THBD are involved in vascular function and hemodynamics. According to Poon et al[20], TGF- β treatment reduces the expression of THBD in cultured human embryoid bodies. This suggests a potential regulatory relationship between TGF- β signaling and THBD expression.

Glycoprotein Ib platelet subunit alpha (GP1BA), together with subunit beta, constitutes a platelet membrane receptor for von Willebrand factor (VWF). After vascular injury, the platelet receptor complex GP Ib-IX-V binds to VWF, initiates the platelet adhesion to endothelium, and facilitates subsequent platelet activation and thrombosis. GP1BA has been proposed as a potential drug target for stroke based on MR and colocalization analysis[21]. In addition, elevated GP1BA levels have also been reported in patients with ischemic stroke undergoing mechanical thrombectomy[22]. Syndecan proteoglycan 4 (SDC4) is a heparan sulfate proteoglycan transmembrane receptor. SDC4 has been linked to myocardial infarction in women, but not to ischemic stroke[23]. Injured cardiac tissue may release SDC4, which could facilitate the attenuation of inflammation[24]. Semaphorin 4D (SEMA4D) is a semaphorin ligand for plexin receptor PLXNB1 that modulates neuronal growth[25-26]. SEMA4D worsens ischemic stroke injury in animal models by disrupting the blood-brain barrier and impairing oligodendrocyte proliferation[27-28]. However, we did not identify direct interactions between GP1BA and SDC4 or between SDC4 and SEMA4D in the current PPI analysis.

Compared with individual proteins, protein level ratios may better reflect relative pathway balance and coordinated biological activity between functionally related proteins. Functional analysis provided additional insight into the

biological mechanisms linking protein ratios to stroke risk. TGFBR2-mediated signaling through the TGF- β signaling pathway may contribute to vascular remodeling and endothelial dysfunction, processes implicated in ischemic stroke pathology. THBD, a critical regulator of anticoagulation, was mapped to complement and coagulation cascades and fibrin clot formation, which aligns with its known role in mitigating thrombosis, supporting a potential role of impaired THBD-related anticoagulant pathways in ischemic stroke risk. GP1BA, a platelet surface receptor, was associated with platelet activation and fibrin clot dynamics, suggesting that its ratio with SDC4 may be associated with microvascular occlusive processes. SDC4-related pathways were enriched in ECM-receptor interaction and heparan sulfate metabolism, suggesting its ratio with SEMA4D may reflect endothelial integrity loss in cerebral small vessels. SEMA4D, linked to axon guidance and nervous system development, may modulate post-stroke neuroinflammation, with its ratio to SDC4 indicating a protective role against secondary neuronal injury. These findings may provide potential targets for future mechanistic and therapeutic investigation. For example, pharmacological modulation of TGF- β signaling or thrombomodulin-related pathways warrants further investigation in the context of stroke prevention and vascular protection.

Our study has the following strengths: 1. Stroke exhibits different pathological mechanisms depending on its subtype. To elucidate the causal relationships more precisely, our MR analysis included specific stroke subtypes. 2. The protein level ratios are formed by biologically connected protein pairs; combined with PPI and enrichment analysis results, our study provides insights into protein interaction networks related to stroke risk. 3. We evaluated bidirectional causal relationships, considering that stroke could affect protein level ratios; however, no significant causal associations of stroke with protein level ratios were observed.

Our study has the following limitations: 1. The GWAS data for both exposure and outcome were derived primarily from populations of European ancestry, so our conclusions were restricted to the European population. 2. For a small part of the 2821 protein level ratios, we applied a relaxed criterion ($p < 1e^{-5}$) during SNP selection, due to a lack of SNPs when using $p < 5e^{-8}$, and this could influence the results because of weak associations between SNPs and exposure. 3. Although MR provides evidence for causal inference, the biological mechanisms underlying these associations still require validation through experimental and clinical studies. Future studies should further clarify the causal relationships between plasma protein level ratios and stroke, ideally using data from diverse populations. Stricter screening thresholds for instrumental variables should be applied where feasible.

5 CONCLUSIONS

Circulating protein level ratios showed potential causal associations with stroke risk: the TGFBR2/THBD ratio was associated with a higher risk of AIS, whereas the GP1BA/SDC4 ratio and SDC4/SEMA4D ratio were associated with an increased and decreased risk of SVS, respectively. These findings highlight the potential value of protein ratio-based biomarkers and pathway-oriented approaches in stroke target prioritization and therapeutic development.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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APPENDIX

Table S1 Characteristics of Instrumental Variables of AS

	SNP	P value	effect allele	other allele	Beta	SE	EAF
1	rs2500281	5.39E-07	A	G	0.0494	0.0099	0.7362
2	rs880315	3.62E-10	T	C	-0.0527	0.0084	0.6
3	rs12057512	7.55E-06	A	C	0.0448	0.01	0.7925
4	rs6695915	4.25E-07	A	G	0.0666	0.0132	0.8637
5	rs114709797	6.37E-06	T	C	-0.1608	0.0356	0.9544
6	rs6593611	4.57E-06	T	C	-0.0383	0.0083	0.6446
7	rs10776752	2.50E-08	T	G	0.0715	0.0128	0.1583
8	rs2842873	5.87E-14	T	C	-0.0613	0.0082	0.3929
9	rs4950915	2.85E-06	T	C	0.0378	0.0081	0.4182
10	rs17015183	2.24E-06	A	C	-0.0481	0.0102	0.8197
11	rs12476527	6.44E-08	T	G	-0.0502	0.0093	0.5167
12	rs355089	2.29E-06	A	T	-0.048	0.0102	0.7847
13	rs58648044	2.56E-06	T	G	-0.0392	0.0083	0.6289

14	rs1995664	1.82E-06	T	C	-0.045	0.0094	0.7288
15	rs6795469	3.41E-06	A	T	0.0578	0.0125	0.2702
16	rs12633109	2.11E-06	T	G	0.0387	0.0082	0.379
17	rs62285242	8.46E-06	A	G	0.0669	0.015	0.1
18	rs10805070	7.71E-06	A	T	0.1291	0.0289	0.1036
19	rs2129977	9.40E-16	A	G	0.073	0.0091	0.3165
20	rs34311906	9.66E-07	T	C	-0.0438	0.0089	0.6006
21	rs149177737	6.94E-06	T	G	0.039	0.0087	0.4374
22	rs6825454	2.62E-09	T	C	-0.0518	0.0087	0.6964
23	rs4460116	3.12E-06	T	C	0.122	0.0262	0.0885
24	rs148159238	8.62E-06	T	C	0.1486	0.0334	0.9762
25	rs10075233	4.77E-06	A	G	0.0616	0.0135	0.1138
26	rs246109	2.70E-06	A	G	0.075	0.016	0.8842
27	rs11957829	1.62E-08	A	G	0.0654	0.0116	0.825
28	rs2585193	5.16E-06	A	G	0.0374	0.0082	0.6411
29	rs73350117	5.77E-07	A	C	-0.056	0.0112	0.8415
30	rs6596445	4.98E-06	T	C	0.0409	0.009	0.2845
31	rs4959130	1.42E-09	A	G	0.0779	0.0129	0.1381
32	rs35276016	1.37E-07	T	C	0.0939	0.0178	0.0835
33	rs16896398	1.30E-08	A	T	-0.0477	0.0084	0.6617
34	rs9486023	8.36E-06	T	C	0.0457	0.0103	0.8184
35	rs556493	4.25E-06	A	G	0.0373	0.0081	0.4839
36	rs7740355	4.70E-06	A	T	-0.0624	0.0136	0.8885
37	rs2107595	4.86E-14	A	G	0.0727	0.0096	0.2204
38	rs42039	7.32E-09	T	C	-0.0604	0.0105	0.2303
39	rs75630045	3.23E-06	A	G	0.2002	0.043	0.0144
40	rs1799983	1.36E-06	T	G	0.0455	0.0094	0.293
41	rs11250183	1.74E-06	T	C	-0.1005	0.021	0.924
42	rs1471859	1.78E-06	A	C	-0.0385	0.0081	0.6094
43	rs7859727	4.22E-10	T	C	0.0494	0.0079	0.5299
44	rs7863844	4.33E-06	T	G	-0.0585	0.0127	0.7814
45	rs10978356	1.60E-06	T	C	-0.0631	0.0131	0.292
46	rs6477843	2.95E-06	A	G	-0.0404	0.0087	0.592
47	rs635634	4.40E-06	T	C	0.0487	0.0106	0.2035
48	rs12416342	7.48E-06	T	G	0.0632	0.0141	0.1251
49	rs7084521	8.35E-06	A	G	-0.0379	0.0085	0.5671
50	rs12774577	2.89E-06	T	C	-0.0556	0.0119	0.8628
51	rs11191833	1.66E-10	A	G	-0.0527	0.0082	0.3942
52	rs60401382	6.76E-08	T	C	-0.0479	0.0089	0.2995
53	rs360139	5.26E-07	A	G	-0.0432	0.0086	0.4222
54	rs7933146	4.89E-07	A	T	0.1208	0.024	0.0485
55	rs9651613	1.16E-06	A	G	0.0452	0.0093	0.3349
56	rs2005108	6.43E-08	T	C	0.0736	0.0136	0.1287
57	rs7304841	1.60E-07	A	C	0.0438	0.0084	0.5923
58	rs10858934	6.68E-07	T	C	0.0548	0.011	0.2363
59	rs3184504	8.63E-12	T	C	0.062	0.0091	0.4542
60	rs35436	2.87E-08	T	C	-0.0462	0.0083	0.3834
61	rs79280766	2.95E-06	A	G	0.1405	0.0301	0.0358
62	rs9316222	4.31E-10	T	C	-0.0599	0.0096	0.2206
63	rs339800	7.11E-08	T	C	0.0568	0.0105	0.2776
64	rs9521634	1.42E-07	T	C	-0.0433	0.0082	0.6593
65	rs12442374	3.70E-07	C	G	-0.0609	0.012	0.8517
66	rs4932370	3.12E-07	A	G	0.045	0.0088	0.3329
67	rs2397816	1.82E-06	A	G	0.0393	0.0082	0.4096
68	rs933562	2.72E-06	A	G	-0.086	0.0183	0.0756
69	rs12932445	2.23E-07	T	C	-0.0502	0.0097	0.7789
70	rs12445022	1.05E-10	A	G	0.0574	0.0089	0.3089
71	rs11869451	1.05E-06	A	G	0.0761	0.0156	0.171
72	rs117426542	5.91E-07	A	G	0.1524	0.0305	0.0313
73	rs8071420	6.49E-06	A	G	-0.0414	0.0092	0.6549
74	rs111254932	2.42E-06	A	C	0.1252	0.0266	0.0334
75	rs2632512	2.21E-07	T	C	0.0566	0.0109	0.1986
76	rs34212978	5.55E-06	T	C	-0.0678	0.0149	0.8986
77	rs8103309	3.40E-08	T	C	0.0501	0.0091	0.655
78	rs6070101	8.82E-06	T	C	-0.0477	0.0107	0.7862
79	rs35947293	9.66E-07	A	G	-0.0419	0.0086	0.3519

Table S2 Characteristics of Instrumental Variables of AIS

SNP	P value	effect allele	other allele	Beta	SE	EAF
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1	rs2500281	3.28E-07	A	G	0.0532	0.0104	0.7353
2	rs17035646	1.34E-09	A	G	0.0536	0.0088	0.405
3	rs12057512	1.54E-06	A	C	0.051	0.0106	0.7895
4	rs6695915	6.14E-07	A	G	0.0687	0.0138	0.8588
5	rs10776752	1.46E-06	T	G	0.0648	0.0135	0.1648
6	rs7553733	4.75E-06	T	C	-0.0393	0.0086	0.3894
7	rs2842873	4.86E-11	T	C	-0.0572	0.0087	0.3955
8	rs12476527	1.30E-06	T	G	-0.0472	0.0098	0.5084
9	rs9309154	6.58E-06	T	G	-0.0447	0.0099	0.2745
10	rs55863310	2.00E-06	A	T	-0.0901	0.019	0.0743
11	rs355089	1.40E-06	A	T	-0.052	0.0108	0.7829
12	rs9874975	2.81E-06	A	G	-0.0528	0.0113	0.2211
13	rs9681992	5.87E-06	C	G	-0.0796	0.0176	0.6143
14	rs9840077	3.69E-06	T	G	-0.0714	0.0154	0.6439
15	rs6795469	9.28E-07	A	T	0.0629	0.0128	0.2811
16	rs6762490	1.18E-06	A	T	0.0409	0.0084	0.3845
17	rs3817581	9.58E-06	T	C	0.0377	0.0085	0.4598
18	rs62285242	2.93E-06	A	G	0.0731	0.0156	0.1019
19	rs7687234	4.38E-06	T	C	0.0406	0.0088	0.4199
20	rs6847935	3.50E-16	A	T	-0.0784	0.0096	0.6743
21	rs34311906	1.19E-07	T	C	-0.0489	0.0092	0.6
22	rs6537481	3.98E-07	A	G	-0.0475	0.0094	0.7115
23	rs6825454	7.43E-10	T	C	-0.0564	0.0092	0.6922
24	rs1511802	2.26E-06	T	C	-0.0412	0.0087	0.6366
25	rs4460116	4.39E-06	T	C	0.1253	0.0273	0.0947
26	rs10075233	1.68E-06	A	G	0.069	0.0144	0.1137
27	rs246109	2.45E-06	A	G	0.079	0.0168	0.8787
28	rs11957829	7.51E-09	A	G	0.0719	0.0124	0.8239
29	rs17615906	6.70E-06	T	C	-0.0528	0.0117	0.8455
30	rs11745259	4.23E-06	T	C	0.0464	0.0101	0.2366
31	rs4959130	2.83E-09	A	G	0.0832	0.014	0.1372
32	rs35276016	1.30E-07	T	C	0.1017	0.0193	0.0833
33	rs762624	2.36E-07	A	C	0.0483	0.0093	0.6273
34	rs2107595	9.25E-14	A	G	0.0759	0.0102	0.2264
35	rs58254777	6.19E-06	A	G	-0.0477	0.0106	0.7629
36	rs42039	6.55E-09	T	C	-0.0656	0.0113	0.2277
37	rs1541861	6.77E-06	A	C	-0.0415	0.0092	0.6429
38	rs11250183	2.48E-06	T	C	-0.1051	0.0223	0.9193
39	rs4298492	9.92E-06	A	G	0.043	0.0097	0.7519
40	rs2294092	3.22E-06	C	G	0.0389	0.0084	0.5786
41	rs1471859	1.85E-06	A	C	-0.0409	0.0086	0.6116
42	rs10813156	6.59E-06	T	C	0.0404	0.009	0.3209
43	rs7859727	1.05E-09	T	C	0.0514	0.0084	0.5355
44	rs10978356	2.90E-06	T	C	-0.0632	0.0135	0.304
45	rs635634	1.79E-06	T	C	0.0529	0.0111	0.2055
46	rs150976965	4.14E-06	T	C	-0.0755	0.0164	0.2108
47	rs871893	6.32E-06	T	C	-0.0501	0.0111	0.8091
48	rs12774577	1.31E-06	T	C	-0.0619	0.0128	0.8646
49	rs11191833	1.11E-07	A	G	-0.0467	0.0088	0.4011
50	rs149070156	5.33E-07	T	C	0.18	0.0359	0.024
51	rs360139	1.57E-07	A	G	-0.0475	0.0091	0.4279
52	rs7933146	2.64E-06	A	T	0.12	0.0255	0.0504
53	rs10501153	3.84E-06	T	C	-0.0445	0.0096	0.3038
54	rs9651613	2.63E-07	A	G	0.0498	0.0097	0.3328
55	rs2005108	3.33E-08	T	C	0.08	0.0145	0.1281
56	rs7304841	4.93E-08	A	C	0.0484	0.0089	0.593
57	rs10876531	3.12E-06	A	C	0.0429	0.0092	0.6424
58	rs117907142	5.67E-06	A	G	-0.0962	0.0212	0.9356
59	rs10858932	5.58E-06	T	C	-0.0509	0.0112	0.7671
60	rs3184504	2.17E-14	T	C	0.0751	0.0098	0.4521
61	rs35436	3.21E-08	T	C	-0.0495	0.0089	0.3814
62	rs79280766	4.71E-06	A	G	0.1486	0.0325	0.0359
63	rs9526212	9.19E-10	A	G	-0.0615	0.0101	0.2386
64	rs73182566	5.65E-06	T	C	0.2021	0.0445	0.0189
65	rs339800	7.62E-08	T	C	0.0597	0.0111	0.2934
66	rs7329411	1.87E-06	A	C	0.0416	0.0087	0.3666
67	rs12886234	6.19E-06	A	G	0.0391	0.0087	0.3772
68	rs2036738	2.38E-07	A	G	-0.0626	0.0121	0.8471
69	rs113802622	1.66E-06	A	C	-0.1442	0.0301	0.9657
70	rs4932370	2.88E-08	A	G	0.0519	0.0094	0.333

71	rs8028726	4.37E-07	T	G	0.0432	0.0085	0.4405
72	rs12932445	1.77E-06	T	C	-0.0488	0.0102	0.7739
73	rs12445022	1.28E-10	A	G	0.0609	0.0095	0.3057
74	rs9909858	3.63E-08	T	C	-0.0893	0.0162	0.812
75	rs11079753	5.49E-06	A	G	-0.0413	0.0091	0.5747
76	rs113225354	1.40E-06	A	G	-0.1324	0.0274	0.9643
77	rs2632512	5.02E-06	T	C	0.054	0.0118	0.1981
78	rs7242591	6.81E-06	A	G	0.0402	0.0089	0.3357
79	rs34212978	2.21E-06	T	C	-0.076	0.0161	0.8991
80	rs1053007	3.58E-08	A	G	-0.0479	0.0087	0.3494
81	rs9749384	8.14E-06	T	C	-0.0375	0.0084	0.541
82	rs2608738	2.12E-06	A	G	-0.0854	0.018	0.7857
83	rs6137856	5.00E-06	A	G	0.0492	0.0108	0.7991
84	rs9653750	7.29E-06	A	G	0.0498	0.0111	0.1797
85	rs7279339	3.54E-06	A	G	0.0446	0.0096	0.2855
86	rs10427961	4.71E-06	T	C	-0.0794	0.0173	0.7703
87	rs9616414	2.66E-06	C	G	-0.0438	0.0093	0.6369

Table S3 Characteristics of Instrumental Variables of LAS

	SNP	P value	effect allele	other allele	Beta	SE	EAF
1	rs2065524	3.56E-06	A	G	-0.2184	0.0471	0.0795
2	rs144415357	8.73E-06	T	C	0.5109	0.1149	0.0184
3	rs12124533	1.22E-08	T	C	0.1529	0.0268	0.2412
4	rs7522794	1.04E-06	T	C	0.1102	0.0226	0.4556
5	rs114667237	1.05E-06	A	G	0.4516	0.0925	0.0195
6	rs115422931	1.43E-06	A	G	0.3225	0.0669	0.0405
7	rs187898661	6.86E-06	T	C	0.3333	0.0741	0.0522
8	rs34048478	8.12E-07	T	C	-0.1212	0.0246	0.365
9	rs2117291	3.71E-06	T	C	0.1733	0.0375	0.0946
10	rs72845421	3.86E-06	T	C	0.4032	0.0873	0.026
11	rs80016789	9.44E-06	A	G	-0.3161	0.0714	0.9751
12	rs4688688	4.53E-06	C	G	0.1202	0.0262	0.1829
13	rs150188940	2.77E-06	A	G	-0.4659	0.0994	0.9805
14	rs142006987	1.49E-06	A	G	0.3495	0.0726	0.0371
15	rs4676799	3.10E-06	T	C	0.0985	0.0211	0.5719
16	rs34585560	5.14E-07	A	G	-0.1062	0.0211	0.4913
17	rs151126490	8.17E-06	C	G	0.4978	0.1116	0.0143
18	rs141329808	2.19E-06	A	C	0.3908	0.0825	0.027
19	rs112146801	3.03E-06	T	C	0.2622	0.0562	0.065
20	rs17612742	1.46E-11	T	C	-0.176	0.0261	0.791
21	rs62332423	6.32E-06	A	G	0.4222	0.0935	0.0219
22	rs62366320	7.81E-06	T	C	0.4877	0.1091	0.0228
23	rs150849782	2.10E-06	C	G	0.6812	0.1436	0.0137
24	rs1556093	1.10E-06	A	C	0.145	0.0298	0.2229
25	rs55741530	9.13E-06	A	T	-0.2444	0.0551	0.9323
26	rs56393506	1.33E-07	T	C	0.1566	0.0297	0.157
27	rs2107595	3.65E-15	A	G	0.1871	0.0238	0.2375
28	rs2868540	4.43E-06	A	C	0.0955	0.0208	0.5246
29	rs9690900	3.48E-06	C	G	0.1399	0.0301	0.3261
30	rs62496825	7.49E-06	T	G	0.4869	0.1087	0.0173
31	rs77886875	9.91E-06	T	C	-0.6072	0.1374	0.9866
32	rs75255626	7.81E-06	C	G	-0.3357	0.0751	0.9697
33	rs75309712	8.80E-06	T	C	-0.249	0.056	0.9414
34	rs7851521	9.63E-06	A	G	-0.1179	0.0267	0.2102
35	rs10990630	1.36E-07	A	G	-0.1365	0.0259	0.2315
36	rs34872471	7.06E-07	T	C	-0.1308	0.0264	0.7153
37	rs2793472	5.78E-06	A	G	0.1071	0.0236	0.7316
38	rs12282853	1.77E-06	T	C	0.4679	0.0979	0.0206
39	rs11232644	9.49E-06	T	G	0.4021	0.0908	0.0269
40	rs61901865	7.14E-06	A	G	0.1657	0.0369	0.1525
41	rs72985562	2.42E-08	T	G	-0.2449	0.0439	0.9166
42	rs35201864	6.53E-06	A	C	0.1671	0.0371	0.088
43	rs71486349	3.08E-06	T	G	0.4222	0.0905	0.0208
44	rs10772977	2.93E-06	A	C	0.0965	0.0206	0.4392
45	rs4766897	6.43E-07	T	C	0.1433	0.0288	0.3308
46	rs78223716	3.15E-06	A	G	-0.4367	0.0937	0.977
47	rs1564454	1.22E-07	A	G	-0.1086	0.0205	0.5764
48	rs35037256	1.45E-06	A	G	-0.0987	0.0205	0.4664
49	rs4792107	9.52E-06	A	G	0.127	0.0287	0.7723

50	rs77158902	7.18E-06	T	C	0.4183	0.0932	0.0223
51	rs12952699	2.10E-06	A	G	0.125	0.0263	0.1756
52	rs142395500	7.71E-07	A	G	0.4295	0.0869	0.0241
53	rs151166754	1.36E-06	T	C	0.4759	0.0985	0.0235
54	rs76263261	3.47E-06	T	C	-0.4149	0.0894	0.9742
55	rs311774	6.08E-06	A	G	0.24	0.0531	0.078
56	rs74461240	1.74E-07	A	G	-0.3245	0.0621	0.9549
57	rs76216590	2.75E-06	T	G	-0.2017	0.043	0.8485
58	rs117105726	3.61E-06	A	G	0.4994	0.1078	0.0167
59	rs6040293	4.37E-06	C	G	-0.0972	0.0212	0.4657
60	rs73128528	3.80E-06	A	T	-0.1514	0.0328	0.8559
61	rs848732	7.26E-06	A	G	-0.1025	0.0228	0.5879

Table S4 Characteristics of Instrumental Variables of CES

	SNP	P value	effect allele	other allele	Beta	SE	EAF
1	rs139069797	3.66E-06	A	G	0.1343	0.029	0.1538
2	rs638704	1.47E-07	T	C	-0.0905	0.0172	0.5686
3	rs61826350	5.69E-06	T	C	0.309	0.0681	0.955
4	rs57167296	9.57E-06	A	G	-0.1773	0.0401	0.8545
5	rs114279112	1.14E-07	T	G	-0.4327	0.0816	0.9809
6	rs72859301	5.01E-06	A	G	-0.1206	0.0264	0.864
7	rs2100192	4.82E-07	A	C	-0.1008	0.02	0.7511
8	rs13143308	1.86E-47	T	G	0.2798	0.0193	0.2817
9	rs1906613	1.83E-08	A	G	0.1019	0.0181	0.3723
10	rs66694617	2.60E-06	T	C	0.2111	0.0449	0.0545
11	rs6536024	3.99E-07	T	C	-0.0892	0.0176	0.4693
12	rs44444878	5.17E-08	A	C	0.0969	0.0178	0.3853
13	rs68189045	3.24E-06	T	C	0.1349	0.029	0.1112
14	rs60701788	7.49E-06	A	C	-0.1037	0.0231	0.8187
15	rs55884259	3.87E-09	A	G	-0.1096	0.0186	0.6576
16	rs7767246	1.87E-06	C	G	0.1069	0.0224	0.7974
17	rs16882237	7.73E-06	T	C	0.1309	0.0293	0.1062
18	rs11772660	1.60E-06	A	G	-0.0884	0.0184	0.6297
19	rs3807989	1.85E-07	A	G	-0.091	0.0174	0.4133
20	rs1549758	9.34E-06	T	C	0.0907	0.0205	0.295
21	rs59498841	5.32E-07	A	G	0.1564	0.0312	0.1992
22	rs60229978	5.50E-06	C	G	0.3413	0.0751	0.0453
23	rs16939239	4.08E-07	A	G	0.1419	0.028	0.1248
24	rs636828	6.55E-06	A	T	0.0882	0.0196	0.26
25	rs78893982	2.65E-06	T	G	-0.1902	0.0405	0.9289
26	rs635634	6.21E-07	T	C	0.1116	0.0224	0.2012
27	rs77908495	9.35E-06	A	G	0.2566	0.0579	0.0413
28	rs2891447	6.92E-06	T	C	-0.1243	0.0276	0.8703
29	rs11596587	7.58E-08	T	C	0.2019	0.0375	0.0953
30	rs74154533	6.08E-07	A	G	0.1131	0.0227	0.1771
31	rs1812258	1.99E-06	T	C	0.1269	0.0267	0.148
32	rs73121964	1.36E-06	A	G	-0.3362	0.0696	0.9747
33	rs12322049	3.23E-06	A	G	0.1435	0.0308	0.1568
34	rs1323182	3.12E-06	A	G	-0.0942	0.0202	0.7206
35	rs535923	2.57E-06	T	G	0.0799	0.017	0.4384
36	rs12874361	7.34E-07	A	T	-0.4982	0.1006	0.9853
37	rs117858373	5.51E-06	C	G	-0.3281	0.0722	0.976
38	rs1964465	6.27E-06	A	G	0.1027	0.0227	0.1914
39	rs150858389	5.07E-06	T	C	0.5018	0.11	0.0144
40	rs12932445	6.86E-18	T	C	-0.1839	0.0213	0.7923
41	rs17677363	8.19E-06	A	T	-0.1235	0.0277	0.8722
42	rs4293488	1.98E-06	T	C	-0.084	0.0177	0.4673
43	rs12607709	5.32E-06	A	G	0.1263	0.0277	0.1171
44	rs8109412	2.84E-06	T	C	0.0981	0.021	0.761
45	rs10407506	2.92E-06	T	C	0.1108	0.0237	0.1772
46	rs76427041	6.71E-06	T	C	0.1407	0.0312	0.1256
47	rs188877744	5.08E-06	T	G	-0.3047	0.0668	0.9669

Table S5 Characteristics of Instrumental Variables of SVS

	SNP	P value	effect allele	other allele	Beta	SE	EAF
1	rs2455132	3.76E-07	T	C	-0.1	0.0197	0.2597
2	rs17035646	1.43E-06	A	G	0.0849	0.0176	0.4674
3	rs2842873	1.49E-07	T	C	-0.09	0.0171	0.3933

4	rs10494434	3.59E-06	A	G	0.1049	0.0226	0.2842
5	rs188186531	3.69E-07	A	T	0.1872	0.0368	0.8862
6	rs13411764	3.32E-06	A	G	0.0857	0.0184	0.7071
7	rs355092	3.96E-06	A	G	-0.1222	0.0265	0.2152
8	rs2060663	9.99E-06	T	C	-0.0835	0.0189	0.7166
9	rs6599175	2.27E-06	T	C	0.1086	0.023	0.7866
10	rs905142	9.26E-06	T	C	-0.0782	0.0176	0.3709
11	rs6790965	8.31E-06	T	C	0.085	0.0191	0.2719
12	rs6845977	6.38E-06	T	C	-0.0824	0.0183	0.7109
13	rs10017904	7.72E-07	A	G	0.1578	0.0319	0.1361
14	rs12520006	6.61E-06	A	G	-0.1629	0.0362	0.9098
15	rs17433120	2.06E-07	A	T	-0.149	0.0287	0.1582
16	rs6936630	1.38E-06	A	T	0.1667	0.0345	0.1077
17	rs2501966	3.09E-06	A	G	0.0771	0.0165	0.5107
18	rs9320625	7.15E-06	A	T	-0.079	0.0176	0.6055
19	rs73198900	4.68E-06	A	G	0.3613	0.0789	0.0196
20	rs58067542	8.04E-06	T	C	0.0916	0.0205	0.4382
21	rs11786691	9.64E-06	A	G	0.1453	0.0328	0.1179
22	rs2411256	2.23E-06	A	G	0.0899	0.019	0.2774
23	rs7016981	9.84E-06	T	C	-0.0905	0.0205	0.7178
24	rs9697029	7.96E-06	C	G	-0.1198	0.0268	0.8854
25	rs12415269	3.10E-06	T	C	-0.0937	0.0201	0.2643
26	rs7079323	2.77E-06	T	C	-0.0856	0.0183	0.5361
27	rs11597695	2.05E-07	T	C	0.0969	0.0187	0.3301
28	rs2142308	7.06E-07	C	G	-0.0919	0.0185	0.3
29	rs537553	9.59E-06	A	G	-0.0945	0.0213	0.749
30	rs12300942	1.04E-06	C	G	0.1163	0.0238	0.1567
31	rs11065979	1.51E-06	T	C	0.1097	0.0228	0.4165
32	rs9521686	5.09E-06	T	C	-0.0863	0.0189	0.2837
33	rs9515201	1.05E-07	A	C	0.1072	0.0202	0.289
34	rs215897	5.93E-06	T	C	-0.0917	0.0202	0.3331
35	rs12445022	2.55E-09	A	G	0.1198	0.0201	0.2764
36	rs9890967	5.42E-06	A	T	-0.1381	0.0304	0.8613
37	rs1119799	4.27E-06	T	G	0.0879	0.0191	0.2507
38	rs10413833	2.94E-06	A	G	-0.192	0.0411	0.9336

Table S6 SNPs as Instrumental Variables in the MR Analysis of the Effect of Plasma Protein Level Ratios on AIS

Exposure	SNP	Effect allele	Other allele	Exposure			Outcome			R ²	F
				Beta	SE	P value	Beta	SE	P value		
TGFB2/THBD protein level ratio	rs1042579	G	A	-0.2425	0.008357	2.65E-183	-0.0345	0.0108	0.001401	0.019768	841.9648
	rs111541957	G	A	-0.10957	0.010418	7.77E-26	-0.0225	0.0189	0.233859	0.002651	110.6019
	rs11605349	T	C	-0.06079	0.010746	1.55E-08	4.00E-04	0.0174	0.981659	0.000766	31.9996
	rs1870702	T	C	0.057222	0.006869	8.27E-17	0.0278	0.0085	0.001073	0.001679	69.40012
	rs2837982	T	C	0.059634	0.007061	3.14E-17	0.0109	0.0091	0.230994	0.001709	71.31499
	rs30535	C	A	-0.06878	0.011407	1.66E-09	0.0128	0.0207	0.53634	0.00087	36.35525
	rs33950747	C	T	-0.17873	0.012516	3.73E-46	-0.0214	0.0232	0.356313	0.004857	203.919
	rs34675647	C	T	-0.08827	0.007519	8.92E-32	0.0014	0.01	0.88866	0.003294	137.8213
	rs34794275	T	C	0.070749	0.009884	8.32E-13	0.0241	0.0142	0.089662	0.001226	51.23501
	rs507666	G	A	-0.28365	0.008499	1.00E-200	-0.0443	0.0112	7.64E-05	0.026018	1113.729
	rs6113722	G	A	0.101596	0.017915	1.43E-08	-0.0111	0.0169	0.511306	0.000769	32.15729
	rs72897585	A	G	-0.07336	0.011557	2.21E-10	0.0011	0.0124	0.929313	0.000965	40.29129
	rs75691219	T	G	0.055512	0.01002	3.04E-08	-0.0139	0.0141	0.324224	0.000738	30.69212
	rs7573901	T	C	0.18373	0.02439	5.09E-1	-0.0018	0.038	0.96290	0.00135	56.7304

5			3	3	4		7	2	6	2
rs9910365	A	G	-0.0649	0.00950	8.62E-1	-0.0101	0.012	0.41156	0.00111	46.6443
			1	4	2		3	8	8	2

Table S7 SNPs as Instrumental Variables in the MR Analysis of the Effect of Plasma Protein Level Ratios on SVS

Exposure	SNP	Effect allele	Other allele	Exposure			Outcome			R ²	F
				Beta	SE	P value	Beta	SE	P value		
GPIBA/SD C4 protein level ratio	rs104789	C	A	0.04741	0.00750	2.63E-10	0.0095	0.020	0.64943	0.00096	39.9484
	1			1	1			9	6	2	1
	rs109141	T	C	0.08099	0.00877	2.75E-20	0.0231	0.020	0.25514	0.00205	85.2430
	44			7	3			3	9	7	3
	rs115464	G	A	0.0936	0.01482	2.76E-10	0.0723	0.036	0.04579	0.00095	39.8551
	798			6	6			2	9	7	7
	rs115962	C	T	-0.0806	0.00750	6.39E-27	-0.0397	0.020	0.04937	0.00278	115.570
	35			7	4			2	4	6	4
	rs117687	A	G	0.2024	0.00975	3.10E-95	0.0371	0.030	0.22535	0.01025	430.910
	61							6	2	5	8
	rs124114	A	G	0.16283	0.00980	9.64E-62	0.0274	0.022	0.21504	0.00658	275.814
	84			7	5			1	2	7	2
	rs126556	C	T	-0.0510	0.00746	7.66E-12	-0.0092	0.018	0.60927	0.00113	46.8764
	6			9	1				3		2
	rs135403	T	C	-0.0967	0.00707	1.73E-42	-0.0323	0.016	0.05309	0.00448	187.039
	4							7	7	2	8
	rs198142	G	T	-0.2518	0.00684	1.00E-20	-0.0381	0.019	0.04837	0.03151	1352.60
	9			2	7	0		3	1	4	1
	rs223308	T	C	-0.0721	0.00781	2.70E-20	-0.013	0.018	0.47746	0.00205	85.2820
	5			7	4			3	7	1	1
rs353043	A	G	0.05305	0.00894	3.07E-09	0.0033	0.020	0.87272	0.00088	35.1554	
00			2	7			6	8	9	8	
rs478318	T	C	-0.0702	0.01045	1.77E-11	0.0051	0.023	0.82451	0.00108	45.2348	
6			9	1				7	5		
rs599349	A	G	0.05715	0.00714	1.31E-15	0.0074	0.017	0.66334	0.00153	63.9499	
4			5	7				9	5	7	
rs6065	C	T	0.09616	0.01344	8.65E-13	9.00E-0	0.027	0.97408	0.00124	51.1579	
			8	5		4		7	5	1	
rs686168	G	A	-0.045	0.00750	2.07E-09	-0.0136	0.022	0.54375	0.00086	35.9225	
1				8			4	6	3	9	
rs689499	G	A	0.04525	0.00693	6.96E-11	0.0108	0.016	0.51276	0.00102	42.5498	
8			5	7			5		1	4	
rs708038	C	A	0.06309	0.00704	3.37E-19	0.0499	0.017	0.00505	0.00192	80.2824	
6			4	2			8	7	5	8	
rs719055	G	A	0.07131	0.00915	6.76E-15	-0.0019	0.026	0.94262	0.00146	60.7104	
1			6	3			4	6	3	2	
rs730589	T	C	-0.0820	0.01413	6.64E-09	-0.0441	0.044	0.32168	0.00080	33.6505	
09			1	7			5		8		
rs755109	T	C	-0.0660	0.0072	4.52E-20	-0.0346	0.020	0.08518	0.00202	84.2617	
			9				1		2	9	
rs779516	A	G	0.07385	0.01303	1.46E-08	0.0465	0.035	0.18774	0.00077	32.1226	
46			9	1			3	5	3	4	
SDC4/	rs104502	C	T	0.05672	0.01033	4.04E-08	-0.0407	0.032	0.20764	0.00071	30.1402
	0			9	3			3	7	7	9
SEMA4D	rs104789	C	A	-0.0416	0.00746	2.44E-08	0.0095	0.020	0.64943	0.00074	31.1217
	1			5	6			9	6	3	9
protein	rs109141	T	C	-0.0624	0.00874	1.00E-12	0.0231	0.020	0.25514	0.00121	50.8721
	44			9	9			3	9	8	2
level	rs115264	C	T	0.06392	0.00759	3.90E-17	-0.018	0.019	0.35100	0.00168	70.8855
	68			5	2			3	5	6	2
ratio	rs115464	G	A	-0.0979	0.01477	3.44E-11	0.0723	0.036	0.04579	0.00104	43.9306
	798			1	1			2	9	6	1
	rs115962	C	T	0.1122	0.00746	5.95E-51	-0.0397	0.020	0.04937	0.00538	226.020
	35				3			2	4	7	2
	rs117687	A	G	-0.2067	0.00969	1.98E-10	0.0371	0.030	0.22535	0.01073	455.013
	61			6	3	0		6	2		8
	rs124114	A	G	-0.1112	0.00979	8.16E-30	0.0274	0.022	0.21504	0.00306	128.825
	84			1	8			1	2		1
	rs128873	T	C	0.06212	0.00931	2.65E-11	-0.0126	0.019	0.51166	0.00106	44.4424
	23				8			2	3	6	5
	rs129205	A	G	-0.0433	0.00694	4.68E-10	0.0075	0.016	0.65719	0.00092	38.8249
	3				9			9	7	5	5

rs1354034	T	C	0.180177	0.007005	8.88E-145	-0.0323	0.0167	0.053097	0.015539	661.5844
rs16948048	A	G	-0.04134	0.00715	7.40E-09	-0.0084	0.0191	0.660089	0.000796	33.43901
rs1981429	G	T	0.242222	0.006829	1.00E-200	-0.0381	0.0193	0.048371	0.029122	1257.853
rs2065500	A	G	-0.05318	0.009481	2.05E-08	0.0194	0.0202	0.336856	0.000748	31.46178
rs2280334	T	C	0.047166	0.007396	1.83E-10	0.0071	0.0176	0.686647	0.00097	40.6622
rs3183927	A	G	0.045179	0.007169	2.99E-10	-0.0323	0.0187	0.084119	0.000945	39.70135
rs35304300	A	G	-0.06845	0.008896	1.46E-14	0.0033	0.0206	0.872728	0.001483	59.19788
rs3816281	G	T	0.046277	0.007988	6.96E-09	-0.0147	0.0181	0.416703	0.000801	33.55764
rs385893	T	C	-0.06946	0.006923	1.15E-23	0.0071	0.0179	0.691627	0.002393	100.6791
rs4783186	T	C	0.081203	0.010395	5.76E-15	0.0051	0.0237	0.824517	0.001451	61.02399
rs667805	A	G	0.056771	0.010148	2.23E-08	0.0074	0.0222	0.738883	0.00075	31.29738
rs6861681	G	A	0.041602	0.007477	2.65E-08	-0.0136	0.0224	0.543756	0.000737	30.95502
rs7034469	T	C	0.043277	0.006952	4.85E-10	0.0056	0.0187	0.764585	0.000923	38.75293
rs7080386	C	A	-0.09014	0.007005	8.10E-38	0.0499	0.0178	0.005057	0.003926	165.5621
rs7190551	G	A	-0.08903	0.009114	1.61E-22	-0.0019	0.0264	0.942626	0.002278	95.43421
rs73185884	C	A	-0.0554	0.00932	2.80E-09	-0.0055	0.0285	0.844275	0.000842	35.33017
rs79312216	T	C	0.180179	0.022144	4.17E-16	-0.0856	0.0423	0.043007	0.001577	66.20386
rs7949566	G	A	-0.09224	0.006974	8.03E-40	-0.0032	0.0172	0.850692	0.004148	174.7728
rs904800	A	G	-0.04114	0.007024	4.74E-09	0.0113	0.0174	0.516064	0.000819	34.30502

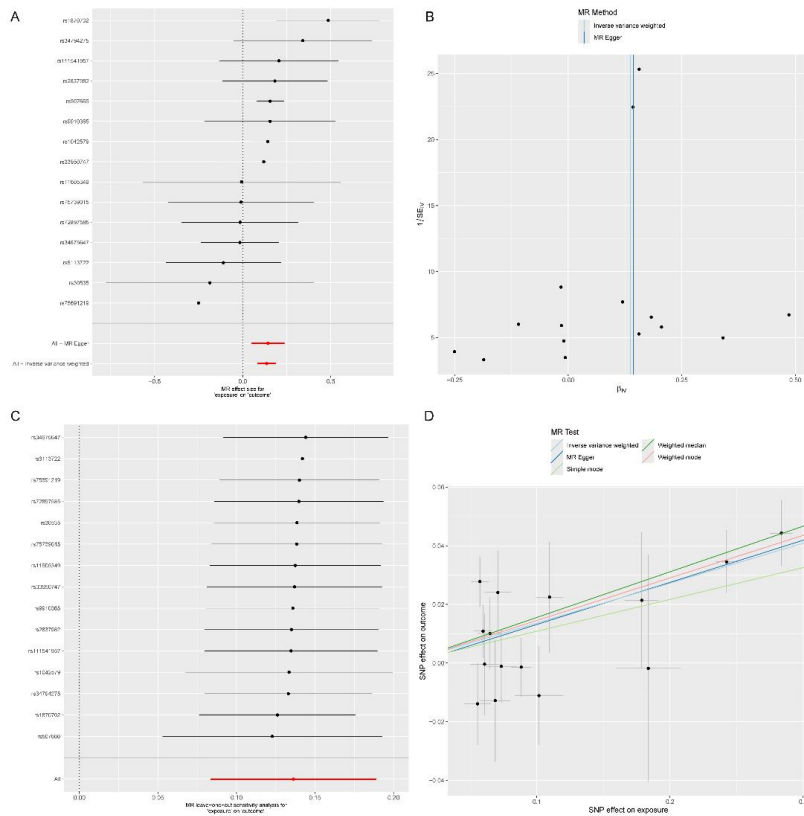


Figure S1 Forest Plot (A), Funnel Plot (B), Sensitivity Analysis (C) and Scatter Plot (D) of the Causal Effect of TGFBR2/THBD Protein Level Ratio on AIS.

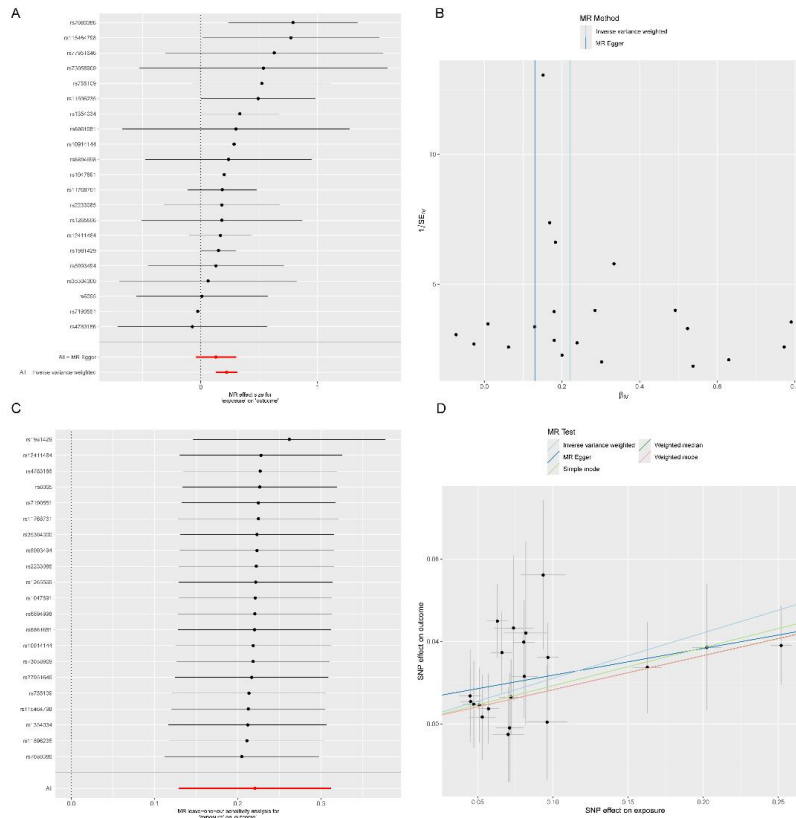


Figure S2 Forest Plot (A), Funnel Plot (B), Sensitivity Analysis (C) and Scatter Plot (D) of the Causal Effect of GP1BA/SDC4 Protein Level Ratio on SVS

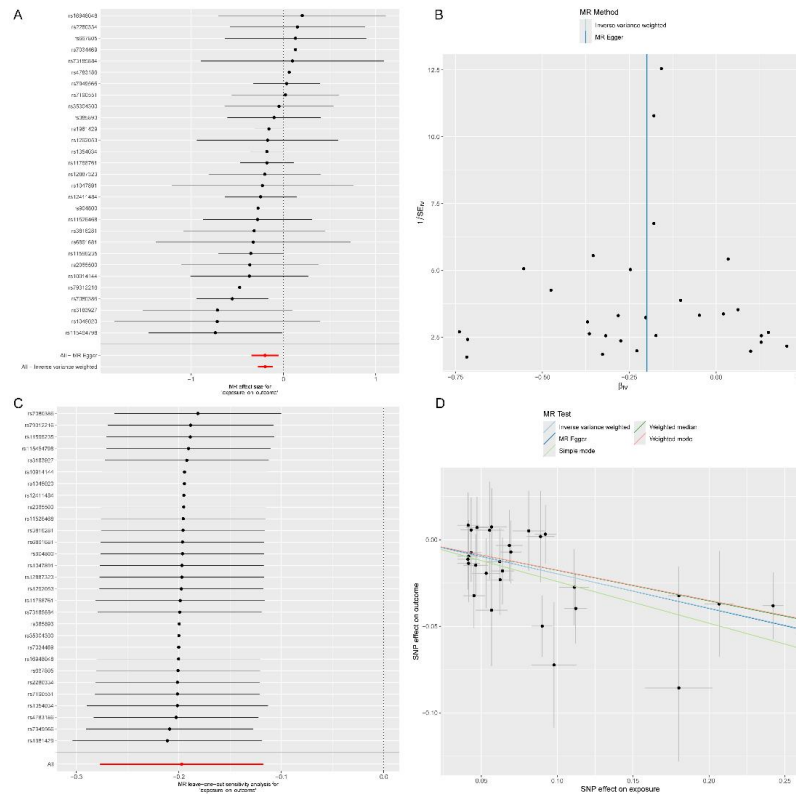


Figure S3 Forest Plot (A), Funnel Plot (B), Sensitivity Analysis (C) and Scatter Plot (D) of the Causal Effect of SDC4/SEMA4D Protein Level Ratio on SVS