Modifiable risk factors for intracranial aneurysms in Asian populations: A univariable and multivariable Mendelian randomization study

Abstract

Background: To investigate the potential modifiable risk factors for intracranial aneurysms in Asian populations using Mendelian randomization analysis.

Methods: Genetic data for intracranial aneurysms and modifiable risk factors in Asian populations were extracted from the IEU Open GWAS project database. Single-nucleotide polymorphisms significantly associated with modifiable risk factors across the genome were used as instrumental variables. Two-sample and multivariate Mendelian randomization analyses were performed to assess the causal relationship between each risk factor and intracranial aneurysms.

Results: In Asian populations, univariable MR analysis revealed that genetically predicted systolic blood pressure, diastolic blood pressure, and ischemic stroke were significantly associated with an increased risk of intracranial aneurysms (OR = 6.14, 95% CI: 3.67-10.26, P = 4.45×10^{-12}; OR = 4.88, 95% CI: 2.69-8.86, P = 1.97×10^{-7}; OR = 1.89, 95% CI: 1.28-2.78, P = 1.38×10^{-3}), while serum low-density lipoprotein cholesterol, total cholesterol, and type 2 diabetes mellitus were significantly associated with a decreased risk of intracranial aneurysms (OR = 0.65, 95% CI: 0.50-0.84, P = 1.13×10^{-3}; OR = 0.62, 95% CI: 0.49-0.79, P = 6.90×10^{-5}; OR = 0.82, 95% CI: 0.76-0.89, P = 3.48×10^{-7}). Multivariate MR analysis showed that systolic blood pressure (OR = 12.33, 95% CI: 2.46-61.74, P = 2.24×10^{-3}), ischemic stroke (OR = 1.50, 95% CI: 1.01-2.12, P = 4.78×10^{-2}), and type 2 diabetes mellitus (OR = 0.79, 95% CI: 0.70-0.89, P = 1.11×10^{-4}) remained significant causal factors for intracranial aneurysms.

Conclusions: In Asian populations, there is a causal relationship between systolic blood pressure, ischemic stroke, and an increased risk of intracranial aneurysms, while type 2 diabetes mellitus is associated with a decreased risk of intracranial aneurysms.

Keywords: Mendelian randomization study, modifiable risk factors, intracranial aneurysms, Asian.

1. Introduction

Intracranial aneurysms (IAs) are localized lesions of the cerebral vascular system, with a prevalence of approximately 3% in the general population.[1] Unruptured intracranial aneurysms (uIAs) are often asymptomatic, but aneurysmal subarachnoid hemorrhage (aSAH) caused by the rupture of IAs leads to approximately 30% of disability and mortality.[2] Considering the significant incidence of IA and the high rate of disability and mortality after rupture, there is an urgent need to identify IA-related risk factors to develop timely prevention strategies. Previous studies have shown that, in addition to immutable factors such as gender, modifiable risk factors associated with aneurysm development mainly include hypertension, smoking, coronary heart disease, and family history of stroke.[3-5]

These traditional epidemiological research methods, such as observational studies and cohort studies, have certain limitations in identifying IA risk factors, which are more prone to the influence of reverse causation and confounding factors. Mendelian randomization (MR) is a novel epidemiological approach that utilizes genetic variants and single-nucleotide polymorphisms (SNPs) as instrumental variables (IVs) based on genome-wide association studies (GWAS) data to reveal the relationship between exposure and outcomes.[6] Current MR studies on IA have almost exclusively used genetic data from individuals of European ancestry, but there are differences in aneurysm incidence among different ethnic groups. This study focuses on modifiable risk factors and protective factors for IA in Asian populations and conducts two-sample MR analysis and multivariate MR analysis separately.

2. Methods

2.1. Modifiable Risk Factors and Data Sources

The risk factors included in this study are divided into two categories. Lifestyle factors include smoking initiation and smoking cessation. Cardiometabolic factors include body mass index (BMI), high-sensitivity C-reactive protein (hs-CRP), systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), total

cholesterol (TC), triglycerides (TG), ischemic stroke, and type 2 diabetes mellitus (T2DM). The genetic data of the above modifiable risk factors and IA were obtained from the Biobank Japan release of disease traits within the IEU (Integrative Epidemiology Unit) Open GWAS project, as detailed in Table 1.

Table 1. Genetic Statistical Data Sources for Modifiable Risk Factors and Intracranial Aneurysms.

Database	Source	GWAS ID	Trait	Sample size	Number of SNPs	Year
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-1	BMI	158,284	5,961,600	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-14	C-reactive protein	75,391	6,108,953	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-17	DBP	136,615	6,108,953	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-24	HDL-c	70,657	6,108,953	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-31	LDL-c	72,866	6,108,953	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-52	SBP	136,597	6,108,953	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-54	TC	128,305	6,108,953	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-55	TG	105,597	6,108,953	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-78	Smoking initiation	165,436	5,961,480	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-81	Smoking cessation	76,047	5,961,480	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-96	Cerebral aneurysm	195,203	8,885,031	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-129	Ischemic stroke	210,054	8,885,705	2019
IEU Open GWAS project	Biobank Japan release of disease traits	bbj-153	T_2DM	210,865	8,885,694	2019

2.2. Univariable MR Analysis

The analysis was conducted using R version 4.3.2 and R packages such as TwoSampleMR and MendelianRandomization.

2.2.1. Selection of IVs

2.2.1.1. Association Analysis

GWAS data for each exposure factor was downloaded, and SNPs strongly associated with the exposure factors were extracted as IVs. A P-value threshold of $< 5 \times 10^{-8}$ was set as the criterion for strong association between the tool variables and exposure factors (if the number of SNPs ultimately used for MR analysis was less than 3, the threshold was adjusted to $P < 5 \times 10^{-6}$).

2.2.1.2. Removal of Linkage Disequilibrium (LD)

SNPs that are more likely to be inherited together due to their proximity in the genome were removed. SNPs with kb > 10000 and $r^2 < 0.001$ were filtered out, ensuring the independence of random distribution among SNPs by retaining the SNP with the lowest P-value associated with the risk factor.

2.2.1.3. Evaluation of Weak Instrument Bias

The R^2 value of each SNP was obtained to calculate the F-statistic for assessing weak instrument bias. $R^2 = 2 \times beta^2 \times eaf \times (1\text{-}eaf)$, where beta is the effect size of the SNP, eaf is the frequency of the SNP's effect allele, and R^2 represents the extent to which a single IV explains the exposure. $F = ((N\text{-}k\text{-}1)/k) \times (R^2/(1\text{-}R^2))$, where N is the sample size of the GWAS study for that exposure factor, and k represents the number of IVs (k=1 since we are calculating the F-statistic for a single SNP). SNPs with F-statistic values > 10 were retained, while those with weak instrument bias were removed.[7]

2.2.1.4. Removal of Confounding Factors

MR Should follow the assumption that the IVs involved in the analysis neither affect IAs through other traits associated with IAs nor are they directly associated with IAs ($P < 1 \times 10^{-5}$). Genome-wide traits significantly associated with these IVs ($P < 1 \times 10^{-5}$) were searched through the PhenoScanner website, and IVs directly associated with IAs were deleted if necessary. Considering that the current research on the risk factors of IAs is still controversial and our study includes many exposure factors, we will not delete the SNPs that may be related to confounding factors in the subsequent statistical analysis. We performed a test for horizontal pleiotropy in sensitivity analyses to minimize the possibility of horizontal pleiotropy. Multivariate Mendelian randomization analysis (MVMR) was added to subsequent analyses to further discuss the effects of possible confounding exposures.

2.2.1.5. Extraction of IVs from GWAS Data of the Outcome Factor

The remaining SNPs screened through the above process were extracted from the GWAS data of IA. SNPs that could not be extracted from the dataset due to poor imputation quality were replaced with proxy SNPs ($r^2 > 0.9$, if available). The information of the extracted SNPs in the exposure data was

merged with the information in the outcome data, and palindromic SNPs with allele frequencies above 0.42 and below 0.58 were removed.[8] The final IVs for the two-sample MR analysis were obtained.

2.2.2. Statistical Analysis

We conducted two-sample MR analyses using the inverse-variance weighted (IVW) method, the weighted median method, and the MR-Egger method to assess the effects of modifiable risk-related variants on IA in Asian populations. Among them, the IVW method with a random-effects model was chosen as the decisive method to determine whether there is a causal relationship between exposure and outcome.[9-11] The impact of exposure on outcomes is expressed using Odds ratio (OR) and 95% confidence interval (95% CI). Since 12 independent exposure hypotheses were tested simultaneously for the same outcome, a Bonferroni-corrected P-value $< 4.17 \times 10^{-3}$ was considered statistically significant. When the P-value was < 0.05 but higher than the Bonferroni Corrected threshold, it was considered indicative evidence of a potential causal relationship.[12]

2.2.3. Sensitivity Analysis

The horizontal pleiotropy was assessed by estimating the deviation of the MR-Egger intercept, with a P-value < 0.05 for the intercept indicating the presence of horizontal pleiotropy, which is not permissible.[13] Heterogeneity was evaluated using the Cochran Q-derived P-value calculated by the IVW method and the MR-Egger method, with Q-pval < 0.05 indicating the presence of heterogeneity.[14] The Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) Outlier test was used to detect and correct biased SNPs, and SNPs with P-values < 0.05 should be removed and the MR analysis should be repeated.[15] The leave-one-out analysis assessed the robustness of the MR analysis by individually removing each SNP.[16]

2.3. MVMR (Multivariate mendelian randomization) Analysis

Exposures that showed significant causal relationships with IA in the two-sample MR analysis were included in the MVMR analysis. The TwoSampleMR, MRPRESSO, and MendelianRandomization R software packages, as well as R Studio, were used for the analysis.

2.3.1. Selection of IVs

Strongly correlated SNPs were selected as IVs using a P-value < 5×10^{-8} as the threshold for strong correlation between IVs and exposure factors. SNPs strongly associated with exposure factors were extracted from the GWAS data of the exposures included in the MVMR analysis. SNPs were filtered for LD using kb > 10000 and $r^2 < 0.001$ as filtering conditions. The remaining SNPs were combined after LD pruning, and duplicate SNPs were removed. LD pruning was repeated according to the above criteria. SNPs were extracted from the GWAS data of each exposure factor and IA, and proxy SNPs were used if necessary. The SNP information extracted from various GWAS databases was merged (while removing palindromic SNPs) to ensure that the SNPs selected satisfied the conditions of being present in all GWAS databases involved in the MVMR analysis and strongly correlated with at least one exposure factor. The remaining SNPs were the IVs used in the MVMR analysis.

2.3.2. Identification of Exposures with High Collinearity

Collinearity refers to a high overlap between two or more exposure-related SNPs with similar effect sizes. Exposures included in the MVMR analysis have a risk of high collinearity, although collinearity is allowed in MVMR analysis, it is not particularly meaningful. The Least Absolute Shrinkage and Selection Operator (Lasso) function in the TwoSampleMR package was used to assess the collinearity of exposure factors and adjust the participating exposures accordingly.

2.3.3. Statistical Analysis

Using the MendelianRandomization R software package, the IVW method and Lasso regression were selected for the multivariate MR analysis to assess the effects of exposures that showed potential causal relationships in the two-sample MR analysis on IA, after adjusting for other exposure factors. The IVW method with a random-effects model was again chosen as the decisive method for determining causality. The Lasso method required regression screening of the IVs participating in the MVMR before analysis. In

the MVMR analysis, a P-value < 0.05 was considered statistically significant for the causal relationship between the exposure and IA.

2.3.4. Sensitivity Analysis

Similar to the sensitivity analysis in the two-sample MR analysis, the deviation of the MR-Egger intercept was estimated to assess horizontal pleiotropy. A P-value < 0.05 for the intercept indicated the presence of horizontal pleiotropy, and pleiotropy was not allowed. Heterogeneity tests were performed using the IVW method and the MR-Egger method, with a P-value < 0.05 indicating the presence of heterogeneity. The MR-PRESSO Outlier test was performed on individual SNPs to detect and correct biased SNPs.

3. Results

3.1. Univariable MR Analysis

Genetic variants predicting higher levels of SBP and DBP were significantly associated with an increased risk of IA (SBP: OR = 6.14, 95% CI: 3.67-10.26, P = 4.45×10^{-12}; DBP: OR = 4.88, 95% CI: 2.69-8.86, P = 1.97×10^{-7}). In the DBP analysis, rs1401982 and rs3856824 were excluded due to potential bias identified by the MR-PRESSO Outlier test. Genetically predicted lower levels of serum LDL-c and TC were significantly associated with a reduced risk of IA (LDL-c: OR = 0.65, 95% CI: 0.50-0.84, P = 1.13×10^{-3}; TC: OR = 0.62, 95% CI: 0.49-0.79, P = 6.90×10^{-5}). Additionally, genetically predicted ischemic stroke was associated with a higher risk of IA (OR = 1.89, 95% CI: 1.28-2.78, P = 1.38×10^{-3}). Genetic variants predicting T2DM were significantly associated with a reduced risk of IA (OR = 0.82, 95% CI: 0.76-0.89, P = 3.48×10^{-7}). The results of the significant associations between SBP, DBP, LDL-c, TC, ischemic stroke, T2DM, and IA using the Weighted Median method were consistent with those obtained using the IVW method (see Figure 1). Sensitivity analysis suggested that none of these causal relationships exhibited horizontal pleiotropy. Heterogeneity tests using the IVW and MR-Egger methods indicated heterogeneity in the causal associations between SBP, DBP, LDL-c, and IA. However, when the IVW method with a random-effects model was used as the decisive method for determining causality, the presence of heterogeneity did not affect the interpretation of the results. We believe that the heterogeneity

may have originated from different analysis platforms, experiments, and populations (see Table 2). The leave-one-out sensitivity analysis suggested that the MR results were robust.

exposure	nsnp	method	pval	OR(95% CI)
BMI	61	MR Egger	0.550	1.251 (0.603 to 2.595)
	61	Weighted median	0.897	1.024 (0.714 to 1.468)
	61	Inverse variance weighted	0.516	1.086 (0.847 to 1.393)
C−reactive protein	7	MR Egger	0.833	0.916 (0.422 to 1.989)
	7	Weighted median	0.900	0.969 (0.599 to 1.569)
	7	Inverse variance weighted	0.892	1.027 (0.703 to 1.501)
SBP	29	MR Egger	**0.012**	18.288 (2.236 to 149.588)
	29	Weighted median	**<0.001**	4.441 (2.549 to 7.739)
	29	Inverse variance weighted	**<0.001**	6.140 (3.673 to 10.264)
DBP	20	MR Egger	0.078	8.868 (0.903 to 87.110)
	20	Weighted median	**<0.001**	4.359 (2.262 to 8.398)
	20	Inverse variance weighted	**<0.001**	4.878 (2.685 to 8.864)
HDL−c	47	MR Egger	0.719	0.950 (0.719 to 1.255)
	47	Weighted median	0.266	0.898 (0.743 to 1.085)
	47	Inverse variance weighted	0.421	0.939 (0.807 to 1.094)
LDL−c	30	MR Egger	0.262	0.722 (0.413 to 1.262)
	30	Weighted median	**<0.001**	0.585 (0.426 to 0.804)
	30	Inverse variance weighted	**0.001**	0.652 (0.504 to 0.843)
Total cholesterol	44	MR Egger	0.178	0.649 (0.350 to 1.204)
	44	Weighted median	**0.008**	0.652 (0.476 to 0.894)
	44	Inverse variance weighted	**<0.001**	0.624 (0.494 to 0.787)
Triglyceride	35	MR Egger	0.209	0.843 (0.648 to 1.095)
	35	Weighted median	0.396	0.906 (0.721 to 1.138)
	35	Inverse variance weighted	0.819	0.981 (0.829 to 1.160)
Smoking initiation	23	MR Egger	0.843	2.515 (0.000 to 20513.540)
	23	Weighted median	0.402	2.594 (0.279 to 24.132)
	23	Inverse variance weighted	0.175	3.284 (0.589 to 18.321)
Smoking cessation	4	MR Egger	0.864	3.934 (0.000 to 4071528.162)
	4	Weighted median	0.380	0.307 (0.022 to 4.289)
	4	Inverse variance weighted	0.222	0.255 (0.028 to 2.287)
Ischemic stroke	4	MR Egger	0.850	2.337 (0.001 to 5465.269)
	4	Weighted median	**0.004**	2.003 (1.242 to 3.231)
	4	Inverse variance weighted	**0.001**	1.887 (1.279 to 2.784)
T2DM	114	MR Egger	**0.028**	0.813 (0.678 to 0.976)
	114	Weighted median	**0.017**	0.870 (0.776 to 0.976)
	114	Inverse variance weighted	**<0.001**	0.821 (0.761 to 0.886)

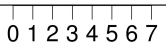

Figure 1 Two-sample Mendelian Randomization Analysis Results of Various Modifiable Risk Factors and Intracranial Aneurysms. When the p-value is less than 0.05, it is bolded and considered to have a potential causal effect. However, a p-value of less than 0.0042 is deemed statistically significant for a causal relationship.

Table 2. Results of Sensitivity Analysis in Two-sample Mendelian Randomization Analysis.

Exposure \ Method	MR-PRESSO	leaveoneout	Heterogeneity				MR-Egger Pleiotropy	
			IVW		MR-Egger			
			Q	P	Q	P	Intercept	P
BMI	removing rs4409766	NA	61.5326	0.4209	61.3624	0.3913	-0.0047	0.6873
C−reactive protein	NA	NA	5.0248	0.6569	5.0073	0.5429	0.0032	0.8989
SBP	NA	NA	58.6349	0.0006	56.3359	0.0008	-0.0359	0.3032
DBP	removing rs1401982、rs3856824	NA	33.7777	0.0195	33.2550	0.0155	-0.0189	0.6013
HDL-c	removing rs12293222	NA	71.2505	0.0099	71.2365	0.0076	-0.0010	0.9254
LDL-c	NA	NA	44.6459	0.0318	44.3873	0.0254	-0.0066	0.6893
TC	NA	NA	49.7269	0.2231	49.7048	0.1933	-0.0019	0.8919
TG	removing rs12293222	NA	38.2920	0.2809	35.9633	0.3314	0.0128	0.1533
Smoking initiation	NA	NA	27.1562	0.2054	27.1517	0.1659	0.0022	0.9534
Smoking cessation	NA	NA	1.5684	0.6666	1.4144	0.4930	-0.0377	0.7327
Ischemic stroke	NA	NA	3.1575	0.3680	3.1529	0.2067	-0.0160	0.9617
T_2DM	NA	NA	133.2469	0.0938	133.2322	0.0835	0.0009	0.9117

3.2. Multivariate MR Analysis

Based on the criteria, we included the exposures with significant causal relationships in the two-sample MR analysis as potential exposures for the MVMR analysis: SBP, DBP, LDL-c, TC, Ischemic stroke, and T2DM. After screening, a total of 114 SNPs were selected as the final IVs for the MVMR analysis. The Lasso function evaluation revealed no need to exclude any exposures due to collinearity. The MVMR analysis results showed that systolic blood pressure (OR = 12.33, 95% CI: 2.46-61.74, P = 2.24×10^{-3}), ischemic stroke (OR = 1.50, 95% CI: 1.01-2.12, P = 4.78×10^{-2}), and type 2 diabetes mellitus (OR = 0.79, 95% CI: 0.70-0.89, P = 1.11×10^{-4}) maintained significant causal relationships with IA after adjusting for the other exposures. After regression screening using the Lasso algorithm, 105 valid IVs were obtained from the 114 SNPs. The analysis showed that the significant associations were consistent with the IVW method (see Figure 2). Sensitivity analysis suggested that there was no horizontal pleiotropy in the MVMR analysis. Heterogeneity tests using the IVW and MR-Egger methods both indicated heterogeneity in the causal relationships in the MVMR analysis. However, when the IVW method with a random-effects model was used as the decisive method for determining causality, the presence of

heterogeneity did not affect the interpretation of the results. We believe that the heterogeneity may have originated from different analysis platforms, experiments, and populations. The MR-PRESSO Outlier test did not detect any outlier SNPs requiring correction (see Table 3).

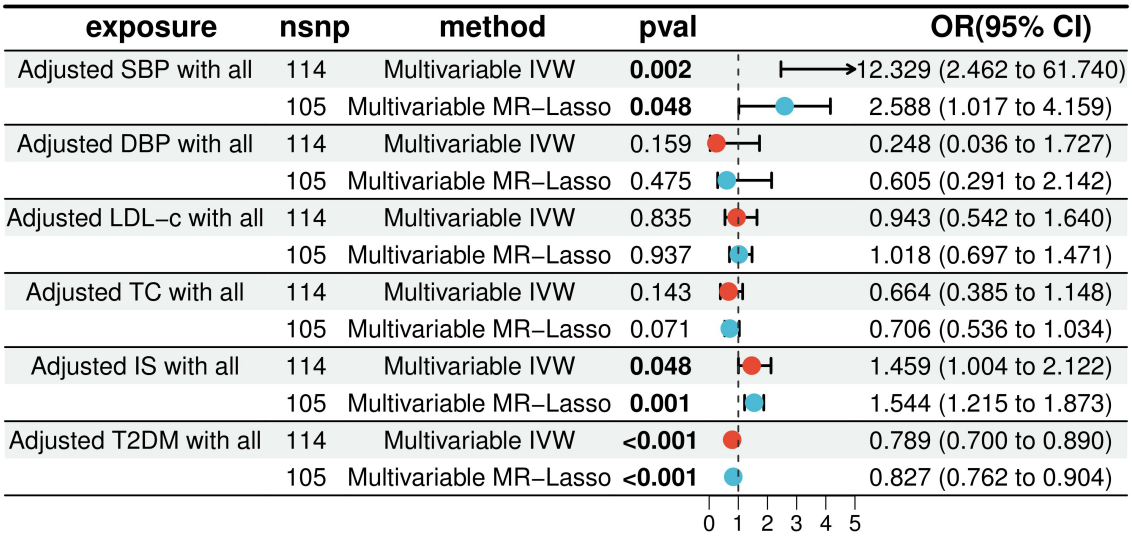

Figure 2 Results of Multivariable Mendelian Randomization Analysis.

Table 3. Results of Sensitivity Analysis in Multivariable Mendelian Randomization.

Exposure \ Method	LASSO	MR-PRESSO outlier test	Heterogeneity		MR-Egger Pleiotropy	
			IVW (P-value)	MR-Egger (P-value)	Intercept	P
SBP+DBP+LDL-c+TC+IS+T_2DM	Removing:NA	No outlier	0.0004	0.0003	-0.002	0.702

4. Discussion

In recent years, researchers have explored the modifiable risk factors of aneurysms through Mendelian randomization methods. For example, Tian et al. showed that daily smoking, smoking initiation, systolic blood pressure, hypertension, and body fat percentage were significantly associated with an increased risk of intracranial aneurysms.[17] Sun et al. demonstrated that blood pressure, smoking, education level, and insomnia were correlated with the risk of IA.[18] However, these studies primarily analyzed data from

European populations, whereas the occurrence of aneurysms differs between Asian and European ethnicities. For instance, studies have shown that the global prevalence of aneurysms averages 3.2%, while epidemiological surveys in China revealed a detection rate of unruptured aneurysms among adults as high as 7.0%.[19,20] Moreover, due to differences in ethnicities, the risk of rupture also varies. For example, the risk of rupture for unruptured aneurysms in the Japanese population is 2.8 times higher than that in Western populations.[21] This study primarily selected data from Asian populations for Mendelian randomization analysis. In addition to the design strengths of the MR Analysis, the strengths of this study include the following. Firstly, both univariate MR analysis and MVMR analysis used multiple MR analysis methods to evaluate potential causal relationships, and the consistency of the obtained effects demonstrated the robustness of our results. Secondly, the IVs currently analyzed all come from relatively uniform Asian populations, reducing bias caused by population differences. Finally, we screened IVs through layers of criteria to reduce possible bias from weak IVs and improve statistical power.

Previous retrospective studies investigating risk factors for IA have consistently shown that hypertension is an independent risk factor for IA.[3] A systematic review and meta-analysis that pooled 174 research reports revealed that hypertension is associated with a higher risk of IA (OR = 1.51, 95% CI: 1.17-1.94), which is also supported by relevant MR analyses.[17,18,22] Our study analyzed blood pressure indicators separately as "SBP" and "DBP", and the results showed that an increased risk of IA was associated with elevated SBP or DBP, consistent with previous studies. Both SBP and DBP, when exceeding normal ranges, can be considered as high-risk factors for IA in clinical risk prediction. The MVMR results indicated that SBP is less influenced by other factors compared to DBP, potentially making it more clinically significant. This aligns with the viewpoint that SBP indicators are better reflectors of vascular issues than DBP indicators.[23] Hypertension, as a systemic disease with atherosclerosis as its basic pathological change, predisposes the arterial walls to hyaline degeneration and hardening, which may promote the occurrence of IA due to decreased vascular adaptability. Recent studies have shown that the occurrence and development of IA are closely related to hemodynamics, and blood pressure, as a fundamental parameter of hemodynamics, may be associated with hemodynamic

stress and participate in the occurrence and development of IA.[24]

A meta-analysis encompassing 23 studies showed that the prevalence of UIA among patients with ischemic stroke was significantly higher than that in the general population (OR = 1.22, 95% CI: 1.01-1.47).[25] Ischemic strokes mainly arise from cerebral atherosclerotic stenosis combined with cerebral infarction caused by thrombosis. Our study revealed a significant association between ischemic stroke and the occurrence of IA. Additionally, although the pathological conditions of the extracellular matrix layer in the vessel walls of IA and cerebral atherosclerosis observed under electron microscopy are opposite, there are more similarities in the pathological processes of cerebral atherosclerosis and IA: phenotypic transformation and even apoptosis of smooth muscle cells in the tunica media of the vascular wall; the tight junctions between endothelial cells may be disrupted; a similar inflammatory cell infiltration process between cerebral atherosclerosis and IA. At the same time, the vascular fitness of both cerebral atherosclerosis and IA decreased.[26-29] This could be a possible reason for ischemic stroke as a risk factor.

The relationship between T2DM and aneurysms is currently controversial. A Korean study showed no association between diabetes and the incidence of unruptured aneurysms, and the same study also found no association between smoking, hypertension, and aneurysms.[30] Early genetic risk studies also did not find evidence of a correlation between T2DM and the risk of IA or abdominal aortic aneurysm.[31] A 2021 MR study also found no connection between the two.[32] However, some observational studies and meta-analyses suggest a negative correlation between T2DM and IA rupture and bleeding.[33,34] Two recent MR studies related to this topic both suggested a causal relationship between diabetes and a reduced risk of IA, which is consistent with our findings.[17,18] A study on the impact of diabetes on abdominal aortic aneurysms suggested that diabetes affects the extracellular matrix remodeling, advanced glycation end products, inflammation, and vascular smooth muscle cell homeostasis of the vessel wall, which may explain why diabetes protects against the occurrence of abdominal aortic aneurysms.[35]

A case-control study suggested that hypercholesterolemia reduces the risk of UIA, and relevant MR analysis indicated that with the increase in TC or LDL-c concentration, the risk of IA decreases.[5,36] Our study provides evidence for the above-mentioned potential causal relationship, but in the MVMR analysis,

the association between TC or LDL-c and IA is no longer statistically significant, which may be attributed to the mediating effect of other exposures. Another MR analysis where IA cases were entirely from European populations showed a potential causal effect between BMI and IA (OR = 1.27, 95% CI: 1.10-1.47, P = .001), but we did not obtain a similar conclusion in our study, which may also be due to ethnic differences.[18]

Previous meta-analyses have shown that smoking is a risk factor for the occurrence of intracranial aneurysms.[37] An MR analysis primarily from European populations indicated that a history of regular smoking and daily smoking volume are positively correlated with the risk of IA (OR = 1.53, 95% CI: 1.32-1.77, P = 9.58×10^{-9}; OR = 2.67, 95% CI: 1.75-4.07, P = 5.36×10^{-6}). Its subsequent MVMR analysis negated the effect of regular smoking history on IA, while daily smoking volume remained significantly associated with IA.[17] Our study revealed that in the two-sample MR analysis of smoking initiation, although the three analytical methods were consistent in assessing the causal relationship between smoking initiation time and IA (OR > 1), none of them considered the association between the two as significant. This is inconsistent with the results of the aforementioned meta-analysis and MR analysis. Firstly, this discrepancy may stem from ethnic differences, suggesting that compared to European populations, regular smoking history is not significantly associated with IA growth in Asian populations. Secondly, there may be other exposures mediating the relationship between this exposure and IA. However, since our study did not include other smoking-related traits such as daily smoking volume in Asian populations, we cannot conclude that smoking-related behaviors or smoking history have no impact on the development of IA in Asian populations. The relationship between smoking-related traits and IA in Asian populations still requires further research.

Meanwhile, it is crucial to consider limitations when interpreting the results. We cannot absolutely avoid the possibility that the SNPs used as IVs are related to uncertain confounders, which is a common issue in almost all MR analyses.

5. Conclusions

This study provides genetic evidence for exploring modifiable risk factors for IA in Asian populations, suggesting a causal relationship between high risks of IA and systolic blood pressure, diastolic blood pressure, and ischemic stroke; as well as a causal relationship between low risks of IA and low-density lipoprotein cholesterol, total cholesterol, and type 2 diabetes. Notably, systolic blood pressure, ischemic stroke, and type 2 diabetes are independent factors associated with aneurysms.

Abbreviations: aSAH = Aneurysmal subarachnoid hemorrhage, BMI = Body mass index, CI = Confidence Interval, DBP = Diastolic blood pressure, GWAS = Genome-Wide Association Studies, HDL-c = High-density lipoprotein cholesterol, hs-CRP = High-sensitivity C-reactive protein, IAs = Intracranial aneurysms, IEU = Integrative Epidemiology Unit, IVs = Instrumental variables, IVW = Inverse-variance weighted, Lasso = Least Absolute Shrinkage and Selection Operator, LDL-c = Low-density lipoprotein cholesterol, LD = Linkage disequilibrium, MR = Mendelian randomization, MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier, MVMR = Multivariate mendelian randomization, OR = Odd ratio, SBP = Systolic blood pressure, SNPs = Single-nucleotide polymorphisms, TC = Total cholesterol, T2DM = Type 2 diabetes mellitus, TG = Triglycerides, uIAs = Unruptured intracranial aneurysms.

Declaration of competing interest

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

This research utilized published studies and consortia that have made their summary statistics publicly available. All original studies included in this research have obtained approval from their respective ethical review boards, and participants have provided informed consent. As a result, no new ethical review board approval was necessary for this research.

Consent for Publication

All authors consent to the publication of this manuscript.

Data Availability Statement

All data needed to evaluate the conclusions in the paper are present in the paper and/or the materials cited herein.

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