Associations of polygenic risk scores with risks of stroke and its subtypes in Chinese

Supplemental Online Content

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Supplemental methods

Definition of the training sets

Among the potential training set (n=22,191), every incident stroke event observed during follow-up was recorded. Only the first event was considered in the present analysis. All stroke events were sorted in order of date of birth ("potential case group"). The potential control group consisted of participants who did not have an incident stroke event during follow-up. In turn, each case was 1:1 matched with control for the study area, sex, and year of birth. The censored age of the control participant(s) should be larger than the age of the case. When multiple potential controls met the above criteria, one control was randomly selected. Each participant could only be selected as a control once. If no control was identified, we expanded the year of birth selection by ±1 year, ±2 years, and ±3 years. If the above procedure still failed to match a case with appropriate control, the case was excluded from the subsequent analysis.

Finally, 7412 (74.3%) of 9977 incident stroke cases were successfully matched with controls. Following a similar procedure, 3844 (74.6%) of 5154 incident ischemic stroke cases, 4296 (95.2%) of 4514 incident intracerebral hemorrhage cases, and 359 (98.4%) of 365 incident subarachnoid hemorrhage cases were successfully matched with controls (**figure 1, supplemental table 1, supplemental table 2**).

Identification of previous PRS

We systematically searched the PGS Catalog,[1] PubMed, and Embase to obtain stroke-related PRS directly from previous studies (Date of searching: 2022-08-06). The detailed search strategies were below:

PGS Catalog

stroke

PubMed

#1: stroke[TI] OR "cerebral infarct*"[TI] OR "intracerebral hemorrhage"[TI] OR "intracerebral haemorrhage"[TI] OR "subarachnoid hemorrhage"[TI] OR "subarachnoid haemorrhage"[TI]

#2: "genetic risk*"[TI] OR "genetic tool*"[TI] OR "polygenic risk*"[TI] OR "polygenic score*"[TI] OR "genomic risk*"[TI]

#3: Review[PT] OR Comment[PT] OR Editorial[PT] OR "Published Erratum"[PT]

#4: "genetic risk factor*"[TI] OR "reply"[TI]

Final: #1 AND #2 NOT (#3 OR #4)

Embase

#1: 'stroke':ti OR 'cerebral infarction':ti OR 'intracerebral hemorrhage':ti OR 'intracerebral haemorrhage':ti OR 'subarachnoid hemorrhage':ti OR 'subarachnoid haemorrhage':ti

#2: 'genetic risk':ti OR 'genetic tool$':ti OR 'polygenic risk':ti OR 'polygenic score$':ti OR 'genomic risk':ti

#3: [article]/lim AND [english]/lim AND [embase]/lim

#4: 'genetic risk factor$':ti

Final: #1 AND #2 AND #3 NOT #4

The inclusion criteria of PRS in the current study were as follows:

- Newly developed.
- The PRS should integrate the information of multiple genetic variants across the whole genome and calculate individual genetic risk by weighted sum.

- The target trait of PRS should be stroke or subtypes of stroke, including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage.
- The primary purpose of the original study was to examine the strength of association between PRS and stroke or subtypes of stroke, or to evaluate the effect of PRS on improving a risk prediction model for stroke or subtypes of stroke.

The exclusion criteria of PRS were as follows:

- The base data of PRS did not include GWAS of stroke or subtypes of stroke. For example, the PRS developed using blood-pressure-related genetic variants.
- Variants in PRS were selected only based on genome-wide significant variants of stroke.
- The training set of PRS was a population with a certain disease (such as individuals with cardiometabolic disease or atrial fibrillation, etc.).
- The information used to construct a PRS (i.e., chromosome, position, effect allele, weight, etc.) was not publicly available from the PGS Catalog website or the supplemental files of the original study.

Following the above search strategy and inclusion and exclusion criteria, four previously reported PRSs were identified. Standard quality control for genetic variants was conducted before subsequent analysis (**Supplemental table 3**).

Identification of previous stroke-related GWAS

We systematically searched previous studies using *gwasfilter*, a customized R script that can efficiently and accurately filter GWASs from the GWAS Catalog Website.[2] GWASs can be filtered based on "whether the GWAS has been replicated", "sample size", "ethnicity of the study population", and other conditions. The source code of this R script is available on GitHub (https://github.com/lab319/gwas_filter). (Date of searching: 2022-08-06)

The detailed search strategies were below:

```
## Step 1: Load this script
source("gwasfilter.R")
## Step 2: Download the latest database from the GWAS Catalog
get_gwasdata()
## Step 3: Determine the filtering strategies for each trait one by one
# any stroke (EFO_0000712)
get_efo(trait="stroke")
obtain_trait(efoindex=1, append=F)
store_trait(traitindex=c(1))
gwasfilter(association=T)
# ischemic stroke (HP_0002140)
get_efo(trait="ischemic stroke")
obtain_trait(efoindex=1, append=T)
store_trait(traitindex=c(1,3,8,17))
# intracerebral hemorrhage (EFO_0005669)
get_efo(trait="intracerebral hemorrhage")
obtain_trait(efoindex=1, append=T)
store_trait(traitindex=c(1,2,10))
# subarachnoid hemorrhage (EFO_0000713)
get_efo(trait="subarachnoid hemorrhage")
obtain_trait(efoindex=1, append=T)
```

```
store_trait(traitindex=c(1:6))
## Step 4: Export the study list
gwasfilter(association=F)
```

Finally, based on ethnicity, sample size, and accessibility of the summary statistics file (SSF), we included 1 stroke SSF, 2 IS SSFs, 2 ICH SSFs, and 2 SAH SSFs from two large-scale GWASs (**supplemental table 4**).[3,4]

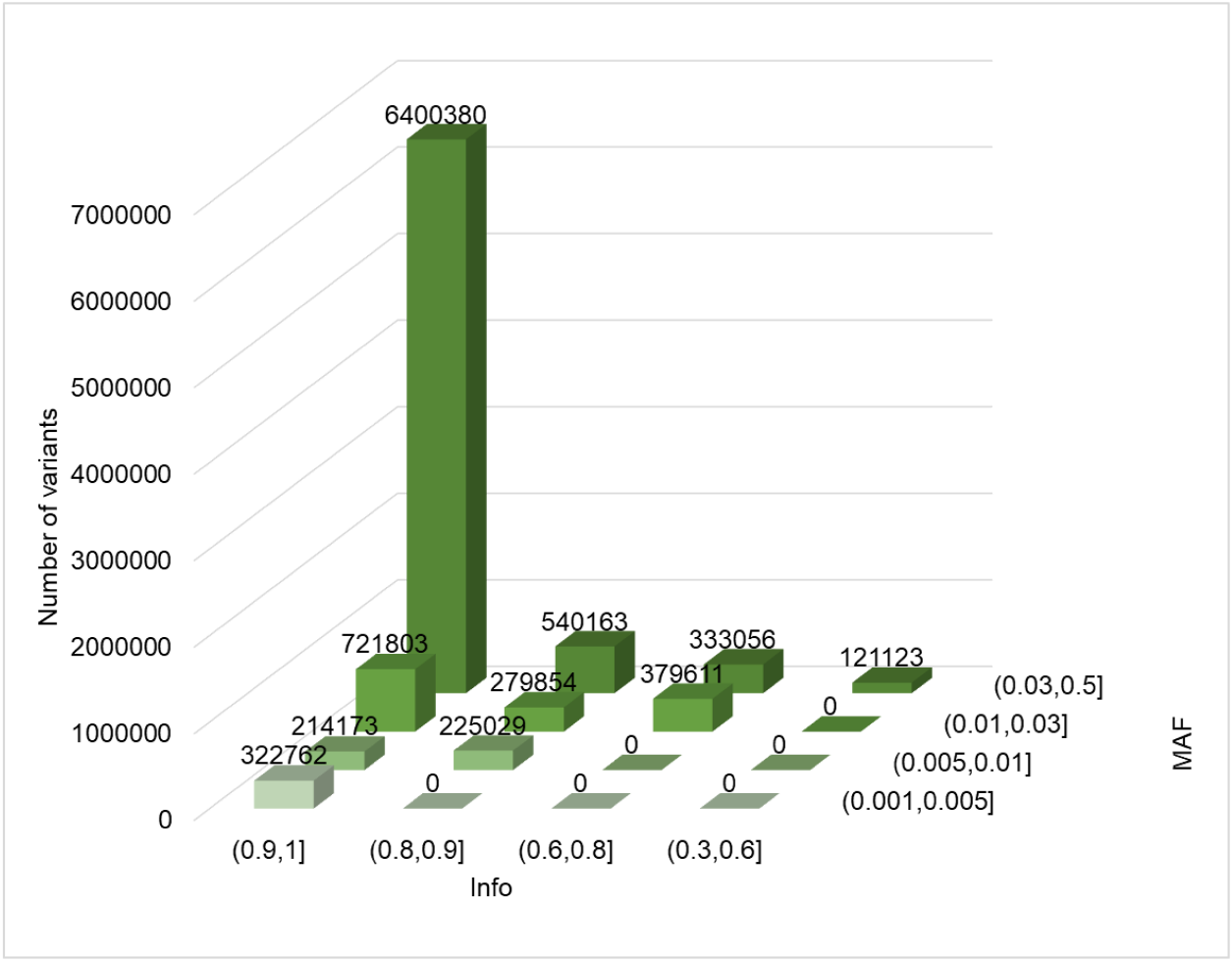
Clumping & thresholding (C+T) method

This approach involves taking the estimated single nucleotide polymorphism (SNP) effects from the largest available GWAS as the SNP weights. In the current study, a grid search strategy was used to construct multiple sets of PRS: we applied the r^2 threshold as 0 (=no pruning), 0.2, 0.4, 0.6, and 0.8, and the P-value threshold from 5×10^{-8} to 1 (40 values in total). For each r^2 threshold, we used PLINK 1.9 [5] to prune variants separately for the 22 autosomes (--clump-kb 250). The threshold on P-value was not applied during linkage disequilibrium (LD) pruning (--clump-p1 1). The reference panel used for LD pruning was 1595 unrelated participants from CKB. We then applied different thresholds to the P-value for associations from the original GWAS. The PRS was computed by a weighted sum of the SNP dosages. After the above process, a GWAS summary statistics file could produce 5×40=200 PRSs with different r^2 thresholds and different P-value thresholds.

LDpred method

This Bayesian approach calculates a posterior mean effect for each variant based on a prior and subsequent shrinkage based on the extent to which this variant is correlated with similarly associated variants in the reference population.[6] Three steps are involved to develop PRS by LDpred (v1.0.10): (1) coordination of SNPs; (2) calculation of SNP posterior effects; (3) calculation of PRS. The variants were restricted to HapMap3 SNPs in the current analysis. Two parameters were required to run LDpred. The first parameter is the LD radius, i.e., the number of SNPs that we adjust for on each side of a given SNP. We used M/3000, the default value recommended by the software, where M is the total number of SNPs used in the analysis. This corresponds to a 2 Mb LD window on average in the genome. The second parameter is the fraction *p* of non-zero effects in the prior. A range of *p* values recommended by the software were used: 1, 0.3, 0.1, 0.03, 0.01, 0.003, and 0.001. In addition, the LD reference panel was required to compute the correlations between genetic variants. East Asians (n=504) and Europeans (n=503) in 1000 Genomes Project Phase 3 were used as LD reference panels, respectively.

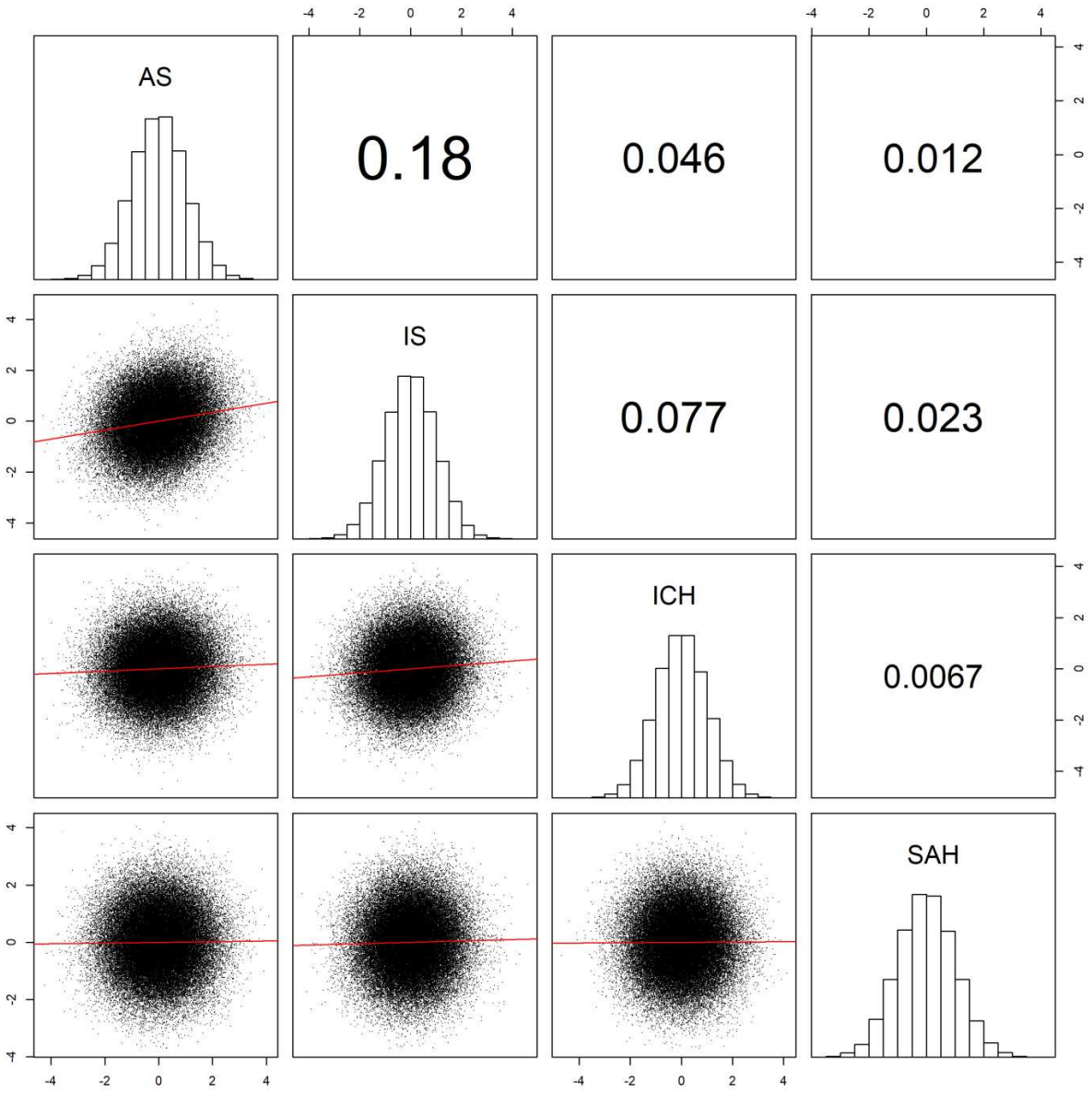
Supplemental figure 1. High-quality variants in CKB



Abbreviations: Info, imputation quality score; MAF, minor allele frequency.

High-quality variants were defined as: (1) Info>0.3 & MAF>0.03; or (2) Info>0.6 & MAF>0.01; or (3) Info>0.8 & MAF>0.005; or (4) Info>0.9 & MAF>0.001.

Supplemental figure 2. Distributions and Correlation plots of the optimal PRSs for stroke and its subtypes in the testing set

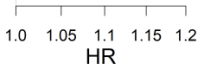


Abbreviations: AS, any stroke; ICH, intracerebral hemorrhage; IS, ischemic stroke; PRS, polygenic risk score; SAH, subarachnoid hemorrhage.

The PRSs reported here are the optimal PRSs for stroke and its subtypes in the training sets (see **table 1** for details). All PRSs were standardized in the testing set (n=72,150) before plotting. The number in the upper-right square of the plot represents the Pearson correlation coefficient. The red line in the lower-left square represents the regression line.

Supplemental figure 3. Associations of PRS with risk of ischemic stroke, stratified by different baseline characteristics

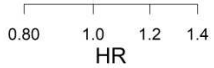
Subgroups	No. of cases	Incidence rate	HR (95% CI)	P for interaction
All	7,507	8.93	1.08 (1.06, 1.11)	
Sex				0.342
women	4,254	8.32	1.07 (1.04, 1.11)	
men	3,253	9.86	1.10 (1.06, 1.13)	
Age, years				0.089
<55	2,643	4.73	1.05 (1.01, 1.09)	
>=55	4,864	17.22	1.10 (1.07, 1.13)	
Current daily smoker				0.067
no	5,673	8.81	1.07 (1.04, 1.10)	
yes	1,834	9.31	1.12 (1.07, 1.17)	
BMI, kg/m2				0.010
<24	3,428	7.33	1.12 (1.08, 1.16)	
>=24	4,079	10.93	1.05 (1.02, 1.09)	
Waist circumference, cm				0.074
women<80,men<85	3,551	7.00	1.10 (1.07, 1.14)	
women>=80,men>=85	3,956	11.87	1.06 (1.03, 1.09)	
Hypertension				0.011
no	3,280	5.79	1.04 (1.01, 1.08)	
yes	4,227	15.40	1.10 (1.07, 1.13)	
Diabetes				0.896
no	6,593	8.25	1.08 (1.06, 1.11)	
yes	914	21.91	1.08 (1.02, 1.16)	
Family history of stroke				0.214
no	5,762	8.30	1.07 (1.05, 1.10)	
yes	1,745	11.86	1.11 (1.06, 1.16)	



The PRS reported here is the optimal PRS for ischemic stroke (see **table 1**), which was standardized (zero mean, unit standard deviation) in the testing set. The incidence rate is reported in unit per 1000 person-years. The Cox models were stratified by sex and ten study regions and adjusted simultaneously for the top 10 principal components of ancestry and array versions, with age as the time scale. The tests for multiplicative interaction were performed using likelihood ratio tests by comparing models with and without cross-product terms. One participant had missing value of body mass index (BMI) and was excluded when stratified by BMI.

Supplemental figure 4. Associations of PRS with risk of intracerebral hemorrhage, stratified by different baseline characteristics

Subgroups	No. of cases	Incidence rate	HR (95% CI)	P for interaction
All	1,193	1.37	1.08 (1.02, 1.14)	
Sex				0.056
women	600	1.14	1.02 (0.94, 1.10)	
men	593	1.73	1.13 (1.05, 1.23)	
Age, years				0.104
<55	389	0.68	1.15 (1.04, 1.27)	
>=55	804	2.66	1.04 (0.97, 1.11)	
Current daily smoker				0.070
no	852	1.28	1.04 (0.97, 1.11)	
yes	341	1.67	1.17 (1.05, 1.30)	
BMI, kg/m2				0.485
<24	662	1.38	1.10 (1.02, 1.18)	
>=24	531	1.36	1.04 (0.95, 1.13)	
Waist circumference, cm				0.661
women<80,men<85	658	1.26	1.08 (1.00, 1.17)	
women>=80,men>=85	535	1.53	1.05 (0.96, 1.14)	
Hypertension				0.755
no	353	0.61	1.08 (0.97, 1.20)	
yes	840	2.88	1.05 (0.98, 1.13)	
Diabetes				0.953
no	1,077	1.31	1.07 (1.01, 1.14)	
yes	116	2.54	1.07 (0.89, 1.29)	
Family history of stroke				0.091
no	954	1.33	1.05 (0.98, 1.12)	
yes	239	1.55	1.20 (1.06, 1.37)	



The PRS reported here is the optimal PRS for intracerebral hemorrhage (see **table 1**), which was standardized (zero mean, unit standard deviation) in the testing set. The incidence rate is reported in unit per 1000 person-years. The Cox models were stratified by sex and ten study regions and adjusted simultaneously for the top 10 principal components of ancestry and array versions, with age as the time scale. The tests for multiplicative interaction were performed using likelihood ratio tests by comparing models with and without cross-product terms. One participant had missing value of body mass index (BMI) and was excluded when stratified by BMI.

Supplemental table 1. The detailed process of case-control matching

Steps	Difference between the year of birth (control - case)	Number of matched cases			
		AS	IS	ICH	SAH
1	0	6825	3458	3978	324
2	-1	267	199	159	20
3	1	104	59	59	4
4	-2	115	65	45	7
5	2	30	20	20	1
6	-3	58	34	27	1
7	3	13	9	8	2
Summing		7412	3844	4296	359

Abbreviations: AS, any stroke; ICH, intracerebral hemorrhage; IS, ischemic stroke; SAH, subarachnoid hemorrhage.

Supplemental table 2. Characteristics of the training sets

	Case	Control
The training set for any stroke		
Number of participants	7412	7412
Array 1	6133 (82.7)	6902 (93.1)
Rural area	5392 (72.7)	5392 (72.7)
Men	3848 (51.9)	3848 (51.9)
Censored age, years	71.0 (63.5-77.9)	65.3 (57.0-72.0)
The training set for ischemic stroke		
Number of participants	3844	3844
Array 1	3010 (78.3)	3681 (95.8)
Rural area	2369 (61.6)	2369 (61.6)
Men	1941 (50.5)	1941 (50.5)
Censored age, years	69.6 (62.3-76.5)	64.1 (56.1-70.6)
The training set for intracerebral hemorrhage		
Number of participants	4296	4296
Array 1	3606 (83.9)	3887 (90.5)
Rural area	3348 (77.9)	3348 (77.9)
Men	2294 (53.4)	2294 (53.4)
Censored age, years	72.1 (64.6-78.9)	65.9 (57.7-73.0)
The training set for subarachnoid hemorrhage		
Number of participants	359	359
Array 1	284 (79.1)	332 (92.5)
Rural area	229 (63.8)	229 (63.8)
Men	138 (38.4)	138 (38.4)
Censored age, years	67.9 (60.8-75.5)	61.0 (53.8-69.2)

Data are presented as n (%) or median (25–75th percentile) unless otherwise specified.

Supplemental table 3. Quality control processes of PRS files from previous studies

Index	PRS ID	Outcomes	Development methods	First Author (Publication year)	The original number of variants	Matched with CKB	Non-ambiguous	Non-Ins/Del	Info ≥ 0.8 in CKB	MAF ≥ 1% in CKB	$P_{HWE} \geq 1\times10^{-6}$ in CKB
1	PGS000038	Stroke	C+T	Rutten-Jacobs LC (2018)	90	73	67	67	67	59	59
2	PGS000039	Ischemic stroke	metaGRS	Abraham G (2019)	3,225,583	2,353,410	2,012,084	2,012,084	1,655,235	1,592,365	1,563,569
3	PGS002259	Stroke	metaGRS	Lu X (2021)	534	532	473	473	467	456	448
4	GRS324	Stroke	metaGRS	Ibrahim-Verbaas CA (2014)	324	321	278	278	278	246	241

Abbreviations: C+T, clumping & thresholding; CKB, China Kadoorie Biobank; HWE, Hardy-Weinberg Equilibrium; Info, imputation quality score; Ins/Del, insertion/deletion; MAF, minor allele frequency; PRS, polygenic risk score.

Supplemental table 4. Quality control processes of GWAS summary statistics files

Items	Source 1	Source 2	Source 3	Source 4	Source 5	Source 6	Source 7
ID in GWAS Catalog	GCST005838	GCST90018703	GCST90018923	GCST90018650	GCST90018870	GCST90018644	GCST90018864
Outcomes	Stroke	Subarachnoid hemorrhage	Subarachnoid hemorrhage	Intracerebral hemorrhage	Intracerebral hemorrhage	Ischemic stroke	Ischemic stroke
Sample size	67,162 multi-ancestry cases / 454,450 multi-ancestry controls	1,203 EAS cases / 152,022 EAS controls	1,693 EUR cases /471,562 EUR controls + 1,203 EAS cases / 152,022 EAS controls	1,456 EAS cases /152,022 EAS controls	1,935 EUR cases / 471,578 EUR controls + 1,456 EAS cases / 152,022 EAS controls	22,664 EAS cases / 152,022 EAS controls	11,929 EUR cases / 472,192 EUR controls + 22,664 EAS cases / 152,022 EAS controls
First Author (Publication year)	Malik R (2018)	Sakaue S (2021)	Sakaue S (2021)	Sakaue S (2021)	Sakaue S (2021)	Sakaue S (2021)	Sakaue S (2021)
The original number of variants	7,675,830	13,425,781	25,841,499	13,425,819	25,841,532	13,429,439	25,844,498
Passed initial quality control	7,627,850 [a]	13,130,774 [b]	24,878,293 [c]	13,130,813 [d]	24,878,319 [e]	13,134,427 [f]	24,881,216 [g]
MAF ≥ 1% in GWAS	7,627,850 [h]	7,440,434	11,513,781	7,440,398	11,513,800	7,440,112	11,515,909
Matched with CKB	6,475,513	7,299,168	9,261,503	7,299,120	9,261,488	7,298,797	9,264,734
Non-ambiguous	5,478,155	6,257,327	7,965,690	6,257,306	7,965,668	6,257,016	7,968,457
Non-Ins/Del	5,477,165	5,778,284	7,025,494	5,778,261	7,025,479	5,777,991	7,028,074
Info ≥ 0.8 in CKB	4,869,469	5,207,701	5,820,101	5,207,708	5,820,133	5,207,526	5,822,588
MAF ≥ 1% in CKB	4,612,892	5,087,906	5,475,815	5,087,897	5,475,832	5,087,676	5,478,538

Items	**Source 1**	**Source 2**	**Source 3**	**Source 4**	**Source 5**	**Source 6**	**Source 7**
$P_{HWE} \geq 1\times10^{-6}$ in CKB	4,557,514	5,028,354	5,402,594	5,028,344	5,402,611	5,028,124	5,405,310
In HapMap3	1,022,347	993,361	1,029,250	993,366	1,027,999	993,337	1,028,074
MAF ≥ 1% in $1KGP_{EAS}$	1,017,531	991,773	1,024,440	991,780	1,023,197	991,768	1,023,272

Abbreviations: 1KGP, 1000 Genomes Project (Phase 3); CKB, China Kadoorie Biobank; EAS, East Asian; EUR, European; GWAS, genome-wide association study; HapMap3, the International HapMap Project Phase 3; HWE, Hardy-Weinberg Equilibrium; Info, imputation quality score; Ins/Del, insertion/deletion; MAF, minor allele frequency;

[a] We excluded 47,087 variants whose chromosomes or positions were not available and 893 variants that were in the same position as other variants.

[b] We excluded 295,007 variants on chromosome X.

[c] We excluded 798,531 variants on chromosome X and 164,675 variants that were at the same position as other variants.

[d] We excluded 295,006 variants on chromosome X.

[e] We excluded 798,538 variants on chromosome X and 164,675 variants that were at the same position as other variants.

[f] We excluded 295,012 variants on chromosome X.

[g] We excluded 798,593 variants on chromosome X and 164,689 variants that were at the same position as other variants.

[h] MAF was not available in the summary statistics file.

Supplemental table 5. Associations of different PRSs with risks of stroke and its subtypes in the training sets

Outcomes	Method	PRS source [a]	Parameter used for developing the PRS in the present study	Number of variants	OR_{SD} (95% CI)	P-value	Note
Any stroke							
	Previous study	PGS000038	—	59	1.058 (1.024, 1.094)	7.66E-04	
	Previous study	PGS002259	—	448	1.125 (1.088, 1.165)	1.44E-11	
	Previous study	GRS324	—	241	1.015 (0.982, 1.050)	3.71E-01	
	C + T	GCST005838	*P*=1E-06, r^2=0	38	1.107 (1.071, 1.145)	1.90E-09	
	LDpred	**GCST005838**	**ρ=0.01, Ref=1KGP-EAS**	**1,017,531**	**1.138 (1.101, 1.177)**	**3.38E-14**	**Optimal**
	LDpred	GCST005838	ρ=0.01, Ref=1KGP-EUR	1,017,496	1.131 (1.094, 1.170)	5.96E-13	
Ischemic stroke							
	Previous study	PGS000039	—	1,563,569	1.065 (1.014, 1.119)	1.16E-02	
	C + T	GCST90018644	*P*=0.07, r^2=0.8	74,670	1.131 (1.077, 1.188)	7.19E-07	
	C + T	**GCST90018864**	***P*=0.02, r^2=0.8**	**32,158**	**1.183 (1.126, 1.244)**	**3.55E-11**	**Optimal**
	LDpred	GCST90018644	ρ=0.001, Ref=1KGP-EAS	991,768	1.116 (1.063, 1.172)	1.12E-05	
	LDpred	GCST90018644	ρ=0.03, Ref=1KGP-EUR	982,412	1.102 (1.050, 1.157)	8.47E-05	
	LDpred	GCST90018864	ρ=0.01, Ref=1KGP-EAS	1,023,272	1.162 (1.106, 1.220)	1.80E-09	
	LDpred	GCST90018864	ρ=0.01, Ref=1KGP-EUR	1,017,672	1.166 (1.110, 1.226)	1.46E-09	
Intracerebral hemorrhage							
	C + T	GCST90018650	*P*=0.2, r^2=0.8	192,079	1.082 (1.037, 1.130)	3.20E-04	
	C + T	GCST90018870	*P*=0.001, r^2=0.2	1,326	1.088 (1.042, 1.136)	1.37E-04	
	LDpred	GCST90018650	ρ=0.003, Ref=1KGP-EAS	991,780	1.066 (1.020, 1.114)	4.17E-03	
	LDpred	GCST90018650	ρ=0.01, Ref=1KGP-EUR	982,436	1.073 (1.028, 1.121)	1.44E-03	
	LDpred	GCST90018870	ρ=0.003, Ref=1KGP-EAS	1,023,197	1.087 (1.041, 1.135)	1.61E-04	
	LDpred	**GCST90018870**	**ρ=0.1, Ref=1KGP-EUR**	**1,017,664**	**1.097 (1.050, 1.146)**	**3.09E-05**	**Optimal**
Subarachnoid hemorrhage							

Outcomes	**Method**	**PRS source [a]**	**Parameter used for developing the PRS in the present study**	**Number of variants**	**OR_{SD} (95% CI)**	**P-value**	**Note**
	C + T	**GCST90018703**	***P*=0.4, r^2=0**	**7,899**	**1.248 (1.056, 1.475)**	**9.21E-03**	**Optimal**
	C + T	GCST90018923	*P*=0.0005, r^2=0.8	889	1.246 (1.064, 1.458)	6.20E-03	
	LDpred	GCST90018703	ρ=0.001, Ref=1KGP-EAS	991,773	1.082 (0.933, 1.255)	2.99E-01	
	LDpred	GCST90018703	ρ=0.001, Ref=1KGP-EUR	982,431	1.126 (0.967, 1.311)	1.26E-01	
	LDpred	GCST90018923	ρ=0.001, Ref=1KGP-EAS	1,024,440	1.129 (0.962, 1.325)	1.37E-01	
	LDpred	GCST90018923	ρ=0.01, Ref=1KGP-EUR	1,017,665	1.147 (0.976, 1.348)	9.61E-02	

Abbreviations: 1KGP, 1000 Genomes Project (Phase 3); CI, confidence interval; C+T, clumping & thresholding; EAS, East Asian; EUR, European; OR, odds ratio; PRS, polygenic risk score; Ref, reference population; SD, standard deviation.

[a] "PGS###" indicates the index in the PGS Catalog. "GCST###" indicates the index in the GWAS Catalog.

Supplemental table 6. Associations of PRSs with risks of stroke and subtypes after adjusting for systolic blood pressure, body mass index, and family history of stroke

Outcomes	PRS	Model 1	Model 2	Model 3
Any stroke				
	PRS_{AS}	**1.10 (1.07, 1.12)**	**1.10 (1.07, 1.12)**	**1.08 (1.06, 1.10)**
	PRS_{IS}	**1.08 (1.06, 1.11)**	**1.08 (1.06, 1.11)**	**1.07 (1.05, 1.09)**
	PRS_{ICH}	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)	1.01 (0.99, 1.03)
	PRS_{SAH}	1.00 (0.98, 1.02)	1.00 (0.98, 1.03)	1.00 (0.98, 1.02)
Ischemic stroke				
	PRS_{AS}	**1.10 (1.07, 1.12)**	**1.10 (1.07, 1.12)**	**1.08 (1.06, 1.11)**
	PRS_{IS}	**1.08 (1.06, 1.11)**	**1.08 (1.06, 1.11)**	**1.07 (1.04, 1.09)**
	PRS_{ICH}	1.02 (0.99, 1.04)	1.02 (0.99, 1.04)	1.01 (0.99, 1.03)
	PRS_{SAH}	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)	1.00 (0.98, 1.02)
Intracerebral hemorrhage				
	PRS_{AS}	**1.13 (1.07, 1.19)**	**1.13 (1.07, 1.20)**	**1.09 (1.03, 1.16)**
	PRS_{IS}	**1.09 (1.03, 1.15)**	**1.09 (1.03, 1.15)**	**1.06 (1.00, 1.12)** [a]
	PRS_{ICH}	**1.08 (1.02, 1.14)**	**1.07 (1.01, 1.14)**	**1.07 (1.01, 1.13)**
	PRS_{SAH}	1.02 (0.96, 1.08)	1.02 (0.96, 1.08)	1.02 (0.96, 1.08)
Subarachnoid hemorrhage				
	PRS_{AS}	1.10 (0.93, 1.30)	1.10 (0.93, 1.31)	1.07 (0.90, 1.27)
	PRS_{IS}	1.02 (0.86, 1.21)	1.03 (0.86, 1.22)	1.01 (0.85, 1.20)
	PRS_{ICH}	1.07 (0.90, 1.27)	1.07 (0.90, 1.27)	1.07 (0.90, 1.27)
	PRS_{SAH}	0.97 (0.81, 1.15)	0.97 (0.82, 1.15)	0.96 (0.81, 1.14)

Abbreviations: AS, any stroke; ICH, intracerebral hemorrhage; IS, ischemic stroke; PRS, polygenic risk score; SAH, subarachnoid hemorrhage.

Model 1 was stratified by sex and ten study regions, with age as the time scale. Model 2 was further adjusted for the top 10 principal components of ancestry and array versions. Model 3 was further adjusted for systolic blood pressure, body mass index, and family history of stroke.

[a] $P<0.05$.

Supplemental table 7. Reclassification based on the continuous NRI and relative IDI

	categorical NRI [a]	continuous NRI	relative IDI [b], %
Ischemic stroke			
Women			
cases	0.001 (-0.005, 0.006)	0.039 (-0.003, 0.080)	–
non-cases	0.001 (-0.000, 0.002)	**0.034 (0.024, 0.044)**	–
total	0.001 (-0.004, 0.007)	**0.073 (0.030, 0.115)**	**0.5 (0.2, 0.9)**
Men			
cases	0.004 (-0.003, 0.012)	0.035 (-0.007, 0.077)	–
non-cases	-0.001 (-0.003, 0.000)	**0.040 (0.029, 0.052)**	–
total	0.003 (-0.004, 0.011)	**0.075 (0.031, 0.120)**	0.4 (-0.1, 0.9)
Hemorrhagic stroke			
Women			
cases	-0.008 (-0.017, 0.001)	0.007 (-0.086, 0.099)	–
non-cases	-0.000 (-0.000, 0.000)	**0.021 (0.011, 0.031)**	–
total	-0.008 (-0.017, 0.001)	0.028 (-0.065, 0.121)	-0.2 (-1.1, 0.7)
Men			
cases	0.008 (-0.008, 0.024)	0.092 (-0.000, 0.184)	
non-cases	0.000 (-0.000, 0.001)	**0.039 (0.028, 0.049)**	
total	0.008 (-0.008, 0.024)	**0.130 (0.037, 0.223)**	0.8 (-0.5, 2.1)

Abbreviations: IDI, integrated discrimination improvement; NRI, net reclassification improvement.

The PRS reported here is the optimal PRS for any stroke (see **Table 1** for details). Numbers in the brackets represent the 95% confidence intervals, which were calculated by 100 bootstrap replications using the BCa method in Stata.

[a] Participants with 10-year risk > 10% were grouped into a high-risk group.

[b] When calculating relative IDI, cases were defined as participants who developed ischemic stroke or hemorrhagic stroke within 10 years of follow-up; non-cases were defined as those who were followed up for more than 10 years, including participants who developed ischemic stroke or hemorrhagic stroke after 10 years.

References

[1] Lambert SA, Gil L, Jupp S, et al. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. *Nat Genet.* 2021;53(4):420-425.

[2] Yang S, Li C, Hu Y, et al. gwasfilter: an R script to filter genome-wide association study. *Chin J Epidemiol.* 2021;42(10):1876-1881.

[3] Malik R, Chauhan G, Traylor M, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet.* 2018;50(4):524-537.

[4] Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet.* 2021;53(10):1415-1424.

[5] Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet.* 2007;81(3):559-575.

[6] Vilhjalmsson BJ, Yang J, Finucane HK, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *Am J Hum Genet.* 2015;97(4):576-592.