

Supplemental Materials

Supplemental Methods

A systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Human Genome Epidemiology Network guidelines.^{1,2} A total of five databases, including PubMed, Embase, Web of Science, China National Knowledge Infrastructure, and Wanfang Databases, were searched without language restrictions for candidate articles up to April 2022. The search terms were (Cerebral AVM OR cerebral arteriovenous malformation OR brain AVM OR brain arteriovenous malformation) AND (pregnancy OR pregnancies OR gestation).

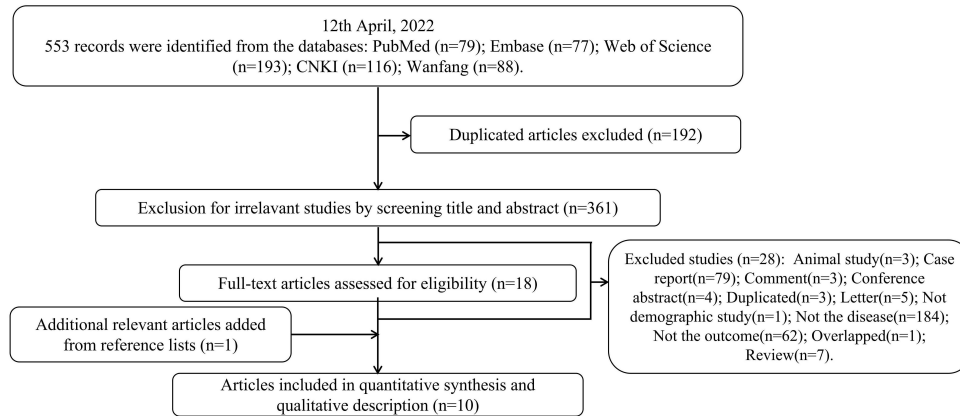
The work of study selection and data extraction were conducted by two independent authors, and any disagreement was resolved by discussion or re-evaluation by a third author. We included all the case-series studies and cohort studies that assessed the haemorrhage risk of bAVM during periods of pregnancy and non-pregnancy in consecutive female cases. Studies with following characteristics were excluded: (1) studies focusing on other vascular malformations such as spine arteriovenous malformation, dural arteriovenous fistulas, cavernous malformations and vein of Galen malformations; (2) studies without clear definitions (recruited individuals, risk and control periods) or sufficient data to calculate relative risks (RRs) and 95% confidence interval (95%CI); (3) conference abstracts, editorials, letters, comments, review articles, case reports, and animal/cellular experimental studies. If multiple studies were published containing the same cohort, the one with the largest sample size were included for further analysis.

The person-years in risk and control periods were firstly adjusted using the numbers of pregnancy and abortion published in articles according to the definition of pregnancy (40-week gestation and 6-week puerperium) and abortion (6-week abortion and 6-week postabortion interval) in this study, then meta-analysis was conducted.

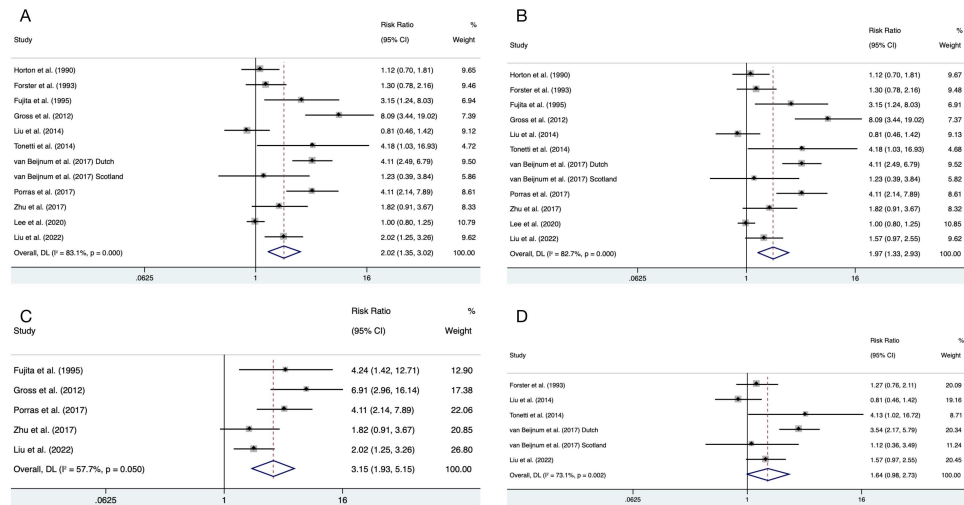
References

1. Minelli C, Thompson JR, Abrams KR, et al. The quality of meta-analyses of genetic association studies: a review with recommendations. *Am J Epidemiol*. 2009;170:1333 – 43. doi:10.1093/aje/kwp350.
2. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009 Jul 21;339:b2535. doi: 10.1136/bmj.b2535.

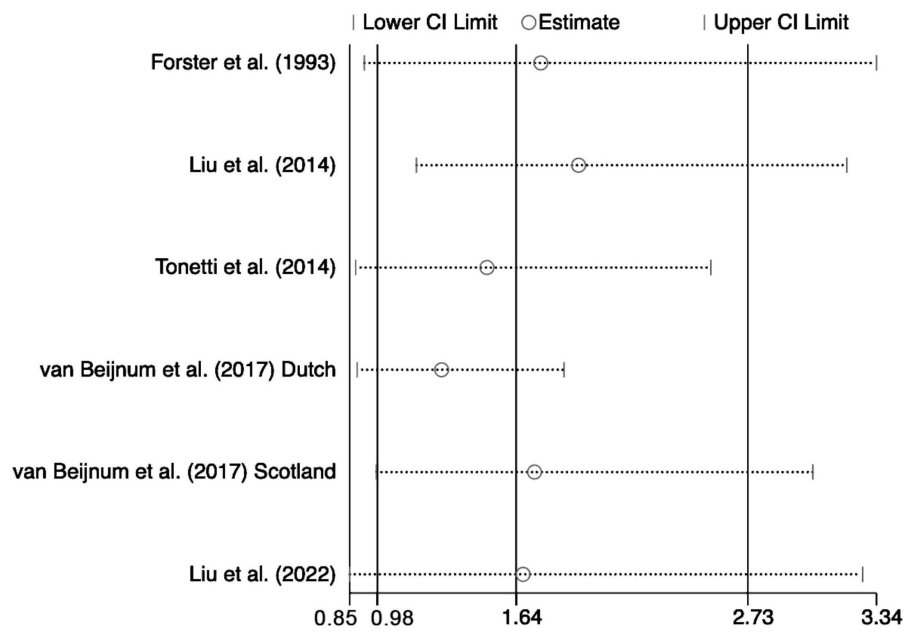
Supplemental Figures



Supplemental Figure 1. Flowchart of literature search results and study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).



Supplemental Figure 2. Forest plots of haemorrhage risk for female brain arteriovenous malformation patients in risk and control periods: (A, B) Meta-analysis performed combining ten published studies with either Scenario I or III in present study; (C) Meta-analysis analysis performed among participants of all ages; (D) Meta-analysis performed among participants of reproductive age (15 - 45 years).



Supplemental Figure 3. The sensitive analysis for the meta-analysis among participants of reproductive age (15 - 45 years).

Supplemental Tables

Supplemental Table 1. Clinical characteristics of brain arteriovenous malformation patients with presentation of haemorrhage

Parameters	Patients with haemorrhage in Risk Period (n=17)	Haemorrhagic Patients of reproductive age with at Least One Previous Pregnancy (Scenario IV, n=106)	Haemorrhagic Patients of reproductive age (Scenario III, n=186)	Haemorrhagic Patients of all ages with at Least One Previous Pregnancy (Scenario II, n=161)	Haemorrhagic patients of all ages (Scenario I, n=311)
Race (%)	Asian (100.0)	Asian (100.0)	Asian (100.0)	Asian (100.0)	Asian (100.0)
Smoking, n (%)	3 (17.6)	17 (16.0)	28 (15.1)	22 (13.7)	33 (10.6)
Alcohol, n (%)	2 (11.8)	12 (11.3)	28 (15.1)	23 (14.3)	39 (12.5)
Hypertension, n (%)	0 (0)	4 (3.8)	4 (2.1)	9 (5.6)	9 (2.8)
Diabetes, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hyperlipidemia, n (%)	4 (23.5)	15 (14.2)	20 (10.8)	27 (16.8)	38 (12.2)
Presenting bAVM Rupture, n (%)	17 (100)	94 (88.7)	165 (89.9)	143 (88.8)	277 (89.7)
Treatment, n (%)					
Non-intervention Treatment	1 (5.9)	8 (7.6)	11 (5.9)	13 (8.1)	20 (6.4)
Microsurgery Only	15 (88.2)	80 (75.5)	131 (70.4)	118 (73.3)	223 (71.7)
Embolism Only	1 (5.9)	10 (9.4)	27 (14.5)	20 (12.4)	45 (14.5)
Radiosurgery Only	0 (0)	3 (2.8)	6 (3.2)	4 (2.5)	8 (2.6)
Microsurgery & Embolism	0 (0)	1 (0.9)	4 (2.1)	1 (0.6)	6 (1.9)
Microsurgery & Radiosurgery	0 (0)	2 (1.9)	3 (1.6)	3 (1.9)	4 (1.3)
Embolism & Radiosurgery	0 (0)	2 (1.9)	4 (2.1)	2 (1.2)	4 (1.3)
Location, n (%)					
Frontal	4 (23.5)	28 (26.4)	40 (21.5)	40 (24.8)	64 (20.6)
Parietal	0 (0)	22 (20.8)	43 (23.1)	32 (19.9)	69 (22.2)
Temporal	5 (29.4)	24 (22.6)	52 (28.0)	43 (26.7)	95 (30.5)
Occipital	3 (17.6)	15 (14.2)	30 (16.1)	27 (16.8)	56 (18.0)
Basal Ganglia & Thalamus	0 (0)	7 (6.6)	15 (8.1)	9 (5.6)	21 (6.8)
Corpus Callosum & Hippocampus	1 (5.9)	7 (6.6)	15 (8.1)	7 (4.3)	21 (6.8)
Cerebellar	1 (5.9)	18 (17.0)	25 (13.4)	32 (19.9)	48 (15.4)
Brain Stem	0 (0)	3 (2.8)	3 (1.6)	4 (2.5)	4 (1.3)
Size, cm, mean (SD)	2.31 (1.16)	2.79 (1.40)	2.90 (1.50)	2.77 (1.43)	2.76 (1.50)
Hemodynamic Related Aneurysm, n (%)	3 (17.6)	22 (20.8)	29 (15.6)	40 (24.8)	53 (17.1)
Deep Venous Drainage, n (%)	7 (41.2)	42 (39.6)	76 (40.9)	72 (44.7)	151(48.6)
Thick Drainage Vein or Venous Bulb, n (%)	3 (17.6)	42 (39.6)	70 (37.6)	65 (40.4)	109 (35.0)
Spetzler-Martin Grading, n (%)					
Grade 1	4 (23.5)	16 (15.1)	27 (14.5)	27 (16.8)	54 (17.4)
Grade 2	9 (52.9)	46 (43.4)	69 (37.1)	65 (40.4)	113 (36.3)
Grade 3	3 (17.6)	28 (26.4)	55 (29.6)	44 (27.4)	91 (29.3)
Grade 4	1 (5.9)	14 (13.2)	28 (15.1)	21 (13.0)	44 (14.1)
Grade 5	0 (0)	2 (1.9)	7 (3.8)	4 (2.5)	9 (2.9)

Supplemental Table 2: Design and analysis of four scenarios on haemorrhage risk of brain arteriovenous malformation during risk and control periods in the Chinese population.

Scenario	Included Individuals	Definition of Risk Period (Pregnancy)	Definition of Risk Period (Abortion)	Definition of Control Period	Risk Period			Control Period			Relative Risk (95% Confidence Interval)	Attributable Risk Percent, %
					Event	Person-Years	Incidence Density	Event	Person-Years	Incidence Density		
I	Haemorrhagic bAVM of all ages (n=311)	40-week gestation and 6-week puerperium	6-week abortion and 6-week postabortion interval	Age at	17	229	7.44%	305	8523	3.58%	2.078(1.275 - 3.387)	51.88
			12-week abortion and 6-week postabortion interval	obliteration or last follow-up	17	255	6.66%	305	8497	3.59%	1.855(1.138 - 3.023)	46.09
		40-week gestation and 12-week puerperium	6-week abortion and 6-week postabortion interval	subtracting risk	17	236	7.20%	305	8516	3.58%	2.010(1.233 - 3.275)	50.25
			12-week abortion and 6-week postabortion interval	period	17	263	6.47%	305	8489	3.59%	1.799(1.104 - 2.933)	44.41
II	Haemorrhagic bAVM of all ages with at least one previous pregnancy (n=161)	40-week gestation and 6-week puerperium	6-week abortion and 6-week postabortion interval	Age at	17	220	7.73%	151	6280	2.40%	3.214(1.946 - 5.306)	68.89
			12-week abortion and 6-week postabortion interval	obliteration or last follow-up	17	228	7.46%	151	6272	2.41%	3.097(1.876 - 5.113)	67.71
		40-week gestation and 12-week puerperium	6-week abortion and 6-week postabortion interval	subtracting risk	17	247	6.88%	151	6253	2.41%	2.850(1.726 - 4.706)	64.91
			12-week abortion and 6-week postabortion interval	period	17	255	6.67%	151	6245	2.42%	2.757(1.670 - 4.552)	63.73
III	Haemorrhagic bAVM of reproductive age (n=186)	40-week gestation and 6-week puerperium	6-week abortion and 6-week postabortion interval	Age at	17	126	13.48%	177	2133	8.30%	1.624(0.987 - 2.671)	38.42
			12-week abortion and 6-week postabortion interval	obliteration or last follow-up	17	140	12.11%	177	2119	8.35%	1.450(0.881 - 2.385)	31.03
		40-week gestation and 12-week puerperium	6-week abortion and 6-week postabortion interval	subtracting both	17	131	13.00%	177	2128	8.32%	1.563(0.950 - 2.571)	36.02
			12-week abortion and 6-week postabortion interval	risk period and 15 yrs	17	145	11.73%	177	2114	8.37%	1.401(0.852 - 2.304)	28.62
IV	Haemorrhagic bAVM with at least one previous pregnancy of reproductive age (n=106)	40-week gestation and 6-week puerperium	6-week abortion and 6-week postabortion interval	Age at	17	118	14.41%	94	1777	5.29%	2.723(1.625 - 4.565)	63.28
			12-week abortion and 6-week postabortion interval	obliteration or last follow-up	17	123	13.82%	94	1772	5.30%	2.605(1.554 - 4.367)	61.61
		40-week gestation and 12-week puerperium	6-week abortion and 6-week postabortion interval	subtracting both	17	132	12.88%	94	1763	5.33%	2.415(1.441 - 4.049)	58.59
			12-week abortion and 6-week postabortion interval	risk period and 15 yrs	17	137	12.41%	94	1758	5.35%	2.321(1.384 - 3.890)	56.92

Supplemental Table 3: Search strategy of potentially related literature.

Pubmed		
Step 1	(((Cerebral AVM[Title/Abstract]) OR (intracranial AVM[Title/Abstract]) OR (cerebral arteriovenous malformation[Title/Abstract]) OR (intracranial arteriovenous malformation[Title/Abstract]) OR (brain AVM[Title/Abstract]) OR (brain arteriovenous malformation[Title/Abstract]))	1924
Step 2	pregnant* OR pregnancy* OR gestation*	1135985
Step 3	1 AND 2	79

Web of Science		
Step 1	(((TS=(Cerebral AVM)) OR TS=(intracranial AVM)) OR TS=(cerebral arteriovenous malformation)) OR TS=(intracranial arteriovenous malformation) OR TS=(brain AVM)	16876
Step 2	TS=(pregnant*) OR TS=(pregnancy*) OR TS=(gestation*)	1365599
Step 3	1 AND 2	577
Step 4	Not review and case report	193

Embase		
Step 1	'cerebral avm':ab,ti OR 'intracranial arteriovenous malformation':ab,ti OR 'brain avm':ab,ti OR 'cerebral arteriovenous malformation':ab,ti OR 'intracranial avm':ab,ti OR 'brain arteriovenous malformation':ab,ti	2368
Step 2	pregnant*:ab,ti OR 'pregnancy*':ab,ti OR 'gestation*':ab,ti	848745
Step 3	1 AND 2	77

CNKI		
Step 1	(SU%=Cerebral AVM) OR (SU%=intracranial AVM) OR (SU%=cerebral arteriovenous malformation) OR (SU%=intracranial arteriovenous malformation) OR (SU%=brain AVM) OR (SU%=brain arteriovenous malformation)	9006
Step 2	(SU%=pregnant) OR (SU%=pregnancy) OR (SU%=gestation)	942704
Step 3	1 AND 2	116

Wanfang		
Step 1	Theme:(Cerebral AVM) or Theme:(intracranial AVM) or Theme:(cerebral arteriovenous malformation) or Theme:(intracranial arteriovenous malformation) or Theme:(brain AVM) or Theme:(brain arteriovenous malformation)	4454
Step 2	Theme:(pregnant) or Theme:(pregnancy) or Theme:(gestation)	368821
Step 3	1 AND 2	88