THE LANCET Neurology

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Horne MA, Flemming KD, Su I-C, et al, and the Cerebral Cavernous Malformations Individual Patient Data Meta-analysis Collaborators. Clinical course of untreated cerebral cavernous malformations: a meta-analysis of individual patient data. *Lancet Neurol* 2015; published online Dec 1. http://dx.doi.org/10.1016/S1474-4422(15)00303-8.

Appendix to:

Margaret A Horne, Kelly D Flemming, I-Chang Su, Christian Stapf, Jin Pyeong Jeon, Da Li, Susanne S Maxwell, Philip White, Teresa J Christianson, Ronit Agid, Won-Sang Cho, Chang Wan Oh, Zhen Wu, Jun-Ting Zhang, Jeong Eun Kim, Karel ter Brugge, Robert Willinsky, Robert D Brown Jr, Gordon D Murray, Rustam Al-Shahi Salman, and the Cerebral Cavernous Malformations Individual Patient Data Meta-analysis Collaborators. Clinical course of untreated cerebral cavernous malformations: a meta-analysis of individual patient data. *Lancet Neurol* 2015 Published Online December 1, 2015 http://dx.doi.org/10.1016/S1474-4422(15)00303-8

Literature search strategies

OVID MEDLINE

1. Hemangioma, Cavernous, Central Nervous System/
2. Hemangioma, Cavernous/
3. (cavernous adj5 (angioma$ or hemangioma$ or malformation$)).tw.
4. cavernoma$.tw.
5. 2 or 3 or 4
6. exp brain/ or central nervous system/ or exp cerebral arteries/
7. exp brain neoplasms/
8. (brain$ or cerebral or intracerebral or central nervous system or intracranial or cerebellar or intraventricular or supratentorial).tw.
9. 6 or 7 or 8
10. 5 and 9
11. 1 or 10

EMBASE

1. Brain Hemangioma/
2. brain ventricle cavernoma/
3. cavernous hemangioma/
4. (cavernous adj5 (angioma$ or hemangioma$ or malformation$)).tw.
5. cavernoma$.tw.
6. 3 or 4 or 5
7. central nervous system/ or exp brain/ or exp brain ventricle/ or exp brain artery/
8. exp brain tumor/
9. (brain$ or cerebral or intracerebral or central nervous system or intracranial or cerebellar or intraventricular or supratentorial).tw.
10. 7 or 8 or 9
11. 6 and 10
12. 1 or 2 or 11

Publications of cohorts eligible for inclusion in individual patient data meta-analysis

Study	Date	Patients	Study design	Other selection criteria
Robinson[WA18]	1991	66	Retrospective; hospital-based	None
Zabramski[WA24]	1994	21	Prospective; 6 families	Familial CCM
Aiba[WA21]	1995	110	Retrospective; hospital-based	None
Kondziolka[WA22]	1995	122	Retrospective + prospective; hospital-based	Conservative management
Kim[WA25]	1997	62	Retrospective; hospital-based	None
Porter[WA34*]	1997	110[†]	Retrospective + prospective; tertiary referral centre	None
Moriarity[WA26]	1999	68	Prospective; hospital-based	None
Porter[WA27]	1999	100	Retrospective; hospital-based	Brainstem CCM location
Barker[WA28]	2001	136	Retrospective; hospital-based	Bled at presentation
Hasegawa[WA29]	2002	82	Retrospective + prospective; radiosurgery unit	High-risk, bled at presentation; pre-treatment
Mathiesen[WA19]	2003	68	Retrospective + prospective; hospital-based	Brainstem CCM location
Wang[WA20]	2003	137	Retrospective; hospital-based	Brainstem CCM location
Ghannane[WA30]	2007	79	Retrospective; hospital-based	None
Flemming[WA35*]	2012	292[†]	Retrospective; tertiary referral centre	None
Schneble[WA36*]	2012	87[†]	Retrospective; tertiary referral centre	None
Al-Shahi Salman[WA37*]	2012	135[†]	Prospective; population-based	None
Al-Holou[WA31]	2012	<50	Retrospective; hospital-based	Children and young adults (≤25 years)
Riant[WA23]	2013	~50	Prospective; hospital-based	Familial CCM
Kalani[WA32]	2013	64	Retrospective; hospital-based	Pregnant women
Kondziolka[WA33]	2013	122	Prospective; hospital-based	Asymptomatic patients
Jeon[WA38*]	2014	326	Retrospective; hospital-based	None
Li[WA39*]	2014	331[†]	Prospective; hospital-based	Brainstem CCM location

* Included in the individual patient data meta-analysis.

[†] Size of the published cohort. Some people in these six cohorts did not meet the inclusion criteria for this meta-analysis and were excluded. Porter *et al.*[WA34] and Al-Shahi Salman *et al.*[WA37] provided unpublished data for this meta-analysis.

Characteristics of included cohorts

Characteristic*	Scotland 1999–2003 (n=135)		Scotland 2006–2010 (n=160)		Hôpital Lariboisière (n=81)		Mayo Clinic (n= 267)		Toronto Western Hospital (n=345)		Seoul National University Hospital (n=326)		Beijing Tiantan Hospital (n=306)	
Median age at diagnosis, years (IQR)	41	32–53	46	34–60	42	28–59	46	31–62	42	33–54	55	43–64	37	29–47
Female sex	80	59%	77	48%	47	58%	143	54%	194	56%	181	56%	145	47%
Mode of presentation														
Incidental	62	46%	67	42%	47	59%	98	37%	101	29%	70	21%	16	5%
Seizure	35	26%	52	33%	10	12%	76	28%	69	20%	95	29%	0	0%
ICH	17	13%	31	19%	10	12%	64	24%	116	34%	107	33%	231	76%
FND	21	15%	10	6%	14	17%	29	11%	59	17%	54	17%	59	19%
Multiple CCM	24	18%	29	18%	27	33%	49	18%	79	23%	49	15%	25	8%
Primary CCM location														
Lobar	90	67%	120	75%	–	–	156	58%	189	55%	193	59%	0	0%
Deep	9	7%	4	2%	–	–	34	13%	30	9%	52	16%	0	0%
Cerebellum	19	14%	11	7%	–	–	14	5%	24	7%	36	11%	0	0%
Brainstem	17	12%	25	16%	17	21%	63	24%	102	29%	45	14%	306	100%
CCM management														
Surgery or stereotactic radiosurgery	23	17%	11	7%	4	5%	73	27%	40	12%	79	24%	83	27%
Conservative management	112	83%	149	93%	77	95%	194	73%	305	88%	247	76%	223	73%
First outcome event in untreated follow-up														
ICH	7	5%	7	4%	4	5%	20	7%	24	7%	52	16%	90	29%
FND	14	10%	6	4%	–	–	–	–	32	9%	–	–	–	–
No outcome event in 5-year follow-up	115	85%	147	92%	77	95%	247	93%	290	84%	274	84%	216	71%
Median censored follow-up, years (IQR)	5·0	2·6–5·0	3·9	2·9–5·0	2·2	0·7–4·2	4·5	1·1–5·0	3·9	1·8–5·0	2·1	1·3–3·3	4·2	2·2–5·0

* Values are *n* (%) unless stated otherwise. ICH denotes intracranial haemorrhage. FND denotes non-haemorrhagic focal neurological deficit.

Assessment of each of the seven cohorts against each of eight risks of bias*

	Scotland 1999–2003	Scotland 2006–2010	Hôpital Lariboisière	Mayo Clinic	Toronto Western Hospital	Seoul National University Hospital	Beijing Tiantan Hospital
Was selection of exposed and non-exposed patients drawn from the same population? (Criterion: all were adults diagnosed with CCM, validated by MRI)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Can we be confident in the assessment of exposure? (Criteria: MRI was used to establish diagnosis, brainstem location, and CCM multiplicity; mode of presentation was determined by brain imaging; sex and age were recorded)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Can we be confident that outcome of interest was not present at start of study? (Criterion: ICH/FND was described at inception and ICH was described during follow-up)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? (Not applicable because the analysis did not assume any associations were known)	na	na	na	na	na	na	na
Can we be confident in the assessment of the presence or absence of prognostic factors? (Criteria: MRI was used to establish diagnosis, brainstem location, and CCM multiplicity; mode of presentation was determined by brain imaging; sex and age were recorded)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Can we be confident in the assessment of outcome? (Criterion: ICH was defined as symptomatic and confirmed by brain imaging)	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
Was the follow-up of cohorts adequate? (Criterion: median follow-up was >2 years)	Definitely yes	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Definitely yes
Were co-interventions similar between groups? (Not applicable because follow-up was censored at the time of any intervention)	na	na	na	na	na	na	na

* An 8-item tool published by the Cochrane Methods Bias group: http://bmg.cochrane.org/sites/bmg.cochrane.org/files/uploads/Tool%20to%20Assess%20Risk%20of%20Bias%20in%20Cohort%20Studies.pdf

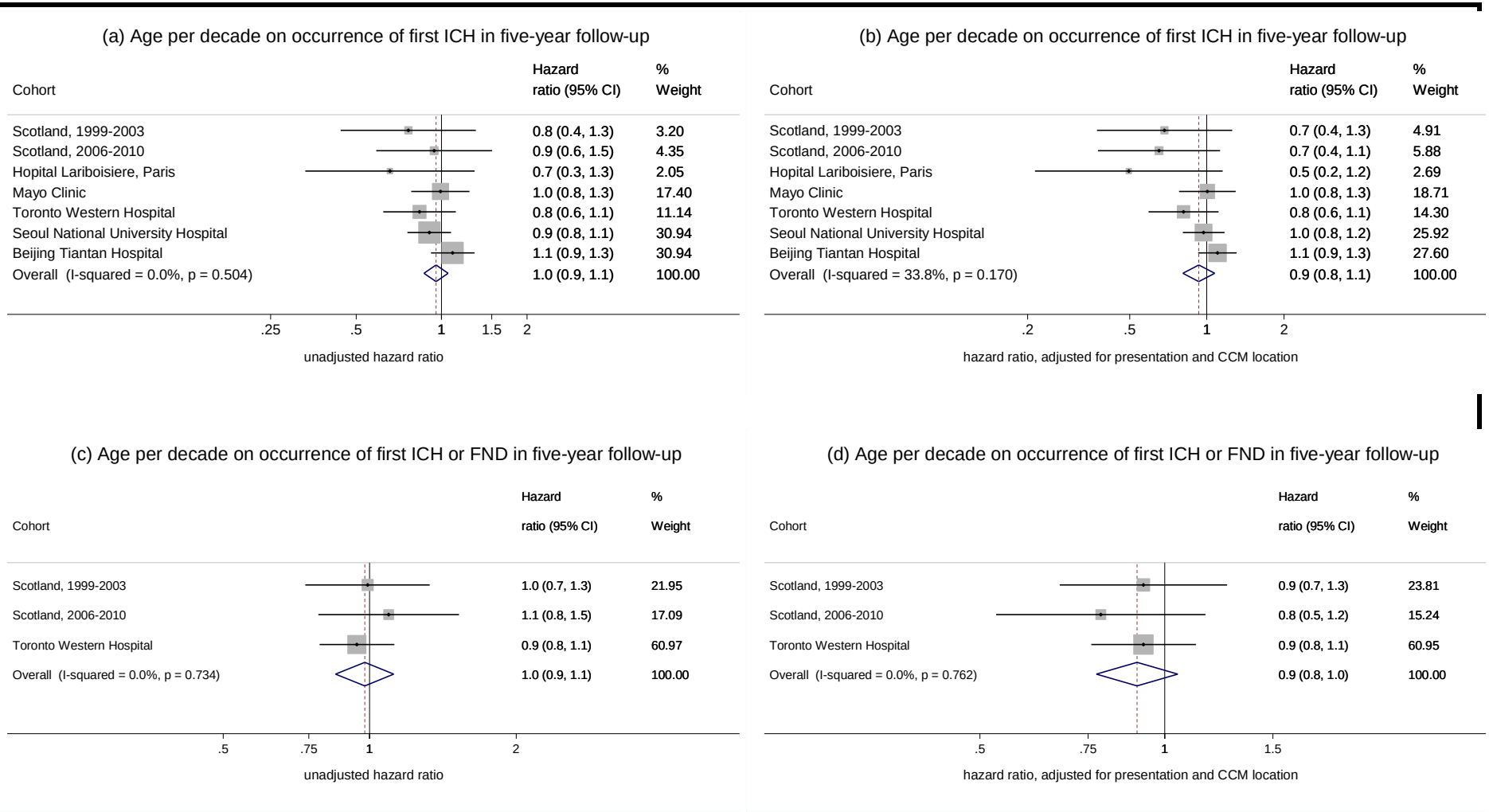
na = not applicable to the present study.

Estimated risk of intracranial haemorrhage in five-year follow-up of each cohort, by mode of presentation

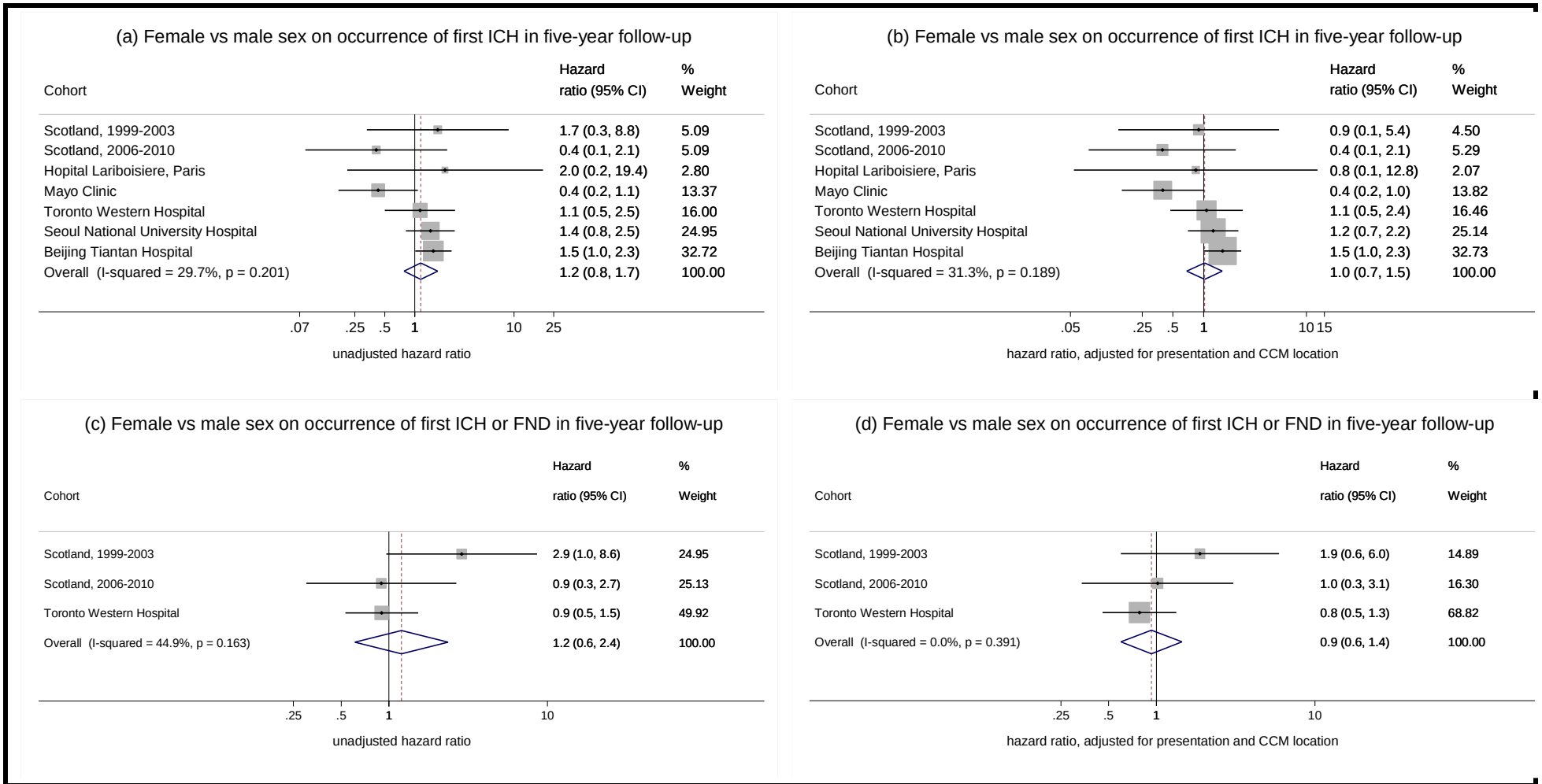
Study	Risk factor	Number of adults	Events	5-year estimated risk (95% confidence interval)	Unadjusted hazard ratio (95% confidence interval)
Scotland, 1999–2003	ICH or FND presentation	38	5	15·9% (3·0 to 28·8)	
	Other presentation	97	2	2·5% (0 to 5·9)	7·5 (1·4 to 38·5)
Scotland, 2006–2010	ICH or FND presentation	41	6	18·3% (4·8 to 31·8)	
	Other presentation	119	1	0·9% (0 to 2·6)	19·3 (2·3 to 160·4)
Hôpital Lariboisière	ICH or FND presentation	24	1	4·2% (0 to 12·2)	
	Other presentation	57	3	10·8% (0 to 22·6)	0·8 (0·1 to 7·5)
Mayo Clinic	ICH or FND presentation	93	15	20·7% (11·2 to 30·1)	
	Other presentation	174	5	4·3% (0·6 to 7·9)	6·4 (2·3 to 17·6)
Toronto Western Hospital	ICH or FND presentation	175	23	15·8% (9·7 to 21·9)	
	Other presentation	170	1	0·6% (0 to 1·8)	23·4 (3·2 to 173·1)
Seoul National University Hospital	ICH or FND presentation	161	42	33·5% (24·2 to 42·8)	
	Other presentation	165	10	10·2% (2·8 to 17·6)	5·0 (2·5 to 9·9)
Beijing Tiantan Hospital	ICH or FND presentation	290	88	32·9% (27·1 to 38·6)	
	Other presentation	16	2	14·4% (0 to 33·1)	3·0 (0·7 to 12·2)

Estimated risk of intracranial haemorrhage in five-year follow-up of each cohort, by primary CCM location

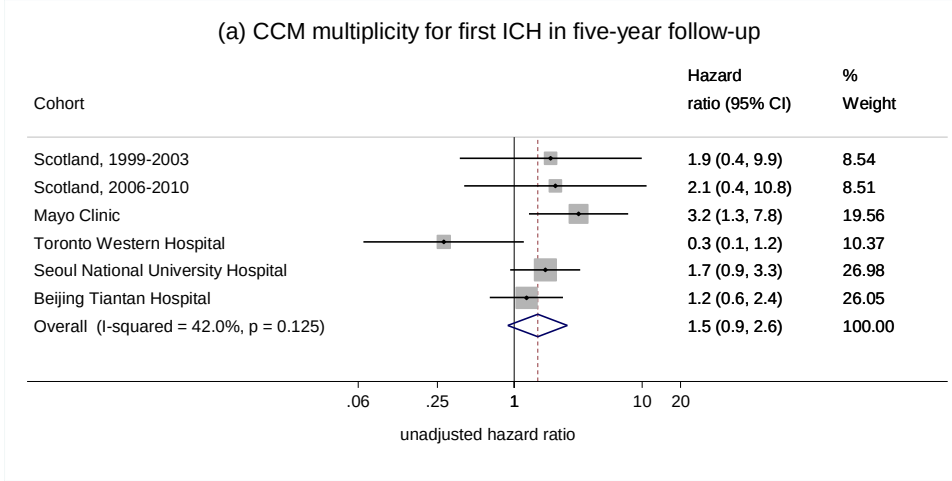
Study	Risk factor	Number of adults	Events	5-year estimated risk (95% confidence interval)	Unadjusted hazard ratio (95% confidence interval)
Scotland, 1999–2003	Brainstem	17	3	18·4% (0 to 37·3)	5·1 (1·1 to 22·6)
	Other location	118	4	4·2% (0·1 to 8·2)	
Scotland, 2006–2010	Brainstem	25	6	29·3% (8·9 to 49·7)	36·0 (4·3 to 299·1)
	Other location	135	1	0·8% (0 to 2·4)	
Hôpital Lariboisière	Brainstem	17	3	25·1% (0 to 50·8)	10·0 (1·0 to 96·8)
	Other location	64	1	3·1% (0 to 9·2)	
Mayo Clinic	Brainstem	63	10	19·5% (8·6 to 30·5)	3·7 (1·5 to 8·9)
	Other location	204	10	7·2% (2·9 to 11·5)	
Toronto Western Hospital	Brainstem	102	16	18·3% (10·0 to 26·6)	5·1 (2·2 to 11·9)
	Other location	243	8	4·3% (1·3 to 7·3)	
Seoul National University Hospital	Brainstem	45	11	29.5% (13.2 to 45.9)	1·8 (0·9 to 3·6)
	Other location	281	41	20.5% (14.0 to 27.1)	
Beijing Tiantan Hospital	Brainstem	306	90	31.9% (26.3 to 37.5)	–
	Other location	0	0	–	

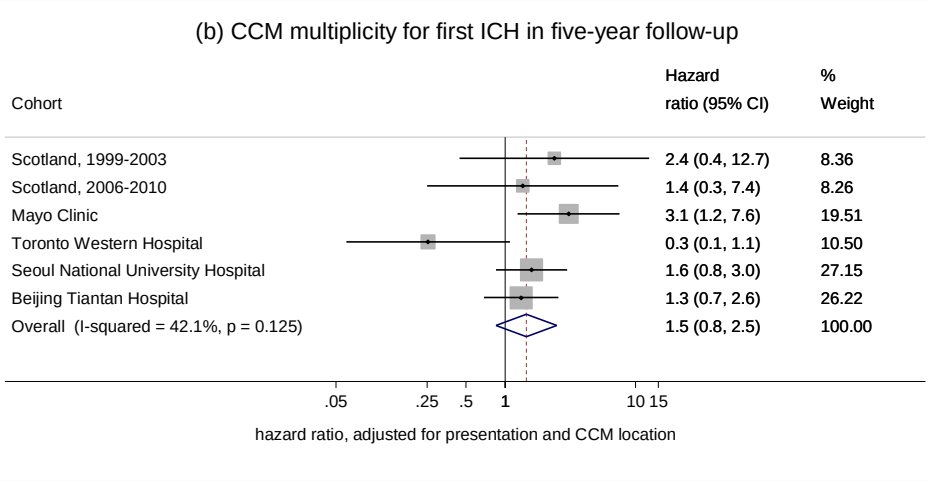


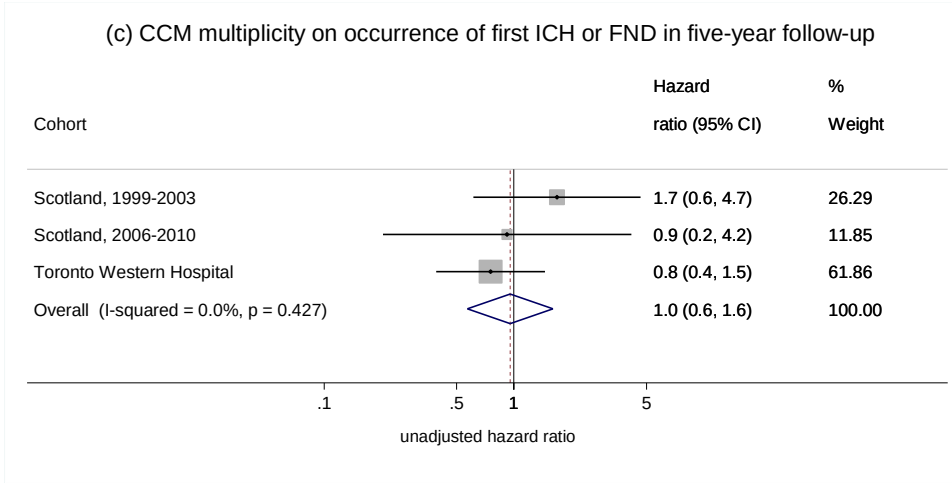
Forest plots displaying cohort-level and pooled estimates of associations between outcome over five years and age per decade, unadjusted (a and c) and adjusted for the two core predictors (b and d).

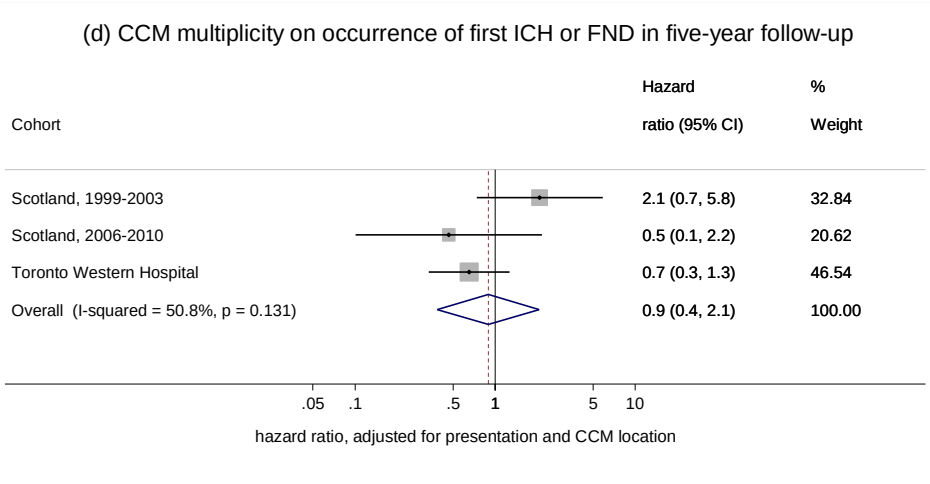


Forest plots displaying cohort-level and pooled estimates of associations between outcome over five years and sex, unadjusted (a and c) and adjusted for the two core predictors (b and d).

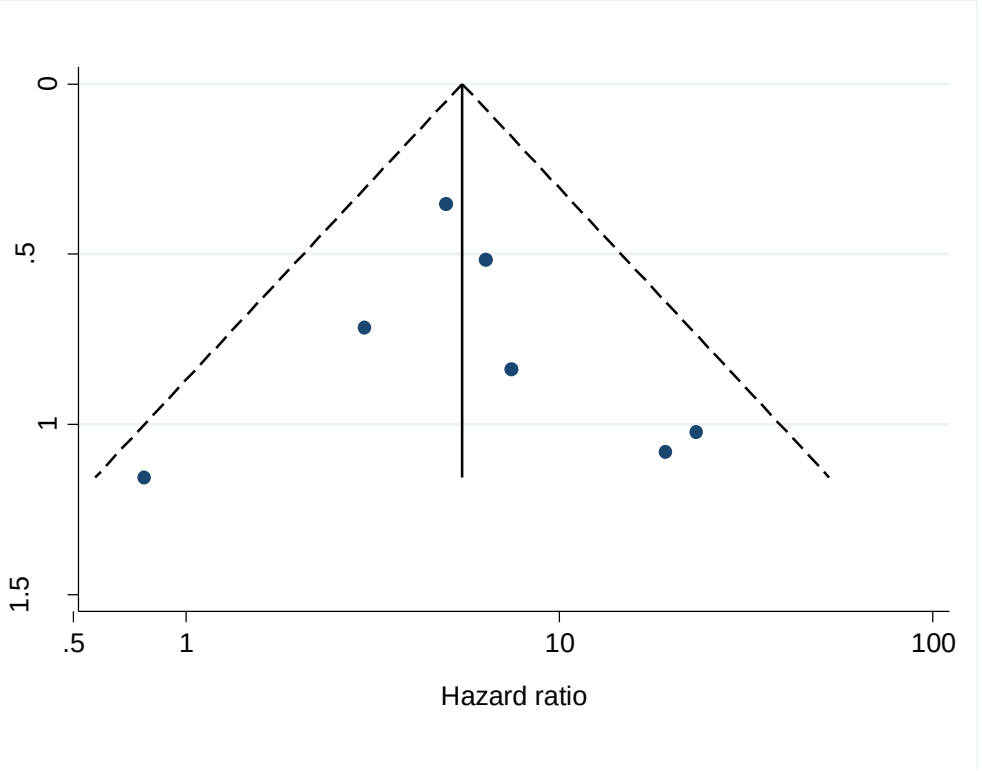




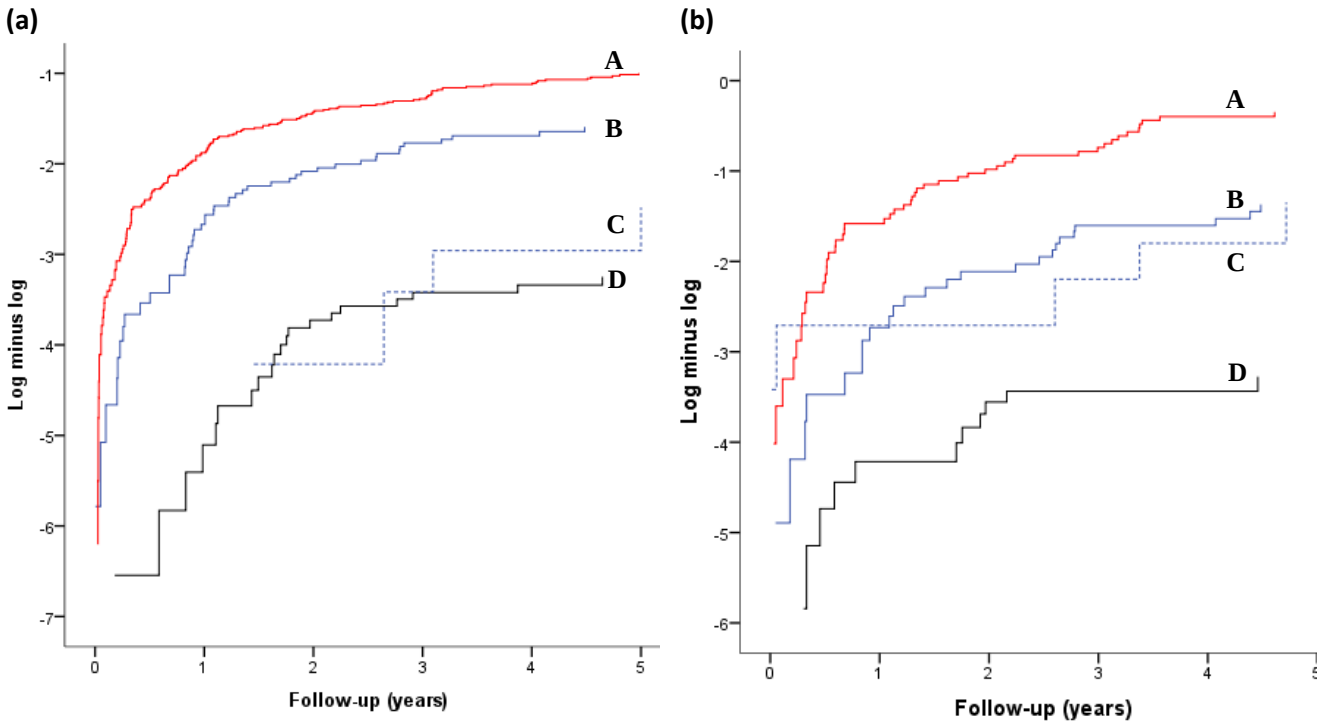




Forest plots displaying cohort-level and pooled estimates of associations between outcome over five years and CCM multiplicity, unadjusted (a and c) and adjusted for the two core predictors (b and d).



Funnel plot based on the association between the primary outcome over five years and intracranial haemorrhage or focal neurological deficit vs other presentation, in each of the seven included cohorts



A – ICH or FND presentation, brainstem location; B – ICH or FND presentation, other location; C – Other presentation, brainstem location; D – Other presentation, other location

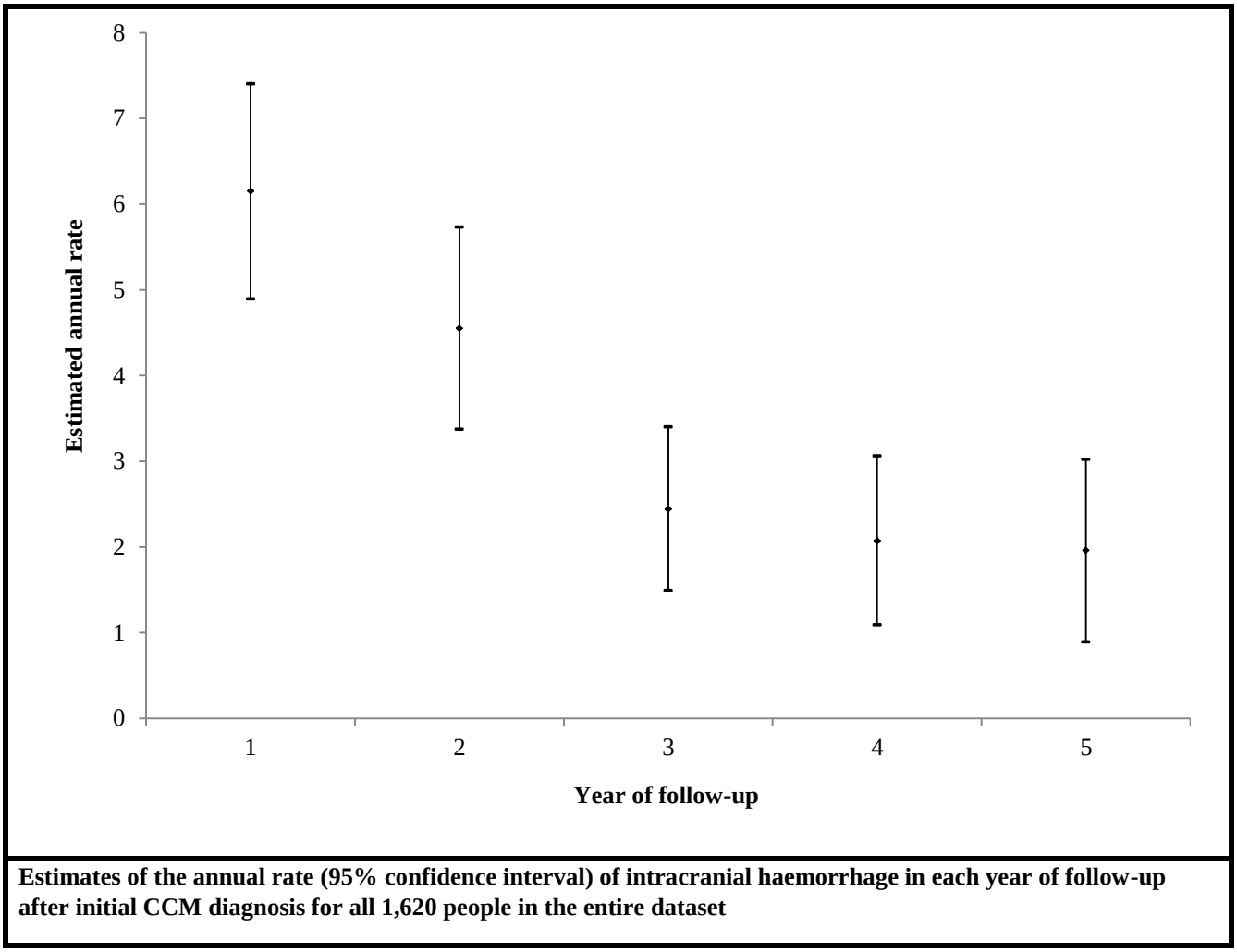
These two plots show the complementary logarithmic function of the survival function $S(t)$ – i.e. $\log\{-\log[S(t)]\}$ – (on the y-axis), plotted against the five-year follow-up (on the x-axis); $S(t)$ is the Kaplan-Meier estimate of the survival function at each successive occurrence of an ICH (a) or ICH or FND (b) at time t. These plots are used to test the assumption of proportional hazards before using Cox proportional hazards regression.

Tests of proportional hazards assumption using complementary log plots: (a) for an outcome of intracranial haemorrhage by presentation and location and (b) for an outcome of intracranial haemorrhage or focal neurological deficit by presentation and location

Estimated risk of intracranial haemorrhage, and intracranial haemorrhage or focal neurological deficit in five-year follow-up of each cohort, by core predictors

Cohort	Other presentation, other location		Other presentation, brainstem location		ICH or FND presentation, other location		ICH or FND presentation, brainstem location	
	Risk (%)	(95% CI)	Risk (%)	(95% CI)	Risk (%)	(95% CI)	Risk (%)	(95% CI)
Outcome: ICH*								
Scotland, 1999–2003	2·7	0 to 6·3	—	—	10·0	0 to 23·5	26·7	0·7 to 52·6
Scotland, 2006–2010	1·0	0 to 2·9	—	—	—	—	46·9	17·5 to 76·3
Hôpital Lariboisière, Paris	3·8	0 to 11·2	46·7	0 to 95·3	—	—	11·1	0 to 31·6
Mayo Clinic	4·6	0·6 to 8·5	—	—	17·8	3·5 to 32·0	24·0	10·9 to 37·0
Toronto Western Hospital	0·7	0 to 2·0	—	—	10·3	2·9 to 17·7	21·7	12·1 to 31·3
Seoul National University Hospital	11·0	3·2 to 18·8	—	—	31·2	21·2 to 41·2	43·0	20·3 to 65·7
Beijing Tiantan Hospital	—	—	14·4	0 to 33·0	—	—	32·9	27·2 to 38·6
Pooled cohorts	3·8	2·1 to 5·5	8·0	0·1 to 15·9	18·4	13·3 to 23·5	30·8	26·3 to 35·2
Outcome: ICH or FND								
Scotland, 1999–2003	8·9	2·6 to 15·1	20·0	0 to 55·1	25·1	5·6 to 44·6	58·3	30·4 to 86·2
Scotland, 2006–2010	2·9	0 to 6·0	—	—	—	—	86·3	62·2 to 100
Toronto Western Hospital	0·7	0 to 2·0	42·8	5·6 to 79·9	27·3	16·3 to 38·2	44·4	32·1 to 56·7
Pooled cohorts	3·7	1·5 to 5·9	22·9	3·7 to 42·2	22·4	14·2 to 30·6	50·7	40·1 to 61·4

***** 1,620 adults contributed data on ICH outcomes. 640 adults contributed data on ICH or FND outcomes.
ICH denotes intracranial haemorrhage. FND denotes non-haemorrhagic focal neurological deficit.



Estimates of the annual rate (95% confidence interval) of intracranial haemorrhage in each year of follow-up after initial CCM diagnosis for all 1,620 people in the entire dataset

Estimates of the annual rate of experiencing an intracranial haemorrhage in each year of follow-up after initial CCM diagnosis by the two core predictors and for all 1,620 people in the entire dataset

Risk factor	Year of follow-up	Number of adults at start of year	Number of outcome events in forthcoming year	Hazard rate (HR)* (%)	95% CI (HR) (%)
Other presentation, other location (n = 718)	1st	718	4	0.59	0 to 1.17
	2nd	634	10	1.74	0.7 to 2.82
	3rd	516	4	0.85	0 to 1.69
	4th	422	1	0.27	0 to 0.79
	5th	331	1	0.32	0 to 0.96
Other presentation, brainstem location (n = 80)	1st	80	0	–	–
	2nd	74	1	1.48	0 to 4.39
	3rd	61	1	1.75	0 to 5.19
	4th	53	1	2.04	0 to 6.04
	5th	45	1	2.63	0 to 7.79
ICH or FND presentation, other location (n = 327)	1st	327	20	6.81	3.83 to 9.80
	2nd	260	13	5.57	2.54 to 8.59
	3rd	207	8	4.48	1.38 to 7.59
	4th	150	2	1.49	0 to 3.56
	5th	118	2	1.92	0 to 4.59
ICH or FND presentation, brainstem location (n = 495)	1st	495	68	15.09	11.52 to 18.67
	2nd	406	33	8.76	5.78 to 11.75
	3rd	347	12	3.77	1.64 to 5.91
	4th	289	13	4.98	2.27 to 7.69
	5th	233	9	4.20	1.46 to 6.94
Entire dataset (n = 1,620)	1st	1,620	92	6.15	4.89 to 7.40
	2nd	1,374	57	4.55	3.37 to 5.73
	3rd	1,131	25	2.44	1.49 to 3.40
	4th	914	17	2.07	1.09 to 3.06
	5th	727	13	1.96	0.89 to 3.02

*Hazard rate is an estimate of the risk of experiencing an ICH during year *x*, given that an individual has survived to the start of year *x*.

Estimated risk of intracranial haemorrhage or focal neurological deficit in five-year follow-up of each cohort, by mode of presentation

Study	Risk factor	Number of adults	Events	5-year estimated risk	95% confidence interval	Unadjusted hazard ratio (95% confidence interval)
Scotland, 1999–2003	ICH/FND presentation	38	12	37·6%	20·5 to 54·7	4·7 (1·9 to 11·5)
	Other presentation	97	8	9·4%	3·2 to 15·6	
Scotland, 2006–2010	ICH/FND presentation	41	10	30·8%	14·5 to 47·2	11·5 (3·2 to 41·9)
	Other presentation	119	3	2·7%	0 to 5·6	
Toronto Western Hospital	ICH/FND presentation	175	50	35·6%	27·2 to 43·9	11·3 (4·5 to 28·3)
	Other presentation	170	5	4·5%	0·4 to 8·6	
Pooled cohorts, un-stratified	ICH/FND presentation	254	72	35·3%	28·4 to 42·1	8·2 (4·8 to 14·2)
	Other presentation	386	16	5·2%	2·6 to 7·8	

Estimated risk of intracranial haemorrhage or focal neurological deficit in five-year follow-up of each cohort, by primary CCM location

Study	Risk factor	Number of adults	Events	5-year estimated risk	95% confidence interval	Unadjusted hazard ratio (95% confidence interval)
Scotland, 1999–2003	Brainstem	17	8	47·1%	23·3 to 70·8	5·2 (2·1 to 12·7)
	Other location	118	12	12·1%	5·7 to 18·6	
Scotland, 2006–2010	Brainstem	25	10	50·3%	26·7 to 73·9	22·6 (6·2 to 82·5)
	Other location	135	3	2·4%	0 to 5·1	
Toronto Western Hospital	Brainstem	102	35	43·4%	31·7 to 55·0	4·9 (2·9 to 8·6)
	Other location	243	20	10·7%	6·1 to 15·4	
Pooled cohorts, unstratified	Brainstem	144	53	44·5%	35·0 to 54·0	6·3 (4·1 to 9·6)
	Other location	496	35	8·8%	6·0 to 11·7	

Articles eligible for inclusion

A. Full text articles excluded

i. Data already included in a separate publication of an eligible cohort

WA1 Li D, Yang Y, Hao S-Y, et al. Hemorrhage risk, surgical management, and functional outcome of brainstem cavernous malformations. *J Neurosurg* 2013; **119**(4): 996–1008.

WA2 Li D, Hao S-Y, Tang J, et al. Clinical course of untreated pediatric brainstem cavernous malformations: hemorrhage risk and functional recovery. *J Neurosurg Pediatr* 2014; **13**(5): 471–83.

WA3 Moore SA, Brown RD, Jr., Christianson TJH, Flemming KD. Long-term natural history of incidentally discovered cavernous malformations in a single-center cohort. *J Neurosurg* 2014; **120**(5): 1188–92.

WA4 Fritschi JA, Reulen HJ, Spetzler RF, Zabramski JM. Cavernous Malformations of the Brain-Stem – a Review of 139 Cases. *Acta Neurochir (Wien)* 1994; **130**(1–4): 35–46.

ii. Diagnosis not certain

WA5 Abe M, Kjellberg RN, Adams RD. Clinical presentations of vascular malformations of the brain stem: comparison of angiographically positive and negative types. *J Neurol Neurosurg Psychiatry* 1989; **52**(2): 167.

WA6 Lobato R, Perez C, Rivas J, Cordobes F. Clinical, radiological, and pathological spectrum of angiographically occult intracranial vascular malformations. Analysis of 21 cases and review of the literature. *J Neurosurg* 1988; **68**(4): 518–31.

iii. Retrospective lifetime period at risk

WA7 Bruneau M, Bijlenga P, Reverdin A, et al. Early surgery for brainstem cavernomas. *Acta Neurochir (Wien)* 2006; **148**(4): 405–14.

WA8 Ferroli P, Sinisi M, Franzini A, Giombini S, Solero C, Broggi G. Brainstem cavernomas: Long-term results of microsurgical resection in 52 patients. *Neurosurgery* 2005; **56**(6): 1203–12.

WA9 Curling OD, Jr, Kelly DL, Elster AD, Craven TE. An Analysis of the Natural History of Cavernous Angiomas. *J Neurosurg* 1991; **75**: 702–8.

WA10 Murillo-Bonilla L, Cantu-Brito C, Arauz-Gongora A, Higuera-Calleja J, Padilla-Rubio J, Barinagarrementeria-Aldatz F. [Cavernous angioma. Clinical observations and prognosis of 133 patients]. *Rev Invest Clin* 2003; **55**(4): 387–93.

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iv. Outcome events were not objective and symptomatic

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WA13 Kupersmith MJ, Kalish H, Epstein F, et al. Natural history of brainstem cavernous malformations. *Neurosurgery* 2001; **48**(1): 47–53.

WA14 Labauge P, Brunereau L, Levy C, Laberge S, Houtteville JP. The natural history of familial cerebral cavernomas: a retrospective MRI study of 40 patients. *Neuroradiology* 2000; **42**(5): 327–32.

v. Duration of follow-up was not adequately quantified

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B. Cohorts eligible for inclusion invited to share but did not provide individual patient data

i. Agreed initially, but no response

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ii. Data no longer available

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iii. Clinical data not available

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C. Cohorts providing individual patient data

WA34 Porter PJ, Willinsky RA, Harper W, Wallace MC. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. *J Neurosurg* 1997; **87**(2): 190–97.

WA35 Flemming KD, Link MJ, Christianson TJH, Brown Jr RD. Prospective hemorrhage risk of intracerebral cavernous malformations. *Neurology* 2012; **78 (9)**: 632–36.

WA36 Schneble HM, Soumare A, Herve D, et al. Antithrombotic therapy and bleeding risk in a prospective cohort study of patients with cerebral cavernous malformations. *Stroke* 2012; **43 (12)**: 3196–99.

WA37 Al-Shahi Salman R, Hall JM, Horne MA, et al. Untreated clinical course of cerebral cavernous malformations: a prospective, population-based cohort study. *Lancet Neurol* 2012; **11**: 217–24.

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