

Economic Burden of Intracranial Vascular Malformations in Adults

Prospective Population-Based Study

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Background and Purpose—Although intracranial vascular malformations (IVMs) are the leading cause of intracerebral hemorrhage (ICH) in young adults, there has not been a cost-of-illness study on an unselected cohort.

Methods—We measured the direct healthcare costs (inpatient, outpatient, intervention, and brain imaging) incurred by every adult within 3 years after their first presentation with a brain arteriovenous malformation (AVM) or cavernous malformation (CM) in a prospective, population-based study. We estimated the indirect cost of lost productivity for the whole cohort over the same period by projecting questionnaire responses from living consenting adults.

Results—369 adults (AVM=229 [62%], CM=140 [38%]) incurred healthcare costs of £5.96 million over 3 years, of which AVMs accounted for 90%, inpatient care accounted for 75%, and the first year of care accounted for 69%. Median 3-year healthcare costs were statistically significantly higher for adults presenting with ICH, aged <65 years, receiving interventional treatment, and adults with AVMs rather than CMs (£15 784 versus £1385, $P<0.0005$). Healthcare costs diminished with increasing AVM nidus size ($P=0.005$). Mean 3-year costs of lost productivity per questionnaire respondent ($n=145$) were £17 111 for AVMs and £6752 for CMs ($P=0.1$), and the projected 3-year cost of lost productivity for all 369 adults was £8.7 million.

Conclusions—The costs of healthcare and lost productivity attributable to IVMs are considerable, and highest in those aged <65 years, presenting with ICH, receiving interventional treatment, and harboring AVMs rather than CMs. Long-term studies of the cost-effectiveness of interventional treatment are needed. (*Stroke*. 2009;40:00-00.)

Key Words: intracranial arteriovenous malformations ■ central nervous system vascular malformations ■ economics ■ cost of illness

Intracranial vascular malformations (IVMs) are the leading cause of spontaneous intracerebral hemorrhage in young adults,¹ whose IVM may leave them disabled or at risk of recurrent hemorrhage or epileptic seizure(s). The two most common subtypes of IVM—arteriovenous malformations (AVMs) and cavernous malformations (CMs)—differ in the frequency and severity of their clinical manifestations.² Furthermore, decisions about whether and how to treat AVMs and CMs tend to differ³: although either IVM may be neurosurgically excised, stereotactic radiotherapy is mostly used for the treatment of AVMs (and some CMs in the brain stem and deep locations), whereas the use of endovascular embolization is confined to AVMs.

IVMs are likely to have a considerable economic burden, because of the healthcare costs incurred by adults' acute care, investigation, interventional treatment, and rehabilitation (especially for those presenting with hemorrhage), as well as the costs of lost productivity incurred by their predilection for

those of working age as well as the long-term morbidity they cause.⁴

Prior economic evaluations of IVMs have not included cost-of-illness studies or analyses alongside randomized control trials; instead, they have focused on estimated costs of different treatment strategies and have restricted their evaluations to AVMs. Cost evaluations of individual procedures have been restricted to endovascular embolization of AVMs (per-person costs of €3975 in France [1997–2001] and €4627 in Germany [1998–1999]).^{5,6} Cost comparison studies have contrasted the costs of multimodality treatment with embolization and surgery versus surgery alone (one American study estimated per-person absolute costs of \$78 400 versus \$49 300 respectively [1998], and another calculated costs per successfully obliterated AVM of \$71 366 versus \$78 506 [1992]),^{7,8} and the costs per person of surgery versus stereotactic radiotherapy (£15 242 versus €7920 in Germany using an indirect comparison of healthcare costs [1998–1999], and

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Can\$33 022 versus Can\$26 085 in a Canadian study considering both healthcare costs and lost productivity [1995]).^{9,10} Per-person lifetime healthcare costs for “operable” AVMs have been estimated using a decision analysis model comparing observation alone (\$33 138) with surgery ± embolization (\$37 484), and a policy of surgery for large- and medium-sized lesions and radiotherapy for small (<3 cm) AVMs (\$32 138; 1991–1995).¹¹

Therefore, we sought to estimate the short-term economic burden attributable to all new AVM and CM diagnoses in a prospective population-based cohort study of adults with IVMs,^{12,13} with a focus on direct healthcare costs and lost productivity. We intended to address the hypotheses that: presentation with hemorrhage confers higher overall (healthcare and productivity) costs than nonhemorrhagic presentation; adults aged <65 years incur higher overall costs than those aged ≥65 years; adults receiving interventional treatment incur higher overall costs than those who do not; AVMs incur greater overall costs than CMs; and AVMs with a small nidus size (<3 cm maximum diameter) incur higher overall costs than those with a larger nidus size.

Methods

Scottish Intracranial Vascular Malformation Study

The Scottish Intracranial Vascular Malformation Study (SIVMS) is a prospective population-based cohort study based on an anonymized extract of data from the Scottish Audit of Intracranial Vascular Malformations (SAIVMs, www.saivm.scot.nhs.uk), which identified Scottish residents aged ≥16 years at the time they were first diagnosed with any type of IVM in the years 1999 to 2003.¹² SAIVMs uses multiple overlapping sources of case ascertainment to identify adults, who are deemed to be incident in the year of their IVM’s definite radiological or pathological diagnosis, and on whom follow-up starts on the date of the clinical presentation that eventually led to the diagnosis being made. Those who do not opt out of medical records surveillance and annual postal questionnaires are followed up on an annual basis by a questionnaire sent to their general (family) practitioner. Participants who opt in then complete annual postal health-related quality-of-life questionnaires. This study included every adult in SIVMS during the years 1999 to 2003 with a definite diagnosis of an AVM or CM. At the time of this analysis in 2007, a maximum of 3 years’ follow-up data were available for the last adult detected in 2003, so we restricted our analyses to data accrued over the first 3 years after every adult’s initial presentation.

Healthcare Costs

We quantified healthcare costs using information obtained from medical records surveillance and national estimates of itemized healthcare costs for the tax year 2005 to 2006.^{14–16} Unfortunately, detailed electronic prescription records held by general practitioners were unavailable, so we did not include costs of pharmaceuticals (in particular, antiepileptic drugs).

Inpatient Stays

For every inpatient stay attributable to an adult’s IVM, we extracted information on length of stay (days) and the responsible specialty (or specialties). We estimated the cost of each inpatient episode using daily costs provided by the Information Services Division (ISD), which are specific to specialty and healthboard.¹⁴ We attributed admissions to intensive care units and neurosurgical, neurological, and rehabilitation wards to the healthboard of the neuroscience center at which the adult had been managed (Greater Glasgow, Lothian, Grampian, or Tayside), whereas we attributed admissions to any other specialty to the healthboard where the adult resided.

Outpatient Appointments

We estimated the cost of hospital outpatient appointments using a 3-year quantification of the total number of attended and unattended appointments documented in each adult’s medical records and the average cost of a neurology/neurosurgery appointment (£202.50).¹⁴

Interventions and Neuroimaging

Costs of computed tomography (£93) and MRI (£150) were estimated from ISD’s Costs Book,¹⁴ whereas the procedure code corresponding to cerebral catheter angiography (“Diagnostic radiology—arteries or lymphatics”) was priced in the Scottish National Tariff Project (£1313).¹⁵ We obtained costs of endovascular embolization and aneurysm coiling (£1765) and linear accelerator stereotactic radiotherapy (£11 698) from the Scottish National Tariff Project,¹⁵ but because Gamma Knife stereotactic radiotherapy was only performed at the National Center for Stereotactic Radiosurgery in Sheffield, England, this was assigned an English reference cost (£8,040).¹⁶ In Scotland, the costs of neurosurgical theater time, materials, and anesthesia are incorporated into the inpatient costs calculated by ISD.¹⁴

Costs of Lost Productivity

We calculated costs of lost productivity using national average weekly gross wage rates published by the Equal Opportunities Commission for Scotland¹⁷ (full-time [≥38 hours per week] £522.90 for men and £423.80 for women, part-time [<38 hours per week] £375.50 for men and £319.40 for women), to estimate unearned income attributable to the loss of employment, or death within 3 years of each adult’s presentation. We determined employment status before and after the clinical presentation that led to IVM diagnosis, using a questionnaire sent in 2007 to living adults who had opted in to completing postal questionnaires. If a respondent had lost full- or part-time employment, the productivity loss was assumed to start on the day after presentation and to continue until the end of the third year of follow-up. We estimated the working patterns of those to whom we were unable to send questionnaires or from whom we did not receive responses, by assuming that they had the same employment patterns as those of the respondents. We tested for bias in the questionnaire-based data by comparing the characteristics of questionnaire respondents and nonrespondents.

Statistical Analysis

We used SPSS (Statistical Package for the Social Sciences [version 13]) and Microsoft Access and Excel for data management and analysis. We used parametric statistics when data obeyed a normal distribution and nonparametric statistics when they did not (Mann–Whitney *U* tests unless otherwise specified). Because of smaller sample size and the large proportion of adults who were unemployed at presentation, we used the mean as a measure of central tendency when reporting cost of lost productivity. We subdivided healthcare costs into 3 major subgroups (age < or ≥65 years, hemorrhagic or nonhemorrhagic presentation, and whether or not interventional treatment was used), and subdivided costs of lost productivity into the latter 2 subgroups because these were likely to be the major influences on employment in adults of working age.

Ethical Approval

The Multicenter Research Ethics Committee for Scotland approved SIVMS (MREC 98/0/48).

Results

369 adult Scottish residents were first diagnosed with a definite AVM (n=229) or CM (n=140) during 1999 to 2003. The median age at presentation was 45 years, 51% were male, and follow-up was complete until 3 years after presentation for all 328 who remained alive, and until death for the 41 who died within 3 years of presentation. Twenty-eight people died during the first year of follow-up, 5 died during the second

Table 1. Estimated Healthcare Costs Over Three Years After Initial Presentation

	Unit Cost (£)	Volumes		Total Costs (£)		Median 3-Year Cost per Adult (£)		p§
		AVM n=229	CM n=140	AVM n=229	CM n=140	AVM n=229	CM n=140	
Inpatient stays, days								
Rehabilitation medicine	Varies by healthboard	4488	157	1 150 030	36 416			
Neurosurgery†		3007	408	2 051 900	256 317			
General internal medicine		1003	101	346 040	32 976			
Geriatric long stay		748	0	121 324	0			
Neurology		160	154	83 240	87 439			
Intensive care		158	1	273 797	1626			
Ear, nose, & throat		0	4	0	4162			
Subtotal			9564	825	4 026 331	418 936	8706	0
Nonsurgical interventions (episodes)								
Radiotherapy—gamma knife	8040	33	0	265 320	0			
Radiotherapy—linear accelerator	11 698	14	0	163 772	0			
Embolization	1765	127	0	224 155	0			
Aneurysm coiling	1765	14	0	24 710	0			
Subtotal		188	0	677 957	0	1765	0	<0.0005
Neuroimaging (episodes)								
Cerebral catheter angiogram	1313	329	25	431 977	32 825			
Computed tomography	93	431	127	40 083	11 811			
Magnetic resonance imaging	150	161	218	24 150	32 700			
Subtotal		921	370	496 210	77 336	1778	300	<0.0005
Outpatient visits (episodes)	203	839	453	169 892	91 741	608	405	0.07
Miscellaneous procedures‡		1	4	1307	3828	0	0	0.7
Total healthcare costs, £				5 371 697	591 841	15 784	1385	<0.0005

†All surgical costs (IVM excision & aneurysm clipping) incorporated in neurosurgical inpatient costs; ‡Miscellaneous procedures=highly complex ocular motility surgery (£1307) & oculoplastic procedures of low complexity (£957)¹⁵; §Comparing median costs per adult.

year, and 8 died during the third year; 16 (39%) of these deaths were directly related to the IVM or its treatment.

Healthcare Costs

Differences Between IVM Types

The total direct healthcare costs incurred by all 369 adults over the 3 years after their first presentation was £5 963 538, of which AVMs accounted for 90% (Table 1). The median healthcare cost per adult over the same time period was £15 784 for AVMs and £1385 for CMs ($P<0.0005$, Table 1). This difference between IVM types was found for inpatient, intervention and imaging costs, but not for outpatient costs (Table 1). The median number of inpatient days over 3 years was greater for AVMs (13, interquartile range 3 to 31) than for CMs (0, interquartile range 0 to 6), $P<0.0005$, although inpatient stays accounted for the majority of the total health-

care costs for both AVMs (75%) and CMs (71%). The majority (69%) of costs were incurred within the first year after presentation (Table 2); median costs were higher in the first than second year for both IVM types ($P<0.0005$), and there was also a significant difference between second and third year costs for AVMs ($P<0.0005$) but not CMs.

Subgroup Analyses

For both AVMs and CMs, adults who presented with hemorrhage, adults who were aged <65 years at presentation, and adults who received interventional treatment incurred higher healthcare costs than those who did not (Table 3). Ordinary least squares regression analysis showed that, for both AVMs and CMs, interventional treatment had the strongest association with healthcare costs, followed by hemorrhagic presentation and then age <65 years at presentation. For adults with

Table 2. Distribution of Estimated Healthcare Costs Over the 3 Years After Initial Presentation

	Year 1			Year 2			Year 3		
	n	Total (£)	Median per Adult (£)	n	Total (£)	Median per Adult (£)	n	Total (£)	Median per Adult (£)
AVM	229	3 755 876	9284	210	1 070 803	870	206	545 018	243
CM	140	339 499	563	131	189 228	236	130	63 114	150

Table 3. Average Estimated Costs of Healthcare and Lost Productivity per Adult in Subgroups and Overall, Over 3 Years After Initial Presentation

	Arteriovenous Malformations				Cavernous Malformations			
	n	Median Healthcare Costs per Adult (£)	n (Responders)	Mean Costs of Lost Productivity per Adult (£)	n	Median Healthcare Costs per Adult (£)	n (Responders)	Mean Costs of Lost Productivity per Adult (£)
Age at presentation								
<65 years	205	16 600	83	17 935	120	1656	54	4662
≥65 years	24	506	4	0	20	344	4	34 960
<i>P</i>		<0.0005		0.3		0.002		0.09
Presentation type								
Hemorrhagic	115	24 815	42	22 522	17	10 257	11	0
Non-hemorrhagic	114	7405	45	12 060	123	1002	47	10 247
<i>P</i>		<0.0005		0.2		<0.0005		0.1
Interventional treatment								
Yes	151	20 763	63	21 368	23	10 257	11	876
No	78	2892	24	5936	117	891	47	8127
<i>P</i>		<0.0005		0.143		<0.0005		0.7
Average 3-year costs per adult (£)	229	15 784	88	17 111	140	1385	57	6752

AVMs, 66% of whom received interventional treatment(s), interventional strategies differed in their median per-person overall healthcare costs (Kruskal-Wallis test $P<0.0005$): embolization followed by radiotherapy was the most expensive (£30 247; $n=22$), then embolization followed by surgery (£23 636; $n=25$), then surgery alone (£18 699; $n=34$), then radiotherapy alone (£18 008; $n=28$), and least expensive was embolization alone (£16 938; $n=41$). Where maximum AVM nidus diameter was known, median overall healthcare costs diminished as size increased (Kruskal-Wallis test $P=0.005$): <30 mm (£19 016; $n=120$), 30 to 59 mm (£13 535; $n=81$), ≥60 mm (£4173; $n=7$).

Productivity Losses

Questionnaire Responses

We sent 214 questionnaires to living consenting participants (127 [55%] AVMs, 87 [62%] CMs), from whom the 3-month response rate was 70% (89 AVMs and 60 CMs). 145 respondents (97%; 88 AVMs and 57 CMs) answered questions about prepresentation employment and subsequent working patterns (Figure). There was little evidence of response bias: comparing questionnaire responders with living nonresponders, there was no significant difference in socioeconomic status, IVM type, healthcare costs, age at presentation, presentation type, or interventional treatment. Before their first presentation with an IVM, 99 (68%) respondents were employed, but afterward only 50 (34%) were employed at an equivalent or greater capacity. There was no evident difference in the likelihood of productivity loss between adults with AVMs (29/60) and CMs (18/39); odds ratio 1.1, 95% confidence interval [CI] 0.5 to 2.4.

Quantification of Costs of Lost Productivity for Questionnaire Respondents

The mean 3-year costs of lost productivity per adult were £17 111 ($n=88$) for AVMs and £6752 ($n=57$) for CMs

($P=0.1$). We found no significant differences between subgroups stratified according to age at presentation, whether adults presented with hemorrhage and whether they received interventional treatment (Table 3). The total 3-year costs of lost productivity were £1 488 646 for all 88 respondents with AVMs and £391 591 for all 57 respondents with CMs.

Costs of Lost Productivity Attributable to Premature Death for the Whole Cohort

For the 16 adults (13 AVMs, 3CMs) who died before the end of the 3-year study period because of their IVM, we assumed that 39% were employed full-time and 29% part-time, before presentation, based on data from questionnaire respondents (Figure). Costs of lost productivity for those who died because of their IVM were then calculated using the number of lost working weeks, defined as the time between the date of death and the date at the end of the third year of follow-up.

Projected Costs of Lost Productivity for the Whole Cohort

To estimate costs of lost productivity for the entire cohort, we used data from the questionnaire respondents to impute the productivity losses for living adults from whom questionnaire data had not been obtained. We extrapolated the changes in employment status of the 145 responders to the whole cohort of 325 adults who were still alive 3 years after initial presentation. For both survivors and decedents, total costs of lost productivity over 3 years were £5.91 million for AVMs ($n=229$) and £2.75 million for CMs ($n=140$).

Discussion

The economic burden incurred by IVMs was considerable over the first 3 years after presentation, the brunt being borne by adults who were aged <65 years, who presented with hemorrhage, and who received interventional treatment. Es-

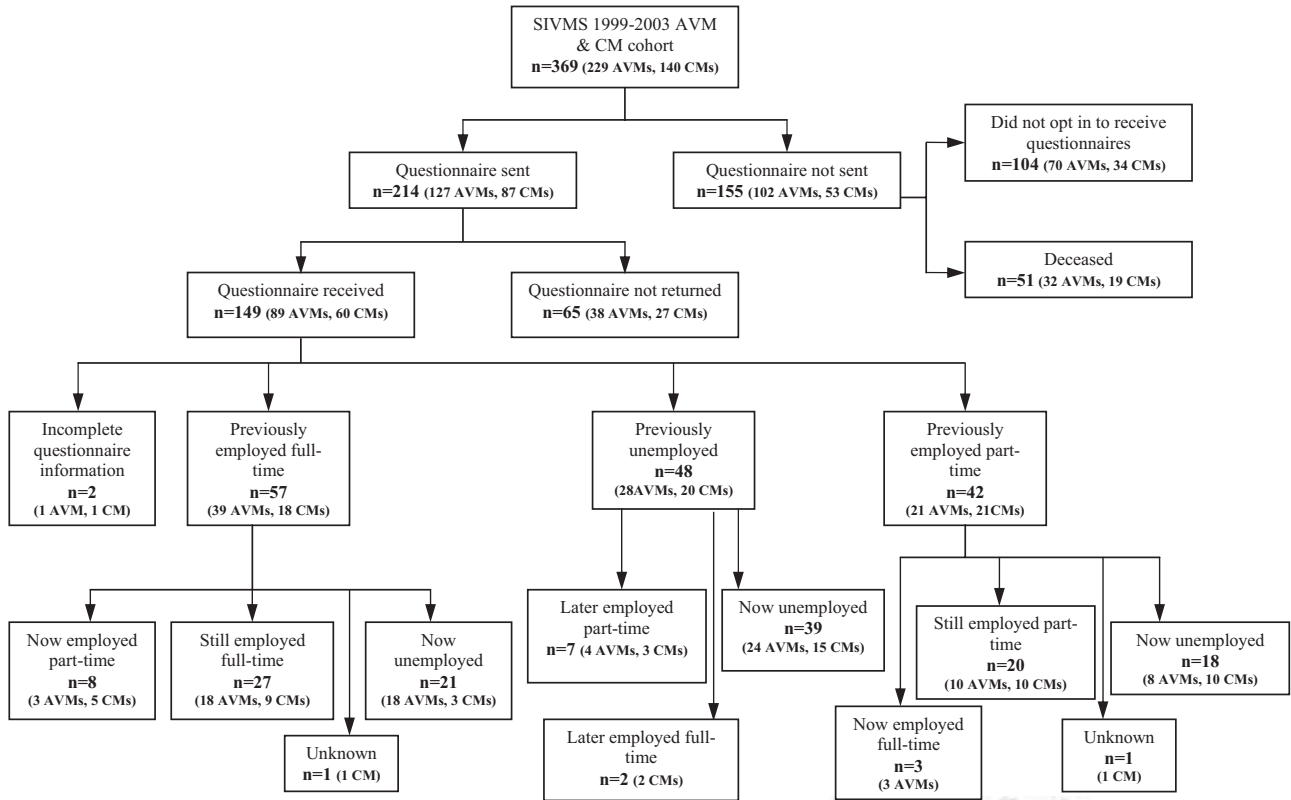


Figure. Employment status of the participants responding to postal questionnaires.

timated costs of lost productivity attributable to IVMs were higher than healthcare costs.

Higher healthcare costs among adults aged <65 years may be explicable by the lower 3-year case fatality in this group (7%, versus 39% among adults aged ≥65 years), fewer younger adults presenting with incidental IVMs (26% versus 55%), and a higher tendency to intervene in younger adults (53% versus 5%). Healthcare costs incurred by adults with AVMs were consistently higher than those incurred by CMs, reflecting the severity of the clinical manifestations of the diseases, and their associated interventional treatment costs—especially for adults presenting with intracranial hemorrhage.¹⁸ Adults receiving interventional treatment inevitably incurred higher direct costs, and the influence of AVM nidus size was likely to be a reflection of the feasibility of treatment (in our dataset, 76% of those with a nidus <30 mm were treated, compared with 57% of those 30 to 59 mm and 14% of those ≥60 mm).¹⁹

The burden associated with lost productivity was even greater than the healthcare costs (especially for those who died prematurely), reflecting the disabling (and sometimes fatal) nature of IVMs predominantly among adults of working age—these costs are likely to be even greater if considered over adults’ lifetimes (especially in view of the risk of recurrent hemorrhage from IVMs). Just as the healthcare costs of CMs were much lower than AVMs, the costs of lost productivity seemed to be lower, too (Table 3, *P*=0.1), but the lack of statistical significance may be a false-negative result attributable to the small sample size and the nonparametric statistics used.

The strength of our data on healthcare costs was that all inpatient stays were captured. Selection bias was minimized by recruiting adults via multiple overlapping sources in a population-based design,¹² and chance was minimized by conducting this study at a time when a reasonable number of adults had been identified. Potential limitations relate to the amalgamation of average neurosurgical costs into the national estimates of inpatient costs (without being able to account for duration of procedure or subsequent high dependency care), and the use of “average” costs of interventions (which vary widely in practice, especially with endovascular techniques). We were unable to account for primary care or prescribing costs because these data were unavailable to us. While this study benefited from obtaining a 70% response rate to a questionnaire about productivity losses attributable to changes in working patterns, the respondents only represented 40% of the entire population cohort. We made various assumptions about the working patterns of the entire cohort by extrapolating data from questionnaire responders, but the lack of any obvious response bias is also reassuring in this respect. We did not quantify other indirect costs—such as the cost of social security benefits, informal care, and loss of caregiver employment—but these are more difficult to measure and could be captured in future studies.

This is the first cost-of-illness study for IVMs on an unselected population-based cohort, and other comparable studies have focused on spontaneous (nontraumatic/“primary”) intracerebral hemorrhage and quantified costs over different time periods to this study, so only a cautious comparison seems appropriate. The economic burden of

spontaneous intracerebral hemorrhage has been quantified in Scotland and found a mean per-patient healthcare cost of £18 629 over 11 years (2005).²⁰ Other European studies of intracerebral hemorrhage have also found lower average per-person healthcare costs than we did for IVM-related hemorrhage: 1-year costs were 11 515 Dutch Guilders (≈£3598) in The Netherlands (1991),²¹ €13 518 (≈£9323) in Germany (1999),²² and 123 200 Danish Krone (≈£10 292) in Denmark (including social services; 1995).²³ Three-year costs in Spain were €10 522 (≈£7207), and 1-year per-person indirect costs were €8158 (≈£5626) including informal care (2004).²⁴ First-year and lifetime costs per intracerebral hemorrhage have been estimated in Australia as Aus\$21 378 (≈£8517) and Aus\$73 542 (≈£29 300; 1997).²⁵ One American study estimated healthcare costs per hospital admission for intracerebral hemorrhage at \$21 535 (≈£13 804; 1992)²⁶; another quoted lifetime healthcare and costs of lost productivity per person of \$123 565 (≈£79,117; 1990).²⁷ Interestingly, several of these estimates are considerably less than the median healthcare cost of £24 815 over 3 years for adults with AVMs presenting with ICH in this study, presumably because some of the other studies omitted imaging and outpatient costs, and mostly included elderly adults who had a high early-case fatality (and thereby incurred a lower economic burden than younger adults^{21–23}).

It will be important to establish both direct healthcare costs and indirect costs (lost productivity, informal care, and loss of caregiver employment) over adults' lifetimes, in particular to investigate whether the costs of intervention are offset by a minimization of indirect costs. In the future, the priority is to establish the clinical and cost-effectiveness of interventions for AVMs and CMs nested within this and other population-based studies,²⁸ and especially in randomized controlled trials like ARUBA (www.arubastudy.org).

Appendix

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Disclosures

None.

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