Trends in the incidence of newly diagnosed cerebral cavernous malformations in Finland: a population-based retrospective cohort study

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Summary

Background The few previous studies that have estimated the incidence of cerebral cavernous malformations (cavernomas) have reported incidence rates of 0.2–1.9/100,000 for diagnosed cavernomas. Our aim was to describe incidence trends of cavernomas by clinical presentation.

Methods We conducted a retrospective cohort study of cavernomas diagnosed at two university hospitals in Finland (Kuopio University Hospital, KUH and Tampere University Hospital, TAUH). Cavernoma diagnoses during 2004–2020 were identified from the KUH and TAUH Care registry databases and verified from medical records and diagnostic imaging studies. We calculated the age-standardized incidence rates using the European standard population and analysed incidence trend and changes in trend by sex, age group, and calendar year using Poisson regression.

Findings A total of 669 cavernoma diagnoses were identified during 2004–2020 in the combined KUH and TAUH population. The age-standardized incidence rate was 2.01/100,000 (95% confidence interval (CI) 1.85–2.16) for all cavernoma diagnoses, 1.25/100,000 (1.13–1.37) for asymptomatic, 0.75/100,000 (0.66–0.85) for symptomatic, and 0.46/100,000 (0.39–0.53) for ruptured cavernomas. No significant difference in the incidence of cavernoma diagnoses was seen between the KUH and TAUH populations or between the sexes. Incidence of cavernomas was highest at ages 40–59 years and low in those under 20 or over 80 years of age. Incidence of diagnosed cavernomas, especially asymptomatic, increased during the study period.

Interpretation In our population-based study, incidence of cavernomas was higher than previously reported and increased during the study period. The burden imposed by cavernomas on healthcare system is considerable and increasing.

Keywords: Cerebral; Cavernoma; Cavernous malformation; Incidence; Symptoms

Introduction

Cerebral cavernous malformations (cavernomas) are a cluster of unmatured dilated vascular structures that arise from the capillaries of the brain and may rupture causing intracerebral haemorrhage.[1] Despite the risk of intracerebral haemorrhage, cavernomas typically show a favourable clinical course and remain mostly asymptomatic. Nevertheless, due to the risk of intracerebral

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Research in context

Evidence before this study

We performed a systematic review of the literature to determine the incidence of diagnosed asymptomatic and symptomatic cerebral cavernous malformations (cavernomas). For the systematic literature search, PubMed database was queried with the following search terms ("cerebral cavernous malformation*" [tw] or "cavernoma*" [tw] or "cavernous angioma*" [tw] or "cavernous hemangioma*" [tw] or "cavernous haemangioma*" [tw] or "Hemangioma, Cavernous, Central Nervous System" [Mesh] or "Hemangioma, Cavernous" [Mesh]) and ("Incidence" [Mesh] or "Epidemiology" [Mesh] or "Prevalence" [Mesh] or incidence*[tw] or epidemiolog*[tw] or prevalence*[tw] or "detection rate*" [tw]) in order to find original research articles. This literature search was updated multiple times during data-analysis and writing of the manuscript, with the last search being made on 20th of April 2024. In addition, we also searched the references of these articles to get a better view of the previous studies concerning incidence or prevalence of cavernomas. With this method, we were able to find only three previous studies concerning the incidence of cavernomas with incidence rates ranging from 0.2 to 1.9 per 100,000 person-years.

Added value of this study

We found a multiple time larger cavernoma incidence than in prior studies, and report that especially the incidence of diagnosed asymptomatic cavernomas has very significantly increased during the last two decades. In addition, we report the trends over time of the age-standardized incidence rate of diagnosed asymptomatic and symptomatic cavernomas stratified according to sex. Our data demonstrates a clear increase in the incidence of diagnosed asymptomatic cavernomas during the first two decades of the 21st century, while the incidence of diagnosed symptomatic cavernomas has remained relatively stable over time.

Implications of all the available evidence

Our findings show that diagnosed cavernomas are more frequent than previously thought, and that in countries with a European type of medical care, cavernomas that likely have a benign clinical course are diagnosed increasingly often. Moreover, our results imply that the average haemorrhage risk of a cavernoma may be higher around middle-age, suggesting that the untreated clinical course of the disease may change age-dependently.

haemorrhage, all diagnosed cavernomas require an expert consultation to determine the possible need for intervention or follow-up, as well as counselling on the possible impact of the diagnosis for the patient.

Since the incidence of cavernoma-related intracerebral haemorrhage is not well established and few studies have estimated the prevalence and incidence of cavernomas, the burden of disease from cavernoma haemorrhage, as well as any incidence-based estimates of overall cavernoma rupture rate remain insufficiently characterized. The few prior studies based on small study populations and short study periods have reported incidence rates of cavernoma diagnoses ranging 0.2–1.9 per 100,000 person-years.[2–4]

Cavernomas are not visualised in cerebral angiography and require magnetic resonance imaging (MRI) for the diagnosis.[1,5] Since the availability of MRI scans has increased over time and the threshold for imaging has lowered, it is to be expected that the incidence of diagnosed cavernomas has increased. As a result, an increasing number of patients with incidentally diagnosed cavernomas will require specialist medical consultation. At the same time, an increasing number of neurological patients are likely to undergo an MRI, likely increasing the number of diagnosed symptomatic cavernomas, as well as the number of incidental cavernomas diagnosed in patients with concomitant but unrelated symptoms.

Our aim was to investigate the incidence rate of cavernomas, the frequency of presentation with haemorrhage or symptoms, and possible changes in the incidence rate of symptomatic and asymptomatic cavernomas over time. We believe that these results will inform about the burden of disease caused by cavernomas and the clinical course of cavernomas. They also have implications for resource needs due to management of cavernomas.

Methods
Study design and participants

This study was a retrospective cohort study of cavernomas diagnosed at two of the five university hospitals in Finland, Kuopio University Hospital (KUH) and Tampere University Hospital (TAUH). KUH is the only neurosurgical referral centre for the population of the Eastern Finland, while the catchment area of TAUH covers the Central Finland and a part of the Western coast (Fig. S1 in the Data supplement). Overall, the catchment population for the two tertiary referral centres encompasses approximately 40% of the national population. Data on sizes of the catchment populations of KUH and TAUH by age, sex and calendar year were obtained from Statistics Finland (KUH roughly 800,000 and TAUH 900,000–1,200,000 the change in size of TAUH catchment population being related to government defined changes in the catchment area geography, Fig. S1 in the Data supplement).[6] This study was approved by the Ethical Review Board of the Hospital

District of Northern Savo (TKU 53/2014) and received a formal research permit from both KUH and TAUH.

Formation of study cohorts

In the Finnish healthcare system, a diagnosis code must be recorded to the Care registry database (HILMO) of the treating institution for all referrals, medical consultations, or patient visits, both in the in-patient and outpatient setting, regardless of whether the lesion treated is an incidental finding or symptomatic. We performed systematic queries of the KUH and TAUH Care registry databases for diagnoses related to intracranial vascular malformations or cavernous malformations (ICD-10 codes: Q28.0–28.3 and D18). Since cavernomas do not have a specific ICD-10 code, these ICD-10 codes were selected based on a survey of which ICD-10 codes the neurosurgeons treating cavernomas in both institutions reported to have used at either hospital during the study period. Given that the initial queries using ICD-10 codes not specific for cavernomas led to a high number of false positives, the medical records and diagnostic imaging studies of all the patients identified in the initial Care registry query were reviewed to confirm the cavernoma diagnosis. For each patient, the confirmed cavernoma diagnosis was based on a typical radiological presentation on MRI scans as reviewed by a neuroradiologist and a neurosurgeon. In addition, we rereviewed the MRI scans of all those patients for whom the scans were available (77%) in order to confirm the radiological diagnosis of a cavernoma according to the Zabramski classification. If the cavernoma was surgically removed, the surgical sample was further analysed by a neuropathologist. The study period at KUH and TAUH was from the first of January 1994 to the 31st of December 2020. Since the frequencies of cavernomas were very low especially at TAUH before 2004 suggesting low completeness, we limited the study period for incidence rate analysis to the years 2004–2020. All the data in the study were complete i.e. there were no missing data points.

Statistical analysis

We calculated the age-standardized incidence rates (ASRs) with 95% confidence intervals (CIs) for cavernomas in the KUH and TAUH populations separately, as well as for the combined population using the European standard population and the direct standardization method.[7,8] The results were stratified by twenty-year age groups and five-year calendar periods (except the last calendar period that was 2019–2020), and according to the clinical presentation (asymptomatic, symptomatic, and ruptured cavernomas). Asymptomatic cavernomas were incidental findings in MRIs. For these patients, the MRI was done for various reasons and the cavernomas was an innocent finding. Cavernomas that presented either with neurological deficits or epilepsy associated with the cavernoma location or rupture, were considered as symptomatic. Cavernomas with headache in the

context of subacute or acute haemorrhage were also considered symptomatic. However, in patients diagnosed with migraine or types of chronic headache disease, the concomitant cavernoma was considered an incidental finding since these types of headaches have not been linked to cavernomas.[9] Ruptured cavernomas had MRI findings showing signs of acute or subacute bleeding. All ruptured cavernomas were symptomatic and thus included in the subcohort of symptomatic cavernomas. We used the z test to evaluate if there was a statistically significant difference in the incidence of cavernomas between the sexes. ASRs of cavernoma diagnoses were calculated using Microsoft Excel version 16.0 (Microsoft, Redmond, WA, USA).

To evaluate temporal trends in cavernoma incidence, we calculated average annual percent changes (APCs) in age-adjusted incidence for all cavernomas as well as for asymptomatic, symptomatic, and ruptured cavernomas in both KUH and TAUH catchment area populations separately and combined. Age-adjusted APCs were calculated using Poisson regression, with number of cases as the outcome and annual population size as the offset term.

We analysed differences in incidence trends between subgroups defined by sex or age group by adding an interaction term (the product of year and sex as well as year and age group) to the Poisson regression model with the main effects only and used the likelihood ratio test to compare the goodness of fit of the two nested models. In addition, we examined possible departure from linearity in the incidence trend by adding calendar year of diagnosis as a categorical variable to the Poisson regression model containing a linear term for year and compared the two nested models with a likelihood ratio test. The Poisson regression analyses were performed using Stata version 17.0 (StataCorp, College Station, TX).

Role of the funding source

The funding source had no role in study design, in the collection, in the data analysis and interpretation of data, nor in the writing of the report or in the decision to submit the paper for publication.

Results

Overall, 669 cavernoma cases were identified in 2004–2020. Of them, 284 patients with one or more cavernomas of the brain were diagnosed during the study period at KUH in Eastern Finland, and 385 patients at TAUH in Central Finland. The annual number of diagnosed cavernomas increased over time (Table 1).

Incidence of cavernomas in the combined population

The overall age-standardized incidence of diagnosed cavernoma patients in 2004–2020 was 2.01/100,000 (95% CI 1.85–2.16) in the combined population. No

	KUH population				TAUH population				KUH and TAUH populations combined			
	Frequency		Standardized incidence rate		Frequency		Standardized incidence rate		Frequency		Standardized incidence rate	
	n	%	Rate	95% CI	n	%	Rate	95% CI	n	%	Rate	95% CI
Total	284	100.0	2.06	1.82–2.30	385	100.0	1.98	1.78–2.17	669	100.0	2.01	1.85–2.16
Sex												
Female	148	52.1	2.15	1.80–2.50	214	55.6	2.17	1.88–2.46	362	54.1	2.16	1.94–2.39
Male	136	47.9	1.96	1.63–2.29	171	44.4	1.80	1.53–2.07	307	45.9	1.86	1.65–2.07
Age group												
0–19	26	9.2	0.88	0.54–1.22	32	8.3	0.74	0.48–0.99	58	8.7	0.80	0.59–1.00
20–39	68	23.9	2.16	1.64–2.67	80	20.8	1.71	1.33–2.08	148	22.1	1.89	1.58–2.19
40–59	111	39.1	2.95	2.40–3.49	141	36.6	2.69	2.25–3.14	252	37.7	2.80	2.45–3.15
60–79	78	27.5	2.44	1.90–2.98	119	30.9	2.83	2.32–3.34	197	29.4	2.66	2.29–3.03
80+	1	0.4	0.13	0.00–0.38	13	3.4	1.24	0.57–1.92	14	2.1	0.76	0.36–1.17
Year period												
2004–2008	77	27.1	1.87	1.45–2.29	69	17.9	1.12	0.86–1.39	146	21.8	1.42	1.19–1.66
2009–2013	87	30.6	2.13	1.68–2.58	126	32.7	2.05	1.69–2.40	213	31.8	2.08	1.80–2.36
2014–2018	93	32.7	2.33	1.86–2.81	147	38.2	2.73	2.29–3.18	240	35.9	2.55	2.23–2.88
2019–2020	27	9.5	1.69	1.04–2.33	43	11.2	2.38	1.66–3.09	70	10.5	2.05	1.57–2.54

Table 1: Frequencies and age-standardized incidence rates (1/100,000) of cerebral cavernous malformation diagnoses in Kuopio University Hospital (KUH) and Tampere University Hospital (TAUH) populations 2004–2020.

significant difference in the incidence was found between the KUH and TAUH population, i.e. between Eastern and Western Finland. There was no significant difference by sex in the age pattern of cavernoma diagnosis (Table 2, likelihood ratio test p = 0.44). No clearly significant difference was observed between the sexes either, though p-value reached borderline significance (z test z = 1.93, p = 0.05): age-standardized incidence was 1.86/100,000 (95% CI 1.65–2.07) for men and 2.16/100,000 (95% CI 1.94–2.39) for women, so confidence intervals were largely overlapping. Age, however, was clearly associated with cavernoma diagnosis, with the highest incidence at 40–59 years of age and the lowest incidence before the age of 20 years or after 80 years (Table 1).

Incidence of asymptomatic, symptomatic, and ruptured cavernomas in the combined population
Most diagnosed cavernomas were asymptomatic: in the combined population in 2004–2020, age-standardized incidence rate was 1.25/100,000 (95% CI 1.13–1.37) for asymptomatic cavernomas, 0.75/100,000 (95% CI 0.66–0.85) for symptomatic cavernomas and 0.46/100,000 (95% CI 0.39–0.53) for ruptured cavernomas. All types of cavernomas were rare below the age of 20 and over 80 years. Incidence rates of symptomatic, asymptomatic, and ruptured cavernomas were similar in men and women (Table 2).

Trends in the incidence of cavernomas in the combined population
Incidence rates of diagnosed cavernomas increased during 2004–2020 in the TAUH population and in the combined population but showed no clear trend in the KUH population (Table 3, Fig. 1). However, the incidence of cavernomas increased significantly at KUH during 1994–2003 (Table S1), with APC of +13.4% (95% CI +5.0, +22.5) during that period. In the combined population, incidence of asymptomatic cavernomas tended to increase faster (APC +5.7%, 95% CI +3.6, +7.8) than incidence of symptomatic cavernomas (APC +2.8%, 95% CI +0.2, +5.5) during 2004–2020, though the 95% CIs overlapped (Table 3, Fig. 2). Incidence of ruptured cavernomas also increased (APC +4.7%, 95% CI +1.3, +8.2) during the study period in the combined population (Table 3, Fig. 2). Incidence trends of cavernoma diagnoses did not differ significantly between the age groups (Table 3, likelihood ratio test p = 0.65) or between the sexes (Table 3, p = 0.95). However, a deviation from linear trend over time, i.e. change in the incidence trend of cavernoma diagnoses was seen during the study period (Fig. 1, p = 0.02). This appeared to occur in the first years of the study period (Figs. 1, 2004–2005). After exclusion of the first two years, no significant departure from linearity was observed any more (Fig. 1, p = 0.09).

Discussion
To our knowledge, our study has a larger population than all previous studies on the incidence of cavernomas combined (in terms of number of cavernomas cases) and is the first cohort study to describe incidence trends of cavernomas after 2004. In a systematic literature search performed in preparation of this study, we were able to find only three previous studies estimating the incidence of cavernomas. These studies reported annual

	Clinical presentation at diagnosis							
	Total		Asymptomatic		Symptomatic		Ruptured	
	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI
Total	2.01	1.85–2.16	1.25	1.13–1.37	0.75	0.66–0.85	0.46	0.39–0.53
Year period								
2004–2008	1.42	1.19–1.66	0.82	0.65–1.00	0.60	0.45–0.75	0.37	0.25–0.49
2009–2013	2.08	1.80–2.36	1.26	1.05–1.48	0.81	0.64–0.99	0.41	0.29–0.53
2014–2018	2.55	2.23–2.88	1.69	1.43–1.96	0.86	0.67–1.05	0.57	0.42–0.73
2019–2020	2.05	1.57–2.54	1.28	0.90–1.66	0.77	0.47–1.07	0.60	0.33–0.87
Age group (both sexes)								
0–19	0.80	0.59–1.00	0.32	0.19–0.44	0.48	0.32–0.64	0.29	0.16–0.41
20–39	1.89	1.58–2.19	1.08	0.85–1.31	0.80	0.60–1.00	0.48	0.33–0.64
40–59	2.80	2.45–3.15	1.76	1.48–2.03	1.04	0.83–1.26	0.62	0.46–0.79
60–79	2.66	2.29–3.03	1.90	1.59–2.22	0.76	0.56–0.95	0.49	0.33–0.65
80+	0.76	0.36–1.17	0.71	0.32–1.10	0.05	0.00–0.16	0.05	0.00–0.16
Sex (according to age group)								
Female	2.16	1.94–2.39	1.34	1.17–1.52	0.82	0.68–0.96	0.52	0.41–0.63
0–19	0.90	0.59–1.21	0.31	0.13–0.49	0.59	0.34–0.84	0.42	0.21–0.63
20–39	2.17	1.70–2.64	1.35	0.98–1.72	0.82	0.53–1.11	0.56	0.32–0.79
40–59	2.91	2.41–3.41	1.87	1.47–2.27	1.04	0.74–1.34	0.56	0.34–0.78
60–79	2.86	2.33–3.39	1.92	1.48–2.35	0.95	0.64–1.25	0.64	0.39–0.89
80+	0.57	0.15–0.99	0.49	0.10–0.88	0.08	0.00–0.24	0.08	0.00–0.24
Male	1.86	1.65–2.07	1.18	1.01–1.35	0.68	0.56–0.81	0.39	0.30–0.49
0–19	0.70	0.43–0.97	0.32	0.14–0.50	0.38	0.18–0.57	0.16	0.03–0.29
20–39	1.62	1.23–2.02	0.84	0.56–1.12	0.79	0.51–1.06	0.42	0.22–0.62
40–59	2.69	2.22–3.17	1.64	1.27–2.01	1.05	0.75–1.35	0.68	0.44–0.92
60–79	2.43	1.92–2.95	1.89	1.43–2.35	0.54	0.30–0.79	0.32	0.13–0.50
80+	1.16	0.30–2.03	1.16	0.30–2.03	0.00	0.00–0.50	0.00	0.00–0.50

Table 2: Age-standardized incidence rates (1/100,000) and 95% confidence intervals (CI) of cerebral cavernous malformation diagnoses in the combined Kuopio University Hospital and Tampere University Hospital population 2004–2020 stratified according to the clinical presentation at diagnosis.

incidence estimates ranging from 0.2 to 1.9 per 100,000 inhabitants.[2–4] The study of Brown Jr et al. in Olmsted County, Minnesota included only five patients with cavernomas and reported an age- and sex-adjusted incidence rate of 0.17/100,000 in 1965–1992 but 0.50/100,000 in 1985–1992, i.e. in the period of increased access to MRI.[4] The Scottish Intracranial Vascular Malformation Study (SIVMS) included 46 cavernoma cases and reported a crude incidence rate of 0.56/100,000 in 1999–2000,[3] which is close to that reported by Brown Jr et al., in 1985–1992. In these studies, the reported incidence of cavernomas was lower than in our study, which is perhaps partly explained by differences in study periods, with improvements in MRI technology and increased availability over time. On the other hand, the largest and the most recent study of El-Koussy et al. had 347 patients with cavernomas (including 10 spinal canal and 5 orbital cavernomas) and reported a total incidence of 1.31/100,000 for symptomatic cavernomas and 0.55/100,000 for asymptomatic cavernomas during 1985–2004.[2] El Koussy et al. reported a total incidence of cavernomas close to our study, though most cavernomas

were symptomatic in that study but asymptomatic in our material. Our study implies that the incidence of cavernomas could be significantly higher than previously thought also in other populations than the Finnish, which merits further studies.

In addition, we found 16 studies estimating the prevalence of cavernomas, with highly variable prevalence estimates ranging from 0.1% to 2.3%.[10–25] Only two of these studies included >100 patients with cavernomas. In thirteen of these studies, the estimated prevalence was in the range of 0.4–1.0%.[10–14,16–18,20–24] The lowest prevalence estimates were reported in two studies estimating incidental findings in brain MRI with low number of included patients with cavernomas; Yue et al. reported a prevalence of 0.14% including five patients with cavernomas, whereas Katzmann et al. reported a prevalence of 0.20% with only two patients with cavernomas.[15,25] A large Chinese study of Meng et al. included 3856 patients with cavernomas and reported a prevalence of 2.33%, which is significantly higher than in other studies.[19] The wide range in these prevalence estimates can be explained by differences in study periods, study populations, or research settings. It is

	Clinical presentation at diagnosis							
	Total		Asymptomatic		Symptomatic		Ruptured	
	APC	95% CI	APC	95% CI	APC	95% CI	APC	95% CI
KUH population								
Total	+1.1	−1.3, +3.5	+0.8	−2.2, +4.0	+1.5	−2.2, +5.5	+4.3	−0.9, +9.9
Age group								
0–19	+1.8	−5.9, +10.1	+9.5	−7.7, +29.9	−0.3	−8.9, +9.0	+6.5	−7.0, +22.1
20–39	−0.2	−5.0, +4.7	−1.9	−7.6, +4.2	+3.0	−5.3, +12.1	+7.7	−4.6, +21.4
40–59	+2.0	−1.8, +6.0	+2.0	−2.8, +7.1	+2.0	−4.0, +8.4	+2.9	−5.0, +11.5
60–79	+0.6	−3.9, +5.3	+0.4	−5.1, +6.2	+0.9	−6.8, +9.2	+3.1	−7.0, +14.2
80+	+19.2	−28.6, +99.0	+19.2	−28.6, +99.0	[a]		[a]	
Sex								
Female	+1.1	−2.2, +4.5	+1.3	−2.7, +5.5	+0.5	−5.1, +6.4	+2.4	−5.1, +10.5
Male	+1.2	−2.3, +4.7	+0.1	−4.5, +4.9	+2.4	−2.7, +7.7	+6.1	−1.1, +13.8
TAUH population								
Total	+7.4	+5.1, +9.7	+9.5	+6.6, +12.5	+3.7	+0.2, +7.5	+5.1	+0.6, +9.7
Age group								
0–19	+8.3	+0.6, +16.6	+9.1	−1.4, +20.8	+7.4	−3.5, +19.6	+3.5	−8.1, +16.5
20–39	+4.6	−0.1, +9.5	+4.3	−2.2, +11.3	+4.8	−1.8, +11.8	+8.9	+0.3, +18.3
40–59	+7.5	+3.9, +11.3	+9.2	+4.6, +14.1	+4.7	−1.2, +10.8	+8.4	+0.6, +16.8
60–79	+8.7	+4.5, +13.1	+12.4	+7.1, +17.8	−0.5	−7.8, +7.3	−3.1	−11.7, +6.4
80+	+10.2	−2.3, +24.4	+12.1	−1.4, +27.5	−8.6	−40.9, +41.2	−8.6	−40.9, +41.2
Sex								
Female	+7.2	+4.2, +10.3	+10.5	+6.4, +14.8	+2.8	−1.7, +7.4	+4.2	−1.3, +9.9
Male	+7.6	+4.2, +11.1	+8.5	+4.4, +12.8	+5.6	−0.4, +11.9	+6.9	−0.8, +15.1
KUH and TAUH populations combined								
Total	+4.6	+2.9, +6.3	+5.7	+3.6, +7.8	+2.8	+0.2, +5.5	+4.7	+1.3, +8.2
Age group								
0–19	+5.3	−0.2, +11.1	+8.9	−0.2, +18.8	+3.1	−3.8, +10.4	+4.8	−4.1, +14.6
20–39	+2.4	−1.0, +5.9	+1.2	−3.1, +5.8	+4.0	−1.2, +9.5	+8.3	+1.2, +15.9
40–59	+5.0	+2.4, +7.8	+6.0	+2.6, +9.5	+3.5	−0.8, +7.9	+5.9	+0.3, +11.8
60–79	+5.2	+2.1, +8.3	+7.3	+3.5, +11.2	+0.2	−5.1, +5.8	−0.3	−6.9, +6.7
80+	+9.5	−2.5, +23.0	+11.3	−1.6, +26.0	−9.5	−41.3, +39.4	−9.5	−41.3, +39.4
Sex								
Female	+4.5	+2.3, +6.8	+6.2	+3.4, +9.2	+1.8	−1.7, +5.4	+3.4	−1.0, +8.0
Male	+4.6	+2.2, +7.1	+5.0	+2.0, +8.2	+4.0	+0.1, +8.1	+6.6	+1.3, +12.2

[a]APC cannot be calculated because there are no CCM cases in this group.

Table 3: Average annual percent changes (APCs) and 95% confidence intervals (CI) in age-adjusted incidence rates of cerebral cavernous malformation diagnoses in Kuopio University Hospital (KUH) and Tampere University Hospital (TAUH) populations 2004–2020.

probable that studies in which people are examined with MRI because of neurological symptoms have more selection bias compared to studies of healthy, asymptomatic population.

Incidence of cavernomas diagnosis in men and women and in different age groups
In our study, the incidence of diagnosed cavernomas overall, as well as asymptomatic, symptomatic, and ruptured cavernomas was similar in men and women. This could imply that sex hormones do not play a major role in the pathogenesis of cavernomas.

The largest age group at diagnosis in our study was adults aged 40–59 years. The age distribution in our study is slightly older than in the previous studies.[2,3,12,16,22] Majority of the cavernoma cases were incidental findings, which suggests that typically a cavernoma is found in conjunction with a neurological symptom that leads to MR imaging and incidental discovery of a cavernoma. That most asymptomatic cavernomas are diagnosed in middle aged population, could suggest that most of them develop in adulthood. The incidence of cavernoma diagnosis in children (<15 years) was unstable and the annual number of cases among children was rather small. Typically, children diagnosed with cavernomas displayed neurological symptoms at diagnosis and true incidental cavernomas were rare in children.
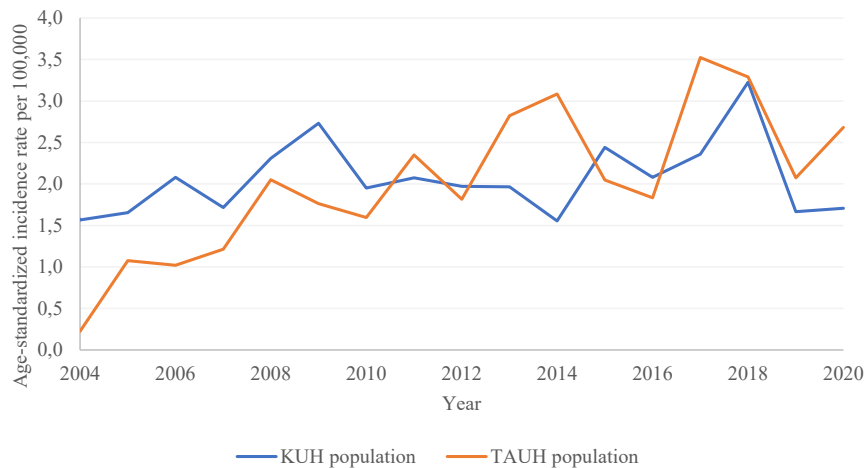
Fig. 1: Age-standardized incidence rates of cerebral cavernous malformation diagnoses in Kuopio University Hospital (KUH) and Tampere University Hospital (TAUH) populations 2004–2020.

Of the cavernoma patients older than 65 years, only 38% (20/52) in the KUH and 20% (18/92) in the TAUH cohort were symptomatic at diagnosis, which highlights the fact that asymptomatic incidental cavernomas are particularly prominent in older patients. The incidence rate of ruptured and symptomatic cavernomas was particularly low after the age of 80 years, 0.05/100,000 for both types. This could imply that risk of cavernoma rupture decreases with age.

Comparison of trends in the incidence of asymptomatic and symptomatic cavernomas

In our study, the majority of the diagnosed cavernomas were asymptomatic at diagnosis, and the incidence rate of the asymptomatic cavernomas increased over two decades, though the temporal pattern was not entirely consistent. The incidence rate of asymptomatic cavernomas was almost twice that of symptomatic cavernomas. Cavernoma diagnosis is likely mainly driven by the frequency of cranial MR imaging, and it seems likely that the not all asymptomatic cavernomas are ever diagnosed. Hence the true number of asymptomatic cavernomas in the population, i.e. the prevalence of asymptomatic cavernomas, is most likely higher than the incidence of asymptomatic cavernomas diagnosed incidentally. Number of head MRI examinations in Finland has increased considerably during the past two decades,[26] which likely explains the increase in the
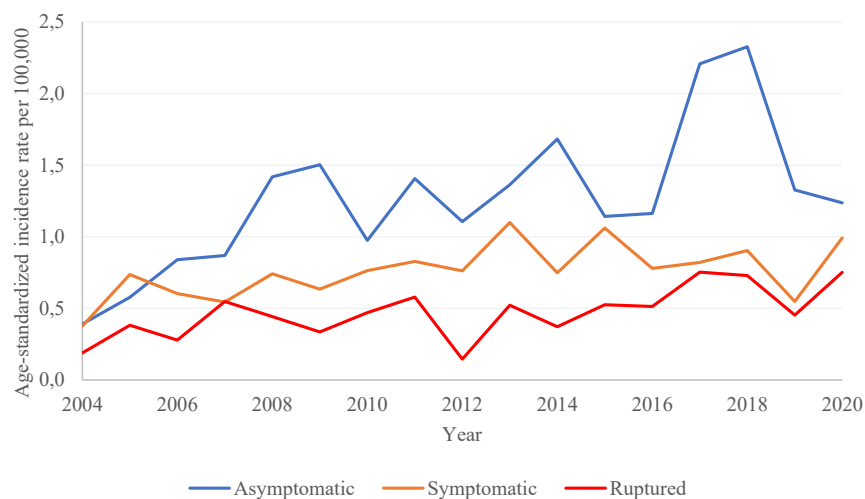

Fig. 2: Age-standardized incidence rates of asymptomatic, symptomatic, and ruptured cerebral cavernous malformation diagnoses in the combined Kuopio University Hospital and Tampere University Hospital population 2004–2020.

incidence of diagnosed asymptomatic cavernomas. The interpretation that increased access to MRI explains the increase in the incidence of cavernomas is supported by our observation that the incidence rates of diagnosed cavernomas increased during different time periods in the two study regions (KUH and TAUH).

The higher than previously thought incidence of asymptomatic cavernomas has an important implication for the estimation of cavernomas rupture risk, since a comparison of the difference between the incidence of asymptomatic and ruptured cavernomas gives a rough estimate of the annual rupture rate of cavernomas. Our observation that the incidence of asymptomatic cavernomas is more than double the incidence of ruptured cavernomas, suggests that a large majority of cavernomas remain unruptured.

Clinical implications

The good prognosis of asymptomatic cavernomas creates a dilemma for their management, since currently the only treatment option is surgical removal. Consequently, it is vital to distinguish, which cavernomas are likely to remain stable.

Our results imply that the patient's sex does not affect the clinical course of cavernoma development, while age does. Asymptomatic cavernomas were most common at ages 40–79 years, while the peak incidence of symptomatic cavernomas, as well as ruptured cavernomas was at ages 40–59 years. This could imply that average haemorrhage risk of cavernomas might be higher near the middle-age years, suggesting that future studies on the untreated clinical course of cavernomas should investigate the possible age-dependent change in the risk of rupture.

Strengths and limitations of the study

By definition, asymptomatic cavernomas are diagnosed as incidental findings, while symptomatic cavernomas can be considered as a form of hemorrhagic stroke since the symptoms are essentially neurological deficits related to major or minor bleeds from the cavernoma. The importance of following and reporting the use of specific methodological criteria for stroke related studies on incidence, has been reviewed and discussed by Sudlow and Warlow in 1996.[27] How this study conforms with the methodological criteria presented by Sudlow and Warlow is summarized in Table S3 of the Data supplement. What should be noted though, is that unlike ischemic stroke or transient ischemic attack, a cavernoma is primarily a radiological diagnosis, whether symptomatic or asymptomatic. Since the cavernoma diagnosis is based on an MRI scan for which the patient needs a referral, and since the physician who made this referral is also responsible for assuring proper management of any finding in the MRI, it is very unlikely that a community-based case ascertainment would differ significantly from a hospital-based one, given that

the prevailing golden standard of practice in Finland during the study period has been to consult a neurosurgical unit for any cavernoma or similar neurovascular anomaly regardless of the context in which it was found.

In general, the valid estimation of incidence requires the following: 1) a well-defined study population, 2) comprehensive, high-quality data sources, and 3) a clear case definition.

Our study population was determined as the catchment area population of the participating university hospitals, namely KUH and TAUH. Finland has a tax-funded, government-maintained, centralized healthcare system, in which specific university hospitals provide service as tertiary referral centres for the population of a specific geographic area. These catchment areas of the university hospitals are defined by the Finnish government and have been followed in referral patterns relatively rigorously until recent years (Data supplement, Fig. S1). Consequently, we could obtain very accurate data of the size, age-distribution, and sex-distribution of our target study population from the Finnish census.

As the primary data source, we used the Care registry of the two participating university hospitals. In the Finnish healthcare system, every patient consultation or visit, be it in an inpatient or outpatient context, leads to an ICD-10 diagnosis code being entered to this registry. Consequently, retrospective data queries of the Finnish Care registry are sensitive for the detection of diagnosed patients, provided that the same ICD-10 diagnosis codes are used for the data query as were used by the treating physicians at the time of data entry. To ensure this, we used in our data query the spectrum ICD-10 diagnosis codes that had been used by the neurosurgeons responsible for cavernoma patients in both institutions. Identification of these ICD-10 codes was easily made through a query thanks to the low number of such colleagues (<12) during the study period. This approach ensures that all cavernoma related entries to the Care registry are caught by the data query, i.e. it is sensitive, but understandably causes a lot of unspecific false positives in the initial query.

For case definition, we used the criteria a radiological presentation typical to a cavernoma on an MRI scan. Given that cavernoma is essentially a radiological diagnosis based on MRI findings, the criteria we used can be considered as the golden standard. Using the MRI based diagnostic criteria, we checked each candidate patient identified in the initial data query and ensured that no false positive cavernoma patients remained in the final study population.

We conclude that our study targeted a well-defined and fairly stable population for which accurate census data was available, and used data sources that can be considered reasonably comprehensive with 100% specificity. Consequently, we consider our incidence results very reliable. Given that there are no false positive

cavernomas in our data thanks to the exhaustive validation check of the original MRI scans or radiologist reports of each patient, the only possible error could be that the true incidence of diagnosed cavernomas would be even higher than detected by our data collection strategy. This would, however, require a major systematic error either in referral or coding practices of either one or both of the university hospitals, leading to underreporting cavernomas in our query of the Care registry databases. This seems very unlikely since the incidence rates in the catchment area of two independent Finnish university hospitals were comparable and significantly higher than most studies have reported previously (Data supplement, Table S2). Moreover, the study group included practicing clinicians in charge of the treatment of cavernoma patients in both participating institutions, and consequently the referral and coding practices in the catchment areas of both participating university hospitals were very familiar to the study group.

In addition to the good quality of our data sources, our study also included more cavernoma diagnoses than most previous studies (Table S2). This leads to significantly more precise incidence estimates. To our knowledge, this is also the first cohort study to describe incidence trends of cavernomas in the past 20 years, i.e. during a period with abundant MR imaging availability. A 17-year study period and classification of cavernomas according to the clinical presentation allowed us to evaluate incidence trends of cavernomas overall and according to clinical presentation, providing valuable information about the disease burden related to them.

Conclusions

The incidence of cavernomas is higher than previously reported and increasing. In our study, incidence of asymptomatic cavernomas was almost twice the incidence of symptomatic cavernomas, and especially the incidence of asymptomatic cavernomas increased considerably during 2004–2020. Symptomatic cavernomas affect mainly population in working ages.

Contributors
Aleksi Halmela: Data analysis, Writing of the manuscript. Emilia Saari: Literature search, Data collection, Writing of the manuscript. Jani Raitanen: Data analysis, Writing of the manuscript. Timo Koivisto: Data collection, Writing of the manuscript. Anssi Auvinen: Study design, Data analysis, Writing of the manuscript. Juhana Frösen: Study design, Data collection, Data analysis, Writing of the manuscript, Supervision of the study. All authors were responsible for the decision to submit the article for publication.

Data sharing statement
Since the data used in this study is subjected to the GDPR regulations of the European Union, it cannot be shared openly. Access to the pseudonymized data can, however, be granted by the administration of KUH or TAUH based on a rational research plan submitted by a qualified researcher.

Declaration of interests
Authors declare no competing interests. Dr. Halmela has received a travel grant from the State funding for university-level health research,

Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.101072.

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