Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

# Size at Which Aneurysms Rupture: A Hospital-Based Retrospective Cohort From 3 Decades

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**BACKGROUND:** The size of the saccular intracranial aneurysm (IA) has been used as the primary indicator for rupture risk. We investigated at which size IAs that rupture did so, and whether this size has significantly changed over time.

**METHODS:** Patients treated for ruptured IAs were identified from the Aneurysm Database of the Tampere University Hospital. The size of the IA at the time of rupture was measured from computed tomographic angiography or digital subtraction angiography made to diagnose the aneurysm. Data for the clinical risk factors for rupture were collected from the patient's medical records.

**RESULTS:** Of the 2545 patients with ruptured intracranial aneurysms (IAs) admitted, the size of the ruptured IA could be determined for 76% (1925 of 2545). Fifty-one percent (984 of 1925) of the studied IAs ruptured at a size <7 mm. Both the mean and the median size of the IA at rupture had a downward trend from 1989 to 1997 (median decrease from 10 mm to 6 mm) but have remained relatively constant since. Forty-six percent (881 of 1925) of the patients with a ruptured IA were not known to have any lifestyle-related aneurysmal subarachnoid hemorrhage risk factor. Of the IAs that ruptured small, 35% were located in the anterior communicating artery and 14% in other small intracranial arteries.

**CONCLUSION:** Small size should not be used to exclude unruptured IAs from prophylactic treatment. The observation that the size at which IAs rupture has previously decreased, suggesting a change in relative importance of risk factors or characteristics of a contemporary patient population compared with older cohorts.

**Key Words:** intracranial aneurysm ■ rupture ■ size ■ subarachnoid hemorrhage ■ temporal trends

Intracranial aneurysms (IAs) may rupture causing aneurysmal subarachnoid hemorrhage (aSAH), a devasting form of intracranial hemorrhage with a high mortality rate.[1] Current treatment options to prevent IA rupture are all invasive procedures, which carry a nonnegligible risk of morbidity and even a small risk of mortality.[2,3] In order to focus these invasive preventive treatments on patients who benefit from them, and whose IAs have a high enough risk of rupture to justify treatment-associated risk, several predictive models have been developed to assess IA rupture risk and the need to treat.[4,5] These predictive models, prospective follow-up studies of unruptured IAs, and American Heart Association and European guidelines all agree that the size and location of the IA are among the most significant determinants of rupture risk.[6–10]

Based on the wealth of data that demonstrate how risk of rupture increases with size, it has been

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suggested that unruptured IAs below a certain threshold size could be, and maybe should be, left untreated unless they grow or show other signs of increased rupture risk.[8–11] Although small IAs may have a low average rupture risk, large consecutive series of aSAH and IA registries, however, clearly show that IAs of all sizes can rupture.[12–14] As a consequence, the existing scientific literature is controversial regarding how small unruptured IAs should be managed. To further complicate the interpretation of existing epidemiological data, a decreasing trend in the size of ruptured IAs has been reported,[15] suggesting that the attributable risk or relative importance of rupture-promoting risk factors may have changed over time, which, in turn, would question the validity of older epidemiological studies in the management of contemporary patient cohorts.

The aim of this study was to investigate at which size IAs that ruptured did so in a previously unpublished consecutive Finnish patient cohort with IAs, whether the threshold size at which IAs rupture has changed over time, and whether there is evidence that the risk factor profile of patients with aSAH has changed over time.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **aSAH** | aneurysmal subarachnoid hemorrhage |
| **IA** | intracranial aneurysm |
| **TAUH** | Tampere University Hospital |

### CLINICAL PERSPECTIVE

- Many of the intracranial aneurysms that benefit from prophylactic treatment are small.
- The relative importance of risk factors for rupture seems to have changed over time.
- Older follow-up studies may not accurately reflect the risk of rupture in contemporary patient populations.

## METHODS

Tampere University Hospital (TAUH) is the only neurosurgical unit providing treatment for ruptured IAs in its catchment area, which is defined by the Finnish government. This makes TAUH the primary referral and consultation center for all patients with aSAH diagnosed at its catchment area. The TAUH Aneurysm Database is a single institution database in which all patients admitted to TAUH for treatment or consultation related to IAs are entered. The database is maintained by a dedicated research nurse of the Department of Neurosurgery at TAUH.

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author at TAUH, Tampere, Finland. Since our study was retrospective and used data collected from medical records and archived imaging studies without contacting the patient directly, the TAUH ethics committee waived the need for informed consent of the participating patients.

Our study cohort was formed by the following steps (presented in a flow chart in the Data supplement):

1. Patients who presented with aSAH were identified from the TAUH Aneurysm Database.
2. Patients with a cause other than a saccular IA for their aSAH (eg, blister aneurysms, traumatic aneurysms, and fusiform aneurysms) were excluded.

To ensure that our study cohort was representative of the overall cohort of patients who experienced an aSAH in the TAUH catchment area and population during our study period we calculated the number of aSAH cases that would have been expected at our catchment area during the study period, based on the published incidence of aSAH in the Finnish population[16] and the size of our catchment population. Population statistics for the TAUH catchment area were obtained from the National Statistics Institution of Finland.

### Measurement of Aneurysm Size

The size of the neck of the ruptured IA, as well as the length and width of the fundus were measured from diagnostic computed tomography angiography or digital substraction angiography as shown in the Data supplement. From the year 1989 to 2003–2004 all images were in analogical form and the aneurysm size measurements were performed using the intracranial carotid artery as a reference, assuming a 5-mm diameter. From year 2004 all images were in digital form and scaled so IA size measurements could be made directly from the digital images (shown in Data supplement).

### Collection of Clinical Variables and Risk Factor Data

The clinical variables, such as age at presentation, sex, diagnosed comorbidities, and history of known risk factors for aSAH or IA formation, are registered to the TAUH Aneurysms Database and were obtained from the database for this study. These clinical

variables were collected retrospectively from the patient's medical records. Risk factor information was registered in patient records during every hospitalization and is based on anamnesis and clinical findings evaluated by the attending physician. History of smoking (current or former), hypertension (treated or untreated), and excess alcohol consumption (prior or current) were coded as binary variables ("yes"/"no") in this study.

### Statistical Analysis

Proportions and percentages were calculated for categorical and ordinal variables and compared with chi-square test between groups. Means, 95% CIs, medians, and ranges were calculated for continuous variables and compared with Mann–Whitney *U* test. Multivariate linear regression was used to investigate the effect of known risk factors for rupture to the size at which aneurysms ruptured over time. The statistics were calculated using SPSS version 21.0 statistical software (IBM).

## RESULTS

### Characteristics of the Study Cohort

During our study period, 2545 patients with ruptured IA were admitted to TAUH. Our study cohort represents 85% of the estimated number of aSAH cases in the catchment area of TAUH (Data supplement, Figure S1), as calculated according to the age distribution of the population in our catchment area and the previously reported incidence of aSAH in the Finnish population.[16]

Of these 2545 patients admitted, the size of the ruptured IA could be determined for 76% (1925 of 2545). Of these patients, 59% (1138 of 1922) were women, and the median age at rupture was 55 years. Patient demographics, risk factor profile, and location of the studied aneurysms are shown in Table 1.

**Table 1. Characteristics of the Consecutive Series of Patients With aSAH Treated at TAUH**

| Clinical variable | Size of the ruptured aneurysm at rupture | | *P* value |
|---|---|---|---|
| | <7 mm (n=984) | ≥7 mm (n=941) | |
| Age at rupture, median (range), y | 55 (0–93) | 55 (11–95) | 0.955 |
| Women, % (N) | 64.1 (631) | 54.0 (508) | <0.001 |
| IA family history, % (N) | 8.2 (81) | 6.8 (64) | 0.235 |
| Lifestyle risk factors, % (N) | | | |
| Smoking history | 29.1 (286) | 39.4 (371) | <0.001 |
| Hypertension | 24.7 (243) | 25.8 (243) | 0.569 |
| Excess alcohol use | 8.2 (81) | 10.4 (98) | 0.099 |
| None of the risk factors listed above | 50.8 (500) | 40.5 (381) | <0.001 |
| Location of ruptured aneurysm, % (N) | | | |
| ICA | 11.0 (108) | 12.4 (117) | 0.320 |
| PCom | 8.5 (84) | 8.0 (75) | 0.652 |
| ACom | 35.0 (344) | 22.8 (215) | 0.001 |
| MCA | 23.6 (232) | 40.4 (380) | <0.001 |
| Other location in the anterior circulation (pericallosa, oftalmica) | 8.3 (82) | 4.6 (43) | 0.001 |
| Basilaris | 6.0 (59) | 8.8 (83) | 0.018 |
| Vertebralis | 0.9 (9) | 0.5 (5) | 0.323 |
| Other location in the posterior circulation (PCA, PICA, SCA) | 5.4 (53) | 1.4 (13) | <0.001 |
| Undetermined | 13 | 10 | |

ACom indicates anterior communicating artery; aSAH, aneurysmal subarachnoid hemorrhage; IA, intracranial aneurysm; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; PCom, posterior communicating artery; SCA, superior cerebellar artery; and TAUH, Tampere University Hospital.

### Size at Which Aneurysms Ruptured Over Time

Overall, 51% (984 of 1925) of the studied IAs ruptured at a size <7 mm, and 49% (941 of 1925) ruptured at a size ≥7 mm (Table 1 and Figure 1). Both the mean and the median size of the IA at rupture had a downward trend from 1989 to 1997 (Table 2, Figures 2 and 3), as the median size decreased from 10 mm to 6 mm. Since 1997, there has been no downward trend in median rupture size. In order to investigate the possible effect that a change in the known risk factor for rupture might have in the size at which IAs ruptured over time, we performed multivariate linear regression analysis. In addition to the year of rupture, age and sex of the patient, history of smoking, and location of the aneurysm were significant factors affecting the size at rupture (Data supplement).

### Differences in Known Risk Factors for Aneurysm Rupture Between Small and Large Ruptured Aneurysms

Age at rupture did not differ among patients with a rupture from a small or ≥7 mm IA (Tables 1 and 2). The decreasing trend in the size of the ruptured IAs was similar in patients older or younger than 50 years (Figures 2 and 3). Female sex was associated with rupture at a size <7 mm (Tables 1 and 2), but the decreasing trend in the size of ruptured aneurysms was seen in both sexes (Figures 2 and 3).

Of the acquired aSAH risk factors related to lifestyle, history of smoking (current or past) was found in 34% (657 of 1925) of the patients with ruptured IA, hypertension in 25% (486 of 1925), and excessive alcohol consumption in 9% (179 of 1925) (Table 1). In our study cohort, 46% (881 of 1925) of the patients with

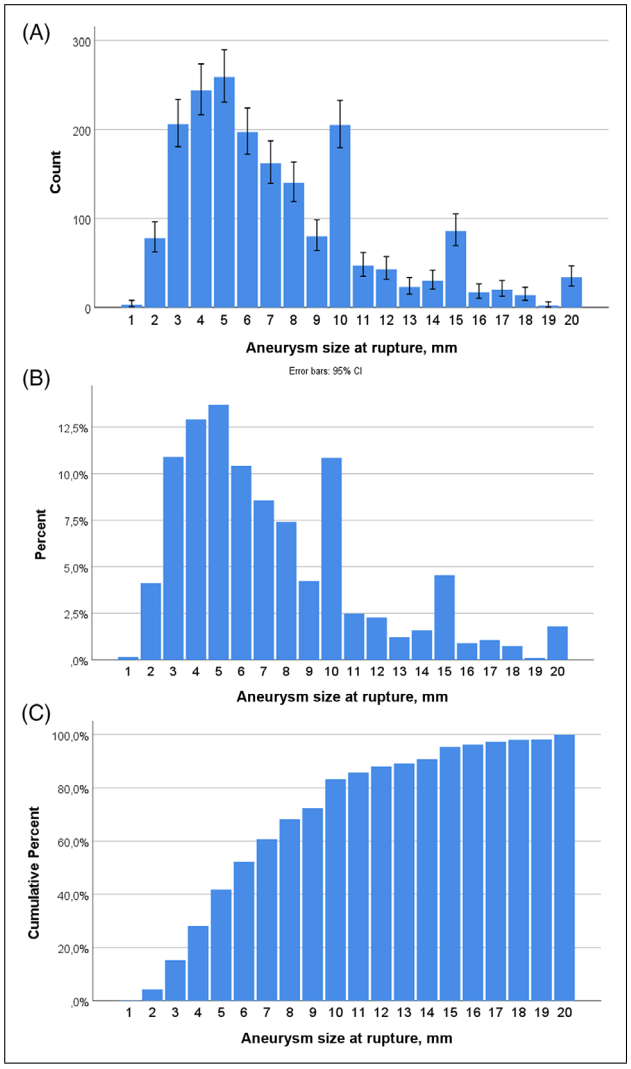


**Figure 1. Size at which intracranial aneurysms (IAs) ruptured.** The number of ruptured IAs of specific size is given in (**A**) (error bars represent 95% CIs), while the same data are presented in (**B**) as a percentage of aneurysms that rupture at a specific size from the total number of ruptured IAs and in (**C**) as the cumulative percentage.

a ruptured IA were not known to have any lifestyle-related aSAH risk factor (Table 1 and Data supplement). Patients with no known smoking history or any other acquired lifestyle-related aSAH risk factor that would explain the IA rupture were more frequent in the group with IAs that ruptured at a size smaller than 7 mm (Table 1).

Location of the aneurysm did differ among the IAs that ruptured at a size smaller or larger than 7 mm (Table 1). Of the IAs that ruptured at a size <7 mm, a larger percentage was located in the anterior communicating artery or other small vessels of the anterior or posterior circulation than of those that ruptured after growing >7 mm (49% versus 29%, respectively). Of the IAs that had grown >7 mm before rupture, 40% were

**Table 2. Mean and Median Size of the Ruptured Aneurysm Stratified According to Patient Demographics and Time Period**

| | Mean, mm | 95% CI | Median, mm | Range, mm |
|---|---|---|---|---|
| All (N=1925) | 7.8 | 7.6–8.0 | 6.0 | 1–55 |
| Women (n=1139) | 7.4 | 7.1–7.7 | 6.0 | 1–44 |
| Men (n=786) | 8.4 | 8.0–8.7 | 7.0 | 1–55 |
| Age, y | | | | |
| ≤50 (n=710) | 7.4 | 7.1–7.7 | 6.0 | 1–30 |
| Women ≤50 (n=349) | 7.0 | 6.6–7.5 | 6.0 | 2–30 |
| Women >50 (n=790) | 7.6 | 7.2–7.9 | 6.0 | 1–44 |
| >50 (n=1215) | 8.0 | 7.7–8.3 | 6.0 | 1–55 |
| Men ≤50 (n=361) | 7.8 | 7.3–8.3 | 7.0 | 1–30 |
| Men >50 (n=425) | 8.9 | 8.3–9.4 | 7.0 | 2–55 |
| 4-y admission groups | | | | |
| 1989–1992 (n=129) | 10.3 | 9.2–11.3 | 10.0 | 2–30 |
| 1993–1996 (n=150) | 8.8 | 7.8–9.7 | 8.0 | 1–30 |
| 1997–2000 (n=197) | 7.3 | 6.6–8.0 | 6.0 | 2–25 |
| 2001–2004 (n=340) | 7.8 | 7.1–8.4 | 6.0 | 2–55 |
| 2005–2008 (n=282) | 7.3 | 6.8–7.8 | 6.0 | 2–24 |
| 2009–2012 (n=338) | 7.6 | 7.2–8.1 | 7.0 | 1–35 |
| 2013–2016 (n=304) | 7.5 | 7.0–7.9 | 7.0 | 1–27 |
| 2017–2020 (n=185) | 7.5 | 6.9–8.2 | 6.0 | 2–37 |

in the middle cerebral artery (Table 1). However, comparison of the relative frequency of ≥7 mm or smaller ruptured IAs at specific anatomical locations over time showed a decreasing trend in percentage of ≥7 mm ruptured IAs in the middle cerebral artery location over time (Data supplement).

## DISCUSSION

We studied the size at which IAs ruptured in a large, single institution database that represents a consecutive series of ruptured IAs with minimal selection bias and covers the majority of aSAH cases in our catchment area (85%). Considering that in the recent nationwide study of aSAH incidence in Finland ≈24% of patients with aSAH had died before reaching the hospital,[16] our study cohort accurately represents those patients with aSAH who made it to a hospital after their bleed during our 30-year study period in the TAUH catchment area. In this patient cohort, half of the IAs that ruptured did so before reaching the size of 7 mm.

### Aneurysm Size as an Indicator for Prophylactic Treatment

It is known that the average annual risk of rupture of a small aneurysm is low, and in many cases lower than the risk associated with prophylactic treatment. In a systematic review conducted by Malhotra et al,[17] the annual rupture rate for aneurysm <7 mm was reported

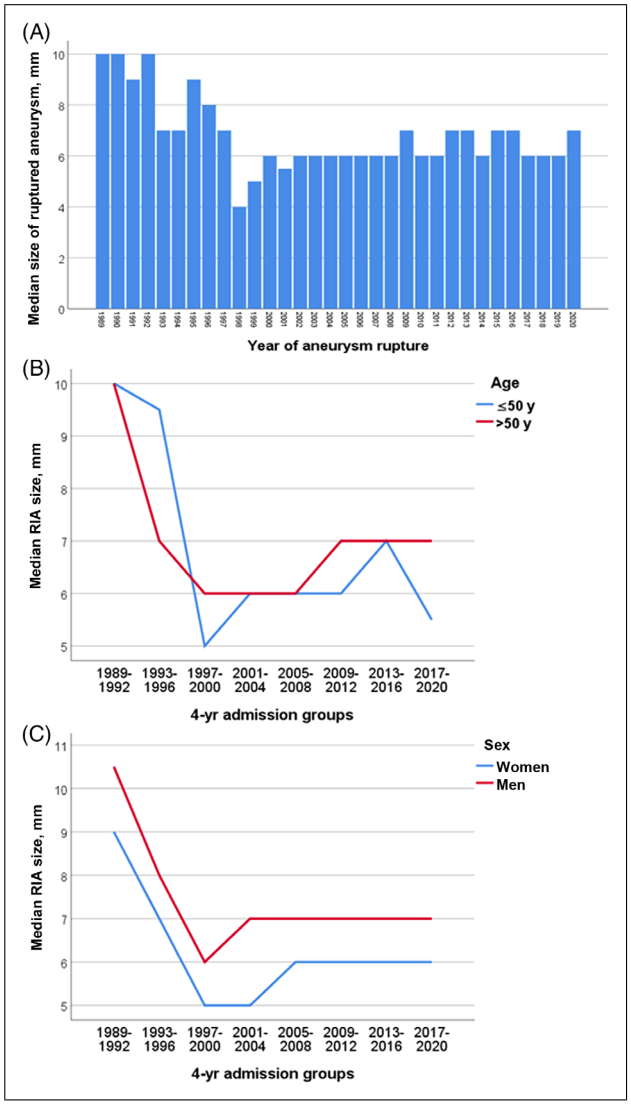


**Figure 2. Change over time in the median size of the aneurysm at rupture.**
The median aneurysm size at rupture over time is shown in (**A**), stratified by age in (**B**) and by sex in (**C**). RIA indicates ruptured intracranial aneurysm.

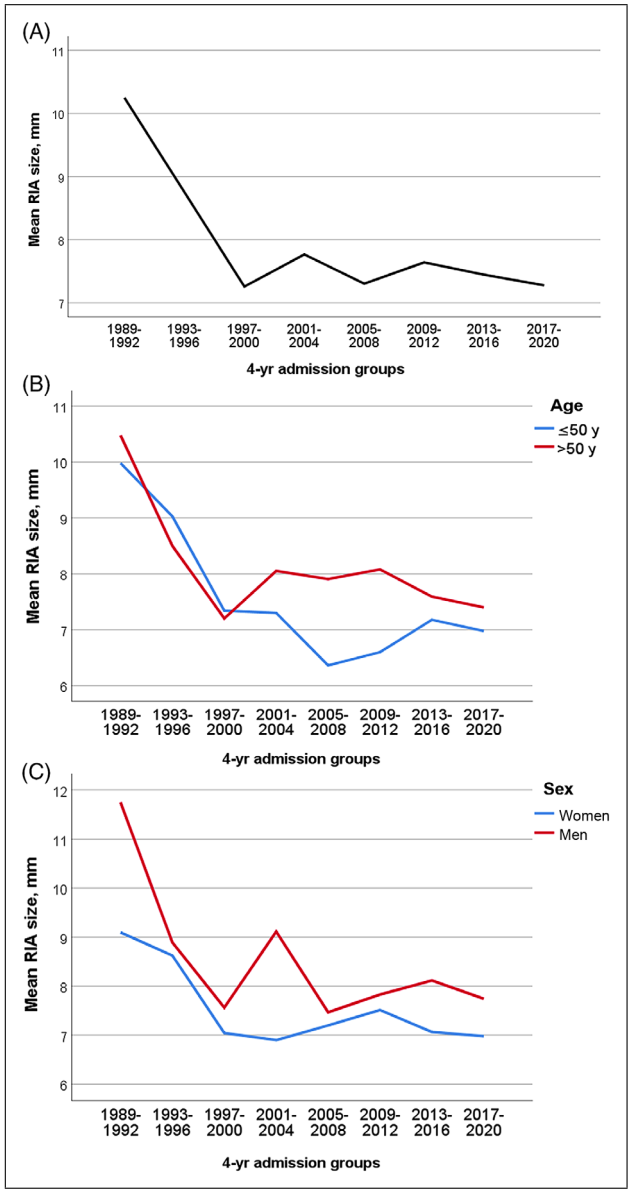


**Figure 3. Change over time in the mean aneurysm size at rupture.**
The mean size of the aneurysm at rupture is shown in (**A**), stratified by age in (**B**), and by sex in (**C**). RIA indicates ruptured intracranial aneurysm.

to be <1% in 12 of 13 studies included in the analysis. Although the annual risk of bleeding has been reported to be low for small aneurysms, our data clearly demonstrate that <7 mm aneurysms should not be excluded from prophylactic treatment based on size alone. This, because at the end it is those IAs which ruptured that should have been treated prophylactically. This may seem somewhat contradictory to the findings by Gondar et al,[11] who showed that a policy of imaging follow-up and prophylactic intervention only when growth occurs, is a safe strategy for small unruptured aneurysms. Although growth during follow-up has been shown to associate with a high risk of rupture,[18,19] our data and the data published by Lindgren et al[14] from another similar large, consecutive Finnish IA database implies that many of the Finnish IAs that rupture do so without preceding significant growth (ie, small size at rupture). This apparent controversy might be explained by different populations, or differences in the prevalence of risk factors in the studied cohorts. Nevertheless, it underlines the importance of not looking just at the IA size but to the whole sum of risk factors when making treatment decisions. What seems to be confirmed in all series is that those aneurysms that do grow during follow-up, as well as those that show signs of past

growth (ie, large size or irregular shape), do have an increased risk of rupture and therefore mandate prophylactic treatment even if relatively small.[19]

## Do Risk Factors for Aneurysm Rupture Change Over Time?

Assessment of the rupture risk of an IA, as well as the patient-specific risk for aSAH, should be based on valid epidemiological data. Epidemiological data change over time when the lifestyle, health behavior, and demographics of populations change. This raises the question of whether older epidemiological studies, or their derivatives, are any more valid in the treatment of contemporary patients, especially in the Finnish population of patients with IA who have a very different risk factor profile now than in the past.[20]

A study conducted in a separate Finnish cohort by Korja et al[15] found that the average size of ruptured IAs has decreased since 1990. Our study found a similar downward trend between 1989 and 1997. After 1997, however, there is no noticeable downward trend in the size of ruptured aneurysms, with the median rupture size remaining at ≈6 mm from 1997 to 2020 (Figure 2A). This decrease in the mean and median size at which IAs rupture during the early 1990s might reflect a change in the lifestyle and health behavior of the Finnish population, which is then reflected in the relative importance of risk factors for IA rupture and subsequently in the pathobiology of the IA disease.

Smoking is a known risk factor for aneurysm rupture and decreasing trends in smoking have been previously associated with decreasing trends in the incidence of aSAH in Finland.[21] Since 1997, smoking has decreased in Finland, especially in men aged 20 to 64 years.[22] However, we did not find a downward trend in annual number of IA ruptures (Data supplement) even though smoking has decreased during the same period.[22] Moreover, in our study cohort, less than one third of the patients with an IA that ruptured before reaching 7 mm presented with a history of smoking. Together, these findings seem to imply that the observed change over time in the size at which IAs rupture is predominantly related to something else besides change in smoking habits.

In our study, overall, only a relatively small proportion of ruptures could be attributed to known risk factors of rupture (Table 1). That a large percentage of patients with aSAH have no history of known aSAH risk factors that would explain the rupture of their IA has been a rather constant phenomenon over the 30-year period of our study (Data supplement). Taken together with the observation that concomitant change in smoking habits poorly explains the change observed in the size of ruptured IAs, seems to suggest that the change in the size at which aneurysms rupture is related to something else besides change in known risk factors, and possibly there are important aSAH risk factors that remain to be discovered and studied.

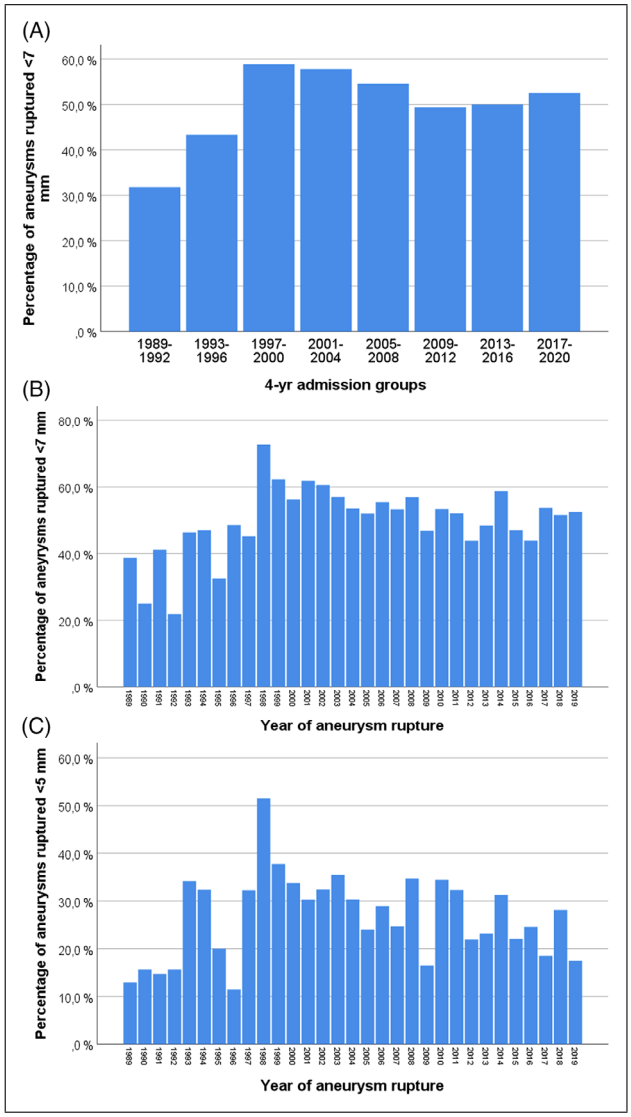


**Figure 4. The proportion of ruptured aneurysms that ruptured at a small size.**

The proportion or percentage of ruptured aneurysms that ruptured before reaching the size of 7 mm is shown over time in (**A**) stratified into 4-year periods and in (**B**) for each year separately. The percentage of ruptured aneurysms that rupture before reaching the size of 5 mm is shown over time in (**C**).

## Clinical Implications

It is worth noting that although the mean and median size at which IAs rupture has decreased over time, the percentage of IAs that ruptured at a small size has not changed over time (Figure 4). Consequently, those IAs that reach a >7 mm size before rupture have had a

tendency over time to rupture on average at a smaller size. In summary, together with the other Finnish studies with similar findings,[14,21] our findings imply that at least in the Finnish population IA size has become an increasingly insensitive indicator of rupture risk. Unfortunately, our data and the data of other similar Finnish cohorts[14,20] also suggest that all of the other established risk factors for IA rupture are too insensitive indicators of rupture risk as well, even if combined in any risk factor score, since 26% (500 of 1925) of all of the studied IAs that ruptured did so at a small size without a history of any known risk factor for rupture (Table 1). It seems therefore paramount to further investigate the pathobiology of IA formation, growth, and eventual rupture, in order to identify the yet unknown or poorly understood risk factors for rupture that seem to explain a large number of ruptures in the contemporary population of patients with IA. A recently discovered association of IA formation and rupture with periodontal infections,[23–25] and prior exposure to periodontal pathogens,[25] is an example of previously undetected factors affecting the clinical course of IA disease.

Because prophylactic treatment of unruptured IAs is still associated with significant risk of morbidity and even mortality,[2,3] not all discovered unruptured IAs should be treated, especially if small, which on average implies a low risk of rupture.[4–10,17] However, treatment should nevertheless also be considered for these small unruptured IAs, and, when presence of known risk factors for rupture, patient age, and suitability of the aneurysm for occlusive treatment favor intervention, it should not be denied based on size alone. Our data imply that especially in the anterior communicating artery location and in IAs arising from smaller or more distal branches of either anterior or posterior circulation, the threshold to treat a small unruptured IA should not be overtly high.

## Limitations

This study had some limitations. First, our study material did not cover all aSAH cases in the study period since some of the ruptures resulted in sudden death before hospitalization. In addition, some patients with aSAH in poor clinical condition may not have been referred to TAUH from the other hospitals in our catchment area. Based on the Finnish SAH incidence[16] and the population of our catchment area of 30 years, 15% of cases were missing from our material. However, even if all of the computational missing cases had been large aneurysms, it would not have significantly altered our conclusion that a significant percentage of the IAs that rupture do so before reaching the size of 7 mm or even 5 mm. Moreover, based on the numbers reported by Rautalin et al[16] from the national Finnish Hospital Discharge Register and Cause of Death Register, ≈24% (2256/9494) of Finnish patients with aSAH die before reaching the hospital. Taking this into account, it should be concluded that our study cohort accurately represents those patients with aSAH who present to the neurosurgeon for emergency treatment, and also rather well the overall population of patients with aSAH.

A second limitation, and a possible source of bias, is the fact that before 2004 in our institution, aneurysm size was measured from analogical images using an estimated 5-mm ICA diameter as a reference, while after 2004 the measurements were made directly from digital imaging studies. Although the difference in the measurement methodology might have introduced a systematic bias, in this series, the decrease in size of the ruptured saccular IAs was in fact observed before entering the era of digital image archive systems. Thus, during the period that we observed a decrease in the size at which aneurysms ruptured, the method for measurement did not essentially change. In turn, after the methodology changed to digital, the size at which aneurysms ruptured did not significantly change. Consequently, measurement error is unlikely to explain the decreasing trend in the size at which saccular IAs ruptured. Moreover, it also would not explain our primary finding, which is that a very large portion of IAs that rupture, do so before reaching 7 mm.

A third limitation is that, because of the retrospective nature of our study, we likely have missed some risk factor history data of some of our patients. The policy at TAUH Neurosurgery has, however, been for a long time to document the status of known aSAH risk factors to the medical records of all patients with IA. Moreover, the observation that a significant percentage of patients with aSAH and those with IA overall do not have a history of established aSAH risk factors, fits with the clinical observations obtained when treating these patients.

Finally, it has been speculated that aneurysms decrease in size after rupture, for which reason the size of an already ruptured aneurysm would not accurately reflect the size before rupture. Although studies on this topic are few, they show that intracranial saccular aneurysms do not usually shrink to a significant extent after rupture.[14,26] Thus, this phenomenon is unlikely to explain our results.

# CONCLUSIONS

We conclude that a significant percentage of IAs that rupture do so at a small size, before growing to 7 mm or even 5 mm in diameter. Although this has been the case in our patient population for the past 30 years, overall, there is a trend that the size at which IAs rupture has decreased, especially in the early 1990s. This may be

attributable to changes in the lifestyle or other health behavior of our patient population.

## ARTICLE INFORMATION

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### Disclosure

None.

### Supplemental Materials

Supporting Information

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