Positive Correlation Between Thoracic Aortic Diameter and Intracranial Aneurysm Size—An Observational Cohort Study

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■ OBJECTIVE: **To investigate the association between intracranial aneurysms (IAs) and thoracic aortic diameter.**

■ METHODS: **This observational cohort study examined thoracic aortic diameters in patients with IA. Patients were categorized by IA size (<7 mm and ≥7 mm) and IA status (ruptured/unruptured) based on radiologic findings. We investigated the association between thoracic aortic diameter and IA size and status using binary and linear regression as univariate and multivariable analyses.**

■ RESULTS: **A total of 409 patients were included. Mean age was 60 (±11.7) years and 63% were women. Thoracic aortic diameters were greater among patients who had an IA ≥7 mm versus IA <7 mm ($P < 0.05$). In the univariate analysis, the diameter of the ascending aorta (odds ratio [OR], 1.07; 95% confidence interval [CI], 1.02—1.129 per 1 mm; $P = 0.002$), aortic arch (OR, 1.10; 95% CI, 1.04—1.15 per 1 mm; $P < 0.001$), and descending aorta (OR, 1.10; 95% CI, 1.03—1.16 per 1 mm; $P = 0.003$) were associated with IAs ≥7 mm. In the multivariable regression model, larger ascending aorta (OR, 1.09; 95% CI, 1.01—1.17 per 1 mm; $P = 0.018$), aortic arch (OR, 1.12; 95% CI, 1.02—1.22 per 1 mm; $P = 0.013$), and descending aorta (OR, 1.20; 95% CI, 1.08—1.33 per 1 mm; $P < 0.001$) were associated with ruptured IA.**

■ CONCLUSIONS: **Greater thoracic aortic diameters are associated with a higher risk of IA being larger than 7 mm and IA rupture. Exploring the concomitant growth tendency in IA and thoracic aorta provides a basis for future considerations regarding screening and risk management.**

INTRODUCTION

The prevalence of intracranial aneurysms (IAs) is generally about 2%—3%. The incidence of aneurysmal subarachnoid hemorrhage is around 10/100,000 per person per year.[1] IAs are known to share similar risk factors with other cardiovascular diseases, and patients with IAs might have an increased atherosclerotic burden.[2]

Key words
- Intracranial aneurysm
- Ruptured intracranial aneurysm
- Thoracic aorta

Abbreviations and Acronyms
β: Linear regression coefficient
ACA: Anterior cerebral artery
AUC: Area under the receiver operating characteristic curve
CI: Confidence interval
CTA: Computed tomography angiography
IA: Intracranial aneurysm
ICA: Internal carotid artery
IFN-γ: Interferon γ
IL-1β: Interleukin 1β
MCA: Middle cerebral artery
MMP: Matrix metalloproteinase
MRA: Magnetic resonance angiography
OR: Odds ratio
RIA: Ruptured intracranial aneurysm
ROC: Receiver operating characteristic
SD: Standard deviation
SE: Standard error
TAA: Thoracic aortic aneurysm
TAD: Thoracic aortic dilatation
TNF-α: Tumor necrosis factor α
UIA: Unruptured intracranial aneurysm
VSMC: Vascular smooth muscle cell

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Citation: World Neurosurg. (2024) 184:e633-e646. https://doi.org/10.1016/j.wneu.2024.02.007

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

IAs might be associated with abdominal aortic aneurysms and thoracic aortic aneurysms (TAAs), which may be explained by shared genetic and lifestyle-related risk factors.[3,4] The coexistence of abdominal aortic aneurysms and atherosclerosis is well established and TAAs are similar in this respect, even though fewer TAAs are clearly associated with atherosclerosis.[5,6] IAs, especially ruptured IAs (RIAs), are associated with inflammation and atherosclerosis.[7-9]

Previously, our group has shown a higher prevalence of thoracic aortic dilatations (TADs) and TAAs among patients with IA.[10] Based on this finding, we hypothesized that increased thoracic aortic diameter would be associated with greater IA size. A test of this hypothesis is novel and aims to lay the background for the coexistence of these entities with diseases.

METHODS

This study protocol was reviewed and approved by the ethics committee of the wellbeing services, county of Southwest Finland, approval number T04/005/18. The need for informed consent was waived by the ethics committee of the wellbeing services, county of Southwest Finland because of the retrospective nature of the study. Patient record data were handled only by qualified staff necessary for the data collection and analysis. Sensitive information was handled confidentially and published results interpreted from the data containing sensitive information were anonymized or pseudonymized when possible and considered to be in accordance with privacy protection required by ethics committee approval.

Study Participants

The participants were consecutive patients treated for their IAs in the Department of Neurosurgery at Turku University Hospital between 2006 and 2016. IA diagnosis was radiologically confirmed by digital subtraction angiography, computed tomography angiography (CTA), or magnetic resonance angiography (MRA). The patients were categorized into different groups as follows: RIA versus unruptured IA (UIA), IA size <7 mm versus IA size ≥ 7 mm, multiple IAs versus single IA, and aortic diameter greater than versus less than threshold cutoff value. The cutoff value was selected based on previous findings, which reported a significantly increased risk for IA rupture after 7 mm.[11]

The 7 mm threshold has been since debated, but current guidelines do not offer another cutoff value and therefore this often-accepted limit is considered sufficient for the purposes of this study. Furthermore, many other studies have also investigated IAs categorized by this same threshold, and therefore our results are more easily comparable to these other results when the same categorization is used.[11-13]

Patients with genetic disorders that predisposed them to arterial malformations (Ehlers-Danlos type IV, Marfan and Loeys-Dietz syndromes) were excluded from this study. Demographic characteristics included other clinically relevant diagnoses and risk factors.

IA Measurements

IA diameters were measured by the authors D.L., M.R., and J.H. RIA (length, height, or width) diameter or the single largest UIA diameter was used in the analyses. Measurements were based on digital subtraction angiography, MRA, or CTA imaging. The location of the measured IA was recorded.

Aortic Measurements

Thoracic aortic diameters were measured from CTA, MRA, or computed tomography by D.L., E.P., T.F., J.G., and J.H. The measurement method used was described in detail in our recent study.[10] The largest diameter of the aorta perpendicular to the axis of the blood flow was measured. The measurement sites were the mid-ascending aorta, the mid-descending aorta at the level of pulmonary artery bifurcation, and the aortic arch at the level of maximum diameter. J.H. is a board-certified radiologist and has validated measurements in a blinded manner.

Statistical Analysis

Continuous variables (age, body mass index [calculated as weight in kilograms divided by the square of height in meters], serum creatinine level, measured maximum diameter or log-transformation of diameter) were reported as mean $\pm$ standard deviation (SD). The independent samples t test was used to compare the groups when normal distribution was assumed. Normal distribution was confirmed visually and using the Kolmogorov-Smirnov test from measured values or from $\log_{10}$-transformed values. The equality of variances was investigated using a Levene test. Categorical variables were reported as numbers (%). Differences between categorical variables were examined using the X^2 test. A P value <0.05 was considered statistically significant. Univariate and multivariable linear regression analyses were used to investigate the relationship between IA and thoracic aortic sizes. Univariate and multivariable binary logistic regression was used to investigate risk factors for RIA or UIA or for IA >7 mm or <7 mm or the threshold cutoff value.

Covariates for regression analyses were determined by their clinical significance and statistical significance as univariates ($P < 0.05$). See also the Supplementary Materials Discussion Section.

Odds ratios (ORs) are reported with 95% confidence intervals (CIs) and regression coefficients βs were reported as β (standard error [SE]). βs and ORs were reported as a change per 1 mm in the thoracic aorta and IA measurements, per 1 cm change in height and 1 year in age. A Youden test for J-index was used to calculate the cutoff threshold values for aortic diameters to further categorize patients. Receiver operating characteristic (ROC) and area under ROC curves (AUCs) were used in the Youden test and to investigate the association between aortic diameters and IAs >7 mm. All statistical analyses were performed using JMP, Version 16.2 (SAS Institute Inc., Cary, North Carolina, USA, 1989–2023).

RESULTS

Baseline Characteristics

A total of 409 patients with IA were included, of whom 225 (62%) were women. The mean age was 60 ($\pm$11.7) years. There were 184 patients (45.0%) with IA >7 mm in diameter. Patients with UIA had significantly more hypertension (48.3% vs. 59.4%; $P = 0.026$), dyslipidemia (18.0% vs. 32.1%; $P = 0.001$), and a history of ischemic stroke (5.8% vs. 29.9%; $P < 0.001$) than did patients with RIA. A total of 144 patients (25.8%) had IA in the anterior cerebral artery (ACA), 134 (23.8%) in the internal carotid artery (ICA), 205

(36.4%) in the middle cerebral artery (MCA), and 80 (14.2%) in the posterior circulation.

The patients with IAs ≥7 mm were more often men (44.3% vs. 32.0%; P < 0.011) smoked more (57.6% vs. 73.7%; P = 0.002), had more often alcohol abuse (1.4% vs. 9.4%; P = 0.027), and presented more often with RIAs (54.9% vs. 32.0%; P < 0.001). The baseline characteristics are shown in Tables 1 and 2 and Supplementary Tables 2 and 6.

Aortic and IA Diameters

Men had greater diameters of the ascending aorta (34.4 mm vs. 32.3 mm; P < 0.001), aortic arch (30.0 mm vs. 28.4 mm; P < 0.001), and descending aorta (26.8 mm vs. 24.0 mm; P < 0.001) than did women. The aortic diameters were also greater among patients with IAs >7 mm (ascending aorta, 33.8 mm vs. 32.5 mm, P = 0.002; aortic arch, 29.7 mm vs. 28.5 mm, P = 0.001; descending aorta, 25.6 mm vs. 24.6 mm, P = 0.003, respectively). The aortic diameters of the patients with RIA and UIA were not significantly different (P > 0.05 for all thoracic aortic diameters). Patients with multiple IAs had a smaller diameter of the ascending aorta (32.2 vs. 34.5; P = 0.006), aortic arch (28.4 vs. 29.3; P = 0.009), and descending aorta (24.4 vs. 25.3; P = 0.014).

The diameter of the aortic arch was greater among the men with an IA >7 mm (30.7 mm vs. 29.3 mm; P = 0.010) than among

Table 1. Baseline Characteristics and Comorbidities

Baseline Characteristics	RIA (n = 233; 42.7%)	UIA (n = 318; 58.3%)	*P* Value
Age (years), mean (SD)	60.5 (11.7)	59.1 (11.8)	0.159
Height (cm), mean (SD)	167.3 (16.8)	167.8 (14.2)	0.752
Body mass index (kg/m^2), mean (SD)	26.2 (4.6)	27.0 (5.3)	0.657
Serum creatinine level (μmol/L), mean (SD)	64.6 (19.7)	80.3 (46.1)	**<0.001**
Glomerular filtration rate (mL/minute/1.73 m^2), mean (SD)	98 (9.8)	86.5 (20.0)	0.080
Female	154 (63.9)	196 (60.7)	0.435
Hypertension	107 (45.7)	186 (58.5)	**0.007**
Dyslipidemia	48 (20.6)	109 (34.3)	**<0.001**
Type 2 diabetes	24 (10.3)	38 (12.0)	0.355
No diabetes	208 (89.3)	280 (88.1)	0.0355
Coronary artery disease	16 (6.9)	29 (9.1)	0.336
Previous myocardial infarct	10 (4.3)	25 (7.9)	0.090
Previous percutaneous coronary intervention	6 (2.6)	10 (3.1)	0.725
Previous coronary artery bypass surgery	3 (1.3)	8 (2.5)	0.313
Peripheral artery disease	7 (3.0)	14 (4.4)	0.391
Subarachnoid hemorrhage or intracranial hemorrhage	9 (3.9)	11 (3.5)	0.801
Ischemic stroke	17 (7.3)	93 (29.3)	**<0.001**
Carotid artery atherosclerosis	12 (5.2)	29 (9.1)	0.074
Active smoker	87 (48.6)	116 (38.5)	0.096
Ex-smoker	34 (19.0)	66 (21.9)	0.096
Nonsmoker	58 (32.4)	119 (39.5)	0.096
Ever-smoker (active + ex)	121 (67.6)	182 (60.5)	0.116
Chronic obstructive pulmonary disease or asthma	33 (14.2)	50 (15.7)	0.612
Polycystic renal disease	2 (1.0)	7 (2.6)	0.205
Alcohol abuse	9 (7.4)	15 (6.9)	0.948
Arteriovenous malformation	1 (0.4)	7 (1.3)	0.087
Rheumatic disease	13 (5.6)	18 (5.7)	0.968
Multiple intracranial aneurysms	78 (32.6)	103 (32.3)	0.871
Liver disease	3 (1.4)	4 (1.3)	0.911

Each disease characteristic means either diagnosed disease or treatment for the disease. Values are number (%) except where indicated otherwise.
Bold indicates statistical significance, $P < 0.05$.

Table 2. Baseline Characteristics by Intracranial Aneurysm Size >7/<7 mm

Baseline Characteristics	<7 mm (n = 225; 55.1%), n (%)	≥7 mm (n = 184; 45.0%), n (%)	*P* Value
Female	153 (68.0)	102 (55.7)	**0.011**
Male	72 (32.0)	81 (44.3)	**0.011**
RIA	72 (32.0)	101 (54.9)	**<0.001**
UIA	153 (68.0)	83 (45.1)	**<0.001**
Active smokers	75 (37.0)	77 (52.0)	**0.004**
Ex-smokers	42 (20.7)	32 (21.6)	**0.004**
Non-smokers	86 (42.4)	39 (26.4)	**0.004**
Ever-smoker (active + ex)	117 (52.0)	109 (59.2)	**0.002**
Alcohol abuse	2 (1.4)	10 (9.4)	**0.027**

Bold indicates statistical significance, $P < 0.05$.

women with an IA >7 mm. Maximum IA diameter was not significantly different among men and women (8.4 mm vs. 7.9 mm; P = 0.315). Maximum IA diameter was greater among the patients with RIA than the UIA (9.4 mm vs. 7.1 mm; P < 0.001) (Supplementary Table 6).

Univariate linear regression found no associations between aortic diameters and IA size, but the diameter of the descending aorta was associated with the log-transformed value of the maximum diameter of IA β 0.02 (0.01), P = 0.034 (Table 3).

The aortic diameters increased the odds of having an IA >7 mm: ascending aorta (OR, 1.07; 95% CI, 1.02–1.12; P = 0.002), aortic arch (OR, 1.10; 95% CI, 1.04–1.15; P < 0.001), and descending aorta (OR, 1.10; 95% CI, 1.03–1.16; P = 0.003). Aortic diameters were not associated with a risk of RIA over UIA (P >

Table 3. Univariate Linear Regression Analyses of Intracranial Aneurysm Maximum Diameter

Characteristic	β (Standard Error)	*P* Value
Age	0.03 (0.03)	0.267
Body mass index	−0.66 (0.35)	0.07
Serum creatinine	0.01 (0.01)	0.080
Aortic diameter		
Ascending aorta	0.09 (0.07)	0.181
Aortic arch	0.15 (0.08)	0.081
Descending aorta	0.12 (0.09)	0.187
Aortic diameter to log-transformed intracranial aneurysm measure		
Ascending aorta	0.01 (0.01)	0.181
Aortic arch	0.01 (0.01)	0.075
Descending aorta	0.02 (0.01)	**0.034**

Each row represents a univariable linear regression analysis with respective unstandardized β.
Bold indicates statistical significance, $P < 0.05$.

Table 4. Odds Ratios for Intracranial Aneurysm Status (Ruptured Intracranial Aneurysm/Unruptured Intracranial Aneurysm), Size >7 mm, Aortic Threshold Values and Multiplicity: Unadjusted Binary Logistic Regression and Simple Odds Ratios

Characteristics	Odds Ratio (95% Confidence Interval)	*P* Value
Logistic binary univariate regression for IA size, dichotomized as IAs <7 mm and ≥7 mm		
Ascending aorta	1.07 (1.02–1.12) per 1 mm	**0.002**
Aortic arch	1.10 (1.04–1.15) per 1 mm	**<0.001**
Descending aorta	1.10 (1.03–1.16) per 1 mm	**0.003**
Logistic binary univariate regression for IA status, rupture, 1= RIA, 0=UIA		
Ascending aorta	1.00 (0.96–1.05)	0.848
Aortic arch	1.01 (0.96–1.06)	0.743
Descending aorta	1.05 (0.99–1.11)	0.108
IA size	1.07 (1.03–1.11)	**<0.001**
Logistic binary univariate regression for multiple IAs		
Ascending aorta	0.94 (0.90–0.98)	**0.006**
Aortic arch	0.93 (0.88–0.98)	**0.009**
Descending aorta	0.93 (0.86–0.99)	**0.014**
IA size	1.01 (0.98–1.04)	0.529
Odds ratio for IA >7 mm by aortic diameter cutoff values		
Ascending aorta >30.8 mm	2.00 (1.27–3.14)	**0.002**
Aortic arch >29.2 mm	1.67 (1.13–2.48)	**0.010**
Descending aorta >25.2 mm	1.57 (1.06–2.32)	**0.025**
Any of the aortic diameter > threshold	2.26 (1.37–3.73)	**0.001**

Logistic binary univariate regression for IA size, dichotomized as IAs <7 mm and ≥7 mm.
Bold indicates statistical significance, $P < 0.05$.

Table 5. Youden J-Index and Area Under the Curve Values for Different Thoracic Aortic Diameters Predicting Intracranial Aneurysm Size >7 mm

	Area Under the Curve	J-Index	Aortic Diameter (mm)*	Probability	Sensitivity	1-Specificity
Ascending aorta	0.578	0.136	30.8	0.411	0.794	0.658
Aortic arch	0.573	0.128	29.2	0.449	0.554	0.427
Descending aorta	0.576	0.129	25.2	0.451	0.560	0.431

Values are from receiver operating characteristic/area under the curve analysis of univariate regression in which each aortic diameter explains IA size > 7 mm; these analyses are presented in Table 4.
*Threshold value at which J-index was greatest.

0.05). The diameter of the ascending aorta (OR, 0.94; 95% CI, 0.90–0.98; P = 0.006), aortic arch (OR, 0.93; 95% CI, 0.88–0.98; P = 0.009), and descending aorta (OR, 0.93; 95% CI, 0.86–0.99; P = 0.014) reduced the odds of having multiple IAs, as shown in Tables 4–6.

The Youden J-index showed that, based on each AUC ROC analysis, the best threshold values were 30.8 mm (sensitivity, 0.79; specificity, 0.34) for the ascending aorta, 29.2 mm (sensitivity, 0.55; specificity, 0.57) for the aortic arch, and 25.2 mm (sensitivity, 0.56; specificity, 0.57) for the descending aorta. Based on these thresholds, having an aortic diameter greater than the threshold cutoff value was associated with increased odds of an IA >7 mm: ascending aorta (OR, 2.00; 95% CI, 1.27–3.14), aortic arch (OR, 1.67; 95% CI, 1.13–2.48), descending aorta (OR, 1.57; 95% CI, 1.06–2.32), or an aortic diameter greater than the cutoff in any location (OR, 2.26; 95% CI, 1.37–3.73). Aortic diameters were more often over the respective threshold cutoff value among patients with an IA >7 mm than among patients with an IA <7 mm: ascending aorta, 79.4% versus 65.8%, P = 0.002, aortic arch, 55.4% versus 42.7%, P = 0.010, descending aorta, 42.7% versus 53.8%, P = 0.025, any aortic location diameter greater than respective cutoff, 72.0% versus 85.3%, P = 0.001, as shown in Table 4.

The diameter of the ascending aorta (OR, 1.09; 95% CI, 1.01–1.17; P = 0.018), aortic arch (OR, 1.12; 95% CI, 1.02–1.22; P = 0.013) and descending aorta (OR, 1.20; 95% CI, 1.08–1.33; P < 0.001) increased the odds of RIA in multivariable binary regression adjusted for age, sex, height, hypertension, dyslipidemia, and smoking. Dyslipidemia was also associated with a risk of RIA in the adjusted models, which is shown in Table 7.

DISCUSSION

The greater thoracic aortic size was associated with a higher risk of having an IA >7 mm and of RIA. Earlier studies have shown that patients with IAs might be at an increased risk of abdominal aortic and TAAs, suggesting shared risk factors.[4,14] Nevertheless, it is unclear which factors affect IA size or how large an IA can grow until it is detected.

Aortopathies (aneurysms, dilatations, and dissections) seem to coexist with IAs, and previous studies have shown that IAs are more common among patients with TAAs and vice versa.[10,15] IAs, TAAs, and TADs share many similarities, including underlying pathophysiology, genetic predispositions, clinical risk factors, and anatomic appearance.[4] We present the correlation between IA diameter and greater thoracic aortic diameters, which further elucidates a plausible connection between IAs and TAAs.

Genome-wide association studies have identified several genetic loci associated with both IAs and TAAs, but the genetic background of TAAs and IAs seems to be mostly unconnected.[3,16] Only some aortic aneurysms and IAs can be explained by Mendelian monogenic diseases, whereas environmental factors such as smoking and high blood pressure may in part explain the occurrence.[17,18] Dysfunctional and diminished vascular smooth muscle cells (VSMCs), degradation of the extracellular matrix, markers of inflammation, alterations in matrix metalloproteinase (MMP) activity, and endothelial layer disruption are all associated with IAs and TAAs.[19-21]

Inflammatory mediators/cytokines with excess expression or upregulation in IAs are tumor necrosis factor α (TNF-α), monocyte chemotactic protein 1, vascular cell adhesion molecule,

Table 6. Categorization of Patients with Intracranial Aneurysm by Aortic Threshold Values Derived From Youden J-Index

	IA <7 mm, n (%)	IA ≥7 mm, n (%)	*P* Value	Odds Ratio (95% Confidence Interval)
Aortic diameter cutoff value				
Ascending aorta >30.8 mm	148 (65.8)	146 (79.4)	**0.002**	**2.00 (1.27–3.14)**
Aortic arch >29.2 mm	96 (42.7)	102 (55.4)	**0.010**	**1.67 (1.13–2.48)**
Descending aorta >25.2 mm	96 (42.7)	99 (53.8)	**0.025**	**1.57 (1.06–2.32)**
Any of above diameters greater than threshold	162 (72.0)	157 (85.3)	**0.001**	**2.26 (1.37–3.73)**

X^2 test categorizing patients with IAs >7 mm by threshold values of thoracic aorta diameter.
Bold indicates statistical significance, *P* < 0.05. Odds ratios with confidence interval not overlapping with 1 are bolded to make notice of statistical significance.

Table 7. Multivariate Model. Binary Regression for RIA instead of UIA.

Characteristics	Odds Ratio (95% Confidence Interval) Adjusted*	*P* Value
Age	0.99 (0.96–1.02)	0.372
Female sex	1.61 (0.73–3.56)	0.239
Height	1.01 (0.97–1.05)	0.734
Dyslipidemia	2.38 (1.16–4.87)	**0.018**
Smoking status	0.78 (0.43–1.40)	0.405
Ascending aorta diameter	1.09 (1.01–1.17)	**0.018**
Hypertension	1.62 (0.89–2.95)	0.114
Age	0.99 (0.96–1.02)	0.370
Female sex	1.57 (0.72–3.43)	0.246
Height	1.00 (0.96–1.04)	0.865
Dyslipidemia	2.64 (1.28–5.53)	**0.007**
Smoking status	0.80 (0.44–1.45)	0.460
Aortic arch diameter	1.12 (1.02–1.22)	**0.013**
Hypertension	1.49 (0.82–2.70)	0.194
Age	0.97 (0.94–1.01)	0.110
Female sex	2.12 (0.93–4.82)	0.062
Height	1.00 (0.996–1.04)	0.851
Dyslipidemia	2.41 (1.16–5.01)	**0.015**
Smoking status	0.89 (0.49–1.63)	0.707
Descending aorta diameter	1.20 (1.08–1.33)	**<0.001**
Hypertension	1.51 (0.83–2.77)	0.180

Each set of variables represents model adjusted for these variables with respective aortic diameter. Covariates in the model are those listed above. Each model contains age, sex, height, dyslipidemia, smoking status, hypertension.
Female is coded as 1 and male as 0, odds ratio <1 indicates that females have diminished risk of IA ≥7 mm.
Bold indicates statistical significance, $P < 0.05$.

macrophage inflammatorty protein 1, interleukin 1β (IL-1β), interferon γ (IFN-γ), IL-6.[22-26] Participating inflammatory cells in IAs are neutrophils, macrophages, Th1 cells, and mast cells. In TAAs, overexpressed or upregulated inflammatory mediators/cytokines are IL-6, IL-1β, transforming growth factor β, TNF-α, IFN-γ, and monocyte chemotactic protein 1. Active inflammatory cells in TAAs are neutrophils, macrophages, T cells especially Th1 cells, and B cells to some extent. Therefore, shared factors are TNF-α, IFN-γ, IL-6, IL-1β, MMPs 2 and 9, and macrophages, neutrophils, and Th cells. Also, a variety of MMPs are involved in the disturbances of extracellular matrix in both IAs and TAAs and especially MMPs 2 and 9 seem to be active in both.[26,27] VSMCs are paramount in healthy artery function. Their ability to switch phenotype is well documented, and this phenomenon is present in atherosclerosis, aortic aneurysms (TAA included), and IAs.[28,29] Dysfunction of endothelial cells is also in play in both IAs and TAAs, with some similarities.[26,27,30] Abnormal flow conditions are established in IAs and possible and suggested in the case of TAAs.[31] In the context of inflammatory markers and cells, the complex interplay involved in inflammation of the artery wall in these diseases is beyond the scope of this study, and only the existence of these in both is pointed out.[19,32]

IA and TAA coprevalence can also be determined by their location. Anterior circulation IAs seem to be associated with coexisting aneurysms in the ascending thoracic aorta, and IAs in the region of the ICA seem to be associated with abdominal aortic aneurysms.[15,33] Embryologically, this kind of location-associated coexistence and possible inheritability is comprehensible. VSMCs, the major cellular components of the aortic wall, of different parts of the aorta are derived from different developmental lineages in conjunction with anterior and posterior intracranial arteries. VSMCs from the anterior intracranial circulation arteries, ascending aorta, and aortic arch are of second heart field and neural crest origin, whereas VSMCs in the posterior intracranial circulation and descending aorta are derived from mesoderm.[34-38]

In the case of IAs, the mere initial size has been found to predict growth, and factors associated with IA rupture are also associated with the growth of IA. Specifically, the demographic factors female sex, hypertension, and smoking are risk factors for IA growth, and the aneurysm-specific factors location and multiplicity of aneurysms are associated with IA growth.[39,40] In particular, posterior circulation IAs seem to possess a greater risk for growth (VSMCs embryologic origin).[41] However, only scarce evidence about thoracic aortic diameter growth exists. As in the case of IAs, the initial size of TAA predicts future growth.[42] Optimal medical therapy for cardiovascular diseases is recommended in the population with established TAAs, even though evidence is scarce about hypertension and dyslipidemia as risk factors for TAA growth. Smoking as a risk factor on the other hand is a shared characteristic compared with IAs.[42]

Dyslipidemia increased the odds for RIA in multivariate models. Conflicting data exist on dyslipidemia and IAs. Although there are multiple studies linking IAs and cardiovascular diseases in patients with IA, there are studies in which dyslipidemia and even coronary artery disease have been associated with decreased odds for IAs. This phenomenon could be a result of the preventive methods applied in patients with dyslipidemia and associated diseases, which may alleviate IA problems as well. Another potential explanation is that IA might be the first hit of cardiovascular disease and, thus, patients with IAs might just be underdiagnosed regarding dyslipidemia.

Limitations

This is a retrospective observational study, which is prone to selection bias, bias generated by insufficient reporting, and uncontrolled bias generated by unmeasured variables. Possible missing values are random and should not affect patient categorization. The risk of missing values affecting the analysis results was estimated to be insignificant. The selection of covariates is bound to introduce a chance of bias. Multicollinearity was not suspected, because demographic factors used in multivariate analysis did not show suspicious distribution in univariate analysis. Potential confounders risk was also estimated to be small because variables

are relevant clinical risk factors in the context of these diseases, but none can be considered a causative agent for thoracic aortic growth or IA formation because their effects are not so great in general.

Significantly more patients are categorized as having UIA than RIA, presumably because UIAs are often found when cranial imaging is performed because of suspected stroke. Because of this bias, stroke was not included as a variable in multivariate analysis. Patients were not categorized by TAA/TAD because the scope of the study was merely a comparison of IA and thoracic aortic diameters.

The study population is limited to a single-country population, which may introduce bias, but population-level predisposition should not obscure results achieved with these methods. The number of patients in this study was also a limitation, especially in terms of subgroup analysis. We measured only the diameter of the aorta and IAs, but their shape and morphologic appearance were not reviewed in this study because we estimated that our approach does not require this categorization.

Conclusions

We found that larger thoracic aortic diameters are associated with a higher risk of IA being larger than 7 mm and IA rupture. We were able to show threshold values for aortic diameters that were associated with increased odds of larger IA. The possible common characteristics that affect IA and TA size growth are still open for exploration. This novel result provides mechanistic evidence inside the frame of epidemiologic coexistence. Exploring the concomitant growth tendency in IA and thoracic aorta provides a basis for future considerations regarding screening and risk management.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Ville Rantasalo: Conceptualization, Formal analysis, Methodology, Writing — original draft, Writing — review & editing. **Jarmo Gunn:** Conceptualization, Formal analysis, Supervision, Writing — original draft, Writing — review & editing. **Emily Pan:** Data curation, Methodology, Writing — original draft, Writing — review & editing. **Tuomas Kiviniemi:** Conceptualization, Methodology, Writing — original draft, Writing — review & editing. **Jussi Hirvonen:** Conceptualization, Methodology, Validation, Writing — original draft, Writing — review & editing. **Melissa Rahi:** Data curation, Methodology, Writing — original draft, Writing — review & editing. **Terhi Fordell:** Data curation, Methodology, Writing — original draft, Writing — review & editing. **Jaakko K. Rinne:** Conceptualization, Data curation, Methodology, Writing — original draft, Writing — review & editing. **Dan Laukka:** Conceptualization, Data curation, Formal analysis, Methodology, Writing — original draft, Writing — review & editing.

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Conflict of interest statement: V.R. reports that financial support was provided by the Finnish Foundation for Cardiovascular Research, Maire Taponen Foundation, and The Finnish Medical Foundation. J.G. declares an unrestricted research grant from Vifor Pharma not related to the current study.

Received 3 January 2024; accepted 2 February 2024

Citation: World Neurosurg. (2024) 184:e633-e646. https://doi.org/10.1016/j.wneu.2024.02.007

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

SUPPLEMENTARY RESULTS

Demographics

The mean age was 59.6 years and did not significantly differ among men and women ($P = 0.126$), patients with ruptured intracranial aneurysm (RIA) and unruptured intracranial aneurysm (UIA) ($P = 0.159$), and patients categorized by intracranial aneurysm (IA) >7/<7 mm ($P = 0.392$). There was no significant difference between the sex distribution of the patients with RIA and UIA (63.9% vs. 60.7%; $P = 0.435$).

Thoracic Aortic Aneurysm and IA Diameter

The aortic diameters were not significantly different when patients were categorized by IA size of 3 mm (all P values >0.05). The aortic arch (29.3 vs. 28.5; $P = 0.038$) and the descending aorta (25.3 vs. 24.6; $P = 0.033$) were greater among patients with IAs >5 mm. The aortic arch (29.8 vs. 28.8; $P = 0.008$) and the descending aorta (25.7 vs. 24.8; $P = 0.015$) were greater among patients with IAs >10 mm. The size of IA was not significantly different among patients with multiple aneurysms ($P > 0.05$).

The diameter of the aortic arch (29.7 mm vs. 28.4 mm; $P = 0.042$, Tukey honestly significant difference [HSD] test) and the descending aorta (25.7 mm vs. 24.3 mm; $P = 0.023$ Tukey HSD) were significantly greater among patients with IA in ACA compared with those who had IA in internal carotid artery (ICA). There was no other significant difference in thoracic aorta (TA) diameter between patients categorized by IA location (ACA, posterior, ICA, MCA]; all other pair comparisons >0.05 Tukey HSD) (**Supplementary Table 1**).

The diameter of the descending aorta was greater among patients who had RIA in ICA than among patients who had UIA in ICA (25.8 mm vs. 23.8 mm; $P = 0.006$). Otherwise, there was no significant difference between the aortic diameters of patients with RIA and UIA categorized as subgroups by IA location (ACA, posterior, MCA, ICA; P value for all other diameters <0.05) (**Supplementary Table 2**).

Logarithmic transformation of IA size was associated with increased diameter of the descending aorta (β (linear regression coefficient) 0.56 (0.27); $P = 0.034$) (**Supplementary Table 3**).

The diameters of the aorta were not associated with a risk of having an IA >7 mm in the adjusted model. Aortic diameters were not associated with increased IA size in the adjusted linear model with the same background variables (P >0.05) (**Supplementary Tables 4** and **5**).

The aortic diameters greater than the threshold cutoff values were not associated with IA status (RIA/UIA), IA size >7/<7 mm or IA maximum diameter in similar multivariable models when the variable for diameter was replaced with the respective dichotomized threshold value. Analysis not shown in Tables.

TAA Diameters Among Patients Categorized by IA Location

Patients were categorized by IA location (ICA, MCA, ACA, posterior). The diameter of the aortic arch and descending aorta of patients with IAs in different locations was statistically different. The significance of this analysis remains inconclusive because only the largest or ruptured IA size and location were recorded. Hence, patients with multiple IAs present bias to this analysis.

TAA Among Patients with ICA Aneurysms

The diameter of the descending aorta was greater among patients who had RIA in ICA than among patients with UIA in ICA (25.8 mm vs. 23.8 mm; $P = 0.006$). The diameter of the aortic arch was greater among patients who had an IA >7 mm in ICA than among patients who had IA <7 mm in ICA (29.5 vs. 27.8; $P = 0.035$).

TAA Among Patients with MCA Aneurysms

There was no significant difference between the aortic dimensions of the patients who had RIA or UIA in MCA. The aortic arch was significantly greater among patients who had an IA >7 mm in MCA than among patients who had an IA <7 mm in MCA (29.4 mm vs. 28.2 mm; $P = 0.038$).

TAA Among Patients with Anterior Circulation Aneurysms

Aortic diameters did not significantly differ among patients who had RIAs or UIAs in ACA ($P > 0.05$ for both).

TAA in Patients with Posterior Circulation Aneurysms

Aortic diameters did not significantly differ among patients with RIAs or UIAs in posterior circulation ($P > 0.05$ for both).

TAA Diameters Among Patients with Different IA Locations: Categorization by IA Status and Size

The aortic arch was greater among patients with IA >7 mm in ICA or in MCA ($P < 0.05$ for both). The descending aorta was greater among patients with RIA in ICA instead of UIA in ICA ($P < 0.05$).

Linear Regressions, Univariate

In the subgroup analysis of patients with UIA, the diameter of the aortic arch was associated with IA size ($\beta = 0.09$; $P = 0.0077$; $R^2 = 0.025$). Among patients with RIA versus UIA and among patients with IA >7 or <7 mm, the aortic diameters were not associated with IA size. Data not shown in Tables.

Among men only, the diameter of the aortic arch was associated with intracranial aneurysm size ($\beta = 0.08$; $P = 0.033$; $R^2 = 0.025$). The diameter of the ascending or descending aorta was not associated with IA size ($P > 0.05$ for both). Among women only, the aortic diameters were not associated with the intracranial aneurysm size ($P > 0.05$ for each).

Among patients with ACA IA, the diameter of the descending aorta was associated with the IA size ($\beta = 0.17$; $P = 0.018$; $R^2 = 0.0482$). Among patients with posterior circulation IA, the aortic diameters were not associated with IA size ($P > 0.05$ for each). Among patients with ICA IA, the diameter of the aortic arch was associated with IA size ($\beta = 0.09$; $P = 0.0294$; $R^2 = 0.044$). In patients with MCA IA, the diameters of the aorta were not associated with IA size ($P > 0.05$ for each).

Patients were also categorized as patients having IA in ACA and patients with no IA in ACA. Among the patients who had an IA in ACA, the diameter of the aortic arch ($\beta = 0.07$; $P = 0.0133$; $R^2 = 0.0143$) was associated with IA size. The diameter of the descending aorta was associated with the log-transformed value of IA size ($\beta = 0.647$; $P = 0.0238$; $R^2 = 0.01338$). None of the aortic dimensions was associated with IA size among patients with no IA in ACA ($P > 0.05$).

IA >7 mm

None of the aortic diameters was associated with IA size ($P > 0.05$ for each)

IA <7 mm

None of the aortic diameters was associated with IA size ($P > 0.05$ for each)

Patients with RIA

None of the aortic diameters was associated with IA size ($P > 0.05$ for each)

Patients with UIA

The diameter of the aortic arch was associated with IA size ($\beta = 0.15$; $P = 0.045$; $R^2 = 0.009$). The ascending and the descending aorta diameters were not associated with IA size ($P > 0.05$ for both).

Binary Regression

The aortic diameters did not increase the odds of having an IA >3 mm ($P > 0.05$ for each).

The ascending aorta diameter did not increase the odds of having IA >5 mm ($P > 0.05$), but the diameter of the aortic arch (odds ratio [OR], 1.06; 95% confidence interval [CI], 1.00–1.12; $P = 0.037$) and the descending aorta (OR, 1.07; 95% CI, 1.01–1.14; $P = 0.031$) increased the odds of having an IA size >5 mm.

The ascending aorta diameter did not increase the odds of having an IA >10 mm ($P > 0.05$), but the diameter of the aortic arch (OR, 1.09; 95% CI, 1.02–1.14; $P = 0.008$) and the descending aorta (OR, 1.08; 95% CI, 1.01–1.16; $P = 0.016$) increased the odds of having an IA size >10 mm.

The diameter of the descending aorta increased the risk for RIA in patients who had IA in ICA (OR, 1.21; 95% CI, 1.06–1.40; $P = 0.005$). The diameters of the ascending aorta or aortic arch were not associated with increased odds of RIA in patients with ICA IA. Odds of RIA were not increased by the diameters of the ascending aorta, aortic arch, or descending aorta diameters among patients with IA in MCA, ACA, or posterior circulation ($P > .05$ and 95% CI overlapping 1 in each comparison), analysis not shown.

RIAs were greater than UIAs in ICA (10.5 mm vs. 7.10 mm; $P = 0.037$), MCA (10.1 mm vs. 7.25 mm; $P < 0.001$) and ACA (7.83 mm vs. 6.28 mm; $P = 0.0126$). RIAs were not significantly larger than UIAs in the posterior circulation ($P = 0.160$) (**Supplementary Table 2**).

SUPPLEMENTARY DISCUSSION

Limitations

Covariates hypertension and dyslipidemia were included because they showed statistically significant differences in UIA and RIA categories. Hypertension is a risk factor for IAs, and as discussed earlier, endothelial dysfunction affects thoracic aortic aneurysm formation and hypertension is known to affect endothelium and other important mechanisms in cardiovascular diseases. On the other hand, dyslipidemia is a common nominator in atherosclerosis-based cardiovascular diseases that is included in analyses to control common cardiovasculardisease–related risk factors in the analysis.

Serum creatinine was excluded from the analysis because renal function impairment is affected by multiple comorbidities and it might add uncontrollable confounding factors and collinearity-related errors to the analysis because impaired renal function might repeat the effect of other factors already included in the analysis. Height and sex were considered important covariates because the aortic diameter is generally greater in men and height is a plausible surrogate marker for the size of patients because taller individuals are more likely to have greater aortic diameter. Smoking is a known risk factor for both IAs and cardiovascular diseases in general and, therefore, we saw that including smoking as a covariate would hinder imbalance between groups. Sex is an important covariate because the risk for IAs has been reported to be different in men and women. Ischemic stroke was statistically significantly more prevalent in patients with RIA than in patients with UIA, but this is likely a result of selection bias because UIAs are often found in patients who undergo imaging studies because of suspected stroke.

Significantly more patients are categorized as having UIA than RIA. Stroke is often an indication for cranial imaging showing UIAs and therefore stroke is plausibly more prevalent in the population with UIA. Because of this bias, stroke was not included as a variable in multivariate analysis. Patients were not categorized by thoracic aortic aneurysm/thoracic aortic dilatation versus none. Our intention was to report an association between increasing sizes of thoracic aorta and IA, and therefore this categorization was not required for our analysis. Thoracic aortic dilatation is not clearly defined and therefore the linear measurement variable is the most feasible instrument for this study.

The study population was from 1 country, Finland, and thus represents the Finnish population and genetics. The Finnish population has been suspected to have a higher prevalence of IAs, but a meta-analysis suggests that UIA prevalence is not increased. Rather the rupture rate of IAs might be increased in the Finnish population.[42] Such phenomenon still should not introduce too much bias to this study: population-level predisposition for the diseases might even help to highlight individuals with extra risk factors, and additional risk factors should emerge to significance even if background noise contains risk associated with the subject. The number of patients in this study was also a limitation, especially in terms of subgroup analysis.

We only measured the diameter of the aorta and intracranial aneurysms, but their shape and morphologic appearance were not reviewed in this study. Although aneurysm morphology is associated with the rupture risk, we left this out of the analysis for the purposes of this study. We see that including classification by morphology in the analysis might act as a confounding factor: Our aim is to visualize aortic diameters association with rupture risk and size of IAs, and this contains IAs that are at risk of rupture for any reason, be it size, unknown characteristics, location, or morphology. All these reasons could represent the very risk to which we are drawing attention.

SUPPLEMENTARY DATA

Supplementary Table 1. Aortic Diameters Among Patients with Intracranial Aneurysm in Different Locations

All patients	Ascending, Mean (SD)	Arch, Mean (SD)	Descending, Mean (SD)	IA, Mean (SD)
IA in internal carotid artery	32.3 (4.3)	28.4 (3.8)	24.3 (0.3)	8.0 (0.3)
IA in middle cerebral artery	32.9 (4.5)	28.7 (3.6)	25.2 (0.3)	8.4 (0.4)
IA in anterior cerebral artery	33.8 (4.4)	29.7 (3.4)	25.7 (0.3)	7.1 (0.3)
IA in posterior circulation	33.4 (4.9)	29.4 (3.8)	24.6 (0.4)	9.4 (0.8)
P value	0.083	0.033*	0.027*	0.072

SD, standard deviation; IA, intracranial aneurysm.
*Tukey HSD, significant difference between patients who had IA in anterior cerebral artery and internal carotid artery.

Supplementary Table 2. Aortic and Intracranial Aneurysm Maximum Diameter Among Intracranial Aneurysm Patients Categorized by Intracranial Aneurysm Location

	Ascending, Mean (SD)	Arch Mean, (SD)	Descending, Mean (SD)	IA, Mean (SD)
IA in internal carotid artery				
RIA	32.9 (4.8)	29.5 (4.2)	25.8 (3.8)	10.5 (6.3)
UIA	32.1 (4.1)	28.0 (3.6)	23.8 (3.0)	7.1 (8.7)
P value	0.344	0.079	0.006	0.037
<7 mm	31.7 (4.5)	27.8 (3.8)	24.0 (3.4)	4.2 (1.4)
≥7 mm	33.2 (4.0)	29.5 (3.7)	24.8 (3.2)	15.5 (10.6)
P value	0.096	0.035	0.210	<0.001
IA in middle cerebral artery				
RIA	32.6 (4.6)	28.8 (3.8)	25.1 (3.4)	10.1 (7.5)
UIA	33.1 (4.3)	28.7 (3.5)	25.3 (3.7)	7.3 (4.1)
P value	0.500	0.881	0.721	<0.001
<7 mm	32.6 (4.1)	28.2 (3.4)	24.7 (3.4)	4.7 (1.6)
≥7 mm	33.7 (4.8)	29.4 (3.6)	25.8 (3.8)	12.2 (6.2)
P value	0.061	0.038	0.055	<0.001
IA in anterior cerebral artery				
RIA	33.6 (4.3)	29.6 (3.3)	25.8 (3.0)	7.8 (4.0)
UIA	33.9 (4.6)	29.7 (3.6)	25.5 (2.9)	6.3 (3.2)
P value	0.733	0.782	0.648	0.013
<7 mm	33.1 (4.3)	29.3 (3.5)	25.3 (3.9)	4.6 (1.4)
≥7 mm	34.7 (4.5)	30.2 (3.3)	26.2 (2.9)	10.7 (3.0)
P value	0.054	0.108	0.108	<0.001
IA in posterior circulation				
RIA	33.0 (5.2)	29.3 (4.0)	24.3 (5.1)	10.2 (6.2)
UIA	33.9 (4.5)	29.4 (3.6)	25.0 (3.0)	8.7 (6.9)
P value	0.475	0.900	0.521	0.380
<7 mm	33.6 (5.1)	28.9 (3.2)	24.6 (2.6)	4.3 (1.6)
≥7 mm	33.4 (4.6)	29.5 (4.5)	25.1 (3.1)	13.1 (6.3)
P value	0.873	0.398	0.567	<0.001

SD, standard deviation; IA, intracranial aneurysm; RIA, Ruptured intracranial aneurysm; UIA, unruptured intracranial aneurysm.

Supplementary Table 3. Univariate Linear Regression Analyses for Thoracic Aorta Diameter

Characteristic	β (Standard Error)	*P* Value
Ascending aorta		
Age	0.14 (0.02)	<0.001
BMI	−0.19 (0.21)	0.397
IA diameter	0.05 (0.03)	0.181
log(IA diameter)	0.47 (0.35)	0.181
Aortic arch		
Age	0.11 (0.01)	<0.001
BMI	0.01 (0.14)	0.909
IA diameter	0.05 (0.03)	0.081
l og(IA diameter)	0.53 (0.30)	0.075
Descending aorta		
Age	0.12 (0.01)	<0.001
BMI	0.13 (0.14)	0.342
l A diameter	0.03 (0.03)	0.187
log(IA diameter)	0.56 (0.27)	0.034

Each row represents univariable linear regression analysis with respective unstandardized β.
BMI, body mass index; IA, intracranial aneurysm.

Supplementary Table 4. Multivariate Binary Regression Models for Intracranial Aneurysm >7 mm

Characteristics	Odds Ratio (95% Confidence Interval) Adjusted	*P* Value
Age	0.98 (0.95—1.01)	0.205
Female sex	0.66 (0.34—1.30)	0.238
Height	1.00 (0.97—1.04)	0.893
Dyslipidemia	0.78 (0.42—1.46)	0.437
Smoking status	0.68 (0.39—1.20)	0.183
Ascending aorta diameter	1.07 (1.00—1.14)	0.060
Hypertension	1.79 (1.02—3.14)	0.043
Age	0.98 (0.95—1.01)	0.223
Female sex	0.66 (0.33—1.28)	0.224
Height	1.00 (0.97—1.03)	0.953
Dyslipidemia	0.84 (0.44—1.58)	0.583
Smoking status	0.70 (0.40—1.22)	0.210
Aortic arch diameter	1.08 (0.99—1.18)	0.072
Hypertension	1.16 (0.65—2.06)	0.620
Age	0.98 (0.95—1.01)	0.162
Female sex	0.74 (0.37—1.48)	0.399
Height	1.00 (0.97—1.03)	0.885
Dyslipidemia	0.76 (0.41—1.42)	0.394
Smoking status	0.73 (0.41—1.28)	0.271
Aortic arch diameter	1.10 (1.00—1.20)	0.057
Hypertension	1.16 (0.65—2.07)	0.613

Model adjusted for these characteristics and run separately with diameter of ascending aorta, aortic arch, and descending aorta.
Covariates in model are those listed above. Each model contains age, sex, height, dyslipidemia, smoking status, hypertension.
Female is coded as 1 and male as 0, odds ratio <1 means that females have diminished risk of intracranial aneurysm ≥7 mm.

Supplementary Table 5. Multivariate Linear Model, Adjusted for These Characteristics and Run Separately with Diameter of Aorta (Ascending, Arch, Descending)

Linear Regression for Intracranial Aneurysm Size

Characteristics	Adjusted β (Standard Error)	*P* Value
Age	0.00 (0.05)	0.953
Sex	0.47 (0.56)	0.407
Height	0.03 (0.05)	0.585
Dyslipidemia	0.03 (0.52)	0.952
Smoking status	-0.41 (0.45)	0.368
Hypertension	0.32 (0.48)	0.508
Ascending aorta diameter	0.09 (0.11)	0.396
Age	0.00 (0.05)	0.883
Sex	0.45 (0.56)	0.420
Height	0.02 (0.05)	0.649
Dyslipidemia	0.11 (0.52)	0.827
Smoking status	−0.38 (0.45)	0.401
Hypertension	0.27 (0.47)	0.570
Aortic arch diameter	0.16 (0.14)	0.259
Age	0.00 (0.05)	0.922
Sex	0.48 (0.58)	0.414
Height	0.03 (0.05)	0.536
Dyslipidemia	0.01 (0.51)	0.989
Smoking status	−0.40 (0.46)	0.381
Hypertension	0.28 (0.48)	0.556
Descending aorta diameter	0.05 (0.15)	0.758

Covariates in the model are those listed above. Each model contains age, sex, height, dyslipidemia, smoking status and hypertension.

Female is coded as 1 and male as 0, odds ratio < 1 would indicate that females have diminished risk for intracranial aneurysm $\geq$7 mm.

Supplementary Table 6. Intracranial Aneurysm and Thoracic Aorta Size of Groups and Sexes

	Ascending, Mean (SD)	Arch, Mean (SD)	Descending, Mean (SD)	IA, Mean (SD)
All patients				
RIA	33.1 (4.6)	29.2 (3.7)	25.3 (3.7)	9.4 (0.4)
UIA	33.1 (4.4)	28.8 (3.6)	24.8 (3.3)	7.1 (0.3)
P value	0.958	0.223	0.207	<0.001
<3 mm IA	33.4 (5.0)	28.9 (4.0)	24.8 (0.5)	2.4 (0.1)
≥3 mm IA	33.1 (4.4)	29.0 (3.7)	25.1 (0.2)	8.7 (0.3)
P value	0.623	0.822	0.667	<0.001
<5 mm IA	32.8 (4.7)	28.5 (3.8)	24.6 (0.3)	3.4 (0.1)
≥5 mm IA	33.2 (4.41)	29.3 (3.6)	25.3 (0.2)	10.3 (0.3)
P value	0.422	0.038	0.0327	<0.001
<7 mm IA	32.5 (4.3)	28.5 (3.6)	24.6 (3.6)	4.5 (1.4)
≥7 mm IA	33.8 (4.6)	29.7 (3.7)	25.6 (3.3)	12.6 (7.8)
P value	0.002	<0.001	0.003	<0.001
<10 mm IA	32.9 (4.5)	28.8 (3.7)	24.8 (0.2)	5.5 (0.1)
≥10 mm IA	33.6 (4.3)	29.8 (3.6)	25.7 (0.3)	16.1 (0.7)
P value	0.144	0.008	0.015	<0.001
1 aneurysm	3.35 (4.7)	29.3 (3.8)	25.3 (0.2)	7.8 (0.3)
Multiple aneurysms	32.2 (4.0)	28.4 (3.2)	24.4 (0.3)	8.3 (0.5)
P value	0.006	0.009	0.014	0.570
Male	34.4	30.0	26.8 (3.2)	8.4 (0.5)
Female	32.3	28.4 (3.5)	24.0 (3.3)	7.9 (0.3)
P value	<0.001	<0.001	<0.001	0.315
Female only				
RIA	32.4 (4.4)	28.5 (3.5)	24.3 (3.6)	9.4 (6.7)
UIA	32.3 (4.0)	28.3 (3.4)	23.7 (3.0)	6.7 (4.7)
P value	0.831	0.562	0.190	<0.001
<7 mm IA	32.0 (4.1)	28.1 (3.5)	23.9 (2.9)	4.6 (1.5)
≥7 mm IA	32.9 (4.3)	28.8 (3.5)	24.3 (3.0)	12.8 (6.1)
P value	0.097	0.076	0.207	<0.001
Male only				
RIA	34.4 (4.8)	30.6 (3.6)	27.1 (3.2)	9.3 (5.2)
UIA	34.3 (4.8)	29.7 (3.8)	26.5 (3.2)	7.8 (7.6)
P value	0.927	0.099	0.243	0.132
<7 mm IA	33.6 (4.7)	29.3 (3.6)	26.3 (3.2)	4.3 (1.4)
≥7 mm IA	35.0 (4.6)	30.7 (3.7)	27.2 (3.1)	12.2 (7.5)
P value	0.068	0.010	0.085	<0.001

SD, standard deviation; IA, intracranial aneurysm; RIA, ruptured intracranial aneurysm; UIA, unruptured intracranial aneurysm.