Prevalence of Intracranial Aneurysm in Patients with Aortopathy: A Systematic Review with Meta-Analyses

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Background and Purpose Patients with aortic disease might have an increased risk of intracranial aneurysm (IA). We conducted this research to assess the prevalence of IA in patients with aortopathy, considering the impact of gender, age, and cardiovascular risk factors.

Methods We searched PubMed and Scopus from inception to August 2019 for epidemiological studies reporting the prevalence of IA in patients with aortopathy. Random-effect meta-analyses were performed to calculate the overall prevalence, and the effect of risk factors on the prevalence was also evaluated. Anatomical location of IAs in patients suffered from distinct aortic disease was extracted and further analyzed.

Results Thirteen cross-sectional studies involving 4,041 participants were included in this systematic review. We reported an estimated prevalence of 12% (95% confidence interval [CI], 9% to 14%) of IA in patients with aortopathy. The pooled prevalence of IA in patients with bicuspid aortic valve, coarctation of the aorta, aortic aneurysm, and aortic dissection was 8% (95% CI, 6% to 10%), 10% (95% CI, 7% to 14%), 12% (95% CI, 9% to 15%), and 23% (95% CI, 12% to 34%), respectively. Gender (female) and smoking are risk factors related to an increased risk of IA. The anatomical distribution of IAs was heterogeneously between participants with different aortic disease.

Conclusions According to current epidemiological evidence, the prevalence of IA in patients with aortic disease is quadrupled compared to that in the general population, which suggests that an early IA screening should be considered among patients with aortic disease for timely diagnosis and treatment of IA.

Keywords Intracranial aneurysm; Aortic diseases; Prevalence; Meta-analysis

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Introduction

The worldwide prevalence of intracranial aneurysm (IA) in the general population is around 3.2%, and the rupture of IA causes subarachnoid hemorrhage, which is life-threatening and mostly attacks relatively young adults.[1] Since most IAs are asymptomatic and concealed, identifying IAs remains arduous, however, indispensable. Due to the advancing availability and quality of brain imaging techniques (e.g., magnetic resonance imaging scanning), the early diagnosis of IA in adults is promising,[2] especially in high-risk patients with selected conditions.[3]

The guidelines for unruptured IAs[4] indicate a higher prevalence of IA in patients with bicuspid aortic valve (BAV) or coarctation of the aorta (CoA). A propositional screening is suggested among patients with either of the two diseases. Recent studies[3,5-8] propose that aortic aneurysm and aortic dissection are also involved with an increased risk of IA. BAV, CoA, aortic aneurysm, and aortic dissection are four aortic diseases which attack aortic valve or segmentation of the aorta with distinct pathological manifestations. Aortic disease and IA are vascular disorders which share similar pathophysiologic mechanism, however, in the disparate area of the cardiovascular system. Both genetic factors and excessive hemodynamic stress caused by hypertension may play an essential role in the pathogenesis of the two diseases.[3] According to previous epidemiological studies,[3,5-13] the disease status of aortopathy might be used to predict the presence of IA.

The relation between IA and aortopathy was revealing, and the prevalence of IA in patients with aortopathy could direct population screening of IA. However, no review had systematically summarized this material. In the present systematic review, our primary goal was to report on an estimated prevalence of IA in patients struggled with aortopathy or different aortic disease (BAV, CoA, aortic aneurysm, and aortic dissection). We wanted to find whether age, gender, and cardiovascular risk factors affect the overall prevalence. Additionally, the anatomical distribution of IAs between different groups of aortic disease was analyzed in this research. The secondary aim was to discuss the presence of aortic disease in patients suffered from IA.

Methods

Search strategy

Results of this systematic review and meta-analysis were reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines (Supplementary Material).[14] We systematically searched PubMed and Scopus to identify studies on the prevalence of IA in patients with aortopathy or the presence of aortic disease in people who suffered from IAs published before August 2019. A combination of keywords was used to grab eligible studies: aorta, aortic dissection, aortic aneurysm, aortic dilatation, CoA, BAV aortopathy, and IA. Searching terms were listed in the Supplementary Material. We did not set any other limitation in this search strategy. References of included studies were manually checked to prevent the omission of eligible research.

Study selection

Two collaborators (X.Y. and L.X.) individually screened the studies from two databases for eligibility according to predefined selection criteria: cohort study, case-control study, and cross-sectional study reported an accurate prevalence of IA in patients with aortic disease; indicated a prevalence of aortic disease in patients suffered from IA. In studies evaluating the prevalence of IA, study population should be patients with brain imaging to avoid the omission of cases. Titles and abstracts from database research were examined and ineligible studies were refused. Full texts of remaining publications were carefully reviewed subsequently. We excluded studies on a specific population (e.g., children). Disagreements were solved in a discussion with a senior author (S.C.).

Data extraction

Two investigators (X.Y. and L.X.) independently extracted data on authors, published year, study country, study design (cohort, case-control, or cross-sectional), event (IA or aortic aneurysm), diagnostic criteria (for IA and aortic diseases), number of events, number of participants from included articles. To investigate the effect of cardiovascular risk determinants on the overall prevalence, risk factors (e.g., gender, smoking) in each study were documented in details. We recorded age and the exact number of patients with or without dichotomous risk factor in two groups (patients with both aortopathy and IA; patients with aortopathy alone). In a previous study,[8] a differing anatomical distribution pattern of IA between subgroups of the aortic aneurysm was reported, and we tended to find whether this site-specific phenomenon exists between different kinds of aortic disease. We extracted the accurate location and size of IAs provided by original work. If prevalence from reports were adjusted by confounding factors, we grabbed primary data to reduce the heterogeneity between studies. Multiple reports in a single article were analyzed separately. A consensus could be reached through group discussion. If the definite number of events/participants was not provided in eligible studies, we tried to contact authors for more information.

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Yu et al.   Intracranial Aneurysm and Aortic Diseases

Definitions

We included BAV, CoA, aortic aneurysm, and aortic dissection as aortopathy (aortic disease) in this literature. BAV was an inherited form of heart disease, but there remained a notable association between BAV and aorta, and we considered BAV an aortic disease in our research. To analyze the site-specific distribution pattern of IA in patients with different aortopathy, IAs were divided into three groups according to their anatomical locations: intracranial internal carotid artery (ICA), anterior choroidal artery, superior hypophyseal artery, and ophthalmic artery (ICA-IA); anterior circulation excluding the ICA, comprising anterior cerebral, anterior communicating, and middle cerebral arteries (anterior circulation-IA [Ant-IA]); and posterior circulation consisted of arteries not included in the ICA-IA or Ant-IA group (Post-IA).[8] This classification for IAs was originally used by Shin et al.[8]

Quality appraisal

The methodological quality of included studies (cross-sectional studies) was evaluated using a modified Newcastle-Ottawa scale developed by Fralick et al.[15] The modified scale covered three perspectives (participant selection; comparability; assessment of outcome) of methodology. Two investigators (X.Y. and L.X.) independently assessed the methodological quality. All results were reviewed by a third investigator (S.C.) with disagreements being resolved through consensus. We did not set any eligibility restrictions on the quality assessment score for the studies that fulfilled inclusion criteria.

Statistical analysis

Three studies reported a prevalence of aortic disease in IA population, and we qualitatively described the result on this issue. The main outcome was a pooled prevalence of IA in patients with aortopathy. The meta-analysis for overall prevalence was conducted in Stata version 14.0 (StataCorp., College Station, TX, USA) and forest plot was prepared in R version 3.6.1 using the forestplot packages (R Foundation for Statistical Computing, Vienna, Austria). Study heterogeneity was fully assessed by the I^2 statistic (0% to 100%) describing the proportion of total variation. Little heterogeneity was defined as $I^2<25\%$, moderate heterogeneity was $25\%<I^2<50\%$, and $I^2>50\%$ stands for a substantial heterogeneity. We expected heterogeneity in the methodology of included studies, hence the meta-analysis was based on a random-effect model. We used the data of participants/events extracted from original articles to calculate prevalence and corresponding 95% confidence interval (CI). Meta-analysis was performed in predefined subgroups of aortopathy (BAV, CoA, aortic aneurysm, and aortic dissection). Publication bias was not detected for the limited number of studies in each subgroup. No sensitivity analysis was planned. We investigated risk factors that may influence the estimated prevalence of IA in patients suffered from aortopathy. All risk factors reported in at least three studies were included in pooled analyses using a random-effect model. Data of dichotomous risk factors were arranged in fourfold tables and odds ratios (ORs) were obtained through calculation. Continuous risk factors were raised as standardized mean differences by Stata version 14.0 and transformed to ORs according to the formula developed in the Cochrane handbook version 5.1.0.[16] We calculated the OR of risk factors on the platform of IBM SPSS Statistics version 24 (IBM Co., Armonk, NY, USA). Primary ORs were pooled on the platform of Stata 14.0, and the final result was displayed in a forest plot produced by R. Continuous variables were compared in analyses of variance or unpaired Student's t-test. All *P*-values were two tails, and *P*-values <0.05 were considered significant.

The present work is a systematic review with meta-analyses of published studies, and data were collected from published materials, and thus ethical approval was not necessary for this article.

Data availability

All extracted data could be made available upon request from qualified investigators to corresponding authors.
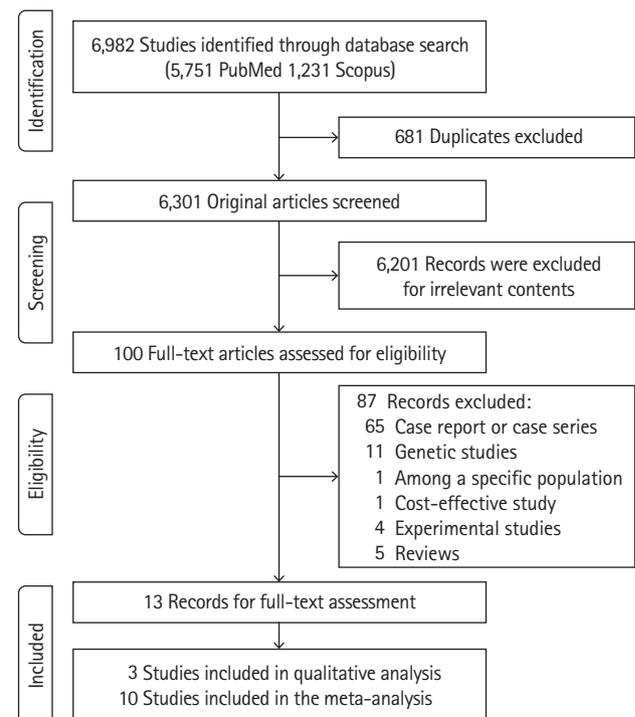
Figure 1. Study screening flow diagram.

Results

Literature search

Figure 1 showed the flow diagram for search strategy and selection procedure of this systematic review. The primary database search yielded 6,982 articles. After removal of duplicates, 6,301 researches were identified and their titles/abstracts were manually retrieved for further evaluation. Of 100 studies considered for eligibility, 13 records were included in the full-text assessment. In the process of screening, one study was conducted in children (mean age 16) with CoA,[17] and we excluded this article for the specific study population, and we also excluded a cohort study in which not all participants were patients with brain imaging.[18] After an inter-observer agreement between reviewers for study inclusion, three studies considering the prevalence of aortic disease in patients with IA were included in qualitative analysis, and a total of ten studies were included in the meta-analysis which reported an estimated prevalence of IA among patients with aortopathy.

Study characteristics

Overall, 13 cross-sectional studies were included in this systematic review (Table 1). Three studies investigated the proportion of patients with aortic aneurysm or BAV in patients suffered from IA.[19-21] Ten studies reported a prevalence of IA in patients with aortopathy: two studies were in patients with BAV;[10,13] three studies considered patients with CoA;[9,11,12] three studies were conducted in patients with aortic aneurysm;[5,7,8] one study investigated aortic dissection;[3] and one study examined both aortic aneurysm and aortic dissection.[6] Seven studies were from the USA, and three studies from South Korea. One study was from Japan, and one study from the UK, and one study from Finland. Of the total 4,041 participants, 1,261 patients were suffered from IA and 3,193 were patients struggled with the aortic disease. IAs were diagnosed by computed tomography angiography, magnetic resonance angiography (MRA) or digital subtraction angiography, and aortic diseases were identified by echocardiography, computed tomography, and MRA. Quality assessment of included studies was displayed in Supplementary Table 1, and overall study quality was moderate (6 to 7 points). We did not exclude any study on the basis of the quality assessment.

Quantitative synthesis

Meta-analysis for the prevalence of intracranial aneurysm in patients with different aortic disease
The meta-analysis of the overall prevalence comprised data of 3,132 patients with four kinds of aortopathy (Figure 2). Based on 10 studies, the pooled analysis reported an estimated prevalence of 12% (95% CI, 9% to 14%; I^2=64.3%) of IA in patients with aortopathy. In the classification of aortic diseases, the pooled prevalence of IA was 8% (95% CI, 6% to 10%; I^2=0.0%) in patients with BAV, 10% (95% CI, 7% to 14%; I^2=0.0%) in participants with CoA, 12% (95% CI, 9% to 15%; I^2=62.7%) in patients suffered from aortic aneurysm, and 23% (95% CI, 12% to 34%; I^2=27.5%) in patients who had a dissection of aorta.

Risk factors
Seven risk factors (Supplementary Figures 1-7) were reported in three or more studies: female gender,[3,6,7,9-13] smoking,[3,6,7,10-13] hypertension,[3,6,7,10-13] age,[6,9,11,13] diabetes,[3,6,7,13] hyperlipidemia,[3,6,7] and the overlapping of two aortic diseases.[7,9,11-13] Pooled analyses yielded effect estimates for the effect of risk factors on the increased prevalence of IAs (Figure 3). Female gender (pooled OR, 1.86; 95% CI, 1.33 to 2.60) and smoking (pooled OR, 1.38; 95% CI, 1.04 to 1.83) were associated with an increased risk of IAs.

Site-specific relationships of intracranial aneurysm with different aortic disease
No significant difference was found in the mean size of IAs between subgroups of aortic disease (P=0.217) (Table 2). However, the anatomical distribution of IAs was heterogeneous between patients with different aortic disorders (Table 2). The Ant-IAs distributed evenly among four groups (0.4 to 0.5 per person), but the distribution of ICA-IAs and Post-IAs were statistically different between patients with different aortic diseases (P<0.001 and P=0.014). ICA-IAs were reported most frequently in patients with aortic aneurysm (0.6 per person), and least frequently in patients with CoA (0.1 per person). The frequency of Post-IAs was highest in the group with CoA (0.4 per person) and least in the group with BAV or aortic aneurysm (0.2 per person).

Heterogeneity
Heterogeneity obtained in the analyses for prevalence and risk factors was not obvious. The prevalence reported by Lee et al.[6] was slightly higher, and this might be associated with a specific methodology of the study, which could induce a significant heterogeneity in the meta-analysis for overall prevalence. Since age was a continuous factor and the population was not strictly limited at included studies, the pooled analysis for age showed substantial heterogeneity (I^2=88.3%).

Table 1. Characteristics of included studies

Study	Country	Study design	Population	Event	Diagnostic criteria for the population	Diagnostic method for the event	No. of participants	No. of patients with the event	No. with event (%)
Miyazawa et al. (2007)[20]	Japan	Cross-sectional	Patients with IAs	AAA	MRA and/or conventional angiography	Ultrasonography followed by either MRA or CT	181	13	7.2
Goyal et al. (2015)[19]	USA	Cross-sectional	Patients treated for IAs	BAV and TAA	NA	Echocardiography, chest CT	317	BAV: 2 TAA:15	BAV: 0.6 TAA: 4.7
Laukka et al. (2019)[21]	Finland	Cross-sectional	Patients with IAs	TAA	DSA	CTA, MRI, and unenhanced CT	411	31	7.5
Connolly et al. (2003)[11]	USA	Cross-sectional	Patients with a history of CoA	IAs	NA	MRA	100	10	10.0
Cook et al. (2013)[9]	USA	Cross-sectional	Patients ≥18 years old with CoA	IAs	NA	CTA	43	5	11.6
Curtis et al. (2012)[12]	UK	Cross-sectional	Patients older than 16 years of age with CoA undergoing MRA of intracranial arteries	IAs	NA	MRA	117	12	10.3
Egbe et al. (2017)[13]	USA	Cross-sectional	Patients ≥18 years old with BAV who underwent intracranial MRA	IAs	Echocardiography	MRA	678	52	7.7
Schievink et al. (2010)[10]	USA	Cross-sectional	Patients with BAV	IAs	Echocardiography, MRI or open surgery	MRA or CTA	61	6	9.8
Rouchaud et al. (2016)[7]	USA	Cross-sectional	Patients ≥18 years old who had an AA and cerebral arterial imaging	IAs	NA	CTA, MRA, or DSA	1,081	128	11.8
Shin et al. (2015)[8]	South Korea	Cross-sectional	Patients ≥18 years old presenting with AA and cerebral arterial imaging	IAs	NA	CTA or MRA	611	71	11.6
Kuzmik et al. (2010)[5]	USA	Cross-sectional	Patients with TAA and high-quality intracranial images	IAs	NA	CTA or MRA	212	19	9.0
Jung et al. (2017)[3]	South Korea	Cross-sectional	Patients with AD and intracranial images	IAs	CTA	CTA or MRA	71	14	19.7
Lee et al. (2017)[6]	South Korea	Cross-sectional	Patients with AD or AA	IAs	Extended aorta CTA	CTA, MRA, or DSA	158	35	22.2

IA, intracranial aneurysm; AAA, abdominal aortic aneurysm; MRA, magnetic resonance angiography; CT, computed tomography; BAV, bicuspid aortic valve; TAA, thoracic aortic aneurysm; NA, not available; DSA, digital subtraction angiography; CTA, computed tomography angiography; MRI, magnetic resonance imaging; CoA, coarctation of the aorta; AA, aortic aneurysm; AD, aortic dissection.
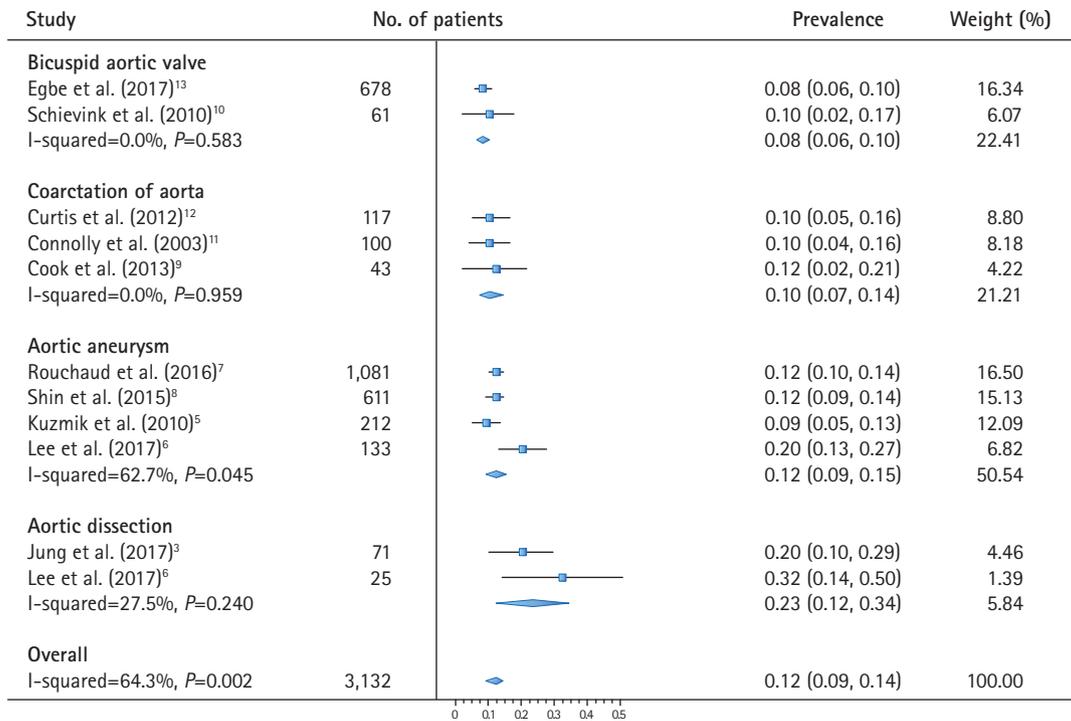
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Yu et al.   Intracranial Aneurysm and Aortic Diseases

Figure 2. Meta-analysis for the prevalence of intracranial aneurysm in patients with aortopathy.
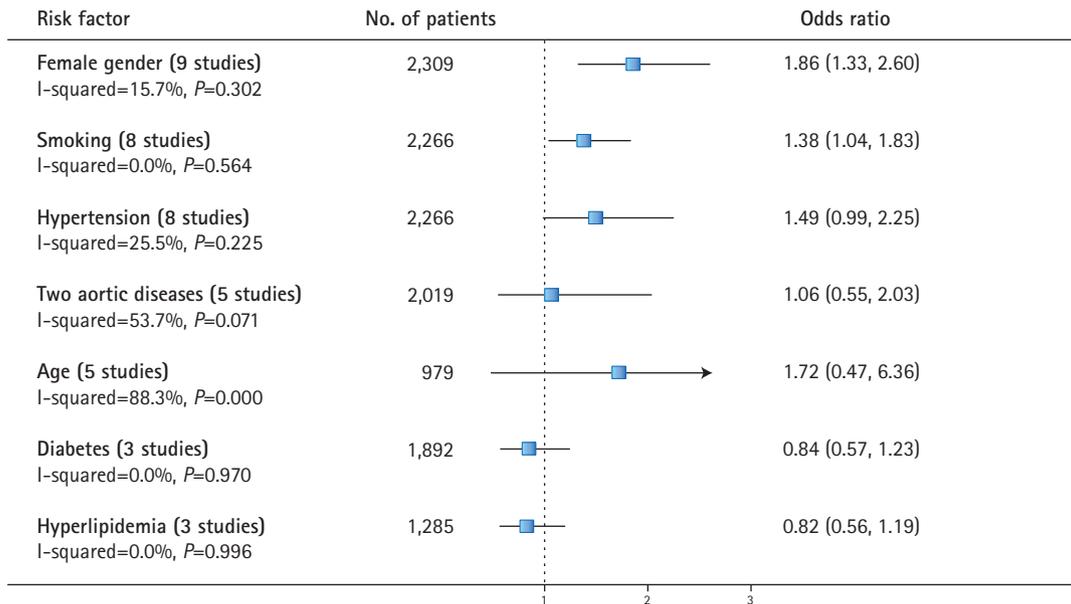

Figure 3. Risk factors for the presence of intracranial aneurysms in patients with aortic diseases.

Qualitative synthesis

Of three included studies, Goyal et al.[19] indicated that the prevalence of BAV and thoracic aortic aneurysm in IA patients were 0.6%, 4.7% respectively. Miyazawa et al.[20] reported a prevalence of 7.2% of abdominal aortic aneurysm in patients with IA. Laukka et al.[21] showed a higher prevalence of thoracic aortic aneurysm (7.5%) in IA patients compared to the general population. Three studies suggested several risk factors (e.g., age and smoking) for this association, but we could not further analyze these factors due to the limited data.

Discussion

Overall, this article suggests that around 12% of patients with

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Yu et al.   Intracranial Aneurysm and Aortic Diseases

Table 2. Location and size of intracranial aneurysm in populations with different aortic disease

| Variable | Total* (n=351) | BAV (n=58) | CoA (n=26) | AD (n=22) | AA | | | P‡ |
					Total† (n=245)	TAA (n=88)	AAA (n=87)	
No. of studies	10	2	3	2	4	4	3	
Size of IA (mm)	5.43±5.01	3.57±1.76	3.78±1.62	5.56±3.47	5.68±5.43	5.82±5.85	5.4±4.4	0.217
No. of IA	431 (1.23)	66 (1.1)	27 (1.0)	22 (1.0)	316 (1.3)	113 (1.3)	110 (1.3)	<0.001
Location of IA								
Ant-IA	163 (0.5)	26 (0.4)	13 (0.5)	10 (0.5)	114 (0.5)	47 (0.5)	34 (0.4)	0.978
ACA	45	9	4	3	29	11	7	
ACoA	35	6	2	0	27	15	9	
MCA	93	11	7	7	58	21	18	
ICA-IA	193 (0.5)	26 (0.4)	3 (0.1)	5 (0.2)	159 (0.6)	51 (0.6)	63 (0.7)	<0.001
ICA	179	15	3	5	156	51	61	
AChoA	8	6	0	0	2	0	1	
SHA	1	0	0	0	1	0	1	
OA	5	5	0	0	0	0	0	
Post-IA	75 (0.2)	14 (0.2)	11 (0.4)	7 (0.3)	43 (0.2)	15 (0.2)	13 (0.1)	0.014
PCoA	7	2	3	0	2	1	0	
PCA	16	7	2	0	7	4	1	
SCA	7	4	2	0	1	0	0	
PICA	9	1	1	0	7	2	1	
VA/BA	36	0	3	7	26	8	11	
Proportions of IA								
Ant-IA (%)	37.8	39.4	48.1	45.5	36.1	41.6	30.9	
ICA-IA (%)	44.8	39.4	11.1	22.7	50.3	45.1	57.3	
Post-IA (%)	17.4	21.2	40.8	31.8	13.6	13.3	11.8	

Values are presented as mean±standard deviation or number (number of intracranial aneurysm per person).
BAV, bicuspid aortic valve; CoA, coarctation of the aorta; AD, aortic dissection; AA, aortic aneurysm; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; IA, intracranial aneurysm; Ant-IA, IA in anterior circulation arteries after bifurcation of the internal carotid artery; ACA, anterior cerebral artery; ACoA, anterior communicating artery; MCA, middle cerebral artery; ICA-IA, IA in internal carotid artery and branches except for Ant-IA; ICA, internal carotid artery; AChoA, anterior choroidal artery; SHA, superior hypophyseal artery; OA, ophthalmic artery; Post-IA, IA in posterior circulation artery; PCoA, posterior communicating artery; PCA, posterior cerebral artery; SCA, superior cerebellar artery; PICA, posterior inferior communicating artery; VA, vertebral artery; BA, basilar artery.
*A combination of bicuspid aortic valve, coarctation of the aorta, aortic aneurysm and aortic dissection; †Abdominal aortic aneurysm and thoracic aortic aneurysm. In several researches, the data of subtypes of aortic aneurysm was not fully provided; ‡P-value for analysis of variance between four aortic diseases of the number of IAs per person.

aortopathy (BAV, CoA, aortic aneurysm, and aortic dissection) suffered from IAs, which is approximately four times that of the general population (3.2%).[1] The prevalence of IA for aortic dissection group is probably twice the prevalence in patients with aortopathy. Gender (female) and smoking are two risk factors related to an increased risk of IAs. Furthermore, a site-specific relationship between different aortic disease and the anatomical location of IAs is mapped.

Potential mechanism

There are several mechanisms for the coexistence of IAs and aortic diseases. The abnormality of cells derived from the neural crest could explain the association between IA and aortopa-thy.[10] The neural crest cells are a group of transient and multi-potent cells in early embryogenesis which is induced to migrate and give rise to several cell lineages. The tunica media of the aortic arch and its branches, including the cervicocephalic arteries are composed of cells derived from neural crest, and the abnormal development of the neural crest cells may result in vascular fragility, and this could cause simultaneous IAs and aortic diseases.[10,22-25]

Furthermore, the genetic relation of IA and aortopathy has been examined in researches.[26-34] Multiple types of gene mutation play a critical role in this relationship: single nucleotide polymorphisms,[27,35] frameshift mutations in exons,[28] and trans-locations of chromosome,[29] which demonstrates that the gene-

related association between IA and aortopathy is rather complicated. In particular, patients with connective tissue diseases such as Loeys-Dietz syndrome, Marfan syndrome, Ehlers-Danlos syndrome, and neurofibromatosis type 1 are thought to be at a higher risk for IAs and aortopathy.[36,37] The widely accepted causal explanation of this relationship is that the genetic mutations in such connective tissue disorders affect the collagen and proteoglycans in extracellular matrix, thus leading to the weakening of the vascular wall.[37]

Acquired risk factors could also increase the risk of IA and aortic disorders. The dominant environmental risk factors for aneurysms include age, gender, smoking, alcohol, and hypertension.[35,38] Hypertension is a known risk factor for the development of IA,[35] aortic aneurysm,[39] and aortic dissection.[40] Blood flow or blood pressure is an important modulator of arterial growth. Wall shear stress is strictly regulated in bodies, with the normal artery enlarging in response to increases in blood flow to maintain normal shear stress.[35] However, high blood pressure in patients with hypertension could significantly affect the shear stress, which could lead to an abnormal expansion of blood vessels.

Prevalence of IA

The pooled prevalence of IA among patients with distinct aortic disease in this research is similar to that of previous observational study.[3,5-13] The estimated prevalence of IA for patients with aortic dissection (23%; 95% CI, 12% to 34%) is much higher compared with that in groups suffered from other aortic diseases. Study quality is moderate and heterogeneity source could be identified through subgroup analysis. The heterogeneity within or between subgroups is limited, which indicates that the relationship between IA and aortopathy is robust regardless of the type of aortopathy. The overall estimated prevalence of IA is around 12% in patients with aortopathy, which is quadrupled compared to that of the general population, and the prevalence of IA in patients suffered from BAV, CoA, aortic aneurysm, aortic dissection is 8%, 10%, 12%, and 23% respectively. BAV and CoA are congenital diseases, and aortic aneurysm or dissection could be induced by acquired factors, and the prevalence of aortic aneurysm or dissection is higher, which indicates that hemodynamic or environmental factors play an essential role in the pathogenesis of IA and aortopathy. The result emphasizes that IA screenings could be conducted among patients with aortic diseases, especially patients with a dissection of the aorta. Importantly, the cost for population screening for IA is considerable, and a cost-effective study in this field is required.

In the surgical intervention of aortopathy, patients could suddenly die for a nubilous reason, and this might be associated with IA or other cerebrovascular accidents. Our findings should be relevant for neurologists, cardiac surgeons, patients with aortopathy and policymakers.

Risk factors

In this research, the effect of gender, age, smoking, hypertension, diabetes, hyperlipidemia, and the overlapping with two aortic diseases on the prevalence of IA in aortopathy sufferers are quantitatively analyzed (Figure 3). Gender (female) and smoking could be risk factors for IAs among patients with aortic diseases. However, study numbers and sample sizes in pooled analyses for risk factors are small (Figure 3), and it could somewhat reduce the statistical power of analyses. Thus, large observational studies are needed to identify precise risk factors for IAs among patients with aortopathy. Priority should be given to patients with special risk factors in population screening for IAs.

Site–specific distribution of IA

A site-specific distribution pattern of IA between groups with different aortopathy is observed in the review. The anatomical distribution of IAs differed significantly in patients with distinct aortic disease. Despite a heterogeneous frequency of ICA-IA and Post-IA among different groups, the frequency of Ant-IA is confoundedly stable among patients suffered from distinct aortopathy. Additionally, the frequency of Ant-IA is the largest in three predefined IA groups. Genetic risk factors are suggested to have a larger role of IA at the middle cerebral artery (contained in Ant-IA) than at other sites of the cerebrovascular system.[41] Consistently, genetic factors are critical in the development of BAV, CoA, aortic aneurysm, and aortic dissection.[42-45] The result suggests a shared pathological mechanism between IA and aortopathy.[8] The stable distribution of Ant-IA might suggest that the connection between aortopathy and IA is strongly associated with the human gene. Distinct allocation of IAs in ICA-IA and Post-IA could accompany with exclusive pathological features of aortic diseases, and this issue should be further explored. We expect subtypes of aortic aneurysm, and we analyze the site of IA in thoracic aortic aneurysm and abdominal aortic aneurysm separately. However, the margin between two groups was not statistically significant, which is inconsistent with a previous study.[8] Shin et al.[8] deliver a differing distribution patterns of IA among subgroups of aortic aneurysm (ascending aneurysm, descending thoracic-suprarenal aneurysms, and infrarenal aneurysm) with 71 participants. We consider the study population is too small to confirm the relationship, and different classifications could somewhat af-

JoS

Yu et al.   Intracranial Aneurysm and Aortic Diseases

fect the result. It is known that genes in the pathogenesis of IA and thoracic aortic aneurysm are closely related, and the pathogenesis of abdominal aortic aneurysm is tended to be more atherosclerotic, but both thoracic aortic aneurysm and abdominal aortic aneurysm affected by hemodynamic and environmental factors. This could explain why the site distribution of IA in two groups is not totally different. Since the sample size of the site-specific analysis is still small, future work is needed on this issue to further test the relationship.

Prevalence of aortopathy

The qualitative part of this review analyzes the presence of aortic disease in patients with IA. Reports from included studies[18-20] lack credible controls that could provide a reliable overall incidence/prevalence of aortic disease in the general population. Unlike IAs, aortic diseases get considerable symptoms and multiple diagnostic methods, and usually it is easier to diagnose aortic disease than IA. However, as increasing small IAs are found incidentally on neuroimaging, a substantial group of patients with IAs may benefit from screening for aortic vascular pathology.

Strengths and limitations

To the best of our knowledge, this study is the first comprehensive systematic review of the relationship between IA and aortopathy. We focus on the impact of cardiovascular risk factors on the overall prevalence, and the result indicates that the presence of aortopathy could be a predictor of IA. The specific distribution pattern of IAs in distinct aortic disease is also mapped in this research. The current review has several limitations. The methodological differences (e.g., diagnostic methods for events) in the original studies lead to inevitable heterogeneity. Although we include 10 studies to quantify the prevalence and the effect of risk factors on the prevalence, the small sample size could somewhat reduce the statistical power and increase the error of statistical analyses. Other risk factors (e.g., alcohol, history of stroke) are also reported, but we are incapable of evaluating these factors due to the limited studies. Complete records of the number and anatomical location for IA in single participants are not fully provided, we are unable to assess the association between different aortopathy and the number of IAs in individuals.

Conclusions

Overall, the present systematic review indicates that the prevalence of IA in patients suffered from aortic disease is quadrupled compared to that in the general population. Gender (female)

and smoking are associated with an increased risk of IA among patients with aortic disease. A heterogeneous distribution pattern of IAs exists among patients with different aortic disease. Since the definite mechanism how aortopathy interact with IA is still unclear, genetic work and biological experiments on this issue are needed. A worldwide epidemiological study, however, with effective controls and large sample size, is also required in this field to produce a credible and conclusive result.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2019.01312.

Disclosure

The authors have no financial conflicts of interest.

Acknowledgments

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Supplementary Material

Search strategy

(1) Pubmed

(aorta OR aortic dissection OR aortic aneurysm OR aortic dilatation OR coarctation of the aorta OR aortic coarctation OR bicuspid aortic valve OR aortopathy) AND (intracranial aneurysm OR brain aneurysm OR cerebral aneurysm)

(2) Scopus

(TITLE-ABS-KEY (aorta) OR TITLE-ABS-KEY (aortic AND dissection) OR TITLE-ABS-KEY (aortic AND aneurysm) OR TITLE-ABS-KEY (aortic AND dilatation) OR TITLE-ABS-KEY (coarctation AND of AND the AND aorta) OR TITLE-ABS-KEY (aortic AND coarctation) OR TITLE-ABS-KEY (bicuspid AND aortic AND valve) OR TITLE-ABS-KEY (aortopathy) AND TITLE-ABS-KEY (intracranial AND aneurysm)

PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4–5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NR
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4–5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4–5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4–5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4–5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5–6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6

| Section/topic	#	Checklist item	Reported on page #
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7–8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8–9, Figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8–9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9, Figures 2-4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8–9, Figures 2-4
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

Adapted from Moher et al.[14] For more information, visit: www.prisma-statement.org.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NR, not reported.

Supplementary Table 1. Modified Newcastle-Ottawa scale for assessing the quality of included studies

Study	Study design	Selection (max=4)				Comparability (max=2)	Outcome (max=3)		Total score (max=9)
		Representa-tive sample	Sample size ade-quate	Non-re-spondents	Ascertain-ment of exposure	Based on design or analysis	Assessment of outcome	Statistical test	
Miyazawa et al. (2007)[20]	Cross-sectional	☺	☺	-	☺	☺☺	☺	☺	7
Goyal et al. (2015)[19]	Cross-sectional	☺	☺	-	☺	☺	☺	☺	6
Laukka et al. (2019)[21]	Cross-sectional	☺	☺		☺	☺☺	☺	☺	7
Connolly et al. (2003)[11]	Cross-sectional	☺	☺	☺	☺	☺	☺	☺	7
Cook et al. (2013)[9]	Cross-sectional	☺	☺	-	☺	☺	☺	☺	6
Curtis et al. (2012)[12]	Cross-sectional	☺	☺	-	☺	☺☺	☺	☺	7
Egbe et al. (2017)[13]	Cross-sectional	☺	☺	-	☺	☺☺	☺	☺	7
Jung et al. (2017)[3]	Cross-sectional	☺	☺	-	☺	☺	☺	☺	6
Kuzmik et al. (2010)[5]	Cross-sectional	☺	☺	-	☺	☺	☺	☺	6
Lee et al. (2017)[6]	Cross-sectional	☺	☺	-	☺	☺	☺	☺	6
Rouchaud et al. (2016)[7]	Cross-sectional	☺	☺	-	☺	☺	☺	☺	6
Schievink et al. (2010)[10]	Cross-sectional	☺	☺	-	☺	☺☺	☺	☺	7
Shin et al. (2015)[8]	Cross-sectional	☺	☺	-	☺	☺	☺	☺	6

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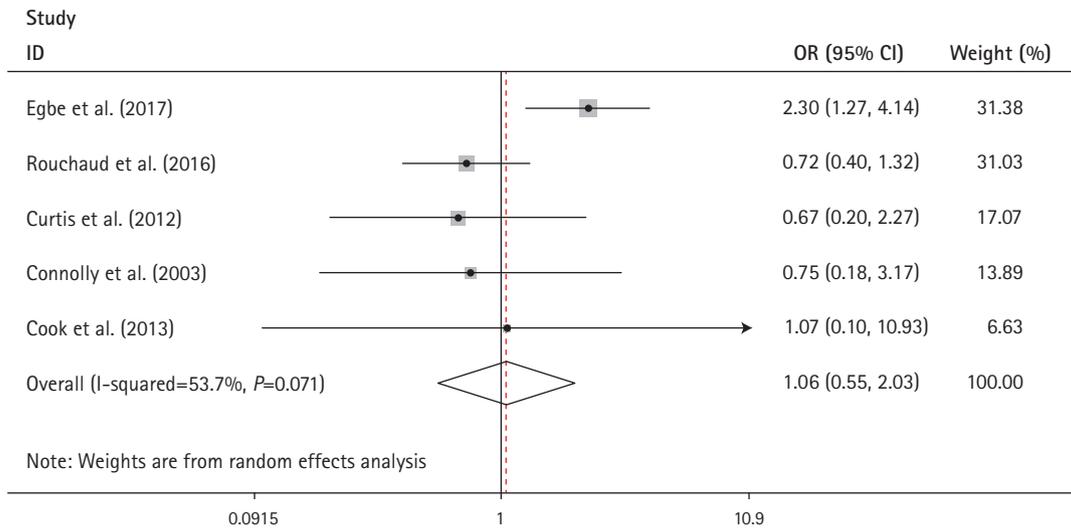Yu et al.   Intracranial Aneurysm and Aortic Diseases
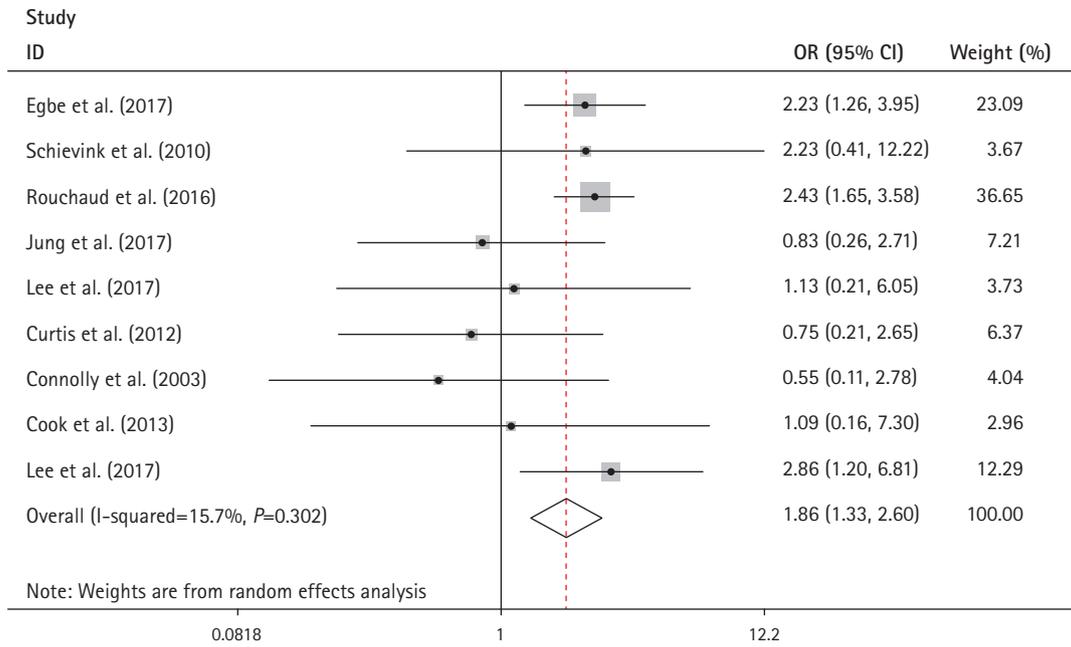
Supplementary Figure 1. Individual analysis of risk factors for the presence of intracranial aneurysms in patients with aortic diseases. Odds ratios (ORs) for female gender on the prevalence of intracranial aneurysm in patients suffered from aortic disease. CI, confidence interval.
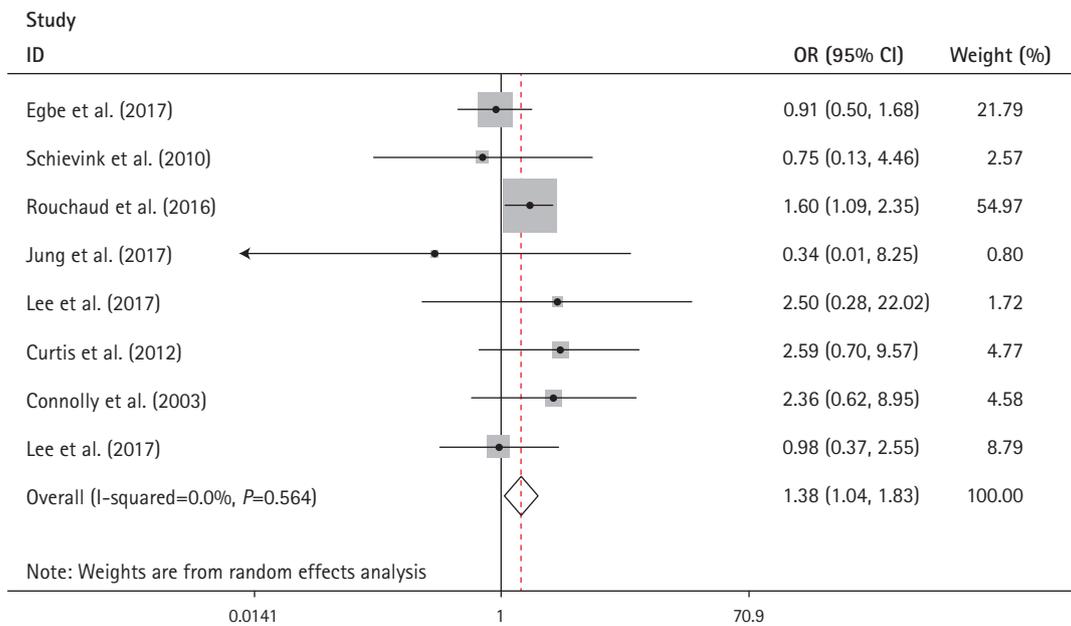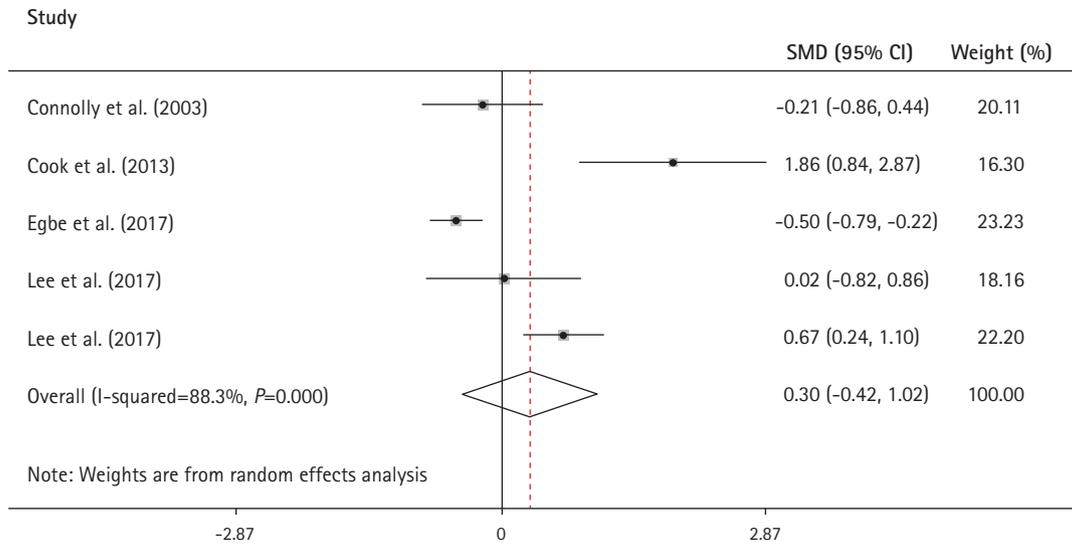

Supplementary Figure 2. Individual analysis of risk factors for the presence of intracranial aneurysms in patients with aortic diseases. Odds ratios (ORs) for smoking on the prevalence of intracranial aneurysm in patients suffered from aortic disease. CI, confidence interval.
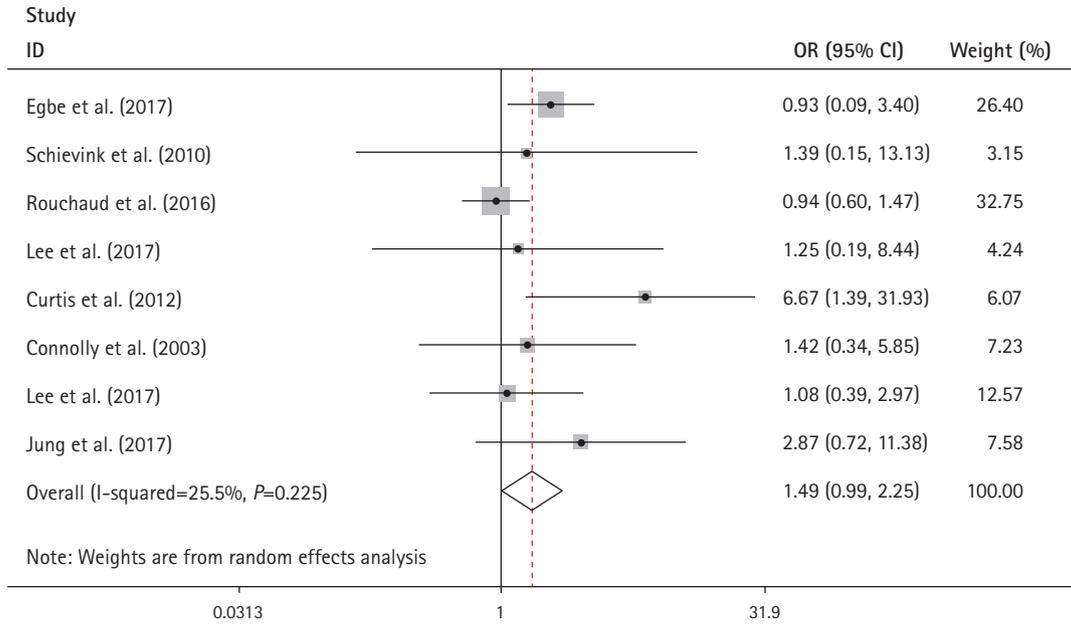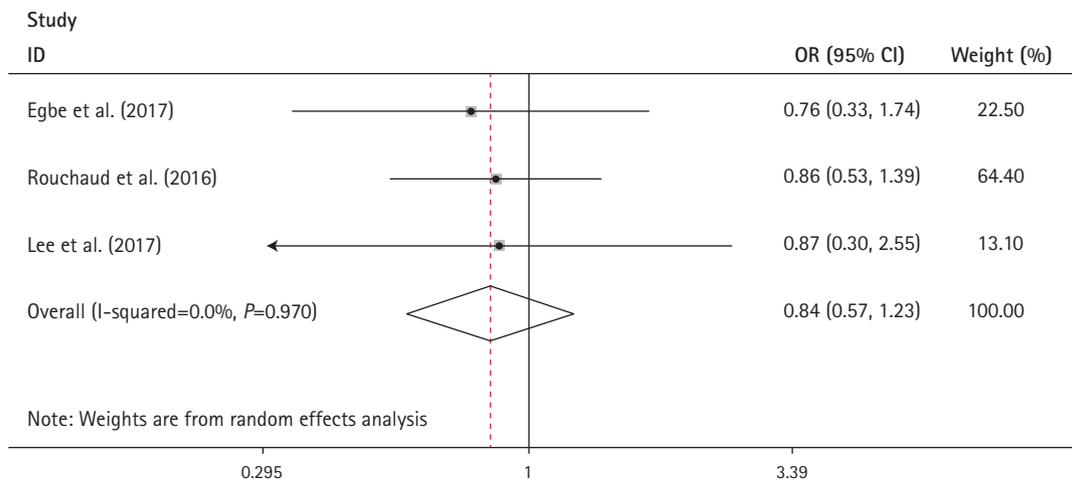
Supplementary Figure 3. Individual analysis of risk factors for the presence of intracranial aneurysms in patients with aortic diseases. Odds ratios (ORs) for hypertension on the prevalence of intracranial aneurysm in patients suffered from aortic disease. CI, confidence interval.
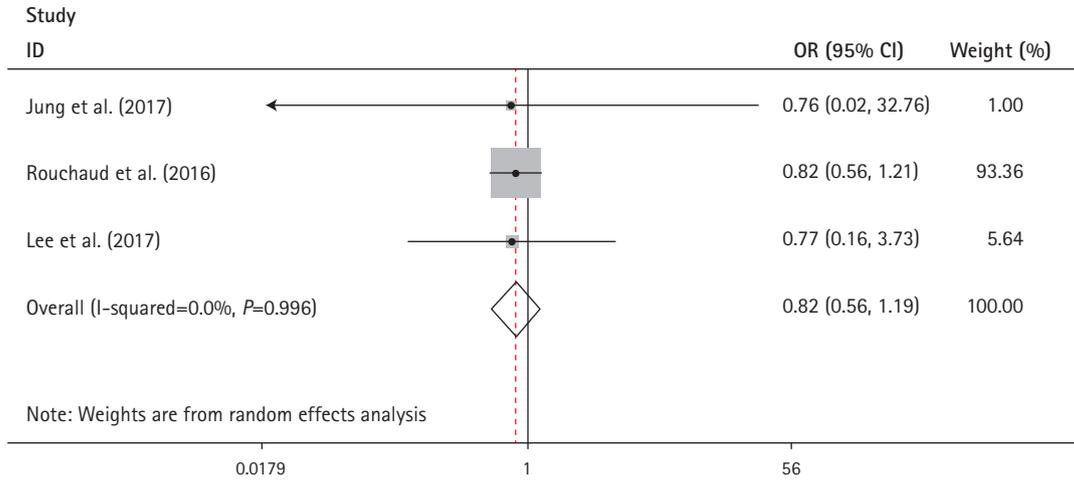

Supplementary Figure 4. Individual analysis of risk factors for the presence of intracranial aneurysms in patients with aortic diseases. Odds ratios (ORs) for the overlapping of two aortic diseases on the prevalence of intracranial aneurysm in patients suffered from aortic disease. CI, confidence interval.

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Yu et al. Intracranial Aneurysm and Aortic Diseases

Supplementary Figure 5. Individual analysis of risk factors for the presence of intracranial aneurysms in patients with aortic diseases. Standard mean difference (SMD) for age on the prevalence of intracranial aneurysm in patients suffered from aortic disease. CI, confidence interval.

Supplementary Figure 6. Individual analysis of risk factors for the presence of intracranial aneurysms in patients with aortic diseases. Odds ratios (ORs) for diabetes on the prevalence of intracranial aneurysm in patients suffered from aortic disease. CI, confidence interval.

Supplementary Figure 7. Individual analysis of risk factors for the presence of intracranial aneurysms in patients with aortic diseases. Odds ratios (ORs) for hyperlipidemia on the prevalence of intracranial aneurysm in patients suffered from aortic disease. CI, confidence interval.