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Review

A systematic review and meta-analysis of risk factors for unruptured intracranial aneurysm growth

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ABSTRACT

Background: Many risk factors are associated with the growth of unruptured intracranial aneurysm; however, the effects of these risk factors on intracranial aneurysm growth remain poorly understood. Here, we performed a meta-analysis to evaluate the effects of these risk factors on intracranial aneurysm growth, incorporating different data types to provide comprehensive estimates of individual effects.

Methods: We searched the Cochrane Library, PubMed, Embase, and Web of Science for cohort studies analyzing risk factors for aneurysm growth prior to January 10, 2019. The hazard ratio (HR) and odds ratio (OR) with its 95% confidence interval (CI) were calculated to assess the effect of individual risk factors on intracranial aneurysm growth. Both univariate analysis (UVA) and multivariate analysis (MVA) were performed. Two reviewers independently assessed the quality of the trials and the associated data. All statistical analyses were performed using standard statistical procedures provided in Review Manager 5.2.

Results: We included 23 studies (N = 7208 participants) in this meta-analysis. A total of 944 patients (13.1%) experienced intracranial aneurysm growth during their follow-up times. Aneurysm size and smoking may have significant effects on the growth of intracranial aneurysm, with pooled ORs of 2.73 (95% CI 2.21–3.36; $P < 0.00001$) and 1.45 (95% CI 1.07–1.98; $P = 0.02$) respectively. However, our results indicated that subarachnoid hemorrhage (SAH) had a negative effect on the growth of intracranial aneurysm (OR 0.64; 95% CI 0.48–0.86; $P = 0.003$). Other risk factors such as irregular shape of intracranial aneurysm, female sex, and multiple aneurysms were inconsistent across studies due to differences in data types and effect estimates.

Conclusions: Our meta-analysis identified aneurysm size and smoking as independent risk factors for the growth of intracranial aneurysm, while prior SAH had a negative effect on the growth of intracranial aneurysm. The roles of other risk factors for intracranial aneurysm growth were inconsistent, with further research necessary to assess fully the roles of these factors in disease outcomes.

1. Introduction

Unruptured intracranial aneurysms have become increasingly common and are an important health-care burden. Approximately 3% of the adult population has an unruptured intracranial aneurysm [1]. Cerebral aneurysms occur in 3%–5% of the general population and are characterized by localized structural deterioration of the arterial wall, with loss of the internal elastic lamina and disruption of the media. The most dreaded complication of cerebral aneurysms is rupture, the likelihood of which is related to several modifiable and nonmodifiable risk factors. Studies have indicated that the growth of a cerebral aneurysm was a strong risk factor for future rupture. As such, many clinicians recommend treating any aneurysm that has increased in size during the follow-up period.

Identification of an unruptured aneurysm offers an opportunity for preventive endovascular or microsurgical occlusion; however, both treatment methods carry risks of complications [2,3]. The risk of aneurysm growth itself may be associated with tobacco smoking and initial size. For small aneurysms, the risk of rupture is considered to be much lower than the risk of treatment complications, hence, the majority of these aneurysms are left untreated [2–4]. Because aneurysms tend to increase in size over time, and larger size is associated with higher risk of rupture, follow-up imaging to assess growth of aneurysms is recommended for aneurysms that are left untreated [5]. Moreover, growth may be a good surrogate marker for rupture in follow-up and treatment studies on unruptured intracranial aneurysms because risk

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prediction models for rupture also predict growth [6].

A large number of risk factors have been identified that may influence the growth of unruptured intracranial aneurysms [6–28], including hypertension, sex, age, previous subarachnoid hemorrhage (SAH), aneurysm size, arterial relationship, irregular shape, smoking, multiple aneurysms, and site. However, the effect of individual risk factors on intracranial aneurysm growth remains poorly understood. Backes et al. reported that most risk factors for aneurysm growth were consistent with risk factors for rupture [29]. Bjorkman et al. indicated that aneurysm size was the strongest risk factor for aneurysm growth in an Eastern Finnish population, though other factors were not found to be risk factors for intracranial aneurysm growth [8]. Here, we performed a meta-analysis to evaluate the effects of these risk factors on intracranial aneurysm growth, incorporating different data types to provide comprehensive estimates of individual effects.

2. Methods and materials

2.1. Inclusion and exclusion criteria

Inclusion criteria:

(1) Both prospective and retrospective studies;
(2) patients included in studies were imageologically diagnosed with unruptured intracranial aneurysm;
(3) studies reporting aneurysm growth as an outcome measure; and
(4) effect estimates for aneurysm growth were given or could be calculated.

Exclusion criteria:

(1) Non-human studies;
(2) articles classified as abstracts, letters, editorials, expert opinions, reviews, case reports or laboratory studies;
(3) studies on vascular malformations other than intracranial aneurysms;
(4) studies without sufficient data for analysis; and
(5) duplicate articles or data were excluded.

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

2.2. Search strategy

We searched the Cochrane Library, PubMed, Embase, and Web of Science for cohort studies analyzing risk factors for aneurysm growth prior to January 10, 2019. Our search terms and procedures were as follows: (1) “aneurysm*“; (2) “incidental” OR “unruptured”; (3) “intracranial” OR “cerebral” OR “brain” OR “intracerebral” OR “cranial”; (4) “grow*” OR “increase” OR “enlarge*” OR “develop*” OR “progress*“. The retrieval formula was as follows: (1) AND (2) AND (3) AND (4). All databases were searched in English using these terms. Two investigators who received normative and unitive training independently screened the titles and abstracts of each study after duplicate references were excluded. Following our initial screening, full texts were obtained for all studies with the potential to meet our minimum inclusion criteria.

2.3. Quality assessment and data extraction

Two assessors independently evaluated the quality of all included studies using the 9-star Newcastle-Ottawa Scale (NOS) [30]. The total NOS scores of each study are shown in Table 1. Studies were judged according to the three aspects of NOS evaluation: selection, comparability, and outcome between the case and control groups. A study with a NOS score ≥ 6 is considered good quality.

The same reviewers extracted all study data and effect estimates (odds ratio, relative risk, and hazard ratio) for risk factors for aneurysm growth; all disagreements were discussed, and a final decision agreed to by both reviewers. Other study-related outcomes, including publication year, sample size, country, study design, aneurysm growth (%), mean age (range/SD), mean aneurysm size (mm), definition of aneurysm growth, follow-up time (years), and imaging method were extracted using a standardized form (Table 1). All data were analyzed using RevMan 5.2 software [31].

2.4. Statistical analysis

In this meta-analysis, the impact of risk factors on the growth of unruptured intracranial aneurysm was measured by estimating the Hazard Ratio (HR), odds ratio (OR), and mean difference (MD) with its 95% confidence interval (CI). The heterogeneity among studies was evaluated by the chi-square-based Q statistical test [32]. $P_{heterogeneity}$ (P_h) ≤ 0.10 was deemed to represent significant heterogeneity, and pooled effect estimates were estimated using a random-effect model (the DerSimonian and Laird method [33]). For variables in which statistical heterogeneity was not observed ($P_h > 0.10$), a fixed effects model (the Mantel–Haenszel method [34]) was used. The effects of outcome measures were considered to be statistically significant if pooled effects with 95% CI did not overlap with 1.0 for HRs or ORs.

Both univariate and multivariate analyses were used to assess the impact of risk factors on the growth of unruptured intracranial aneurysm. For HR outcomes, we estimated risk factors including hypertension, age, previous SAH, aneurysm size, arterial relationship, irregular shape, female sex, multiplicity, smoking, and multiple aneurysms. For OR outcomes, estimated risk factors included age, current smoking, female sex, hypertension, prior SAH, and aneurysm size. For studies with dichotomous data, we compared MCA vs. ICA, ACA vs ICA, female vs. male, multiple vs. single, age, aneurysm size (mm), multiplicity, hypertension, diabetes mellitus, smoking, prior SAH, anterior artery, and irregular shape. Association between age and the growth of intracranial aneurysm were estimated using continuous variables.

Finally, publication bias was assessed by contour-enhanced funnel plots. If the shape of funnel plots revealed no obvious evidence of asymmetry, we considered that there was no obvious publication bias. All statistical analyses were performed using standard statistical procedures provided in Review Manager 5.2 [31].

3. Results

3.1. Retrieval of literature and study characteristics

The primary literature search revealed 2423 records, of which 570 were deemed duplicates. The remaining 1853 records were screened for possible inclusion based on titles and abstracts. From these studies, 1513 were excluded based on their titles and abstracts. Full texts were obtained for the remaining 340 studies, of which 317 were excluded (309 studies for wrong aims or insufficient data, seven for review articles, one for repeated data), yielding a final set of 23 studies covering 7208 participants [6–28]. Of these 23 studies, seven were designed as prospective trials and sixteen were retrospective trials. The sample size ranged from 32 to 1507 patients, with 17 studies consisting of sample sizes > 100 patients. A total of 944 patients (13.1%) experienced intracranial aneurysm growth during their respective follow-up periods. A detailed search process and summary of studies is shown in a study flow diagram (Fig. 1). Additional characteristics of each study are shown in Table 1.

Table 1
The characteristics of included studies for the present meta-analysis.

Study (author/year)	Country	Study design	Participants	Aneurysm Growth (%)	Mean age (range/ SD)	Mean Aneurysm Size (mm)	Definition of Aneurysm Growth	Follow-up time (years)	Imaging method	NOS score
Backes D et al., 2015	The Netherlands	Retrospective	557	86 (15%)	55 (18–84)	4.3 (1–33)	≥1-mm increase	3.4 (0.5–10.8)	CTA, DSA, autopsy	8
Burns JD et al., 2009	United States	Retrospective	165	17 (10%)	64 (13)	4.9 (2–18)	≥1-mm increase	4.6 (1.0–14.3)	MRA	7
Chien A et al., 2013	United States	Retrospective	235	34 (14%)	62 (14)	3.6 (1–7)	Overall change in size > 0.75 mm	2.4 (0.3–6.8)	CTA	8
Ferns SP et al., 2011	The Netherlands	Retrospective	32	3 (9%)	50 (35–68)	2.6 (1–7)	≥1-mm increase	4.7 (4.5–5.4)	MRA	7
Igase M et al., 2013	Japan	Prospective	200	21 (11%)	68 (31–91)	3.3 (2–10)	≥1-mm increase	2.0 (1.0–2.2)	MRA	7
Inoue T et al., 2012	Japan	Retrospective	1002	18 (2%)	65 (29–89)	NR	≥1.5 × increase of diameter	1.0 (0.4–1.9)	MRA	6
Jeon JS et al., 2014	South Korea	Retrospective	524	17 (3%)	59 (11)	3.6 (0.8)	≥1.5 × increase of aneurysm size	2.9 (1.5)	DSA, MRA	6
Juvela S et al., 2001	Finland	Retrospective	87	39 (45%)	38 (9)	5.1 (2–26)	≥1-mm increase	18.9 (1.2–38.9)	CTA, DSA, autopsy	8
Kubo Y et al., 2014	Japan	Prospective	79	8 (10%)	74 (3)	4.9 (2–15)	≥2-mm increase	3.2 (0.3–7.0)	CTA, MRA	5
Matsubara S et al., 2004	Japan	Retrospective	140	9 (6%)	63 (29–82)	4.1 (2–20)	≥0.5-mm increase	1.5 (0.3–7.0)	CTA	7
Matsumoto K et al., 2013	Japan	Retrospective	111	13 (12%)	65 (11)	4.9	≥1-mm increase	3.5 (0.3–7.0)	MRA	6
Mehan WA Jr et al., 2014	United States	Retrospective	146	4 (3%)	62	5.4 (2–35)	≥2-mm increase	3.4 (1.0–9.3)	CTA	8
Miyazawa N et al., 2006	Japan	Retrospective	130	14 (11%)	69 (9)	4.2 (2–22)	≥2-mm increase	2.4 (0.8–5.8)	MRA	7
So TY et al., 2010	Australia	Retrospective	208	95 (45.7%)	51 (14–81)	4.0 (2–24)	NR	1.8 (0.1–11.4)	Angiographic film	7
Sonobe M et al., 2010	Japan	Prospective	374	25 (7%)	62 (23–89)	3.3 (1–5)	NR	3.5 (0.5–7.0)	CTA, MRA, DSA	5
Backes D et al., 2017	Japan	Prospective	1507	257 (17%)	61 (18–97)	NR	≥1-mm increase	2.5 (0.5–14.3)	Angiography, CTA	6
Bjorkman J et al., 2018	Finland	Prospective	350	36 (10.3%)	48.6	3.6	≥1-mm increase	1.7	CTA, DSA	6
Brinjikji W et al., 2018	Canada	Retrospective	352	40 (11%)	55.8 (0.6)	3.9 (0.1)	≥1-mm increase	4.8 (0.5)	CTA, MRA, DSA	6
Choi HH et al., 2018	Korea	Prospective	173	28 (16.2%)	57.4 (11.1)	2.4 (1.1–6.9)	≥1-mm increase	6 (2–12)	CTA, MRA	7
Juvela S et al., 2018	Finland	Prospective	87	40 (46%)	38.4 (9.1)	5.1 (4.1)	≥1-mm increase	21.7 (1.2–51)	CTA	8
Moon J et al., 2018	Korea	Retrospective	82	7 (8.5%)	56.7 (11.7)	NR	≥2-mm increase	4 (1–15)	NR	8
Phan TG et al., 2002	United States	Retrospective	57	4 (7%)	60 (31–78)	5.0 (2–15)	NR	3.9 (1.4–7.5)	MRA	5
Wermer MJ et al., 2005	The Netherlands	Retrospective	610	129 (16%)	53.5 (24–70)	NR	NR	NR	CTA	7

CTA, computed tomography angiography; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; NR, not report.

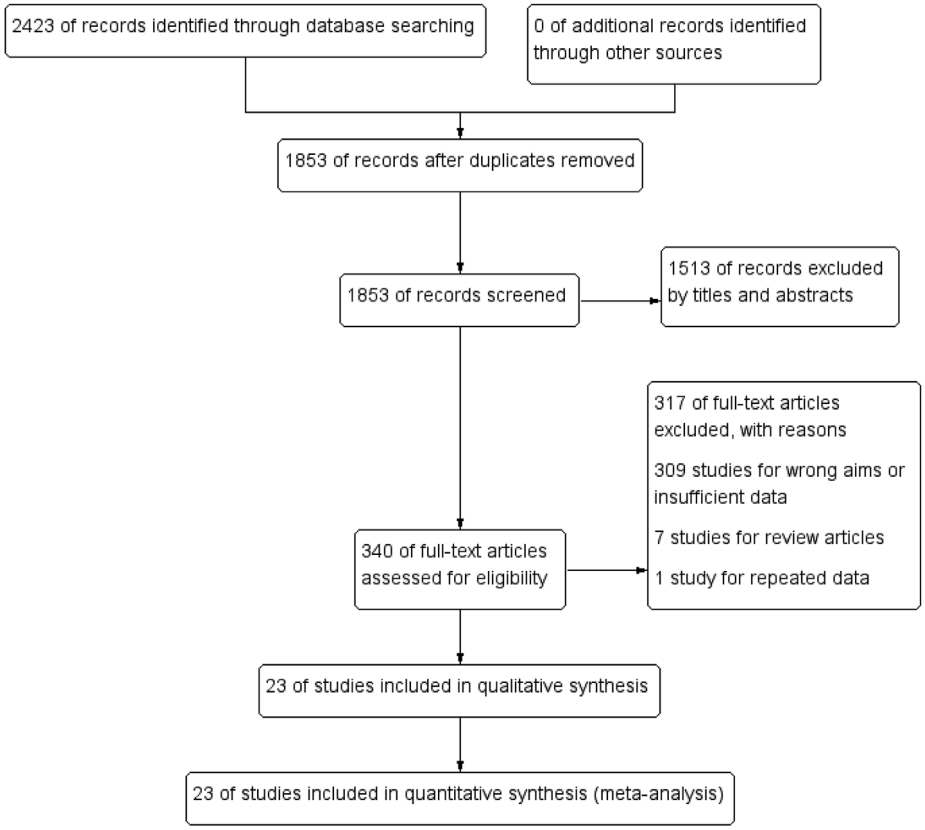

Fig. 1. Flow diagram of literature search and selection of included studies for meta-analysis.

3.2. Quality assessment

As shown in Table 1, there were six studies with a NOS score of 8, eight studies with a NOS score of 7, six studies with a NOS score of 6, and three studies with a NOS score of 5. Based on these assessments, 86.9% of studies met our standard for good quality.

Next, risk of bias graphs were generated for each of our included studies. The risk of bias for each RCT was presented as a percentage across all included studies (Fig. 2), as well as individually (Fig. 3). The risk of bias graphs indicated generally good methodological quality. Good quality was strongest in "selection", including items of representativeness of the exposed cohort and selection of the non-exposed cohort. Comparability of outcome issues was deemed to be a low risk of bias in these studies. High risk of bias items accounted for a small proportion in our included studies. Unclear risks of bias were seen for the criteria "follow long enough for outcomes to occur" and "demonstration that outcome of interest was not present at the start of the study".

3.3. Association between risk factors and the growth of intracranial aneurysm estimated with hazard ratios

Correlations between risk factors and the growth of intracranial aneurysm were performed based on predicted hazard ratios. As shown in Table 2, significant correlations were observed between the growth of intracranial aneurysm and previous SAH (UVA: HR 0.47; 95% CI 0.35–0.63; $P < 0.00001$, and MVA: HR 0.60; 95% CI 0.43–0.83; $P = 0.002$), aneurysm size (UVA: HR 1.42; 95% CI 1.10–1.83; $P = 0.007$, and MVA: HR 1.55; 95% CI 1.10–2.17; $P = 0.01$), smoking (HR 1.57; 95% CI 1.02–2.42; $P = 0.04$), and multiple aneurysms (HR 2.49; 95% CI 1.35–4.61; $P = 0.003$). In contrast, no significant associations were found between the growth of intracranial aneurysm and hypertension, age, arterial relationship, irregular shape, female sex, and multiplicity. These analyses were estimated using a random-effect

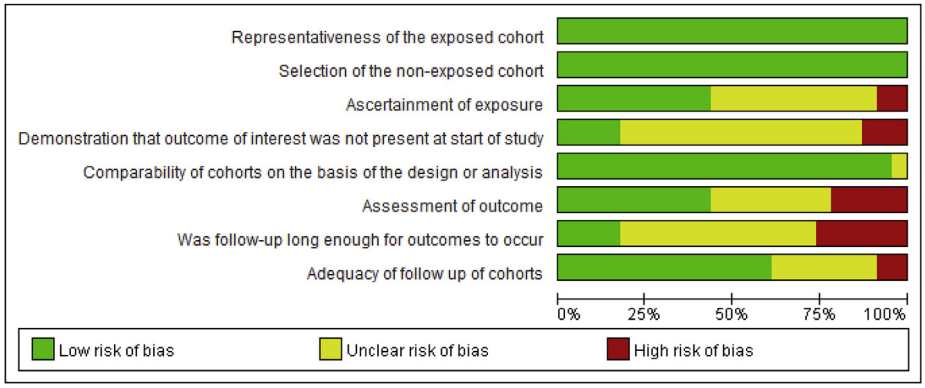

Fig. 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

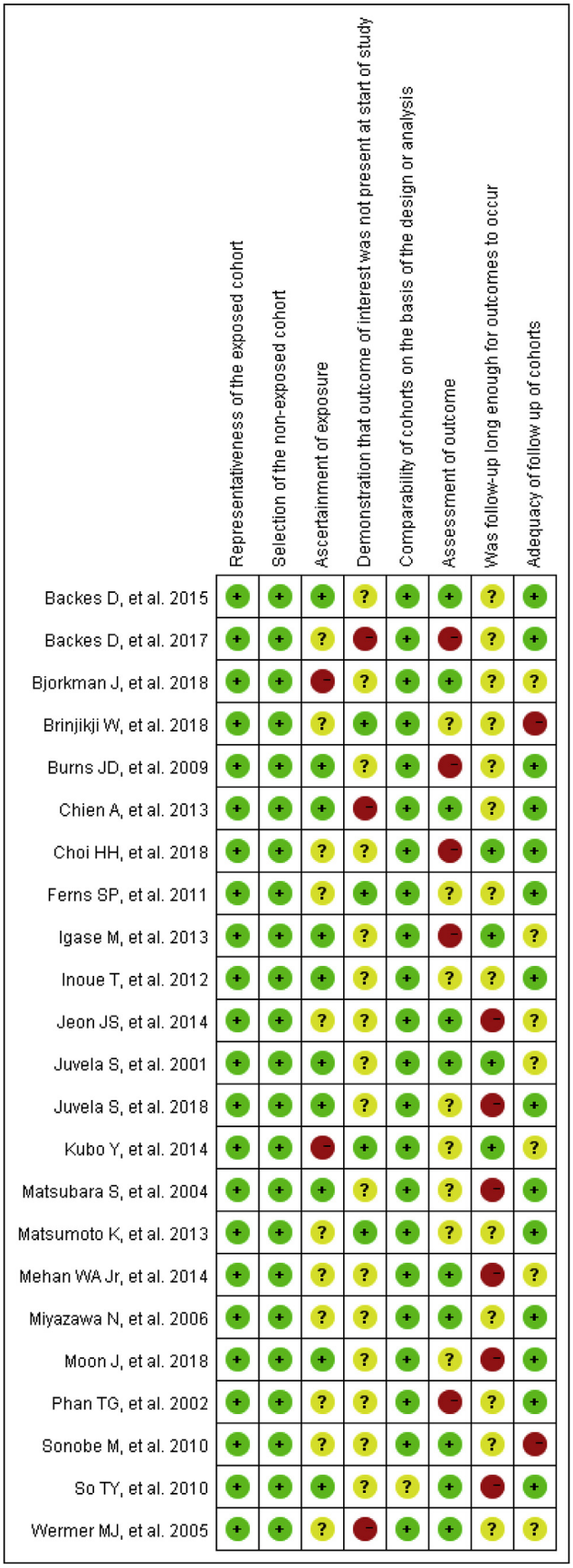

Fig. 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

model, as significant heterogeneity was found among all variables, with the exception of previous SAH, multiple aneurysms, and smoking.

3.4. Association between risk factors and the growth of intracranial aneurysm estimated with odds ratios

Many of the included studies assessed potential correlations between risk factors and the growth of intracranial aneurysm using odds ratios (ORs). For this study, we pooled these data, and reanalyzed them as part of a combined analysis. Our pooled analysis revealed significant correlations between the growth of intracranial aneurysm and current smoking (UVA: OR 1.95; 95% CI 1.02–3.76; $P = 0.05$, and MVA: OR 4.35; 95% CI 2.17–8.72; $P < 0.00001$), female sex (OR 2.02; 95% CI 1.43–2.86; $P < 0.0001$), hypertension (MVA: OR 1.18; 95% CI 1.05–1.32; $P = 0.006$), and aneurysm size (UVA: OR 1.41; 95% CI 1.23–1.62; $P < 0.00001$, and MVA: OR 1.34; 95% CI 1.15–1.56; $P = 0.0002$). No significant associations were found between the growth of intracranial aneurysm and age, hypertension (UVA), or prior SAH. These analyses were estimated using a fixed-effect models, as no significant heterogeneity was found between studies, with the exception of age (UVA) and current smoking (Table 3).

3.5. Association between risk factors and the growth of intracranial aneurysm estimated as dichotomous variables

We also collected data that displayed as dichotomous in our included studies and performed pooled analysis. Our results indicated significant correlation between the growth of intracranial aneurysm and aneurysm size (mm) (OR 2.73; 95% CI 2.21–3.36; $P < 0.00001$; Fig. 4), prior SAH (OR 0.64; 95% CI 0.48–0.86; $P = 0.003$; Fig. 5), and smoking (OR 1.45; 95% CI 1.07–1.98; $P = 0.02$; Fig. 6) and irregular shape (OR 2.12; 95% CI 1.60–2.80; $P < 0.00001$). No significant associations were observed in the growth of intracranial aneurysm in analyses of MCA vs. ICA, ACA vs. ICA, female vs. male, multiple vs. single, age, multiplicity, hypertension, diabetes mellitus, and anterior artery (Table 4).

3.6. Publication bias

Funnel plots were generated to assess the potential for publication bias among the included studies. The absence of any significant asymmetry across plots suggests no clear evidence of publication bias in any of the studies used in this analysis (Fig. 7).

4. Discussion

A large number of risk factors have been identified that may have influenced the growth of unruptured intracranial aneurysms; these include hypertension, sex, age, previous history of SAH, aneurysm size, arterial relationship, irregular shape, smoking, multiple aneurysms, and anatomic site. However, the precise relationship between these risk factors and the growth of intracranial aneurysms remains poorly understood.

Our systematic review and meta-analysis of various data types revealed significant correlations between the growth of intracranial aneurysms, aneurysm size, and smoking status. Aneurysm size was of particular importance in these analyses, with large aneurysm size associated with an increased risk of growth of intracranial aneurysms by UVA and MVA for both hazard ratios and odds ratios (Tables 2 and 3). These results suggest that aneurysm size may represent an independent risk factor for intracranial aneurysm growth. For smoking, significant associations were observed for three different types of collected data, including MVA, which identified current smoking status as an independent risk factor for the growth of intracranial aneurysms (OR 4.35; 95% CI 2.17, 8.72; $P < 0.00001$). These observations reveal a partial overlap with a previous meta-analysis, which reported

Table 2
The pooled results of the association between risk factors and the growth of intracranial aneurysm estimated with hazard ratios.

Subgroups	Number of participants	Pooled results			heterogeneity		
		HR	95% CI	*P* value	I^2	P_h value	Analytical effect model
Hypertension							
UVA	3396	1.22	0.87, 1.71	0.25	68%	0.009	Random-effect model
MVA	1431	1.57	0.59, 4.19	0.37	79%	0.008	Random-effect model
Age							
UVA	3049	1.07	0.97, 1.19	0.18	87%	< 0.00001	Random-effect model
MVA	2414	1.02	0.92, 1.13	0.70	65%	0.06	Random-effect model
Previous SAH							
UVA	2899	0.47	0.35, 0.63	< 0.00001*	42%	0.14	Fixed-effect model
MVA	2414	0.60	0.43, 0.83	0.002*	0%	0.79	Fixed-effect model
Aneurysm size							
UVA	2866	1.42	1.10, 1.83	0.007*	80%	0.0004	Random-effect model
MVA	2381	1.55	1.10, 2.17	0.01*	65%	0.06	Random-effect model
Arterial relationship							
UVA	2381	1.60	0.51, 5.02	0.42	79%	0.009	Random-effect model
MVA	2381	2.21	0.51, 9.55	0.29	86%	0.001	Random-effect model
Irregular shape							
UVA	1857	1.66	0.57, 4.81	0.35	83%	0.02	Random-effect model
MVA	1857	0.96	0.36, 2.58	0.94	75%	0.05	Random-effect model
Female sex	3476	1.27	0.76, 2.13	0.37	59%	0.03	Random-effect model
Multiplicity	365	1.27	0.08, 20.61	0.87	92%	0.0005	Random-effect model
Smoking	1969	1.57	1.02, 2.42	0.04*	41%	0.14	Fixed-effect model
Multiple aneurysms	984	2.49	1.35, 4.61	0.003*	0%	0.50	Fixed-effect model

HR, hazard ratio; CI, confidence intervals; UVA, univariate analysis; MVA, multivariate analysis; SAH, subarachnoid hemorrhage.

Table 3
The pooled results of the association between risk factors and the growth of intracranial aneurysm estimated with odds ratios.

Characteristics	Number of participants	Pooled results			heterogeneity		
		OR	95% CI	*P* value	I^2	P_h value	Analytical effect model
Age							
UVA	547	0.95	0.85, 1.08	0.45	80%	0.002	Random-effect model
MVA	339	1.03	0.98, 1.09	0.18	42%	0.18	Fixed-effect model
Current smoking							
UVA	634	1.95	1.02, 3.76	0.05	55%	0.06	Random-effect model
MVA	374	4.35	2.17, 8.72	< 0.00001	16%	0.31	Fixed-effect model
Female sex	548	2.02	1.43, 2.86	< 0.0001	0%	0.49	Fixed-effect model
Hypertension							
UVA	547	1.01	0.86, 1.18	0.93	0%	0.41	Fixed-effect model
MVA	374	1.18	1.05, 1.32	0.006	19%	0.29	Fixed-effect model
Prior SAH	373	0.89	0.57, 1.39	0.61	45%	0.18	Fixed-effect model
Aneurysm size							
UVA	629	1.41	1.23, 1.62	< 0.00001	0%	1.0	Fixed-effect model
UVA	539	1.34	1.15, 1.56	0.0002	0%	0.75	Fixed-effect model

OR, odds ratio; CI, confidence intervals; UVA, univariate analysis; MVA, multivariate analysis.; SAH, subarachnoid hemorrhage.

significant associations between aneurysm growth rates and age (> 50 years of age; 3.8% per year versus 0.9% per year, $P < 0.01$), female sex (3.2% per year versus 1.3% per year, $P < 0.01$), smoking history (5.5% per year versus 3.5% per year, $P < 0.01$), cavernous carotid artery location (14.4% per year), non-saccular shape (14.7% per year versus 5.2% per year for saccular, $P < 0.01$), and aneurysm size ($P < 0.01$) [35]. The author also stated that aneurysm growth was associated with a rupture rate of 3.1% per year compared with 0.1% per year for stable

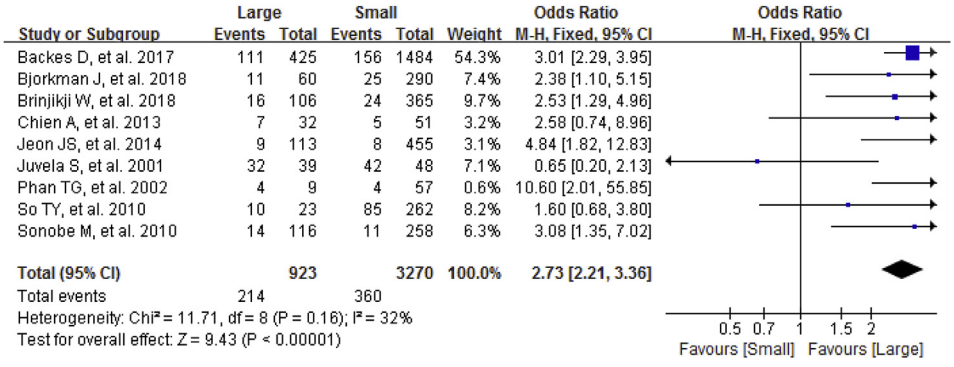

Fig. 4. Forest plot of the aneurysm size (mm) as one of growth factors for intracranial aneurysm.

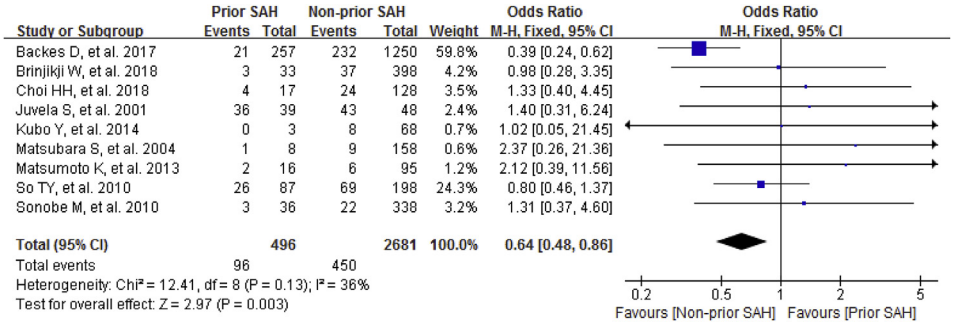

Fig. 5. Forest plot of the association between prior SAH and the growth of intracranial aneurysm.

aneurysms ($P < 0.01$). While the association between large aneurysm size, faster growth, and higher incidence of aneurysm rupture is not surprising, many of the other associations observed in this study were not replicated here. In particular, our study found the association between intracranial aneurysm growth and female sex to be inconsistent across data types. Comparisons of odds ratios were significant in this study; however, similar analyses of both hazard ratios and categorical variables failed to reach statistical significance. In addition, no significant differences were observed for either age or arterial relationship in any of the data types analyzed. Other variables, such as irregular shape and multiple aneurysms will require further investigation due to inconsistencies within the data.

Prior SAH had a negative effect on the growth of intracranial aneurysms, an effect that was consistently observed across studies and data types. A study by Backes et al. proposed a combination of earlier SAH, location of the aneurysm, population, age > 60 years, size of the aneurysm, and shape of the aneurysm (ELAPSS score) as a method for predicting aneurysm growth [7]. A subsequent study by Brinjikji et al. revealed similar outcomes, with aneurysm size, smoking status, PHASES score, and ELAPSS score all significantly associated with aneurysm growth [9].

This work has important limitations, which need to be taken into account when designing future studies. First, the imaging methods that were used to assess the growth of intracranial aneurysms were inconsistent in different studies. For example, some studies only used magnetic resonance angiography as the assessment tool of growth of aneurysm [13–15,21], while others relied on computed tomography angiography [17,20,22,28], digital subtraction angiography [6,8] or, in some cases, a combination of these methods [9,12,16,18,27]. This variability between methods represents an important risk for bias. Second, the risk factors found in this analysis may not account for aneurysms with a high risk of rupture, because the majority of patients in the included studies had aneurysms with a low risk of rupture and, therefore, had follow-up imaging instead of preventive aneurysm treatment. Third, there was significant variability between studies with regard to the definition of aneurysm growth. In our analysis, the majority of studies defined aneurysm growth as ≥ 1-mm increase [6–10,12–14,17,21], though a few studies used a definition of either 1.5 × increase of diameter [15,16] or ≥ 2-mm increase [19,22–24]. Due to limitations in the number of studies, we were unable to perform a subgroup analysis to identify differences based on the definition of aneurysm growth. Fourth, the baseline of aneurysm size used in these studies exhibited a large range of variation. The majority of studies used mean aneurysm size of ~4 mm as the baseline to evaluate the growth of aneurysm. Further, researchers should use clear cut-off values for the baseline aneurysm size used to predict the growth, and indicate the size of aneurysms that exhibit faster growth or higher rates of rupture. Fifth, the reported follow-up periods were inconsistent among studies, in terms of both the duration and completeness of patient data. Another factor that hampers our assessment of aneurysm growth as a risk factor for rupture is the fact that most centers will treat patients with aneurysm growth to prevent aneurysm rupture, a practice that may result in an underestimation of the rupture risk in patients with aneurysm growth. Also, aneurysm growth may have occurred before aneurysm rupture, but may not have been detected because of the long interval between follow-up scans, leading to an underestimation of the rupture risk in patients with aneurysm growth.

In conclusion, our meta-analysis suggests that aneurysm size and smoking status may be independent risk factors for intracranial aneurysm growth, while prior SAH may have a negative effect on the growth of intracranial aneurysms. The role of other risk factors previously implicated in the growth of intracranial aneurysms, including female sex, irregular shape, and multiple aneurysms, were inconclusive. Further studies will be necessary to assess fully the significance of these factors.

Ethical Approval

Ethical Approval is not applicable.

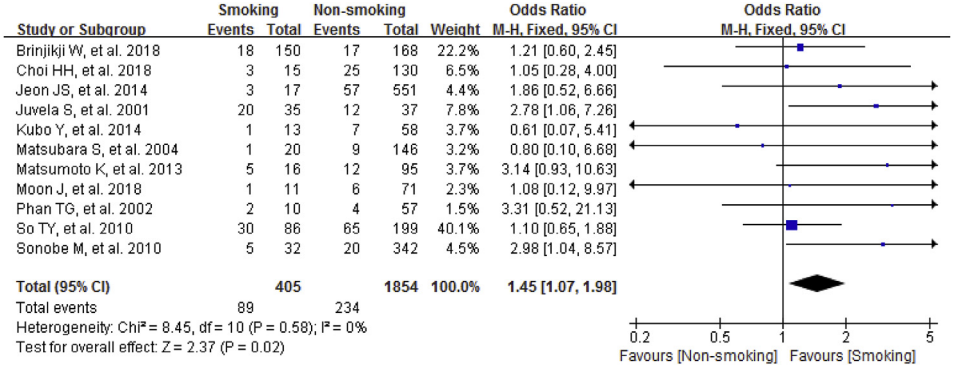

Fig. 6. Forest plot of smoking as one of growth factors for intracranial aneurysm.

Table 4
The pooled results of the association between risk factors and the growth of intracranial aneurysm estimated with dichotomous.

Characteristics	Number of participants	Pooled results			heterogeneity		
		OR	95% CI	*P* value	I^2	P_h value	Analytical effect model
MCA vs ICA	1429	1.42	0.96, 2.09	0.08	44%	0.11	Fixed-effect model
ACA vs ICA	1779	0.90	0.54, 1.52	0.70	0%	0.81	Fixed-effect model
Female vs Male	2895	1.15	0.92, 1.43	0.22	3%	0.41	Fixed-effect model
Multiple vs single	2744	1.64	0.97, 2.76	0.06	60%	0.02	Random-effect model
Age	2670	1.04	0.60, 1.80	0.88	64%	0.02	Random-effect model
Aneurysm size (mm)	4807	2.73	2.21, 3.36	< 0.00001	32%	0.16	Fixed-effect model
Multiplicity	198	1.35	0.07, 25.67	0.84	95%	< 0.0005	Random-effect model
Hypertension	3381	1.22	0.86, 1.73	0.27	46%	0.06	Random-effect model
Diabetes mellitus	998	1.01	0.47, 2.18	0.97	0%	0.66	Fixed-effect model
Smoking	2187	1.45	1.07, 1.98	0.02	0%	0.58	Fixed-effect model
Prior SAH	2858	0.64	0.48, 0.86	0.003	36%	0.13	Fixed-effect model
Anterior artery	2465	1.11	0.53, 2.34	0.77	57%	0.07	Random-effect model
Irregular shape	2209	2.12	1.60, 2.80	< 0.00001	22%	0.28	Fixed-effect model

OR, odds ratio; CI, confidence intervals; BMI, body mass index; SAH, subarachnoid hemorrhage; ACA, anterior cerebral arteries; ICA, internal carotid artery; MCA, middle cerebral artery.

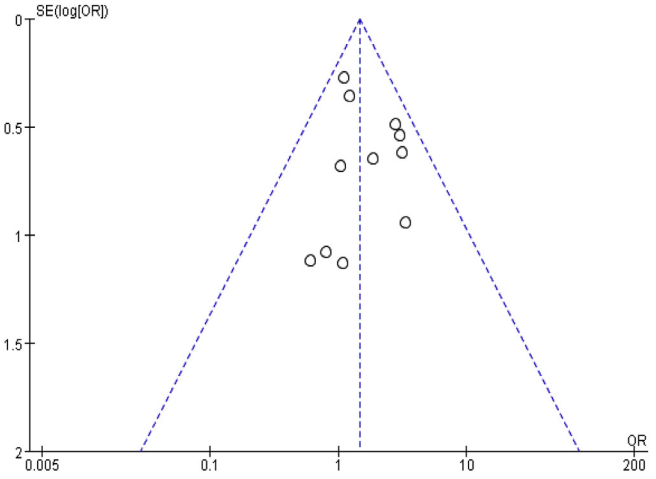

Fig. 7. Forest plot for detecting publication bias of the association between risk factors and intracranial aneurysm growth.

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Conflicts of interest

The authors declare no relevant conflict of interest.

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Appendix A. Supplementary data

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