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Original Article

Prevalence and risk factors of unruptured intracranial aneurysms in ischemic stroke patients – A global meta-analysis

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ABSTRACT

Background: Unruptured intracranial aneurysms (UIAs) have an estimated global prevalence of 2.8% in the adult population; however, UIA was identified among more than 10% of ischemic stroke patients. Many epidemiological studies and reviews have pointed to the presence of UIA among patients with ischemic stroke; yet, the extent of this association is not fully known. We performed a systematic review and meta-analysis to determine the prevalence of UIA in patients admitted to hospitals with ischemic stroke and transient ischemic attack (TIA) at both global and continental levels and evaluate factors associated with UIA in this population.

Methods: We identified, in five databases, all studies describing UIA in ischemic stroke and TIA patients between January 1, 2000, and December 20, 2021. Included studies were of observational and experimental design.

Results: Our search yielded 3581 articles of which 23 were included, with a total of 25,420 patients. The pooled prevalence of UIA was 5% (95% confidence interval [CI] = 4–6%) with stratified results showing 6% (95% CI = 4–9%), 6% (95% CI = 5–7%), and 4% (95% CI = 2–5%) in North America, Asia, and Europe, respectively. Significant risk factors were large vessel occlusion (odds ratios [OR] = 1.22, 95% CI = 1.01–1.47) and hypertension (OR = 1.45, 95% CI = 1.24–1.69), while protective factors were male sex (OR = 0.60, 95% CI = 0.53–0.68) and diabetes (OR = 0.82, 95% CI = 0.72–0.95).

Conclusion: The prevalence of UIA is notably higher in ischemic stroke patients than the general population. Physicians should be aware of common risk factors in stroke and aneurysm formation for appropriate prevention.

Keywords: Computed tomography angiography, Ischemic stroke, Magnetic resonance angiography, Prevalence, Adults, Unruptured intracranial aneurysm

INTRODUCTION

Unruptured intracranial aneurysms (UIAs) have an estimated global prevalence of 2.8% in the adult population.[50] Frequent vascular imaging and improved technologies largely increased the detection

of UIA,[52] which has helped optimize risk stratification of aneurysms prone to rupture.[48] The rupture of an intracranial aneurysm is life-threatening, associated with high rates of morbidity and mortality. Annually, 10% of intracranial aneurysms rupture,[20] with nearly 20% of patients dying before hospitalization,[31] and 30% dying within 3 months.[32]

Many epidemiological studies and reviews have pointed to the presence of UIA among patients with ischemic stroke;[8,40,23] yet, the extent of this association is not fully known. Moreover, data on the prevalence of UIA in patients with ischemic stroke are important for healthcare planning.[49] To address this gap in the literature, we performed a systematic review and meta-analysis to determine the prevalence of UIA in patients admitted to hospitals with ischemic stroke and transient ischemic attacks (TIA) at both global and continental levels and evaluate factors associated with UIA in this population.

MATERIALS AND METHODS

Search strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[37] A comprehensive search of PubMed, Embase, VHL, African Index Medicus, and Google Scholar was conducted for studies published from January 1, 2000, to December 20, 2021, to identify all relevant human studies of UIA in stroke and TIA patients. No built-in filters were used for language, region, or sex.

A search strategy consisting of 14 MeSH terms was developed in MEDLINE. The keywords for the search strategy were ((“Intracranial Aneurysm”[Mesh])) AND (“Stroke”[Mesh] OR “Embolic Stroke”[Mesh] OR “Thrombotic Stroke”[Mesh] OR “Ischemic Stroke”[Mesh] OR “Infarction, Middle Cerebral Artery”[Mesh] OR “Infarction, Anterior Cerebral Artery” [Mesh] OR “Stroke, Lacunar”[Mesh] OR “Transitory ischemic attack”) OR “Cerebrovascular accident”) OR “Cerebral Infarction”) OR “Brain Infarction”) OR “Acute Ischemic Stroke”) AND “Prevalence”[Mesh].

To locate additional relevant publications, we identified references from the articles that fit our inclusion criteria using a snowball approach. We also hand-searched five additional pre-selected, high-impact neurosurgery, and neurointerventional radiology journals: Journal of Neurology, Neurosurgery and Psychiatry, American Journal of Neuroradiology, Journal of Neurosurgery, and World Neurosurgery.

Eligibility criteria

We included observational studies (cohort, cross-sectional, case–control, and case series) and clinical trials in our search. The population of interest included patients aged ≥18 years that were admitted to the hospital for having an ischemic stroke or TIA but had no known predisposing genetic or autoimmune diseases. The identified exposure was UIA detected by imaging modalities (computed tomography, computed tomography angiography, magnetic resonance imaging, magnetic resonance angiography, or fluoroscopy angiography) in the population of interest.

We excluded studies that were determined to be of poor quality, according to the National Institutes of Health (NIH) Quality Assessment tool, and those lacking sufficient information to calculate prevalence. We also excluded study designs, such as reviews, editorials, commentaries, and case reports. In addition, if multiple studies used the same dataset or cohort, only the study with the largest sample size was included.

Study selection process

Articles identified by the search strategy were imported into the reference management software, Mendeley, version 1.19.5/2019 (London, United Kingdom). Duplicates were deleted and the remaining articles were screened by title and abstract for inclusion. For articles that passed the initial screen and for those where titles and abstracts were not sufficient to make a decision, full texts were retrieved and further assessed for final inclusion. Manuscripts not written in English were translated. Two investigators carried out the entire process independently and disagreements in the study selection were resolved through consensus.

Data collection and missing data

All of the data were extracted into a preconceived and standardized form in Microsoft Excel (Office 365: Microsoft, Redmond, Washington, United States).

The following qualitative data were extracted from each study: authors, year of publication, country of publication, study type, number of patients with ischemic stroke or TIA, number of patients with UIA, mean age, location of aneurysms, mean aneurysm size, and imaging method used to detect the aneurysm. The qualitative and quantitative data were extracted by all investigators and reviewed by two independent investigators. For the primary outcome, the numerical data extracted from each study included the total number of patients with ischemic stroke or TIA, number of patients with UIA, and subgroups according to continent. For the secondary outcome, the data extracted included first author, year of publication, number of exposed cases, exposed controls, unexposed cases, and unexposed controls. In the case of missing data or lack of relevant information in studies, authors were contacted.

Outcome variables

The primary outcome was the prevalence of UIA among patients with ischemic stroke and TIA, which was assessed

globally and by continent. The secondary outcome was associated factors related to UIA in patients with stroke and TIA. Associated factors included were sex, size of occluded vessel (large or small), hypertension, smoking, diabetes, dyslipidemia, stroke in anterior/posterior circulation, and atrial fibrillation.

Risk of bias

Quality assessment of the included studies was evaluated by the NIH Study Assessment Tools. Each study was assessed based on eight to fourteen questions, according to study type. After assessment, studies were given a rating of good, fair, or poor quality. A "good" study has the least risk of bias, a "fair" one is susceptible to some bias that is not sufficient to invalidate its results, and a "poor" study holds significant bias.

Statistical analysis

The software STATA (StataCorp LLC, College Station, Texas, United States) was used to perform all statistical analyses in this study.

For the primary outcome, we measured prevalence of UIA in stroke and TIA patients using the following formula:

$$P = \frac{Number\ of\ UIA\ in\ the\ population\ of\ interest\ *}{N}$$

P = Prevalence; N = Total sample size of patients with ischemic stroke or TIA.

*Population of interest = Patients with ischemic stroke or TIA.

The results of the primary outcome were expressed as relative frequencies and pooled in a quantitative synthesis to determine the overall effect. Heterogeneity among studies was assessed using Cochran's Q tests and I^2 statistics, with Cochran's $Q < 0.05$ and $I^2 > 50\%$ indicating substantial heterogeneity.[33] We applied a fixed-effects model when $I^2 < 50\%$, and a random-effects model when $I^2 > 50\%$.[55] In the case of discrepancies between Cochran's Q and I^2 statistics, a random-effects model was used to guarantee a conservative approach, since the random-effects model redistributes the weight of the studies almost proportionally.[16] Sensitivity analysis was conducted to evaluate robustness of the primary outcome. To detect publication bias, the Egger's test was used. $P > 0.05$ on the Egger's test was considered indicative of statistically significant publication bias.

To account for patients' characteristics and risk factors that might explain differences in the prevalence of UIA in the stroke/TIA population, we calculated OR using a 2 × 2 table for all the variables of the secondary outcomes, then we pooled the results in a quantitative synthesis. Heterogeneity for these differences was assessed using Cochran's Q test and I^2 test.

RESULTS

Study selection and characteristics

Our database search identified a total of 3664 articles. After excluding 3372 articles based on relevance to our primary objective and removing 83 duplicates, 209 articles remained. Of these, we filtered 186 articles because they failed to provide sufficient information regarding effect size or could not be found. Ultimately, we included 23 articles with a total sample size of 25,420 patients, spanning 13 different countries [Figure 1].

Among the studies included in this systematic review and meta-analysis, 22 were observational (15 retrospective, six prospective, and one descriptive) and one was a randomized clinical trial. The highest proportion of articles was from the United States (n = 8) and South Korea (n = 5). The remaining articles were from China, Japan, Taiwan, Singapore, Thailand, Germany, Greece, Italy, the United Kingdom, the Netherlands, and Canada. China and Japan alone contributed vastly to our final sample size, accounting for approximately 13,000 subjects.

For each of the 23 studies included, the items evaluated were first author, year of publication, country of publication, study type, number of patients with UIA, sample size, mean age, location of UIA, mean UIA size, and imaging modality [Table 1]. Mean age ranged from 62.4 to 79 years, and the mean size of UIA ranged from 2.93 to 7.45 mm. In 16 articles, aneurysms were more frequent in the internal carotid artery or the middle cerebral artery. Imaging modalities varied between studies, with computed tomography angiography and magnetic resonance angiography being the most common.

Risk of bias

The risk of bias was assessed according to the NIH Quality Assessment Tool.[17] Of the 23 articles included, 14 were considered of good quality, nine were considered of fair quality, and none were considered to be of poor quality. More details on this assessment are available in Appendix A.[2,8,9,11-13,15,18,19,21,23,25-28,35,38, 40,41,45,46,53,54]

Prevalence of UIA in stroke and TIA patients

Global prevalence

Pooled estimates of UIA prevalence were calculated for 23 studies totaling 25,420 stroke and TIA patients. Globally, the pooled prevalence was 5% (95% CI = 4–6%). Heterogeneity was statistically significant, with I^2 = 90.3% and Cochran's $Q < 0.001$ [Figure 2].[2,8,9,11-13,15,18,19,21,23,25-28,35,38,40,41,45,46,53,54]

Prevalence by continent

Pooled estimates of UIA prevalence were stratified by continent. Our study shows results from North America, Europe, and

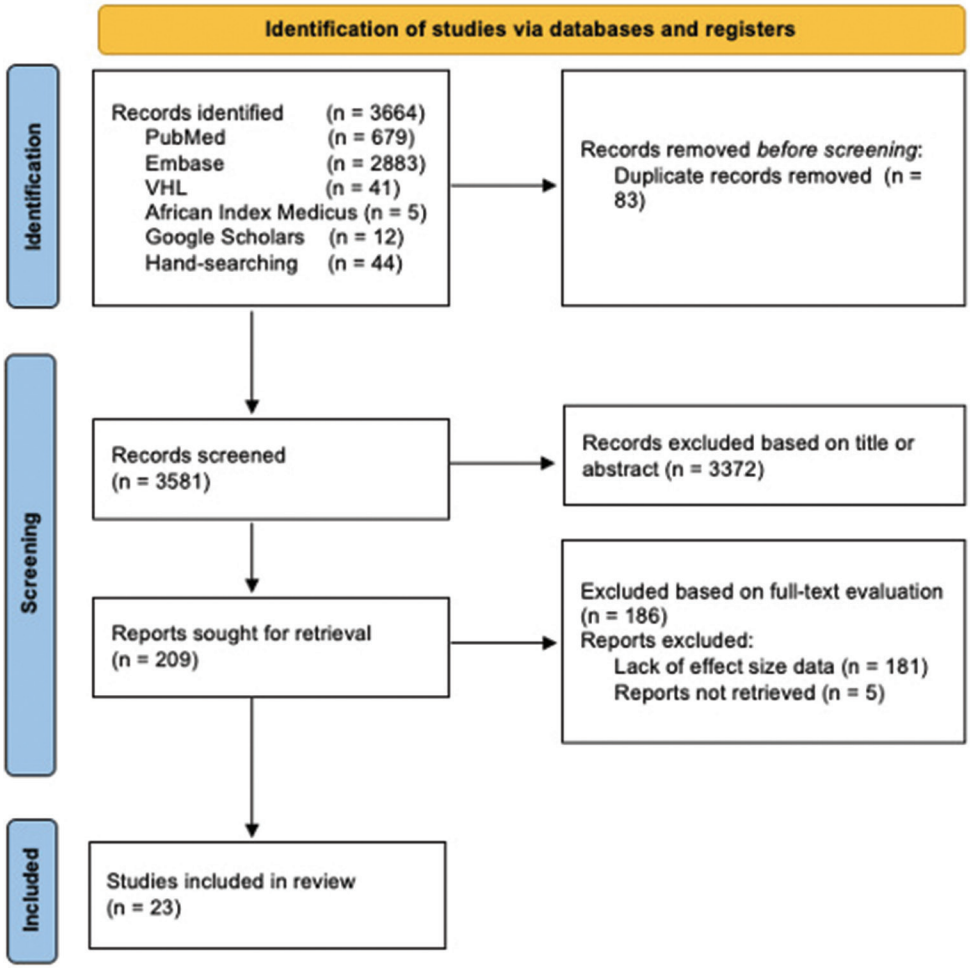

Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow diagram. n: Number

Asia. No data was available for Africa, South America, or Oceania. In North America, data from eight studies with a total of 5976 patients showed a pooled prevalence of 6% (95% CI = 4–9%) with substantial heterogeneity (I^2 = 90.7%) [Figure 3].[2,8,9,11-13,15,18,19,21,23,25-28,35,38,40,41,45,46,53,54] In Europe, data from five studies with a total of 3975 patients showed a pooled prevalence of 4% (95% CI = 2–5%) with substantial heterogeneity (I^2 = 66.55%). Finally, in Asia, data from ten studies with a total of 15,469 patients showed a pooled prevalence of 6% (95% CI = 5–7%) with substantial heterogeneity (I^2 = 71.43%). Cochran's Q tests were applied in all analyses and showed significance ($P \leq 0.001$) among the variables in our study. Original data for the primary and secondary outcomes is provided in Appendix B.[2,8,9,11,12,13,15,18,19,21,23,25-28,35,38, 40,41,45,46,53,54]

Sensitivity analysis and publication bias

A sensitivity analysis was performed to measure the effect of each study on the pooled estimate, revealing no change in the direction of the results [Figure 4].[2,8,9,11-13,15,18,19,21,23,25-28,35,38,40,41,45,46,53,54] An Egger's test was used and yielded *P*-value of 0.089, indicating no publication bias.

Factors associated with UIA in stroke and TIA patients

To identify the factors associated with UIA in stroke and TIA patients, we used a fixed-effects model and subsequently calculated pooled estimates for the following extracted factors: male sex, large vessel occlusion, hypertension, smoking, diabetes, dyslipidemia, stroke in the anterior circulation, and atrial fibrillation [Table 2].

There was a statistically significant association between the presence of UIA in our study population and both large vessel occlusion (OR = 1.22, 95% CI = 1.01–1.47) and hypertension (OR = 1.45, 95% CI = 1.24–1.69). In contrast, male sex (OR = 0.60, 95% CI = 0.53–0.68) and diabetes (OR = 0.82, 95% CI = 0.72–0.95) demonstrated a significantly lower association with UIA presence, suggesting a protective role.

Smoking, dyslipidemia, atrial fibrillation, and anterior circulation stroke were not found to be significantly associated with UIA in stroke and TIA patients. Calculated I^2 was <50%, confirmed by Cochrane Q tests that presented *P*-value >0.05 for all variables in our study, suggesting no substantial heterogeneity.

Table 1: Summary of study findings.

Author	Year	Country	Study type	Patients with UIA	Sample size	Mean age	Location of UIA	Mean UIA size (mm)	Imaging method
Zibold *et al.*[54]	2016	Germany	Observational, Retrospective	11	300	67.7	- ICA: 3 (27%) - MCA: 7 (63%) - BA: 1 (9%)	4.81	CTA, MRA, DSA
Chen *et al.*[8]	2018	USA	Observational, Retrospective (Case-Control)	176	1541	71.0	- ICA: 87 (49%) - ACA+AComA: 34 (19%) - MCA: 16 (9%) - PCA: 4 (2%) - PComA: 18 (10%) - BA: 6 (3%)	4.16	CTA, MRI, MRA, DSA
Wu *et al.*[53]	2021	China	Observational, Retrospective	260	4033	70.0	- ICA: 190 (73%) - ACA: 8 (3%) - MCA: 22 (8.5%) - PCA: 8 (1.9%) - AComA: 9 (3.5%) - PComA: 8 (3%) - BA+VA: 15 (6%)	2.93	MRI, DSA
Oh *et al.*[41]	2008	South Korea	Observational, Prospective	17	258	73.0	- ICA: 9 (52%) - MCA: 6 (35%) - BA: 1 (6%) - VA: 1 (6%)	5.10	CTA, MRA
Mowla *et al.*[38]	2015	USA	Observational, Retrospective	33	637	72.6	- ICA: 22 (66.6%) - MCA: 7 (15.8%) - BA: 5 (11.3%) - Others: 10 (22.7%)	4.70	CT, MRI
Oh *et al.*[40]	2013	South Korea	Observational, Prospective	19	314	72.2	- ICA: 11 (58%) - MCA: 6 (31.6%) - BA: 2 (10.5%)	4.57	CTA, MRA
Kim *et al.*[27]	2016	South Korea	Observational, Retrospective	74	955	64.9	- ICA: 48 (52.2%) - MCA: 22 (24%) - AComA: 9 (9.8%) - PComA: 6 (6.5%) - BA+VA: 7 (7.6%)	3.75	MRA
Shono *et al.*[46]	2018	Japan	Observational, Retrospective	412	8857	74.0	- ICA: 152 (31.9%) - ACA: 26 (5.4%) - MCA: 130 (27.3%) - PCA: 4 (0.8%) - AComA: 59 (12.4%) - PComA: 54 (11.3%) - BA+VA: 52 (10.9%)	4.10	CT, MRI
Mittal *et al.*[35]	2013	USA	Observational, Retrospective	10	104	79.0	- ICA: 2 (17%) - MCA: 3 (25%) - AComA: 4 (33%) - PComA: 3 (25%)	3.20	CTA, MRA,
Goyal *et al.*[13]	2015	Germany, Greece, USA, Singapore	Observational, Prospective+ Meta Analysis of Case Series	42	1398	63.0	- ICA+MCA+ AComA+OA: 34 (71%) - PCA+PComA+ BA+VA: 14 (29%)	4.30	CT, MRA, DSA

(Contd...)

Table 1: *(Continued).*

Author	Year	Country	Study type	Patients with UIA	Sample size	Mean age	Location of UIA	Mean UIA size (mm)	Imaging method
Chiu *et al.*[9]	2017	China, Taiwan	Observational, Retrospective	11	144	74.8	- ICA: 6 (54%) - MCA: 3 (27%) - AComA: 1 (9%) - BA: 1 (9%)	3.80	CTA, MRA,
Jiranukool *et al.*[23]	2020	Thailand	Observational, Descriptive	13	186	67.7	- ICA: 9 (69.1%) - ACA: 1 (7.7%) - MCA: 1 (7.7%) - BA (Tip): 2 (15.4%)	3.2	MRA
Hurford *et al.*[19]	2020	UK	Observational, Prospective (Cohort)	82	1609	70.4	- ICA: 22 (21.4%) - ACA+AComA: 40 (38.8%) - MCA: 29 (28.2%) - PCA+ PComA+BA: 12 (11.7%)	4.20	CTA, MRA
Edwards *et al.*[12]	2012	USA	Observational, Retrospective	22	236	74.0	- ICA: 11 (49.9%) - ACA: 1 (4.5%) - MCA: 4 (18.1%) - AComA: 2 (9%) - PComA: 4 (18.1%) - OA: 1 (4.5%) - BA: 1 (4.5%) - VA: 2 (9%)	4.20	CT, CTA, MRI, MRA
Kim *et al.*[28]	2012	South Korea	Observational, Retrospective	8	194	69.5	- ICA: 2 (25%) - ECA: 1 (12.5%) - ACA: 1 (12.5%) - MCA: 1 (12.5%) - PComA: 2 (25%) - BA+VA: 1 (12.5%)	5.40	CTA, MRA
Ishikawa *et al.*[21]	2010	Japan	Observational, Retrospective	13	374	76.9	- ICA: 4 (31%) - MCA: 3 (23%) - AComA: 4 (31%) - BA: 3 (23%) - Multiple Sites: 1 (8%)	4.90	MRI, MRA
Hokari *et al.*[18]	2014	South Korea	Observational, Retrospective	5	130	73.0	- ICA+PComA: 3 (30%) - MCA: 7 (70%)	5.10	MRA
Sheth *et al.*[45]	2012	USA	Observational, Retrospective	8	172	62.4	- ICA: 3 (37.5%) - ACA: 2 (25%) - OA: 2 (25%) - VA: 1 (12.5%)	6.25	CTA
Doyle *et al.*[11]	2018	USA	Observational, Retrospective	5	200	68.4	- Intracranial: 4 (80%) - Cervical Artery: 1 (20%)	Not provided and cannot be calculated.	CTA
Kanesa-Thasan *et al.*[25]	2018	USA	Observational, Retrospective	16	225	65.0	- ICA: 9 (50%) - ACA: 1 (6%) - MCA: 2 (11%) - PCA: 1 (6%) - AComA: 2 (11%)	3.00	CTA

(Contd...)

Table 1: *(Continued).*

Author	Year	Country	Study type	Patients with UIA	Sample size	Mean age	Location of UIA	Mean UIA size (mm)	Imaging method
Kappelle *et al*.[26]	2000	USA, Canada	Experimental (Randomized Clinical Trial)	90	2885	66.0	- PComA: 1 (6%) - BA: 1 (6%) - VA: 1 (6%) - ICA: 31 (34.3%) - MCA: 18 (20%) - AComA: 11 (12.2%) - PComA: 38 (42.2%) - SCA: 1 (1.1%)	3.92	CTA
Ballotta *et al*.[2]	2006	Italy	Observational, Prospective	11	474	72.0	- ACA: 2 (18%) - MCA: 9 (81.8%) - SCA: 1 (9%)	7.45	CTA, MRA
Héman *et al*.[15]	2009	Netherlands	Observational, Prospective	8	194	70.0	- ACA: 1 (12.5%) - MCA: 5 (62.5%) - PICA: 1 (12.5%) - BA: 1 (12.5%)	5.55	CTA

*ICA: Internal carotid artery, MCA: Middle cerebral artery, PCA: Posterior cerebral artery, CTA: Computed tomography angiography, CT: Computed tomography, BA: Basilar artery, PICA: Posterior inferior cerebellar artery, ACA: Anterior cerebral artery, SCA: Superior cerebellar artery, AComA: Anterior communicating artery, PComA: Posterior communicating artery, VA: Vertebral artery, OA: Ophthalmic artery, ECA: External carotid artery, MRA: Magnetic resonance angiography, DSA: Digital subtraction angiography, MRI: Magnetic resonance imaging, UIA: Unruptured intracranial aneurysm, USA: United States of America.

DISCUSSION

Intracranial aneurysms are not passively enlarging vascular structures, rather they are active, complex formations that exhibit features of inflammation, with pathophysiology similar to endothelial dysfunction found in vascular disease of stroke and TIA patients.[4] Several studies in the past have reported an increase in the prevalence of UIA in stroke and TIA patients, but results were limited in terms of sample size, study design, population, and geographic distribution.[23,41,19,21]

In this meta-analysis, we determined the prevalence of UIA among ischemic stroke and TIA patients admitted to hospitals and identified factors associated with the development of UIA in this population by pooling data from 23 individual studies, totaling 25,420 stroke patients. We found the global prevalence rate to be 5% (95% CI = 4–6%), notably higher than the 2.8% reported in the general population.[50] We discovered a 6% prevalence rate of UIA in North America and Asia and a 4% prevalence rate in Europe. Data from North American studies exhibited a wider confidence interval margin compared to other continents, which could be explained by the heterogeneity among these studies. In contrast, European studies demonstrated an overall lower prevalence rate of UIA, which could be attributed to differences in risk factor profiles. The lack of studies in Africa, South America, and Oceania limited calculating the prevalence of UIA in these continents, constraining the worldwide applicability of our results [Appendix C].

Our results revealed that factors such as female sex, hypertension, and large vessel occlusion were significantly associated with the presence of UIA in stroke and TIA patients. Prior studies suggest that the risk of intracranial aneurysms increases among females after menopause, especially those with early menopause.[10,50] This can be explained by the lack of estrogen, the latter playing a role in preventing formation of intracranial aneurysms through its vasoprotective effects on the cerebral vasculature, which was explored in animal models and observed in retrospective hormone replacement therapy studies.[22,36]

Similar to a previous study conducted by Vlak *et al*.,[51] our results showed that systemic hypertension (OR = 1.45, 95% CI = 1.24–1.69) is an associated risk factor for aneurysm formation. Evidence suggests that the hemodynamic stress resulting from high blood pressure influences tissue remodeling and inflammation of the aneurysmal wall. It also results in endothelial dysfunction and, ultimately, vascular disruption, which contribute to aneurysm formation.[5,34] Furthermore, smoking showed no significant relationship with aneurysm formation, in contrast to the findings of multiple studies,[6,24,30] which demonstrated an association between the two. However, our included study data on smokers did not specify the duration and frequency of smoking, which may have impacted this correlation.

We also found that large vessel occlusion (OR = 1.22, 95% CI = 1.01–1.47) significantly correlated with UIA formation. We hypothesize that the high flow acceleration and turbulent

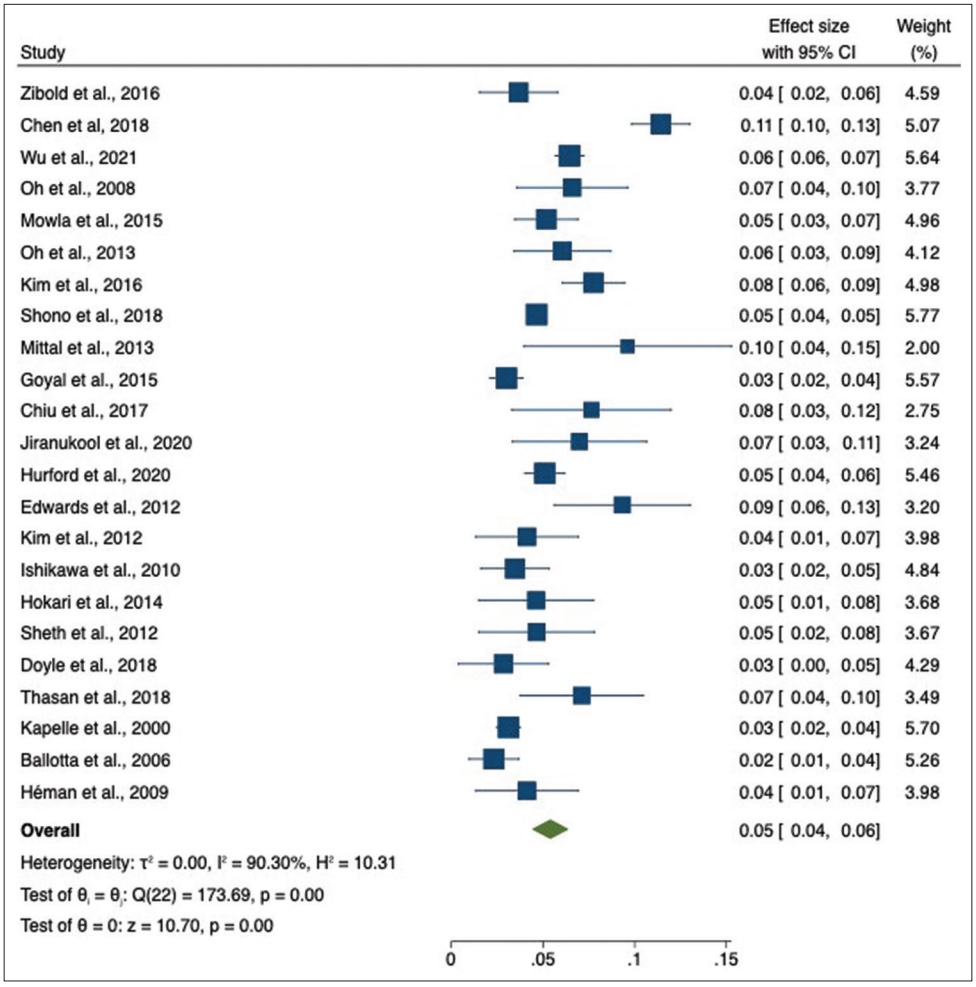

Figure 2: Forest plot of unruptured intracranial aneurysms global prevalence in patients with ischemic stroke and transient ischemic attacks. The blue squares represents the prevalence of UIA in ischemic stroke patients. The lateral lines represents the confidence interval. The green rectangle represents the pool estimate of the prevalence in all studies. CI: Confidence interval.

hemodynamics may affect vessel walls in a similar mechanism to that of hypertension. These occlusions promote maladaptive inflammatory changes, remodeling, and repair pathways that ultimately create defective endothelial wall architecture, forming intracranial aneurysms.[1,7,47] More research is still needed to corroborate this finding.

Patients with diabetes were found to have lower odds of developing intracranial aneurysms (OR = 0.82, 95% CI = 0.72–0.95). Paradoxically, this protective effect may be explained by the use of medications used to treat diabetes.[3,49] Diabetic medications such as metformin,[43] insulin,[14] and glibenclamide[44] have been shown to play a role in inhibiting the enzyme matrix metalloproteinase-9.[42] This enzyme is present and active in large concentrations in cerebral aneurysmal tissue,[29] playing a role in local connective tissue degradation and formation.[39] Diabetic medications interfere with these degradation pathways and, as a result, may protect against the formation of aneurysms.[29] However, it is important to highlight that not all included studies were clear in regards to patients' use of anti-diabetic drugs so that our analysis may encompass both diabetic patients under treatment and without treatment. This must be considered for adequate assessment of results.

Our work has important strengths and limitations. To date, this is one of the most thorough studies performed to evaluate UIA and their associated characteristics in stroke and TIA patients. The large number of patients and extensive search strategy contributed to the reliability of this study. In addition, our meta-analysis is the first to perform sensitivity analyses for the prevalence rate of UIA in stroke and TIA patients. The analyses revealed that excluding each of the studies from the pooled estimate had no influence on the prevalence rate across all studies globally, indicating the robustness of our findings. Nonetheless, the results of our

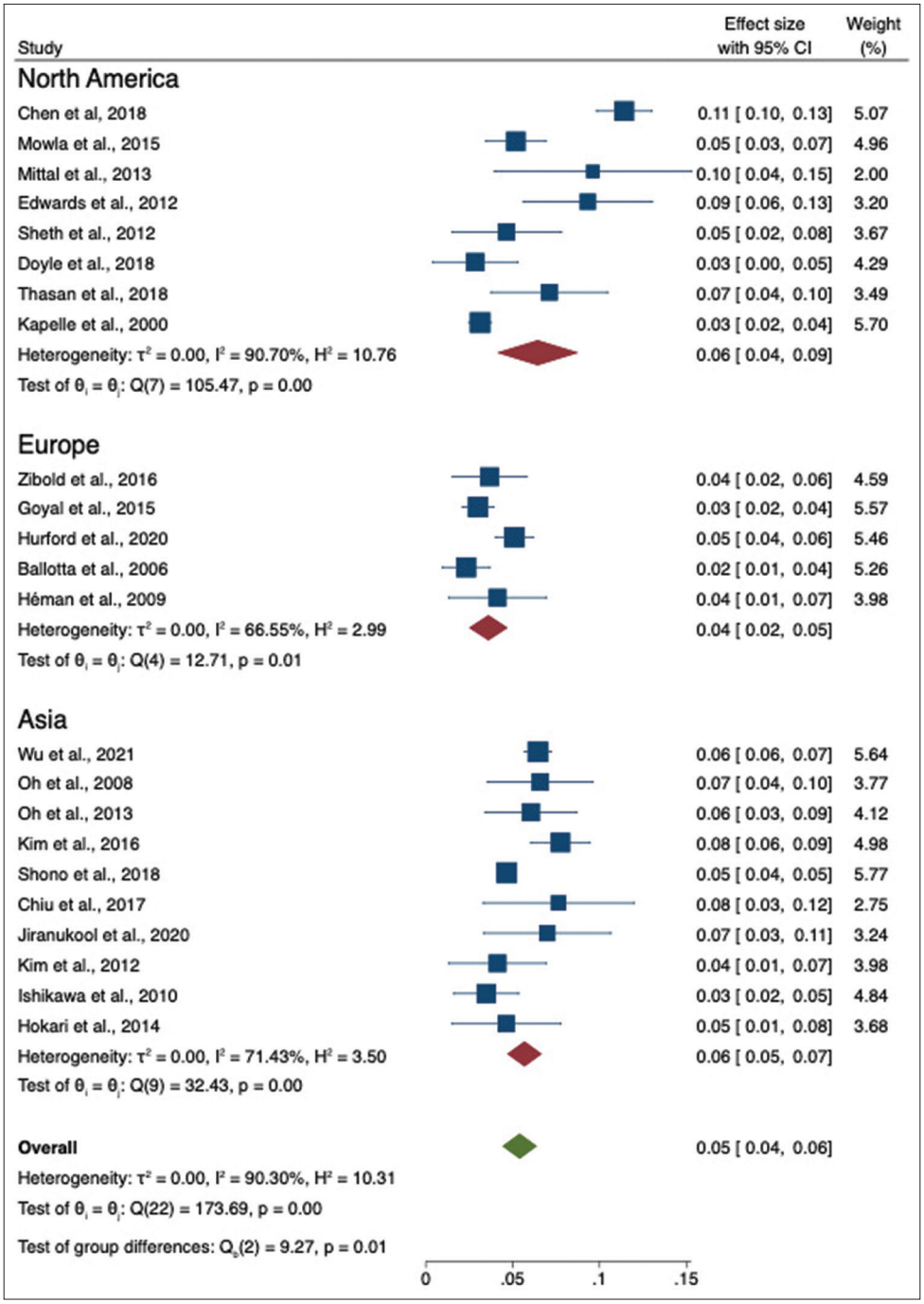

Figure 3: Forest plot of prevalence of unruptured intracranial aneurysms in patients with ischemic stroke or transient ischemic attacks by continent. The blue squares represents the prevalence of UIA in ischemic stroke patients in that study. The lateral lines represents the confidence interval. The red rectangle represents the pooled prevalence for that continent. The green rectangle represents the overall prevalence of all continents.

primary outcome demonstrated considerable heterogeneity (I^2 = 90.3%, P < 0.001) among all studies. To take this into consideration, we used the random-effects model to evenly redistribute the statistical weight of each study for analysis. Finally, data on the prevalence of UIA in stroke and TIA patients was limited to North America, Europe, East Asia, and Southeast Asia. Additional research should aim to assess UIA in stroke and TIA patients in South America, Africa,

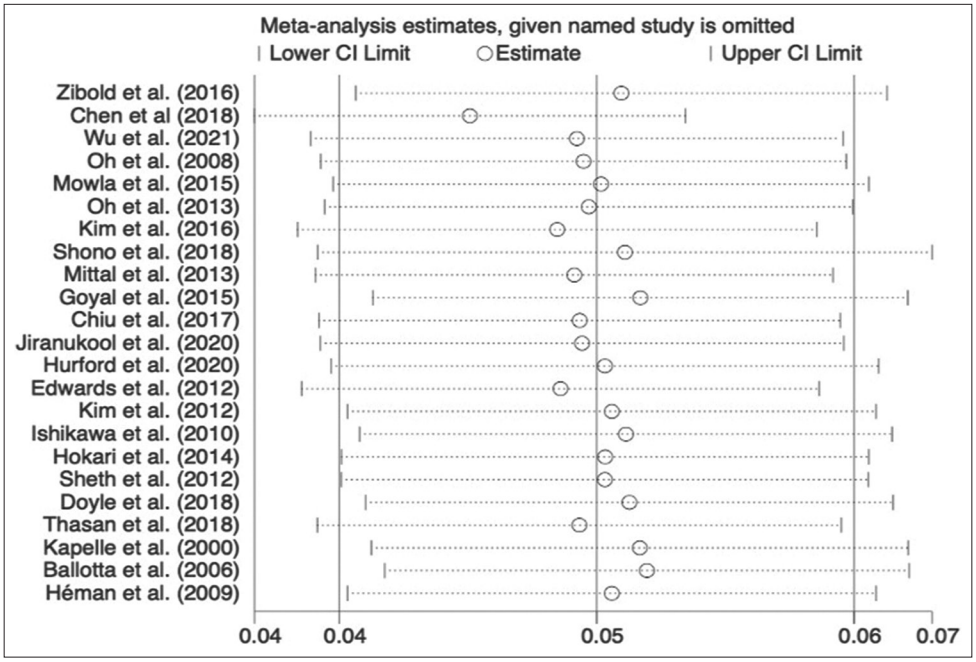

Figure 4: Sensitivity analysis of the prevalence of unruptured intracranial aneurysms in patients with ischemic stroke or transient ischemic attacks. The white circle represents the overall prevalence when removing the study that is on the left side. The lateral lines represents the confidence interval.

Table 2: Factors associated with UIA in stroke and TIA patients.

Characteristic	Number of studies	Number of patients	Odds ratio (95% CI)	I^2 value (%)	Cochran's Q test *P*-value
Male	13	18667	0.60 (0.53–0.68)	31.8	0.121
Large vessel occlusion	8	8083	1.22 (1.01–1.47)	<0.001	0.655
Hypertension	13	18667	1.45 (1.24–1.69)	<0.001	0.695
Smoking	13	18667	1.01 (0.88–1.16)	4.7	0.399
Diabetes	12	18367	0.82 (0.72–0.95)	<0.001	0.729
Dyslipidemia	11	18173	1.07 (0.94–1.22)	<0.001	0.715
Stroke in the anterior circulation	2	542	1.45 (0.39–5.40)	<0.001	0.861
Atrial fibrillation	7	16460	0.99 (0.83–1.17)	<0.001	0.445

UIA: Unruptured intracranial aneurysm, TIA: Transient ischemic attacks, OR: Odds ratio, CI: Confidence interval.

Oceania, and the rest of Asia for global applicability of these analyses.

CONCLUSION

Our meta-analysis suggests that pooled estimates of prevalence of UIA among patients with ischemic stroke and TIA admitted to hospitals is 5% worldwide, with a higher prevalence observed in North America and East Asia. Medical conditions and characteristics such as hypertension and large vessel occlusion were associated with increased risk of UIA in stroke and TIA patients, whereas diabetes and male sex were protective factors. However, the development of UIA in stroke and TIA patients had no association with smoking, dyslipidemia, atrial fibrillation, and stroke in the anterior circulation. Our findings provide helpful information for the recognition of UIA in high-risk populations to provide targeted and prompt control measures to prevent unfavored prognoses.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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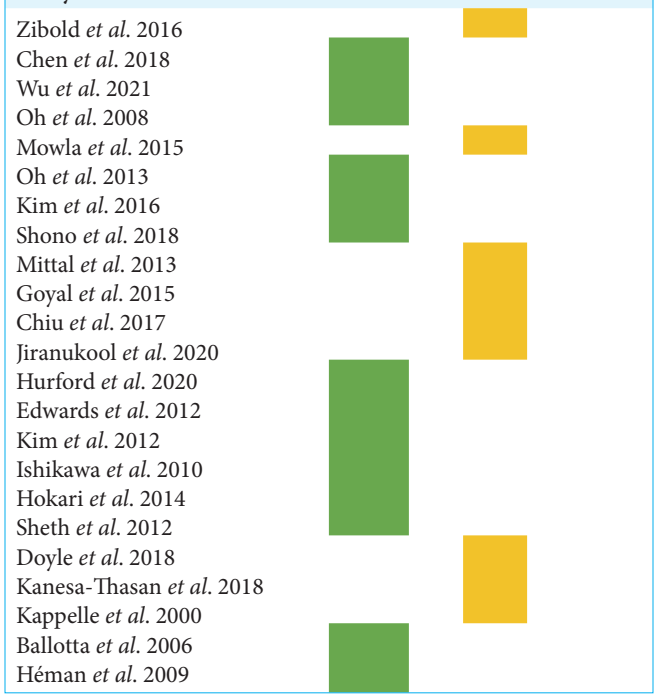
APPENDICES

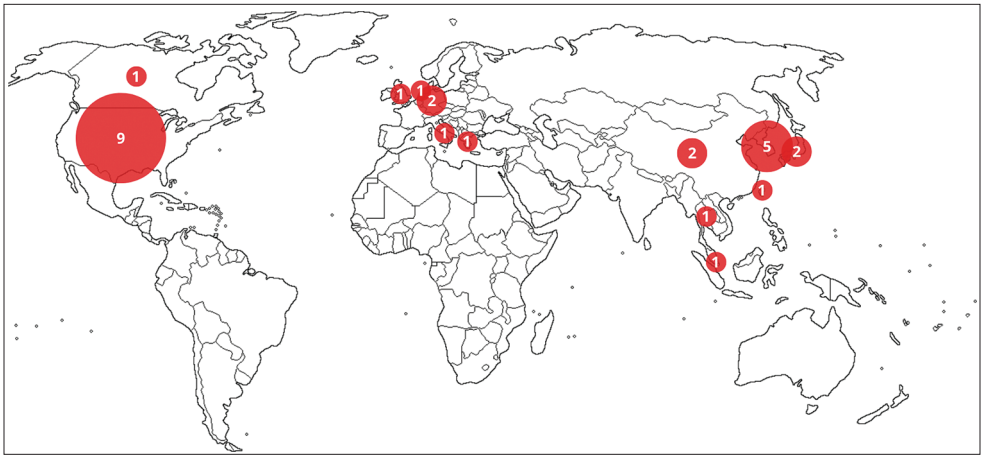
Appendix A: Quality assessment of the articles included.



Appendix B: Raw data for the primary and secondary outcomes.

Author	Year	a	b	c	d
Chen *et al*	2018	31	223	145	1142
Wu *et al.*	2021	39	523	221	3250
Shono *et al.*	2018	95	2056	317	6389
Mittal *et al.*	2013	0	17	10	77
Chiu *et al.*	2017	5	37	6	96
Hurford *et al.*	2020	9	228	73	1299
Sheth *et al.*	2012	3	32	5	132
Chen *et al.*	2018	31	223	145	1142

a: Exposed cases, b: Exposed controls, c: Unexposed cases, d: Unexposed controls



Appendix C: Map providing data on number of studies conducted worldwide. The numbers showed represents the number of studies conducted in each region.