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ABOUT COVER

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Risk factors for stroke recurrence in young patients with first-ever ischemic stroke: A meta-analysis

Yu Xia, Han Liu, Rui Zhu

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Abstract

BACKGROUND

At present, the incidence rate of ischemic stroke in young people is increasing yearly, and the age of onset is increasingly young. Therefore, primary and secondary prevention of ischemic stroke in young people, especially secondary prevention, is particularly crucial.

AIM

We aimed to comprehensively evaluate risk factors for stroke recurrence in first-ever young ischemic stroke (YIS) patients.

METHODS

The meta-analysis was used to quantitatively analyze the research results on risk factors for stroke recurrence in first-ever YIS patients both domestically and internationally. Stata12.0 software was used for heterogeneity testing, publication bias analysis, sensitivity analysis, and the calculation of combined odds ratios and 95% confidence intervals.

RESULTS

The odds ratio (OR) values of the relationship between hypertension and hyperlipidemia and recurrence of first-ever YIS were 1.54 (1.05-2.26) and 1.12 (1.00-1.25), respectively. The OR values of male sex, type 2 diabetes, smoking, drinking and YIS recurrence were 1.66 (0.98-2.79), 1.01 (0.64-1.59), 1.21 (0.83-1.76), and 1.28 (0.82-2.53), respectively. The relationship between male sex, type 2 diabetes, smoking, drinking and YIS recurrence was ambiguous.

CONCLUSION

Hypertension and hyperlipidemia are important risk factors for stroke recurrence in first-ever YIS patients, and active intervention should be taken.

Key Words: Young ischemic stroke; First-ever; Risk factors; Recurrence; Meta-analysis

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Core Tip: This article mainly uses the meta-analysis technology to retrieve stroke risk factors. The meta-analysis is used to quantitatively analyze the research results on risk factors for stroke recurrence in first-ever young ischemic stroke (YIS) patients both domestically and internationally. Finally, we find that hypertension and hyperlipidemia are important risk factors for stroke recurrence in first-ever YIS patients, and active intervention should be taken, in order to realize the precise target intervention of young people with ischemic stroke and reduce the disability rate and mortality rate.

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INTRODUCTION

Worldwide, stroke is the main cause of death and disability and is characterized by high disability rates, high mortality rates, and high recurrence rates[1]. With the rapid development of the economy and society, the incidence rate of ischemic stroke in young people is gradually increasing, and the age of onset is gradually becoming younger. Compared with ischemic stroke in elderly individuals, the etiology of ischemic stroke in young people is more diversified, which leads to certain difficulties in diagnosis.

Research has shown that there are approximately 2 million new youth strokes worldwide each year, with ischemic stroke being the main cause and a high recurrence rate of stroke[2]. However, its treatment methods and effects are still limited. Young people are the backbone of families, society, and even the country. Once they are disabled or even killed, significant damage to society and families occurs. This study used the meta-analysis method in evidence-based medicine to systematically evaluate the research results of risk factors for stroke recurrence in first-ever young ischemic stroke (YIS) patients, explore risk factors for stroke recurrence in first-ever YIS patients, and provide a theoretical basis for formulating preventive measures for YIS patients.

MATERIALS AND METHODS

Literature selection criteria

Inclusion criteria were as follows: (1) The study subjects were YIS patients and met the diagnostic criteria for acute ischemic stroke, as well as the age limit for young stroke (18-50 years of age)[3,4]; (2) the research objective was to explore the risk factors for recurrent stroke after the onset of the first stroke; (3) the experimental design was a case control study or a current or retrospective study that was divided into a case group and a control group, and exposure factors were compared between the two groups; (4) the length of time the research had been conducted or the date that the study occurred had been publicly published; (5) there were clear regulations for sample sizes; and (6) the original data provided odds ratio (OR) values and 95% confidence intervals (95% CIs), or the corresponding data formulas could be used to calculate OR values and 95% CIs.

Exclusion criteria were as follows: Lichtenstein's[5] standards and custom standards were used to evaluate the quality of literature and eliminate literature with poor quality, duplicate reports, incomplete data, and incorrect calculations.

Retrieval methods

Internationally recognized system evaluation retrieval strategies were adopted. The search databases included the China National Knowledge Infrastructure Database (2003-2023), the VIP Database (1989-2023), the Wanfang Database (1981-2023), PubMed, and Web of Science. Published literature on the risk factors for stroke recurrence in first-ever YIS were screened and collected. "Young ischemic stroke", "young cerebral infarction", "young brain infarction" or "young ischemic infarction" and "risk factors" were used as search terms; "risk factors" and "young ischemic stroke" or "ischemic stroke of young adults" were used as search terms; and a combination of subject words and keywords was used to search.

Literature screening and quality evaluation

All retrieved literature was checked for duplicates based on the author, year, and title of the literature. One researcher independently selected the literature, extracted the data, and checked each one before another researcher conducted a review. When selecting literature, we first read the title and abstract, and after excluding significantly unrelated literature, we further read the entire text to determine whether it was ultimately included. For literature that met the inclusion

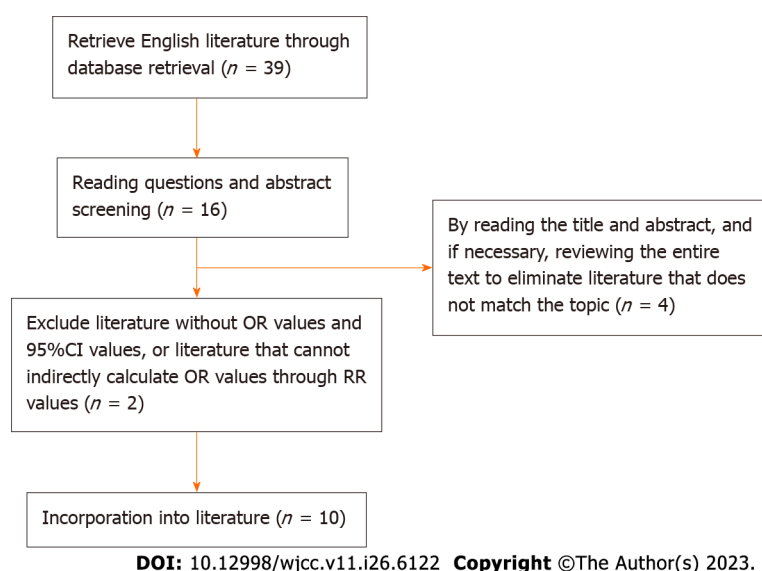


Figure 1 Flow chart showing the search strategy. OR: Odds ratio RR: Relative risk.

criteria, the content of data extraction mainly included author, year, sample size, and journal name.

Data extraction

According to the above retrieval method, a total of 39 English studies were retrieved and screened according to the inclusion and exclusion criteria. Finally, a total of 10 studies were found to be consistent with the research topic of this article. Please refer to the flowchart in [Figure 1](#) for details.

Statistical methods

The statistical software Stata 12.0 provided by the International Evidence Based Medicine Collaboration Network was used to conduct heterogeneity testing on the collected data and to calculate the combined OR values and 95% CIs. (1) When heterogeneity test results of $P > 0.05$ were obtained, a fixed-effects model was used for meta-analysis; when heterogeneity test results of $P \leq 0.05$ were obtained, a random-effects model was used; (2) The merged OR value and 95%CI and whether there was statistical significance were determined based on whether the OR value was within the 95%CI; and (3) When the number of included studies was ≥ 6 , a funnel plot analysis was used to determine whether there was publication bias.

RESULTS

Basic information of the included literature

According to the above retrieval strategy, a total of 39 English studies were retrieved and screened according to the inclusion and exclusion criteria. Finally, a total of 10 studies were included in this study, with a total of 3291 cases and 8270 controls. The basic information of the included literature is detailed in [Table 1](#).

Literature quality evaluation and risk assessment

Researchers used the NOS to evaluate the quality of the literature. If there were any differences, they could resolve them through consultation or consultation with third parties. NOS includes 4 items for "research object selection" (4 points), 1 item for "inter group comparability" (2 points), and 3 items for "outcome measurement" (3 points), with a maximum score of 9 points. A score of ≥ 6 points was considered high-quality literature, and a score of < 6 points was considered low-quality literature ([Table 2](#)).

Main meta-analysis results of risk factors for stroke recurrence in first-ever YIS

According to the research contents included in the literature and the number of references for each risk factor, this study selected six risk factors for systematic evaluation: male sex, hypertension, hyperlipidemia, type 2 diabetes, smoking, and drinking.

Heterogeneity test: A heterogeneity test was carried out on the references of various risk factors. The literature on the relationship between hyperlipidemia, type 2 diabetes, drinking and the incidence of YIS had good consistency ($P > 0.05$); therefore, the fixed-effects model was used. There was heterogeneity ($P < 0.05$) in the literature on the relationship between male sex, hypertension, smoking, and the onset of YIS; therefore, a random-effects model was used.

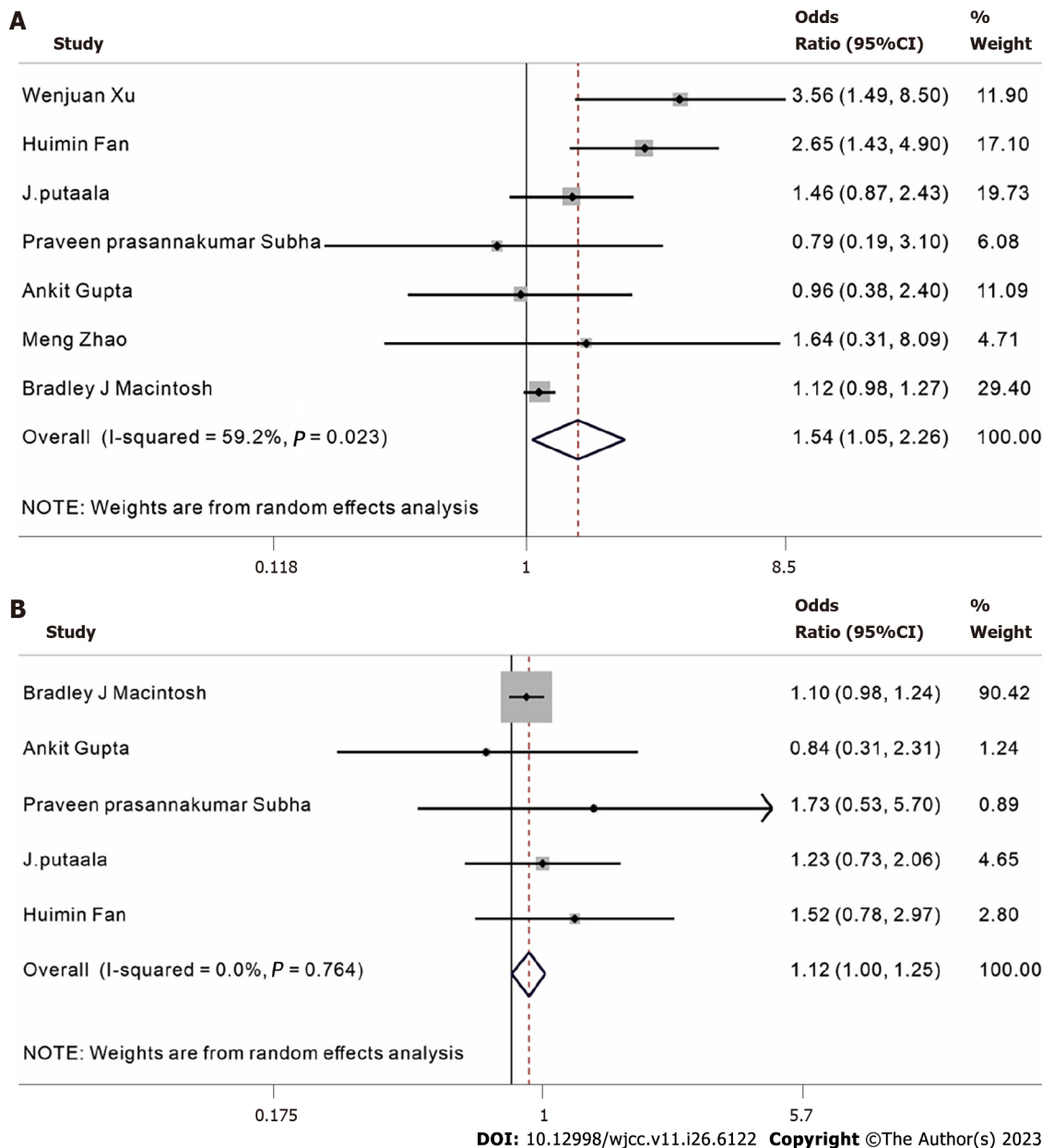


Figure 2 Forest map. A: The impact of hypertension on stroke recurrence in young ischemic stroke (YIS) patients; B: The impact of hyperlipidemia on stroke recurrence in YIS patients.

Meta-analysis results: The results showed that the combined OR values of hypertension and hyperlipidemia were both greater than 1 and statistically significant. Therefore, it was a risk factor for stroke recurrence in first-ever YIS patients (Figure 2). The combined OR values of male sex, type 2 diabetes, smoking and drinking were 1.66, 1.01, 1.21 and 1.28, respectively, but the 95%CI included "1", so this study cannot consider male sex, type 2 diabetes, smoking and drinking as risk factors for stroke recurrence in patients with first-ever YIS (Table 3).

Publication bias analysis

The publication bias analysis of hypertension was conducted using $\text{se}[\log(\text{or})]$ as the x-axis and $\log[\text{or}]$ as the y-axis to plot a funnel plot of the relationship between hypertension and first-ever YIS stroke recurrence. The results showed that the funnel plot symmetry of hypertension was poor, indicating the presence of publication bias (Figure 3A).

The published bias analysis of type 2 diabetes used $\text{se}[\log(\text{OR})]$ of the reference as the abscissa and $\log[\text{OR}]$ as the ordinate to draw a funnel chart of the relationship between type 2 diabetes and first-ever YIS stroke recurrence. The results showed that the funnel plot symmetry of type 2 diabetes was relatively poor, suggesting that there might be publication bias (Figure 3B).

Sensitivity analysis of hypertension

Sensitivity analysis was conducted on hypertension using a one-by-one exclusion method. The sensitivity analysis results suggested excluding any study (except for the research paper published by Bradley Macintosh in 2021), and the combined

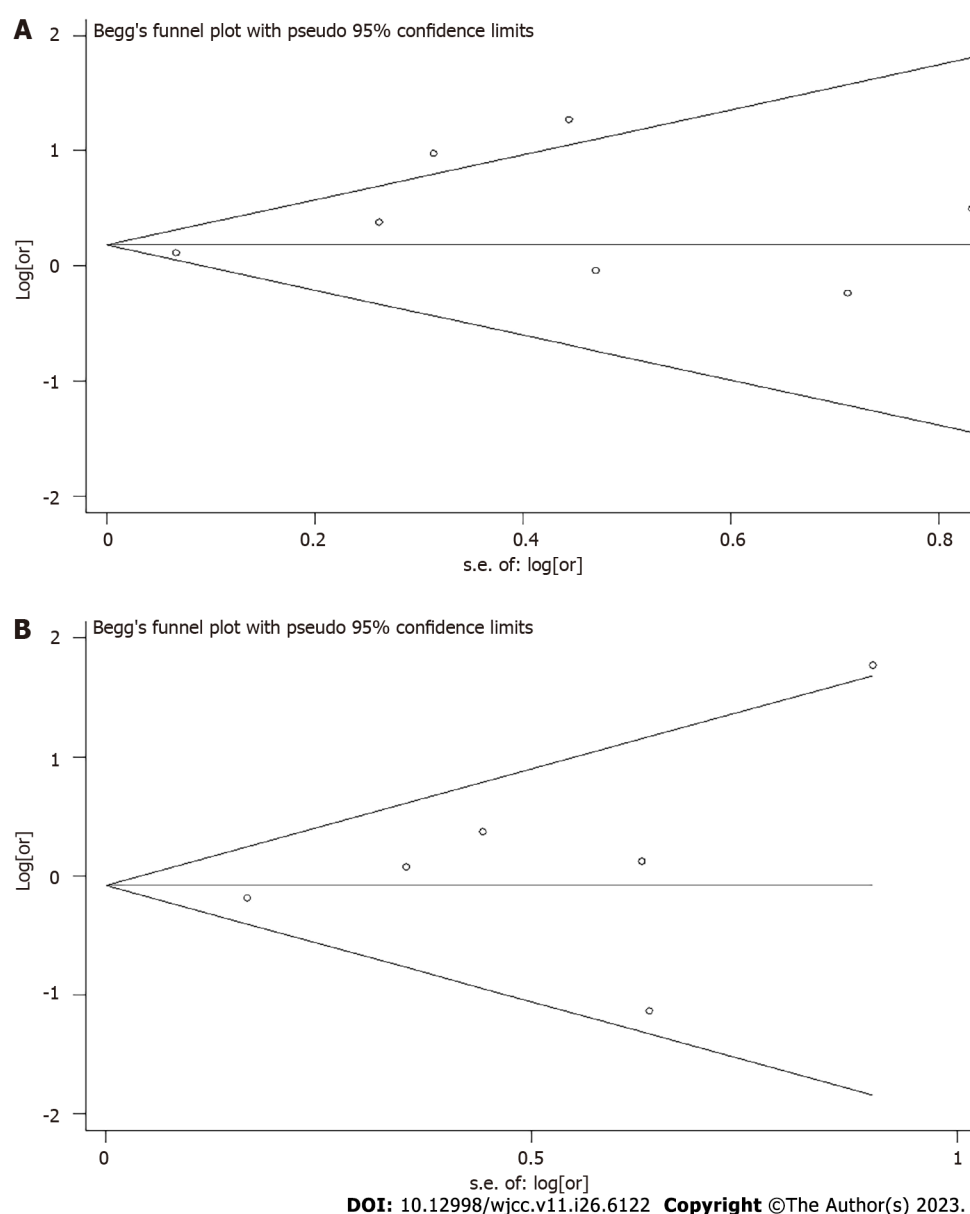


Figure 3 Funnel plot. A: The relationship between hypertension and recurrence of young ischemic stroke (YIS); B: The relationship between type 2 diabetes and YIS stroke recurrence.

results of the remaining studies were statistically significant (95%CI value excluding 1), consistent with the original merged results (95%CI value excluding 1), indicating that the research results were relatively stable. The slightly higher heterogeneity of hypertension might be related to the research paper published by MacIntosh *et al*[6] in 2021, but the overall results were relatively stable and had high credibility (Figure 4).

DISCUSSION

Ischemic stroke is a disease with a high incidence rate, high recurrence rate and high disability rate, affecting approximately 12 million patients worldwide every year, of which approximately 10% occur in individuals under 50 years old[7, 8]. At present, the definition of youth stroke is not yet unified, and different studies have different definitions of its age limit. We defined young ischemic stroke based on the age range used in multiple large-scale studies, which was 18-50 years old[8-10]. Compared with elderly ischemic stroke, there were certain differences in the risk factors and etiology of the first onset and recurrence of YIS, and different studies had similar or conflicting views[11-19]. Therefore, this article adopted the method of meta-analysis to eliminate false information while retaining true information and to eliminate relatively unreliable research conclusions, and we strived to identify high-risk key factors that led to recurrent stroke in YIS patients after their first onset to minimize the disability or even mortality rate of YIS patients as much as possible.

This study showed that the combined OR values of hypertension and hyperlipidemia were both greater than 1, and that result was statistically significant. Therefore, it was a risk factor for stroke recurrence in first-ever YIS patients

Table 1 Basic Information of selected literature

| Number | Ref. | Number of cases | Number of controls | Publication of journals |
|--------|----------------------------------|-----------------|--------------------|--|
| 1 | Yang <i>et al</i> [11], 2016 | 64 | 171 | <i>Neuroscience</i> |
| 2 | Xu <i>et al</i> [12], 2021 | 110 | 139 | <i>BMC Neurology</i> |
| 3 | Fan <i>et al</i> [13], 2018 | 74 | 358 | <i>Medicine</i> |
| 4 | Putala <i>et al</i> [14], 2009 | 86 | 550 | <i>Neurology</i> |
| 5 | Song <i>et al</i> [15], 2017 | 293 | 64 | <i>International Journal of Neuroscience</i> |
| 6 | Subha <i>et al</i> [16], 2015 | 15 | 85 | <i>Ann Indian Acad Neurol</i> |
| 7 | Gupta <i>et al</i> [17], 2022 | 63 | 63 | <i>Annals of Indian Academy</i> |
| 8 | Vibo <i>et al</i> [18], 2021 | 273 | 164 | <i>European Stroke</i> |
| 9 | Zhao <i>et al</i> [19], 2017 | 121 | 575 | <i>World Neurosurgery</i> |
| 10 | MacIntosh <i>et al</i> [6], 2021 | 2192 | 6101 | <i>Journal of the American Heart Association</i> |

Table 2 Methodological quality evaluation results of included literature (Unit: Points)

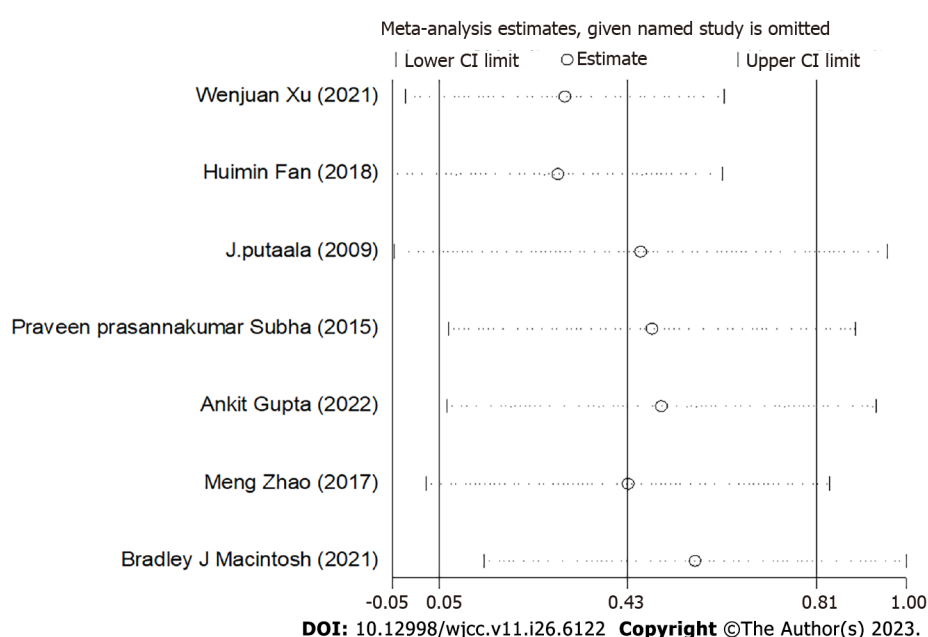
| Ref. | Research selection | Intergroup comparability | Result measure | Literature quality |
|----------------------------|--------------------|--------------------------|----------------|--------------------|
| Yang <i>et al</i> [11] | 4 | 2 | 3 | 9 |
| Xu <i>et al</i> [12] | 4 | 1 | 3 | 8 |
| Fan <i>et al</i> [13] | 3 | 2 | 3 | 8 |
| Putala <i>et al</i> [14] | 3 | 2 | 3 | 8 |
| Song <i>et al</i> [15] | 4 | 2 | 2 | 8 |
| Subha <i>et al</i> [16] | 4 | 2 | 2 | 8 |
| Gupta <i>et al</i> [17] | 3 | 2 | 3 | 8 |
| Vibo <i>et al</i> [18] | 4 | 2 | 3 | 9 |
| Zhao <i>et al</i> [19] | 3 | 2 | 3 | 8 |
| MacIntosh <i>et al</i> [6] | 3 | 2 | 2 | 7 |

(Figure 2). The combined OR values of male sex, type 2 diabetes, smoking and drinking were 1.66, 1.01, 1.21 and 1.28, respectively, but the 95% CI included "1", so this study cannot consider male sex, type 2 diabetes, smoking and drinking as risk factors for stroke recurrence in patients with first-ever YIS (Table 3). Research has shown that hypertension changes the cerebrovascular system through the deposition of fibrin in blood vessels and the hypertrophy of smooth muscles, thus causing atherosclerosis and ultimately leading to stenosis or occlusion of blood vessels in the affected area and secondary cerebral ischemia[20]. Many scholars believe that hypertension destroys the integrity of the blood-brain barrier and increases the vascular permeability of the brain, which is the precursor of serious cerebrovascular damage and one of the primary causes of stroke[21-25]. This study found that hypertension was an independent risk factor for stroke recurrence in first-ever YIS patients. Therefore, YIS patients must reduce their blood pressure in a timely manner, but excessive blood pressure reduction should be avoided, as that could lead to hypoperfusion injury. Grade-3 hypertension blood pressure management concepts could be followed (gentle, morning rise, long-term compliance), and more attention should be given to the systolic blood pressure of first-ever YIS patients. Several studies[26-29] showed that platelet activation was closely related to the degree of atherosclerosis. Atherosclerosis is mainly caused by dyslipidemia. Plasma lipids existed in the form of lipoproteins. Plasma endogenous triglycerides were bound to low-density lipoprotein (LDL) and very low density lipoproteins (VLDL) and transported. The increase in endogenous triglycerides in plasma was essentially an increase in LDL and VLDL. Cells absorb more cholesterol from LDL and VLDL particles, leading to an increase in cholesterol and phospholipid content in patients' platelets and enhanced platelet activity. Therefore, it could be considered that the effect of endogenous triglycerides on platelet aggregation function was essentially the effect of elevated LDL and VLDL on platelet aggregation function.

Some scholars have reported that compared with women, men might have more bad habits (such as smoking, excessive drinking, staying up late, heavy physical labor, *etc.*) due to high social pressure, which may be related to the formation of carotid atherosclerotic plaques, but male sex might not have a fundamental impact or role in the recurrence of ischemic stroke[30,31]. This study also concluded that there was no clear correlation between male sex and recurrent cerebral infarction after the first ischemic stroke in young people. It is well known that chronic hyperglycemia leads to endothelial dysfunction, inflammation and accelerated atherosclerosis processes, resulting in macrovascular complica-

Table 3 Meta-analysis results of stroke recurrence in young ischemic stroke patients

| Risk factor | Number of merged literature | Case group | Control group | P , % | P value | Metaanalysis model | Merge OR values | 95%CI |
|-----------------|-----------------------------|------------|---------------|---------|-----------|---------------------|-----------------|-------------|
| Male | 5 | 2678 | 7049 | 80.80 | < 0.001 | Random effect model | 1.66 | (0.98-2.79) |
| Hypertension | 7 | 2661 | 7871 | 59.20 | 0.023 | Random effect model | 1.54 | (1.05-2.26) |
| Hyperlipidemia | 5 | 2430 | 7157 | 0.00 | 0.764 | Fixed effect model | 1.12 | (1.00-1.25) |
| Type 2 diabetes | 6 | 2551 | 7732 | 42.70 | 0.12 | Fixed effect model | 1.01 | (0.64-1.59) |
| Smoking | 5 | 2430 | 7157 | 71.10 | 0.008 | Random effect model | 1.21 | (0.83-1.76) |
| Drinking | 3 | 152 | 506 | 41.10 | 0.183 | Fixed effect model | 1.28 | (0.82-2.53) |

**Figure 4 Sensitivity analysis of the relationship between hypertension and young ischemic stroke recurrence.**

ations due to the effects of increased oxidant production, lipoprotein enrichment and the formation of advanced glycation end products. Long-term hyperglycemia could also damage vascular endothelial cells, increase the adhesion of blood-forming components, and lead to circulatory dysfunction leading to ischemia[32-34]. However, this article did not find that type 2 diabetes was a risk factor for the recurrence of ischemic stroke in young people who had ischemic stroke for the first time. According to our speculation, the reason may be that the recurrence of ischemic stroke may mainly depend on the blood sugar control level of type-2 diabetes patients (the blood sugar control level can be monitored by glycosylated hemoglobin and other indicators). If the blood sugar of patients is well controlled, it may not quickly lead to the serious damage to endothelial cells that could cause severe atherosclerotic plaque formation. In addition, this article did not find a fundamental impact of smoking and alcohol consumption on first-ever ischemic stroke in young people, which may be due to bias in the records of previous medical history by relevant scholars (such as whether they quit smoking, specific daily smoking counts and durations, whether they quit drinking, specific daily alcohol consumption and durations, *etc.*). In the end, when comparing and analyzing the results, due to insufficient data, recording accuracy and incomplete typing, there would be bias in the classification and statistical results. This may also be due to the limited impact of smoking and alcohol consumption on endothelial cell damage, which would not directly lead to the recurrence of ischemic stroke.

In conclusion, among the six risk factors screened above, hypertension and hyperlipidemia were important risk factors for stroke recurrence in patients with first-ever YIS. Although male sex, type 2 diabetes, smoking, and alcohol consumption may damage vascular endothelial cells, their role in the recurrence of ischemic stroke may be limited. Therefore, we must attach great importance to the blood pressure levels of young first-ever ischemic stroke patients, especially the control of ambulatory blood pressure levels. In addition, hyperlipidemia was also a key risk factor for

stroke recurrence, and it was necessary to actively monitor blood lipid levels and control them within a reasonable range. Finally, it is hoped that more large-scale, prospective, and high-quality clinical studies will be conducted in the future to observe the relevant risk factors for first-ever ischemic stroke in young people while striving to minimize the disability and even mortality rates of patients, thereby improving the quality of life and health level of young people.

CONCLUSION

This meta-analysis revealed that hypertension and hyperlipidemia were important risk factors for stroke recurrence in first-ever YIS patients, and active intervention should be taken.

ARTICLE HIGHLIGHTS

Research background

At present, the incidence rate of ischemic stroke in young people is increasing yearly, and the age of onset is increasingly young. Therefore, primary and secondary prevention of ischemic stroke in young people, especially secondary prevention, is particularly crucial.

Research motivation

We aimed to comprehensively evaluate risk factors for stroke recurrence in first-ever young ischemic stroke (YIS) patients.

Research objectives

We aimed to comprehensively evaluate risk factors for stroke recurrence in first-ever young ischemic stroke (YIS) patients.

Research methods

The meta-analysis was used to quantitatively analyze the research results on risk factors for stroke recurrence in first-ever YIS patients both domestically and internationally. Stata12.0 software was used for heterogeneity testing, publication bias analysis, sensitivity analysis, and the calculation of combined odds ratios and 95% confidence intervals.

Research results

The OR values of the relationship between hypertension and hyperlipidemia and recurrence of first-ever YIS were 1.54 (1.05-2.26) and 1.12 (1.00-1.25), respectively. The OR values of male sex, type 2 diabetes, smoking, drinking and YIS recurrence were 1.66 (0.98-2.79), 1.01 (0.64-1.59), 1.21 (0.83-1.76), and 1.28 (0.82-2.53), respectively. The relationship between male sex, type 2 diabetes, smoking, drinking and YIS recurrence was ambiguous.

Research conclusions

Hypertension and hyperlipidemia are important risk factors for stroke recurrence in first-ever YIS patients, and active intervention should be taken.

Research perspectives

This paper investigates the independent recurrence risk factors of first-ever young ischemic stroke patients and assesses the importance and criticality of traditional risk factors.

FOOTNOTES

Author contributions: Xia Y is responsible for statistical processing and writing of papers; Liu H is responsible for reviewing the paper; Zhu R is responsible for the quality control, review, and supervision of paper data.

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