

Review

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# Risk and Cumulative Risk of Acute Ischemic Stroke Recurrence in China: A Systematic Review and Meta-Analysis

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## Abstract

**Objective:** To comprehensively evaluate the risk of recurrence after initial ischemic stroke, and to provide a relatively comprehensive reference for the prevention and control of stroke recurrence.

**Methods:** CNKI, VIP, Wanfang, PubMed, Web of Science, Embase and other databases were collected to investigate the status of recurrence after initial ischemic stroke, the search period of which was from the establishment of databases to March 2019. And then quality evaluation and data extraction were carried out. The overall cumulative risks of stroke recurrence at 3 months, 6 months, 1 year, 2 years and 5 years after initial ischemic stroke were calculated, and heterogeneity analysis was performed.

**Results:** A total of 29 studies from 19 provinces (cities, autonomous regions) in China were included. The cumulative total sample size was 22 484 cases, the cumulative recurrent sample size was 3 309 cases. The pooled cumulative risk was 4.5% (95% CI: 3.1-5.8) at 3 months, 7.8% (95% CI: 5.6-10.0) at 6 months, 13.6% (95% CI: 11.0-16.2) at 1 year, 17.5% (95% CI: 12.4-22.6) at 2 years and 30.9% (95% CI: 20.2-41.7) at 5 years after initial ischemic stroke.

**Conclusions:** The recurrence rate of acute ischemic stroke in China is high. It is recommended that all levels of medical and health departments strengthen the prevention and treatment of ischemic stroke recurrence to reduce the recurrence of ischemic stroke and improve the prognosis of patients.

**Key words:** Acute ischemic stroke; Recurrence; Meta-analysis; Frequency

## Introduction

Acute ischemic stroke (AIS) has long been the focus of global stroke prevention and control, which is attributed to its high disability, high mortality and high recurrence rate.

The recurrence of AIS will aggravate the deterioration of neurological function, and increase the risk of bad clinical outcome of stroke. It brings irreparable loss to the patients' life and health. The overall situation of stroke recurrence has been reported in foreign countries<sup>[1]</sup>. Although a large number of epidemiological investigations have been carried out on the recurrence of AIS in China,

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there is still a lack of overall description and systematic evaluation of the related situation. Based on this, a meta-analysis was used to comprehensively analyze the pooled cumulative risk of stroke recurrence at 3, 6 months and 1, 5, 10 years after initial ischemic stroke in China, in order to fully understand the epidemic situation of stroke recurrence in China in an all-round way. It provides a relatively comprehensive reference for medical workers and researchers.

## Materials and Methods

### Search strategy

The literatures on the risk of recurrence of acute ischemic stroke were systematically collected according to the principle of free subject words. The sources of the literatures included CNKI, Wanfang Database, VIP Database, PubMed, Web of Science, The Cochrane Library, CINAHL, EMBASE. And the search period was from the establishment of databases to March 2019. Chinese retrieval terms included: “中风 / 缺血性中风 / 脑血管病 / 脑血管意外 / 脑栓塞 / 脑血栓 / 脑梗塞”, “复发”. English retrieval terms included: “stroke / ischemic stroke / ischemia cerebra / cerebral ischemia / cerebral infarction / cerebrovascular disease / cerebral vascular accident / cerebrovascular accident / brain vascular accident / PostStroke”, “recurrent / recurrence”. In addition, there was in the way of snowball to trace back to the citation.

### Correlation definition

**Initial ischemic stroke:** The patients with initial stroke were diagnosed according to the diagnostic criteria of ischemic stroke established by the 4<sup>th</sup> National Conference on Cerebrovascular Diseases in 1995 and supported by CT or MRI.

**Recurrent ischemic stroke:** The initial attack was relieved, and more than 28 days later, the new central nervous system damage appeared again, the localization signs or the original symptoms were aggravated, which was confirmed by the skull CT or MRI.

### Selection Criteria

**Inclusion criteria:** (1) Chinese stroke patients were

diagnosed in China; (2) There were clear diagnoses of ischemic stroke and its recurrence; (3) The study was designed as a cohort study; (4) The recurrence rate of ischemic stroke was provided directly or indirectly.

**Exclusion criteria:** (1) Lectures, reviews, case reports, etc; (2) Experimental studies of basic medicine; (3) Literatures with repeated publication of the same data, incomplete original data, no full text, unclear types of research, and erroneous data statistics.

### Literature screening and data extraction

Endnote X8 was used for screening and data extraction, and 2 researchers independently browsed the papers and abstracts for the preliminary screening, read through the full text and completed the re-screening. In case of disagreement, the third party decided. Data extraction included: first author, published year, region, recurrence cases, total follow-up cases, etc.

### Literature quality evaluation

The Newcastle-Ottawa quality assessment table (Newcastle-Ottawa Scale, NOS) was used to evaluate the quality of the included literature based on the following 3 aspects: the selection of the study population, the comparability between groups, and the exposure factors. Those with score  $\geq 5$  points could be included in meta analysis. If the score was more than 5 points, the meta analysis could be carried out. The 2 researchers independently and mutual-blindly completed the process, and then compared the evaluation results with each other. In case of disagreement, the results were decided by a third party.

### Statistical analyses

The double-chord transform method was used to transform the data. And then Metaprop of the Stata software was used to calculate the progressive rate of the data. The heterogeneity between the included literature was tested by  $I^2$  value and Q test. When  $P > 0.1$ ,  $I^2 \leq 50\%$ , the studies were considered to be homogeneous, and then the fixed effect model was used to combine the effect values, otherwise the random effect model was used. The sensitivity analysis was carried out to verify the stability

of the combined effect values by item-by-item exclusion of the single included study. The publication bias was quantitatively evaluated based on the Egger test. The difference was statistically significant when  $P < 0.05$ .

## Results

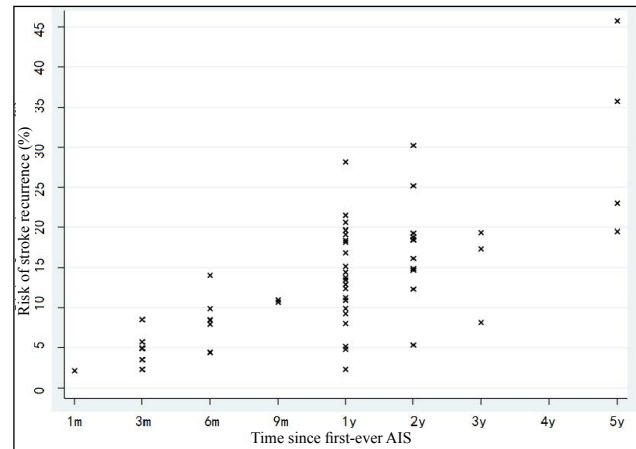
### Literature inclusion and quality evaluation

Three-thousand five-hundred eighty-one studies were identified by the electronic database searches. After re-checking, browsing the abstracts, reading the full text and other layers of screening, there was finally ended up with 29 documents<sup>[3-31]</sup>. The cumulative total sample size was 22 484 cases, and the cumulative recurrent sample size was 3 142 cases. The recurrent time of the subjects ranged from 1991 to 2016, and the follow-up time ranged from 3 months to 5 years. The research sites covered 19 provinces in China. The quality evaluation score of the included literature was at least 5 points, with a maximum of 8 points. The estimates of risk of acute ischemic stroke recurrence across all the included studies was shown in Figure 1.

### Meta analysis results

**The recurrence rate at 3 months after first-ever AIS:** 6 studies<sup>[6, 14, 20, 21, 25, 31]</sup> (a total of 4 450 patients) reported the recurrence rate at 3 months after AIS, with a cumulative recurrence rate of 2.28% to 8.52%. Statistical heterogeneity was found among the studies ( $P = 0.001$ ,  $I^2 = 76.1\%$ ), so random effect model was used to analyze the combined effects. The results showed that the cumulative recurrence rate was 4.5% (95% CI: 3.1-5.8) at 3 months after initial AIS, as shown in Figure 2.

**The recurrence rate at 6 months after first-ever AIS:** 7 studies<sup>[6, 14, 18, 20, 21, 25, 31]</sup> (a total of 4 626 patients) reported the recurrence rate at 6 months after acute ischemic stroke, with a cumulative recurrence rate of 4.39% to 14.07%. Statistical heterogeneity was found among the studies ( $P < 0.001$ ,  $I^2 = 86.1\%$ ), so random effect model was used to analyze the combined effects. The results showed that the cumulative recurrence rate was 7.8% (95% CI: 5.6-10.0) at 6 months after first-ever AIS, as shown in Figure 3.



**Figure 1 Risk of AIS recurrence across all studies**

Notes: “m” refers to month(s); “y” refers to year(s)

**The recurrence rate at 1 year after first-ever AIS:** 23 studies<sup>[3, 6, 8, 10-17, 19-27, 29-31]</sup> (a total of 20 618 patients) reported the recurrence rate of AIS at 1 year after acute ischemic stroke, with a cumulative recurrence rate of 4.8% to 28.19%. Statistical heterogeneity was found among the studies ( $P = 0.000$ ,  $I^2 = 97.9\%$ ), so random effect model was used to analyze the combined effects. The results showed that the cumulative recurrence rate was 13.6% (95% CI: 11.0-16.2) at 1 year after first-ever AIS, as shown in Figure 4.

**The recurrence rate at 2 years after first-ever AIS:** 11 studies<sup>[4-5, 7, 10-11, 13, 15, 20, 22, 24, 28]</sup> (a total of 11 427 patients) reported the recurrence rate at 2 years after initial AIS, with a cumulative recurrence rate of 5.34% to 30.26%. Statistical heterogeneity was found among the studies ( $P < 0.001$ ,  $I^2 = 97.8\%$ ), so random effect model was used to analyze the combined effects. The results showed that the cumulative recurrence rate was 17.5% (95% CI: 12.4-22.6) at 2 years after initial AIS, as shown in Figure 5.

**The recurrence rate at 5 years after first-ever AIS:** 4 studies<sup>[9, 13, 19-20]</sup> (a total of 2 508 patients) reported the recurrence rate at 5 years after initial AIS, with a cumulative recurrence rate of 19.55% to 45.78%. Statistical heterogeneity was found among the studies ( $P < 0.001$ ,  $I^2 = 97.3\%$ ), so random effect model was used to analyze the combined effects. The results showed that the cumulative recurrence rate was 30.9% (95% CI: 20.2-41.7) at 5 years after AIS, as shown in Figure 6.

**Table 1** The basic situation and quality evaluation of AIS recurrence risk in literature

| Authors                         | Year of publication | Initial study period | Area         | Sample size     |             | Cumulative risk of stroke recurrence (%) |     |     |     |     | NOS score |
|---------------------------------|---------------------|----------------------|--------------|-----------------|-------------|--|-----|-----|-----|-----|-----------|
|                                 |                     |                      |              | Recurrent cases | Total cases | 3 m                                      | 6 m | 1 y | 2 y | 5 y |           |
| Chen Peng <sup>[3]</sup>        | 2014                | 2011-2012            | Ningxia      | 79              | 401         | ...                                      | ... | 79  | ... | ... | 7         |
| Zheng Jianghuan <sup>[4]</sup>  | 2015                | 2010-2013            | Guizhou      | 30              | 162         | ...                                      | ... | ... | 30  | ... | 8         |
| Li Qi <sup>[5]</sup>            | 2014                | 2011-2014            | Hainan       | 27              | 143         | ...                                      | ... | ... | 27  | ... | 8         |
| Luan Mei <sup>[6]</sup>         | 2016                | 2013-2015            | Chongqing    | 41              | 270         | 23                                       | 38  | 41  | ... | ... | 8         |
| Su Changqing <sup>[7]</sup>     | 2014                | 2011-2014            | Fujian       | 31              | 123         | ...                                      | ... | ... | 31  | ... | 7         |
| Song Li <sup>[8]</sup>          | 2008                | 2005-2007            | Liaoning     | 58              | 421         | ...                                      | ... | 58  | ... | ... | 8         |
| Cheng Yuefeng <sup>[9]</sup>    | 2017                | 2011-2016            | Heilongjiang | 206             | 450         | ...                                      | ... | ... | ... | 206 | 7         |
| An Yachen <sup>[10]</sup>       | 2017                | 2013-2016            | Hebei        | 184             | 1058        | ...                                      | ... | 98  | 158 | ... | 8         |
| Chen Yunxia <sup>[11]</sup>     | 2011                | 2008-2010            | Hebei        | 79              | 408         | ...                                      | ... | 55  | 79  | ... | 8         |
| Zhang Shenning <sup>[12]</sup>  | 2008                | 2004-2006            | Jiangsu      | 160             | 834         | ...                                      | ... | 160 | ... | ... | 7         |
| Zheng Shengbang <sup>[13]</sup> | 2017                | 2010-2015            | Shanghai     | 233             | 651         | ...                                      | ... | 140 | 197 | 233 | 7         |
| Wang Jing <sup>[14]</sup>       | 2016                | 2013-2015            | Zhejiang     | 35              | 282         | 14                                       | 24  | 35  | ... | ... | 8         |
| Tang Meilian <sup>[15]</sup>    | 2016                | 2014-2015            | China        | 647             | 6450        | ...                                      | ... | 148 | 345 | ... | 8         |
| Zhang Changqing <sup>[16]</sup> | 2018                | 2007-2009            | China        | 95              | 1978        | ...                                      | ... | 95  | ... | ... | 7         |
| Zhao Yan <sup>[17]</sup>        | 2014                | 2010-2012            | Henan        | 105             | 812         | ...                                      | ... | 105 | ... | ... | 6         |
| Ma Juanjuan <sup>[18]</sup>     | 2015                | 2013-2015            | Jiangsu      | 14              | 176         | ...                                      | 14  | ... | ... | ... | 5         |
| Yan Zhongrui <sup>[19]</sup>    | 1998                | 1991-1996            | Shandong     | 112             | 573         | ...                                      | ... | 46  | ... | 112 | 7         |
| Wang Liping <sup>[20]</sup>     | 2005                | 1994-1999            | Henan        | 192             | 834         | 19                                       | 37  | 94  | 135 | 192 | 6         |
| Duan Kangli <sup>[21]</sup>     | 2018                | 2014-2015            | Shanxi       | 115             | 2230        | 78                                       | 98  | 115 | ... | ... | 6         |
| Yang Junping <sup>[22]</sup>    | 2014                | 2009-2013            | Henan        | 97              | 786         | ...                                      | ... | 78  | 97  | ... | 5         |
| Zhang Ming <sup>[23]</sup>      | 2016                | 2010-2015            | Shandong     | 49              | 269         | ...                                      | ... | 49  | ... | ... | 6         |
| Xue Min <sup>[24]</sup>         | 2013                | 2008-2011            | Anhui        | 90              | 612         | ...                                      | ... | ... | 90  | ... | 6         |
| Wang Xiaoqing <sup>[25]</sup>   | 2018                | 2014-2016            | Hebei        | 76              | 450         | 22                                       | 38  | 76  | ... | ... | 6         |
| Chen Jingfei <sup>[26]</sup>    | 2015                | 2012-2014            | Ningxia      | 43              | 233         | ...                                      | ... | 43  | ... | ... | 5         |
| Xu Lina <sup>[27]</sup>         | 2018                | 2014-2016            | Shanxi       | 45              | 311         | ...                                      | ... | 45  | ... | ... | 5         |
| Zhang Youlin <sup>[28]</sup>    | 2012                | 2007-2009            | Beijing      | 37              | 200         | ...                                      | ... | ... | 37  | ... | 6         |
| Sun Shuju <sup>[29]</sup>       | 2013                | 2008-2011            | Hubei        | 42              | 149         | ...                                      | ... | 42  | ... | ... | 5         |
| Gelin Xu <sup>[30]</sup>        | 2007                | 2003-2006            | Jiangsu      | 172             | 834         | ...                                      | ... | 172 | ... | ... | 7         |
| Wang Weiyang <sup>[31]</sup>    | 2016                | 2014-2015            | Beijing      | 42              | 384         | 22                                       | 38  | 42  | ... | ... | 5         |

**Notes:** “m” refers to month(s); “y” refers to year(s)

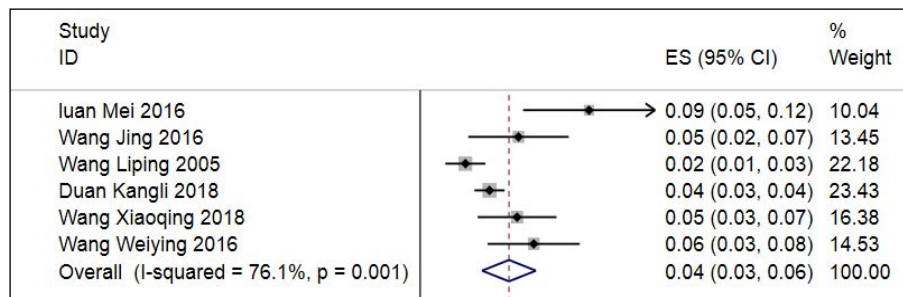


Figure 2 Cumulative risk of stroke recurrence 3 months after first-ever AIS

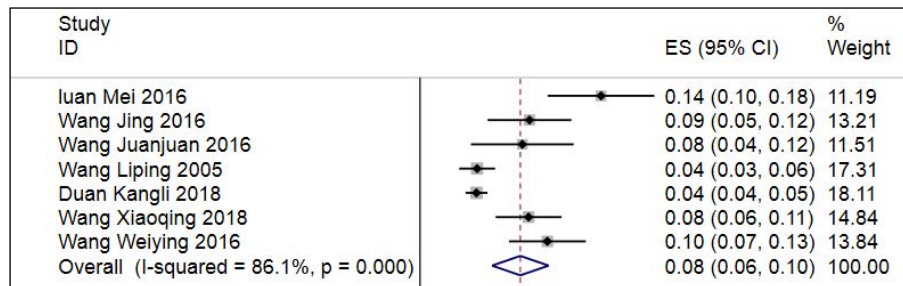


Figure 3 Cumulative risk of stroke recurrence 6 months after first-ever AIS

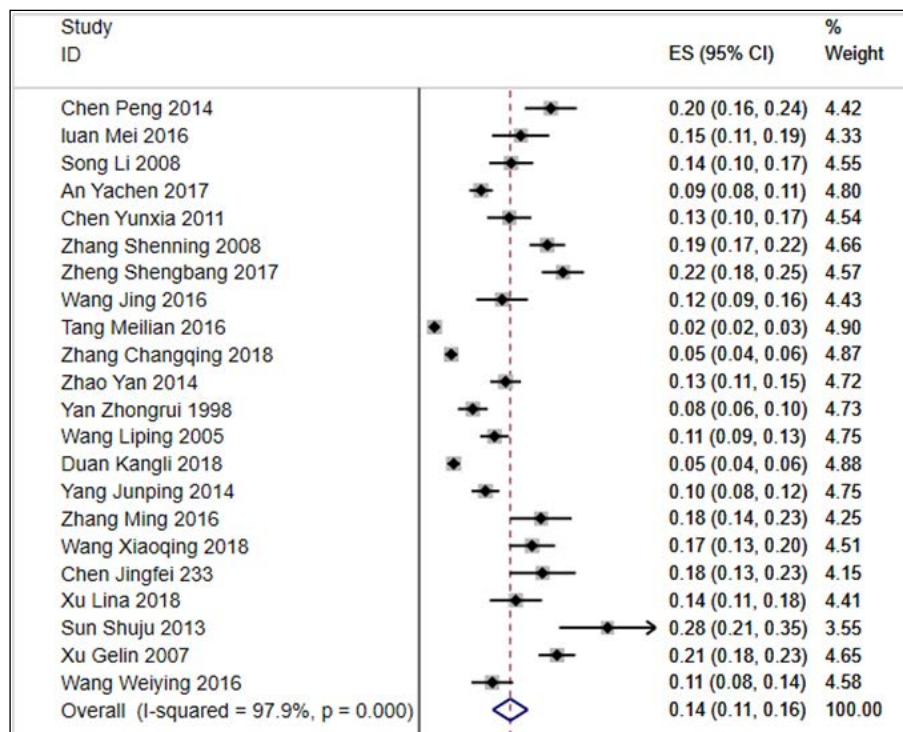


Figure 4 Cumulative risk of stroke recurrence 1 year after first-ever AIS

### Sensitivity analysis

The cumulative recurrence rate at 3 months, 6 months, 1 year, 2 years, and 5 years after AIS were calculated respectively by the fixed effect model and the random effects model, as shown in Table 3. The results showed that the combined results of different effect models at 6

months, 5 years after AIS were consistent, suggesting that the results of meta analysis of cumulative recurrence rates were more stable and reliable. In the sensitivity analysis of cumulative recurrence rate at 3 months, 1 year and 2 years after AIS, it was found that the results of the meta-analysis of the 2 cumulative relapse rates were

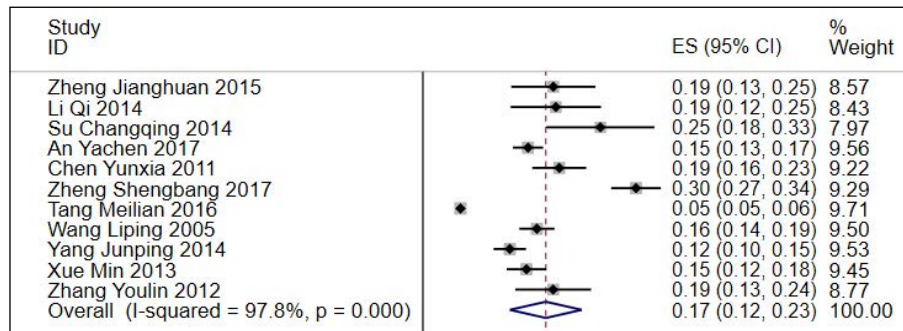


Figure 5 Cumulative risk of stroke recurrence 2 years after first-ever AIS

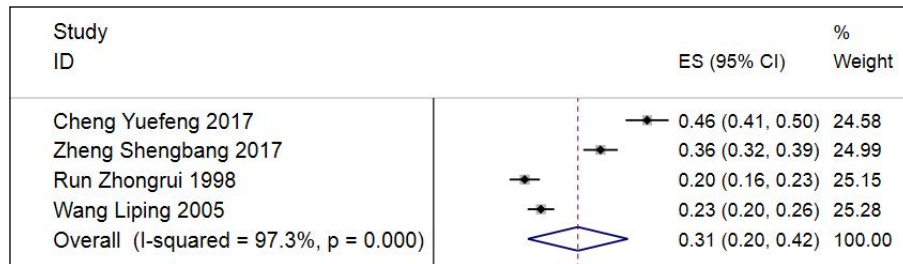


Figure 6 Cumulative risk of stroke recurrence 5 years after first-ever AIS

inconsistent, suggesting that the stability coefficient of the results of meta analysis of the 2 cumulative recurrence rates were lower.

### Publication bias analysis

The results of Egger's test showed that there might be publication bias in the literature which reported the cumulative recurrence rate at 6 months, 1 year and 2 years after the initial ischemic stroke ( $P < 0.05$ ). However, there was no significant publication bias in the literature which reported the cumulative recurrence rate at 3 months and 5 years after the initial AIS ( $P > 0.05$ ).

## Discussion

Acute ischemic stroke has a higher recurrence rate. Compared with initial AIS patients, the mortality and disability rate of recurrent ischemic stroke patients are significantly increased, causing great troubles and burdens for patients and families. There are different reports on the recurrence rate of ischemic stroke in China, and the results of different literature reports are quite different. Therefore, it is necessary to summarize and analyze the recurrence rate of AIS in China. The study included 29 studies covering 19 provinces (cities and autonomous regions) in China, with a total of 22 484 cases. The prevalence of

recurrent ischemic stroke in China in recent years was well described in this study. Through meta analysis, the pooled cumulative recurrence risk at 3 months, 6 months, 1 year, 2 years, and 5 years after initial AIS in China was 4.5%, 7.8%, 13.6%, 17.5%, and 30.9%, respectively. According to the 2017 Chinese Stroke Prevention Report, the 1-year recurrence rate of patients with AIS in China was 13.2%<sup>[32]</sup>. The result is basically consistent with the result of this study, which also verified the accuracy and reliability of this study. However, a foreign meta analysis involving 13 studies<sup>[1]</sup> indicates that the pooled cumulative risk was 11.1% (95% CI: 9.0-13.3) at 1 year, 26.4% (95% CI: 20.1-32.8) at 5 years after initial stroke, which was lower than the pooled cumulative recurrence risk obtained in this study. It is speculated that the reasons for this difference may be related to the regional and ethnic differences in the recurrence of ischemic stroke and the different inclusion criteria of the 2 studies. Differences in sample sizes are also taken into account.

The study strictly follows the reporting specification of observational meta-analysis, but there are still some limitations that need to be explained. (1) Restricted to the characteristics of single-rate meta analysis, there may be a high degree of heterogeneity<sup>[33]</sup>. It is consistent with the meta analysis of single rate published at home and



**Table 3 Sensitivity analysis results**

| Cumulative risk of stroke recurrence | Fixed effect model    |               | Random effect model   |               |
|--------------------------------------|-----------------------|---------------|-----------------------|---------------|
|                                      | Combined effect value | 95% CI        | Combined effect value | 95% CI        |
| 3 months after first-ever AIS        | 1.036                 | 1.031 – 1.042 | 0.045                 | 0.031 – 0.058 |
| 6 months after first-ever AIS        | 0.054                 | 0.048 – 0.061 | 0.078                 | 0.056 – 0.100 |
| 1 years after first-ever AIS         | 0.049                 | 0.046 – 0.052 | 0.136                 | 0.110 – 0.162 |
| 2 years after first-ever AIS         | 0.079                 | 0.074 – 0.083 | 0.175                 | 0.124 – 0.226 |
| 5 years after first-ever AIS         | 0.280                 | 0.263 – 0.297 | 0.309                 | 0.202 – 0.417 |

abroad<sup>[34-35]</sup>. (2) The results of the study were scattered. Considering that the cumulative recurrence rate of AIS was influenced by time factors, the total recurrence rate was not calculated in this study. And the subgroup analysis of sex, age, region and so on could not be carried out without calculating the total recurrence rate. (3) The severity of the patient's condition is different, resulting in a large heterogeneity among the studies. (4) Due to the fact that the literature included in this study were limited to publicly published and accepted research in the database, and some of the literature had shorter follow-up time, non-reported response rate, non-reported data integrity and methods of handling missing values, and so on, the publication bias of the literature relatively large. It may affect the accuracy of the results. Therefore, the results of this study still need to be further verified by random sampling and large-scale national epidemiological surveys.

To sum up, the recurrence risk after acute ischemic stroke in China is relatively high. It is suggested that medical and health departments at all levels must pay more attention to the prevention and treatment of recurrent ischemic stroke, and attach importance to the recurrence factors of ischemic stroke. We should take appropriate interventions to reduce the recurrence of ischemic stroke, improve the prognosis, lower the fatality rate and disability rate.

## Declaration

The authors of this article declare no conflict of interest.

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