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The association between homocysteine and ischemic stroke subtypes in Chinese

A meta-analysis

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Abstract

Background: The findings on the association between elevated plasma homocysteine levels and the risk of the trial of org 10172 in acute stroke treatment (TOAST) of ischemic stroke have been inconsistent in Chinese. So far, there is no meta-analysis about the association between Hcy and the TOAST subtypes of ischemic stroke in Chinese. This study; therefore, aimed to evaluate whether elevated homocysteine levels are associated with the TOAST subtypes of ischemic stroke using a meta-analysis.

Materials and methods: A systematic search of electronic databases were conducted for studies reporting homocysteine levels in ischemic stroke and the TOAST of ischemic stroke to April 18, 2018. The data were extracted after the application of inclusion and exclusion criteria. All the data were analyzed using Stata software version 9.0 (Stata Corp LP, College Station, TX). The standardized mean difference (SMD) and 95% confidence interval (CI) were used to compare continuous variables.

Results: Thirteen studies comprising 3114 participants (2243 patients and 871controls) met the eligibility criteria and were included in the meta-analysis. The meta-analysis revealed that the ischemic stroke group had significantly higher levels of homocysteine than controls (SMD = 1.15, 95% CI = 0.85–1.45, $P < .05$). The subgroup analyses suggested that the groups of patients with large-artery atherosclerosis, small-vessel occlusion, cardioembolism, stroke of other determined etiology and stroke of undetermined etiology had significantly higher levels of homocysteine compared to those in the control group (large-artery atherosclerosis: SMD = 2.12, 95% CI = 1.40–2.84, $P < .05$; small-vessel occlusion: SMD = 1.10, 95% CI = 0.72–1.48, $P < .05$; CE: SMD = 1.17, 95% CI = 0.64–1.71, $P < .05$; stroke of other determined etiology: SMD = 0.88, 95% CI = 0.53–1.24, $P < .05$; stroke of undetermined etiology: SMD = 1.50, 95% CI = 0.66–2.33, $P < .05$, respectively).

Conclusion: This meta-analysis found that ischemic stroke patients and the TOAST of ischemic stroke patients in Chinese had significantly higher homocysteine levels than the controls, suggesting that serum homocysteine levels may be a risk factor for ischemic stroke and the TOAST subtypes of ischemic stroke in Chinese.

Abbreviations: CE = cardioembolism, CI = confidence interval, Hcy = homocysteine, LAA = large-artery atherosclerosis, SAO = small-vessel occlusion, SMD = standardized mean difference, SOE = stroke of other determined etiology, SUE = stroke of undetermined etiology, TOAST = the trial of org 10172 in acute stroke treatment.

Keywords: homocysteine, ischemic stroke, meta-analysis, TOAST

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1. Introduction

A stroke is defined as "a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in the case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin.[1]" Ischemic stroke, also known as cerebral infarction, which accounts for 85% of all strokes,[2] is one of the most common cerebrovascular diseases. It is characterized by a high incidence, morbidity, and mortality and endanger the health and lives of patients. It is the major cause of disability and the second leading cause of death in the world.[3] According to the trial of org 10172 in acute stroke treatment (TOAST) criteria,[4] ischemic stroke can be divided into large-artery atherosclerosis (LAA), small-vessel occlusion (SAO), cardioembolism (CE), stroke of other determined etiology (SOE), and stroke of undetermined etiology (SUE). In addition to the traditional risk factors such as hypertension, diabetes, and smoking, studies have found that homocysteine (Hcy) is an independent risk factor for cardiovascular and cerebrovascular diseases.

Hcy, a sulfhydryl-containing amino acid, is an important intermediate product of methionine and cysteine metabolism. Its serum level can increase in specific conditions such as congenital enzyme defects, chronic renal and liver dysfunction, and treatment with several drugs. High Hcy levels caused by metabolic disorders of Hcy are an independent risk factor for hypertension,[5] myocardial infarction,[6–8] peripheral arterial occlusive disease,[9,10] venous thrombosis,[11,12] hemorrhagic strokes,[13,14] and ischemic stroke.[15–19] In recent years, researchers have placed increasing emphasis on high Hcy levels, and a number of case-control studies have been conducted to explore the correlation between Hcy and ischemic stroke.[20] Nevertheless, the results have been inconsistent. Stroke has become the first leading cause of death in Chinese, and the most common type is the ischemic stroke.[21] But only a few research papers have explored the relationship between Hcy and the TOAST subtypes of ischemic stroke in Chinese. What's more, the correlations between Hcy and the TOAST subtypes of ischemic stroke are thus still unclear in Chinese. So far, there is no meta-analysis about the association between Hcy and the TOAST subtypes of ischemic stroke in Chinese. The published studies on Hcy and ischemic stroke have also had only modest sample sizes, which has limited their significance. By performing a meta-analysis, the prevailing method for the quantitative summary of different results, the data can be assessed using a reasonable sample size. The purpose of the present meta-analysis was to quantitatively assess the findings from prospective studies on plasma Hcy levels and the risk of ischemic stroke and its TOAST subtypes.

2. Methods

This protocol is conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement.[22] Ethical approval was unnecessary in this study because this paper was a statistical analysis based on the previous articles.

2.1. Publication search

A comprehension search was conducted on the PubMed, EMBASE, and Chinese biomedicine databases for articles up to April 18, 2018. The following keywords were used: "stroke" OR "ischemic stroke" OR "cerebral ischemia," "brain ischemia," and "plasma homocysteine" OR "homocysteine" OR "Hcy" OR "plasma Hcy." Case-control studies that included the subtype of TOAST in ischemic stroke were chosen. Of the studies with overlapping data published by the same author, only the most recent or complete study was included in this meta-analysis.

2.2. Inclusion and exclusion criteria

The following criteria were used to identify eligible studies that had investigated the association between plasma Hcy levels and ischemic stroke:

(1) case-control studies written in English and Chinese;
(2) studies that assessed the correlation between Hcy and patients with ischemic stroke;
(3) studies that included ischemic stroke patients and healthy controls;
(4) studies that provided information on the plasma Hcy levels in the case and control groups at the onset of ischemic stroke; and
(5) studies that used the TOAST classification standard.

The exclusion criteria were as follows:

(1) not using TOAST classification standard;
(2) publications with duplications or studies with overlapping data from the same author;
(3) abstracts, case reports, proceedings, letters, reviews, and meta-analyses;
(4) incomplete outcome data; and
(5) a score of 6 points on the Newcastle–Ottawa scale (NOS).

2.3. Data extraction and quality assessment

Two reviewers independently extracted the following data from each included study using a standard form: first author's name, year of publication, country of origin, ethnicity, Hcy levels (mean ± standard), and the TOAST subtypes. A quality assessment was conducted according to the NOS criteria for retrospective studies.[23]

2.4. Statistical analysis

All the meta-analyses were performed using Stata version 9.0 (Stata Corp LP, College Station, TX). The standardized mean difference (SMD) with a 95% confidence interval (CI) was used for the continuous variables. Heterogeneity among the studies was measured via I^2 tests, and studies with an I^2 higher than 50% were considered to have high heterogeneity. A fixed effects model was used when there was no significant heterogeneity among the studies; otherwise, a random effects model was used. To identify possible sources of heterogeneity within the included studies, subgroup analyses were performed based on the TOAST subtypes. Funnel plots were used to evaluate potential systematic bias in the studies. Two-sided P-values $< .05$ were considered statistically significant.

3. Results

3.1. Study characteristic

After screening the abstracts, 229 possible studies were identified considered, and 20 studies in Chinese people were considered eligible after a detailed review. Notwithstanding 7 for scoring <6 points using the NOS criteria (Fig. 1). This process resulted in selection of 13 studies[24–36] involving 3114 participants (2243 patients and 871 controls) for the meta-analysis. Of the included studies, 12 reported on ischemic stroke,[24–32,34–36] 13 on the LAA subtype,[24–36] 13 on the SAO subtype,[24–36] 9 on the CE subtype,[26,27,29,30,32–36] 8 on the SOE subtype,[27,29,30,32–36] and 8 on the SUE subtype[27,29,30,32–36] (Table 1). The studies included in the meta-analysis were generally of high quality.

3.2. Association between Hcy and the TOAST of ischemic stroke

There was heterogeneity among the studies reporting differences of plasma Hcy levels between ischemic stroke, LAA and the healthy controls ($I^2 = 89.9\%$, $I^2 = 97.2\%$). The ischemic stroke and the TOAST subtypes in the 13 included studies showed obvious heterogeneity. Thus, a random effects model was used to pool the data. An incorporate analysis showed that the ischemic stroke patients had significantly higher levels of Hcy compared to

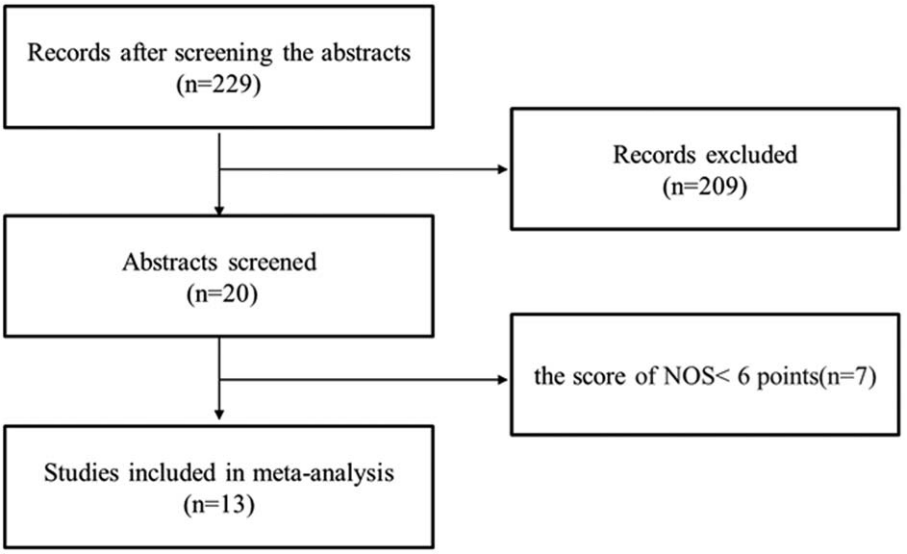

Figure 1. Study selection flow.

Table 1

Study characteristics.

Author	Year	Country	Control (Num)	IS (Num)	TOAST subtypes					NOS (points)
					LAA (Num)	SAO (Num)	CE (Num)	SOE (Num)	SUE (Num)	
Yin	2004	China	40	65	40	25	–	–	–	6
Li	2005	China	50	105	56	49	–	–	–	7
Wu	2006	China	41	82	32	27	13	–	–	6
Wang	2007	China	60	98	23	26	13	19	15	6
Li	2009	China	30	73	34	29	7	3	–	6
Yue	2011	China	28	97	32	29	19	10	7	7
Liu	2012	China	56	173	61	63	16	7	26	6
Zhang	2014	China	30	153	55	98	–	–	–	6
Zhou	2015	China	50	121	53	48	12	3	5	8
Pan	2015	China	100	498	171	176	45	20	86	6
Yu	2015	China	146	328	88	105	53	–	73	7
Wu	2016	China	90	110	35	37	13	6	19	8
Zhang	2016	China	150	340	164	69	38	9	60	6

CE = cardioembolism, IS = ischemic stroke, LAA = large-artery atherosclerosis, Num = number, SAO = small-vessel occlusion, SOE = stroke of other determined etiology, SUE = stroke of undetermined etiology.

the controls (SMD = 1.15, 95% CI = 0.85–1.45, $P < .05$) (Fig. 2). In the subgroup analysis, in which the participants were stratified by the TOAST subtypes of ischemic stroke, the TOAST subtypes had significantly higher levels of Hcy compared to the controls (LAA: SMD = 2.12, 95% CI = 1.40–2.84, $P < .05$; SAO: SMD = 1.10, 95% CI = 0.72–1.48, $P < .05$; CE: SMD = 1.17, 95% CI = 0.64–1.71, $P < .05$; SOE: SMD = 0.88, 95% CI = 0.53–1.24, $P < .05$; SUE: SMD = 1.50, 95% CI = 0.66–2.33, $P < .05$) (Fig. 3). The LAA patients had higher serum Hcy levels compared to the SAA, CE, SOE, SUE patients (SMD = 1.03, 95% CI = 0.45–1.61, $P < .05$; SMD = 1.54, 95% CI = 0.60–2.48, $P < .05$; SMD = 1.18, 95% CI = 0.56–1.79, $P < .05$; SMD = 1.42, 95% CI = 0.47–2.37, $P < .05$, respectively) (Fig. 4). While the SAO patients had higher serum Hcy levels compared to the SUE (SMD = -0.05, 95% CI = −0.52–0.43, $P < .05$). There were no significant differences between SAO and CE, SOE patients (SMD = 0.27, 95% CI = 0.03–0.50, $P > .05$; SMD = 0.44, 95% CI = 0.08–0.81, $P > .05$). The CE patients had higher serum Hcy levels compared to the SUE (SMD = −0.32, 95% CI = −0.81–0.16, $P < .05$), and there were no statistical differences between the CE and SOE patients plasma Hcy levels (SMD = 0.28, 95% CI = −0.01–0.57, $P > .05$). Additionally, there were no statistically significantly differences between the SOE and SUE patients (SMD = −0.35, 95% CI = −0.64 to −0.07, $P > .05$).

3.3. Regression analysis

A regression analysis was conducted based on the ischemic stroke and the TOAST subtypes. We conducted a regression analysis on the data through "year." We concluded that heterogeneity accounted for 87.65% of residual variation, and "year" could explain 33.41% of the studies' variations for the ischemic stroke patients.

3.4. Publication bias

The funnel plot and Egger tests were performed to quantitatively evaluate the publication bias of the literature on ischemic stroke.

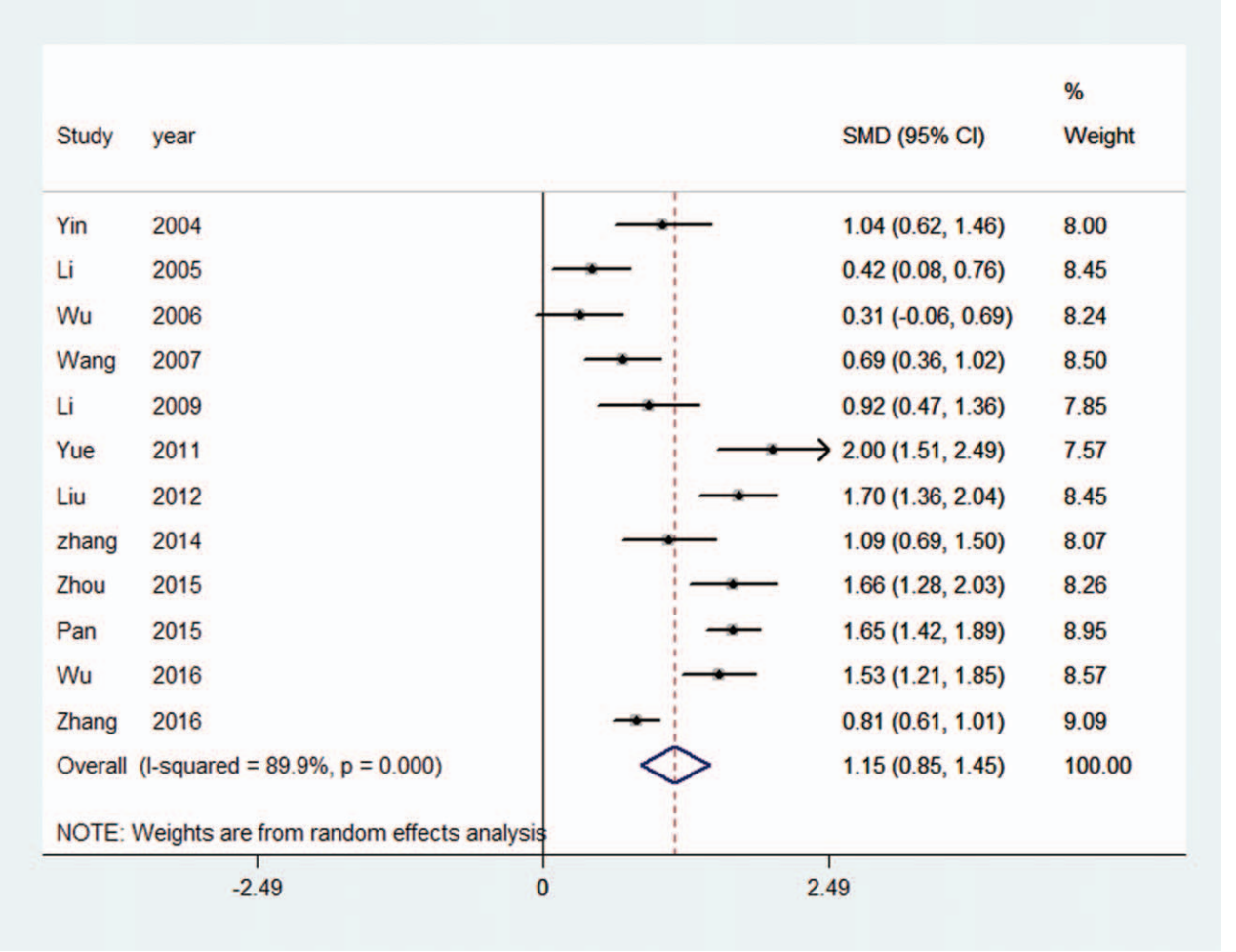

Figure 2. Meta-analysis of 12 studies reporting on homocysteine levels in patients with ischemic stroke compared to the controls.

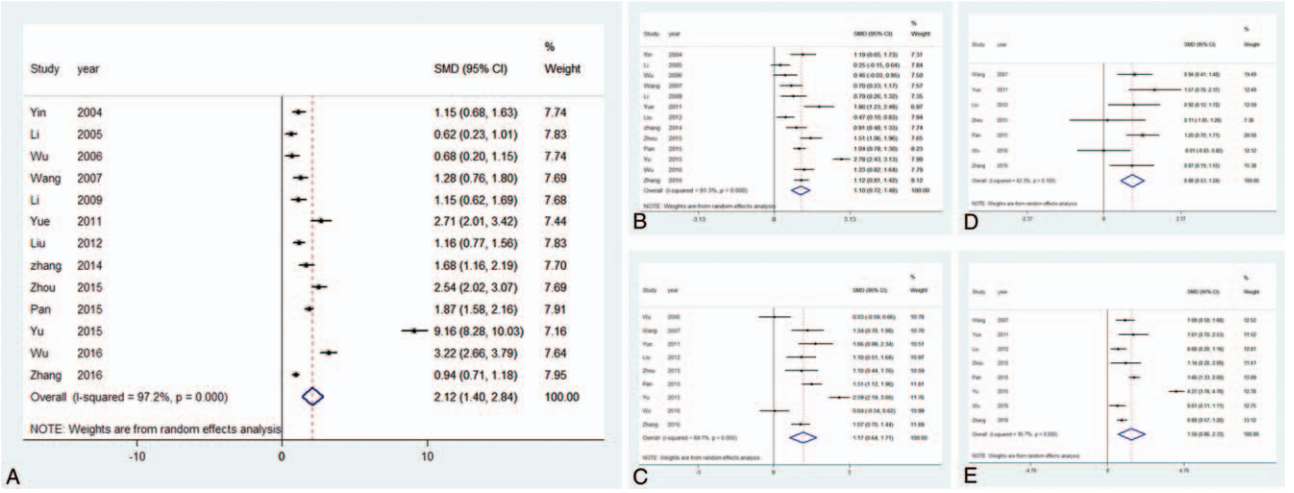

Figure 3. The TOAST of ischemic stroke, A (LAA vs Con), B (SAO vs Con), C (CE vs Con), D (SOE vs Con), E (SUE vs Con). CE = cardioembolism, CI = confidence interval, Con = control, LAA = large-artery atherosclerosis, SAO = small-vessel occlusion, SOE = stroke of other determined etiology, SUE = stroke of undetermined etiology, TOAST = the trial of org 10172 in acute stroke treatment.

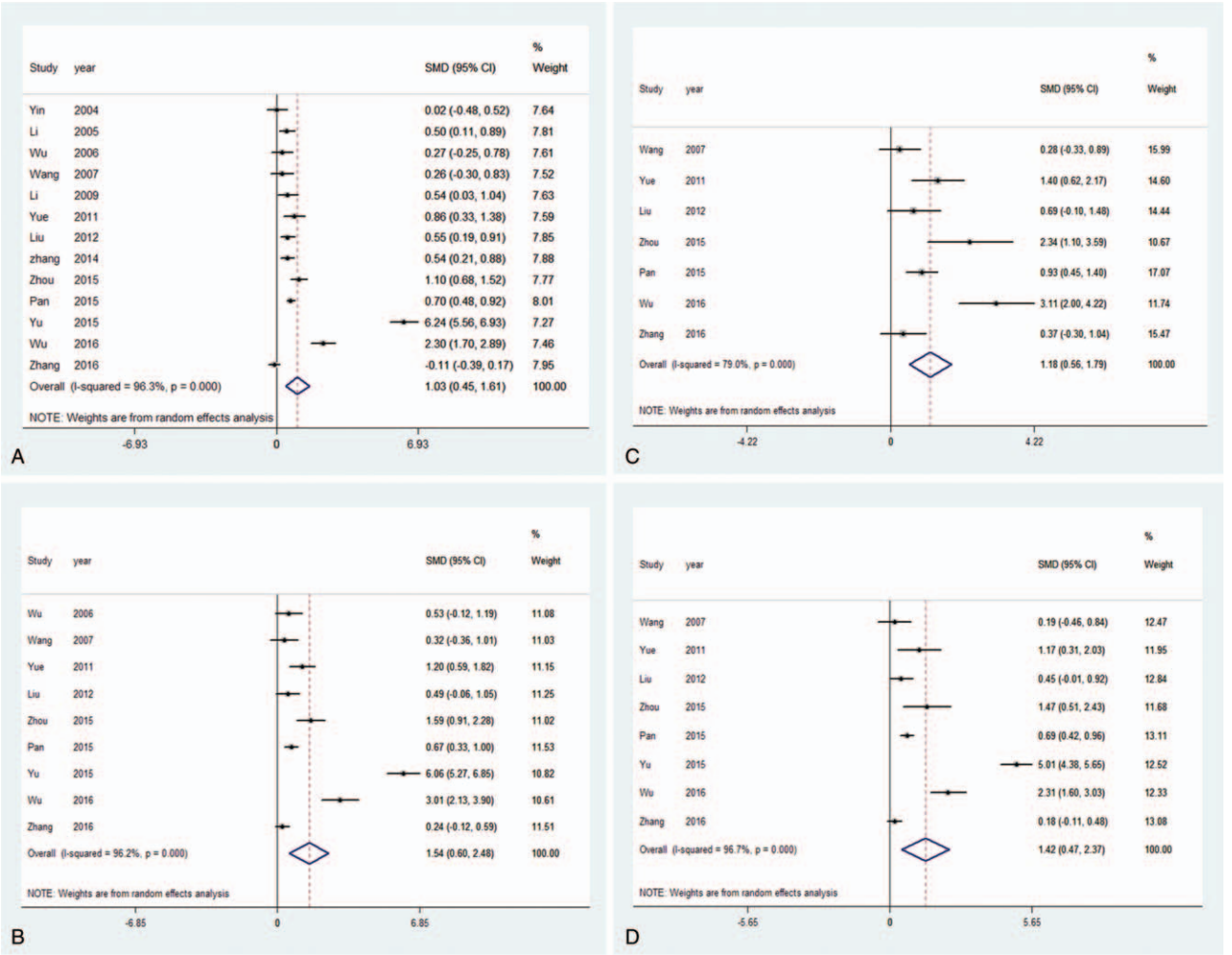

Figure 4. Meta-analysis on homocysteine levels in patients with large-artery atherosclerosis stroke compared to the other TOAST subtypes. A (LAA vs SAO), B (LAA vs CE), C (LAA vs SOE), D (LAA vs SUE). CE = cardioembolism, LAA = large-artery atherosclerosis, SAO = small-vessel occlusion, SOE = stroke of other determined etiology, SUE = stroke of undetermined etiology, TOAST = the trial of org 10172 in acute stroke treatment.

The results of the Egger test provided statistical evidence for funnel plot symmetry ($P = .123$) in the overall results, suggesting the absence of publication bias. No significant publication bias was detected using funnel plot tests in the subgroup analyses for differences between the Hcy levels of ischemic stroke and the TOAST subtypes patients and the controls (Fig. 5).

4. Discussion

Ischemic stroke, an important clinical problem, has been well studied but the mechanism of ischemic stroke is still relatively unclear. Hcy is not only a risk factor for, but also correlated with, stroke severity, worse prognosis,[18,37–39] and stroke recurrence.[40–42] Furthermore, some studies have found that patients who have high Hcy levels are roughly twice as likely to have a stroke as normal people.[17,40]

Although increasing evidence has demonstrated that elevated Hcy levels may be an important contributor in the development of ischemic stroke, a handful of studies have suggested the different view.[13,43] At present, there are few research papers about the relationship between Hcy and the TOAST subtypes of ischemic stroke in the Chinese. The correlations between Hcy and the TOAST subtypes of ischemic stroke in Chinese are thus still unclear. In China, studies have shown that Hcy is correlated with ischemic stroke closely especially in the subtype of SAO and LAA.[24,35,36] Some studies have indicated that Hcy is only related to LAA.[32–34,44] But research on the relationship between Hcy and CE, SOE, SUE is rare, and to date, only 2 studies showed that Hcy is related to the all the subtypes of TOAST,[35,36] 1 study showed that Hcy has not related with SOE.[34] In this study, we extracted data on Hcy levels from 13 studies and found that the Hcy levels in the Chinese patients with ischemic stroke and the TOAST subtypes were significantly higher than in the healthy controls, suggesting that Hcy levels could be an aggravating factor in atherosclerosis, and high Hcy levels might be one of the risk factors for ischemic stroke. The precise mechanism of Hcy on the susceptibility of ischemic stroke remains unresolved. Most of the studies on high Hcy levels as a cause of ischemic stroke have found that Hcy damages endothelial cells, increase vascular smooth muscle, the inflammatory process, oxidative insult, and enhances the production of fibrinogen leading to abnormal coagulation together with platelet dysfunction.[1,45–49]

We also found Hcy significantly higher in LAA patients than the other TOAST subtypes patients in Chinese. Indeed, Hcy is

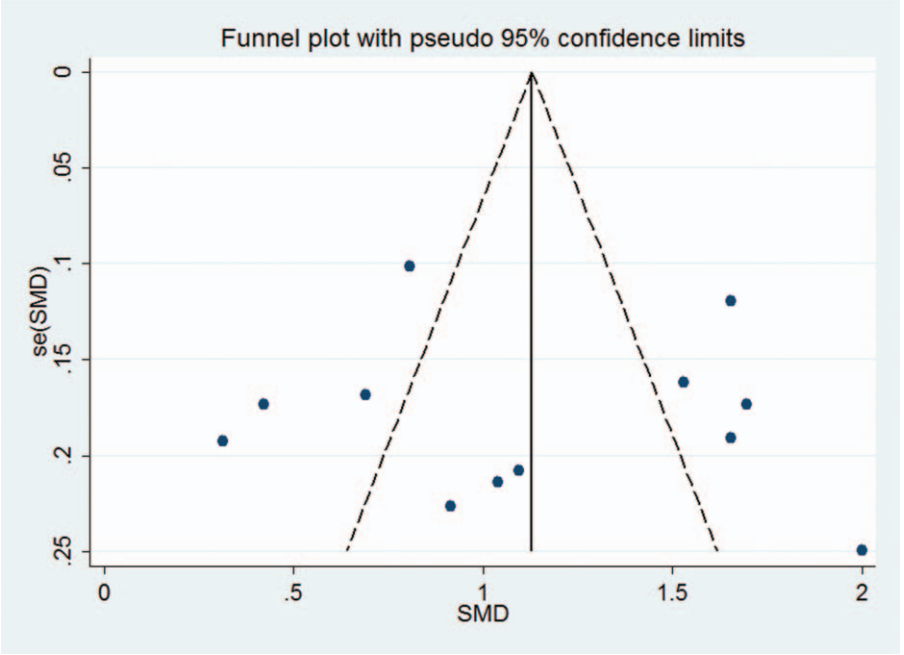

Figure 5. Funnel plot to detect risk of publication bias in the meta-analysis.

more likely higher in patients with the LAA subtype of ischemic stroke. It can be speculated that the increased plasma Hcy may promote atherosclerosis of the great vessels, and atherosclerosis plays a key role in the occurrence of LAA. The increased production of reactive oxygen species caused by Hcy may directly injury endothelial cells especially hydrogen peroxide[50–52] and decline nitric oxide bioavailability which is concomitant with diminishing of nitric oxide including vasoconstriction, smooth muscle proliferation, increase platelet activation and leucocyte recruitment.[52,53] In addition, Hcy enhances the release of arachidonic acid from platelets to generate reactive oxygen species, leading to calcium and lipid deposits in the endothelial wall. Together, these changes degrade arterial elasticity and accelerate the process of atherosclerosis.[12,54–58] In our study, Hcy in SAO patients were higher than SOE patients, and the CE patients were higher than SUE patients in Chinese.

There was no meta-analysis about Hcy and ischemic stroke subtypes in non-Chinese people. Studies which have evaluated the relationship between Hcy levels and stroke subtypes have shown different results in non-Chinese people. Eikelboom et al[59] reported that Hcy was associated with a higher risk of LAA and SAO compared with controls. Ashjazadeh et al[60]conducted a study in 171 Iranian patients with acute ischemic stroke and concluded that Hcy has a strong association with cardioembolic subtype. A South London study in 457 stroke patients reported Hcy was significantly greater in small vessel disease and cardioembolic compared with controls.[61] An Italy study reported that Hcy is an independent risk factor for all subtypes of ischemic stroke.[62] Two other studies in a Turkish population demonstrated that Hcy had a significant role in large vessel atherothrombotic and cardioembolic stroke.[63,64] The different results in non-Chinese people and Chinese people caused by racial difference, regional difference, difference food habits and other factors. The methylene tetrahydrofolate reductase (MTHFR), cystathionine β-synthase (CBS), and methionine synthase (MS) are the key enzymes in Hcy metabolism. Studies have shown that the heterozygous mutation frequency of MTHFR C677T in Chinese[65] is higher than that which reported abroad,[66] and the homozygous mutation frequency of MTHFR C677T in Chinese[65] is the same with reported abroad.[66] The mutation frequency of CBS 844ins68 and MS A2756G in Chinese[65,67] was significantly lower than that in abroad[68,69] and the mutation frequency of MS A2756G in Chinese[65] is lower than that in Caucasians.[70,71] These genes play an important role in the synthesis and metabolism of Hcy. Some studies have shown that the MTHFR C677T polymorphism is associated with ischemic stroke,[72–75] while some studies have showed the different opinion.[76,77] A domestic meta-analysis[78] provided evidence that CBS T833C genetic polymorphism was associated with the risk of stroke. Nevertheless, the results from subgroups of Chinese and Caucasian are different. In the Chinese subgroup, the result showed CBS T833C polymorphism lead to increased incidence of stroke. Furthermore, the staple food is grains and the non-staple food is vegetables and some meat in China. In western countries, meat (such as: cattle, sheep, fish, pig, etc) is the main diet and the proportion of meat in the diet is higher than Chinese.

The finding of a few studies suggest that a 3 mmol/L lower total Hcy level could be associated with a 10% lower risk of recurrent strokes.[79] Recent studies have indicated that the risk of ischemic stroke in populations with high Hcy levels is 1.71 higher than among those with low levels.[80] Some studies have indicated founded that lowering Hcy levels can reduce the risk of ischemic stroke.[80,81] Accordingly, clarifying the correlation between Hcy and ischemic stroke, and reducing the Hcy levels of at-risk patients may play a role in the prevention of ischemic stroke.

The present study had several limitations. First, the different detection methods employed in the indicated studies to determine plasma Hcy levels may have sensitivity and reliability issues. Second, we were unable to analyze the effect of the acute stress

reaction of ischemic stroke on plasma Hcy levels since there were insufficient data about Hcy levels before the onset of ischemic stroke. Third, few studies reported on other risk factors, such as blood pressure, blood glucose, obesity, and sexuality, in the results of their subgroup analyses. There is thus certainly a need for larger and wider case-control studies to explore the role of other factors that are likely to cause ischemic stroke.

5. Conclusions

Our meta-analysis found that the patients with ischemic and the TOAST subtypes in our study had significantly higher Hcy levels than in the healthy controls, and elevated Hcy levels may; therefore, be a risk factor for ischemic stroke and the TOAST subtypes of ischemic stroke in Chinese. However, further prospective population-based studies are needed to longitudinally evaluate the association between Hcy levels and the progression of different ischemic stroke subtypes. Additionally, the relatively limited number of eligible studies may influence the sensitivity of statistical analyses. Further randomized controlled trials with larger numbers of participants are necessary to confirm these findings.

Author contributions

Data curation: Tao Zhang, Yaogang Zhang, Jianhua Li.
Formal analysis: Tao Zhang, Yuan Jiang.
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Validation: Yan Cheng, Xiaoming Su, Zhu Man, Jing Hou, Li Sun.
Writing – original draft: tao zhang, Yuan Jiang.
Writing – review & editing: Yuan Jiang, Yanyan Ma.

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