Review Article

Homocysteine Levels and Ischemic Stroke: A Systematic Review

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Abstract

The most common type of stroke is ischemic stroke. Given that death due to stroke is one of the three leading causes of death globally, it is essential to identify its risk factors, especially modifiable risk factors. Nowadays, High homocysteine is recognized as one of the risk factors for stroke. Our aim in this study was to investigate the association between homocysteine levels and ischemic stroke. We searched the keywords in Scopus, Web of Science, Google Scholar, PubMed, and Science Direct with a 15-year time limit. At first, 3884 studies were found, and after further investigation and based on inclusion and exclusion criteria, only nine studies were selected. Of the nine selected studies was a clinical trial and eight observational studies, and in total, there were 16227 participants in these studies. The prevalence of ischemic stroke was higher in people with high homocysteine levels than in people with normal homocysteine levels (14.1% vs. 9.8%). The prevalence was generally higher in men, but among people with high homocysteine levels, the prevalence of ischemic stroke was slightly higher in women than in men (12% vs. 11%), and also, in women and men, the prevalence of ischemic stroke was higher in people with high homocysteine levels than in people with normal levels. Based on selected studies, increased homocysteine levels in men and women increases the risk of ischemic stroke. Because homocysteine levels are a modifiable risk factor, diet and prevention of vitamin B12 decrease can help prevent an increased risk of ischemic stroke.

Keywords: Homocysteine; Ischemic stroke, Systematic review

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Introduction

Death of some neuron cells and their dysfunction due to lack of oxygen can lead to a brain stroke, which can change the body's function or perception of its condition (1, 2). Stroke is divided into hemorrhagic and ischemic due to the Pathological processes that occur (3). The most common type of stroke is ischemic stroke, which causes 85% of strokes. Ischemic stroke (IS) is caused by an obstruction in one of the brain arteries that can cause cell death (1, 4).

Determining the risk factors and treatment of stroke depends on its specific pathogenesis. Risk factors for IS can be divided into modifiable and non-

modifiable types. Non-modifiable risk factors including sex, age, ethnicity, inherited diseases, family history, and low birth weight, and modifiable risk factors including smoking, high blood pressure, diet, physical inactivity, metabolic syndrome, and dyslipidemia, heart disease, body mass index, and alcohol consumption (5-7). The results of studies show that controlling for modifiable risk factors prevents ischemic stroke (8, 9).

High homocysteine can increase oxidative stress, reduce vasodilation, stimulate vascular smooth muscle cell proliferation, and alter the elastic properties of vascular walls, which ultimately increase the risk of atherosclerosis (10). Therefore, in addition to the common risk factors mentioned in the previous paragraph, plasma homocysteine can also be considered as one of the risk factors for IS (11). A study by Wang et al. (12) shows that the rate of IS is higher in people with high homocysteine levels (hHcy) than in people with normal homocysteine levels (nHcy). Another study on this subject was conducted in 2020 (13), which confirms the claim of the previous study. However, a study by Halddin et al. in Sweden (14) shows that the rate of IS is slightly higher in people with nHcy than in those with hHcy.

This systematic review study aimed to investigate the association between IS in people with hHcy and nHcy, given that homocysteine levels in individuals can be modified, and its modification can decrease the incidence of stroke. Therefore, it is necessary to carefully survey the studies to determine the relationship between the rate of IS and homocysteine levels.

Methods

The present systematic review study was performed based on the PRISMA checklist (15). To avoid any bias in the study in the search process, study selection for inclusion in the study, assessment of article quality, and data extraction were used by two authors (PP) and (AS) and in case of any disagreement between the two authors from the author's comments third (MA) was used.

Search Strategy: We searched the keywords "Homocysteine", "Hcy", "plasma Homocysteine", "plasma Hcy", "ischemic stroke", "cerebral ischemia", "brain ischemia" and "stroke" in PubMed, web of science, Scopus, Science Direct and Google scholar databases. To be sure, the sources of the selected articles for data mining were also manually reviewed so that a study would not be missed. Search results were limited to English and articles in languages other were excluded. First, duplicate articles from the study selection process were removed, then the title and abstract of the articles were carefully reviewed, and articles with titles and abstracts unrelated to our aims and subject were excluded from the study. Finally, the full text of the remaining articles was carefully studied, and articles were selected using the inclusion and exclusion criteria of the studies and after evaluating their quality, the required data were extracted. We considered the 15-year time limit for search, so we only reviewed articles from 2005 to October 2020.

Study Selection: PICOT (Population, Intervention, Comparison, Outcome, and Time) was used as a criterion for entering articles into the study (Table1), and original research articles were reviewed based on the PICOT criteria. The exclusion criteria excluded articles without full text, duplicate articles, case reports, letters to the editor, commentaries, editorials, case series, animal studies, conference abstracts, and articles other than English. In some studies, stroke was not of the IS type, or IS data were indistinguishable from data on other types of stroke were excluded. Also, articles that examined the association of homocysteine levels only with the severity or recurrence of ischemic stroke were excluded. Several studies have examined the association between homocysteine levels and IS in people with other diseases, such as diabetes or high blood pressure. These studies were also excluded.

Quality assessment and Data extraction: After reviewing the full text of the selected articles, nine articles were selected for quality assessment. The CONSORT (16) and STROBE (17) checklists were used for quality assessment. The CONSORT checklist was used to evaluate one study and the STROBE checklist was used for the other eight studies. Extraction of data related to the first author, year of publication of the article, countries in which studies were conducted, age range, mean age and

genders of study participants, total number and number of women and men separately with high and normal homocysteine levels and total number and number of men and women with high and normal homocysteine who have suffered a stroke were performed by two reviewers (A.S and P.P). The extracted data was reviewed by the third reviewer (M.A.) to match the data of the two reviewers (A.S and P.P).

Results

After searching for the keywords "Homocysteine," "Hcy," "plasma Homocysteine," "plasma Hcy," "ischemic stroke," "cerebral ischemia," "brain ischemia," and "stroke" in PubMed, web of science, Scopus, Science Direct and Google scholar databases, 3884 articles were obtained. First, 1086 duplicate articles were identified and deleted. The titles and abstracts of 2798 articles were carefully studied and reviewed. Studies that did not have titles and abstracts related to our topic and purpose were excluded from case report articles, letters to the editor, commentaries, editorials, Case series, animal studies, conference abstracts, and articles other than English. Three hundred-one articles were selected for full-text review, their full-text was carefully reviewed, and if there was data needed for extraction, the articles were selected for inclusion in the study. Finally, nine studies were selected for data extraction, and the required data were entered in a pre-prepared table. The process of searching and selecting studies is summarized in Table 1.

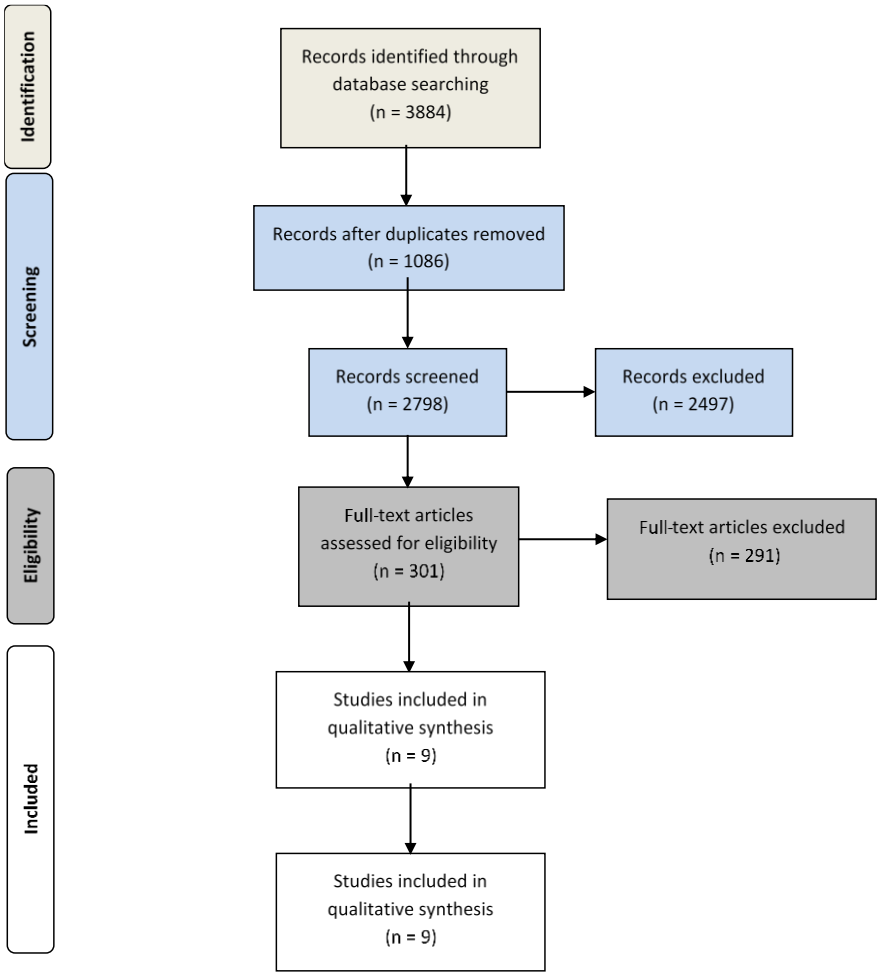

Figure 1. The diagram of the study.

Table 1: PICOT (Population, Intervention, Comparison, Outcome, Time) criteria for inclusion of studies.

Parameter	Inclusion Criteria
Population	Adults (18≤)
Intervention	Hyperhomocysteinemia
Comparison	Hyperhomocysteinemia vs. Normal homocysteine levels
Outcome	Risk of ischemic stroke event
Time	The last 15 years (2020-2005)

Of the nine selected studies was a clinical trial (13) and eight observational studies (12, 14, and 18-23), and in total, there were 16227 participants in these studies. Homocysteine levels were normal in 10,738 people, and homocysteine levels were high in 5489 people, the number of participants in each study ranged from 85 to 5935, and male and female genders were present in all studies. The age range of the participants was over 18 years, and their mean age was 59.7±11.3. Most studies have been done in China, one of the reasons being the high mortality rate due to stroke in China; a study by Donkor et al. Shows that the death rate due to stroke in China per 100,000 people is 151 to 251 people (24). A summary of the characteristics of the nine articles used in this study is shown in Table 2.

Prevalence of ischemic stroke: Of the nine studies selected, data from 8 studies show that the rate of ischemic stroke is higher in people with high homocysteine levels (12, 13, and 18-23). However, in one study, the rate of ischemic stroke was higher in people with normal homocysteine levels than in people with high homocysteine (14). The overall prevalence of ischemic stroke was 11.3%, and the prevalence of ischemic stroke was 14.1% in people with high homocysteine and 9.8% in people with normal homocysteine levels. The highest prevalence of ischemic stroke was 73.3%, which was related to people with high homocysteine levels (22) and the lowest prevalence was 2.6%, which was related to people with normal homocysteine levels (20).

Differences in the prevalence of ischemic stroke in men and women: In only four studies, the prevalence of IS in men and women with high and normal homocysteine levels were reported separately (12, 13, 18, and 20). In other studies, the prevalence has generally been expressed, and the prevalence of IS in men and women cannot be extracted separately. In these four studies, the prevalence of IS was generally higher in both men and women with hHcy than in men and women with nHcy. The prevalence of IS in men and women with hHcy and nHcy was 11% vs. 7.5% and 12% vs. 5.2%, respectively. Data from four studies show that the prevalence of IS is generally higher in men than in women (9.2% vs. 6.5%).

Discussion

This study aimed to investigate the relationship between homocysteine levels and the prevalence of IS using a systematic review method. Nowadays, increased plasma total homocysteine levels are considered as one of the reasons that are independent of other cerebrovascular risk factors such as hypertension, smoking, age, body mass index, diabetes, creatinine, high-density lipoprotein cholesterol levels, alcohol consumption, and Social class can increase a person's risk of stroke (25-27). Results of this systematic review study show that elevated total plasma homocysteine levels can be a risk factor for IS, and it also shows that the prevalence of IS is generally higher in people with hHcy than in people with nHcy. According to the results of this study, the prevalence of IS is generally higher in men; a study by Wang et al., Which examined the relationship between gender and the prevalence of stroke, confirms this finding (28-31). However, it should be noted that the prevalence of IS

Table 2: Prevalence of IS in people with normal and high homocysteine levels.

First author (year),[Ref]	Country	Type of Study	Gender	Age range	Mean age	Sample size hHCY (male/female), n	Sample size nHCY (male/female), n	hHcy patients with IS (male/female), %	nHcy patients with IS (male/female), %
Li, J. J. (2020)[13]	China	Randomized Clinical Trial	Both	55-72	62.4	1515 (1167/348)	1529 (860/669)	20.5 (21.3/17.8)	**17.7 (19.8/15.1)**
Wang, C. Y. (2015)[12]	China	Case-Control	Both	35-85	65.7±9.3	205 (112/93)	395 (218/177)	39.5 (38.3/40.8)	**30.1 (30.7/29.3)**
Han, L. (2015)[18]	China	cohort	Both	20≤	—	1505 (1104/401)	3656 (1465/2191)	6.1 (5.1/8.9)	**2.8 (2.2/3.2)**
Choi, S. H. (2015)[19]	South Korea	cohort	Both	—	60±12.1	58 (46/11)	145 (87/58)	73.2 (—)	**60 (—)**
Wang, Chang-yi. (2014)[20]	China	cross-sectional	Both	20≤	59±12.1	1863 (1360/503)	4072 (1568/2504)	5 (4.9/5.1)	**2.6 (2.6/2.7)**
Hultdin, J. (2011)[14]	Sweden	Case-Control	Both	25-74	55±8.1	219 (—)	617 (—)	31.9 (—)	**34.1 (—)**
*Cui, Renzhe. (2008)[21]	Japan	case–control	Both	40-79	68.2	54 (—)	148 (—)	59.2 (—)	**46.6 (—)**
Angelova, E. A. (2008)[22]	Bulgaria	case-control	Both	18-55	47±6.7	15 (—)	70 (—)	73.3 (—)	**40 (—)**
Bos, M. J. (2005)[23]	Netherlands	prospective study	Both	45≥	36.6	55 (30/25)	106 (42/64)	75 (—)	**64.1 (—)**

Ref: Reference; hHcy: high homocysteine level; nHcy: normal homocysteine level

is slightly higher in women with hHcy than men with hHcy (12% vs. 11%).

In 2005 a study by Bos et al., in the Netherlands among people under the age of 45 (23) was performed that the results show the prevalence of IS was higher in people with hHcy. Bos study used people under the age of 45, and the mean age of the participants was 36.6 (23), while in most studies, the mean age of the participants was over 55 years. In the study by Cui et al., Which had a higher mean age than the other studies (68.2 years), the prevalence of ischemic stroke was higher in people with hHcy than

in people with nHcy (21), so it seems that increased homocysteine can be a risk factor for increasing the risk of IS in adults (18≤), regardless of age.

Among the selected studies, four have been performed in China (12, 13, 18, and 20); the importance of conducting this study in China is because China has the highest incidence of stroke with standardized age in the world (32). These studies can be very effective in identifying the risk factors for stroke, especially modifiable risk factors, to prevent the further prevalence of the stroke. The results of studies conducted in China show that the prevalence of IS is higher in people with hHcy than in people with nHcy (12, 13, 18, and 20). In 3 studies, the prevalence of IS was higher in women with hHcy than in men with hHcy (12, 18, and 20), but in one study, the prevalence of IS was higher in men with hHcy than in women. The prevalence of IS was higher in men with nHcy in 2 studies than women with nHcy (12, 13), and in 2 studies, women were more than men (18, 20).

The results of a study by Angelova et al. show that the prevalence of IS is higher in people with high homocysteine levels than in people with nHcy (22); the results of the study by Choi et al., conducted in South Korea, also confirm the association between homocysteine levels and IS (19). It should be noted that the results of the study by Hultdin et al. show that the prevalence of ischemic stroke is slightly higher in people with nHcy than in people with hHcy, but the difference was not significant (14).

The present systematic review study has some limitations, the number of cohort studies in this field is not enough, so due to the importance of the topic of stroke, it is necessary to conduct more cohort studies in this field to examine and conclude this topic more carefully. Also, due to the lack of access to the Embase database, we could not search for keywords in this database. Studies have been conducted in a limited number of countries, including four studies in China (12, 13, 18, and 20) and other studies in South Korea (19), Sweden (14), Japan (21), Bulgaria (22) and The Netherlands (23), which covers only the regions of East Asia and Eastern and Western Europe. For a more accurate and better conclusion, it is necessary to conduct this study in other countries.

Conclusion

The results of this study could confirm the association between homocysteine levels and the risk of IS. Therefore, it is necessary to use an appropriate diet to treat high homocysteine levels and consume enough calories and animal proteins (33-36). Deficiency of folic acid or vitamin B12 can also increase homocysteine levels and cause Hyperhomocysteinemia in a person; high homocysteine levels due to folic acid or vitamin B12 deficiency can be corrected with supplementation (34-38).

Acknowledgment

None.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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