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# The role of homocysteine levels as a risk factor of ischemic stroke events: a systematic review and meta-analysis

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**Introduction:** Among numerous risk factors, homocysteine (Hcy) has been linked to cerebral infarction; however, results have been inconsistent. This review aimed to conduct a meta-analysis of published studies to investigate the relationship between plasma Hcy levels and the risk of ischemic stroke.

**Methods:** A systematic literature search was conducted until November 2022 to obtain articles reporting Hcy levels in ischemic stroke patients. Review Manager software was used to perform all statistical analyses (version 5.3).

**Results:** Initial investigation yielded 283 articles. The final evaluation included 21 articles, including two prospective studies, one retrospective cohort, and 18 case–control studies. These studies included 9888 participants, of which 5031 were admitted patients with ischemic stroke. An integrated analysis revealed that ischemic stroke patients had significantly higher levels of Hcy than controls (mean difference (MD) = +3.70, 95% confidence interval (CI) = 2.42–5.81, $p < 0.001$).

**Conclusion:** This meta-analysis and systematic review indicate that ischemic stroke patients have significantly higher homocysteine levels than controls. Detecting hyperhomocysteinemia and reducing homocysteine levels should be explored among individuals at increased risk for ischemic stroke.

KEYWORDS

**homocysteine, ischemic stroke, risk factor, systematic review, meta-analysis**

## Introduction

The cerebrovascular disease has emerged as the leading cause of disability and the second leading cause of death worldwide. Ischemic stroke is one of the most common cerebrovascular diseases, constituting 85% of all strokes (1). Older age, gender, hypertension, diabetes mellitus, hypercholesterolemia, and smoking are the traditional risk factors for cerebrovascular disease (2). Among a variety of risk factors, studies have found that homocysteine (Hcy) is an independent risk factor and correlated with cerebral infarction due to intracranial small-vessel disease and extracranial vascular disease, including myocardial infarction and peripheral artery disease (3–6).

Homocysteine (Hcy) is a naturally sulfhydryl-containing amino acid and is closely linked with endothelial dysfunction and extracellular matrix proliferation that may cause vessel damage (7). Recent studies reported a possible association between hyperhomocysteinemia and thrombotic vascular events,

including ischemic stroke (8–10), but these studies have suggested mixed conclusions, and the mechanism by which homocysteine affects stroke prognosis is still unclear. In recent years, researchers have conducted numerous case–control studies to explore the possible correlation between Hcy and cerebral infarction (11, 12). Nevertheless, the results have been inconsistent. Most of the published studies on Hcy and ischemic stroke only had modest sample sizes and were not well-designed, affecting their significance. Current guidelines did not recommend any treatment for Hcy levels. However, if the role of Hcy levels may affect stroke outcomes, controlling Hcy levels may be a novel treatment option for stroke treatment and prevention.

Therefore, the aim of this review was to perform a meta-analysis of published studies to assess the relationship between plasma Hcy levels and the risk of ischemic stroke.

# Methods

This review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (13).

## Literature search and selection criteria

Initially, three independent reviewers screened the databases of the included studies on PubMed, and MedRvix up to November 2022, using specific keywords: "ischemic stroke" OR "cerebral infarct" AND "homocysteine." We used the following criteria to identify eligible studies that investigated the association between Hcy levels and ischemic stroke: (1) studies that reported the relationship between baseline plasma Hcy levels (measured at admission) and patients with ischemic stroke and (2) studies that compared ischemic stroke patients and healthy controls (case–control). The literature search was also restricted to English-language articles only. The exclusion criteria were as follows: (1) single-arm trials (no control/comparison group); (2) outcomes out of interest (studies that did not estimate the mean differences between ischemic stroke patients and healthy controls); and (3) data cannot be extracted (incomplete data). The primary outcome was the differences in the plasma Hcy levels between ischemic stroke patients and the control group, and the secondary outcome was the differences in the plasma Hcy levels between male and female ischemic stroke patients.

## Data extraction and quality assessment

In total, three authors independently screened and examined the titles and abstract, followed by a full-text review using the inclusion and exclusion criteria. In the event of disagreement between the three authors, the main author would help to resolve the issue and make a final decision. Studies that entirely fulfilled our inclusion criteria were retrieved and additional articles were added based on the bibliography of the articles retrieved through the outlined search strategy. If the reviewers could not reach an agreement, the first author will be consulted for the final decision.

We extracted and tabulated the following data: author(s), year of publication, study design, country of origin, baseline characteristics, homocysteine levels (mean ± standard deviation), and clinical outcomes. The quality of each included study was assessed using the Oxford Center for Evidence-Based Medicine Quality ratings and classified the evidence ratings ranged from one to five, with one representing high-quality studies such as randomized controlled trials (RCT) and five representing case reports (14).

## Statistical analysis

All the analyses were performed using Review Manager software (version 5.3). Standardized mean difference (SMD) with a 95% confidence interval (CI) was used for continuous variables to compare the homocysteine levels between groups. The I2 tests measured heterogeneity among studies, and studies with I2 higher than 50% were considered to have high heterogeneity. A fixed-effects model was used when there was no significant heterogeneity among studies; otherwise, a random-effects model was used when data were considered heterogeneous. Two-sided *P*-values of $<0.05$ were regarded as statistical significance (15, 16).

# Results

## Study characteristics

The search strategy initially generated 283 articles. After removing duplicates and abstract screening, 104 full-text articles were assessed for eligibility. Finally, 21 articles were included in the final review, including two prospective studies, one retrospective cohort, and 18 case–control studies. Figure 1 shows the PRISMA flow chart of study selection.

This process resulted in the selection of 21 studies involving a total of 9888 participants, of whom 5031 were patients admitted with ischemic stroke, for the meta-analysis. Of the included studies, first author, publication year, total sample participants, country location, ethnicity, age, and study quality level were assessed. The studies included in the meta-analysis were generally of moderate quality rating (Table 1).

## Homocysteine levels in patients with ischemic stroke

This study compared the differences in the plasma Hcy levels between ischemic stroke patients and the control group, and other features were listed (Table 2). There was high heterogeneity among the studies reporting differences in Hcy levels between ischemic stroke patients and control ($I^2 = 100\%$). Thus, a random-effects model was used to analyze the data. An incorporated analysis showed that the AIS patients had significantly higher levels of Hcy compared to the controls (MD = +3.70, 95% CI = 2.42–5.98, $p < 0.001$) (Figure 2). Additional analysis of sex differences showed that male acute ischemic stroke patients had higher levels of Hcy

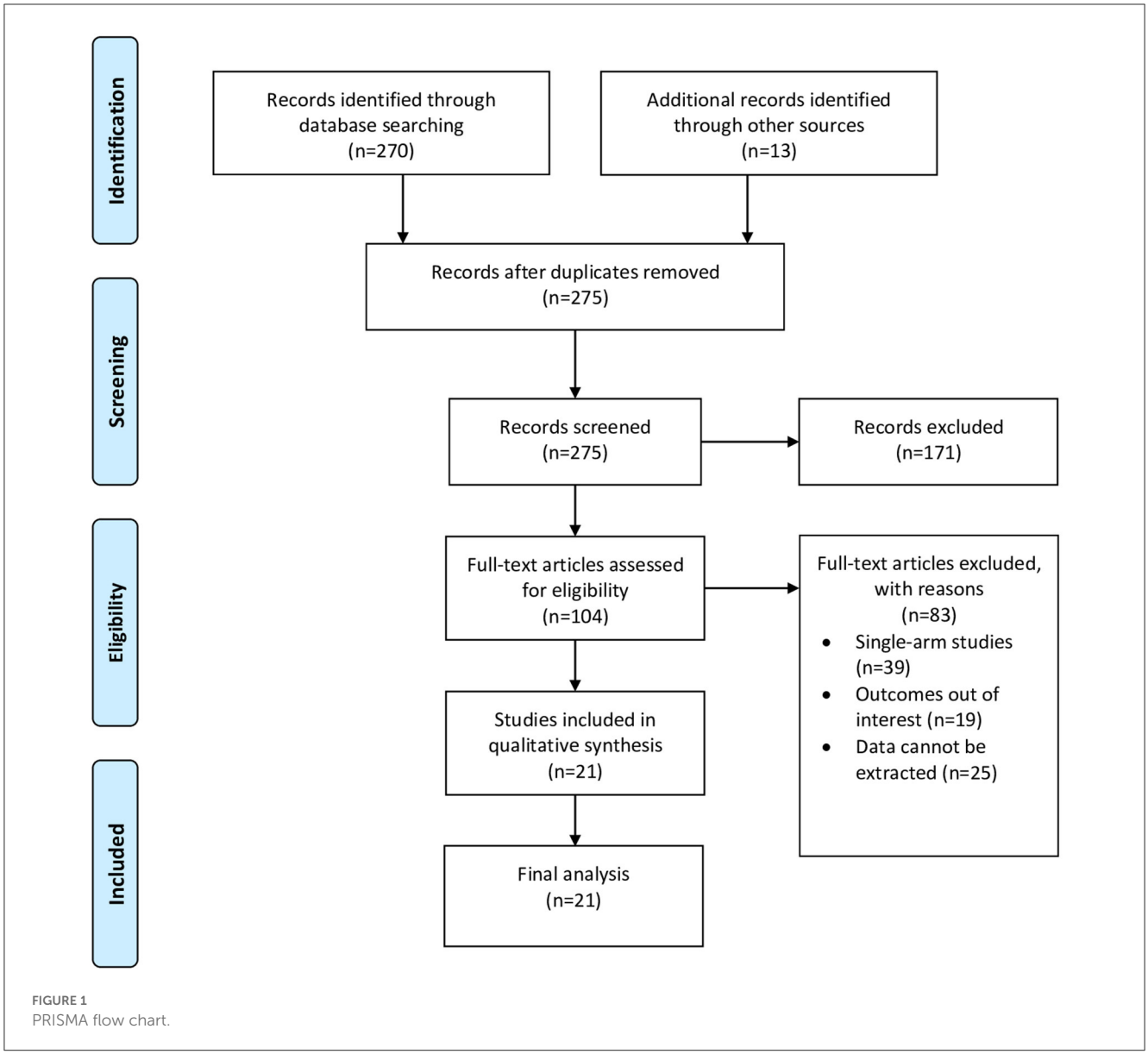


FIGURE 1
PRISMA flow chart.

compared to female patients (MD = +0.42, 95% CI = −1.20–2.05, $p = 0.61$) (Figure 3).

## Discussion

Homocysteine is a non-dietary amino acid that can be transformed into cysteine or recycled into methionine, a necessary amino acid, with the assistance of certain B vitamins. Normal homocysteine ranges in men and women vary between 5 and 10 micromol/L (micromoles per liter). If homocysteine levels surpass 10 micromol/L, this condition is called hyperhomocysteinemia (38, 39). Data from our systematic review and meta-analysis suggested the following: (1) patients with ischemic stroke had greater homocysteine levels than controls and (2) homocysteine could be an independent risk factor for the outcome of ischemic stroke patients. Homocysteine levels are often classified as mild (slightly above 10 micromol/L), moderate (16–30 micromol/L), intermediate (31–100 micromol/L), and severe (above 100 micromol/L) (40). Even mild hyperhomocysteinemia may increase the risk for ischemic stroke, as demonstrated by numerous studies in this systematic review and meta-analysis (18, 23, 25, 27, 28, 31, 36, 37). In total, three studies did not find homocysteine levels that meet the criteria for hyperhomocysteinemia, but all showed a tendency for greater homocysteine levels in stroke patients compared to controls (29, 30, 34). A prior study concludes that the effect of blood homocysteine level on stroke severity and outcome begins to appear between 8 and 10 micromol/L (41).

A higher homocysteine level raises the risk of vascular diseases, including stroke. Conversely, a decrease in homocysteine levels is correlated with a reduced risk of ischemic stroke (42). Elevated homocysteine levels can lead to stroke through a variety of pathways. Homocysteine promotes the transcription of the factor in the neural tissue, which enhances inflammation

TABLE 1 Baseline characteristics of patients in the included studies.

| Authors | Study type | Country location | No. of participants, (n) | Ethnicity | Age, Median (IQR, y) or Mean ± SD | Study quality level |
|---|---|---|---|---|---|---|
| Alfieri et al. (17) | Prospective cohort | Brazil | 352 | Caucasians | IS group: 67.7 ± 12.1, Control group: 63.1 ± 11.3 | 2 |
| Jin et al. (18) | Case-control | China | 3575 | Asians | IS group: 62.71 ± 11.86, Control group: 50.82 ± 8.87 | 3 |
| Ma et al. (19) | Retrospective Cohort | China | 314 | Asians | IS group: 53.8 ± 6.2, Control group: 54.0 ± 7.0 | 3 |
| Shademan et al. (20) | Case-control | Turkey | 240 | Asians | IS group: 58.2 ± 8.5, Control group: 55.1 ± 6.6 | 3 |
| Yurekli et al. (21) | Prospective trial | Turkey | 118 | Asians | IS group: 61.07 ± 6.28, Control group: 58.71 ± 5.66 | 2 |
| Wang et al. (22) | Case-control | China | 202 | Asians | IS group: 61.07 ± 11.56, Control group: 62.49 ± 8.93 | 3 |
| Kawamoto et al. (23) | Case-control | Japan | 91 | Asians | IS group: 81 ± 7, Control group: 79 ± 6.5 | 3 |
| Yoldas et al. (24) | Case-control | Turkey | 80 | Asians | IS group: 69 ± 11, Control group: 70 ± 9 | 3 |
| Salem-Berrabah et al. (25) | Case-control | Tunisia | 147 | Africans | IS group: 57.62, Control group: 30 to 70 years | 3 |
| Omrani et al. (26) | Case-control | Iran | 186 | Arabs | IS group: 62.2 ± 9.8, Control group: 61.8 ± 9.9 | 3 |
| Wei et al. (27) | Case-Control | China | 1108 | Asians | IS group: 59.34 ± 9.25, Control group: 59.88 ± 10.12 | 3 |
| Luo et al. (28) | Case-Control | China | 601 | Asians | IS group: 60.70 ± 12.33, Control group: 60.17 ± 10.32 | 3 |
| Modi et al. (29) | Case-Control | India | 87 | Asians | NR | 3 |
| Xiao et al. (30) | Case-Control | China | 304 | Asians | IS group: 60.37 ± 12.02, Control group: 60.45 ± 12.23 | 3 |
| Narayan et al. (31) | Case-Control | India | 175 | Asians | IS group: 53.3 ± 14.6, Venous stroke group: 30.9 ± 6.6, Control group: 51.8 ± 9.3 | 3 |
| Al-Allawi and Jubrael. (32) | Case-Control | Iraq | 120 | Arabs | IS group: 60, Control group: 62 | 3 |
| Lu et al. (33) | Case-Control | China | 320 | Asians | IS group: 63.91 ± 11.49, Control group: 61.65 ± 11.47 | 3 |
| Zheng et al. (34) | Case-Control | China | 418 | Asians | MCA stroke group: 64 ± 12, CA stroke group: 62 ± 11, BA stroke group: 60 ± 13, Control group: 64 ± 11 | 3 |
| Chen et al. (35) | Case-Control | China | 610 | Asians | IS group: 64.40 ± 12.90, Control group: 65.16 ± 11.95 | 3 |
| Zhou and Qi. (36) | Case-Control | China | 216 | Asians | IS group: 66.32 ± 11.51, Control group: 64.46 ± 12.77 | 3 |
| Chen et al. (37) | Case-Control | China | 730 | Asians | IS group: 65.7 ± 11.5, Control group: 66.3 ± 10.2 | 3 |

BA, Basilar Artery; IS, Ischemic Stroke; MCA, Middle Cerebral Artery; NR, Not Reported in detail; PCA, Posterior Cerebral Artery.

by elevating the concentration of inflammatory cytokines. Homocysteine accumulation within cells has been demonstrated to impede methyltransferases, reduce deoxyribonucleic acid (DNA) repair, and promote apoptosis. Autooxidation of homocysteine metabolites generates $H_2O_2$ and results in necrotic cell death (43, 44). Plasma homocysteine levels are frequently associated with the development of atherosclerosis and the degradation of vascular endothelium. Homocysteine induces the formation of serine elastase in vascular smooth muscle cells, which results in elastolysis by dissolving the extracellular matrix and generating reactive oxygen species (45).

One of the studies in this systematic review and meta-analysis comparing large-artery atherosclerosis stroke patients and healthy controls found a significant difference in homocysteine blood levels (18). Similar results were reported in a previous meta-analysis comparing homocysteine blood levels among

TABLE 2 Patients group and clinical characteristics of patients in the included studies.

| Authors | Ischemic stroke group (no. of patients) | Control group (no. of patients) | Ischemic stroke group Hcy levels, μmol/L (Mean ± SD) | Control group Hcy levels, μmol/L (Mean ± SD) | Stroke subtypes | Follow-up | Covariates adjustment | Other outcomes |
|---|---|---|---|---|---|---|---|---|
| Alfieri et al. (17) | 176 | 176 | 16.6 ± 1.3 | 12.0 ± 1.5 | NR | 3 months | Age, sex, ethnicity, BMI, smoking, and previous medications (antihypertensive, hypolipemiant, and hypoglycemic drugs) | The main findings of the study are that IS associated with increased WBC counts, high hsCRP, IL-6, lipid hydroperoxides (LOOH), NOx, homocysteine, ferritin, ESR, glucose, and insulin, and lowered iron, 25(OH)D level, total cholesterol, and HDL cholesterol |
| Jin et al. (18) | 1810 (male: 965; female: 845) | 1765 (male: 570; female: 1195) | 13.67 ± 6.62 (male: 13.86 ± 6.74; female:14.45 ± 6.26) | 12.49 ± 4.36 (male: 11.93 ± 5.46; female: 12.86 ± 5.74) | large-artery atherosclerosis (LAA) | NR | Age, sex | In LAA-IS patients, the TT homozygous genotype correlated with an increased risk of developing LAAIS, The plasma homocysteine level was genotype-dependent according to the following trend: TT > CT > CC |
| Ma et al. (19) | 92 hypertensive patients with IS | 114 hypertensive patients without IS | 61.1 ± 8.8 | 55.7 ± 10.2 | NR | 6 months | NR | In hypertensive patients with IS, serum cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), ischemia-modified albumin (IMA), lipoprotein-associated phospholipase A2 (Lp-PLA2), glial fibrillary acidic protein (GFAP), and homocysteine (HCY) levels were significantly higher compared to controls ($p < 0.05$) |
| Shademan et al. (20) | 120 | 120 | 16.1 ± 1.20 | 13.2 ± 0.82 | NR | NR | Blood pressure, glucose, and cholesterol | The mean serum levels of apolipoprotein B 48, interleukin-1β, and Homocysteine, were significantly increased in the experimental group compared to the control group with a $p$-value of 0.001 |
| Yurekli et al. (21) | 54 | 64 | 29.28 ± 10.9 | 12.83 ± 6.8 | NR | 24 h after admission | NR | Compared to the control group, IS patients had lower serum vitamin D ($p < 0.0001$) and brain-derived neurotrophic factor ($p < 0.0001$) levels and higher homocysteine levels ($p < 0.0001$). There was a correlation between vitamin D levels and BDNF levels in patients with IS |
| Wang et al. (22) | 101 | 101 | 18.48 ± 10.29 | 15.27 ± 6.35 | NR | NR | Age, sex, BMI, TG, TC, HDL, and LDL | Serine hydroxymethyl transferase 1 (SHMT1) gene hypermethylation was significantly associated with high Hcy concentration in ischemic stroke patients |
| Kawamoto et al. (23) | 44 | 47 | 14.6 ± 5.6 | 12.9 ± 6.6 | NR | NR | Age, gender, albumin, creatinine, hypertension, diabetes, smoking, BMI, TG, TC, HDL, and uric acid | There was an association between elevated Hcy levels (>10 μ**mol/L)** and IS among the elderly Japanese |
| Yoldas et al. (24) | 40 | 40 | 21.0 ± 0.6 | 11.2 ± 1.1 | NR | NR | NR | Subjects with stroke have higher circulating serum hsCRP and homocysteine levels |
| Salem-Berrabah et al. (25) | 50 (male: 30; female: 15) | 97 (male: 50; female: 46) | 15.83 ± 10.60 (male: 16.73 ± 12.45; female:14.03 ± 5.23) | 13.78 ± 6.29 (male: 14.7 ± 6.03; female: 12.78 ± 6.47) | NR | NR | NR | In Tunisian subjects, the risk of developing ischemic stroke in hyperhomocysteinemic subjects was 2.4 times more than in subjects with normal Hcy levels (OR = 2.4; 95% CI: 1.13–5.06; $p < 0.05$). |
| Omrani et al. (26) | 93 | 93 | 20.59 ± 19.7 | 14.1 ± 9.5 | NR | NR | Smoking | In this study, 41% of patients had hyperhomocysteinemia. Hcy plasma levels in the acute phase of ischemic stroke (within 24 h) were significantly higher than normal limits |

*(Continued)*





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TABLE 2 (Continued)

| Authors | Ischemic stroke group (no. of patients) | Control group (no. of patients) | Ischemic stroke group Hcy levels, μmol/L (Mean ± SD) | Control group Hcy levels, μmol/L (Mean ± SD) | Stroke subtypes | Follow-up | Covariates adjustment | Other outcomes |
|---|---|---|---|---|---|---|---|---|
| Wei et al. (27) | 548 | 560 | 12.14 ± 2.61 | 8.92 ± 2.43 | NR | NR | Gender, age, smoker, diabetes and hypertension | Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p < 0.001$). Higher levels of homocysteine were reported in patients with ischemic stroke who had the rs2666433AA genotype compared to those who carried the rs2666433 GG+GA genotypes ($p < 0.001$) |
| Luo et al. (28) | 298 | 303 | 13.98 ± 7.15 | 8.96 ± 7.02 | NR | NR | Gender, age, smoking situation, diabetes, hypertension | Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p < 0.001$) |
| Modi et al. (29) | 57 (male: 41; female: 16) | 30 (male: 22; female: 8) | 9.91 ± 2.25 (male: 10.24 ± 2.34; female: 9.08 ± 1.81) | 8.00 ± 2.74 (male: 8.45 ± 2.72; female: 6.79± 2.60) | NR | NR | Gender, smoking, hypertension, obesity | Hyperhomocysteinemia is a significant independent risk factor for ischemic stroke ($p < 0.01$). A considerable positive correlation was also found between hypertension, smoking, and elevated levels of homocysteine |
| Xiao et al. (30) | 152 | 152 | 1.18 ± 0.23 | 1.14 ± 0.16 | NR | NR | Telomere length, glucose, TC, HDL | Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p$: 0.047). Telomere length and homocysteine (HCY) were inversely associated in ischemic stroke patients ($r = -0.176$, $p$: 0.03) |
| Narayan et al. (31) | 75 IS patients and 25 venous stroke patients | 75 | IS group: 12.88 ± 10.27, venous stroke group: 8.08 ± 4.17 | 8.62 ± 6.13 | Ischemic stroke and venous stroke | NR | NR | Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p$: 0.02). Ischemic stroke and venous stroke patients were younger than 45 years old |
| Al-Allawi and Jubrael. (32) | 70 | 50 | 20.9 ± 22.2 | 12.3 ± 10.2 | NR | NR | NR | Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p$: 0.02). TT and CT genotypes had greater homocysteine levels than the CC genotype ($p < 0.001$ and $p$: 0.04, consecutively). No interquartile ranges for age were available |
| Lu et al. (33) | 152 | 168 | 16.628 ± 12.0426 | 14.78 ± 9.494 | NR | NR | Age, gender, smoking, alcohol consumption, SBP, DBP, blood glucose, TC, TG, LDL, HDL, UA, plasma fibrinogen level | NR |
| Zheng et al. (34) | 209 | 209 | MCA stroke group: 8.89 ± 2.32, PCA stroke group: 7.99 ± 2.20, BA stroke group: 8.09 ± 2.54 | 8.35 ± 1.93 | MCA, PCA, and BA stroke | NR | NR | MCA stroke patients had significantly higher homocysteine levels than PCA ($p = 0.016$) and BA stroke patients ($p$: 0.013) |
| Chen et al. (35) | 400 | 210 | 8.93 ± 1.32 | 9.59 ± 1.74 | NR | NR | NR | NR |
| Zhou and Qi. (36) | 108 | 108 | 14.43 ± 5.43 | 11.14 ± 3.78 | NR | NR | NR | Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p < 0.001$) |
| Chen et al. (37) | 382 | 348 | 12.43 ± 6.09 | 10.12 ± 5.19 | NR | NR | NR | Homocysteine was significantly higher in ischemic stroke patients than in the controls ($p < 0.001$). Homocysteine levels were statistically lower in ischemic stroke patients with the GG or AG genotype than in those with the AG or AA genotype |

BA, Basilar Artery; IS, Ischemic Stroke; MCA, Middle Cerebral Artery; NR, Not Reported in detail; PCA, Posterior Cerebral Artery; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure, TC, Total Cholesterol, TG, Triglycerides, LDL, low-density lipoprotein, HDL, high-density lipoprotein, UA, uric acid.





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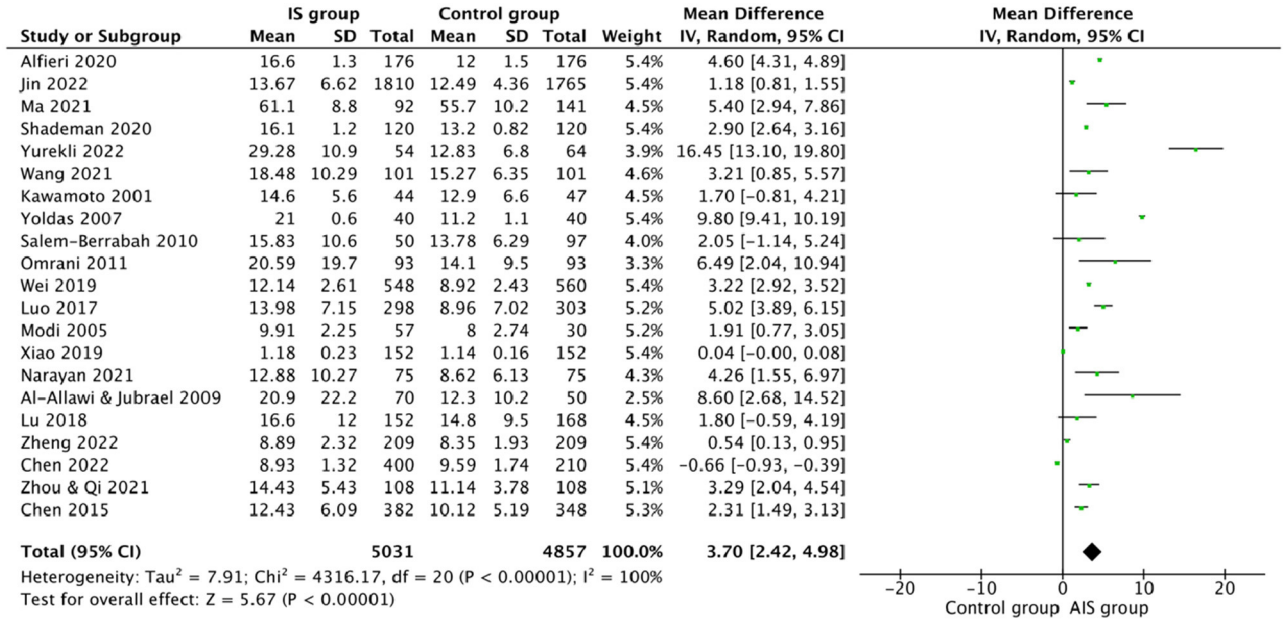


FIGURE 2
Forest plots for comparing plasma Hcy levels between ischemic stroke (AIS) patients and controls.

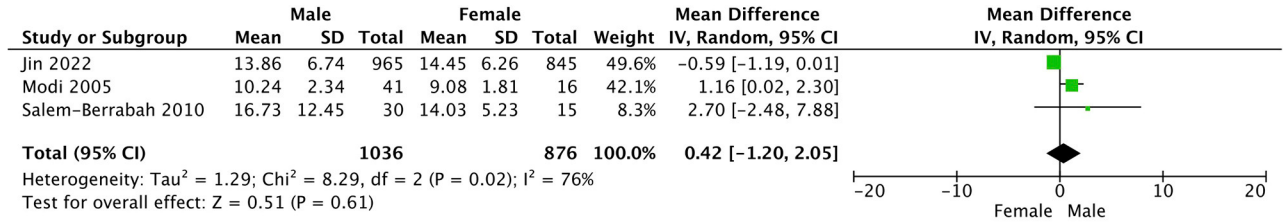


FIGURE 3
Forest plots of sex differences comparing plasma Hcy levels in ischemic stroke (AIS) patients.

acute stroke patients (2,243 patients) and a control group (871 patients). Hyperhomocysteinemia is most often related to the subtypes "small-vessel occlusion" and "large-artery atherosclerosis" (46).

Depending on their locations, individuals with middle cerebral artery (MCA) stroke had significantly higher homocysteine levels than patients with the posterior cerebral artery (PCA) and basilar artery (BA) stroke (34). Higher homocysteine levels in MCA stroke patients compared to BA stroke patients may be indicative of a higher risk of post-stroke cardiovascular disorders in MCA stroke patients related to a hypercoagulable state (47).

Hyperhomocysteinemia is also a risk factor for other stroke subtypes, including intracerebral hemorrhage, the second-leading subtype of stroke (48). In an earlier meta-analysis involving 667 patients with intracerebral hemorrhage, 1821 patients with ischemic stroke, and 2500 healthy controls, homocysteine levels in intracerebral hemorrhage patients were significantly higher than in healthy controls, indicating that the exact pathophysiology of intracerebral hemorrhage inevitably involves increased homocysteine levels (49). The plasma homocysteine level was found to be an exacerbating factor in atherosclerosis, resulting in the pathogenesis of endothelial degeneration and vessel wall necrosis, which could increase the risk of ischemic stroke as well as intracerebral hemorrhage (50). Additionally, a raised homocysteine level was significantly associated with an increased risk of recurrent stroke within 15 months after the initial cerebrovascular event (51). A plasma homocysteine level above the 75th percentile 3 months following an ischemic stroke was predictive of vascular events, including stroke recurrence (52).

Vitamin B deficiency is a potential challenge that might impair homocysteine metabolism and lead to hyperhomocysteinemia (53). Nonetheless, vitamin B supplementation and homocysteine reduction remain the subjects of several debates. In the

Vitamins to Prevent Stroke (VITATOPS) trial, daily B vitamins supplementation did not appear to be over the placebo in reducing the incidence of major vascular events (54). It was hypothesized that antiplatelet therapy, administered to approximately 80% of patients in the VITATOPS trial, might have modulated the beneficial impact of B vitamins on homocysteine levels. Patients who were receiving antiplatelet therapy at the baseline were separated from those who were not in the *post-hoc* analysis. There was no significant difference in the primary outcome between the placebo and vitamin B groups in patients receiving antiplatelet medication at the baseline (14.8% vs. 15.7%). However, for patients who did not receive antiplatelet therapy at the baseline, vitamin B treatment correlated with a significant reduction in primary outcome events (16.8% vs. 21.0%) (55). According to the Vitamin Intervention for Stroke Prevention (VISP) trial, moderate homocysteine reduction did not affect vascular outcomes (56). However, there were a few issues with the VISP trial. It appears that VISP gave too much cobalamin in the low-dose vitamin arm of the study (6 mcg daily; at least the recommended daily intake [RDI] or, by some measures, three times the RDI) as well as insufficient cobalamin in the high-dose vitamin arm (400 mcg daily) for geriatric patients (57). A dose–response study revealed that geriatric patients with cobalamin levels below 221 pmol/L require 1000 g daily for optimal absorption (58). It became clear that the ability to absorb sufficient levels of cobalamin was the primary determinant of response to vitamin therapy in homocysteine reduction. Mecobalamin, one of the active analogs of cobalamin, has been shown to reduce plasma homocysteine concentrations. An earlier study revealed that after 4 weeks, 8 weeks, 3 months, and 6 months of supplementation, the homocysteine level in the group receiving 500 μg of mecobalamin three times a day was lower than in the group receiving only conventional therapy. In addition, the treatment group had significantly higher scores on the National Institutes of Health Stroke Scale (NIHSS) after 3 and 6 months of mecobalamin supplementation than the control group. (59). Similar to cobalamin, folate is an essential regulator in the homocysteine metabolic process; a previous meta-analysis comprising 14 randomized controlled trials with a total of 39,420 participants showed that homocysteine reduction after folic acid supplementation was significantly higher in regions without folate fortification than in regions with folate fortification (60).

Despite all the contrasts, multiple studies indicate that daily vitamin B intake has a strong preventive effect against stroke or transient ischemic attack (61). Reducing homocysteine levels prior to the onset of atherosclerosis may have preventative benefits for vascular events. In other words, homocysteine must be decreased as promptly as possible. Yet another issue that must be addressed is attempting to determine the impact of modifiable risk factors, including hyperhomocysteinemia, on medical care, such as suggesting homocysteine-lowering interventions, including supplementation with vitamin B, to decrease the probability of stroke or achieving better prognosis of stroke patients.

There were some limitations in our study. (1) Most of the included studies only measured homocysteine levels at hospital admission. There was a lack of data on changes in homocysteine levels during follow-up. Therefore, further studies assessing the average time of measurement of homocysteine levels following an ischemic stroke or during hospitalization would help understand whether homocysteine is a risk factor or a consequence of stroke. (2) Our primary outcome was to compare the homocysteine levels between the ischemic stroke and control group. Further studies are needed to analyze other covariates (different types of strokes and comorbidity) or predict the risk estimates of hyperhomocysteinemia.

## Conclusion

This meta-analysis and systematic review indicate that ischemic stroke patients have significantly higher homocysteine levels than controls. Detecting hyperhomocysteinemia and reducing homocysteine levels should be explored among individuals at increased risk for ischemic stroke.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

RP: supervision, study concept, writing of the initial draft, and data extraction. VW: writing of the initial draft, data extraction, analysis, and interpretation. VV: full-text review, manuscript preparation, and data extraction and analysis. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

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