INPLASY PROTOCOL

To cite: Zhao et al. Association of methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism with ischemic stroke risk in different populations: an updated meta-analysis. Inplasy protocol 2022110037. doi: 10.37766/inplasy2022.11.0037

Received: 08 November 2022

Published: 08 November 2022

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Support: **NSFC(No. 81971116).**

Review Stage at time of this submission: **Formal screening of search results against eligibility criteria.**

Conflicts of interest:
None declared.

Association of methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism with ischemic stroke risk in different populations: an updated meta-analysis

Zhao, LL[1]; Li, T[2]; Dang, MJ[3]; Li, Y[4]; Fan, H[5]; Hao, Q[6]; Song, DL[7]; Lu, JL[8]; Lu, ZW[9]; Jian, YT[10]; Wang, HY[11]; Wang, XY[12]; Wu, YL[13]; Zhang, GL[14].

Review question / Objective: **Recently, increasing evidence has implicated methylenetetrahydrofolate reductase (MTHFR) gene mutation as a risk factor for ischemic stroke (IS) in the general population. However, studies have been inconclusive and lack evidence on specific populations. We aim to determine whether the MTHFR C677T variant is linked to an increased risk of IS in different age groups andregions.**
Information sources: **A systematic search of PubMed, EMBASE, Cochrane Library, Web of Science, and CNKI databases for relevant observational studies will be undertaken.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 November 2022 and was last updated on 08 November 2022 (registration number INPLASY2022110037).

INTRODUCTION

Review question / Objective: **Recently, increasing evidence has implicated methylenetetrahydrofolate reductase (MTHFR) gene mutation as a risk factor for ischemic stroke (IS) in the general population. However, studies have been inconclusive and lack evidence on specific populations. We aim to determine whether the MTHFR C677T variant is linked to an increased risk of IS in different age groups andregions.**

Condition being studied: **Ischemic strokes (IS) is acute neurological deficits caused by**

vascular occlusion. It is one of the leading causes of death and disability worldwide. Although its rate increases with age, IS occurs in more than two million young adults (<45 years) per year worldwide, having an even more relevant clinical and socioeconomic impact on health care costs and loss of productivity. Reperfusion therapy, as a milestone in treatment of ischemic stroke, is the most effective treatment, including intravenous thrombolysis and arterial thrombectomy. But there are still a lot of patients can not benifit from these treatment. It is important to figure out ways to prevent the incidence of stroke. Hyperhomocysteinemia is reported to have an independent association with the risk of stroke. Folate metabolism is largely controlled by the methylenete-trahydrofolate reductase (MTHFR), which catalyzes the conversion of 5,10-methylenetetrahydrofolate into 5-methylenetetrahydrofolate. 5-methylenetetrahydrofolate provides a methyl group in the methylation reaction of homocysteine to methionine. Thus MTHFR enzyme activity is very important to the homeostasis of serum homocysteine level. C677T was a common mutant in MTHFR. The replacement of C with T at nucleotide 677 results in converting an alanine to valine amino acid residue in the enzyme. These missense mutations cause 50-60% decreased enzyme activity in patients who have the homozygous variant (TT), which contributes to hyperhomocysteinemia. Thus, it is important to figure out the association between MTHFR C677T polymorphism and the risk of IS on the point of primary and secondary prevention of IS.

METHODS

Participant or population: Case-control or cohort studies that enrolled patients diagnosed with ischemic stroke (IS) for the first time will be included. Studies that only included patients diagnosed with IS will be excluded. All studies provide MTHFR C677T genotype frequency will be included. Only studies with P value of Hardy–Weinberg equilibrium (HWE) test > 0.05 are considered eligible.

Intervention: The frequency of "T" in the allele model, "TT+TC" in the dominant model, "TT" in the recessive mode, "TC" in the heterozygote model, and "TT" in the homozygote model.

Comparator: The frequency of "C" in the allele model, "CC" in the dominant model, "CC+TC" in the recessive mode, "CC" in the heterozygote model, and "CC" in the homozygote model.

Study designs to be included: Case-control or cohort studies of English and Chinese are eligible for this review.

Eligibility criteria: Publications with Newcastle–Ottawa scale score of 7–9 will be considered eligible.

Information sources: A systematic search of PubMed, EMBASE, Cochrane Library, Web of Science, and CNKI databases for relevant observational studies will be undertaken.

Main outcome(s): Stroke susceptibility will be evaluated by odds ratios (OR)and its 95% confidence intervals (95% CI) in each genetic model.

Additional outcome(s): None.

Quality assessment / Risk of bias analysis: Two reviewers will independently assess risk of bias based on the following domains from recommendations from the Newcastle-Ottawa Scale: 1. adequate definition of cases; 2. Representativeness of the cases; 3. Selection of Controls; 4. Definition of Controls; 5. Comparability of cases and controls on the basis of the design or analysis; 6. Ascertainment of exposure; 7. Same method of ascertainment for cases and controls; 8. Non-Response rate. Sensitivity analysis will be conducted based on the bias assessment to assess robustness of results.

Strategy of data synthesis: MTHFR C677T polymorphism and stroke susceptibility by calculating odds ratios (OR) and 95%

confidence intervals (CI). I2 will be used to evaluate heterogeneity among genetic comparison models, while the pooled OR will be estimated via the random effect model of Mantel-Haenszel. Heterogeneity between studies is indicated by an I2 > 50% In addition, we will study the impact of a single study on pooled OR by performing sensitivity analyses on different genetic comparison models. Egger's, Begg's, and funnel plots will be used to evaluate the potential publication bias in our study. Stata 17.0 will be used to perform statistical analysis of all genetic comparison models.

Subgroup analysis: Two subgroup analyses will be undertaken: The first to assess if the stroke susceptibility of people with "T" allele are different in different ethnical groups (Asia, Africa, Europe, North America, South America, and Oceania); The second to investigate whether the stroke susceptibility are different in different age groups (Young: < 18; Middle-aged: 18-60; Elderly: >60).

Sensitivity analysis: We will studied the impact of a single study on pooled OR by performing sensitivity analyses on different genetic comparison models.

Language restriction: English and Chinese.

Country(ies) involved: China.

Keywords: MTHFR C677T, polymorphism, Ischemic stroke, Subgroup analysis, Meta-analysis.

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