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MTHFR C677T Polymorphism and Ischemic Stroke Susceptibility: A Meta-Analysis of Publicly Accessible Case-Control Studies

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Abstract

Genetic association studies have repeatedly examined the common MTHFR C677T polymorphism (rs1801133) in relation to ischemic stroke, yet estimates differ across populations and study settings. We searched publicly accessible full-text records in Europe PMC and reconstructed unadjusted genotype effects when complete CC, CT, and TT tables were available. Ten records were recovered, and six independent case-control datasets supplied compatible counts. DerSimonian–Laird random-effects synthesis showed associations with ischemic-stroke case status for TT versus CT+CC (odds ratio [OR] 1.71, 95% confidence interval [CI] 1.25–2.34), CT+TT versus CC (OR 1.42, 95% CI 1.18–1.71), and T versus C (OR 1.38, 95% CI 1.17–1.63). Heterogeneity was substantial (I2 70.7%, 66.7%, and 76.9%, respectively). Exact control Hardy–Weinberg equilibrium sensitivity analysis also retained pooled ORs above one. The available public data support an association in the analysed datasets, but heterogeneity, predominantly Chinese sampling, and unadjusted estimates preclude causal or clinical-prediction interpretation.

Keywords

MTHFR C677T, ischemic stroke, case-control studies, genetic association, meta-analysis

1. Introduction

Ischemic stroke is a clinically heterogeneous endpoint, and inherited variation may contribute to susceptibility alongside vascular, metabolic, and environmental factors. A focused synthesis is useful when a variant has been tested repeatedly but individual reports differ in design, ancestry, phenotype definition, and covariate handling. The MTHFR C677T polymorphism (rs1801133) is a recurring candidate because it has been examined alongside homocysteine-related phenotypes and stroke risk. Full-text repositories such as Europe PMC provide an auditable route to original genotype tables when access permits [1].

Database visibility does not by itself make evidence combinable. Catalog entries can point to an association or a publication, whereas a count-based meta-analysis additionally needs a clear phenotype, an independent comparison group, and enough genotype detail to reconstruct the same contrast in every study. This distinction is especially important for candidate-variant literature, in which an article can report a related biomarker, a stroke subtype, or a multivariable model without providing the three genotype cells required for a compatible calculation. The present study therefore uses public databases as an evidence-recovery and verification route,

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not as a substitute for the study-level data structure required by meta-analysis. Its central unit of analysis is a reported case-control genotype table whose provenance can be checked in the accessible full text.

The published MTHFR literature does not yield a single directly comparable effect estimate. Several case-control studies in Chinese populations reported genotype distributions for ischemic-stroke cases and controls [2–5]. A study restricted to Chinese people with type 2 diabetes reported the same locus in a different clinical setting [6], whereas a Hungarian study considered MTHFR among genotype combinations and classical risk factors [7]. Their unadjusted tables cannot on their own settle the cross-study direction, but they supply a checkable basis for a common count-based synthesis.

This paper narrows the broad question of genetic variants and disease susceptibility to a reproducible locus–phenotype pair: MTHFR C677T and ischemic stroke. It pools only independently reported case-control datasets with directly verified CC, CT, and TT counts. Its contribution is methodological rather than a claim of a new biomarker: it reconstructs comparable unadjusted effects from traceable tables, evaluates three genetic contrasts, and tests their direction with leave-one-out and control Hardy–Weinberg equilibrium (HWE) sensitivities. The purpose is association evidence synthesis, not causal, diagnostic, prognostic, or treatment analysis.

This scope addresses a practical reproducibility gap in short conference papers. A public database can identify a relevant record, but the reported association cannot be combined unless case status, genotype definition, and all three genotype cells can be verified. By retaining a path from each pooled contrast to the source table, the analysis makes both its calculation and its exclusions inspectable. The same design also makes its limits visible: the effect estimates are crude case-control associations and cannot substitute for harmonised adjusted analyses.

2. Related Work and Evidence Gap

The recovered reports do not describe one uniform study population. Huang et al. examined MTHFR C677T, homocysteine, and stroke severity in a southwest Chinese case-control sample, whereas Jin et al. provided a large Han Chinese series [2, 3]. Zhou et al. assessed tagging variants in MTHFR, and Li et al. examined C677T alongside homocysteine variation [4, 5]. Ma et al. analysed C677T in people with type 2 diabetes; Szolnoki et al. reported a Hungarian case-control dataset within a multigene risk-factor framework [6, 7]. The studies differ in sampling frame, phenotype ascertainment, and adjustment, so the pooled analysis uses only genotype counts that could be verified.

Four other public records were kept for context rather than added to the reconstructed primary set. They comprised a prospective low-folate Chinese cohort, a subtype-focused European analysis, a young-patient study of prothrombotic variants, and a case-control SNP-screening report [8–11]. Their design or reporting did not provide a compatible, non-overlapping three-genotype case-control table for every prespecified contrast, so they were left out of the main calculation. A larger cohort or a stroke-subtype analysis can still be valuable evidence; it is simply not interchangeable with the genotype-count input required here.

Zhao et al. provide a broader reference point: their searches of several bibliographic databases yielded 96 eligible studies and associations across genetic models [12]. That evidence base is more comprehensive than the present reconstruction. Our narrower aim is to make a small set of publicly accessible case-control tables auditable, apply one common unadjusted estimand, and report explicit robustness checks. The approach is consistent with reporting guidance that calls for transparent descriptions of participant selection, genotyping, and analytic choices [13].

3. Methods

3.1 Protocol, Source Recovery, and Eligibility

The search question was whether the MTHFR C677T polymorphism was associated with ischemic-stroke case status. Europe PMC was used as the primary public full-text source. The search combined “MTHFR C677T”, “rs1801133”, “ischemic stroke”, “case-control”, and “genotype”, and was last run on 27 August 2026. The recovery route and accessible source identifiers were retained with the run record, allowing the ten

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recovered records to be checked against public metadata. This targeted public-accessibility search is not presented as a database-wide systematic review.

The primary pool required an independently reported ischemic-stroke case-control dataset with countable CC, CT, and TT genotypes in a source table. We excluded prospective studies, incompatible phenotypes or subtype-only estimates, reports without a compatible three-genotype table, and records whose independence could not be established. One investigator entered the verified counts in a structured file, retaining the PMCID, DOI, and original table location for each included dataset. This compact extraction follows the transparency goals of STREGA [13].

For the six accessible reports, we used a small study-level checklist rather than a formal risk-of-bias scale. Each dataset was checked for a case-control comparison, an ischemic-stroke phenotype, complete case and control genotype counts, and a traceable source location. We then examined control HWE as a signal relevant to genotype quality and selection. The checklist makes the minimum data-quality checks visible without assigning an overall score when reporting was incomplete.

3.2 Effect Construction and Synthesis

For each study, unadjusted odds ratios were reconstructed from reported counts for three prespecified contrasts: recessive (TT versus CT+CC), dominant (CT+TT versus CC), and allelic (T versus C). Control HWE was assessed from genotype counts with the exact test of Wigginton et al.; $P < 0.05$ was considered evidence of departure from HWE for sensitivity analysis [14]. For a two-by-two table, a is the exposed case count, b the unexposed case count, c the exposed control count, and d the unexposed control count. The study estimate was

$$\mathrm{OR} = \frac{ad}{bc}, \qquad \mathrm{Var}[\log(\mathrm{OR})] = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}. \tag{1}$$

Here, a denotes the exposed case count, b denotes the unexposed case count, c denotes the exposed control count, and d denotes the unexposed control count. The analysis script applied a 0.5 continuity correction only if a cell was zero; no correction was required for the included contrast tables. Because the studies differed in population and clinical setting, the log odds ratios were pooled with the DerSimonian–Laird random-effects estimator [15]. The pooled estimate was exponentiated to obtain an OR and 95% CI.

Cochran's Q and I^2 were used to describe between-study dispersion; I^2 is the share of observed variation not attributed to within-study sampling error [16]. We repeated each contrast after removing one dataset in turn. This leave-one-out check asks whether any single study reverses the pooled direction, but it cannot address confounding, population stratification, genotype-quality concerns, or phenotype misclassification. All quantitative outputs were generated deterministically from the preserved genotype-count file.

The calculation did not estimate a population attributable fraction, a risk score, a genotype-by-environment interaction, or a causal effect. It also did not conduct subgroup meta-analysis because six datasets do not support stable estimates across ancestry, diabetes status, stroke subtype, or folate exposure. Publication-bias tests were not performed because fewer than ten independent datasets were available, making funnel-plot asymmetry tests unreliable. The source table locations are retained so that another analyst can reproduce the contrasts or evaluate a different eligibility rule.

Table 1: Included datasets and directly verified MTHFR C677T genotype counts. Population is given in parentheses; CN, Chinese; SW, Southwest China; Hei, Heilongjiang; T2D, type 2 diabetes; control HWE results are reported in the text

Study (population)	N_{case}	$N_{control}$	Case CC/CT/TT	Control CC/CT/TT
Huang (CN-SW)	198	168	94/72/32	101/62/5
Jin (CN-Hei)	1,810	1,765	1320/460/30	1330/420/15
Zhou (CN-Tianjin)	542	654	160/270/112	242/308/104
Ma (CN-T2D)	236	390	36/106/94	88/183/119
Li (CN-Central)	300	261	71/134/95	106/110/45
Szolnoki (Hungarian)	867	743	415/338/114	386/268/89

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4. Evidence Synthesis

4.1 Study Selection and Extracted Evidence

The public-accessibility search recovered ten full-text records. Six met quantitative eligibility criteria, and four were retained only as contextual evidence. The selection account records ten recovered records, six included genotype-count datasets, and four exclusions from the primary pool. Table 1 presents the extracted counts and clinical variation. Five datasets were Chinese and one was Hungarian; the Ma dataset was restricted to people with type 2 diabetes.

Figure 1 summarizes this bounded recovery. The four contextual records were retained narratively but not pooled under the prespecified contrasts.

Across the six datasets, the reconstructed tables contained 3,953 cases and 3,981 controls. The smallest control TT cell occurred in Huang et al. (five controls), while Jin et al. contributed the largest series. The table reports underlying cells rather than only study-level ORs, allowing inspection of the data used in each transformation. The source reports did not provide one common covariate set, so the pooled estimates remain unadjusted.

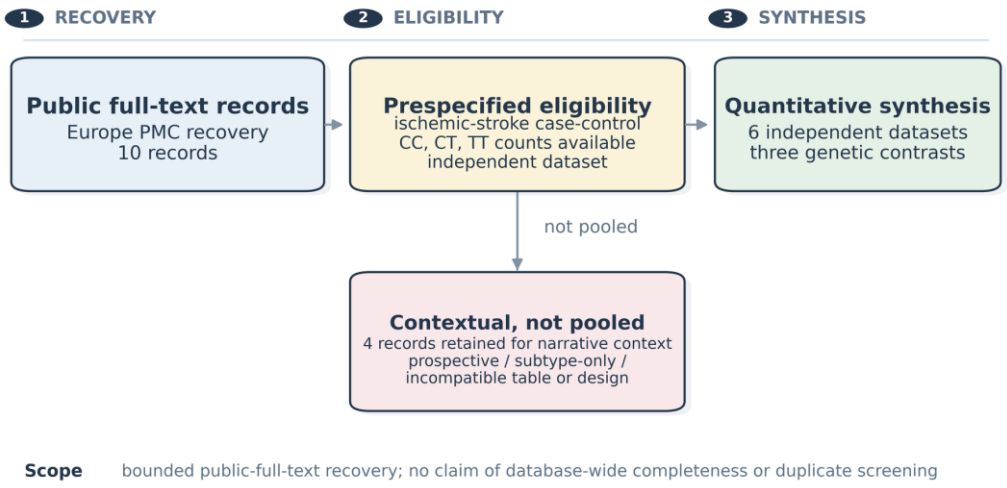
Exact control HWE testing identified departure in Jin et al. ($P = 0.0026$) and Szolnoki et al. ($P = 0.00016$); the other four studies had $P \geq 0.05$. These departures do not establish study error, but they motivated a prespecified sensitivity analysis excluding the two datasets.

The HWE screen should be interpreted cautiously. A small control-group P value can reflect genotyping error, population structure, control selection, or chance in the context of multiple study features. It does not identify which explanation applies to a particular report. Its role here is therefore limited to testing whether the pooled direction depends on studies whose control distributions depart from HWE, rather than to exclude those reports from the primary evidence without disclosure.

4.2 Random-effects Estimates and Sensitivity Diagnostics

All three random-effects contrasts were above one. The recessive TT contrast produced OR 1.71 (95% CI 1.25–2.34; Q = 17.05 on 5 degrees of freedom; I^2 = 70.7%). Figure 2 displays the six study-level and pooled estimates for this contrast. The plot is based on unadjusted genotype counts and a DerSimonian–Laird random-effects calculation, so its rightward pooled effect is an association estimate rather than evidence of causation.

Figure 1: Public-record recovery and eligibility flow. The diagram reports the bounded Europe PMC full-text recovery used in this study, not a database-wide PRISMA flow. Contextual records were retained for interpretation but not pooled under the prespecified genotype-count contrasts



The dominant contrast yielded OR 1.42 (95% CI 1.18–1.71; Q = 15.01; I^2 = 66.7%), and the allelic contrast yielded OR 1.38 (95% CI 1.17–1.63; Q = 21.68; I^2 = 76.9%). Table 2 summarizes these results together with

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the leave-one-out ranges. Removing any one study did not move a pooled OR below one in any contrast. Heterogeneity nevertheless remained substantial for most recalculations, and the intervals of the study-specific recessive effects were wide. The forest plot displays that spread alongside the pooled line.

After excluding the two studies with control HWE $P < 0.05$, the four-study random-effects estimates remained above one: OR 1.93 (95% CI 1.29–2.90) for TT versus CT+CC, 1.65 (1.35–2.03) for CT+TT versus CC, and 1.56 (1.27–1.92) for T versus C. This sensitivity analysis strengthens robustness of direction, but does not remove the limitations of unadjusted counts or heterogeneous settings.

We did not replace the primary estimates with the HWE-restricted results, because doing so would discard two independently reported datasets on the basis of a screening result alone. The two analyses are therefore shown together. This makes it possible to see that the direction persists after the HWE restriction while keeping the uncertainty in magnitude and generalisability explicit.

For the recessive contrast, study-specific unadjusted ORs ranged from 1.11 to 6.28, illustrating the dispersion that motivates random effects. After one-study removal, the recessive pooled OR ranged from 1.51 to 1.91; corresponding ranges were 1.28 to 1.52 for the dominant contrast and 1.29 to 1.46 for the allelic contrast. These ranges are sensitivity descriptors rather than tests of equivalence between studies. High I^2 values therefore remain part of any comparison across settings.

Figure 2: Recessive genetic contrast (TT versus CT+CC) for MTHFR C677T and ischemic-stroke case status. Study estimates were reconstructed from unadjusted genotype counts. The pooled line is the DerSimonian–Laird random-effects estimate (OR 1.71, 95% CI 1.25–2.34; I2 = 70.7%). The figure supports an association interpretation only

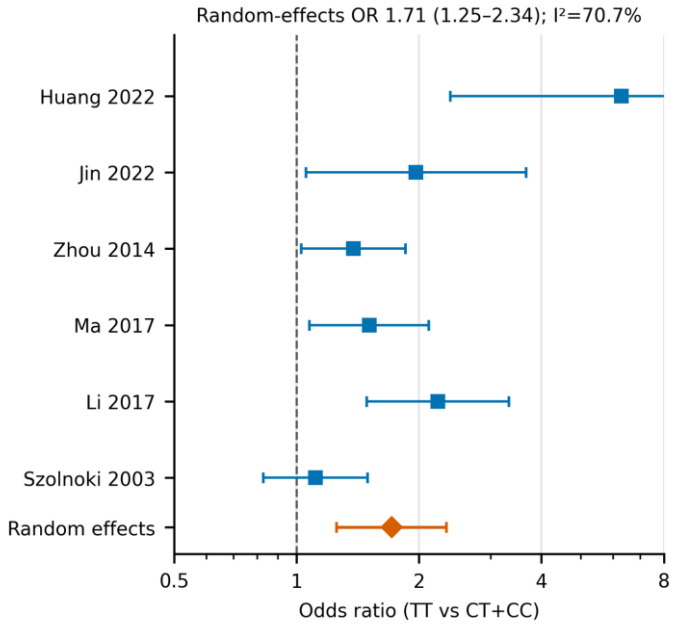

Table 2: Random-effects estimates and leave-one-out diagnostics across six datasets

Contrast	OR (95% CI)	Q	I^2 (%)	LOO OR range
TT vs CT+CC	1.71 (1.25–2.34)	17.05	70.7	1.51–1.91
CT+TT vs CC	1.42 (1.18–1.71)	15.01	66.7	1.28–1.52
T vs C	1.38 (1.17–1.63)	21.68	76.9	1.29–1.46

LOO, leave-one-out; CI, confidence interval. All leave-one-out estimates remained above one.

5. Discussion

Across the recessive, dominant, and allelic contrasts, the reconstructed estimates pointed in the same direction. The largest pooled magnitude was for TT versus CT+CC, which also showed substantial heterogeneity. These models are different summaries of the same genotype-count corpus, not causal models. The direction did not change when studies were removed one at a time or when the two control-HWE-deviating

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studies were excluded. Folate exposure, homocysteine, diabetes, vascular risk, and ancestry-related structure were not available for adjustment.

Several features plausibly contribute to the observed dispersion. The primary pool combines five Chinese datasets with one Hungarian dataset, includes different geographic settings, and contains one diabetes-restricted sample. Clinical case definitions and covariate adjustment also differed across source reports. The direct extraction strategy has a compensating strength and weakness: table counts can be audited and recomputed, whereas adjusted effects cannot be pooled without harmonising the original covariates. The present analysis deliberately retains that weakness in view rather than presenting the unadjusted ORs as a clinical risk model.

The restricted analysis should be read against broader database-wide syntheses. Zhao et al. pooled 96 studies found through searches of multiple databases, whereas this paper reconstructs a smaller set of publicly accessible, directly checkable tables [12]. The dominant and allelic estimates here (OR 1.42 and 1.38) were close to Zhao et al.'s corresponding values (OR 1.47 and 1.37); the recessive estimate was higher (1.71 versus 1.52). The agreement in direction supports interpretation of the restricted reconstruction, but does not make it comprehensive. We did not add the four contextual records simply to increase the study count. Broader searches, duplicate screening, ancestry- and subtype-aware definitions, and harmonised adjusted estimates remain future requirements. Publication-bias testing also needs more than the six independent datasets available here.

The control-HWE findings sharpen, rather than eliminate, this caution. The persistence of all three pooled directions after excluding Jin and Szolnoki indicates that the primary direction is not driven solely by those two control distributions. It does not show that the remaining studies are free of bias, nor does it establish a biological mechanism. The more conservative interpretation is that the observed association survives a basic genotype-distribution sensitivity check while still requiring confirmation in broader, better harmonised datasets.

The public-data approach remains useful because it leaves a verifiable trail from manuscript statement to source table and deterministic calculation. It does not replace individual-participant-data meta-analysis, formal risk-of-bias assessment, or functional work on MTHFR. A future synthesis could distinguish lacunar, large-artery, and cardioembolic phenotypes before pooling. Until then, association wording remains the defensible interpretation.

6. Conclusion

This meta-analysis reconstructed three unadjusted genetic contrasts from six independently reported, publicly accessible MTHFR C677T case-control datasets. Each pooled estimate was above one, and the direction persisted in leave-one-out and control-HWE sensitivity analyses. The available data therefore support an association between MTHFR C677T and ischemic stroke susceptibility in the analysed datasets. Heterogeneity, predominantly Chinese sampling, a diabetes-restricted dataset, and non-harmonised covariate adjustment preclude causal or clinical-prediction interpretation. The value of this short synthesis lies in traceable genotype counts and explicit limits.

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Conflicts of Interest

The authors declare no conflict of interest.

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