

# Does CYP2C19 polymorphisms affect neurological deterioration in stroke/TIA patients?

## A systematic review and meta-analysis of prospective cohort studies

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### Abstract

**Background:** The association between cytochrome P450 2C19 (CYP2C19) polymorphisms and neurological deterioration in stroke or transient ischemic attack (TIA) patients is not completely understood. Hence, we performed a systematic review and meta-analysis of prospective cohort studies to quantify this association.

**Methods:** PubMed, Cochrane Library, Excerpta Medica Database, China National Knowledge Infrastructure and WanFang databases were searched for studies published up to April 2019. Prospective cohort studies that reported an association between CYP2C19 polymorphisms and neurological deterioration in stroke/TIA patients were included. Data on risk ratio (RR) and 95% confidence intervals (CI) were extracted and pooled by the authors. Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines were followed.

**Results:** Twelve eligible studies were included. Twelve studies reported CYP2C19\*2, \*3 loss-of-function alleles and 5 studies reported CYP2C19\*17 gain-of-function allele. Compared to non-carriers, carriers of CYP2C19\*2, \*3 loss-of-function alleles had a significantly higher risk of neurological deterioration (RR, 1.63; 95%CI, 1.32–2.02). Conversely, carriers of CYP2C19\*17 gain-of-function allele had a significantly lower risk of neurological deterioration (RR, 0.520; 95%CI, 0.393–0.689) compared to non-carriers.

**Conclusions:** This meta-analysis demonstrated that the carriers of CYP2C19\*2, \*3 loss-of-function alleles have an increased risk of neurological deterioration compared to non-carriers in stroke or TIA patients. Additionally, CYP2C19\*17 gain-of-function allele can reduce the risk of neurological deterioration.

**Abbreviations:** CI = confidence interval, CYP2C19 = cytochrome P450 2C19, mRS = modified Rankin Scale, NIHSS = National Institute of Health Stroke Scale, RR = risk ratio, TIA = transient ischemic attack.

**Keywords:** cytochrome P-450 2C19, ischemic attack transient, meta-analysis, neurological deterioration, stroke

### 1. Introduction

Globally, stroke is the second most common cause of death and the leading cause of major, long-term disability.<sup>[1]</sup> The CHANCE study revealed that the combination of clopidogrel and aspirin, compared to aspirin alone, reduced the risk of stroke recurrence

among stroke or transient ischemic attack (TIA) patients.<sup>[2]</sup> The combination of clopidogrel and aspirin has become a recommended treatment option for patients with symptomatic intracranial atherosclerosis stenosis, the incidence of intracranial atherosclerosis stenosis in patients with ischemic stroke or TIA in

Editor: Qinhong Zhang.

This work was supported by the National Key R&D Program of China (grant numbers 2018YFC1312902) and Science and Technology Innovation Platform of Jiangxi Department of Science and Technology (grant numbers 20171BCD40024).

Funding Source: National Natural Science Foundation of China; Award ID: 81960609). This funding is responsible for the publishing costs of the manuscript.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Wang J, Kuang J, Yi Y, Peng C, Ge Y, Yin S, Zhang X, Chen J. Does CYP2C19 polymorphisms affect neurological deterioration in stroke/TIA patients? A systematic review and meta-analysis of prospective cohort studies. *Medicine* 2021;100:11(e25150).

Received: 17 November 2019 / Received in final form: 13 March 2020 / Accepted: 24 February 2021

<http://dx.doi.org/10.1097/MD.00000000000025150>

China is 46.6%.<sup>[3]</sup> However, Wang Y et al found that, compared to aspirin-only treatment, the use of clopidogrel plus aspirin reduced the risk of a new stroke only in the subgroup of patients who were not carriers of the cytochrome P450 2C19 (CYP2C19) loss-of-function alleles.<sup>[3,4]</sup> The effect of CYP2C19 polymorphisms on clopidogrel pharmacodynamics and clinical outcomes (subsequent stroke, composite vascular events, bleeding) in stroke or TIA patients has been well researched, however its effect on neurological deterioration is less well understood.

Stroke patients are at a high risk of developing neurological deterioration. About 30% of stroke patients develop neurological deterioration, a situation related to increased mortality and long-term functional disability.<sup>[5]</sup> Once deterioration has occurred, spontaneous reversal with conservative management occurs only in one-third of these patients, most patients with deterioration do not recover full function.<sup>[6]</sup> The underlying mechanisms and prevention strategies for neurological deterioration have no consensus. Previous studies have reported several factors associated with neurological deterioration, such as diabetes,<sup>[7]</sup> aspirin use,<sup>[8]</sup> thrombus extension,<sup>[9]</sup> clopidogrel resistance,<sup>[10]</sup> and homocysteine.<sup>[5]</sup> CYP2C19 polymorphisms have been linked to clopidogrel resistance, thus, they may influence neurological deterioration as well. CYP2C19\*2, \*3 are common loss-function variants that result in a decrease in enzyme activity and clopidogrel resistance.<sup>[11]</sup> It has been estimated that the CYP2C19\*2, \*3 alleles occurs in 18% of Hispanics, 33% of African Americans and 58.8% of East Asian populations.<sup>[11–15]</sup> Meanwhile, the CYP2C19 gain-of-function allele (\*17) is associated with increased catalytic activity, and occurs in approximately 0.5% to 4% of the total population.<sup>[16]</sup> Patients were categorized by CYP2C19 metabolizer status based on \*2, \*3, \*17 genotypes: patients with at least two \*2 or \*3 alleles (\*2/\*2, \*2/\*3, \*3/\*3) were defined as poor metabolizers (PM); those with 1 \*2 or \*3 allele (\*1/\*2, \*1/\*3) were defined as intermediate metabolizers (IM); and those without a \*2, \*3, or \*17 allele (\*1/\*1) were defined as extensive metabolizers (EM). Individuals carrying at least 1 \*17 allele (\*1/\*17, \*17/\*17) were defined as ultra-metabolizers (UM).<sup>[4]</sup>

The association between CYP2C19 polymorphisms and neurological deterioration is not well understood. Thus, a systematic review and meta-analysis was performed to explore the association between CYP2C19 polymorphisms and neurological deterioration in stroke and/or TIA patients.

## 2. Methods

### 2.1. Search strategy

A comprehensive search of PubMed, Excerpta Medica Database, Cochrane library, China National Knowledge Infrastructure, and WanFang database from their inceptions to May 24, 2019 was conducted to identify studies describing the association between CYP2C19 polymorphisms and neurological deterioration in stroke/TIA patients. The search terms included the following 3 items and were combined using the Boolean operator AND: neurological deterioration (including “National Institute of Health Stroke Scale (NIHSS),” “national institute of health stroke scale,” “modified Rankin Scale (mRS),” “modified rankin scale” or “neurologic deterioration”); CYP2C19 polymorphisms (including “Cytochrome P-450CYP2C19,” “CYP11C19,” “cytochrome P4502C19,” “CYP2C19,” “ABCB1,” “PON-1,” “paraoxonase-1,” “cytochrome P450 2C9,” “CYP2C8,” “cytochrome

P4502C8,” “CYP3A4,” “cytochrome P4503A4,” “CYP3A5,” “cytochrome P4503A5,” “CYP2B6,” “cytochrome P4502B6,” “ITGB3,” “P2RY12,” “P2Y12” or “COX-1”); and patients (including “stroke,” “transient ischemic attack,” “transient ischemic attack” or “TIA”). Appropriate modifications were used for searches in China National Knowledge Infrastructure and WanFang databases. No restrictions were used in the search strategy. The detailed search strategy is available upon request.

### 2.2. Selection criteria

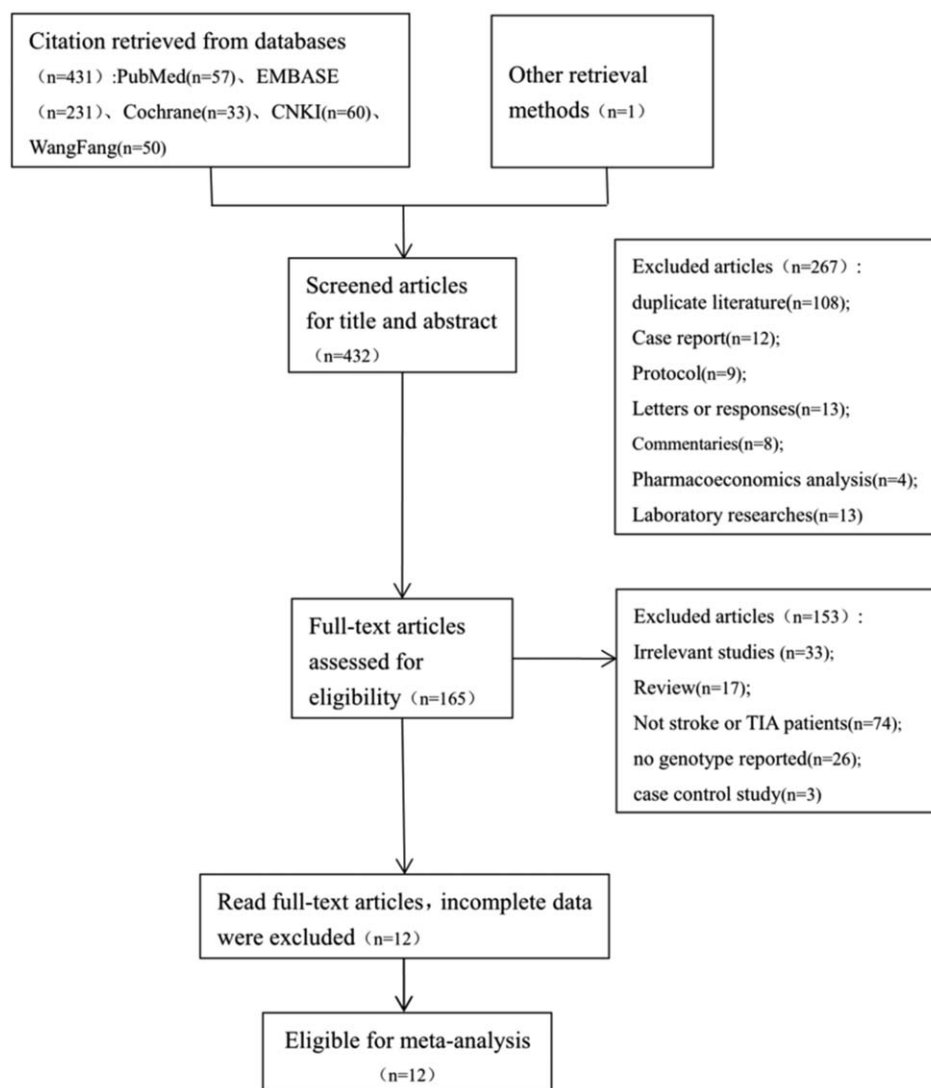
Two researchers (J.K. and Y.P.Y.) identified studies eligible for further review by performing an initial screen of identified titles or abstracts. Discrepancies were resolved by consensus or determined by a third researcher (J.J.W.). Articles were considered for inclusion in the meta-analysis if they reported original data on neurological deterioration and CYP2C19 polymorphisms in stroke/TIA patients. Reviews, editorials and letters were excluded. Both reviewers fully agreed on the eligibility of the included articles in the first screening. A second screening based on a detailed full text review was then performed. Cohort studies were included in the criteria. Given the research objectives, studies were restricted to those concerning stroke/TIA patients. Additionally, studies were excluded if neurological deterioration and CYP2C19 polymorphisms had not been reported.

### 2.3. Data extraction and quality assessment

The primary data were risk ratio (RR) for neurological deterioration with 95% confidence intervals (CI), or any data that could be used to calculate RRs and 95% CIs. RRs calculated from multivariate analysis were extracted if both univariate and multivariate analyses were provided. The study and patients' characteristics included first author, publication year, patient race, number of patients, median or mean age of patients, study type, gender, Stroke type, CYP2C19 genotype, follow up period, indicators of neurological deterioration (mRS/NIHSS score). Data were extracted independently by 2 researchers (J.K. and Y. P.Y.) using a standardized form. Any discrepancies were reviewed by a third reviewer (J.J.W.) and resolved by consensus. The quality of the observational studies were assessed using the Newcastle-Ottawa scale.<sup>[16]</sup>

### 2.4. Statistical analysis

The outcome event was neurological deterioration, which was defined as: ①mRS score >2 point;<sup>[17]</sup> ②NIHSS score ≥4;<sup>[18,19]</sup> ③an increase in NIHSS score by ≥2 points.<sup>[17]</sup> Random-effects meta-analyses were performed to calculate overall pooled estimates of the association between CYP2C19\*2, \*3 loss-of-function alleles and neurological deterioration using the generic inverse variance method, and fixed-effects meta-analysis was used to calculate overall pooled estimates of the association between CYP2C19\*17 gain-of-function allele and neurological deterioration with the Mental-Haenszel method. Heterogeneity was evaluated by calculating the  $I^2$  statistic, with a  $P$  value of .10 set for significance. Potential publication bias of studies with different sample sizes was examined by visual inspection of funnel plots and trim-and-fill analysis. All statistical analyses were performed with Stata 14.0 (Stata Corp, College Station, TX).  $P$  values were 2-sided with a significance level of .05. As our research is a review without intervention, ethical



**Figure 1.** Flow diagram of the systematic review process. CNKI = China National Knowledge Infrastructure, EMBASE = Excerpta Medica Database, TIA = transient ischemic attack.

approval is not applicable. Supplemental Content, <http://links.lww.com/MD/F923>

### 3. Results

#### 3.1. Study selection and characteristics

A total of 432 potentially relevant studies were identified in the initial search (Fig. 1). After reviewing titles and abstracts, 267 articles were excluded. Full texts for the remaining 165 articles were reviewed in detail, and subsequently 153 of these articles were excluded: review or meta-analysis ( $n=17$ ), not stroke or TIA patients ( $n=74$ ), no gene or neurological outcome reported ( $n=26$ ), case control study ( $n=3$ ).

Therefore, twelve studies from 3805 citations were considered based on inclusion criteria, and included in the meta-analysis. The literature screening process and results are shown in Figure 1. In the twelve included studies, eleven were from China,<sup>[20–30]</sup> and 1 was from Japan.<sup>[30]</sup> All were prospective cohort studies. The main outcome of the 12 studies was neurological deterioration (defined as NIHSS/mRS score or poor prognosis in included

researches). CYP2C19\*2, \*3, \*17 alleles were reported in included studies.<sup>[20–31]</sup> Other alleles like \*4, \*5, \*6, \*7 were not detected and reported in the study population. Four studies reported \*1 and \*17 alleles<sup>[20,22,26,31]</sup> (2 of them described \*1, \*17 as extensive metabolizers, EM<sup>[20,31]</sup>). The Newcastle Ottawa Scale score of the 12 studies ranged from 6 to 9. Four of them reached nine points,<sup>[22,28–30]</sup> and all others were between 7 to 8 points.<sup>[20,21,23–27]</sup> One study, which lacked research details, only scored 6 points.<sup>[30]</sup> There were deficiencies in the quality of evaluation for gene detection: 2 studies did not carry out Hardy-Weinberg balance on the distribution of the CYP2C19 gene.<sup>[22,31]</sup> Most genotype information from included studies was available with the Hardy-Weinberg balance. The detailed characteristics of included studies are shown in Table 1.

#### 3.2. Effects of CYP2C19\*2, \*3 loss-of-function alleles

All 12 studies included data regarding the association between CYP2C19\*2,\*3 loss-of-function alleles and neurological deterioration in stroke/TIA patients.<sup>[20–31]</sup>  $I^2$  test showed that there

**Table 1**  
**Characteristics of the studies included in the systematic review and meta-analysis.**

Source	Sample size	Study Type	Country	Age, mean	Men(n,%)	Smoker (n,%)	Stroke type	CYP2C19* Alleles Reported	Follow-up	Quality Score
Dongmei Jia 2013	206	Cohort	China	66.5 ± 11.8	NR	NR	Cerebral embolism and small vessel disease	CYP2C19*1,*2,*3,*17	6 mo	8
LiNa Qiu 2014	198	Cohort	China	67.47 ± 13.6	95, 45%	74, 35%	Acute ischemic stroke	CYP2C19*2,*3	6 mo	7
Yuting Zhao 2014	114	Cohort	China	65.97 ± 10.38	86, 75.44%	43, 37.7%	Ischemic stroke	CYP2C19*1,*2,*3,*17	12 mo	9
LiNa Qiu 2015	410	Cohort	China	64.8 ± 12.1	228, 55.6%	162, 39.5%	Acute ischemic stroke	CYP2C19*1,*2,*3	31 mo	8
Chun Wang 2016	363	Cohort	China	69.96 ± 10.98	234, 62%	158, 42%	Atherothrombotic, Small artery disease	CYP2C19*2,*3	6 mo	9
Xingyang Yi 2016	550	Cohort	China	68.78 ± 12.26	112, 67.5%	212, 38.5%	Ischemic stroke	CYP2C19*2	6 mo	8
Yingting Wang 2016	321	Cohort	China	62.0 ± 3.5	82, 25.5%	169, 52.6%	Ischemic stroke	CYP2C19*2,*3	12 mo	9
Hanqin Gao 2017	232	Cohort	China	60.09 ± 4.99	82, 71%	57, 49%	Symptomatic intracranial atherosclerotic stenosis	CYP2C19*2,*3	7 d	7
K. Fukuma 2017	195	Cohort	Japan	72.1	140, 58.6%	NR	Acute atherothrombotic stroke, TIA	CYP2C19*1,*2,*3	3 mo	6
Chen 2018	189	Cohort	China	66.0 ± 10.9	117, 60.9%	53, 27.6%	Ischemic stroke	CYP2C19*2,*3	12 mo	9
Jing Lin 2018	375	Cohort	China	70.2 ± 11.4	242, 64.5%	158, 42.1%	Ischemic stroke	CYP2C19*2,*3	7 mo	8
Xingyang Yi 2018	570	Cohort	China	70.9 ± 11.6	313, 55%	228, 40%	Ischemic stroke	CYP2C19*2	10 d	7

CYP2C19=cytochrome P450 2C19, TIA=transient ischemic attack.

was significant heterogeneity in the included articles ( $I^2=64.7\%$ ,  $P=.001$ ), so the random-effect model was used for combining the results. The results showed that carriers of CYP2C19\*2, \*3 loss-of-function alleles were at increased risk of neurological deterioration (RR, 1.63; 95%CI, 1.32–2.02) (Fig. 2). Additionally, carriers of 2 CYP2C19 loss-of-function alleles presented a higher risk of neurological deterioration than carriers with only 1 loss-of-function allele (RR, 1.63; 95%CI, 1.26–2.12) (Fig. 3).

**3.3. Effects of CYP2C19\*17 gain-of-function allele**

There were 4 studies that reported CYP2C19\*17 gain-of-function allele and neurological deterioration of stroke/TIA patients.<sup>[21,23,27,32]</sup> The  $I^2$  test showed low heterogeneity ( $I^2=0.01\%$ ,  $P>.05$ ), thus the fixed effect and Mental-Haenszel methods were used to combine effect size. The results showed that the CYP2C19\*17 gain-of-function allele was associated with reducing in the risk of neurological deterioration (RR, 0.52; 95% CI, 0.39–0.69) (Fig. 4).

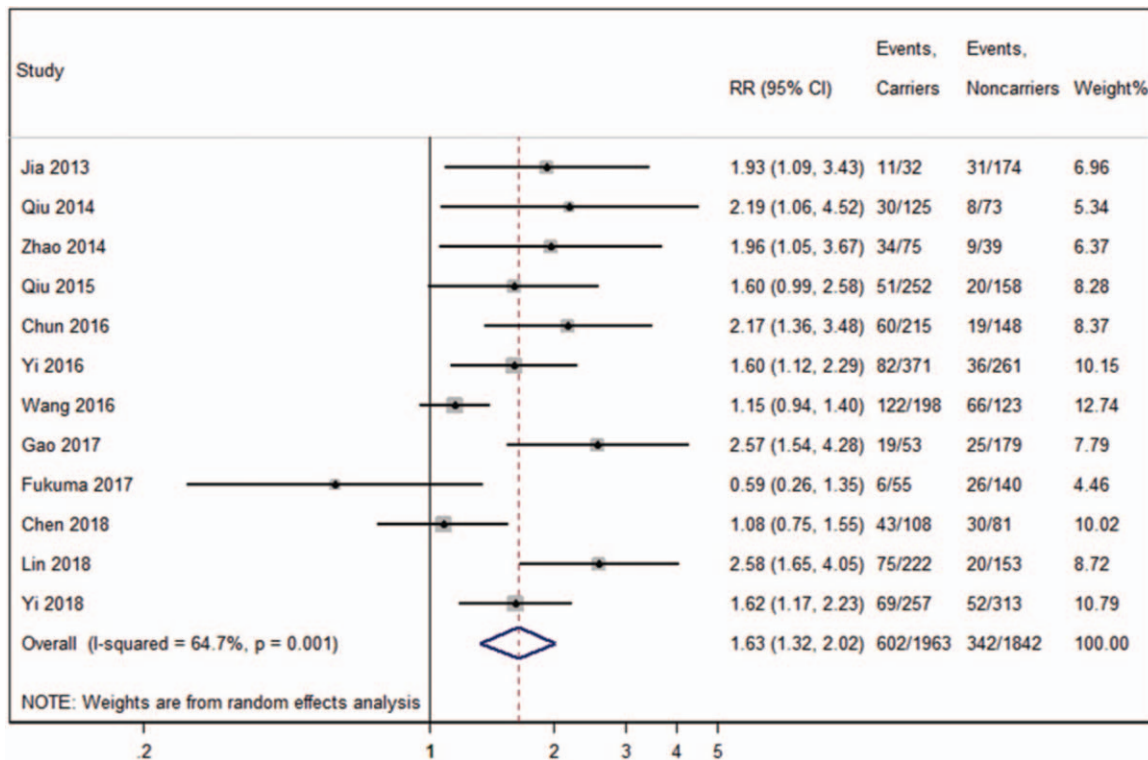


Figure 2. Risk of neurological degeneration for stroke patients with CYP2C19\*2, \*3 loss-of-function alleles. CI=confidence interval.

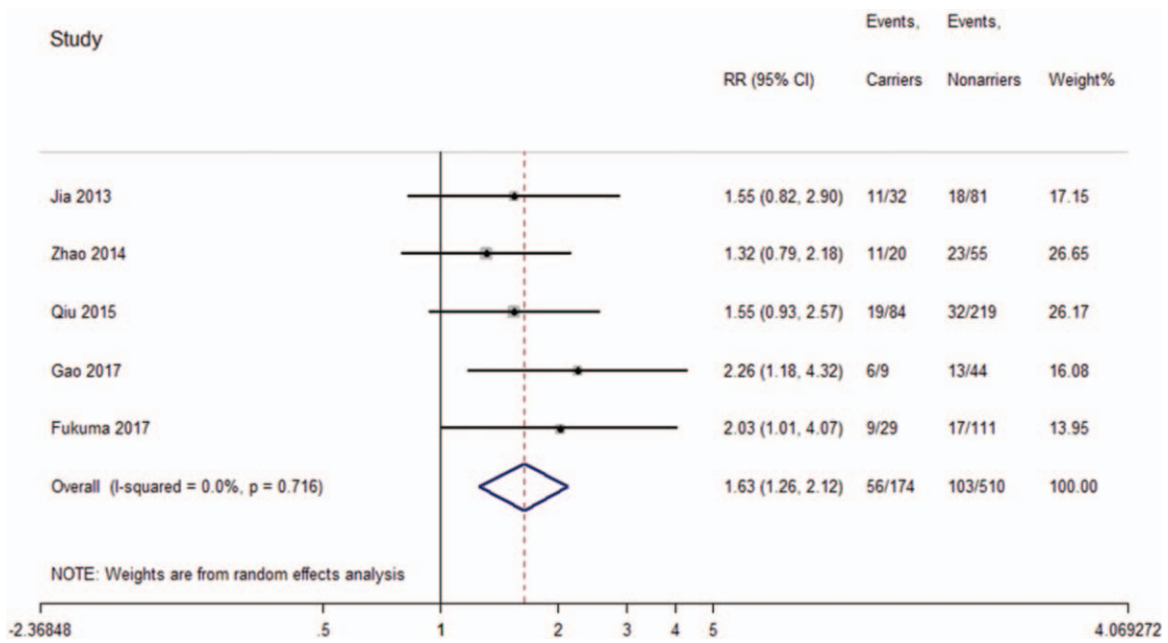


Figure 3. Risk of neurological degeneration for carriers of 2 loss-of-function alleles in comparison with carriers of 1 loss-of-function allele. CI=confidence interval.

### 3.4. Publication bias

Publication bias was assessed with the Egger test, with  $P > .05$ , indicating no significant publication bias. We quantified the potential effect of small study bias using trim-and-fill analysis (Fig. 5). Only 1 hypothetical missing study reduced the original RR from 1.753 to 1.674 for the random-effect model.

### 4. Discussion and conclusions

In this meta-analysis, data from published studies was combined to evaluate the association between CYP2C19 polymorphisms and neurological deterioration. The results revealed that CYP2C19 loss-of-function alleles (\*2, \*3) carriers were at an increased risk of neurological deterioration in comparison to noncarriers among stroke or TIA patients. Furthermore, carriers

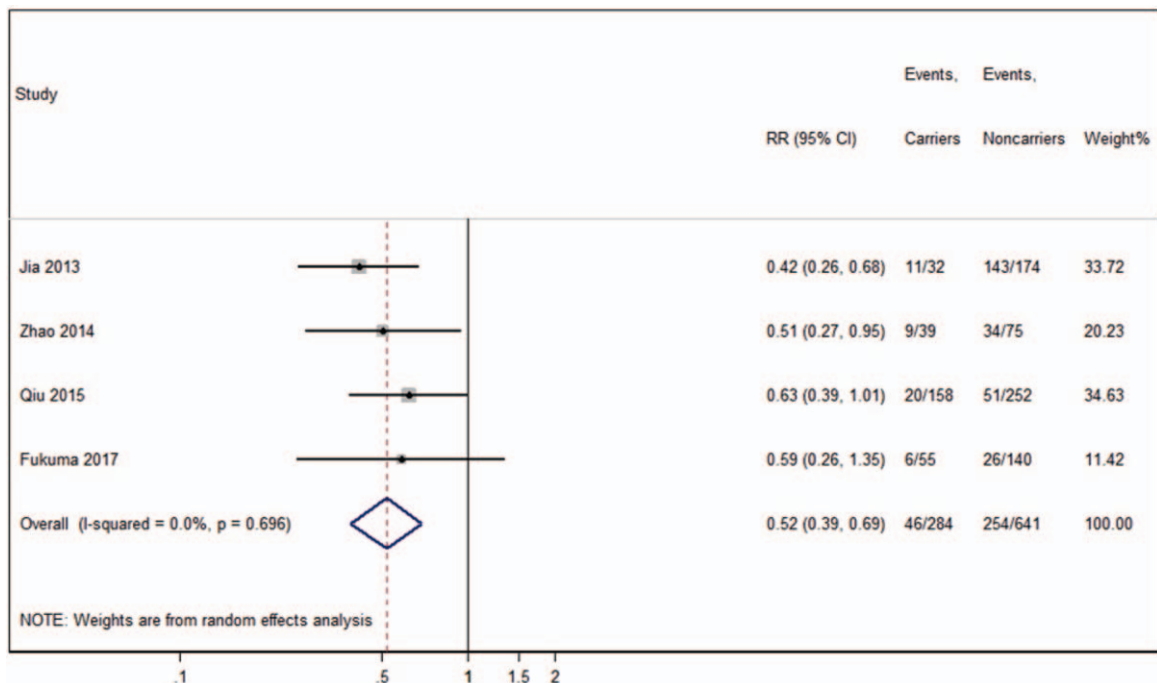
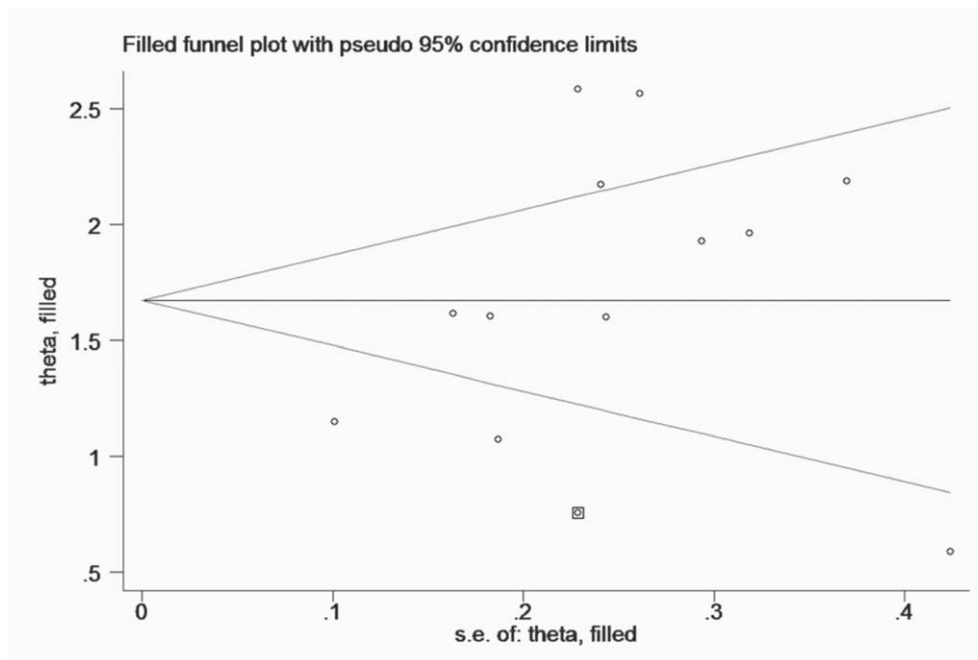


Figure 4. Risk of neurological degeneration for stroke patients with CYP2C19\*17. CI=confidence interval.



**Figure 5.** Filled funnel plot with pseudo 95% confidence limits of CYP2C19\*2, \*3 loss-of-function alleles. Circles are original data, whereas squares are imputed filled values. s.e.=indicates standard error.

of 2 CYP2C19 loss-of-function alleles presented a higher risk of neurological deterioration than carriers with 1 loss-of-function allele. Conversely, the CYP2C19\*17 gain-of-function allele was a protective factor against neurological deterioration.

Recognizing the relationship between CYP2C19 polymorphisms and neurological deterioration based on a systematic review and meta-analysis is critically important to optimize precise treatment and prognosis for stroke or TIA patients. For CYP2C19\*2, \*3 loss-of-function alleles carriers, clinicians may pay more attention to the deterioration of neurological function. Stroke or TIA prognosis can be optimized with CYP2C19 gene-oriented individualized antiplatelet therapy. More assessments of neurological function and health care are essential as well. In clinical settings, varying the dose of clopidogrel or shifting to new antiplatelet agents (eg, prasugrel, ticagrelor) based on genetic results may be alternatives for CYP2C19\*2, \*3 loss-of-function alleles carriers, who have a weakened response to clopidogrel.<sup>[32–34]</sup> Additionally, the use of neurologic agents (eg, levodopa, amantadine) can be adjusted based on genotypes as well. The CYP2C19\*17 allele exhibited a protective function against neurological deterioration among stroke/TIA patients. This effect should be taken into consideration for precise treatment.

Carriers of CYP2C19 loss-of-function alleles account for 30% of white people, and 50% to 60% of East Asian people.<sup>[35–37]</sup> CYP2C19 polymorphisms are a significant factor of neurological deterioration in stroke and TIA patients. Therefore, genetic testing should be popularized, and clinicians should be prompted to personalize antiplatelet therapy. This is especially in East Asian populations with a high prevalence of the CYP2C19 loss-of-function allele.<sup>[4,38]</sup> Furthermore, the CYP2C19\*17 gain-of-function allele can reduce the risk of neurological deterioration, which factors into individualized treatment programs as well. Apart from CYP2C19 polymorphisms, other influencing factors

such as dietary habit, smoking, thrombolytic therapy, and anticoagulant drug use may also contribute to neurological deterioration. Further investigation through randomized controlled trials are needed.

Our study is the first systematic review and meta-analysis that focus on the CYP2C19 polymorphisms and neurological deterioration due to stroke or TIA. All included references are studies with robust power and precision. However, there are some limitations to this study:

- (1) Due to the low prevalence of \*17 carriers, there is limited research on the association between CYP2C19\*17 gain-of-function allele and neurological deterioration;
- (2) most of the included studies were from China, there presented racial restrictions.

In conclusion, CYP2C19\*2, \*3 carriers are at increased risk of neurological deterioration compared to noncarriers among stroke or/and TIA patients. Furthermore, carriers with 2 loss-of-function alleles presented a higher risk of neurological deterioration than carriers with only 1 loss-of-function allele. Conversely, the CYP2C19\*17 gain-of-function allele is a protective factor against neurological deterioration. These findings support the idea that CYP2C19 polymorphisms affect neurological deterioration, and genetic testing for these alleles should be facilitated.

### Author contributions

**Data acquisition and analysis:** Jiajing Wang, Yanqiu Ge, Chen Peng.

**Formal analysis:** Shujuan Yin.

**Methodology and Software:** Xiaolin Zhang, Jibiao Chen.

**Study concept and design:** Yingping Yi, Jie Kuang, Jiajing Wang.

**Writing & revision:** Jie Kuang, Jiajing Wang.

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