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Association between interleukin-10-819T/C polymorphism and risk of ischemic stroke

A meta-analysis

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Abstract

Background: The interleukin-10 (IL-10)-819T/C polymorphism has been indicated to be correlated with ischemic stroke susceptibility, but this relationship remains controversial. A meta-analysis was conducted to investigate the potential association between IL-10-819T/C polymorphism and ischemic stroke risk.

Methods: Databases including Pubmed, Embase, and CNKI were searched. Data were extracted and odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Results: Eight case-control studies with 1832 cases and 1520 controls were included in this meta-analysis. IL-10-819T/C polymorphism may decrease the risk of ischemic stroke (C vs T: OR = 1.01, 95% CI: 0.91–1.12; CC vs TT: OR = 0.91, 95% CI: 0.73–1.14; CT vs TT: OR = 1.10, 95% CI: 0.95–1.28; CC + CT vs TT: OR = 1.06, 95% CI: 0.92–1.22; CC vs CT + TT: OR = 0.91, 95% CI: 0.75–1.11). In the stratified analysis by sample size, and case-control matched status, significant associations were still not observed in all genetic models. In the subgroup meta-analysis based on source of controls, IL-10-819T/C polymorphism had decreased ischemic stroke risk for recessive model in population-based controls' subgroup (CC vs CT + TT: OR = 0.69, 95% CI: 0.50–0.95), but not in the hospital-based controls' subgroup. In the stratified analysis based on ethnicity, IL-10-819T/C polymorphism had decreased ischemic stroke risk for recessive model in Asian populations (CC vs CT + TT: OR = 0.78, 95% CI: 0.62–0.99), but not in Caucasian populations.

Conclusions: In conclusion, the results suggest that the IL-10-819T/C polymorphism is not associated with ischemic stroke risk. Larger scale studies are needed for confirmation.

Abbreviations: 95% CI = 95% confidence interval, CNKI = China National Knowledge Infrastructure, HWE = Hardy–Weinberg equilibrium, IL-10 = interleukin-10, NOS = Newcastle–Ottawa scale, OR = odds ratios.

Keywords: interleukin-10-819T/C, ischemic stroke, meta-analysis, polymorphism

1. Introduction

Ischemic stroke is the leading cause of death and disability worldwide.[1] A complex interaction between modifiable and non-modifiable conventional risk factors and genetic factors could be behind the pathogenesis of ischemic stroke.[2] Weyrich et al reported that chronic low-grade inflammation and activation of the innate immune system are closely involved in the pathogenesis of ischemic stroke.[3] Inflammatory reactions have been identified in the pathogenesis of cerebral ischemia.[4] So, ischemic stroke has been recognized as an inflammation-related disease. Several candidate genes of inflammatory cytokines are implicated in the pathogenesis of ischemic stroke, one of which is interleukin-10 (IL-10).

IL-10 is a multifunctional cytokine with anti-inflammatory properties, which has been shown involving in the inflammatory process of ischemic stroke.[5–8] IL-10 is a pleiotropic cytokine that modulates the function of several adaptive immunity-related cells.[9] IL-10 is known to suppress the functions of both T lymphocytes and macrophages, working as a general dampener of the immune and inflammatory responses.[10]

IL-10 gene is located on chromosome 1, has five exons, and has been mapped to the junction between 1q31 and 1q32.[11] Several polymorphic loci have been identified and characterized in the IL-10 gene, and one of the most widely evaluated is C-819T (rs1800871) in the promoter region. Several studies examined the impact of IL-10-819T/C polymorphism and the risk of ischemic stroke,[12–19] but the findings were inconsistent and controversial. So, we conducted an updated meta-analysis to obtain a more precise approximation of the association between this polymorphism and ischemic stroke susceptibility.

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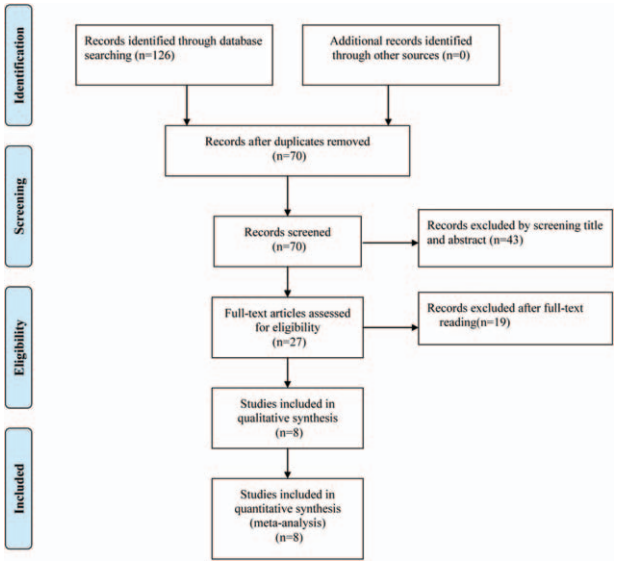

Figure 1. Flowchart of included studies in the current meta-analysis.

2. Methods

2.1. Publication search

We conducted the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[20] The electronic databases Pubmed, Embase, and CNKI were searched using the following terms: (interleukin-10 OR interleukin 10 OR IL-10 OR IL10) AND (cerebral infarction OR ischemic stroke) AND (polymorphism OR mutation OR variant) up to August 2019. The reference lists of retrieved article were hand searched.

2.2. Inclusion and exclusion criteria

All selected studies complied with the following criteria:

(1) case-control study on the IL-10 polymorphism and ischemic stroke risk; and
(2) sufficient published data for estimation of the odds ratio (OR) with a 95% confidence interval (CI).

Studies were excluded, if one of the following existed:

(1) not relevant to ischemic stroke or IL-10,
(2) not a case-control study,
(3) genotype frequencies or number not specified,
(4) animal studies,
(5) editorials, reviews, and abstracts.

If more than one study by the same author using the same case series was published, either the studies with the largest sample size or the most recently published study was included. Ethical approval was not necessary as this study is a meta-analysis.

2.3. Data extraction

Data were extracted independently by two reviewers and entered into separate databases from each qualified study: the first author, year of publication, ethnicity, sample size, genotype distributions in cases and controls, and *P* values for the Hardy–Weinberg equilibrium (HWE) of genotype distribution of controls. We evaluated the quality of all the studies included according to Newcastle–Ottawa scale (NOS).[21] The NOS contains three categories which are selection (0–4 points), comparability (0–2 points), and exposure (0–3 points). The total scores ranged from 0 to 9.

2.4. Statistical analysis

The ORs with 95% CI were calculated under five genetic models: the allele model (C vs T), the homozygote model (CC vs TT), the heterozygote model (CT vs TT), the dominant model (CC + CT vs TT), and the recessive model (CC vs CT + TT). Heterogeneity was calculated by using both χ^2-based *Q*-statistic and I^2-statistic.[22] When *Q* test reported a *P*-value of more than .10 and $I^2 < 50\%$, fixed effects model was used to calculate the pooled ORs,[23] otherwise random effects model was used.[24] Predefined subgroup analyses were conducted by ethnicity, source of controls, sample size, and case-control matched status. Sensitivity analysis was conducted to examine the effect of individual studies on pooled results and the stability of results. Publication bias was assessed with funnel plots and Egger regression test.[25] All statistical tests were carried out using Stata 12.0 software (Stata Corporation, College Station, TX). A *P*-value of $<.05$ was considered significant. All the *P* values were two sided.

Table 1

Main characteristics of eligible studies.

Study	Year	Ethnicity	Source of control	Cases/controls	Sample size	Matched status	Case	Control	HWE	NOS
							CC/CT/TT	CC/CT/TT		
Zhang et al	2007	Asian	HB	204/131	335	No	28/90/86	27/48/56	0.07	8
Jin et al	2011	Asian	HB	189/92	281	No	12/82/95	7/37/48	0.97	8
Tuttolomondo	2012	Caucasian	HB	96/48	144	Yes	63/14/19	26/17/5	0.39	8
He et al	2015	Caucasian	HB	260/260	520	Yes	43/113/104	33/111/116	0.43	8
Jiang et al	2015	Asian	HB	181/115	296	Yes	32/73/76	18/44/53	0.09	7
Tong et al	2016	Asian	PB	100/100	200	Yes	26/56/18	30/48/22	0.74	8
Tong et al	2018	Asian	PB	648/648	1296	Yes	49/281/318	73/259/316	0.08	8
Yuan et al	2018	Asian	HB	154/126	280	No	27/62/65	20/48/58	0.07	8

HB = hospital-based, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa scale, PB = population-based.

3. Results

3.1. Study characteristics

A total of 126 studies were retrieved from Pubmed, Embase, and CNKI. Finally, eight eligible studies were included in this meta-analysis.[12–19] A flowchart of the included and excluded studies was shown in Figure 1. The characteristics of the selected studies are summarized in Table 1. All studies of control were in HWE ($P > .05$).

3.2. Meta-analysis

A summary of the meta-analysis findings on the associations between IL-10-819T/C polymorphism and susceptibility to ischemic stroke was provided in Table 2. The pooled analysis indicated that the significant association between IL-10-819T/C polymorphism and ischemic stroke under five genetic models (C vs T: OR = 1.01, 95% CI: 0.91–1.12, $I^2 = 0.0\%$, $P_H = 0.663$; CC vs TT: OR = 0.91, 95% CI: 0.73–1.14, $I^2 = 15.9\%$, $P_H = 0.305$; CT vs TT: OR = 1.10, 95% CI: 0.95–1.28, $I^2 = 8.9\%$, $P_H = 0.361$; CC + CT vs TT: OR = 1.06, 95% CI: 0.92–1.22, $I^2 = 0.0\%$, $P_H = 0.790$; CC vs CT + TT: OR = 0.91, 95% CI: 0.75–1.11, $I^2 = 37.7\%$, $P_H = 0.129$; Figs. 2–6).

Similarly, in the stratified analysis by sample size, and case-control matched status, no significant results were observed in all the genetic models (Table 2). In the subgroup meta-analysis based on source of controls, IL-10-819T/C polymorphism had decreased ischemic stroke risk in population-based controls' subgroup under this model (CC vs CT + TT: OR = 0.69, 95% CI: 0.50–0.95), but no obvious association existed in the hospital-based controls' subgroup.

In the stratified analysis based on ethnicity, IL-10-819T/C polymorphism had decreased ischemic stroke risk in Asian populations under this model (CC vs CT + TT: OR = 0.78, 95% CI: 0.62–0.99), but not in Caucasian populations.

3.3. Sensitivity analysis

To evaluate the stability of this meta-analysis, we excluded the included studies one by one and compared the differences between the effect values before and after each elimination (Fig. 7). This analysis showed that the results were stable.

3.4. Publication bias

The shape of the funnel plot did not reveal obvious asymmetry (Fig. 8) and the Egger test suggested the absence of publication bias ($P = .318$ for C vs T; $P = .646$ for CC vs TT; $P = .390$ for CT vs TT; $P = .878$ for CC + CT vs TT; $P = .330$ for CC vs CT + TT).

4. Discussion

IL-10 is a potent anti-inflammatory cytokine and a potent upregulator of B cell production and differentiation.[26] Levels of IL-10 production are important in immune regulation, and IL-10 is associated with several autoimmune diseases.[27,28] A large number of studies have shown that IL-10 gene polymorphisms are associated with various diseases and play a central role in the pathophysiology and clinical courses of these diseases. The SNP at position -819 of IL-10 gene promoter have been shown to alter IL-10 mRNA and protein levels.[29] Although previous case-control

Table 2

Main characteristics of relevant studies selected for meta-analysis.

Analysis	OR (95% CI)	P	Heterogeneity I^2	Heterogeneity P
Overall (8)				
C vs T	1.01 (0.91–1.12)	.910	0.0%	.663
CC vs TT	0.91 (0.73–1.14)	.420	15.9%	.305
CT vs TT	1.10 (0.95–1.28)	.221	8.9%	.361
CC + CT vs TT	1.06 (0.92–1.22)	.422	0.0%	.790
CC vs CT + TT	0.91 (0.75–1.11)	.358	37.7%	.129
Source of control				
HB (6)				
C vs T	1.08 (0.94–1.24)	.284	0.0%	.760
CC vs TT	1.06 (0.80–1.40)	.699	0.0%	.451
CT vs TT	1.09 (0.89–1.34)	.404	30.3%	.208
CC + CT vs TT	1.10 (0.91–1.33)	.321	0.0%	.697
CC vs CT + TT	1.09 (0.84–1.41)	.518	18.3%	.294
PB (2)				
C vs T	0.92 (0.79–1.08)	.306	0.0%	.663
CC vs TT	0.73 (0.51–1.04)	.078	0.3%	.317
CT vs TT	1.11 (0.89–1.38)	.369	0.0%	.475
CC + CT vs TT	1.01 (0.82–1.24)	.916	0.0%	.480
CC vs CT + TT	0.69 (0.50–0.95)	.023	0.0%	.515
Ethnicity				
Asian (6)				
C vs T	0.97 (0.86–1.09)	.575	0.0%	.758
CC vs TT	0.84 (0.65–1.08)	.167	0.0%	.486
CT vs TT	1.13 (0.96–1.33)	.149	0.0%	.985
CC + CT vs TT	1.05 (0.90–1.23)	.515	0.0%	.956
CC vs CT + TT	0.78 (0.62–0.99)	.037	0.0%	.484
Caucasian (2)				
C vs T	1.17 (0.93–1.48)	.171	0.0%	.663
CC vs TT	1.23 (0.77–1.96)	.382	44.3%	.180
CT vs TT	0.55 (0.11–2.76)	.468	84.8%	.010
CC + CT vs TT	0.86 (0.36–2.09)	.747	63.9%	.096
CC vs CT + TT	1.44 (0.96–2.15)	.077	0.0%	.699
Matched status				
Yes (5)				
C vs T	1.01 (0.90–1.14)	.856	0.0%	.431
CC vs TT	0.93 (0.72–1.20)	.564	40.9%	.149
CT vs TT	1.07 (0.90–1.28)	.418	46.2%	.115
CC + CT vs TT	1.05 (0.89–1.24)	.564	0.0%	.446
CC vs CT + TT	1.02 (0.71–1.46)	.929	54.9%	.065
No (3)				
C vs T	0.99 (0.81–1.21)	.933	0.0%	.569
CC vs TT	0.88 (0.58–1.33)	.549	0.0%	.470
CT vs TT	1.17 (0.87–1.56)	.303	0.0%	.971
CC + CT vs TT	1.09 (0.83–1.43)	.551	0.0%	.924
CC vs CT + TT	0.81 (0.55–1.20)	.303	0.0%	.381
Sample size				
≥300 (3)				
C vs T	0.97 (0.85–1.10)	.646	46.2%	.156
CC vs TT	0.86 (0.52–1.44)	.759	66.5%	.051
CT vs TT	1.11 (0.93–1.33)	.257	0.0%	.894
CC + CT vs TT	1.04 (0.88–1.24)	.634	0.0%	.628
CC vs CT + TT	0.81 (0.49–1.34	.419	69.7%	.037
<300 (5)				
C vs T	1.07 (0.90–1.28)	.416	0.0%	.983
CC vs TT	1.05 (0.74–1.51)	.771	0.0%	.854
CT vs TT	1.07 (0.82–1.40)	.611	46.3%	.114
CC + CT vs TT	1.10 (0.86–1.41)	.468	0.0%	.586
CC vs CT + TT	1.09 (0.80–1.48)	.591	0.0%	.668

CI = confidence interval, HB = hospital-based, OR = odds ratio, PB = population-based.

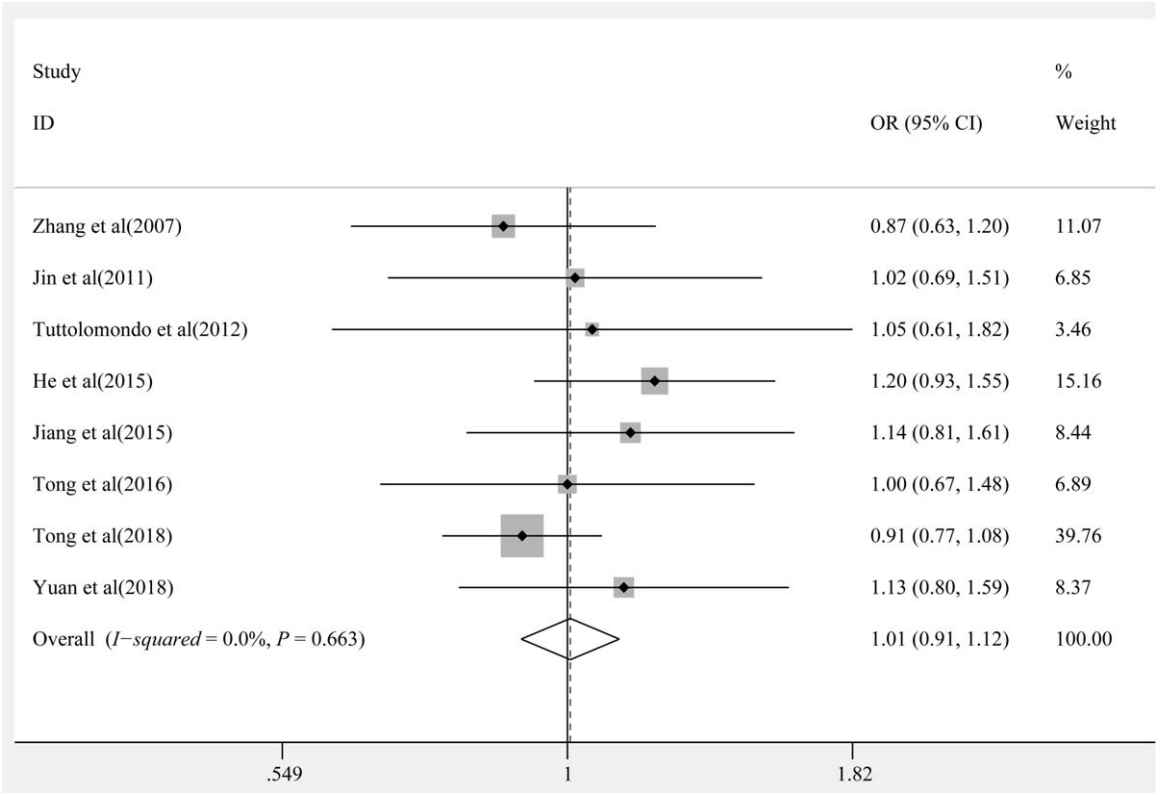

Figure 2. Forest plot of the association between the IL-10-819T/C polymorphism (C vs T) and ischemic stroke risk.

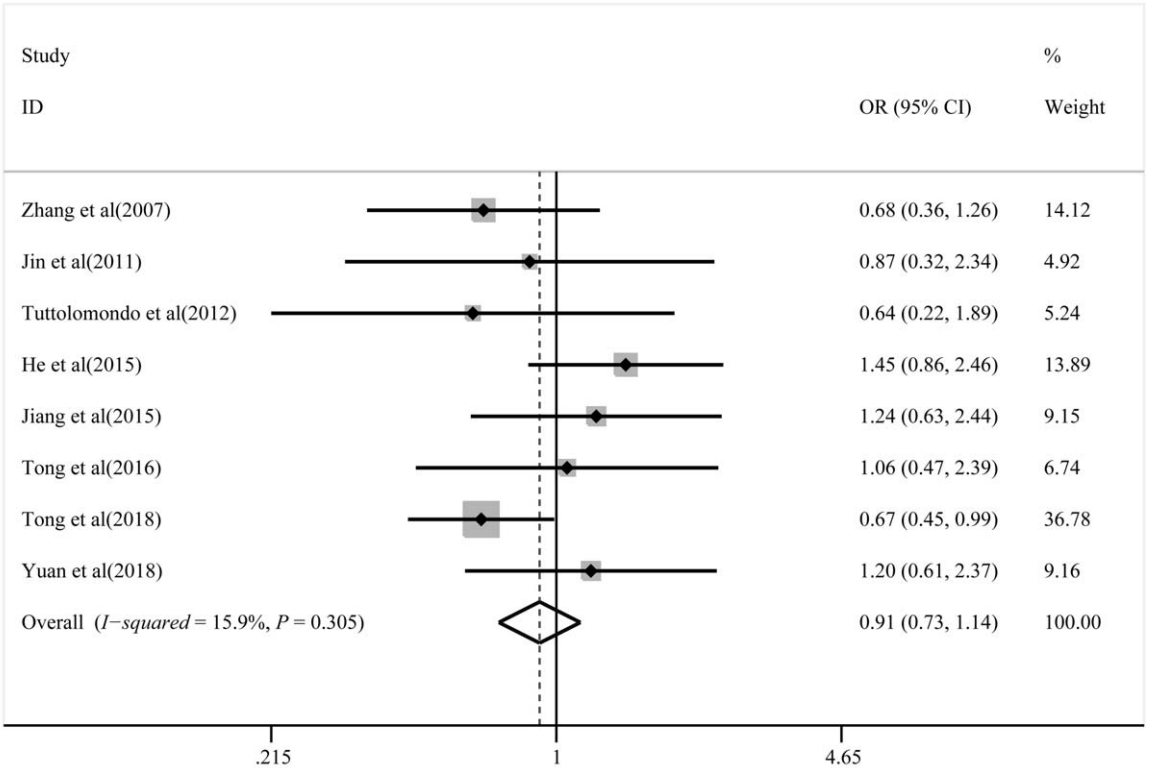

Figure 3. Forest plot of the association between the IL-10-819T/C polymorphism (CC vs TT) and ischemic stroke risk.

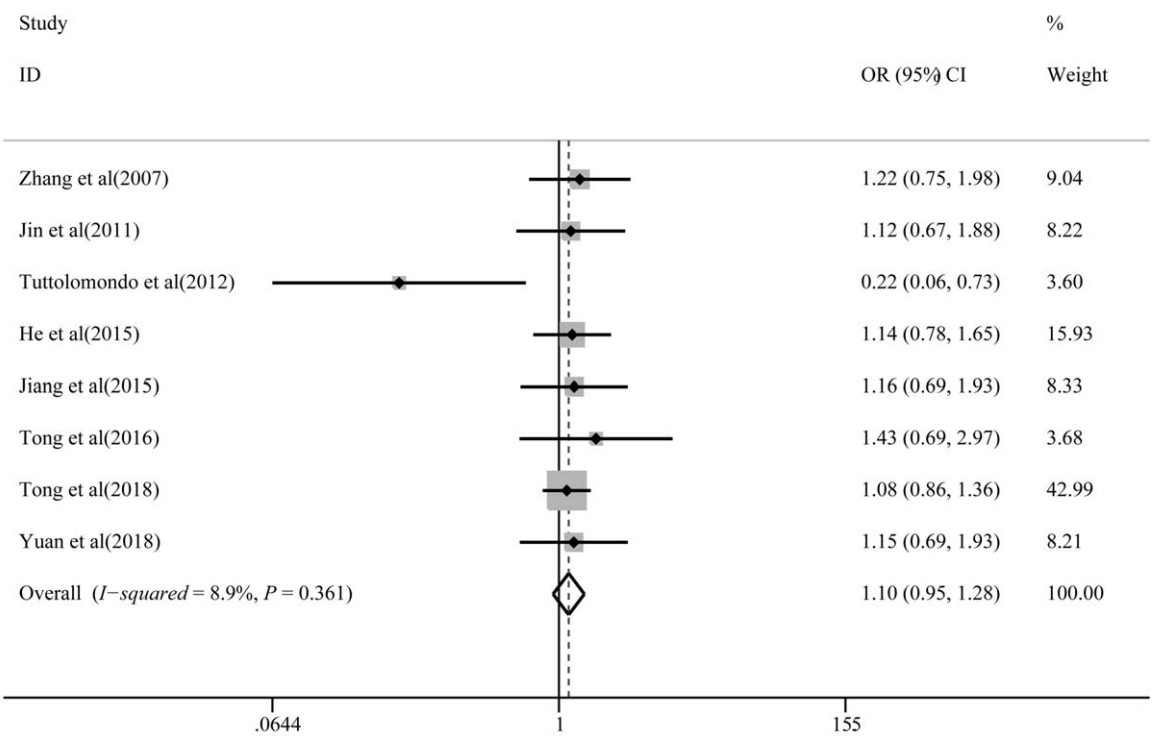

Figure 4. Forest plot of the association between the IL-10-819T/C polymorphism (CT vs TT) and ischemic stroke risk.

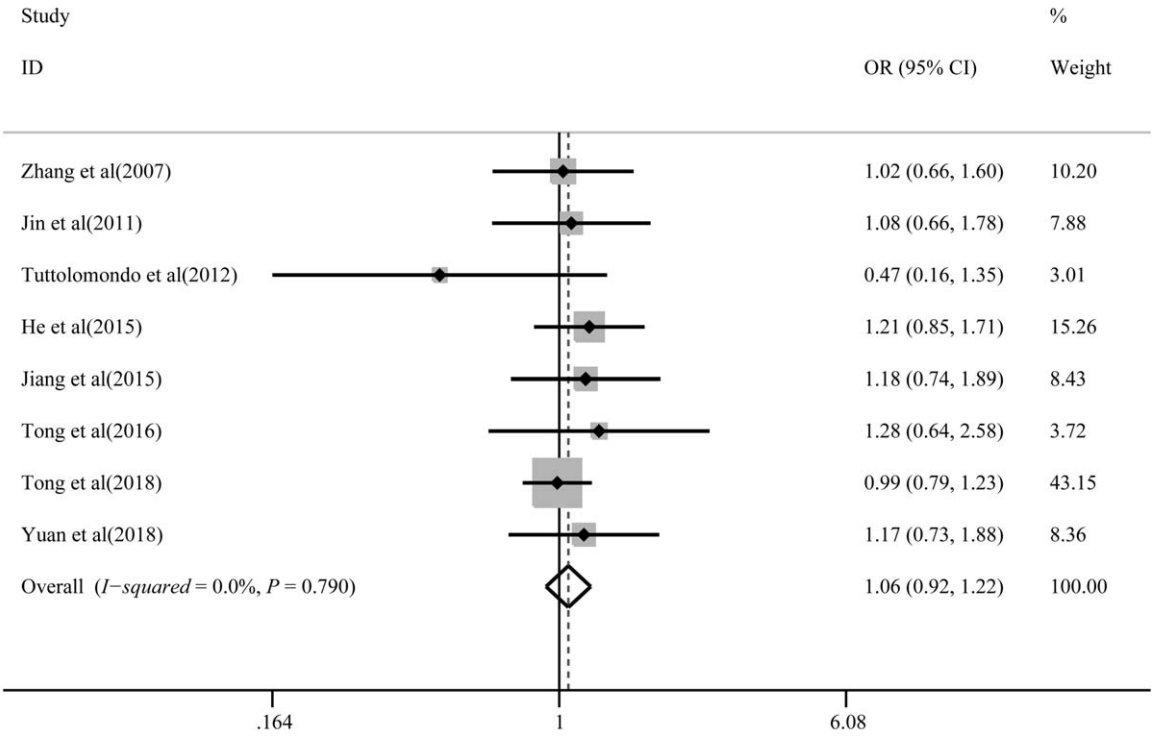

Figure 5. Forest plot of the association between the IL-10-819T/C polymorphism (CC + CT vs TT) and ischemic stroke risk.

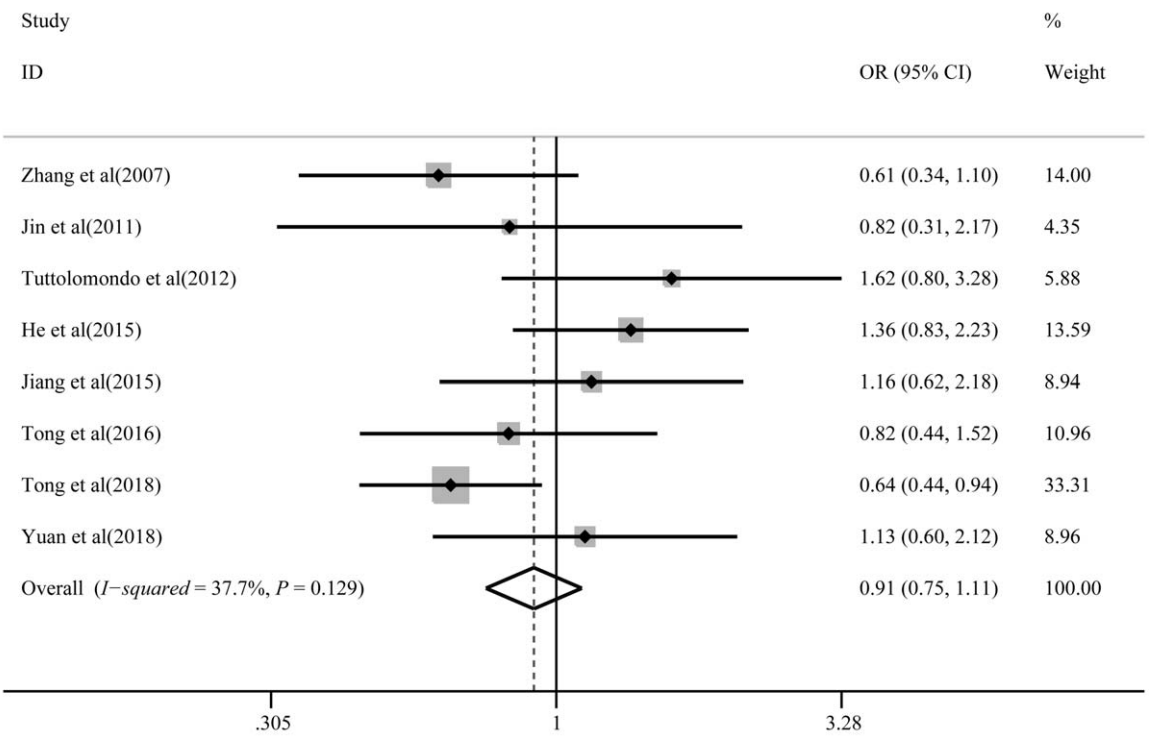

Figure 6. Forest plot of the association between the IL-10-819T/C polymorphism (CC vs CT + TT) and ischemic stroke risk.

studies showed that the IL-10 polymorphism might contribute to the risk of ischemic stroke, and the sample size of the studies was too small. Thus, this meta-analysis was performed.

Our results suggest that the IL-10-819T/C polymorphism is not associated with risk of ischemic stroke in the overall studied populations. Similarly, in the stratified analysis by sample size, and case-control matched status, no significant results were observed in all the genetic models. However, our subgroup meta-analysis based on source of controls suggests the IL-10-819T/C polymorphism is significantly associated with ischemic stroke risk for the recessive model (CC vs CT + TT) in the population-based controls' subgroup. This result needs further investigation because only two of the total eight eligible studies belong to the hospital-based controls' subgroup, so the sample size is relatively small and not quite reliable. In the stratified analysis based on ethnicity, IL-10-819T/C polymorphism had decreased ischemic stroke risk in Asian populations under this model (CC vs CT + TT: OR = 0.78, 95% CI: 0.62–0.99), but not in Caucasian populations. This discrepancy in ischemic stroke risk may be explained by geographic climate, differences in alleles and genotypes in various ethnic populations, daily lifestyle, ethnic diversity, and dietary habits. However, this finding should be

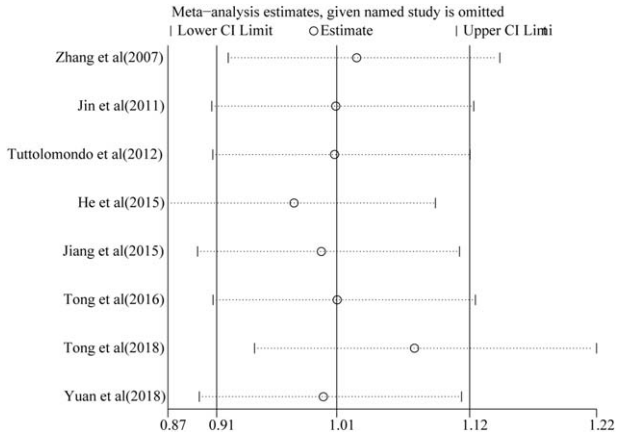

Figure 7. Sensitivity analysis of the association between the IL-10-819T/C polymorphism(C vs T) and ischemic stroke risk.

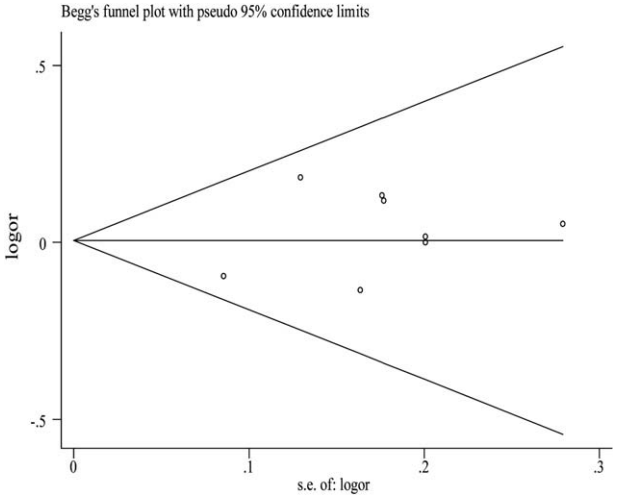

Figure 8. Begg funnel plot of the association between the IL-10-819T/C polymorphism(C vs T) and ischemic stroke risk.

interpreted with caution. Because in our meta-analysis for IL-10-819T/C polymorphism, only two articles were conducted in Caucasian populations.

Some limitations of this meta-analysis should be considered in interpreting the results. First, we have only focused those published studies in English and Chinese in the current meta-analysis. Second, only one promoter polymorphism, -819T/C in the *IL-10* gene, was evaluated in this meta-analysis, which might not be sufficient to address the complex genetic architecture of ischemic stroke. Third, the source of articles is uneven in geographical distribution, the majority of the included studies were conducted in Asians, which may introduce ethnicity bias, and further studies should focus on Africans and Caucasians. Fourth, meta-analysis is a type of retrospective study, and the recall and selection bias may be present.

In conclusion, our meta-analysis suggests that the IL-10-819T/C polymorphism is not associated with ischemic stroke risk in overall population. Due to limitations showed above in this analysis, it is critical that larger and well-designed studies are needed to confirm our results.

Author contributions

Data curation: Shuang Zuo.
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Investigation: Shuang Zuo.
Project administration: Haishan Li.
Software: Shuang Zuo, Haishan Li, Tingting Zheng.
Supervision: Shuang Zuo, Haishan Li
Writing – original draft: Shuang Zuo.
Writing – review & editing: Shuang Zuo, Haishan Li, Tingting Zheng.

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