Meta-Analysis of Observational Studies in Epidemiology

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Association between interleukin-10 -1082A/G polymorphism and risk of ischemic stroke

A meta-analysis

Shuang Zuo, BS*, Tingting Zheng, BS, Haishan Li, BS

Abstract

The Interleukin-10 -1082A/G polymorphism has been indicated to be correlated with ischemic stroke susceptibility, but the results of studies are still debatable. Thus, a meta-analysis was carried out.

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

12 case-control studies with 2722 cases and 2405 controls were included in this meta-analysis. IL-10 -1082A/G polymorphism may decrease the risk of ischemic stroke (G vs A: OR = 0.72, 95% CI: 0.59–0.87; GG vs AA: OR = 0.59, 95% CI:0.48–0.74; AG vs AA: OR = 0.69, 95% CI: 0.51–0.93; GG+AG vs AA: OR = 0.65, 95% CI: 0.50–0.84; GG vs AG+AA: OR = 0.71, 95% CI: 0.55–0.93). Meanwhile, similar results were also observed in matched studies, hospital-based subgroup, Asians, and large sample-size studies.

In conclusion, this meta-analysis suggested that the IL-10 -1082A/G polymorphism contributes to decreased ischemic stroke risk. Further large-scale and well-designed studies are still needed to confirm the results of our meta-analysis.

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 -1082A/G, ischemic stroke, meta-analysis, polymorphism

1. Introduction

Ischemic stroke is a major cause of adult disability and death in the world,[1] which is a heterogeneous multifactorial disease associated with genetic and environmental factors.[2] During the past few years, more and more evidence showed that inflammatory molecules and the genetic variation of the genes which encoded these inflammatory cytokines might take part in the pathogenesis of stroke.[3] Inflammatory mechanisms may not only play important roles in the manifestation and development of ischemic stroke, but also may be vulnerable to ischemic stroke in time via accumulation of atherosclerotic disease and maintain of atrial fibrillation.[4] 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] IL-10 is mainly produced by macrophages, T-helper-2 cells, and B lymphocytes, which can both stimulate and suppress immune responses, such as cytokine production, antigen presentation, macrophage activation and antigen-specific T-cell proliferation.[6] Several polymorphic loci have been identified and characterized in the IL-10 gene, and one of the most widely evaluated is -1082A/G (rs1800896) in the promoter region. It is believed that the A/G substitution is relevant to low/high amount of IL-10 secretion, respectively.[7]

Recently, many molecular epidemiological studies[3,8–18] were performed to investigate the association between the IL-10 -1082A/G polymorphism and ischemic stroke; however, no definitive conclusion has yet been reached. This discrepancy might be due to studies with small sample size, ethnic differences, and publication bias. Therefore, it is necessary to conduct meta-analysis to explore this association between IL-10 -1082A/G polymorphism and ischemic stroke risk.

2. Methods

2.1. Publication search

The electronic databases PubMed, Embase, and CNKI were searched using the following terms: (interleukin-10 OR interleukin 10 OR IL-10 OR IL10) AND (stroke OR cerebrovascular accident OR cerebral ischemia OR cerebral infarction) AND (polymorphism OR mutation OR genotype OR allele OR variation OR variant) up to August 2019. To avoid missing

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relevant studies, the reference lists of some major articles and reviews were manually checked.

2.2. Inclusion and exclusion criteria

All selected studies complied with the following criteria:

(1) case-control study on the IL-10 polymorphism and risk of ischemic stroke;
(2) sufficient published data for estimation of the odds ratio (OR) with a 95% confidence interval (CI); and
(3) genotype frequencies in the control group consistent with Hardy-Weinberg equilibrium (HWE) *(P > .05)*.

Studies were excluded if one of the following existed:

(1) not relevant to ischemic stroke or IL-10,
(2) not designed as case-control studies,
(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 since 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 HWE of genotype distribution of controls. We evaluated the quality of all of the studies included according to Newcastle–Ottawa scale (NOS).[19] The NOS contains 3 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 (G vs A), the homozygote model (GG vs AA), the heterozygote model (AG vs AA), the dominant model (GG+AG vs AA), and the recessive model (GG vs AG+AA). Heterogeneity was calculated by using both χ^2 based Q-statistic and I^2-statistic.[20] 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,[21] otherwise random effects model was used.[22] 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.[23] All statistical tests were carried out using Stata 12.0 software (Stata Corporation, College Station, TX). A P value of less than .05 was considered significant. All of the P values were 2 sided.

3. Results

3.1. Study characteristics

A total of 122 studies were retrieved from PubMed, Embase, and CNKI. Finally, 12 eligible studies were included in this meta-analysis.[3,8–18] A flow chart of the included and excluded studies was shown in Figure 1. The characteristics of the selected studies are summarized in Table 1.

3.2. Meta-analysis

A summary of the meta-analysis findings on the associations between IL-10-1082A/G polymorphism and susceptibility to ischemic stroke was provided in Table 2. The pooled analysis indicated that the significant association between IL-10-1082A/G polymorphism and ischemic stroke under five genetic models (G vs A: OR = 0.72,95% CI:0.59–0.87, $I^2 = 66.9\%$, $P_H < .001$; GG vs AA: OR = 0.59,95% CI:0.48–0.74, $I^2 = 17.1\%$, $P_H = .291$; AG vs AA: OR = 0.69, 95% CI:0.51–0.93, $I^2 = 56.9\%$, $P_H = .008$; GG+AG vs AA: OR = 0.65, 95% CI: 0.50–0.84, $I^2 = 50.6\%$, $P_H = .022$; GG vs AG+AA: OR = 0.71,95% CI: 0.55–0.93, $I^2 = 64.5\%$, $P_H = .004$. Figs. 2–6).

In a stratified analysis by case-control matched status, significant associations of IL-10-1082A/G polymorphism with decreased risk of ischemic stroke were found in matched group of the four genetic models (G vs A: OR = 0.75, 95% CI:0.62–0.91; GG vs AA: OR = 0.59, 95% CI: 0.48–0.74; GG+AG vs AA: OR = 0.68, 95% CI: 0.52–0.90; GG vs AG+AA: OR = 0.72, 95% CI: 0.55–0.95).

Subgroup analysis by source of control showed significant associations of IL-10-1082A/G polymorphism with decreased risk of ischemic stroke were found in hospital-based subgroup of all the five genetic models (G vs A: OR = 0.67, 95% CI: 0.53–0.84; GG vs AA: OR = 0.53, 95% CI: 0.40–0.72; AG vs AA: OR = 0.63, 95% CI: 0.43–0.91; GG+AG vs AA: OR = 0.59, 95% CI: 0.43–0.79; GG vs AG+AA: OR = 0.67, 95% CI: 0.47–0.94). No significant association was detected in the population-based subgroup in all genetic models.

When studies were stratified for ethnicity, significant associations of IL-10-1082A/G polymorphism with decreased risk of ischemic stroke were found for Asian populations in all genetic models (G vs A: OR = 0.67, 95% CI: 0.53–0.85; GG vs AA: OR = 0.51, 95% CI:0.39–0.68; AG vs AA: OR = 0.68, 95% CI: 0.47–0.97; GG+AG vs AA: OR = 0.60, 95% CI: 0.44–0.83; GG vs AG +AA: OR = 0.63, 95% CI: 0.45–0.89). No significant association was detected under five genetic models in the Caucasian populations.

By sample size, significant associations of IL-10-1082A/G polymorphism with decreased risk of ischemic stroke were found in large studies (total sample size ≥500) under all genetic models (G vs A: OR = 0.70, 95% CI: 0.56–0.88; GG vs AA: OR = 0.52, 95% CI:0.40–0.66; AG vs AA: OR = 0.74, 95% CI: 0.57–0.94; GG+AG vs AA: OR = 0.62, 95% CI: 0.49–0.78; GG vs AG+AA: OR = 0.66, 95% CI: 0.49–0.89), but not in small studies (total sample size < 500).

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

No obvious visual asymmetry was observed in Begg funnel plots (Fig. 8), and the results of Egger test revealed no statistical evidence for publication bias among studies ($P = .400$ for G vs A;

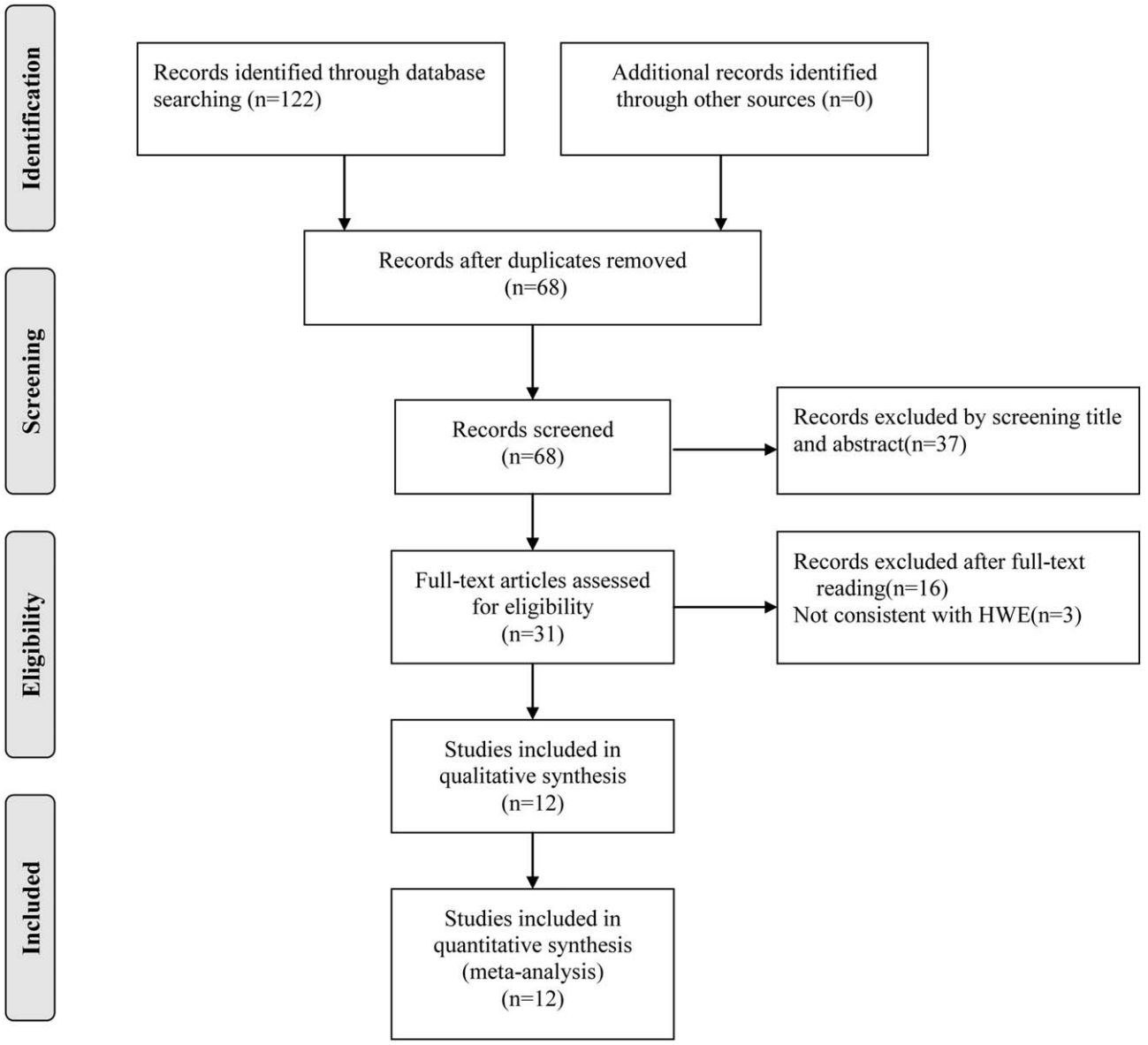

Figure 1. Flow chart of included studies in the current meta-analysis.

Table 1

Main characteristics of eligible studies.

Study	Year	Ethnicity	Source of control	Cases/Controls	Sample size	Matched status	Case	Control	HWE	NOS
							GG/AG/AA	GG/AG/AA		
Zhang et al	2007	Asian	HB	204/131	335	no	0/2/202	0/11/120	0.616	8
Munshi et al	2010	Asian	PB	480/470	950	yes	147/241/92	189/218/63	0.991	7
Jin et al	2011	Asian	HB	189/92	281	no	1/27/161	2/12/78	0.087	8
Marousi et al	2011	Caucasian	PB	145/145	290	yes	27/71/47	21/71/53	0.723	8
Tuttolomondo	2012	Caucasian	HB	96/48	144	yes	24/14/58	11/17/20	0.065	8
He et al	2015	Caucasian	HB	260/260	520	yes	95/124/41	123/108/29	0.475	8
Ozkan et al	2015	Asian	HB	42/48	90	yes	5/26/11	11/18/19	0.113	8
Jiang et al	2015	Asian	HB	181/115	296	yes	0/28/153	0/32/83	0.083	8
Li et al	2016	Asian	HB	335/335	670	yes	130/151/54	158/143/34	0.844	7
Kumar et al	2016	Asian	HB	250/250	500	yes	162/77/11	209/37/4	0.127	7
Liu et al	2017	Asian	HB	386/386	772	yes	313/68/5	308/75/3	0.498	8
Yuan et al	2018	Asian	PB	154/125	279	no	0/24/130	0/35/90	0.069	8

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

Table 2

Main characteristics of relevant studies selected for meta-analysis.

Analysis	OR (95% CI)	*P*	Heterogeneity	
			I^2	*P*
Overall (12)				
G vs A	0.72 (0.59–0.87)	.001	66.9%	<.001
GG vs AA	0.59 (0.48–0.74)	<.001	17.1%	.291
AG vs AA	0.69 (0.51–0.93)	.015	56.9%	.008
GG+AG vs AA	0.65 (0.50–0.84)	.001	50.6%	.022
GG vs AG+AA	0.71 (0.55–0.93)	.014	64.5%	.004
Source of control				
HB (10)				
G vs A	0.67 (0.53–0.84)	<.001	63.2%	.004
GG vs AA	0.53 (0.40–0.72)	<.001	0.0%	.862
AG vs AA	0.63 (0.43–0.91)	.015	57.8%	.011
GG+AG vs AA	0.59 (0.43–0.79)	.001	41.6%	.080
GG vs AG+AA	0.67 (0.47–0.94)	.021	66.7%	.006
PB (2)				
G vs A	0.91 (0.53–1.47)	.700	84.5%	.011
GG vs AA	0.84 (0.32–2.24)	.730	83.7%	.013
AG vs AA	0.87 (0.64–1.17)	.349	34.6%	.216
GG+AG vs AA	0.86 (0.48–1.57)	.632	75.0%	.046
GG vs AG+AA	0.89 (0.44–1.79)	.742	77.0%	.037
Ethnicity				
Caucasian (3)				
G vs A	0.85 (0.59–1.21)	.368	68.0%	.044
GG vs AA	0.82 (0.45–1.53)	.539	57.6%	.094
AG vs AA	0.69 (0.35–1.37)	.292	72.1%	.028
GG+AG vs AA	0.75 (0.44–1.28)	.294	62.8%	.068
GG vs AG+AA	0.92 (0.55–1.55)	.766	59.2%	.086
Asian (9)				
G vs A	0.67 (0.53–0.85)	.001	67.4%	.002
GG vs AA	0.51 (0.39–0.68)	<.001	0.0%	.863
AG vs AA	0.68 (0.47–0.97)	.033	54.9%	.023
GG+AG vs AA	0.60 (0.44–0.83)	.002	46.6%	.060
GG vs AG+AA	0.63 (0.45–0.89)	.009	69.8%	.086
Matched status				
Yes (9)				
G vs A	0.75 (0.62–0.91)	.004	68.4%	.001
GG vs AA	0.59 (0.48–0.74)	<.001	23.2%	.245
AG vs AA	0.74 (0.54–1.01)	.059	50.8%	.039
GG+AG vs AA	0.68 (0.52–0.90)	.006	44.1%	.074
GG vs AG+AA	0.72 (0.55–0.95)	.020	67.9%	.003
No (3)				
G vs A	0.48 (0.21–1.08)	.076	68.3%	.043
GG vs AA	0.24 (0.22–2.71)	.250	-	-
AG vs AA	0.47 (0.17–1.26)	.131	75.1%	.018
GG+AG vs AA	0.46 (0.18–1.15)	.096	72.3%	.027
GG vs AG+AA	0.24 (0.02–2.68)	.246	-	-
Sample size				
≥500 (5)				
G vs A	0.70 (0.56–0.88)	.002	71.8%	.007
GG vs AA	0.52 (0.40–0.66)	<.001	0.0%	.885
AG vs AA	0.74 (0.57–0.94)	.015	0.0%	.975
GG+AG vs AA	0.62 (0.49–0.78)	<.001	0.0%	.889
GG vs AG+AA	0.66 (0.49–0.89)	.006	74.1%	.004
<500 (7)				
G vs A	0.71 (0.49–1.03)	.069	66.6%	.006
GG vs AA	1.00 (0.62–1.63)	.994	0.0%	.396
AG vs AA	0.64 (0.36–1.12)	.119	75.9%	<.001
GG+AG vs AA	0.66 (0.41–1.08)	.101	70.8%	.002
GG vs AG+AA	1.01 (0.65–1.56)	.968	27.1%	.249

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

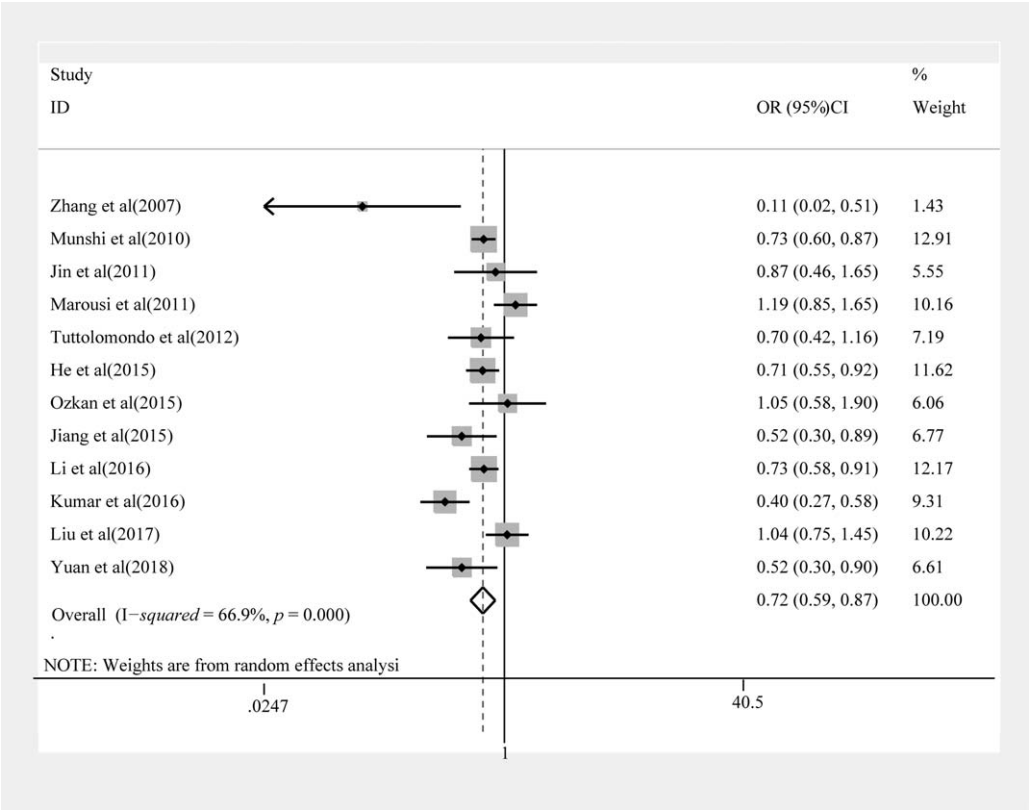

Figure 2. Forest plot of the association between the IL-10-1082A/G polymorphism (G vs A) and ischemic stroke susceptibility.

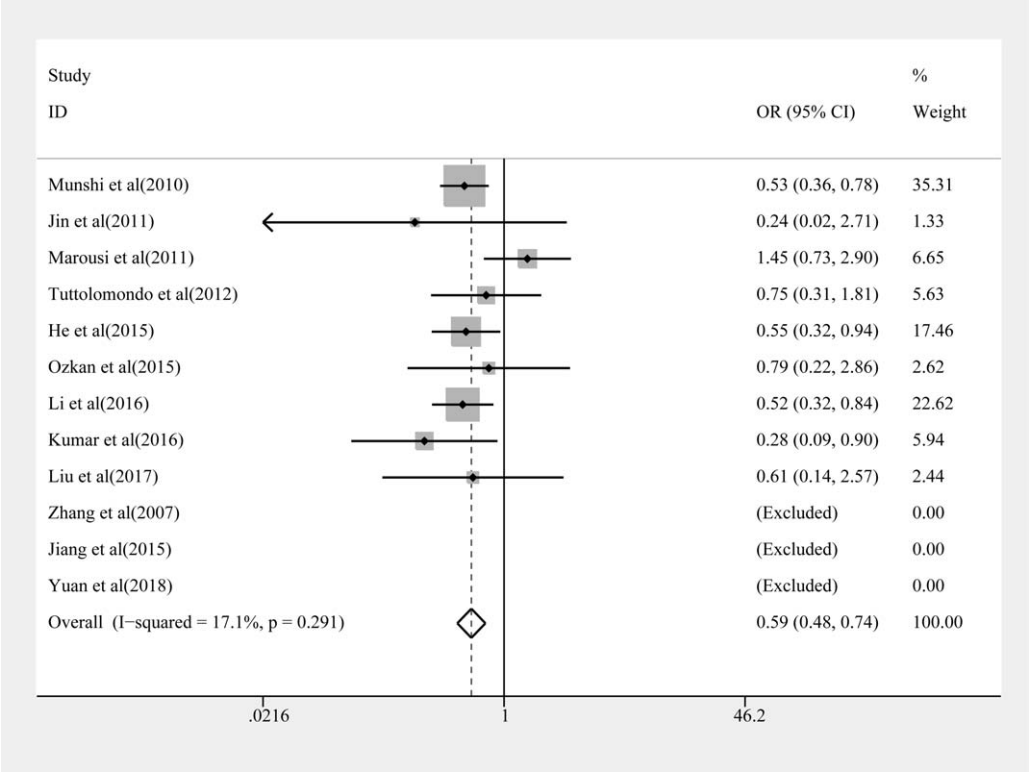

Figure 3. Forest plot of the association between the IL-10-1082A/G polymorphism (GG vs AA) and ischemic stroke susceptibility.

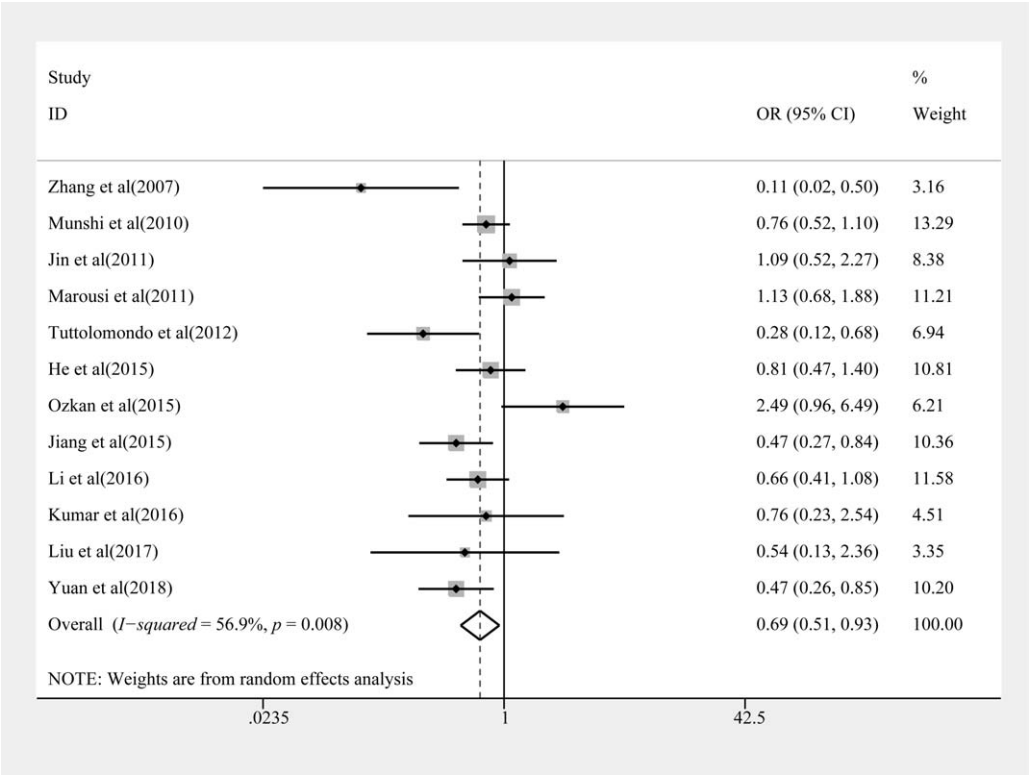

Figure 4. Forest plot of the association between the IL-10-1082A/G polymorphism (AG vs AA) and ischemic stroke susceptibility.

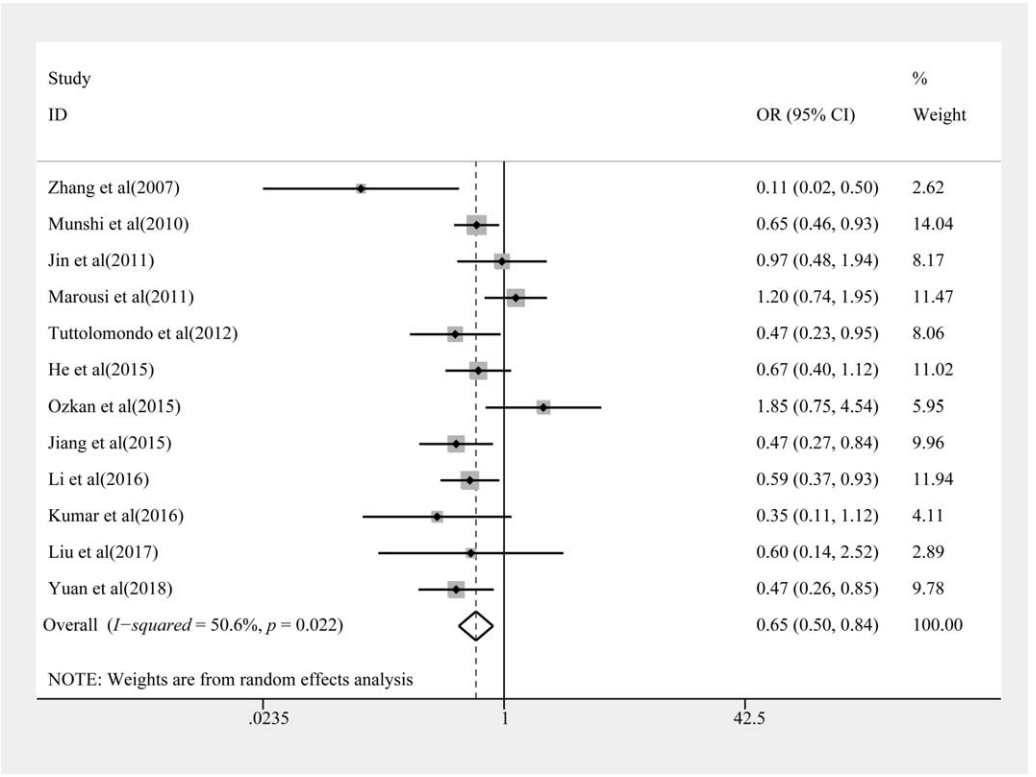

Figure 5. Forest plot of the association between the IL-10-1082A/G polymorphism (GG+AG vs AA) and ischemic stroke susceptibility.

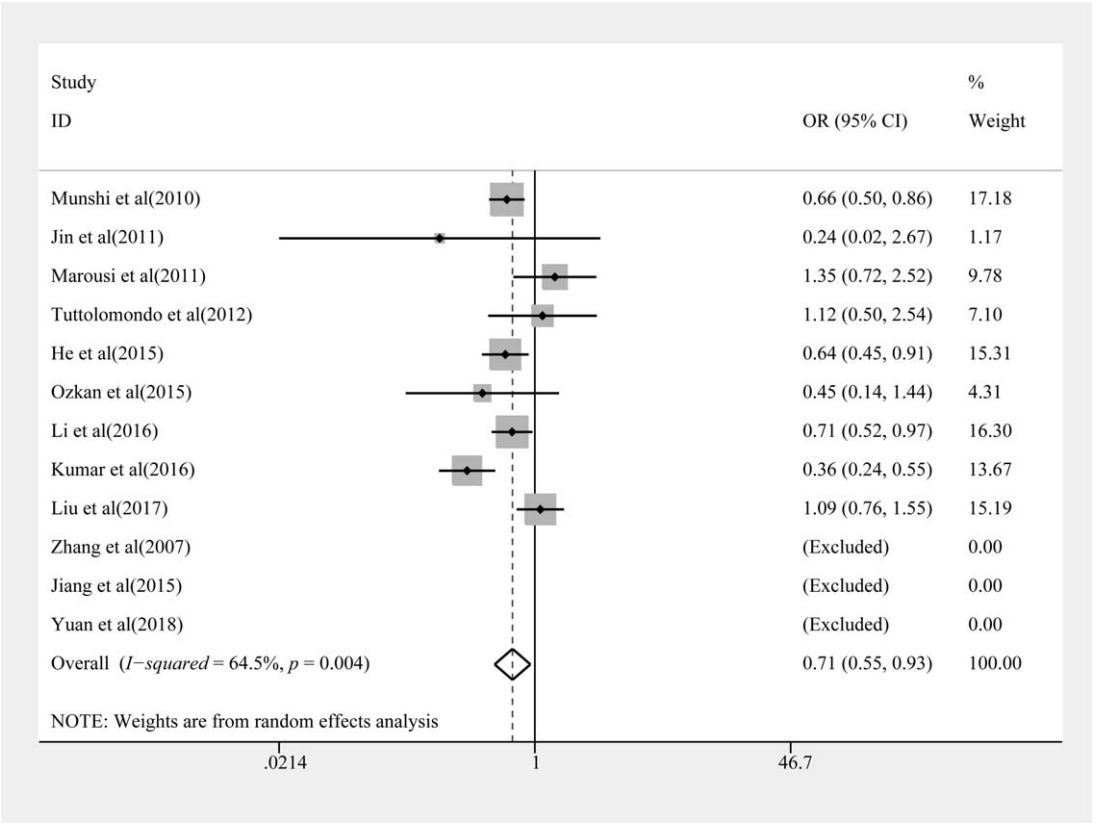

Figure 6. Forest plot of the association between the IL-10 -1082A/G polymorphism (GG vs AG+AA) and ischemic stroke susceptibility.

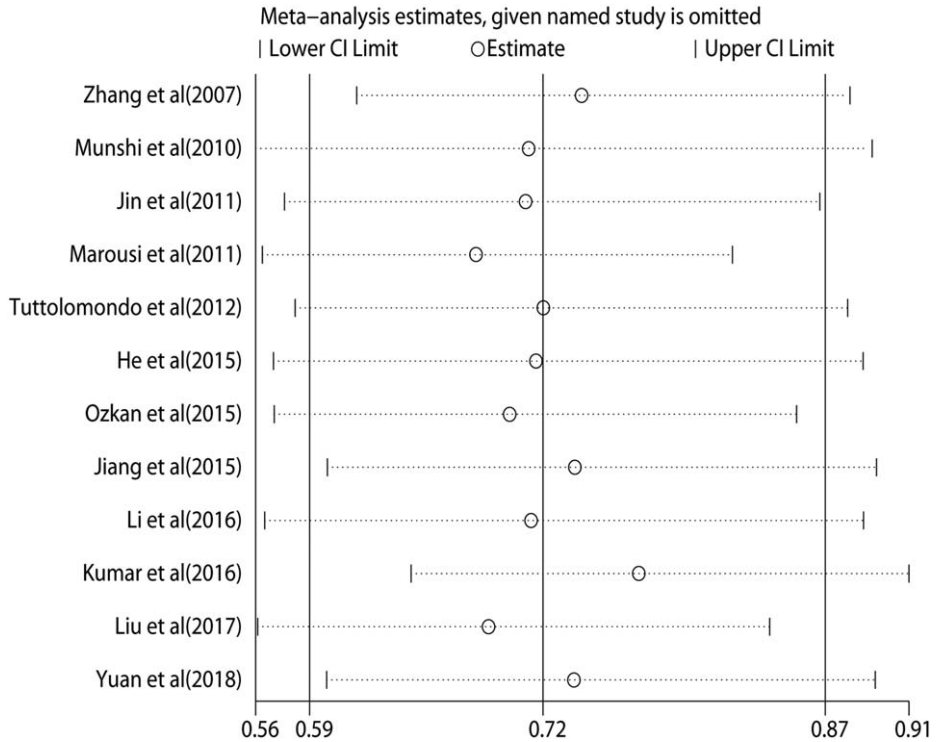

Figure 7. Sensitivity analyses of the association between the IL-10 -1082A/G polymorphism (G vs A) and ischemic stroke susceptibility.

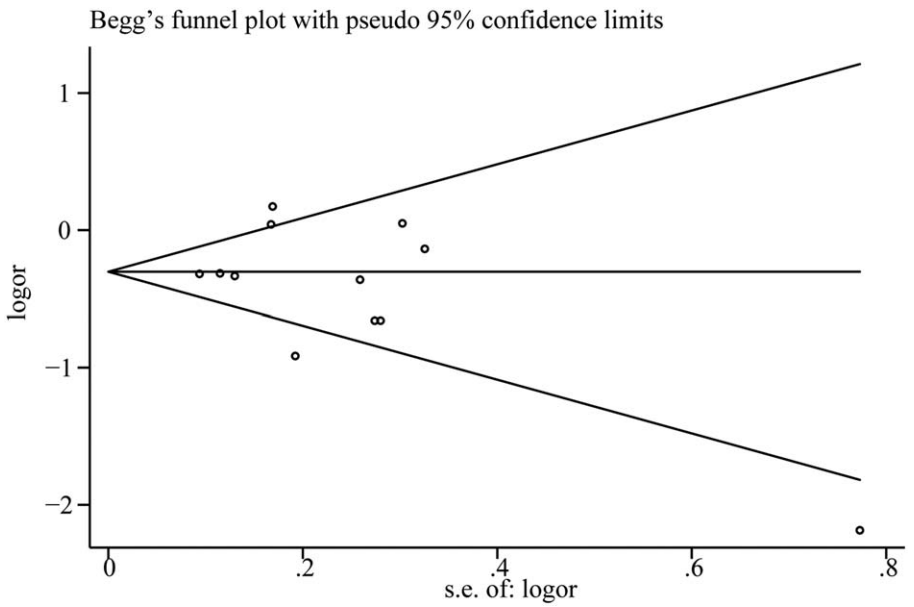

Figure 8. Begg funnel plot of the association between the IL-10 -1082A/G polymorphism (G vs A) and ischemic stroke susceptibility.

$P = .972$ for GG vs AA; $P = .476$ for AG vs AA; $P = .431$ for GG +AG vs AA; $P = .976$ for GG vs AG+AA).

4. Discussion

It is now accepted that genetics and environmental factors contribute to ischemic stroke susceptibility and outcome. Similarly, the inflammation reaction is also relevant to ischemic stroke. IL-10 is a potent anti-inflammatory cytokine with multiple functions taking part in inflammation reaction as well as the development of ischemic stroke. Recently, the associations between IL-10 -1082 A/G polymorphism and the risk of ischemic stroke have been intensively investigated, however, the results are inconsistent. Thus, we conducted a comprehensive meta-analysis involving published data, to assess the strength of association between the IL-10 -1082 A/G polymorphism and ischemic stroke risk. In this present meta-analysis, 12 studies with 2722 cases and 2405 controls concerning the IL-10 -1082 A/G polymorphism were included.

In the overall population, we found that IL-10 -1082 A/G polymorphism had a decreased association with ischemic stroke risk in all five genetic models (G vs A: OR = 0.72, 95% CI: 0.59–0.87; GG vs AA: OR = 0.59, 95% CI:0.48–0.74; AG vs AA: OR = 0.69, 95% CI: 0.51–0.93; GG+AG vs AA: OR = 0.65, 95% CI: 0.50–0.84; GG vs AG+AA: OR = 0.71, 95% CI: 0.55–0.93).

Significant heterogeneity among the studies was shown in our results; we performed stratified analyses in terms of case-control matched status, source of controls, ethnicity, and sample size. In a stratified analysis by case-control matched status, similar results were revealed in matched group of the four genetic models. Subgroup analysis by source of control showed significant associations of IL-10 -1082A/G polymorphism with decreased risk of ischemic stroke were found in hospital-based subgroup of all the five genetic models, but not in the population-based subgroup in all genetic models. In hospital-based studies, poor comparability between cases and controls might exert a confounding effect on the true association in light of a regional specialty for the disease under study and the differential hospitalization rates between cases and controls.[24] In contrast, subjects drawn from community might be representative of the true population, leading us to believe that results from population-based studies might be more representative. In this meta-analysis, most studies have recruited subjects from hospital, and only two studies from population. So, more studies are required to confirm this result.

In the stratified analysis based on ethnicity, IL-10 -1082 A/G polymorphism had decreased ischemic stroke risk in Asian populations based on all five genetic models, 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 interpreted with caution. Because in our meta-analysis for IL-10 -1082A/G polymorphism, only three articles were conducted in Caucasian subgroup totally.

By sample size, significant associations of IL-10 -1082A/G polymorphism with decreased risk of ischemic stroke were found in large studies (total sample size $\geq$500) under all genetic models, but not in small studies (total sample size $<$ 500). The discrepancy might due to the small sample size in some studies, which are underpowered to detect a slight effect.

In order to make the conclusion more credible, we performed the publication bias analysis and sensitivity analysis. Funnel plots suggested that no obvious publication bias was observed. The sensitivity analysis by excluding studies showed that the results are robust and convincing.

Some limitations of this meta-analysis should be considered in interpreting the results. First, the included studies were published in English and Chinese, while studies published in other languages were ignored. Second, because of the high heterogeneity in our present meta-analysis, the reliability of the findings may be weakened. Despite the application of the random-effects

model in our meta-analysis, the findings on the overall susceptibility should be taken cautiously. 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, our analysis did not consider the possibility of gene-gene or SNP-SNP interactions or the possibility of linkage disequilibrium between polymorphisms. Further investigations of the haplotypic effect of a gene and the study of multiple polymorphisms in different genes are needed.

In our meta-analysis, the pooled results of our meta-analysis demonstrated that the IL-10 -1082A/G polymorphism may play an important role in decreasing ischemic stroke susceptibility. 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.
Formal analysis: Tingting Zheng.
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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