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A meta-analysis on associations of *IL-6* and *IL-10* polymorphisms with susceptibility to ischemic stroke

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ABSTRACT

Background: Some previous studies already explored associations of interleukin-6 (*IL-6*) and interleukin-10 (*IL-10*) polymorphisms with ischemic stroke (IS). However, the results were conflicting. In this meta-analysis, we aimed to better analyze the relationship between *IL-6/IL-10* polymorphisms and IS in a larger pooled population.
Methods: We performed a systematic search of PubMed, Web of Science, Embase and CNKI. We calculated pooled odds ratios (ORs) and 95% confidence intervals (CIs) to estimate associations between *IL-6/IL-10* polymorphisms and IS.
Results: Totally 37 studies were included for analyses. A significant association with IS was observed for *IL-10* rs1800896 polymorphism in AA versus GG + GA (recessive model, $p = .001$, OR = 1.42, 95%CI 1.15–1.75) in overall population. Further subgroup analyses showed that *IL-6* rs1800795 was significantly associated with IS in Asians in GG versus GC + CC (dominant model, $p = .0005$, OR = 0.74, 95%CI 0.62–0.88), CC versus GG + GC (recessive model, $p = .003$, OR = 1.61, 95%CI 1.17–2.21) and G versus C (allele model, $p = .01$, OR = 0.74, 95%CI 0.58–0.93), whereas *IL-10* rs1800896 polymorphism was significantly associated with cerebral infarction (CI) in GG versus GA + AA (dominant model, $p = .02$, OR = 2.04, 95%CI 1.14–3.64), GA versus GG + AA (overdominant model, $p = .03$, OR = 0.50, 95%CI 0.27–0.93) and G versus A (allele model, $p = .01$, OR = 1.92, 95%CI 1.16–3.17).
Conclusions: Our findings indicated that *IL-6* rs1800795 polymorphism was significantly associated with individual susceptibility to IS in Asians, but not in Caucasians. In addition, *IL-10* rs1800896 polymorphism was also significantly associated with individual susceptibility to IS, especially for CI.

1. Introduction

Ischemic stroke (IS), characterized by ischemia (Transient ischemic attack, TIA) or even necrosis (Cerebral infarction, CI) of brain tissue resulted from obstruction of cerebral arteries, is the major cause of death and disability all over the world (Global Burden of Disease Study, 2013). During the past two decades, more and more evidence showed that genetic factors might play crucial roles in the pathogenesis of IS. First, many genetic variations were found to be associated with an increased susceptibility to IS by previous genetic association studies (Markus and Bevan, 2014; Kopyta et al., 2014; Meschia et al., 2011). Second, screening of common causal variations was also proved to be a cost-efficient way to predict the individual risk of developing IS (Chauhan and Debette, 2016). Overall, these findings jointly indicated that genetic predisposition was crucial for the development of IS.

Interleukins (ILs) are potent regulators of inflammatory processes (Scheller et al., 2014; Fietta et al., 2014; Hutchins et al., 2013; Sanjabi et al., 2009). It is well established that excessive inflammation serves as an etiological factor of atherosclerotic/thrombotic vascular diseases including IS (Anrather and Iadecola, 2016; Jin et al., 2013). Consequently, it is possible that functional *interleukin* polymorphisms, which may affect normal function of interleukins, may also impact individual susceptibility to IS. Recently, some studies already investigated potential associations between *IL-6/IL-10* polymorphisms and IS. However, the results of these studies were inconsistent and the sample size of individual studies was relatively statistical inadequate (Belisário et al., 2017; Jiang et al., 2015; Kumar et al., 2016; Marousi et al., 2011; Ozkan et al., 2015; Yang et al., 2014; Han, 2015). In this study, a meta-analysis was performed to better analyze the relationship between *IL-6/IL-10* polymorphisms and IS in a larger pooled population.

2. Materials and methods

We reported this meta-analysis as requested by the Reporting Items

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for Systematic Reviews and Meta-analyses (PRISMA) guideline (Moher et al., 2009).

2.1. Literature search and inclusion criteria

PubMed, Web of Science, Embase and CNKI were searched for potentially eligible articles using the combination of following terms: "interleukin-6", "IL-6", "interleukin 6", "IL 6", "interleukin-10", "IL-10", "interleukin 10", "IL 10", "polymorphism", "variant", "variation", "mutation", "SNP", "ischemic stroke", "cerebral infarction", "brain infarction", "cerebral ischemia", "brain ischemia", "transient ischemic attack" and "cerebrovascular disease". Additionally, the reference lists of all retrieved articles were also screened.

Included studies must meet all the following criteria: (1) case-control study about *IL-6/IL-10* polymorphisms and IS in human beings; (2) providing sufficient data for calculating odds ratios (ORs) and 95% confidence intervals (CIs); (3) full text in English or Chinese available. Studies were excluded if one of the following criteria was fulfilled: (1) not related to *IL-6/IL-10* polymorphisms and IS; (2) reviews/comments/letters; (3) case reports or case series. If duplicate reports by the same authors were found, we only included the most complete study for pooled analyses.

2.2. Data extraction and quality assessment

We extracted the following information from eligible studies: name of the first author, year of publication, country and ethnicity of participants, type of disease, sample size and the genotypic distribution of *IL-6/IL-10* polymorphisms in cases and controls. The probability value (*p* value) of Hardy-Weinberg equilibrium (HWE) was also calculated.

We used the Newcastle-Ottawa scale (NOS) to evaluate the quality of eligible studies (Stang, 2010). The NOS has a score range of zero to nine, and studies with a score of more than seven were thought to be of high quality.

Two reviewers conducted data extraction and quality assessment independently. When necessary, we wrote to the corresponding authors for extra information. Any disagreement between two reviewers was solved by discussion until a consensus was reached.

2.3. Statistical analyses

In this meta-analysis, statistical analyses were performed with Review Manager Version 5.3.3. We calculated ORs and 95% CIs to estimate potential associations between *IL-6/IL-10* polymorphisms and IS in dominant, recessive, over-dominant and allele models, with a *p* value of 0.05 or less was defined as statistically significant. Between-study heterogeneities were evaluated with I^2 statistic. Random-effect models (DerSimonian-Laird method) would be used for analyses if I^2 was > 50%. Otherwise, analyses would be conducted with fixed-effect models (Mantel- Haenszel method). We also conducted subgroup analyses by ethnicity of participants and type of disease. Stabilities of synthetic results were tested in sensitivity analyses. Publication biases were assessed by funnel plots.

3. Results

3.1. Characteristics of included studies

The initial literature search identified 414 articles. After excluding irrelevant or duplicate articles, 65 articles were retrieved for further evaluation. Another 28 articles were subsequently excluded after reading the full text. Totally 37 eligible studies were ultimately included for pooled analyses (see Fig. 1). Characteristics of included studies were summarized in Table 1.

3.2. Overall and subgroup analyses

A significant association with IS was observed for *IL-10* rs1800896 polymorphism in AA versus GG + GA (recessive model, $p = .001$, OR = 1.42, 95%CI 1.15–1.75, $I^2 = 48\%$) in overall population. Further subgroup analyses showed that *IL-6* rs1800795 was significantly associated with IS in Asians in GG versus GC + CC (dominant model, $p = .0005$, OR = 0.74, 95%CI 0.62–0.88, $I^2 = 25\%$), CC versus GG + GC (recessive model, $p = .003$, OR = 1.61, 95%CI 1.17–2.21, $I^2 = 43\%$) and G versus C (allele model, $p = .01$, OR = 0.74, 95%CI 0.58–0.93, $I^2 = 51\%$), whereas *IL-10* rs1800896 polymorphism was significantly associated with CI in GG versus GA + AA (dominant model, $p = .02$, OR = 2.04, 95%CI 1.14–3.64, $I^2 = 59\%$), GA versus GG + AA (overdominant model, $p = .03$, OR = 0.50, 95%CI 0.27–0.93, $I^2 = 64\%$) and G versus A (allele model, $p = .01$, OR = 1.92, 95%CI 1.16–3.17, $I^2 = 53\%$). However, no any positive findings were detected for rs1800796, rs1800871 and rs1800872 polymorphisms in pooled analyses (see Table 2).

3.3. Sensitivity analyses

We conducted sensitivity analyses to test the effects of individual study on pooled results. No any altered results were detected in sensitivity analyses, which suggested that our findings were statistically robust.

3.4. Publication biases

We used funnel plots to evaluate potential publication biases. The shape of funnel plots was symmetry for every comparison, which indicated that our pooled results were unlikely to be impacted by severe publication biases.

4. Discussion

The genetic distributions of investigated *IL-6/IL-10* polymorphisms among included studies were presented in Table 1, and from this Table, the readers can see clearly that the results of previous studies were not consistent. Additionally, from Table 2, you can see that for rs1800795, rs1800796 and rs1800896 polymorphisms, obvious heterogeneities existed among included studies in overall analyses, which suggested that genetic distribution of these polymorphisms vary greatly across included studies. In this case, a meta-analysis is of course warranted to get a more conclusive result. Therefore, we conducted this meta-analysis to more comprehensively analyze associations between *IL-6/IL-10* polymorphisms and IS, and the pooled results revealed that *IL-6* rs1800795 polymorphism was significantly associated with individual susceptibility to IS in Asians, but not in Caucasians. In addition, *IL-10* rs1800896 polymorphism was also found to be significantly associated with individual susceptibility to IS, especially for CI. No any altered results were observed in sensitivity analyses, which suggested that our findings were statistically robust.

Several points should be noted about this meta-analysis. Firstly, previous studies demonstrated that rs1800795 (−174G > C), rs1800796 (−572G > C), rs1800871 (−819C > T), rs1800872 (−592C > A) and rs1800896 (−1082A > G) polymorphisms located in the promoter region of *IL-6/IL-10* gene were all associated with altered transcription activity (Turner et al., 1997; de Oliveira et al., 2015; Toker et al., 2017; Kazemi et al., 2016). Thus, it is theoretically possible that these three functional polymorphisms may impact biological function of IL-6/IL-10 or cause changes in IL-6/IL-10 expression levels, which may lead to immune dysfunction as well as excessive inflammation, and ultimately influence individual susceptibility to IS. Therefore, considering the relatively small sample size of the current meta-analysis, maybe our study was still statistically inadequate to detect the actual associations between *IL-6/IL-10* polymorphisms and

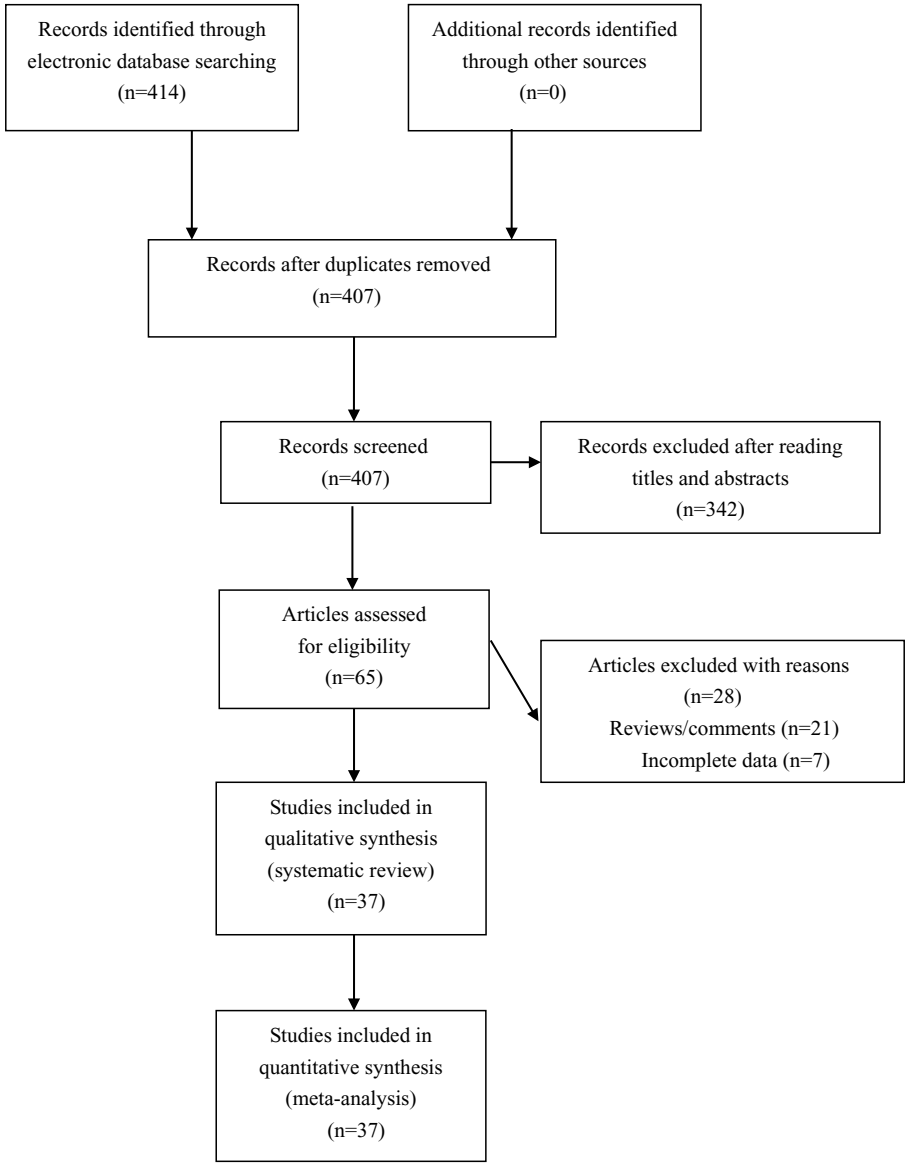

Fig. 1. Flowchart of study selection for the present study.

IS. Secondly, it was well established that IL-6 serves as a pro-inflammatory cytokine whereas IL-10 serves as an anti-inflammatory cytokine. Previous studies found that rs1800795 polymorphism was associated with increase transcription activity of IL-6 and high inflammation environment, while rs1800896 polymorphism was associated with increase transcription activity of IL-10 and less inflammation environment (Turner et al., 1997; de Oliveira et al., 2015; Toker et al., 2017; Kazemi et al., 2016). Based on these findings, the mutant allele of rs1800795 polymorphism should be associated with an elevated susceptibility to IS, whereas the mutant allele of rs1800896 polymorphism should be associated with a reduced susceptibility to IS, and the positive findings of our meta-analysis were basically consistent with these theoretical assumptions. Thirdly, the trends of associations for rs1800795 and rs1800896 polymorphisms in Asians and Caucasians were opposite, which suggested that genotypic distribution of rs1800795 and rs1800896 polymorphisms in different ethnicities may be extremely different. The same phenomenon might also apply to other functional *IL-6/IL-10* polymorphisms like rs1800796, rs1800871 and rs1800872. Nevertheless, since most of eligible studies for these three polymorphisms were conducted in Asians, we could not perform subgroup analyses by ethnicity accordingly. Therefore, future studies in Caucasians are still warranted to confirm our speculations. Moreover, the obvious heterogeneities existed between included studies for rs1800795, rs1800796 and rs1800896 polymorphisms in overall analyses indicated that the distribution of these polymorphisms varies greatly from population to population. Therefore, the genetic associations between these polymorphisms and IS may be ethnic-specific, and we should not generalize the subgroup analyses results to a broader population. Fourthly, the etiology of IS is extremely complex, consequently, to better elucidate potential roles of genetic variations in IS, we strongly recommend future studies to conduct haplotype analyses and investigate potential gene-gene interactions (Morgan and Humphries, 2005). Fifthly, it should be noted that two recent meta-analyses conducted by Ye et al. (2012) and Jin et al. (2014) also tried to explore potential associations between *IL-6/IL-10* polymorphisms and IS. However, the current meta-analysis was much more comprehensive than previous works because the following two points, (1) many related studies were published in the last 5 years. Therefore, an update meta-analysis was warranted and the sample sizes of our analyses were also significantly larger than previous meta-analyses, which could significantly reduce the risk of obtaining false positive or false negative results; (2) The previous meta-analyses of Ye et al. and Jin et al. only

Table 1
The characteristics of included studies.

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotypes (wtwt/wtmt/mtmt)		*P*-value for HWE	NOS score
					Cases	Controls		
rs1800795-174 G/C								
Balcerzyk 2012	Poland	Caucasian	IS	80/138	21/43/16	40/76/22	0.157	7
Balding 2004	Ireland	Caucasian	IS	105/389	33/60/12	123/198/68	0.445	7
Banerjee 2008	India	Asian	IS	176/212	123/53/0	156/52/4	0.890	8
Bazina 2015	Croatia	Caucasian	IS	114/187	39/53/22	63/98/26	0.214	8
Chakraborty 2013	India	Asian	IS	100/120	57/35/8	73/39/8	0.380	8
Chamorro 2005	Spain	Caucasian	IS	273/105	104/134/35	46/50/9	0.370	7
Flex 2004	Italy	Caucasian	IS	237/223	100/115/22	56/99/68	0.102	8
Greisenegger 2003	Italy	Caucasian	IS	214/214	81/96/37	76/108/30	0.394	8
Han 2015	China	Asian	CI	305/326	196/74/35	243/69/14	0.003	8
Karahan 2005	Turkey	Caucasian	IS	86/83	54/24/8	55/22/6	0.090	8
Lalouschek 2006	Austria	Caucasian	IS	404/415	143/187/74	156/192/67	0.540	8
Ma 2003	China	Asian	CI	42/18	42/0/0	18/0/0	NA	7
Mansoori 2012	India	Asian	IS	50/120	27/20/3	88/29/3	0.742	7
Ozkan 2015	Turkey	Caucasian	IS	42/48	16/22/4	14/21/13	0.388	8
Pola 2002	Italy	Caucasian	CI	122/134	63/47/12	29/58/47	0.170	7
Pola 2003	Italy	Caucasian	IS	119/133	56/48/15	28/58/47	0.206	7
Revilla 2002	Spain	Caucasian	IS	82/82	27/40/15	37/39/6	0.320	7
Tong 2010	China	Asian	IS	648/648	648/0/0	645/3/0	0.953	8
Tuttolomondo 2012	Italy	Caucasian	IS	96/48	40/46/10	14/33/1	< 0.001	7
Yang 2014	China	Asian	IS	430/461	205/170/55	246/171/44	0.079	8
You 2007	China	Asian	CI	177/112	177/0/0	112/0/0	NA	7
rs1800796-572 G/C								
Han 2015	China	Asian	CI	305/326	117/149/39	139/151/36	0.599	8
Liu 2012	China	Asian	CI	70/80	34/33/3	51/24/5	0.354	8
Tong 2010	China	Asian	IS	648/648	341/269/38	401/212/35	0.319	8
Yamada 2006	Japan	Asian	IS	636/2010	412/199/25	1138/760/112	0.309	8
Yang 2014	China	Asian	IS	429/461	267/127/35	318/122/21	0.041	8
rs1800871-819 C/T								
Belisário 2017	Brazil	Mixed	IS	26/369	12/13/1	150/173/46	0.721	7
He 2015	China	Asian	IS	260/260	104/113/43	116/111/33	0.427	8
Jiang 2015	China	Asian	CI	181/115	76/73/32	53/44/18	0.093	8
Jin 2011	China	Asian	CI	189/92	95/82/12	48/37/7	0.972	7
Tong 2016	China	Asian	IS	100/100	26/56/18	30/48/22	0.735	8
Tong 2018	China	Asian	IS	648/648	318/281/49	316/259/73	0.076	8
Tuttolomondo 2012	Italy	Caucasian	IS	96/48	63/19/14	26/17/5	0.390	8
Yuan 2016	China	Asian	CI	154/126	65/62/27	58/48/20	0.069	8
Zhang 2007	China	Asian	CI	204/131	86/90/28	56/48/27	0.008	8
rs1800872-592 C/A								
Balding 2004	Ireland	Caucasian	IS	105/389	65/35/5	235/139/15	0.317	7
Belisário 2017	Brazil	Mixed	IS	26/369	12/13/1	150/173/46	0.721	7
Tong 2016	China	Asian	IS	100/100	77/22/1	76/24/0	0.173	8
Tong 2018	China	Asian	IS	648/648	337/301/10	345/294/9	< 0.001	8
Xie 2013	China	Asian	IS	106/1369	54/40/12	561/642/166	0.393	8
Zhang 2007	China	Asian	CI	204/131	86/90/28	56/48/27	0.008	8
rs1800896-1082 G/A								
Belisário 2017	Brazil	Mixed	IS	26/369	9/13/4	152/170/47	0.960	7
He 2015	China	Asian	IS	260/260	95/124/41	123/108/29	0.475	8
Jiang 2015	China	Asian	CI	181/115	153/28/0	83/32/0	0.083	8
Jin 2011	China	Asian	CI	189/92	161/27/1	78/12/2	0.087	7
Kumar 2016	India	Asian	IS	250/250	162/77/11	209/37/4	0.127	8
Liu 2017	China	Asian	IS	386/386	313/68/5	308/75/3	0.498	8
Marousi 2011	Greece	Caucasian	IS	145/145	47/71/27	53/71/21	0.723	8
Munshi 2010	India	Caucasian	IS	480/470	147/241/92	189/218/63	0.991	7
Ozkan 2015	Turkey	Caucasian	IS	42/48	11/26/5	19/18/11	0.113	8
Sultana 2011	India	Caucasian	IS	238/226	154/44/40	163/47/16	< 0.001	8
Tong 2016	China	Asian	IS	100/100	94/6/0	92/8/0	0.677	8
Tong 2018	China	Asian	IS	648/648	641/5/2	634/10/4	< 0.001	8
Tuttolomondo 2012	Italy	Caucasian	IS	96/48	58/24/11	20/17/11	0.065	8
Yuan 2016	China	Asian	CI	154/125	130/24/0	90/35/0	0.069	8
Zhang 2007	China	Asian	CI	204/131	202/2/0	120/11/0	0.616	8

Abbreviations: IS, Ischemic stroke; CI, Cerebral infarction; wt, Wild type; mt, Mutant type; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-ottawa scale; NA, Not available.

focused on the most common investigated *IL-6/IL-10* polymorphisms (rs1800795 and rs1800896), whereas our meta-analysis explored associations between five common *IL-6/IL-10* polymorphisms and IS. So our work could be considered as an important supplement to pre-existing literatures. Sixthly, we also aimed to investigate associations between other *interleukin* (*IL-4, IL-8 and IL-12*) polymorphisms and IS in this meta-analysis. Nevertheless, no any *IL-4/IL-8/IL-12* polymorphisms were explored by at least two original studies. Thus, pooled analyses of

Table 2
Results of overall and subgroup analyses.

Variables	Sample size	Dominant comparison	Recessive comparison	Overdominant comparison	Allele comparison
		P value OR (95%CI) I^2 statistic	*P* value OR (95%CI) I^2 statistic	*P* value OR (95%CI) I^2 statistic	*P* value OR (95%CI) I^2 statistic
rs1800795-174 G/C					
Overall	3902/4216	0.51 1.09 (0.85–1.39) 79%	0.77 0.94 (0.62–1.42) 83%	0.51 1.04 (0.93–1.15) 10%	0.62 1.06 (0.84–1.33) 87%
Asian	1928/2017	**0.0005 0.74 (0.62–0.88)** 25%	**0.003 1.61 (1.17–2.21)** 43%	0.05 1.19 (1.00–1.43) 0%	**0.01 0.74 (0.58–0.93)** 51%
Caucasian	1974/2199	0.10 1.29 (0.95–1.74) 79%	0.39 0.81 (0.50–1.32) 84%	0.58 0.96 (0.85–1.10) 0%	0.17 1.21 (0.92–1.60) 88%
CI	646/590	0.65 1.52 (0.25–9.24) 97%	0.84 0.77 (0.06–10.41) 97%	0.78 1.04 (0.77–1.41) 27%	0.74 1.34 (0.25–7.30) 98%
rs1800796-572 G/C					
Overall	2088/3525	0.30 0.83 (0.58–1.18) 88%	0.67 1.05 (0.83–1.33) 50%	0.33 1.17 (0.85–1.62) 84%	0.34 0.87 (0.66–1.15) 87%
Asian	2088/3525	0.30 0.83 (0.58–1.18) 88%	0.67 1.05 (0.83–1.33) 50%	0.33 1.17 (0.85–1.62) 84%	0.34 0.87 (0.66–1.15) 87%
CI	375/406	0.13 0.74 (0.50–1.09) 30%	0.64 1.12 (0.71–1.76) 0%	0.26 1.41 (0.77–2.58) 64%	0.12 0.85 (0.68–1.04) 0%
rs1800871-819 C/T					
Overall	1858/1889	0.52 0.96 (0.83–1.10) 0%	0.16 0.86 (0.70–1.06) 25%	0.98 1.00 (0.85–1.17) 38%	0.82 1.01 (0.91–1.12) 0%
Asian	1736/1472	0.31 0.93 (0.81–1.07) 0%	0.17 0.86 (0.70–1.07) 30%	0.74 1.03 (0.87–1.21) 31%	0.94 1.00 (0.90–1.11) 0%
CI	728/464	0.39 0.90 (0.71–1.14) 0%	0.53 0.90 (0.65–1.25) 0%	0.19 1.17 (0.93–1.49) 0%	0.76 0.97 (0.82–1.16) 0%
rs1800872-592 C/A					
Overall	1189/3006	0.51 1.05 (0.90–1.23) 0%	0.25 0.81 (0.57–1.16) 0%	0.89 0.99 (0.85–1.16) 12%	0.34 1.06 (0.94–1.20) 0%
Asian	1058/2248	0.61 1.04 (0.88–1.24) 24%	0.31 0.82 (0.56–1.20) 0%	0.96 1.00 (0.84–1.18) 44%	0.44 1.05 (0.92–1.21) 0%
rs1800896-1082 G/A					
Overall	3399/3413	0.87 1.03 (0.76–1.39) 78%	**0.001 1.42 (1.15–1.75)** 48%	0.61 0.93 (0.71–1.22) 73%	0.85 1.02 (0.80–1.31) 79%
Asian	2372/2107	0.36 1.26 (0.77–2.06) 84%	0.08 1.45 (0.96–2.19) 20%	0.31 0.79 (0.50–1.25) 81%	0.33 1.24 (0.81–1.91) 84%
Caucasian	1001/937	0.25 0.82 (0.58–1.15) 61%	0.59 1.17 (0.67–2.03) 72%	0.71 1.06 (0.78–1.45) 50%	0.33 0.86 (0.64–1.16) 72%
CI	728/463	**0.02 2.04 (1.14–3.64)** 59%	0.25 0.24 (0.02–2.67) NA	**0.03 0.50 (0.27–0.93)** 64%	**0.01 1.92 (1.16–3.17)** 53%

Abbreviations: OR, Odds ratio; CI, Confidence interval; NA, Not available; S, Ischemic stroke; CI, Cerebral infarction.
The values in bold represent there is statistically significant differences between cases and controls.

these polymorphisms were infeasible and future studies should try to analyze potential associations between other *interleukin* polymorphisms and IS.

Some limitations of this meta-analysis should also be noted when interpreting our findings. First, our pooled results were derived from unadjusted analyses due to lack of raw data, and we have to admit that failure to perform further adjusted analyses may impact the reliability of our findings (Xie et al., 2017). Second, associations between *IL-6/IL-10* polymorphisms and IS may also be modified by gene-environmental interactions. However, most studies did not investigate the effects of these potential interactions, which impeded us to conduct relevant analyses (Wu et al., 2016). Thirdly, grey literatures that were not formally published in academic journals were not included for analyses in this meta-analysis since it is hard to assess their quality. Nevertheless, since grey literatures were not analyzed, although funnel plots indicated that severe publication biases were unlikely, it is still possible that our findings may be influenced by potential publication biases (Hu et al., 2017). Considering the above mentioned limitations, our findings should be interpreted with caution.

5. Conclusion

In summary, our meta-analysis suggested that *IL-6* rs1800795 polymorphism was significantly associated with individual susceptibility to IS in Asians, but not in Caucasians. In addition, *IL-10* rs1800896 polymorphism was also significantly associated with individual susceptibility to IS, especially for CI. Further studies with larger sample sizes are still needed to confirm our findings.

Authors' contributions

Miao Chen and Yue Yang conceived of the study, participated in its design. Miao Chen and Yue Yang conducted the systematic literature review. Miao Chen and Yue Yang performed data analyses. Miao Chen and Yue Yang drafted the manuscript. All authors have read and approved the final manuscript.

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Declaration of Competing Interests

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors, thus ethical approval is not required.

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