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ORIGINAL RESEARCH

Association between *CD14* rs2569190 C>T polymorphism and ischemic stroke susceptibility: a meta-analysis based on 5,277 subjects

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Introduction: Previous epidemiological studies have suggested that *CD14* rs2569190 C>T polymorphism plays an important role in ischemic stroke (IS) risk, but the results were inconsistent. Therefore, we conducted a meta-analysis to determine the association between *CD14* rs2569190 C>T polymorphism and IS susceptibility.

Methods: Online databases were searched from inception up to July 1, 2018, for studies concerning *CD14* rs2569190 C>T polymorphism and its association with IS susceptibility. ORs and corresponding 95% CIs were calculated in the genetic models of each polymorphism locus with Stata Version 14.0. Furthermore, heterogeneity, meta-regression, accumulative analyses, sensitivity analyses, and publication bias were examined.

Results: Overall, 10 observed studies involving 5,277 subjects were included in this meta-analysis on *CD14* rs2569190 C>T polymorphism. Generally, no significant associations were found between *CD14* rs2569190 C>T polymorphism and IS risk (allele contrast of T vs C: OR =1.03, 95% CI =0.96–1.12, P=0.41, I^2=27.8%; co-dominant models of CT vs CC: OR =1.01, 95% CI =0.81–1.25, P=0.95, I^2=51.9%; co-dominant models of TT vs CC: OR =1.04, 95% CI =0.89–1.22, P=0.62, I^2=25.1%; dominant model of CT + TT vs CC: OR =1.02, 95% CI =0.84–1.25, P=0.82, I^2=51.4%; recessive model of TT vs CC + CT: OR =1.07, 95% CI =0.95–1.22, P=0.28, I^2=0%), similar to the results in the subgroup analysis.

Conclusion: The current evidence indicated that *CD14* rs2569190 C>T polymorphism was not a critical risk factor for IS development.

Keywords: CD14, ischemic stroke, polymorphism

Introduction

Stroke is the second most common cause of mortality, accounting for more than 11.8% of all deaths globally.[1] The World Health Organization estimated that stroke affects 9.0 million people and causes 6.15 million deaths worldwide, and the number of deaths is expected to increase to 7.8 million in 2030.[2,3] Stroke and its complications, such as hemiplegia, depression, and death, have been considered the sixth common cause of reduced disability-adjusted life years and impose intolerable economic and mental burden on individuals and the society in general.[4] Ischemic stroke (IS) is a major type of stroke, accounting for more than 80% of all stroke cases, and its most common pathological presentation is arterial atherosclerosis.[5] Multiple factors, such as high blood pressure, intracranial atherosclerosis, dyslipidemia, and cigarette smoking, contribute to the development of IS. However, these factors do not account for all IS cases and the pathogenesis of IS is still unclear.

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Recent evidence indicated that multiple pro- and anti-inflammatory factors are involved in the pathogenesis of IS. CD14 is the receptor of bacterial lipopolysaccharide (LPS), which is an important glycoprotein expressed as membrane CD14 on the surface of monocytes, neutrophils, and macrophages and soluble CD14 (sCD14) in the serum.[6] CD14 transfers the LPS and other bacterial signals through the LPS-binding protein/CD14/myeloid differentiation factor 2 (MD-2)/Toll-like receptor (TLR) 4 complex.[7] This multimolecule complex triggers cascade signal amplification and activates innate host defense mechanisms, thereby promoting the release of cytokines and increase in antigen presentation, which stimulate an immune response.[8]

Animal research had suggested that low-dose LPS intraperitoneal injection results in IS and systemic inflammatory conditions, aggravates cerebrovascular balance, enhances blood–brain barrier injury and leads to brain edema formation.[9,10] Moreover, considerably high levels of plasma sCD14 are reported in patients with IS and closely associated with the risk of death.[11,12] *CD14* is a 3.9-kb gene located on chromosome 5q23-31, which encodes a 55 kDa glycoprotein with 375 amino acids.[13] rs2569190 (C-260T, sometimes referred to as C-159T) is the most common polymorphism locus in the promoter region of the *CD14* gene, and this single-nucleotide polymorphism is related to the Sp proteins.[14] The T allele of rs2569190 decreases the strength of the bond between the *CD14* promoter GC box and Sp consensus sequence, changes the transcriptional capacity, and increases the protein expression level of CD14.[15,16] In 2000, Ito et al[17] conducted the first case–control study and reported that rs2569190 C>T polymorphism is not associated with IS susceptibility. Since then, other case–control studies on the association between rs2569190 C>T polymorphism and IS susceptibility have been conducted, but the results were inconsistent. Thus, we conducted this meta-analysis on the basis of all published studies to explore a precise assessment of the association between the rs2569190 C>T polymorphism and IS susceptibility.

Methods

This current meta-analysis was conducted according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[18] All collected data were extracted from published studies, and there is no ethical issue.

Search strategy

Three online databases (PubMed, Embase, and Web of Science) were searched for all published case–control studies that focused on the association between rs2569190 C>T polymorphism and IS susceptibility from inception up to July 1, 2018. Only English studies were included. The bibliographies of the included studies were reviewed for the inquiry of some potential studies. The search terms were "((cluster of differentiation 14) OR CD14 OR rs2569190) AND (polymorphism OR variant OR mutation) AND (stroke OR (ischemic stroke) OR (cerebral infarction))", and the strategy was listed (eg, in PubMed) as follows:

#1 cluster of differentiation 14
#2 CD14
#3 rs2569190
#4 #1 OR #2 OR #3
#5 polymorphism
#6 variant
#7 mutation
#8 #5 OR #6 OR #7
#9 stroke
#10 ischemic stroke
#11 cerebral infarction
#12 #9 OR #10 OR #11
#13 #4 AND #8 AND #12.

Inclusion criteria

In this meta-analysis, all included studies met the following criteria: 1) case–control studies focused on the association between rs2569190 C>T polymorphism and IS susceptibility, 2) patients with IS were diagnosed with magnetic resonance imaging or computed tomography, 3) there were sufficient data of the genotypes in the case–control groups to evaluate the ORs and 95% CIs, 4) studies were published only in the English language, and 5) duplicate publications or overlapping data were deleted and only the largest or most recently updated data were retained.

Data extraction and quality evaluation

Two investigators (Yan-Qiong Wu and Shi-Yan Cheng) independently reviewed and collected the eligible information from the selected studies, such as surname of the first author, date of publication, country or region, ethnicity, control design, genotyping method, sample sizes of the cases and controls, and frequency data of the genotype distribution. Moreover, the Hardy–Weinberg equilibrium (HWE) and minor allele frequency assessment in the controls were calculated and presented in Table 1. The qualities of all the selected studies were evaluated by the first two authors according to the modified Newcastle–Ottawa scale (NOS).[19] The scores ranged from 0 (worst) to 11 points (best) (Table 1), and the studies with the score of 8 or higher were considered

Table 1 Scale for quality evaluation

Criteria	Score
Representativeness of cases	
Time, consecutive/randomly cases with clearly defined sampling frame	2
Without time or consecutive/randomly case, without clearly defined sampling frame	1
Not described	0
Source of controls	
Population based	2
Hospital based or Healthy based	1
Not described	0
Hardy–Weinberg equilibrium in controls	
Hardy–Weinberg equilibrium	2
Hardy–Weinberg disequilibrium	1
Not available	0
Genotyping examination	
Genotyping done under "blinded" condition and repeated again	2
Genotyping done under "blinded" condition or repeated again	1
Unblinded done or not mentioned and unrepeated	0
Subjects	
Number ≥500	1
Number <500	0
Association assessment	
Assess association between genotypes and ischemic stroke with appropriate statistics and adjustment for confounders	2
Assess association between genotypes and ischemic stroke with appropriate statistics and without adjustment for confounders	1
Inappropriate statistics used	0

as high quality. Potential divergences were solved by discussion with all the authors.

Statistical analysis

The association between rs2569190 C>T polymorphism and IS susceptibility was evaluated by calculating the pooled ORs and 95% CIs. Heterogeneity between the included studies was first determined with Cochran's Q test and I^2 test. The presence of $I^2>40\%$ and $P<0.1$ was considered as an indicator of significant heterogeneity. When $P>0.1$ or $I^2\leq40\%$, the fixed-effect model was adopted (the Mantel–Haenszel method), otherwise a random-effects model was applied (I–V heterogeneity method).[20,21] Four genetic models were examined, including allele contrast (T vs C), co-dominant models (heterozygote comparison: CT vs CC and homozygote comparison: TT vs CC), dominant model (CT + TT vs CC), and recessive model (TT vs CC + CT). Subgroup analyses were conducted according to HWE status, ethnicity, control design, subject number, and NOS evaluation. Meta-regression was conducted to identify potential factors that contribute to existing heterogeneity. Cumulative meta-analyses and sensitivity analyses were performed to assess the statistical tendency and stability of the results of each study. Egger's linear regression test and Begg's funnel plots were used for the identification of publication biases.[22] All the statistical outcomes were processed with Stata Version 14.0 (StataCorp LP, College Station, TX, USA). A two-sided P-value <0.05 was considered statistically significant.

Results

Study characteristics

In total, we identified 74 potential case–control studies through a systematic literature search. Figure 1 presents the inclusion procedures of the related studies. A total of 62 studies were excluded. Ten eligible studies involving 2,535 patients and 2,742 controls were included in the meta-analysis.[17,23–31] Five studies focus on Asian population,[17,26,29–31] and five studies focus on Caucasian population.[23–25,27,28] Three studies deviated from the HWE in terms of the genotype distributions in the control groups.[25,29,31] Nine studies used PCR-restriction fragment length polymorphism (PCR-RFLP) method, and one study used PCR-fluorescent-labeled oligonucleotide hybridization (PCR-FLOH) method.[28] All included characteristics are shown in Table 2.

Quantitative and subgroup analyses

The pooled results on the association between *CD14* rs2569190 C>T polymorphism and IS susceptibility are presented in Table 3. Overall, no significant association between the *CD14* rs2569190 C>T polymorphism and IS susceptibility was observed in all genetic models (T vs C: OR =1.03, 95% CI =0.96–1.12, P=0.41, I^2=27.8%, Figure 2; CT vs CC: OR =1.01, 95% CI =0.81–1.25, P=0.95, I^2=51.9%; TT vs CC: OR =1.04, 95% CI =0.89–1.22, P=0.62, I^2=25.1%; CT + TT vs CC: OR =1.02, 95% CI =0.84–1.25, P=0.82, I^2=51.4%; TT vs CC + CT: OR =1.07, 95% CI =0.95–1.22, P=0.28, I^2=0%) (Table 3). In the subsequent analysis, some similar negative associations were demonstrated between *CD14* rs2569190 C>T polymorphism and IS susceptibility, such as in the subgroup of the Asian (T vs C: OR =1.01, 95% CI =0.91–1.11, P=0.92, I^2=0%; CT vs CC: OR =0.94, 95% CI =0.71–1.23, P=0.65, I^2=50.4%; TT vs CC: OR =0.97, 95% CI =0.79–1.19, P=0.80, I^2=0%; CT + TT vs CC: OR =0.96, 95% CI =0.82–1.14, P=0.66, I^2=37.8%; TT vs CC + CT: OR =1.05, 95% CI =0.90–1.23, P=0.56, I^2=0%) and Caucasian population groups (T vs C: OR =1.07, 95% CI =0.85–1.35, P=0.56, I^2=52.8%; CT vs CC: OR =1.02, 95% CI =0.75–1.67, P=0.58, I^2=59.9%; TT vs CC: OR =1.13, 95% CI =0.75–1.70, P=0.57, I^2=50.2%;

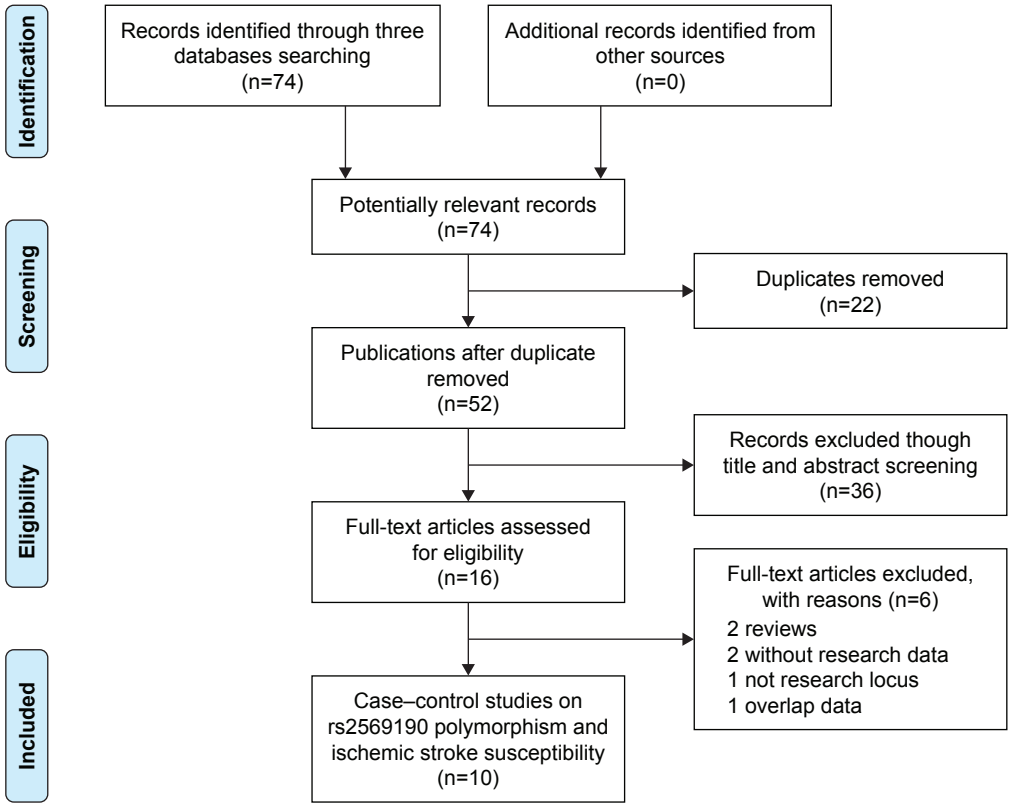

Figure 1 Flow diagram of the study selection process.

CT + TT vs CC: OR =1.12, 95% CI =0.75–1.66, P=0.58, I^2=63.9%; TT vs CC + CT: OR =1.12, 95% CI =0.90–1.38, P=0.30, I^2=0%) (Table 3).

Furthermore, heterogeneity was observed in the heterozygote comparison and dominant model. Meta-regression analysis was performed according to the abovementioned stratified factors, but no apparent factor was found to contribute to the existing heterogeneity (for CT vs CC: P_{HWE}=0.63, $P_{ethnicity}$=0.52, $P_{control\ design}$=0.19, $P_{subjects}$=0.23, P_{NOS}=0.86; for CT + TT vs CC: P_{HWE}=0.50, $P_{ethnicity}$=0.53, $P_{control\ design}$=0.16, $P_{subjects}$=0.28, P_{NOS}=0.85). Accumulative (Figure 3 for T vs C model) and sensitive (Figure 4 for T vs C) analyses were conducted based on the published date. No significant fluctuations were found, which indicated that the results of all genetic models were stable and credible.

Publication bias was measured and did not present any significant asymmetry in the five funnel plots. These results were confirmed using Egger's test (T vs C, P=0.91; Figure 5; CT vs CC: P=0.65; TT vs CC, P=0.88; CT + TT vs CC, P=0.81; TT vs CC + CT, P=0.24).

Discussion

According to the new published report by Wang et al, IS is one of the most important leading causes of morbidity and mortality in China. More than 47 billion China Yuan (CNY) was spent in the treatment of IS, and the average annual growth rate has been 24.96% since 2004.[32] IS can lead to serious injury to the nervous system and results in a series of complications. IS has become one of the major public health problems and imposed heavy economic and spiritual burden to families and society.

CD14 has been considered as a major component of LPS receptor complex and known to trigger immune cell recognition along with TLR-4 and MD-2.[33] Increased serum CD14 levels have been suggested with the development of IS and contributes to a series of neuroinflammation in cerebral ischemia.[34,35] Furthermore, high CD14 levels may be associated with vascular endothelial cell damage, which facilitates atherosclerosis formation and increases the risk of IS subsequently.[36,37] rs2569190 C>T polymorphism located at the 5′ untranslated region (UTR) of *CD14* gene. The T allele had been proven to be a risk factor for myocardial infarction in European ethnicity,[38] suggesting that the T allele can increase the CD14 level by evaluating *CD14* gene transcription and expression.[39]

In 2000, Ito et al[17] investigated whether rs2569190 C>T polymorphism contributes to a disposition to IS and did not find any significant association between rs2569190 C>T

Table 2 Characteristics of case–control studies on CD14 rs2569190 C>T polymorphism and ischemic stroke risk

Study	Year	Country	Ethnicity	Control design	Genotype method	Case	Control	Genotype distribution						*P* for HWE	MAF	NOS evaluation
								Case			Control					
								CC	CT	TT	CC	CT	TT			
Ito et al[17]	2000	Japan	Asian	PB	PCR-RFLP	235	309	53	125	57	71	155	83	0.93	0.52	8
Grau et al[23]	2001	Germany	Caucasian	HB	PCR-RFLP	20	21	5	12	3	6	9	6	0.51	0.50	6
Zee et al[24]	2002	US	Caucasian	PB	PCR-RFLP	279	279	75	132	72	62	146	71	0.43	0.52	10
Lichy et al[25]	2002	Germany	Caucasian	PB	PCR-RFLP	151	149	37	75	39	73	71	35	0.02	0.39	7
Park et al[26]	2006	Korea	Asian	PB	PCR-RFLP	125	125	19	79	27	29	72	24	0.09	0.48	9
Lalouschek et al[27]	2006	USA	Caucasian	PB	PCR-RFLP	404	415	113	187	104	123	200	92	0.53	0.46	8
Kis et al[28]	2007	Hungary	Caucasian	HB	PCR-FLOH	59	52	20	24	15	15	20	17	0.10	0.52	7
Lin et al[29]	2008	China	Asian	HB	PCR-RFLP	450	450	75	213	162	61	244	145	0.01	0.59	6
Banerjee et al[30]	2008	India	Asian	HB	PCR-RFLP	112	212	27	50	35	36	112	64	0.27	0.57	6
Das et al[31]	2017	India	Asian	HB	PCR-RFLP	700	700	171	394	135	174	391	135	<0.01	0.47	7

Note: HWE is control.

Abbreviations: HB, hospital or healthy based; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; NOS, Newcastle–Ottawa scale; PB, population based; PCR-FLOH, PCR fluorescent-labeled oligonucleotide hybridization; PCR-RFLP, PCR-restriction fragment length polymorphism.

Table 3 Summary of ORs and 95% CI of CD14 rs2569190 C>T polymorphism and ischemic stroke risk

	N[a]	T vs C				CT vs CC				TT vs CC				CT + TT vs CC				TT vs CC + CT			
		OR	95% CI	*P*-value	I^2 (%)	OR	95% CI	*P*-value	I^2 (%)	OR	95% CI	*P*-value	I^2 (%)	OR	95% CI	*P*-value	I^2 (%)	OR	95% CI	*P*-value	I^2 (%)
Total	10	1.03	0.96–1.12	0.41	27.8	1.01	0.81–1.25	0.95	51.9	1.04	0.89–1.22	0.62	25.1	1.02	0.84–1.25	0.82	51.4	1.07	0.95–1.22	0.28	0
HWE, yes	7	1.00	0.90–1.11	0.98	0	0.96	0.79–1.15	0.64	19.5	0.99	0.80–1.23	0.93	0	0.97	0.81–1.16	0.73	15.3	1.03	0.86–1.23	0.77	0
HWE, no	3	1.13	0.90–1.41	0.28	71.5	1.11	0.67–1.84	0.67	81.6	1.19	0.77–1.84	0.43	67.4	1.16	0.72–1.87	0.54	81.6	1.12	0.94–1.34	0.21	0
Ethnicity																					
Asian	5	1.01	0.91–1.11	0.92	0	0.94	0.71–1.23	0.65	50.4	0.97	0.79–1.19	0.80	0	0.96	0.82–1.14	0.66	37.8	1.05	0.90–1.23	0.56	0
Caucasian	5	1.07	0.85–1.35	0.56	52.8	1.12	0.75–1.67	0.58	59.9	1.13	0.75–1.70	0.57	50.2	1.12	0.75–1.66	0.58	63.9	1.12	0.90–1.38	0.30	0
Control design																					
PB	5	1.11	0.93–1.32	0.23	56.6	1.18	0.84–1.65	0.33	64.2	1.22	0.88–1.70	0.24	50.0	1.20	0.87–1.67	0.27	67.0	1.10	0.92–1.32	0.30	0
HB	5	0.98	0.88–1.09	0.75	0	0.89	0.73–1.07	0.22	17.7	0.91	0.73–1.15	0.44	0	0.99	0.75–1.08	0.27	0	1.05	0.88–1.25	0.60	0
Subjects																					
>500	5	1.01	0.93–1.10	0.83	0	0.93	0.80–1.08	0.36	7.4	1.00	0.82–1.19	0.97	0	0.96	0.83–1.11	0.56	0	1.07	0.93–1.23	0.36	0
<500	5	1.18	0.81–1.44	0.58	57.1	1.23	0.71–2.14	0.36	63.8	1.14	0.65–2.01	0.64	55.1	1.19	0.70–2.05	0.52	67.1	1.09	0.82–1.44	0.56	0
NOS evaluation																					
NOS ≥8	4	1.03	0.92–1.16	0.61	0	1.00	0.82–1.23	0.98	31.9	1.07	0.84–1.36	0.59	8.3	1.02	0.84–1.25	0.81	32.0	1.06	0.87–1.29	0.56	0
NOS <8	6	1.04	0.88–1.22	0.66	48.0	1.00	0.69–1.44	0.98	65.0	1.01	0.87–1.17	0.93	43.3	1.00	0.71–1.42	0.98	64.5	1.08	0.92–1.27	0.36	5.0

Notes: [a]Numbers of comparisons. I^2 is for heterogeneity test.

Abbreviations: HB, hospital or healthy based; HWE, Hardy–Weinberg equilibrium; NOS, Newcastle–Ottawa scale; PB, population based.

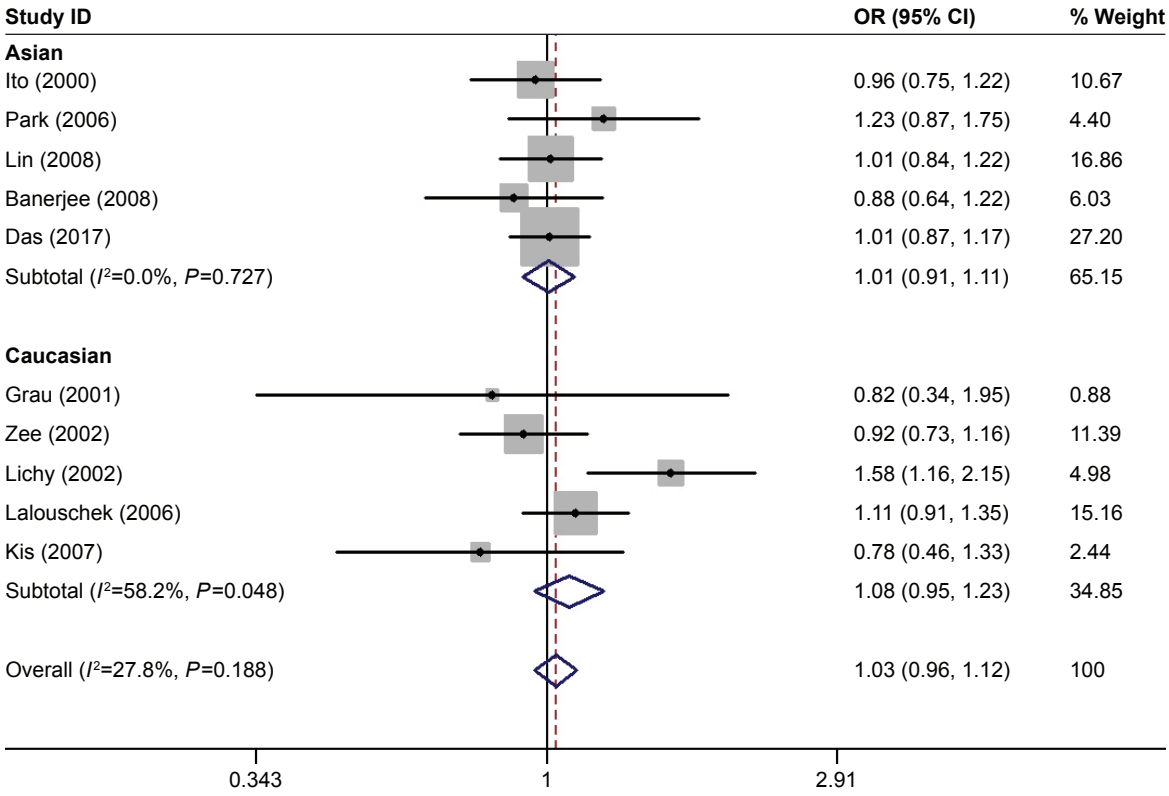

Figure 2 OR and 95% CIs of the associations between *CD14* rs2569190 C>T polymorphism and ischemic stroke susceptibility in T vs C model.

polymorphism and IS susceptibility. Since then, a number of studies were conducted to evaluate the role of rs2569190 C>T polymorphism in IS events in different ethnicities. Grau et al,[23] Banerjee et al,[30] and Das et al[31] reported a negative association between rs2569190 C>T polymorphism and IS susceptibility. However, Lichy et al[25] found that the TT genotype is associated with a risk of the stratified micro- or macroangiopathic IS. In contrast, Cole et al[40] suggested that

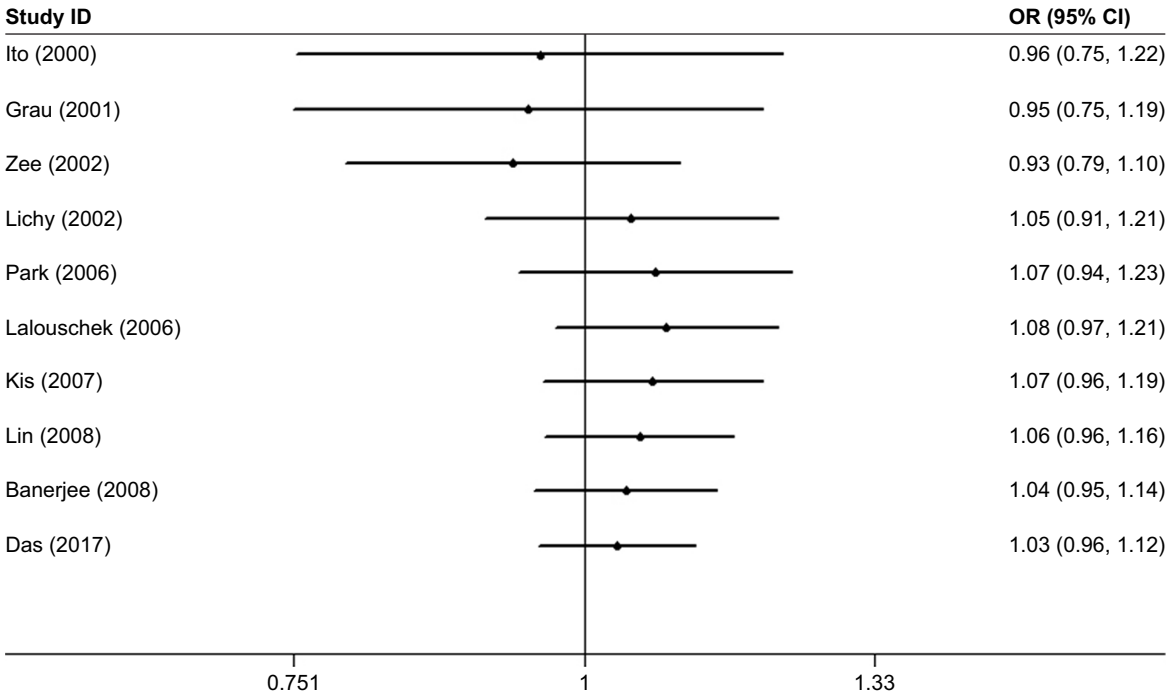

Figure 3 Cumulative meta-analyses according to publication year in T vs C model of *CD14* rs2569190 C>T polymorphism.

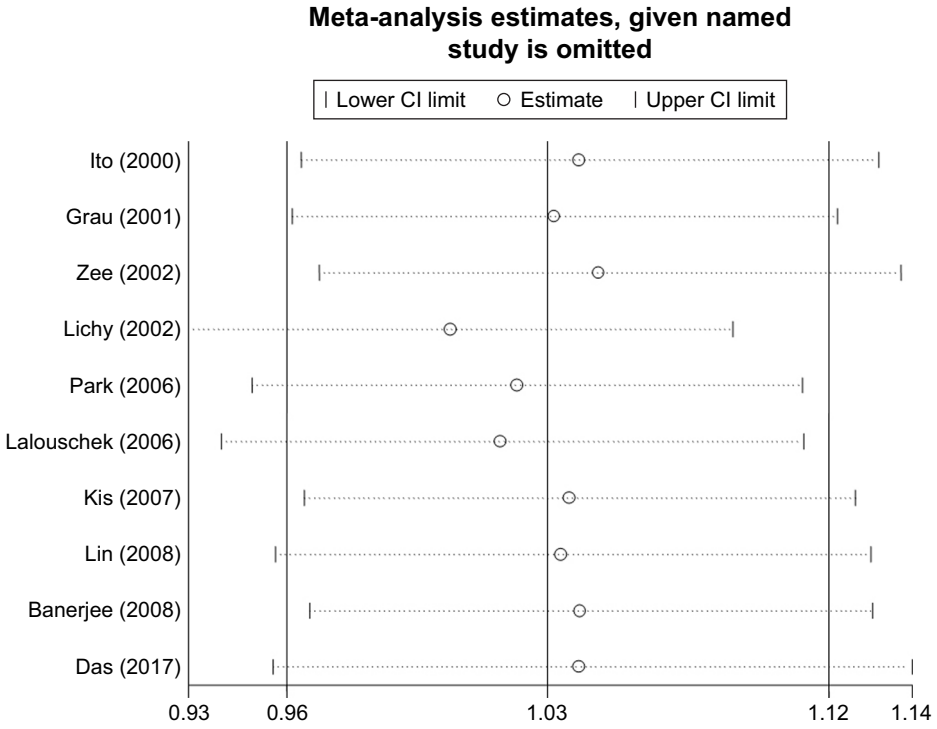

Figure 4 Sensitivity analysis through deleting each study to reflect the influence of the individual dataset to the pooled ORs in T vs C model of *CD14* rs2569190 C>T polymorphism.

C allele rs2569190 C>T polymorphism increases the risk of IS among smokers (OR =2.05, 95% CI =1.09–3.86).

In epidemiological studies, small sample sizes may contribute to a low statistical power of the results and lead to an inaccurate conclusion. To our knowledge, a meta-analysis is an effective method of combining the quantitative results of previous studies in order to derive a pooled summary conclusion through statistical measures, which can reduce the risk of drawing incorrect conclusions based on small sample sizes.

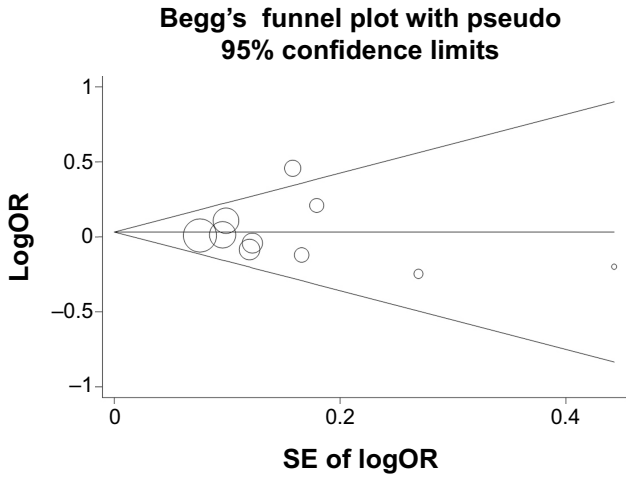

Figure 5 Funnel plot analysis to detect publication bias for T vs C model of *CD14* rs2569190 C>T polymorphism.
Note: Circles represent the weight of the studies.

Therefore, we conducted this meta-analysis using eligible case–control studies to explore a more reliable association between rs2569190 C>T polymorphism and IS risk by increasing the sample number of subjects. In this meta-analysis, the overall pooled results revealed that rs2569190 C>T polymorphism had no significant influence on IS risk in all genetic models. Moreover, no significant association between rs2569190 C>T polymorphism and IS risk was found in Asian or Caucasian populations, indicating no significant correlation with ethnicity. In addition, the stratified analyses were conducted on the basis of HWE status, control design, subject number, and NOS evaluation, but no significant results could be found. The possible explanation may be that *CD14* rs2569190 C>T polymorphism is not involved in IS susceptibility directly but plays a pathogenic role in synergy with other abnormally expressed proteins or gene polymorphisms.

In 2009, Banerjee[41] conducted a meta-analysis on the association between *CD14* rs2569190 C>T polymorphism and cerebrovascular diseases but did not conduct a subgroup analysis on IS susceptibility. Thereafter, Misra et al conducted a meta-analysis with only six published case–control studies and failed to find any significant association between *CD14* rs2569190 C>T polymorphism and IS susceptibility.[42] We conducted this meta-analysis by integrating 10 published case–control studies with a comprehensive research strategy

and large sample size. In addition, more rigorous methodology, such as stratified analysis, cumulative analyses, sensitivity analyses, meta-regression, and quality evaluation, was adopted to guarantee the accuracy of all results. However, some limitations in this meta-analysis should be addressed. First, heterogeneity was observed in the heterozygote model and dominant models and meta-regression was conducted but no apparent factor that contributes to the current heterogeneity was found. The heterogeneity can be partly alleviated in the subgroup analysis. Second, only English language studies were included and all included studies were from Asian and Caucasian populations; thus, a population bias may be present and may restrict the application of our conclusion to other races. Finally, these results were conducted on the basis of a single factor (genotype distribution in the case and control groups) and the potential interaction mechanisms with age, sex and other risk factors cannot be interpreted because of insufficient original data.

Conclusion

The evidence obtained suggested that rs2569190 C>T polymorphism may not be an independent risk factor for IS susceptibility. Considering the importance of *CD14* in IS development, further larger studies with gene–environment interactions in diverse populations should be conducted to clarify the association between *CD14* rs2569190 C>T polymorphism and IS susceptibility.

Disclosure

The authors report no conflicts of interest in this work.

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