

# Association of *RAGE* gene Gly82Ser polymorphism with coronary artery disease and ischemic stroke

## A systematic review and meta-analysis

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### Abstract

**Background:** The receptor for advanced glycosylation end products (RAGE) has been widely linked to diabetic atherosclerosis, but its effects on coronary artery disease (CAD) and ischemic stroke (IS) remain controversial. The Gly82Ser polymorphism is located in the ligand-binding V domain of RAGE, suggesting a possible influence of this variant on RAGE function. The aim of the present study is to clarify the association between the *RAGE* Gly82Ser polymorphism and susceptibility to CAD and IS.

**Methods:** Eligible studies were identified through a comprehensive literature search. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the association of Gly82Ser polymorphism with CAD and IS risk. Fixed- or random-effects model was used depending on the heterogeneity between studies. A funnel plot and Egger linear regression test were applied to assess publication bias. We also performed subgroup analyses to investigate potential sources of heterogeneity.

**Results:** A total of 16 eligible articles containing 18 studies were analyzed. The pooled analysis indicated that the Gly82Ser polymorphism significantly increased CAD risk in recessive and homozygous genetic models (SS vs GS + GG: OR = 1.34, 95% CI = 1.09–1.64; SS vs GG: OR = 1.38, 95% CI = 1.12–1.71). A significant association between the Gly82Ser polymorphism and IS risk was observed in all tested models except the heterozygous genetic model (GS + SS vs GG: OR = 1.20, 95% CI = 1.04–1.38; SS vs GS + GG: OR = 2.20, 95% CI = 1.74–2.78; SS vs GG: OR = 2.23, 95% CI = 1.72–2.91; S vs G: OR = 1.32, 95% CI = 1.05–1.65). Subgroup analysis suggested an association between CAD and IS risk and the Gly82Ser polymorphism in the Chinese population, but not in the non-Chinese population.

**Conclusions:** The current meta-analysis suggests that the *RAGE* Gly82Ser polymorphism is associated with an increased risk of CAD and IS, especially in the Chinese population. However, better-designed studies with larger sample sizes are needed to validate the results.

**Abbreviations:** AGE = advanced glycosylation end product, CAD = coronary artery disease, CI = confidence interval, HWE = Hardy–Weinberg equilibrium, IS = ischemic stroke, OR = odds ratio, RAGE = receptor for advanced glycosylation end products.

**Keywords:** coronary artery disease, Gly82Ser, ischemic stroke, meta-analysis, RAGE

## 1. Introduction

Coronary artery disease (CAD) and ischemic stroke (IS) share risk factors, frequently coexist, and remain major health burdens worldwide.<sup>[1,2]</sup> Both CAD and IS are manifestations of atherosclerosis.<sup>[2]</sup> Epidemiological studies have revealed that

individuals with diabetes mellitus are more likely to suffer from atherosclerotic diseases.<sup>[3,4]</sup> Meanwhile, evidence has indicated that sustained hyperglycemia could result in the formation and accumulation of advanced glycosylation end products (AGEs), accelerating vascular dysfunction and atherogenesis.<sup>[5]</sup> However, these factors apply only to a proportion of the pathogenesis of atherosclerosis. Genetic evidence suggests that both CAD and IS are highly heritable and have substantial overlap of genetic risk.<sup>[4,6–8]</sup>

The receptor for AGEs (RAGE) is a member of the immunoglobulin superfamily of cell surface molecules.<sup>[9]</sup> RAGE expression occurs in most tissues, including the heart, brain, liver, and kidney.<sup>[10]</sup> The *RAGE* gene is located on chromosome 6p21.3 and is overexpressed in atherosclerotic plaques.<sup>[11,12]</sup> It was identified as a likely candidate gene associated with vascular and neurological complications, such as atherosclerosis, CAD, IS, and Alzheimer disease.<sup>[9,13,14]</sup> More than 50 polymorphisms have been identified in the region of the *RAGE* gene.<sup>[15]</sup> Of these, the *RAGE* Gly82Ser polymorphism (rs2070600), representing a glycine (G) to serine (S) substitution, is of interest because of its localization in the N-linked glycation site (position 82), which could influence AGE–RAGE interaction.<sup>[16]</sup> Some studies in humans and animals have yielded conflicting results concerning the potential role of the *RAGE* Gly82Ser polymorphism in the pathogenesis of atherosclerosis. Several studies have indicated that Gly82Ser polymorphism is a possible risk factor for the

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The authors have no conflicts of interest to disclose.

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development of CAD,<sup>[17,18]</sup> while others failed to specifically link this variant to CAD.<sup>[19,20]</sup> Meanwhile, the role of Gly82Ser polymorphism in IS susceptibility remains controversial.<sup>[21,22]</sup>

Consequently, there appears a need for a meta-analysis to investigate the association between the *RAGE* Gly82Ser polymorphism and the risk of CAD and IS.

## 2. Methods and materials

### 2.1. Literature search strategy

A comprehensive search strategy was performed using electronic databases, including PubMed, Embase, Web of Science, ScienceDirect, Cochrane Library, Wanfang database, and the Chinese National Knowledge Infrastructure Database. Databases were searched using the following search terms: (“*RAGE*” OR “the receptor for advanced glycosylation end products” OR “Gly82Ser” OR “rs2070600”) and (“polymorphism” OR “genotype” OR “variant”) and (“cerebral infarction” OR “ischemic stroke” OR “coronary artery disease” OR “myocardial infarction” OR “angina” OR “atherosclerosis”). The deadline of publication for inclusion in the meta-analysis was March 2016. Manual searching was also performed to find potentially relevant records.

### 2.2. Inclusion and exclusion criteria

Studies included in our meta-analysis were qualified on the basis of the following criteria: studies on the association between the Gly82Ser polymorphism and susceptibility to CAD or IS; total CAD cases that were documented by angiographic evidence of at least 50% stenosis of 1 major coronary artery, myocardial infarction, a history of prior angioplasty, or coronary artery bypass surgery; studies in which magnetic resonance imaging or computed tomography was used to confirm the diagnosis of IS; studies in which the data in the references were sufficient for present estimation; and studies in which the publication language was English and/or Chinese. However, all reviews, abstracts, meta-analyses, letters to the editor, animal studies, case-only studies, and studies containing overlapping data were excluded.

### 2.3. Data extraction

The data were extracted by 2 independent reviewers (W-QM and YZ) according to the selection criteria. Disagreements were resolved through discussion, or by a third reviewer (N-FL). The following information was extracted from each study: author, publication date, region, country, total number of cases and controls, number of different genotypes in cases and controls, genotyping methods, and Hardy–Weinberg equilibrium (HWE) in controls.

### 2.4. Statistical analysis

Statistical analyses were performed with Stata software package (version 12.0; StataCorp, College Station, TX). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the association between susceptibility to CAD and IS and the *RAGE* Gly82Ser polymorphism. Pooled ORs were calculated for the dominant (GS+SS vs GG), recessive (SS vs GS+GG), homozygous (SS vs GG), heterozygous (GS vs GG), and allele (S vs G) genetic models. The Cochrane Q-test and index ( $I^2$ ) were used to measure heterogeneity between the

studies.  $P > 0.10$  in the Q-test or  $I^2 < 50\%$  indicated no heterogeneity among the studies. The fixed-effects model was used when there was no significant heterogeneity; otherwise, the random-effects model was applied. Subgroup analyses according to ethnicity (Chinese and non-Chinese populations), HWE status, and sample size (studies with  $>500$  subjects were categorized as “large,” and studies with  $<500$  subjects were categorized as “small”) were performed to detect sources of heterogeneity among the studies. To assess the stability of the results, sensitivity analysis was performed by removing each individual study at a time. Possible publication bias was tested by funnel plot and Egger linear regression test.

### 2.5. Ethics

Ethical approval was not required for the present meta-analysis.

## 3. Results

### 3.1. Selection and characteristics of studies

The initial literature search identified 1415 potentially relevant articles, of which 859 articles were excluded because they were duplicates. Twenty-six articles were obtained from the literature search after screening titles and abstracts. Then, 10 articles were excluded due to being reviews and meta-analyses, and including insufficient data. Finally, 16 articles meeting the inclusion criteria were preserved.<sup>[17–32]</sup> A flow diagram of the literature selection process is shown in Fig. 1.

The main characteristics of the eligible studies are summarized in Table 1. A total of 18 studies, covered in 16 articles, were identified. One article reported 2 separate studies on the association between the *RAGE* Gly82Ser polymorphism and CAD susceptibility,<sup>[18]</sup> and another reported the association between the Gly82Ser polymorphism and susceptibility to CAD and IS.<sup>[21]</sup> Thus, 18 studies were eligible for our meta-analysis. There were 12 and 6 studies concerning the association between the Gly82Ser polymorphism and susceptibility to CAD and IS, respectively. The countries in which these studies were conducted included the United States, South Korea, China, and Turkey. Two articles reported 2 separate studies. Three studies did not satisfy the HWE for the control group.<sup>[2,3,26,27]</sup>

### 3.2. Association between the *RAGE* Gly82Ser polymorphism and susceptibility to CAD

All studies analyzed indicated an increased risk associated with the Gly82Ser polymorphism and CAD susceptibility in recessive and homozygous genetic models (SS vs GS+GG: OR = 1.34, 95% CI: 1.09–1.64; SS vs GG: OR = 1.38, 95% CI: 1.12–1.71). No significant associations were observed between the Gly82Ser polymorphism and CAD susceptibility in dominant, heterozygous, and allele genetic models. Heterogeneity inspection showed high between-study heterogeneity under dominant, heterozygous, and allele genetic models. Subgroup analysis stratified by simple size indicated that large sample sizes, rather than small sample sizes, showed a significant association between the Gly82Ser polymorphism and CAD susceptibility under recessive and homozygous genetic models. Stratification analysis stratified by ethnicity also suggested the existence of a significant association between the Gly82Ser polymorphism and CAD risk in the Chinese population under all tested models except the heterozygous genetic model (Table 2; Fig. 2).

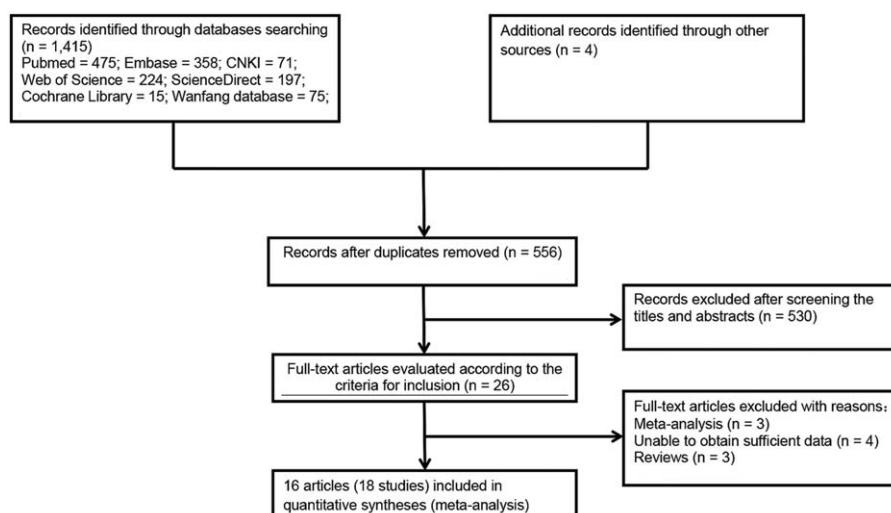


Figure 1. Flow diagram of the literature selection process. CNKI = Chinese National Knowledge Infrastructure Database.

### 3.3. Association between the RAGE Gly82Ser polymorphism and susceptibility to IS

Meta-analysis of the RAGE Gly82Ser polymorphism showed an elevated risk of IS in all tested models except the heterozygous genetic model (GS + SS vs GG: OR = 1.20, 95% CI: 1.04–1.38; SS vs GS + GG: OR = 2.20, 95% CI: 1.74–2.78; SS vs GG: OR = 2.23, 95% CI: 1.72–2.91; S vs G: OR = 1.32, 95% CI: 1.05–1.65). Heterogeneity inspection showed high between-study heterogeneity under dominant, heterozygous, and allele genetic models. When we conducted subgroup analysis by ethnicity, significant associations were observed in the Chinese population under all tested models except heterozygous genetic model, with a reduction in heterogeneity. Stratification by sample size indicated that the polymorphism of Gly82Ser was significantly associated with IS risk for small sample sizes under

dominant, recessive, homozygous, and allele genetic models, with low between-study heterogeneity (Table 2; Fig. 3).

### 3.4. Sensitivity analysis

The influence of each study on the pooled ORs and 95% CIs was evaluated by excluding each study at a time. No individual study significantly affected the OR (Fig. 4).

### 3.5. Publication bias

Funnel plots and Egger linear regression tests were performed to assess the publication bias of the included studies. The funnel plot appeared to be symmetrical (Fig. 5) and no statistically significant asymmetry was observed by Egger linear regression test for CAD (GS + SS vs GG,  $P_{Egger} = 0.094$ ). Because of the limited number of

**Table 1**  
Characteristics of eligible studies included in the meta-analysis.

References	Country	Region	Disease	Genotyping methods	Sample size, cases/controls	Cases, GG/GS/SS	Controls, GG/GS/SS	PHWE
Hofmann et al <sup>[19]</sup>	The USA	America	CAD	PCR-RFLP	132/1500	123/8/1	1380/120/0	0.760
Zee et al <sup>[21]</sup>	The USA	America	CAD	TaqMan	341/341	314/27/0	311/30/0	0.395
Yoon et al <sup>[20]</sup>	South Korea	Asia	CAD	TaqMan	747/802	562/173/12	560/229/13	0.055
Lu et al <sup>[23]</sup>	China	Asia	CAD	PCR-RFLP	214/352	127/81/6	210/140/7	0.003
Peng et al <sup>[25]</sup>	China	Asia	CAD	PCR-RFLP	370/370	234/115/21	223/138/9	0.200
Zhi and Liu <sup>[24]</sup>	China	Asia	CAD	PCR-RFLP	707/422	405/284/18	281/133/8	0.083
Gao et al <sup>[18]</sup>	China	Asia	CAD	PCR-RFLP	175/170	91/77/7	127/41/2	0.514
Gao et al <sup>[18]</sup>	China	Asia	CAD	PCR-RFLP	155/200	92/58/5	140/55/5	0.884
Lu et al <sup>[32]</sup>	China	Asia	CAD	PCR-RFLP	270/112	170/85/15	72/33/7	0.238
Aydogan et al <sup>[26]</sup>	Turkey	Europe	CAD	PCR-RFLP	87/52	52/34/1	24/28/0	0.007
Kucukhuseyin et al <sup>[27]</sup>	Turkey	Europe	CAD	PCR-RFLP	113/55	52/60/1	26/29/0	0.008
Yu et al <sup>[17]</sup>	China	Asia	CAD	PCR-LDR	1142/1106	482/507/153	496/489/121	>0.050
Gao et al <sup>[28]</sup>	China	Asia	IS	PCR-RFLP	46/50	22/24/0	28/21/1	0.190
Zee et al <sup>[21]</sup>	The USA	America	IS	TaqMan	259/259	248/9/2	237/22/0	0.475
Gao et al <sup>[29]</sup>	China	Asia	IS	PCR-RFLP	261/50	114/144/3	28/21/1	0.189
Zhu <sup>[30]</sup>	China	Asia	IS	PCR	1034/1015	655/326/53	670/320/25	0.066
Cui et al <sup>[22]</sup>	China	Asia	IS	PCR-RFLP	384/425	91/149/144	135/197/93	0.188
Sheng et al <sup>[31]</sup>	China	Asia	IS	PCR-RFLP	124/125	36/33/55	44/52/29	0.081

CAD = coronary artery disease, HWE = Hardy–Weinberg equilibrium, IS = ischemic stroke, PCR-LDR = polymerase chain reaction-ligase detection reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

**Table 2**

**Summary of meta-analysis of the association between the Gly82Ser polymorphism and coronary artery disease and ischemic stroke.**

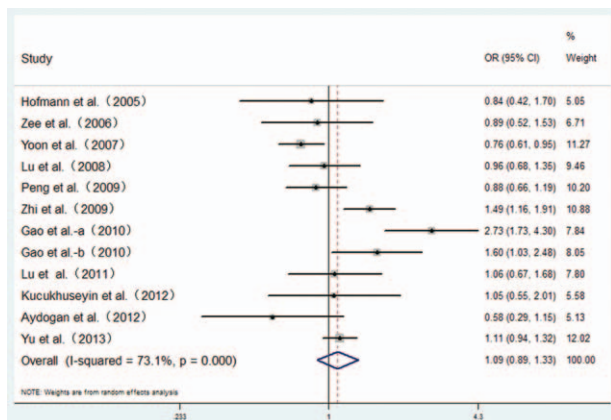
Genetic model	Overall and subgroup	CAD				IS			
		N	OR (95% CI)	I <sup>2</sup> , %	P <sub>Heterogeneity</sub>	N	OR (95% CI)	I <sup>2</sup> , %	P <sub>Heterogeneity</sub>
GS+SS versus GG	Overall	12	1.09 (0.89–1.33)	73	0.000	6	1.20 (1.04–1.38)	48	0.087
	All in HWE	9	1.16 (0.91–1.47)	78	0.000	6	1.20 (1.04–1.38)	48	0.090
	Large sample	7	0.99 (0.82–1.21)	66	0.007	3	1.16 (1.00–1.35)	75	0.020
	Small sample	5	1.28 (0.79–2.07)	77	0.002	3	1.44 (1.01–2.07)	0	0.870
	Chinese	7	1.27 (1.01–1.61)	75	0.000	5	1.24 (1.08–1.44)	0	0.480
	Non-Chinese	5	0.79 (0.65–0.94)	0	0.760	1	0.48 (0.23–1.01)	N/A	N/A
SS versus GS+GG	Overall	12	1.34 (1.09–1.64)	0	0.610	6	2.20 (1.74–2.78)	0	0.800
	All in HWE	9	1.33 (1.08–1.64)	22	0.250	6	2.20 (1.74–2.78)	0	0.800
	Large sample	7	1.34 (1.07–1.66)	13	0.330	3	2.16 (1.67–2.80)	0	0.860
	Small sample	5	1.35 (0.71–2.55)	0	0.690	3	2.38 (1.41–4.01)	0	0.380
	Chinese	7	1.35 (1.09–1.63)	0	0.600	5	2.19 (1.73–2.76)	0	0.730
	Non-Chinese	5	1.23 (0.62–2.44)	11	0.340	1	5.04 (0.24–105.47)	N/A	N/A
GS versus GG	Overall	12	1.06 (0.86–1.31)	73	0.001	6	0.77 (0.45–1.35)	86	0.000
	All in HWE	9	1.13 (0.88–1.44)	79	0.000	6	0.77 (0.45–1.35)	86	0.000
	Large sample	7	0.96 (0.78–1.16)	67	0.005	3	0.50 (0.19–1.33)	93	0.000
	Small sample	5	1.27 (0.79–2.04)	75	0.003	3	1.22 (0.74–2.01)	39	0.190
	Chinese	7	1.24 (0.97–1.60)	76	0.000	5	0.87 (0.48–1.59)	88	0.000
	Non-Chinese	5	0.77 (0.64–0.93)	0	0.750	1	0.39 (0.18–0.87)	N/A	N/A
SS versus GG	Overall	12	1.38 (1.12–1.71)	0	0.470	6	2.23 (1.72–2.91)	0	0.930
	All in HWE	9	1.38 (1.11–1.72)	27	0.210	6	2.23 (1.72–2.91)	0	0.930
	Large sample	7	1.37 (1.09–1.72)	22	0.270	3	2.27 (1.69–3.05)	0	0.870
	Small sample	5	1.51 (0.79–2.87)	0	0.520	3	2.10 (1.16–3.81)	0	0.610
	Chinese	7	1.41 (1.13–1.76)	0	0.570	5	2.22 (1.70–2.89)	0	0.900
	Non-Chinese	5	3.36 (0.57–2.36)	35	0.200	1	4.78 (0.23–100.06)	N/A	N/A
S versus G	Overall	12	1.10 (0.94–1.28)	67	0.000	6	1.32 (1.05–1.65)	63	0.020
	All in HWE	9	1.15 (0.96–1.38)	73	0.000	6	1.32 (1.05–1.65)	63	0.020
	Large sample	7	1.04 (0.89–1.20)	58	0.030	3	1.20 (0.84–1.69)	82	0.004
	Small sample	5	1.24 (0.85–1.81)	73	0.005	3	1.52 (1.17–1.98)	0	0.520
	Chinese	7	1.23 (1.04–1.46)	42	0.006	5	1.41 (1.17–1.65)	49	0.100
	Non-Chinese	5	0.83 (0.71–0.98)	0	0.830	1	0.58 (0.29–1.16)	N/A	N/A

CAD = coronary artery disease, CI = confidence interval, HWE = Hardy–Weinberg equilibrium, IS = ischemic stroke, N = number of studies, N/A = not applicable, OR = odds ratio, P<sub>Heterogeneity</sub> = P value for heterogeneity.

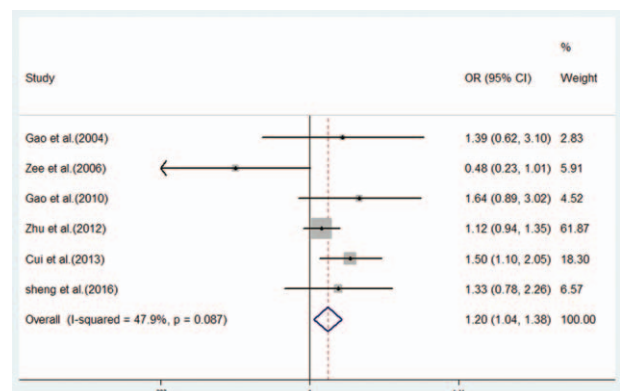
the studies included in IS, the power of the funnel plots for detecting bias will be low.<sup>[33]</sup> Consequently, only the Egger linear regression test was used to evaluate the publication bias for IS (GS+SS vs GG, P=0.426).

**4. Discussion**

The current meta-analysis has consolidated and reanalyzed 18 eligible studies of the effect of the Gly82Ser polymorphism on the incidence of CAD and IS. All of the results suggest that the RAGE Gly82Ser polymorphism is associated with an increased risk of

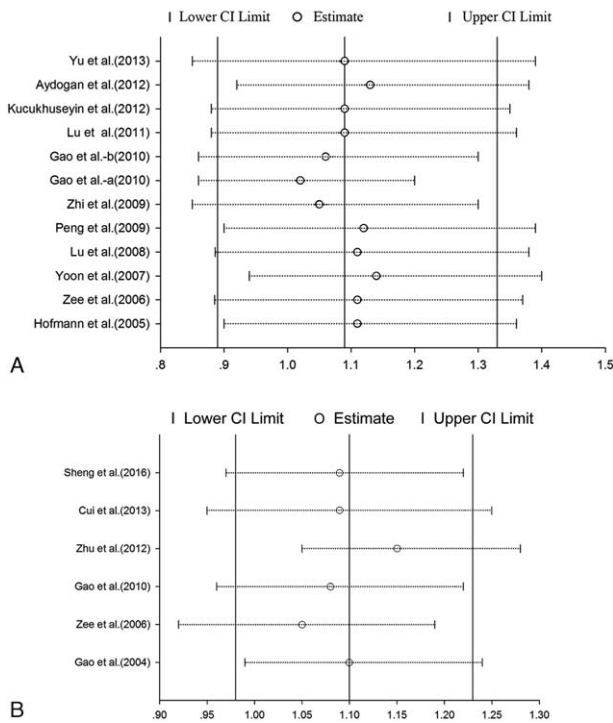


**Figure 2.** Forest plot from the meta-analysis for the association of the RAGE Gly82Ser polymorphism and CAD risk in dominant genetic model (GS+SS vs GG). Compared to the GG genotype, GS+SS genotypes showed no increased risk of CAD. CAD = coronary artery disease, CI = confidence interval, OR = odds ratio.



**Figure 3.** Forest plot from the meta-analysis on the association between the RAGE Gly82Ser polymorphism and IS risk in dominant genetic model (GS+SS vs GG). Compared to the GG genotype, GS+SS genotypes showed an increased risk of IS. CI = confidence interval, IS = ischemic stroke, OR = odds ratio.

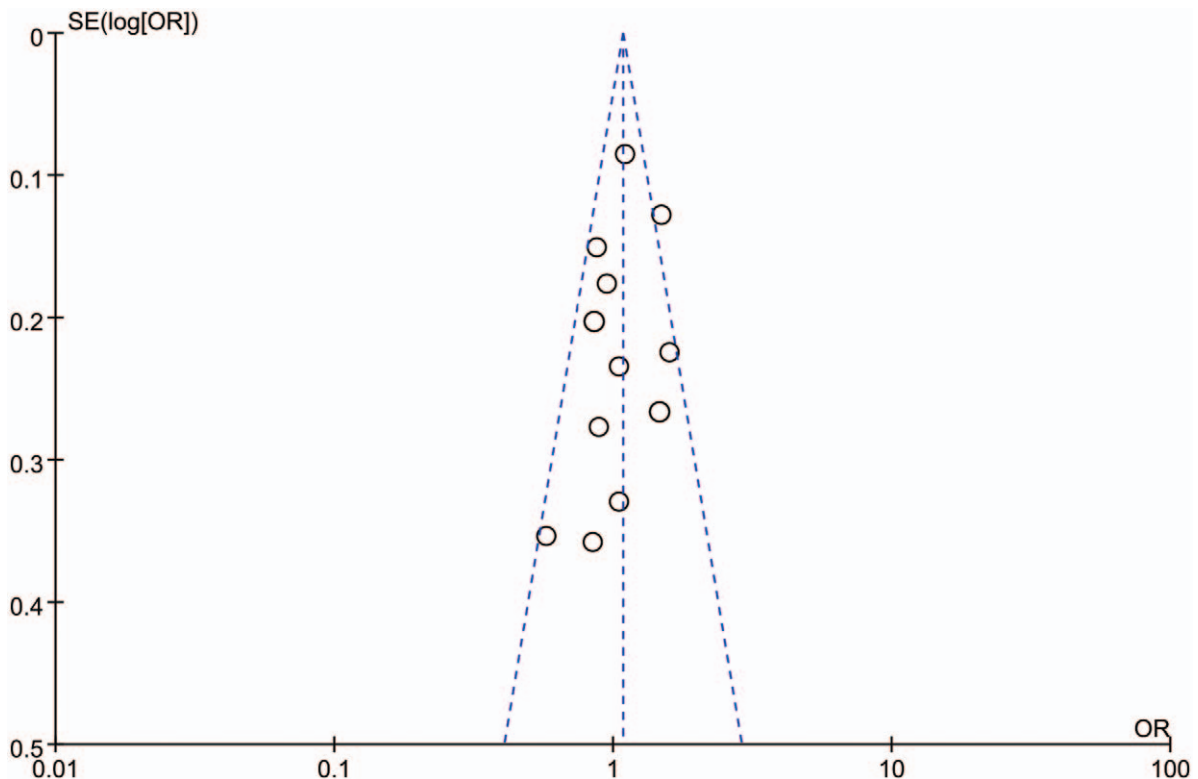




**Figure 4.** (A and B) Sensitivity analysis of pooled OR coefficients on the correlation between the *RAGE* Gly82Ser polymorphism and susceptibility to CAD (A) and IS (B). Results were evaluated by excluding each study 1 at a time. CAD = coronary artery disease, CI = confidence interval, IS = ischemic stroke, OR = odds ratio.

CAD and IS. Furthermore, subgroup analysis indicated that the subjects with the Ser82 allele were at higher risk of CAD and IS in the Chinese population, than in the non-Chinese population. On the other hand, stratified analysis by ethnicity was successfully applied to relieve heterogeneity bias in the polymorphism analysis within the Chinese population, suggesting that ethnicity may potentially be the source of the heterogeneity. Although 3 studies did not comply with HWE in the non-CAD controls, removing these studies during the stratification analysis by HWE status did not alter the conclusions made in the meta-analysis. Sensitivity analysis also confirmed the stability of our results.

Atherosclerosis is the main cause of CAD and IS.<sup>[2]</sup> Although much of work has identified the significant association between *RAGE* gene polymorphisms and diabetic atherosclerosis,<sup>[34,35]</sup> it is difficult to draw a causal link between *RAGE* gene polymorphisms and the risk of CAD and IS. Sustained hyperglycemia could lead to the formation and accumulation of AGEs, and *RAGE* mediates most of the adverse effects of AGEs.<sup>[36]</sup> The AGE-*RAGE* interaction alters cellular signaling, promotes gene expression, and enhances the release of proinflammatory molecules, involved in the pathogenesis of vascular diabetic complications.<sup>[37]</sup> Previous studies have identified that significantly higher levels of *RAGE* are observed in human atherosclerotic plaques.<sup>[38]</sup> The Gly82Ser mutation exhibits potentially enhanced ligand-binding affinity, which may predispose or exasperate diabetic atherosclerosis.<sup>[16,39]</sup> Meanwhile, evidence has indicated that pharmacological blockage of *RAGE*, or genetic deletion, resulted in significant suppression of atherosclerosis progression.<sup>[34,40]</sup> In our study, we found its efforts on CAD and IS, especially in the Chinese population, and the reason may partly depend on genetic diversity among different ethnic groups.<sup>[41]</sup>



**Figure 5.** Funnel plot for studies investigating the effect of the *RAGE* Gly82Ser polymorphism on the risk of CAD under the domain model. The studies of the *RAGE* Gly82Ser polymorphism were symmetrically distributed within the funnel plot. CAD = coronary artery disease, OR = odds ratio; SE = standard error.

Although several relevant meta-analyses have analyzed the relationship between the Gly82Ser polymorphism and CAD susceptibility,<sup>[42,43]</sup> there are some differences. More eligible studies were included in our study and 5 genetic models gave us a comprehensive understanding of the relationship between the Gly82Ser polymorphism and susceptibility to CAD. Furthermore, the present meta-analysis is the first one to assess the association between the Gly82Ser polymorphism and IS risk.

Several limitations of our meta-analysis should be mentioned. First, heterogeneity in our study may influence the reliability of our results, although subgroup analysis was performed to detect the source of heterogeneity and sensitivity analysis was used to assess the stability of the results. Second, the data extracted from each record were based on unadjusted estimates, which may lead to misleading results. Third, the language of eligible studies was limited to English and Chinese, and despite no evidence of publication bias from our statistical tests, some may remain.

In conclusion, our meta-analysis supports an association between the RAGE Gly82Ser polymorphism and the risk of CAD and IS, especially in the Chinese population. Although subgroup analysis was used to investigate the significant heterogeneity among studies, these results should be interpreted with caution. Further well-designed studies with large sample sizes are needed to validate the present results.

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