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Original Article

Intercellular adhesion molecule 1 rs5498 A>G polymorphism is associated with coronary artery disease risk: a meta-analysis

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Abstract: Objectives: The association of *intercellular adhesion molecule 1* (*ICAM-1*) rs5498 A>G (K469E) polymorphism with coronary artery disease (CAD) susceptibility has been widely explored; however, these studies have yielded conflicting results. To address the correlation more precisely, we performed this pooled analysis. Design and Methods: EmBase, PubMed and China Biology Medicine (CBM) databases were independently searched by two authors for eligible studies before January 15, 2016. Fixed-effects or random-effects model was used to calculate the odds ratios (ORs) and their 95% confidence intervals (CIs) when appropriate. Results: Meta-analysis of total studies demonstrated that variants of ICAM-1 rs5498 A>G were significantly correlated with the decreased susceptibility of CAD. Subgroup analyses by different types of CAD and different populations also identified a significant correlation. In addition, sensitivity analysis further suggested a relationship of ICAM-1 rs5498 A>G polymorphism with CAD risk. Conclusions: In summary, the present meta-analysis of available data indicates that the ICAM-1 rs5498 A>G polymorphism probably decreases the susceptibility of CAD, especially in Caucasians and myocardial infarction subgroups.

Keywords: Polymorphism, *ICAM-1*, coronary artery disease, myocardial infarction susceptibility, meta-analysis

Introduction

Coronary artery disease (CAD) is the leading cause of death in developed countries, and the prevalence is expected to promote worldwide [1]. The incidence and mortality rate of CAD boost largely for aging of the population, as well as an increasing prevalence of established CAD-related lifestyles, such as physical inactivity, heavy smoking, drinking and 'westernized' diets. However, the mechanism of atherosclerosis is very complicated and remains unclear, although it has been considered a chronic inflammation process.

The *intercellular adhesion molecule 1* (*ICAM-1*) gene, a member of the immunoglobulin (Ig) superfamily, is located on chromosome 19q-13.3. ICAM-1 is a cell adhesion molecule and plays an important role in leukocytes adhering to the vascular endothelial cells. ICAM-1 has five extracellular IgG-like binding domains on the surface of cell, a transmembrane region and a cytoplasmic tail that correlate with some cytoskeletal linker proteins [2-4]. ICAM-1 is presented on the surface of a few cells including fibroblasts, leukocytes, endothelial cells, epithelial cells and keratinocytes [5]. An increased level of soluble ICAM-1 (sICAM) was observed in cases with confirmed CAD or cerebral atherosclerosis [6-8]. ICAM-1 mediates the cell-cell and cell-extracellular matrix reciprocities, and then induces the invasion of multiple activated cells into damaged tissue during the immune and inflammatory responses. These findings suggested that ICAM-1 exerted a vital role in the development of the inflammation reaction, atherosclerosis and thrombosis [9].

Accumulating evidences indicate single nucleotide polymorphisms (SNPs) of *ICAM-1* gene may play crucial roles in atherosclerotic processes. *ICAM-1* gene is polymorphic, and a lot of SNPs have been identified, such as rs5498 A>G (K469E), rs1799969 G>A, rs3093030 C>T, rs5030382 A>G, rs281432 C>G, rs5496 A>G, rs5490 A>C and rs281428 C>T polymorphisms etc. Among them, the rs5498 A>G (K469E) polymorphism of *ICAM-1* gene was the most extensively studied for its implication in CAD risk. Some previous studies showed that *ICAM-1* rs5498 A>G polymorphism was involved in the etiology of CAD and myocardial infarction (MI). However, the findings of previous studies remain inconsistent rather than conclusive. Considering the important role of *ICAM-1* rs5498 A>G polymorphism in atherosclerotic processes, we conducted a pooled analysis on all available data to assess the CAD risk correlated with *ICAM-1* rs5498 A>G polymorphism. To the best of our knowledge, the present meta-analysis is the most comprehensive study with respect to the relationship of *ICAM-1* rs5498 A>G variants with CAD risk.

Materials and methods

Search strategy

We carried out an extensively online search of the PubMed, Embase and China Biology Medicine (CBM) databases from the inception up to January 15, 2016. Search terms for *ICAM-1* polymorphism and CAD risk were: 'Intercellular adhesion molecule-1' or 'intercellular adhesion molecule 1' or 'ICAM 1' or 'ICAM-1', 'SNP' or 'polymorphism' or 'variant' or 'mutation' and 'coronary artery disease' or 'CAD' or 'coronary heart disease' or 'CHD' or 'myocardial infarction' or 'MI'. No language restriction was imposed. In addition, all references cited in the retrieved publications were manually searched to identify additional publications.

Inclusion and exclusion criteria

The major selection criteria were: (1) case-control studies which evaluated the relationship of *ICAM-1* rs5498 A>G polymorphism with CAD susceptibility, (2) genotype distribution of controls consistent with Hardy-Weinberg Equilibrium (HWE), (3) containing data on genotype and allele frequency for estimating odds ratios (ORs) with 95% confidence intervals (95% CIs). Accordingly, publications without sufficient data, duplicated data, not case-control study design, reviews, meta-analysis and comments were excluded.

Data extraction

Two reviewers (X. Zheng and W. Tang) extracted the corresponding information independently. Disagreements were resolved based on discussion among all authors. The extracted information contained: the surname of first author, year of publication, country, ethnicity, type of CAD, genotyping method and genotype frequencies.

Statistical analysis

The association of *ICAM-1* rs5498 A>G variants with CAD risk was assessed by calculating ORs with 95% CIs, based on the genotype number in cases and controls. The pooled ORs and their CIs were calculated for four genetic models, such as dominant model, recessive model, homozygote comparison and allele comparison model. A Chi-square-based statistic I^2 test was used to evaluate heterogeneity [10] and an I^2<25% indicates low heterogeneity, 25%≤I^2≤ 50% indicates moderate heterogeneity and I^2>50% indicates large heterogeneity [11]. Mantel-Haenszel method (the fixed effects model) was harnessed when there was no significant heterogeneity [12]; otherwise, Der Simonian-Laird method (the random effects model) was used [13]. One-way sensitivity analysis was performed by omitting each individual study at a time from the total and re-calculating the remainder [21]. Sub-group analyses were performed to identify the source of heterogeneity, such as ethnicity, the type of CAD, sample size and source of control. Publication bias was assessed with Begg's funnel plot and Egger's regression method [14] (P<0.05 was defined representative of statistical publication bias). All p values were two-sided. All available data were analyzed using STATA version 12.0 software (Stata Corp, College Station, Texas USA).

Results

Characteristics

In total, 259 potentially relevant articles were retrieved from the initial search. **Figure 1** showed the detailed screening procedure. Finally, a total of sixteen publications with eigh-

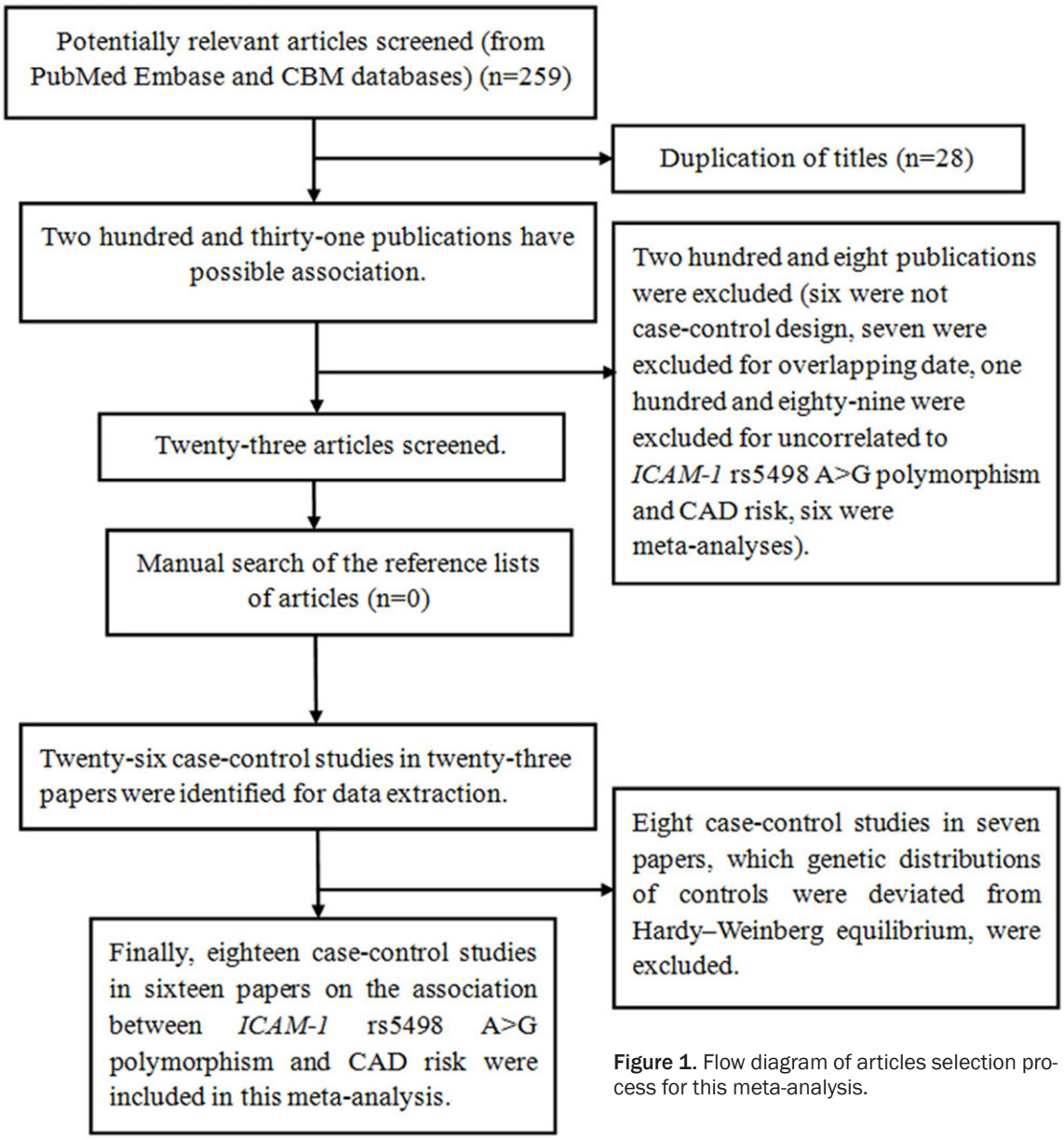

Figure 1. Flow diagram of articles selection process for this meta-analysis.

teen comparisons were identified [15-30]. Of these articles, eight investigated MI [15, 18-23, 25], nine investigated non-MI [16, 17, 21, 22, 26-30] and one investigated mixed CAD [24]. Among eighteen case-control studies, ten were from Caucasians [15, 18-23, 30] and eight were from Asians [16, 17, 24-29]. The detailed characteristics of these eligible studies and the distribution of *ICAM-1* rs5498 A>G variants as well as alleles are shown in **Tables 1** and **2**, respectively.

Quantitative synthesis

Eighteen eligible studies with 3,484 cases and 3,911 controls met the major inclusion criteria. The results of the meta-analysis on *ICAM-1* rs5498 A>G polymorphism and CAD risk are listed in **Table 3**. Overall, there was a significantly decreased risk of CAD risk in four genetic models: OR, 0.76; 95% CI, 0.62-0.94; *P*=0.011 for G vs. A; OR, 0.63; 95% CI, 0.42-0.93; *P*=0.019 for GG vs. AA; OR, 0.77; 95% CI, 0.61-0.98; *P*=0.030 for GG+AG vs. AA and OR, 0.70; 95% CI, 0.51-0.95; *P*=0.023 for AG vs. AA (**Figure 2** and **Table 3**). In a subgroup analysis by ethnicity, a significantly decreased CAD risk was found among Caucasians (OR, 0.64; 95% CI, 0.46-0.89; *P*=0.008 for G vs. A; OR, 0.48; 95% CI, 0.26-0.89; *P*=0.020 for GG vs. AA; OR, 0.67; 95% CI, 0.48-0.95; *P*=0.023 for GG+AG

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

Study	Year	Country	Ethnicity	Type	No. of cases/ controls	Source of control	Genotype Method
Nasibullin *et al.* [15]	2016	Russian Federation	Caucasians	Myocardial infarction	315/286	HB	PCR-RFLP
Chou *et al.* [16]	2015	China	Asians	Coronary artery disease	339/186	HB	TaqMan
Luo *et al.* [17]	2014	China	Asians	Coronary artery disease	674/779	PB	PCR-RFLP
Gazi *et al.* [18]	2014	Turkey	Caucasians	Myocardial infarction	48/67	HB	Real-time PCR
Buraczynska *et al.* [19]	2012	Poland	Caucasians	Myocardial infarction	118/824	HB	Nested PCR
Mohamed *et al.* [21]	2010	Egypt	Caucasians	Coronary artery disease	127/50	HB	PCR-RFLP
Mohamed *et al.* [21]	2010	Egypt	Caucasians	Myocardial infarction	73/50	HB	PCR-RFLP
Sakowicz *et al.* [20]	2010	Poland	Caucasians	Myocardial infarction	163/140	PB	PCR-RFLP
Aminian *et al.* [22]	2007	Iran	Caucasians	Myocardial infarction	152/140	HB	PCR-RFLP
Aminian *et al.* [22]	2007	Iran	Caucasians	Coronary artery disease	148/140	HB	PCR-RFLP
Milutinovic *et al.* [23]	2006	Slovenia	Caucasians	Myocardial infarction	152/215	HB	PCR-RFLP
Zhang *et al.* [24]	2006	China	Asians	Mixed type	173/141	HB	PCR-RFLP
Wang *et al.* [25]	2005	China	Asians	Myocardial infarction	165/199	HB	PCR-RFLP
Wang *et al.* [26]	2005	China	Asians	Coronary artery disease	211/206	HB	PCR-RFLP
Liu *et al.* [27]	2011	China	Asians	Coronary artery disease	312/302	HB	PCR-RFLP
Li *et al.* [28]	2010	China	Asians	Coronary artery disease	93/101	HB	PCR-SSP
Mo *et al.* [29]	2009	China	Asians	Coronary artery disease	97/35	PB	PCR-RFLP
Yusup *et al.* [30]	2009	China	Caucasians	Coronary artery disease	124/50	PB	PCR-RFLP

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PCR-SSP: polymerase chain reaction-sequence specific primer.

Table 2. Distribution of *ICAM-1* polymorphism genotype and allele

Study	Year	Case			Control			Case		Control		HWE
		AA	AG	GG	AA	AG	GG	G	A	G	A	
Nasibullin *et al.* [15]	2016	101	152	62	90	145	51	276	354	247	325	Yes
Chou *et al.* [16]	2015	177	143	19	94	80	12	181	497	104	268	Yes
Luo *et al.* [17]	2014	339	278	57	461	273	45	392	956	363	1195	Yes
Gazi *et al.* [18]	2014	12	27	9	8	33	26	45	51	85	49	Yes
Buraczynska *et al.* [19]	2012	69	44	5	272	379	173	54	182	725	923	Yes
Mohamed *et al.* [21]	2010	23	46	58	2	11	37	162	92	85	15	Yes
Mohamed *et al.* [21]	2010	17	28	28	2	11	37	84	62	85	15	Yes
Sakowicz *et al.* [20]	2010	54	N/A	106*	48	69	14	N/A	N/A	97	165	Yes
Aminian *et al.* [22]	2007	42	77	33	36	69	35	143	161	139	141	Yes
Aminian *et al.* [22]	2007	48	67	33	36	69	35	133	163	139	141	Yes
Milutinovic *et al.* [23]	2006	47	72	33	65	109	41	138	166	191	239	Yes
Zhang *et al.* [24]	2006	111	52	10	69	59	13	72	274	85	197	Yes
Wang *et al.* [25]	2005	96	61	8	91	90	18	77	253	126	272	Yes
Wang *et al.* [26]	2005	117	82	12	92	95	19	106	316	133	279	Yes
Liu *et al.* [27]	2011	124	84	17	101	103	26	118	332	155	305	Yes
Li *et al.* [28]	2010	47	39	7	52	36	13	53	133	62	140	Yes
Mo *et al.* [29]	2009	15	35	47	12	12	11	129	65	34	36	Yes
Yusup *et al.* [30]	2009	55	54	15	21	26	3	84	164	32	68	Yes

*The combined number of GG and AG genotypes; HWE: Hardy-Weinberg equilibrium; N/A: not available.

vs. AA and OR, 0.59; 95% CI, 0.36-0.96; *P*= 0.035 for GG vs. AG+AA), but not Asians (**Figure 2** and **Table 3**). In a subgroup analysis by the type of CAD, *ICAM-1* rs5498 A>G polymorphism was correlated with a significantly decreased risk of MI (OR, 0.63; 95% CI, 0.44-0.91; *P*= 0.012 for G vs. A; OR, 0.43; 95% CI, 0.21-0.86; *P*=0.017 for GG vs. AA; OR, 0.67; 95% CI, 0.47-

Table 3. Meta-analysis of the *ICAM*-1 rs5498 A>G polymorphism and CAD risk

	No. of study	G vs. A			GG vs. AA			GG+AG vs. AA			GG vs. AG+AA		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Total	18	0.76 (0.62-0.94)	0.011	<0.001	0.63 (0.42-0.93)	0.019	<0.001	0.77 (0.61-0.98)	0.030	<0.001	0.70 (0.51-0.95)	0.023	<0.001
Ethnicity													
Caucasians	10	0.64 (0.46-0.89)	0.008	<0.001	0.48 (0.26-0.89)	0.020	<0.001	0.67 (0.48-0.95)	0.023	<0.001	0.59 (0.36-0.96)	0.035	<0.001
Asians	8	0.89 (0.68-1.17)	0.415	<0.001	0.80 (0.48-1.34)	0.396	<0.001	0.88 (0.63-1.22)	0.439	<0.001	0.84 (0.58-1.23)	0.381	0.028
Type of CAD													
MI	8	0.63 (0.44-0.91)	0.012	<0.001	0.43 (0.21-0.86)	0.017	<0.001	0.67 (0.47-0.97)	0.033	<0.001	0.54 (0.31-0.93)	0.028	<0.001
Non-MI	9	0.90 (0.68-1.17	0.421	<0.001	0.85 (0.51-1.41)	0.525	<0.001	0.90 (0.66-1.24)	0.537	<0.001	0.86 (0.57-1.29)	0.455	0.002
Sample size													
>500	4	0.99 (0.75-1.31)	0.954	0.001	1.01 (0.62-1.65)	0.972	0.024	0.97 (0.68-1.39)	0.885	0.001	1.12 (0.88-1.43)	0.367	0.142
≤500	14	0.69 (0.54-0.89)	0.004	<0.001	0.52 (0.32-0.86)	0.010	<0.001	0.70 (0.54-0.92)	0.012	<0.001	0.60 (0.41-0.89)	0.011	<0.001
Source of control													
Hospital based	14	0.68 (0.55-0.82)	<0.001	<0.001	0.50 (0.35-0.72)	<0.001	<0.001	0.67 (0.54-0.83)	<0.001	0.001	0.58 (0.43-0.80)	0.001	<0.001
Population based	4	1.37 (1.17-1.59)	<0.001	0.208	1.90 (1.31-2.74)	0.001	0.465	1.38 (1.15-1.65)	< 0.001	0.184	1.65 (1.16-2.33)	0.005	0.730

CAD: coronary artery disease. MI: myocardial infarction.

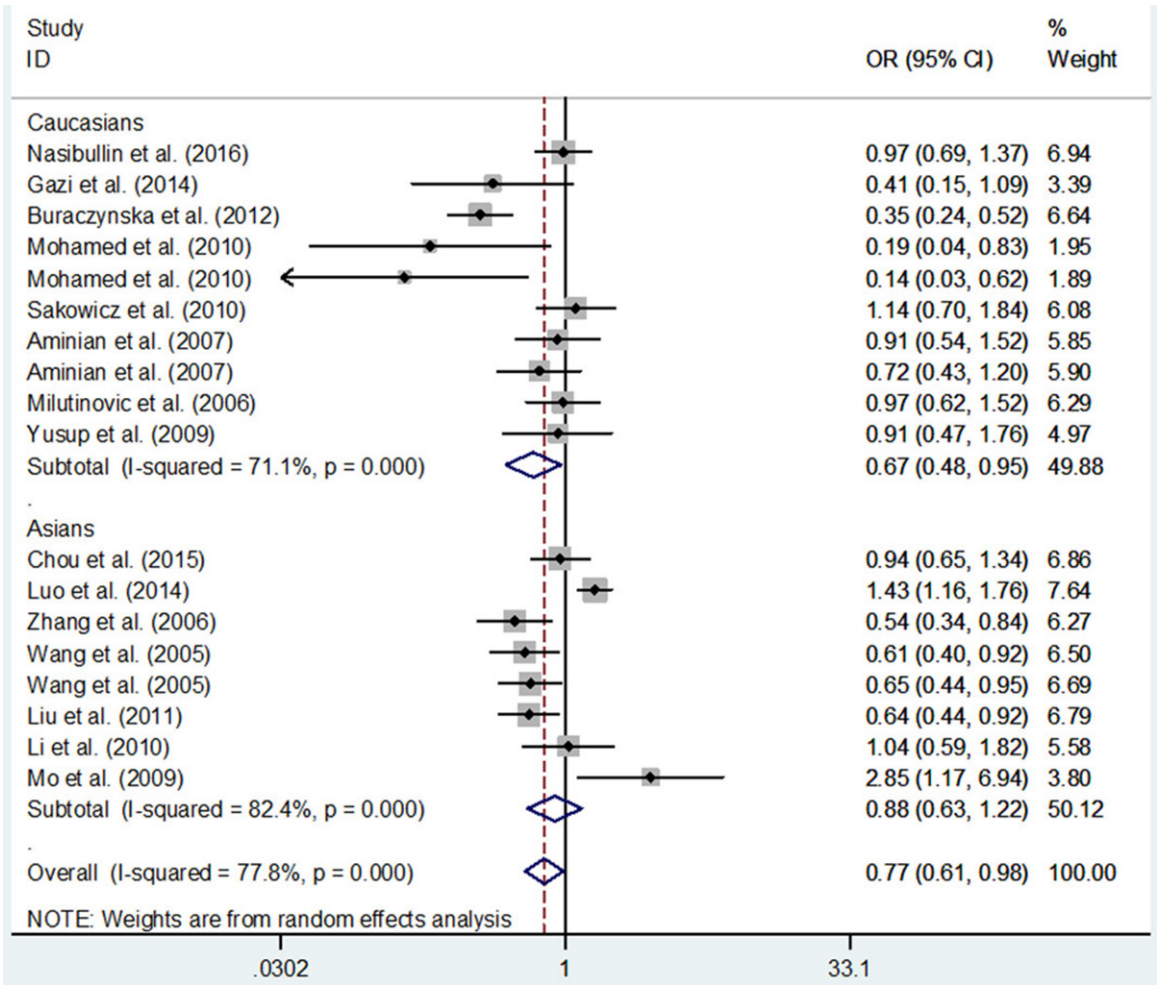

Figure 2. Meta-analysis with a random-effects model for the relationship between *ICAM-1* rs5498 A>G polymorphism and CAD risk in different ethnicity (GG+AG vs. AA genetic model).

0.97; *P*=0.033 for GG+AG vs. AA and OR, 0.54; 95% CI, 0.31-0.93; *P*=0.028 for GG vs. AG+AA), but not of non-MI (**Figure 3** and **Table 3**).

Tests for publication bias

We carrieded out Begg's funnel plot and Egger's test to measure the publication bias of eligible studies. No evidence of publication bias was found in our findings (GG+AG vs. AA: Begg's test *P*=0.325, Egger's test *P*=0.059) (**Figure 4**).

Tests for sensitivity analyses

Influence of an individual case-control study involved in the present meta-analysis on the pooled ORs and CIs was evaluated by removing each study in turn and repeating the meta-analysis. As shown in **Figure 5**, the corresponding pooled ORs and CIs were not materially altered (data not shown).

Tests for heterogeneity

As shown in **Table 3**, significant heterogeneity between included studies was found in overall comparisons. Thus, we examined the source of heterogeneity by subgroup analysis (**Table 3**). The results indicated that Caucasians, MI, small sample size and hospital-based subgroups may contribute to the major source of heterogeneity (**Table 3**).

Discussion

ICAM-1 induces adhesion of circulating leukocytes to activated endothelium, and migration to the vascular intima, which is a vital patho-

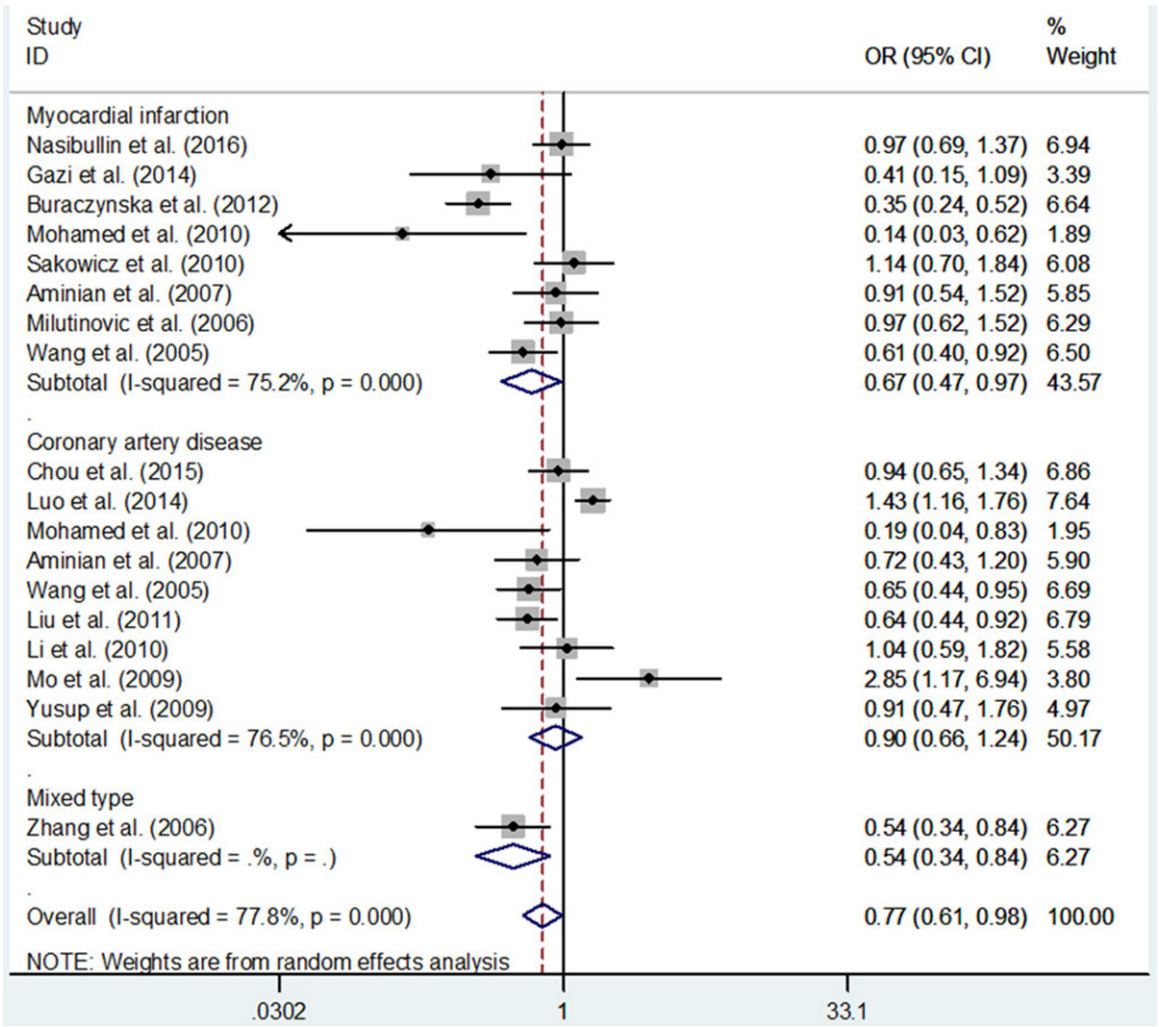

Figure 3. Meta-analysis with a random-effects model for the relationship between *ICAM-1* rs5498 A>G polymorphism and CAD risk in different CAD type (GG+AG vs. AA genetic model).

genic process of inflammatory diseases, atherosclerosis and thrombosis [31-34]. During inflammation reaction, sICAM-1 is produced by several cells, such as fibroblasts, leukocytes, endothelial cells and epithelial cells, which is activated by multiple cytokines and then produce a number of membrane ICAM-1 [35]. The level of serum sICAM-1 was relatively low in healthy controls; however, it was elevated with acute coronary syndrome [6, 36].

Recently, accumulating studies focused on the relationship between *ICAM-1* rs5498 A>G variants and CAD risk. In the present study, we conducted a meta-analyses to assess the association between CAD risk and *ICAM-1* rs5498 A>G polymorphism. The findings suggested that the *ICAM-1* rs5498 G allele was a protective factor for CAD. Several meta-analyses have been performed on this SNP correlated with the susceptibility of CAD [37-40]. However, none of them have comprehensively covered all eligible studies on *ICAM-1* rs5498 A>G polymorphism. In the present pooled analysis, we included all the potential papers published to date on this SNP correlated with CAD risk, and thus incorporated more eligible case-control studies than the previously published studies. To the best of our knowledge, our study was the most comprehensive meta-analysis in this field.

The rs5498 A>G polymorphism, a SNP in exon 6 of *ICAM-1*, encodes a glutamate→lysine substitution at amino acid residue 469 (E469K). The previous study indicated that *ICAM-1* rs5498 A>G polymorphism affected mRNA

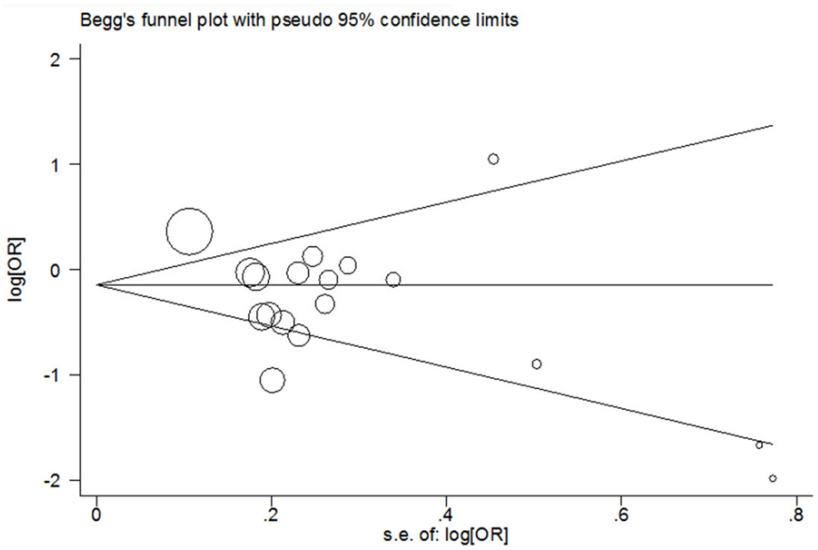

Figure 4. Begg's funnel plot of meta-analysis of the relationship between the *ICAM-1* rs5498 A>G polymorphism and the risk of CAD (GG+AG vs. AA genetic model).

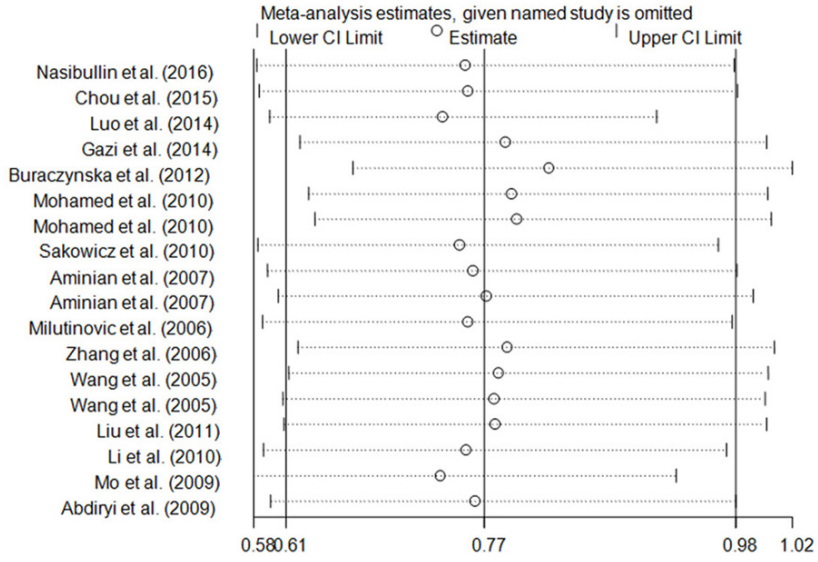

Figure 5. Sensitivity analysis of the influence of GG+AG vs. AA genetic model in CAD meta-analysis (random-effects estimates for *ICAM-1* rs5498 A>G polymorphism).

splicing patterns which resulted in AA genotype may have a lower sensitivity to apoptosis than GG genotype [41], then altered the ability of cell-cell interactions and inflammatory response. In the present study, we found that *ICAM-1* rs5498 A>G locus conferred the decreased susceptibility to CAD, suggesting the presence of the G allele, which was correlated with apoptosis, might decrease the susceptibility of CAD. In a subgroup analysis by ethnicity, a significant association between *ICAM-1* rs5498 A>G polymorphism and the decreased CAD risk was found in Caucasians, but not Asians. Results of the present study indicated the influence of *ICAM-1* rs5498 A>G polymorphism and diversity in different races to the risk of CAD. In a subgroup analysis by the type of CAD, *ICAM-1* rs5498 A>G polymorphism was correlated with the decreased risk of MI, but not of non-MI. We first confirmed that *ICAM-1* rs5498 A>G polymorphism conferred a decreased risk to MI. However, these findings should be interpreted with caution. For MI, only eight small sample sizes studies with 1186 cases and 1921 controls were included in this meta-analysis, which may have limited power to obtain a real influence. Large heterogeneity also should be considered.

Some cautions of this meta-analysis should be addressed. Firstly, only published papers were pooled together to analyze. Therefore, selection bias may inevitably exist, although no bias was identified in the Begger's funnel plot and Egger's tests. Secondly, due to lack of background data, the results of this meta-analysis were based on the crude estimates. Thirdly, large heterogeneity was found in our study, thus the results should be interpretated with cautions. Fourth, the sample size of the eligible studies was relatively small. Simultaneously, in this meta-analysis, no genome-wide association studies (GWAS) was recruited. Compared to the classical candidate-gene approach, GWAS is a powerful approach to assess the common genetic variants. Finally, in this study, we only focused

on *ICAM-1* rs5498 A>G polymorphism, and did not ponder other locus in *ICAM-1* gene or risk genes.

In summary, the present meta-analysis suggests that the *ICAM-1* rs5498 A>G polymorphism probably decreases the susceptibility of CAD, especially in Caucasians and myocardial infarction subgroups. To further confirm the findings, large-scale epidemiological studies with different ethnic groups assessing gene-environment and gene-gene interactions are needed.

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Disclosure of conflict of interest

None.

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