ICAM-1 gene rs5498 polymorphism decreases the risk of coronary artery disease

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Abstract
Background: Many studies investigated the association between intercellular adhesion molecule 1 (ICAM-1) gene rs5498 polymorphism and the risk of coronary artery disease (CAD). However, the results were inconsistent.
Methods: To clarify convincing association, we conducted a comprehensive meta-analysis by searching in PubMed, Embase, Web of sciences, Sciences citation index, Google scholar, Cochrane Library, and the CNKI databases. Pooled odds ratios (ORs) and 95\% confidence intervals (CIs) were calculated.
Results: A total of 29 case-control studies with 5,494 cases and 6,364 controls for rs5498 polymorphism were included. The studied populations of this meta-analysis included Caucasians and Asians. Meta-analysis showed that rs5498 polymorphism was associated with the decreased risk of CAD. Stratification analysis of ethnicity found that rs5498 polymorphism decreased the risk of CAD among Caucasians, but not among Asians. Stratification by type of CAD revealed that ICAM-1 gene rs5498 polymorphism was also correlated with the decreased risk of myocardial infarction (MI).
Conclusion: In conclusion, this meta-analysis indicates that ICAM-1 gene rs5498 polymorphism decreases the risk of CAD.
Abbreviations: CAD = coronary artery disease, CIs = confidence intervals, ICAM-1 = intercellular adhesion molecule 1, MI = myocardial infarction, ORs = odds ratios, SNP = single nucleotide polymorphism.
Keywords: coronary artery disease, ICAM-1, meta-analysis, polymorphism

1. Introduction
Coronary artery disease (CAD) is a significant risk factor for human life.\textsuperscript{[1]} The main pathogenesis of CAD is atherosclerosis, in which raised areas of degeneration and cholesterol deposits form on the inner surfaces of the arteries obstructing blood flow. Although a chronic inflammation is considered, the mechanism of atherosclerosis is not clear enough to explain. Adhesion molecules are primary markers of endothelial dysfunction, which causes atherosclerosis.\textsuperscript{[2]} It is necessary to investigate the genetic factors of adhesion molecules.

The intercellular adhesion molecule 1 (ICAM-1) is a part of immunoglobulin (IG) superfamily which is a member of adhesion molecules.\textsuperscript{[3]} ICAM-1 is located on chromosome 19, including 7 exons and 6 introns that code a 90-kDa transmembrane glycoprotein. ICAM-1 mediates adhesion of circulating leukocytes to the blood vessel wall and activated endothelium, which is important for pathogenetic processes of atherosclerosis.\textsuperscript{[4]}

ICAM-1 might play a leading role in the development of the inflammation reaction and atherosclerosis.\textsuperscript{[5]} Therefore, it is reasonable to hypothesize that the ICAM-1 may be a candidate gene for CAD susceptibility.
Rs5498 is a single-base A-G transition polymorphism, which is located in exon 6 of the ICAM-1 gene. The missense mutation results in an amino acid substitution from glutamine (E) to lysine (K). Rs5498 polymorphism plays a vital role in the etiology of atherosclerosis.\textsuperscript{[6]} Studies have demonstrated that the risky and protective alleles of rs5498 polymorphism were G and A allele respectively.

Recently, lots of studies provide evidences that single nucleotide polymorphisms (SNPs) of ICAM-1 gene are important for atherosclerotic processes. Among them, the rs5498 (K469E) polymorphism of ICAM-1 gene was the most extensively studied for its implication in CAD and myocardial infarction (MI) risk.\textsuperscript{[7-32]} However, the results of these studies were conflicting and inconclusive because of the clinical heterogeneity, different ethnic populations, and small sample sizes. In order to precisely elucidate the genetic roles for ICAM-1 gene rs5498 polymorphism in the development of CAD, we performed a comprehensive meta-analysis to clarify the association between this SNP and CAD risk.

2. Materials and methods
2.1. Literature search and criteria of inclusion
We searched the PubMed, Embase, Web of sciences, Sciences citation index, Google scholar, Cochrane Library, and CNKI databases to identify studies through July 6, 2018. The following search terms were used: “Intercellular adhesion molecule-1” or “intercellular adhesion molecule 1” or “ICAM-1,” “SNP” or “polymorphism” and “coronary artery disease” or...
Figure 1. Selection for eligible citations included in this meta-analysis.

Table 1

Characteristics of included studies.

| Study           | Year | Nationality | Type                  | No. of cases/controls | Genotype method   |
|-----------------|------|-------------|-----------------------|-----------------------|-------------------|
| Nasibullin et al| 2016 | Russian     | Myocardial infraction | 315/286               | PCR-RFLP          |
| Chou et al      | 2015 | China       | Coronary artery disease | 339/186              | TaqMan            |
| Yang et al      | 2014 | China       | Coronary artery disease | 604/468              | PCR               |
| Luo et al       | 2014 | China       | Coronary artery disease | 674/779              | PCR-RFLP          |
| Gaz et al       | 2014 | Turkey      | Myocardial infraction  | 48/67                 | Real-time PCR     |
| Buraczynska et al| 2012 | Poland      | Myocardial infraction  | 118/824              | Nested PCR        |
| Mohamed et al   | 2010 | Egypt       | Coronary artery disease | 100/50               | PCR-RFLP          |
| Mohamed et al   | 2010 | Egypt       | Myocardial infraction  | 73/50                | PCR-RFLP          |
| Sadowsicz et al | 2010 | Poland      | Myocardial infraction  | 163/140              | PCR-RFLP          |
| Sarecka et al   | 2009 | Poland      | Coronary artery disease | 191/203              | PCR-RFLP          |
| Aminian et al   | 2007 | Iran        | Myocardial infraction  | 148/140              | PCR-RFLP          |
| Aminian et al   | 2007 | Iran        | Myocardial infraction  | 152/140              | PCR-RFLP          |
| Podgoranski et al| 2006 | America     | Myocardial infraction  | 52/382               | MALDI-TOF-MS       |
| Milutinovic et al| 2006 | Slovenia    | Myocardial infraction  | 152/215              | PCR-RFLP          |
| Zak et al       | 2005 | Poland      | Coronary artery disease | 146/121              | PCR-RFLP          |
| Jiang et al     | 2002 | German      | Coronary artery disease | 349/213              | PCR               |
| Jiang et al     | 2002 | German      | Myocardial infraction  | 179/213              | PCR               |
| Luo et al       | 2013 | China       | Coronary artery disease | 245/377              | PCR               |
| Liu et al       | 2011 | China       | Coronary artery disease | 312/302              | PCR-RFLP          |
| Li et al        | 2010 | China       | Coronary artery disease | 93/101               | PCR-SSP           |
| Mo et al        | 2009 | China       | Coronary artery disease | 97/35                | PCR-RFLP          |
| Yusup et al     | 2009 | China       | Coronary artery disease | 124/50               | PCR-RFLP          |
| Wen et al       | 2008 | China       | Coronary artery disease | 71/164               | Nested PCR        |
| Zhou et al      | 2006 | China       | Coronary artery disease | 103/197              | PCR-SSP           |
| Zhang et al     | 2006 | China       | Coronary artery disease | 173/141              | PCR-RFLP          |
| Wei et al       | 2006 | China       | Myocardial infraction  | 225/230              | PCR               |
| Wang et al      | 2005 | China       | Myocardial infraction  | 165/199              | PCR-RFLP          |
| Wang et al      | 2005 | China       | Coronary artery disease | 211/206              | PCR-RFLP          |
| Shang et al     | 2005 | China       | Coronary artery disease | 122/97               | Nested PCR        |

PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; SSP = sequence specific primer.
| Author and year | SOC | Ethnicity | Case Control | MAF | Case/Control | NOS |
|----------------|-----|-----------|--------------|-----|-------------|-----|
| Nasibullin 2016 | HB  | Caucasian | AA 101 AG 152 GG 62 | AA 145 | 0.438/0.432 | 6   |
|                 |     |           | AA 32.1% AG 48.3% GG 19.6% | AA 50.7% | 17.8% |
| Chou 2015       | HB  | Asian     | AA 177 AG 143 GG 19 | AA 80 | 0.267/0.280 | 7   |
|                 |     |           | AA 52.2% AG 42.2% GG 5.6% | AA 43.0% | 6.5% |
| Yang 2014       | HB  | Asian     | AA 305 AG 251 GG 48 | AA 160 | 0.287/0.261 | 6   |
|                 |     |           | AA 50.5% AG 41.6% GG 7.9% | AA 34.2% | 9.0% |
| Luo 2014        | PB  | Asian     | AA 339 AG 278 GG 57 | AA 273 | 0.291/0.233 | 7   |
|                 |     |           | AA 50.5% AG 41.2% GG 8.5% | AA 35.0% | 5.8% |
| Gazi 2014       | HB  | Caucasian | AA 12 AG 27 GG 9 | AA 33 | 0.469/0.634 | 7   |
|                 |     |           | AA 25.0% AG 56.2% GG 18.8% | AA 49.3% | 38.8% |
| Burazynska 2012 | HB  | Caucasian | AA 69 AG 44 GG 5 | AA 379 | 0.638/0.850 | 7   |
|                 |     |           | AA 58.5% AG 37.3% GG 4.2% | AA 22.0% | 74.0% |
| Mohamed 2010    | HB  | Caucasian | AA 23 AG 46 GG 2 | AA 11 | 0.575/0.850 | 7   |
|                 |     |           | AA 18.1% AG 36.2% GG 45.7% | AA 22.0% | 74.0% |
| Mohamed 2010    | HB  | Caucasian | AA 17 AG 28 GG 2 | AA 11 | 0.575/0.850 | 7   |
|                 |     |           | AA 23.2% AG 38.4% GG 38.4% | AA 22.0% | 74.0% |
| Sakowicz 2010   | PB  | Caucasian | AA 54 AG N/A GG 106* | AA 69 | 0.575/0.850 | 7   |
|                 |     |           | AA 31.9% AG 61.8% GG 6.3% | AA 46.0% | 21.0% |
| Sarecka 2009    | PB  | Caucasian | AA 61 AG 44 GG 12 | AA 122 | 0.372/0.340 | 8   |
|                 |     |           | AA 31.9% AG 61.8% GG 6.3% | AA 46.0% | 21.0% |
| Aminian 2007    | HB  | Caucasian | AA 48 AG 67 GG 33 | AA 69 | 0.448/0.496 | 8   |
|                 |     |           | AA 32.4% AG 45.3% GG 22.3% | AA 49.3% | 25.0% |
| Aminian 2007    | HB  | Caucasian | AA 42 AG 77 GG 33 | AA 69 | 0.470/0.496 | 8   |
|                 |     |           | AA 27.6% AG 50.7% GG 21.7% | AA 49.3% | 25.0% |
| Podgoreanu 2006 | HB  | Caucasian | AA 14 AG 26 GG 12 | AA 50 | 0.481/0.637 | 8   |
|                 |     |           | AA 26.9% AG 50.0% GG 23.1% | AA 46.3% | 40.6% |
| Milutinovic 2006| HB  | Caucasian | AA 47 AG 72 GG 33 | AA 65 | 0.454/0.444 | 6   |
|                 |     |           | AA 30.9% AG 47.4% GG 21.7% | AA 50.7% | 19.1% |
| Zak 2005        | PB  | Caucasian | AA 48 AG 86 GG 12 | AA 68 | 0.377/0.347 | 6   |
|                 |     |           | AA 32.0% AG 58.9% GG 8.2% | AA 56.2% | 6.6% |
| Jiang 2002      | PB  | Caucasian | AA 139 AG 148 GG 62 | AA 66 | 0.390/0.563 | 7   |
|                 |     |           | AA 39.8% AG 58.2% GG 17.8% | AA 46.3% | 40.6% |
| Jiang 2002      | PB  | Caucasian | AA 63 AG 78 GG 38 | AA 66 | 0.430/0.563 | 7   |
|                 |     |           | AA 35.2% AG 43.6% GG 21.2% | AA 31.0% | 40.8% |
| Luo 2013        | PB  | Caucasian | AA 110 AG 101 GG 34 | AA 186 | 0.345/0.406 | 6   |
|                 |     |           | AA 44.9% AG 41.2% GG 13.9% | AA 49.4% | 19.1% |
| Liu 2011        | HB  | Asian     | AA 124 AG 84 GG 17 | AA 101 | 0.262/0.337 | 8   |
|                 |     |           | AA 39.7% AG 26.9% GG 5.4% | AA 34.1% | 8.6% |
| Li 2010         | HB  | Asian     | AA 47 AG 39 GG 7 | AA 36 | 0.285/0.307 | 7   |
|                 |     |           | AA 50.6% AG 41.9% GG 7.5% | AA 35.6% | 12.9% |
| Mo 2009         | PB  | Asian     | AA 15 AG 35 GG 47 | AA 12 | 0.665/0.486 | 6   |
|                 |     |           | AA 15.5% AG 36.1% GG 48.4% | AA 34.3% | 31.4% |
| Yusup 2009      | PB  | Caucasian | AA 55 AG 54 GG 15 | AA 26 | 0.339/0.320 | 6   |
|                 |     |           | AA 44.4% AG 43.5% GG 12.1% | AA 52.0% | 6.0% |
| Wen 2008        | HB  | Asian     | AA 28 AG 30 GG 13 | AA 65 | 0.394/0.558 | 6   |
|                 |     |           | AA 39.4% AG 42.3% GG 18.3% | AA 39.6% | 36.0% |
| Zhou 2006       | HB  | Asian     | AA 38 AG 45 GG 20 | AA 102 | 0.413/0.325 | 6   |
|                 |     |           | AA 39.4% AG 42.3% GG 18.3% | AA 39.6% | 36.0% |
| Zhang 2006      | HB  | Asian     | AA 111 AG 52 GG 10 | AA 59 | 0.208/0.301 | 5   |
|                 |     |           | AA 64.1% AG 30.1% GG 5.8% | AA 41.8% | 9.3% |
| Wei 2006        | PB  | Asian     | AA 124 AG 84 GG 17 | AA 103 | 0.262/0.337 | 8   |
|                 |     |           | AA 55.1% AG 37.3% GG 7.6% | AA 44.8% | 11.3% |
| Wang 2005       | HB  | Asian     | AA 96 AG 61 GG 8 | AA 90 | 0.233/0.317 | 7   |
|                 |     |           | AA 58.2% AG 37.0% GG 4.8% | AA 45.2% | 9.1% |
| Wang 2005       | HB  | Asian     | AA 117 AG 82 GG 12 | AA 95 | 0.251/0.323 | 7   |
|                 |     |           | AA 55.4% AG 38.9% GG 5.7% | AA 46.1% | 9.2% |
| Shang 2005      | PB  | Asian     | AA 48 AG 50 GG 24 | AA 33 | 0.402/0.531 | 6   |
|                 |     |           | AA 39.3% AG 41.0% GG 19.7% | AA 34.0% | 36.1% |

*Note: MAF = minor allele frequencies, NOS = Newcastle–Ottawa scale, N/A = not available, SOC = source of controls. The combined number of AG and GG genotypes.*
“CAD” or “coronary heart disease” or “CHD” or “myocardial infarction” or “MI.” No restrictions were placed on the search. Additional initially omitted studies (such as reference lists of identified studies) have been identified by hand screening. The identified studies conformed to the following criteria: studies that evaluated the association between CAD risk and ICAM-1 gene rs5948 polymorphism, studied on human beings, studies provided sufficient data to calculate the ORs and 95% confidence interval (CIs), and P value, and case–control studies. We obtained approval for the study protocol from the Ethics Committee of the Second Affiliated Hospital of Zhejiang Chinese Medical University. The ethical approval of our study was in line with the standards of the Declaration of Helsinki.

2.2. Data extraction and quality assessment

Related information was carefully extracted from all eligible studies. The extracted information from all eligible studies including: name of first author, publication year, country of origin, type of CAD, ethnicity, genotype method, source of controls, and genotype numbers of cases and controls. Two reviewers independently performed the extraction of data and assessed the study quality based on the Newcastle–Ottawa scale scores (NOS). All disagreements were discussed and resolved with consensus.

2.3. Statistical analysis

All statistical analyses were performed using the Stata 11.0 software (Stata Corp, College Station, TX). ORs and 95%CIs were used to assess the strength of associations between ICAM-1 gene rs5948 polymorphisms and CAD risk. Stratification analysis was carried out by ethnicity, SOC, type of CAD, and genotype methods. P < .05 was considered statistically significant. When a Q test indicated P < .1 or I² > 50% indicated heterogeneity across studies, a random-effect model was used. Otherwise, the fixed-effects model was applied. Pooled ORs were calculated for allele model, dominant model, recessive model, homozygous model, and heterozygous model. We performed sensitivity analyses by omitting each study in turn to determine the effect on the test of heterogeneity and evaluated the stability of the overall results. Potential publication bias was assessed by Begg’s and Egger’s linear regression test; P < .05 was considered to indicate statistically significant.

3. Results

3.1. Characteristics of the included studies

We yielded a total of 399 citations after incipient search. 46 citations were selected for further full text review. Around 23 citations were excluded due to the following reasons:

Figure 2. Forest plot shows odds ratio for the association between ICAM-1 gene rs5948 polymorphism and CAD risk (A: G vs A; B: AG + GG vs AA; C: GG vs AA + AG; D: GG vs AA). CAD = coronary artery disease, ICAM-1 = intercellular adhesion molecule 1.
9 investigated other SNPs of ICAM-1 gene; 3 citations did not provide detailed genotyping data; 2 were reviews; 5 were meta-analyses; and 1 was not case-control study. Eventually, we identified 26 eligible citations (5,494 cases and 6,364 controls) containing 29 studies. Selection for qualified studies was presented in Figure 1. The characteristics of included studies are summarized in Tables 1 and 2. The NOS of all included studies ranged from 6 to 8 stars, suggesting that these studies were of high methodological quality.

| Table 3 | Meta-analysis of association between ICAM-1 rs5498 polymorphism and coronary artery disease. |
|----------|------------------------------------------------------------------------------------------|
| Comparison | OR (95%CI) | P-value | P for heterogeneity | $I^2$ (%) | Model |
| G vs A | 0.77 (0.66,0.89) | .001 | <.001 | 84.7 | Random |
| AG+GG vs AA | 0.79 (0.66,0.94) | .007 | <.001 | 76.5 | Random |
| GG vs AA+AG | 0.67 (0.53,0.84) | .001 | <.001 | 73.0 | Random |
| GG vs AA | 0.63 (0.48,0.83) | .001 | <.001 | 76.0 | Random |
| AG vs AA | 0.87 (0.75,1.01) | .066 | <.001 | 64.1 | Random |

ICAM-1 = intercellular adhesion molecule 1.

Figure 3. Stratification analyses of ethnicity shows odds ratio for the association between ICAM-1 gene rs5948 polymorphism and CAD risk (AG+GG vs AA). CAD = coronary artery disease, ICAM-1 = intercellular adhesion molecule 1.
3.2. Meta-analysis of rs5948 polymorphism

In the general analysis, we detected a significant association between ICAM-1 gene rs5948 polymorphism with a decreased risk of CAD (G vs A: OR, 0.77; 95% CI, 0.66–0.89, P = .001; Fig. 2; AG + GG vs AA: OR, 0.79; 95% CI, 0.66–0.94, P = .007; GG vs AA + AG: OR, 0.67; 95% CI, 0.53–0.84, P = .001; GG vs AA: OR, 0.63; 95% CI, 0.48–0.83, P = .001, Table 3). Data indicated that GG or AG genotype and G allele were regarded as protective factors for CAD. Stratification analyses were conducted according to ethnicity, source of controls (SOC), type of CAD and genotype methods. Our data indicated that rs5498 polymorphism was significantly associated with a decreased risk of CAD among Caucasians (G vs A: OR, 0.68; 95% CI, 0.55–0.85, P = .001; AG + GG vs AA: OR, 0.72; 95% CI, 0.58–0.83, P = .001, Table 4), but not among Asians. In the subgroup analysis by type of CAD, ICAM-1 rs5498 polymorphism was correlated with a significantly decreased risk of MI (G vs A: OR, 0.62; 95% CI, 0.47–0.82, P = .001; AG + GG vs AA: OR, 0.71; 95% CI, 0.48–0.88, P = .006; GG vs AA + AG: OR, 0.51; 95% CI, 0.33–0.79, P = .003; GG vs AA: OR, 0.42; 95% CI, 0.24–0.72, P = .002, Table 4).

We assessed sensitivity analysis by omitting each study once at a time in every genetic model for rs5498 polymorphism. The pooled ORs for the effects of the SNP on the risk for CAD risk indicated that our data was stable and trustworthy. Both Egger’s and Begg’s tests (AG + GG vs AA, Fig. 4) were used to evaluated

| Table 4 | Summary of the subgroup analyses in this meta-analysis. |
| --- | --- |
| **Comparison** | **Category** | **Studies** | **OR (95% CI)** | **P-value** |
| G vs A | Ethnicity | Caucasian | 15 | 0.68 (0.55, 0.85) | <.001 |
| | | Asian | 13 | 0.87 (0.71, 1.06) | .172 |
| | SOC | HB | 18 | 0.71 (0.59, 0.85) | <.001 |
| | | PB | 10 | 0.89 (0.68, 1.16) | .384 |
| | Type | MI | 9 | 0.62 (0.47, 0.82) | .001 |
| | | CAD | 19 | 0.84 (0.71, 1.01) | .060 |
| | Genotype method | PCR-RFLP | 15 | 0.65 (0.69, 1.03) | .105 |
| | | PCR | 9 | 0.61 (0.48, 0.79) | <.001 |
| | | Other methods | 4 | 0.91 (0.61, 1.34) | .626 |
| AG + GG vs AA | Ethnicity | Caucasian | 16 | 0.72 (0.58, 0.90) | .003 |
| | | Asian | 13 | 0.88 (0.68, 1.13) | .328 |
| | SOC | HB | 18 | 0.70 (0.56, 0.89) | .003 |
| | | PB | 11 | 0.93 (0.72, 1.20) | .574 |
| | Type | MI | 10 | 0.65 (0.48, 0.88) | .006 |
| | | CAD | 19 | 0.86 (0.71, 1.06) | .158 |
| | Genotype method | PCR-RFLP | 15 | 0.87 (0.69, 0.98) | .206 |
| | | PCR | 9 | 0.63 (0.46, 0.85) | .003 |
| | | Other methods | 4 | 0.96 (0.57, 1.61) | .870 |
| GG vs AA + AG | Ethnicity | Caucasian | 15 | 0.61 (0.43, 0.86) | .004 |
| | | Asian | 13 | 0.86 (0.68, 1.10) | .056 |
| | SOC | HB | 18 | 0.61 (0.47, 0.79) | <.001 |
| | | PB | 10 | 0.84 (0.53, 1.34) | .465 |
| | Type | MI | 9 | 0.51 (0.33, 0.79) | .003 |
| | | CAD | 19 | 0.76 (0.58, 1.01) | .048 |
| | Genotype method | PCR-RFLP | 15 | 0.85 (0.63, 1.15) | .287 |
| | | PCR | 9 | 0.46 (0.33, 0.65) | <.001 |
| | | Other methods | 4 | 0.73 (0.45, 1.18) | .203 |
| GG vs AA | Ethnicity | Caucasian | 15 | 0.54 (0.36, 0.80) | .002 |
| | | Asian | 13 | 0.74 (0.51, 1.07) | .110 |
| | SOC | HB | 18 | 0.53 (0.38, 0.74) | <.001 |
| | | PB | 10 | 0.87 (0.52, 1.44) | .577 |
| | Type | MI | 9 | 0.42 (0.24, 0.72) | .002 |
| | | CAD | 19 | 0.75 (0.54, 1.03) | .076 |
| | Genotype method | PCR-RFLP | 15 | 0.83 (0.58, 1.19) | .309 |
| | | PCR | 9 | 0.41 (0.28, 0.61) | <.001 |
| | | Other methods | 4 | 0.71 (0.33, 1.53) | .384 |
| AG vs AA | Ethnicity | Caucasian | 15 | 0.81 (0.68, 0.97) | .019 |
| | | Asian | 13 | 0.94 (0.74, 1.18) | .580 |
| | SOC | HB | 18 | 0.79 (0.65, 0.97) | .022 |
| | | PB | 10 | 1.00 (0.60, 1.29) | .991 |
| | Type | MI | 9 | 0.74 (0.58, 0.94) | .014 |
| | | CAD | 19 | 0.90 (0.78, 1.04) | .436 |
| | Genotype method | PCR-RFLP | 15 | 0.87 (0.71, 1.06) | .165 |
| | | PCR | 9 | 0.80 (0.60, 1.06) | .114 |
| | | Other methods | 4 | 1.07 (0.67, 1.71) | .779 |

CAD = coronary artery disease, HB = hospital-based controls, MI = Myocardial infarction, PB = population-based controls, SOC = source of controls.
4. Discussion

In this current meta-analysis, we found that ICAM-1 gene rs5498 polymorphism was associated with the decreased risk of CAD. Stratification analysis of ethnicity found that rs5498 polymorphism decreased the risk of CAD only among Caucasians. Stratification by type of CAD detected that ICAM-1 gene rs5498 polymorphism was related with the decreased risk of MI.

ICAM-1 induces adhesion of circulating leukocytes to activated endothelium, and migration to the vascular intima, which is a vital pathogenic process of inflammatory diseases, atherosclerosis and thrombosis. During inflammation reaction, Soluble ICAM-1 is produced by several cells, such as fibroblasts, leukocytes, endothelial cells and epithelial cells. These cells were activated by multiple cytokines and then produced a number of membrane ICAM-1. Previous studies indicated that ICAM-1 was significantly elevated among acute coronary syndrome groups compared with healthy controls, suggesting that ICAM-1 was associated with the pathogenesis of CAD.

Several meta-analyses investigated ICAM-1 gene rs5498 polymorphism with CAD susceptibility before. They all indicated that rs5498 polymorphism was a risk factor of CAD. We included additional studies and found support for conflicting results regarding this SNP. Our meta-analysis demonstrated that rs5498 polymorphism was significantly associated with an increased risk of CAD. Stratification analysis of ethnicity in their meta-analysis suggested that rs5498 polymorphism was associated with an increased risk of CAD among Asians and Caucasians. It is of note that the meta-analysis by Li Yanyan showed rs5498 polymorphism was related with increased risk for CAD in Chinese Han population. However, subgroup of this meta-analysis found that rs5498 polymorphism was significantly associated with a decreased risk of CAD among Caucasians, but not among Asians, indicating that diversity inheritance of different ethnicities. It is obvious that the findings of this study were different from those of previous meta-analyses. We hypothesized varied sample sizes mainly contributed to conflicting results.

We think previous meta-analyses had several limitations. First, Li et al and Zou et al falsely extracted genotype data from included studies. For instance, the correct genotype numbers from a Chinese study by Shang et al were as following: case, AA = 48, AG = 50, GG = 24; control, AA = 29, AG = 33, GG = 35, but unlike the extracted data of these previous meta-analyses. We also suspected the correctness of data from 2 studies. Therefore, we re-conducted the meta-analysis combined with the correct data of these studies included by previous meta-analyses (not containing these new emerging studies). We found that rs5498 polymorphism was associated with the decreased risk of CAD, which was in accord with our later results. Second, Li et al did not include 9 studies while Zou et al did not include 11 studies. Third, Li et al identified a Chinese study, but we did not find the genotype numbers of rs5498 polymorphism in this study. However, we did not find the genotype numbers of rs5498 polymorphism in this study. Consequently, the reliability of their conclusions should be interpreted with caution. Fourth, Li did not investigate other races except Chinese. Due to these above limitations of previous meta-analyses, we performed a new meta-analysis. We observed that ICAM-1 rs5498 polymorphism conferred a protective factor of CAD. We believed our meta-analysis has some strength over previous meta-analyses for the following reasons. One, we identified 29 studies including 5494 cases and 6364 controls with regard to rs5498 polymorphism and the sample size of this meta-analysis was large. Two, sensitivity analysis indicated that our data about rs5498 polymorphism was trustworthy and robust.
In a subgroup analysis by the type of CAD, we also found that ICAM-1 rs5498 polymorphism was correlated with the decreased risk of MI. We did not obtain positive finding among other types of CAD. We hypothesized that these discordances regarding ICAM-1 gene rs5498 polymorphism may be partly due to the inherent heterogeneity of diseases in different CAD types. However, other factors including environmental exposure, sample sizes, genotyping methods, and clinical heterogeneity may also account for these inconsistencies. In the future, more studies are needed to verify above assumptions.

Several potential limitations should be addressed in this meta-analysis. First, due to limited data, we could not conduct further stratification analyses of other potential factors, such as age and gender. Second, our results were based on unadjusted estimates for confounding factors, which might have affected the final results. Third, we could not assess potential gene–gene and gene–environment interactions because of the lack of relevant data. Fourth, the heterogeneity of this meta-analysis was high in many genetic models. Fifth, the conclusions of some stratification analyses about rs5498 polymorphism should be interpreted with caution due to limited sample size. Lastly, only 2 Asian countries were included in the analysis, and most Asian data were from China.

In conclusion, this meta-analysis confirms that ICAM-1 gene rs5498 polymorphism is associated with the decreased risk of CAD. Further studies with large sample sizes are necessary to validate whether ICAM-1 gene rs5498 polymorphism contribute to CAD susceptibility in other ethnic groups.

Author contributions
Conceptualization: Ailing Liu, Ailing Wan.
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Writing – original draft: Ailing Liu, Bingzhi Zhou.
Writing – review & editing: Ailing Wan, Aifang Feng, Ruping Rui, Bingzhi Zhou.

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