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# Strong association between the interleukin-8-251A/T polymorphism and coronary artery disease risk

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**Abstract**

Several reports have suggested a possible association between the interleukin (IL)-8-251A/T single-nucleotide polymorphism (SNP) and the susceptibility to coronary artery disease (CAD). Due to inconclusive results of the studies so far, we conducted a meta-analysis to systematically summarize the studies on the association between this SNP and CAD risk. A systematic literature search identified 9 case-control studies (3752 cases and 4219 controls) on the IL-8-251A/T polymorphism. We observed a significant association between different genetic forms of −251A/T SNP and CAD risk, like the allele model (A vs T: odds ratio [OR] 1.14, 95% confidence interval [CI] 1.02–1.27, $P = .02$), dominant model (AA + AT vs TT: OR 1.20, 95% CI 1.01–1.43, $P = .042$), recessive model (AA vs AT + TT: OR 1.15, 95% CI 1.03–1.27, $P = .01$), and homozygous model (AA vs TT: OR 1.26, 95% CI 1.01–1.56, $P = .037$), whereas the heterozygote model did not show any significant association (AT vs TT: OR 1.16, 95% CI 0.98–1.38, $P = .091$). Furthermore, significant heterogeneity was observed among studies in terms of all genetic models, except the recessive model. Analysis of the ethnic subgroups revealed a significantly higher risk of CAD in the East Asian population carrying this SNP, and the heterogeneity among the studies regarding the East Asian population was decreased after subgroup analysis. The results of this meta-analysis suggest that the IL-8-251A/T SNP may increase the risk of CAD, especially in people of East Asian ethnicity. Further large-scale, multicenter epidemiological studies are warranted to validate this finding.

**Abbreviations:** CAD = coronary artery disease, CI = confidence interval, HWE = Hardy–Weinberg equilibrium, MAF = minor allele frequency, MALDI-TOF =Matrix Adsorbed Laser Desorption-Ionisation-Time of Flight, ORs = odds ratios, PCR-RFLP = polymerase chain reaction–restriction fragment length polymorphism, SNP = single-nucleotide polymorphism.

**Keywords:** −251A/T, coronary artery disease, gene, interleukin-8, single-nucleotide polymorphism

## 1. Introduction

Coronary artery disease (CAD), 1 of the most common heart diseases, is a group of clinical manifestations including stable and unstable angina, myocardial infarction, and sudden coronary death.[1] It is associated with high mortality and morbidity in both developed and developing countries.[2] CAD develops over a long period of time and involves several lifestyle factors, including diet, hypertension, hypercholesterolemia, diabetes, obesity, and lack of physical activity.[3–6] Nevertheless, only a small percentage of individuals with these high-risk factors develop CAD, suggesting a hereditary basis of CAD pathology.

The interleukin 8 (IL-8) gene is located on chromosome 4q13-q21, and comprises of 4 exons, 3 introns, and a proximal promoter region.[7] IL-8 plays an important role in regulating both inflammatory and immune processes.[7,8] Since its discovery in the late 1980s, IL-8 has been shown to participate in all stages of atherosclerosis, from vascular inflammation to cardiac remodeling after myocardial infarction (MI),[9] suggesting an association between *IL-8* gene and CAD risk. Several studies have examined the association between 2 common *IL-8* gene polymorphisms, −251A/T (rs4073) and 781C/T (rs2227306), and the risk of CAD.[10,11] The polymorphism at the −251 position of the promoter region of the *IL-8* gene affects its transcriptional activity, and the homozygous −251A allele is correlated with increased expression.[12,13] To date, many studies had assessed the association between the *IL-8*-251A/T single-nucleotide polymorphism (SNP) and CAD risk, but the results have been inconclusive.[10,11,14–20] Therefore, we conducted a meta-analysis on 9 published case-control studies examining this association.

## 2. Methods

### 2.1. Search strategy and eligibility of relevant studies

The PubMed database was searched for articles published from 1948 to present, and EMBASE from 1974 to present (last search June 20, 2018). Combinations of the following phrases were used: "coronary artery disease or coronary heart disease or

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cardiovascular diseases," "polymorphism or variation or variant or mutation," and "Interleukin 8 or IL-8 or rs4073." To retrieve the most eligible studies, we evaluated all articles and manually searched their references. The inclusion criteria were as follows: English-language papers and human-associated studies; case-control studies; evaluating the association between −251A/T SNP and risk of CAD; containing useful genotypic frequency. The study was reviewed and approved by the Ethics Committee of Wuxi People's Hospital Affiliated to Nanjing Medical University.

### 2.2. Study selection

The literature search was conducted by 1 investigator (Y.W.). Two researchers (Y.W. and W.W.) independently selected the studies for inclusion according to eligibility criteria. Disagreements between reviewers were resolved by consensus; if the disagreement pertained, a third author (R.X.W.) made the final decision.

### 2.3. Data extraction

Two investigators extracted the data independently and reached consensus on all items. For each of the eligible publications, the following data were extracted: first author's surname, year of publication, country of study population, ethnicity, total number of cases and controls, genotyping methods and matching criteria, and the numbers of all individuals with the TT, TA, and AA genotypes.

### 2.4. Assessment of study quality

The quality of the included studies was assessed using the Newcastle–Ottawa Quality Assessment Scale for case-control studies. A study can be given a maximum of 1 star for each numbered item within the selection and exposure categories. A maximum of 2 stars can be awarded for comparability. The total quality scores ranged from 0 to 9 stars.

### 2.5. Statistical analysis

The statistical analyses were performed with the STATA software version 12.0 (STATA Corp., College Station, TX). To measure the strengths of the genetic associations of the *IL-8*-251A/T SNP with CAD risk, the pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A chi-square test was performed to determine whether the genotypic frequencies deviated from the Hardy–Weinberg equilibrium (HWE). The heterogeneity among studies was analyzed using the Q statistic test. *P* values less than .10 were considered statistically significant.[21] If significant heterogeneity was observed, the DerSimonian–Laird method was used to evaluate the pooled ORs (95% CIs) in random-effects model. If no significant heterogeneity was observed, the Mantel–Haenszel test was used to calculate the pooled ORs (95% CIs) in fixed-effects models.[22] To explore the effect of heterogeneity among the studies, subgroup analyses were performed. Sensitivity analysis was performed by omitting each study to assess the quality and consistency of the results. We also performed Egger test to examine publication bias, and $P < .05$ was considered statistically significant.[23]

## 3. Results

### 3.1. Characteristics of studies

A total of 103 published articles were obtained by keyword-related and manual search. Figure 1 illustrates the process of inclusion and exclusion of associated studies, which finally identified 9 articles including a total of 3752 cases and 4219 controls suitable for our meta-analysis.[10,11,14–20] For 2 studies[18,19] that involved 2 stage groups, each group was analyzed separately. The quality scores of all of the included studies were greater than 5 stars. The characteristics of eligible studies are summarized in Table 1. Five studies were on East Asian populations and 4 on Caucasians. All studies used blood samples for DNA extraction. Polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assay was used in 6 studies, 2 studies used TaqMan (Applied Biosystems, Foster City, CA) method, and 1 study used Matrix Adsorbed Laser Desorption-Ionisation-Time of Flight (MALDI-TOF) to detect the genotypes. CAD was confirmed by coronary angiography in all studies. In addition, 8 studies were hospital-based and 1 was population-based.[11] The distribution of genotypes among the controls of the studies was in agreement with HWE in 6 studies.[10,15,17] The genotypic frequencies of the −251A/T SNP in the studies included in the meta-analysis are listed in Table 2.

### 3.2. Association between the IL-8-251A/T polymorphism and CAD risk

As shown in Table 3, the pooled results indicate a significant association between *IL-8*-251A/T SNP and CAD risk in most genetic models: allele model (A vs T: OR 1.14, 95% CI 1.02–1.27, $P = .02$) (Fig. 2); dominant model (AA + AT vs TT: OR 1.20, 95% CI 1.01–1.43, $P = .042$); recessive model (AA vs AT + TT: OR 1.15, 95% CI 1.03–1.27, $P = .01$); and homozygous genetic model (AA vs TT: OR 1.26, 95% CI 1.01–1.56, $P = .037$). The heterozygous model (AT vs TT) did not show any significant association with CAD risk (OR 1.16, 95% CI 0.98–1.38, $P = .091$).

### 3.3. Publication bias

Begg funnel plot and Egger test were used to assess the publication bias. As shown in Fig. 3, the funnel plots did not reveal any obvious asymmetry in all genotypes in overall population. Neither test showed any statistical evidence for publication bias in our meta-analysis ($P > .05$).

### 3.4. Heterogeneity and sensitivity analyses

Substantial heterogeneity was observed among studies for all genetic models (AA + AT vs TT: $I^2 = 62.6\%$, $P = .006$; AT vs TT: $I^2 = 55.9\%$, $P = .020$; AA vs TT: $I^2 = 61.0\%$, $P = .009$; A vs T: $I^2 = 61.3\%$, $P = .008$), except AA vs AT + TT model ($I^2 = 28.7\%$, $P = .190$) (Table 3). Next, we assessed the source of heterogeneity in all genetic models by comparing the ethnicities of the study groups. The heterogeneity was significantly decreased in the East Asian population after subgroup analysis, whereas significant heterogeneity was observed among Caucasians (Table 3).

Sensitivity analyses showed that the study by Velásquez et al[11] was the major contributor of heterogeneity for the allele model ($I^2 = 61.3\%$, $P = .008$). After excluding this study, the heterogeneity was significantly reduced ($I^2 = 21.1\%$, $P = .262$) (Table 4). As expected, similar results were observed for other genetic models (ie, AT vs TT and AA vs TT). However, the statistical significance of the results was not altered when any single study was omitted, confirming the stability of the results.

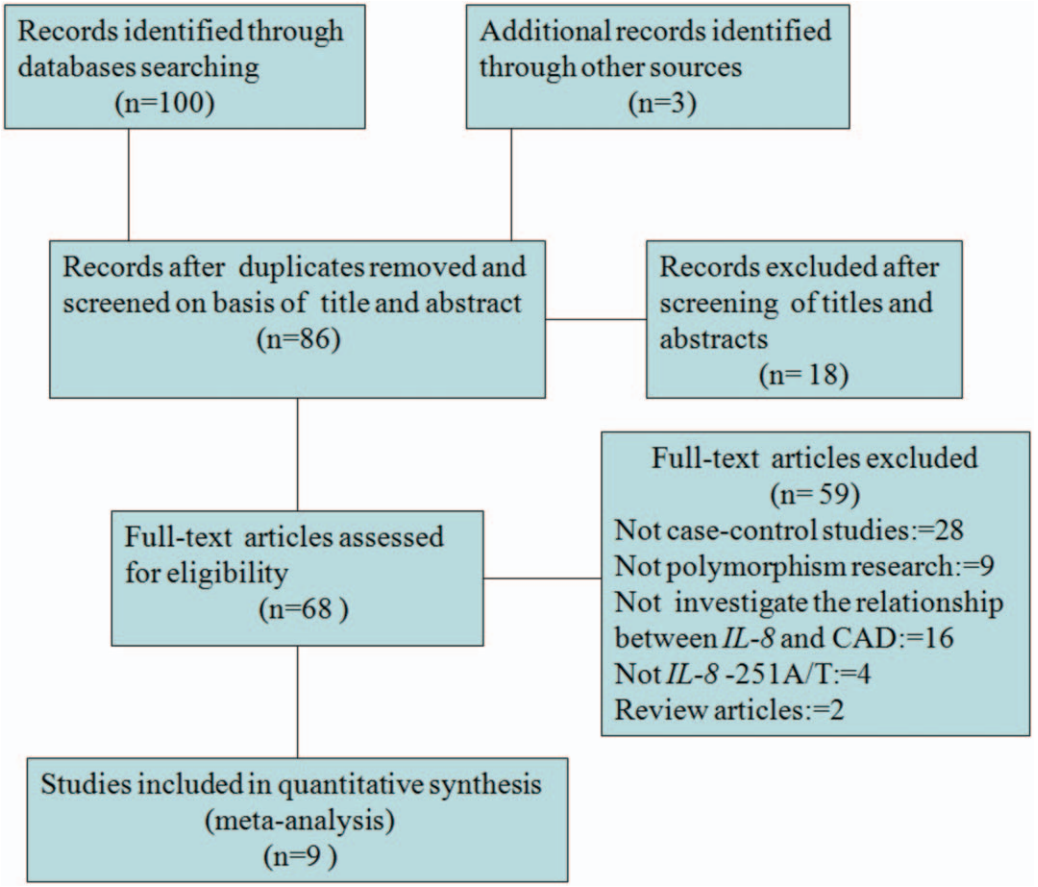


**Figure 1.** Flow diagram of study selection process.

## 4. Discussion

Coronary artery disease is caused by a combination of genetic and environmental factors. The individual differences in CAD susceptibility, despite similar environmental risk factors,[24] suggests a vital role of gene variants in the pathogenesis of CAD. Therefore, increasing numbers of studies in recent times have focused on the association of the SNPs of genes related to CAD and its pathogenesis.[25,26] Genome-wide association study has helped identify gene variants in different ethnic populations that are associated with increased susceptibility to CAD. Mutations in the CDKN2A/2B/ANRIL gene cluster, PHACTR1, NHGRI, and KCNE2, have been identified as the risk factors of CAD.[27] Numerous studies have found an association between the *IL-8*-251A/T SNP and CAD risk. Four studies[10,11,14,19] have indicated a significant association between the −251A/T SNP and CAD, whereas the other studies showed no association.[15–18,20] Therefore, we performed a comprehensive meta-analysis with the aim of clarifying whether there is a significant association of the *IL-8*-251A/T SNP (rs4073) with CAD susceptibility. To the best of our knowledge, this is the first meta-analysis that systematically explores this association.

Rus et al[28] hypothesized that IL-8 expression is induced by complement activation, which may contribute to the increased

**Table 1**

**Characteristics of studies selected in the meta-analysis.**

| First author | Year | Country | Ethnicity | Control source | Subjects, n cases/controls | Endpoint of assessment | Genotyping method | MAF in controls | HWE | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| Zhang[14] | 2017 | China | East Asian | HB | 217/245 | coronary artery disease | PCR-RFLP | 0.45 | Y | 5 |
| Yang[15] | 2015 | China | East Asian | HB | 410/410 | coronary artery disease | PCR-RFLP | 0.49 | N | 5 |
| Ren and She[16] | 2015 | China | East Asian | HB | 325/342 | coronary artery disease | Taqman | 0.47 | Y | 5 |
| Wang[17] | 2015 | China | East Asian | HB | 260/285 | myocardial infarction | PCR-RFLP | 0.47 | N | 6 |
| Velásquez[11] | 2014 | Sweden | Caucasian | PB | 867/1035 | myocardial infarction | MALDI-TOF | 0.56 | Y | 6 |
| Zhang[19] | 2011 | China | East Asian | HB | 1035/996 | coronary artery disease | PCR-RFLP | 0.35 | Y | 5 |
| La Manna[18] | 2010 | Italy | Caucasian | HB | 196/602 | cardiovascular disease | Taqman | 0.57 | Y | 6 |
| Vogiatzi[20] | 2010 | Greece | Caucasian | HB | 201/147 | coronary artery disease | PCR-RFLP | 0.46 | Y | 6 |
| Vogiatzi[10] | 2008 | Creece | Caucasian | HB | 241/157 | coronary artery disease | PCR-RFLP | 0.42 | N | 6 |

CAD = coronary artery disease, HB = hospital-based, HWE = Hardy–Weinberg equilibrium, MAF = minor allele frequency, MALDI-TOF = Matrix Adsorbed Laser Desorption-Ionisation-Time Of Flight, ND = not determined, PB = population-based, PCR-RFLP = polymerase chain reaction–restriction fragment length polymorphism.

**Table 2**

**Genotype frequencies in the studies included in the meta-analysis.**

| | | Genotype frequency (n) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cases | | | | | Controls | | | | |
| Reference | Year | TT | TA | AA | A | T | TT | TA | AA | A | T |
| Zhang et al[14] | 2017 | 47 | 101 | 69 | 239 | 195 | 80 | 108 | 57 | 222 | 268 |
| Yang et al[15] | 2015 | 118 | 178 | 114 | 406 | 414 | 134 | 171 | 105 | 381 | 439 |
| Ren and She[16] | 2015 | 85 | 147 | 93 | 333 | 317 | 108 | 149 | 85 | 319 | 365 |
| Wang et al[17] | 2015 | 72 | 113 | 75 | 263 | 257 | 89 | 119 | 77 | 273 | 297 |
| Velásquez et al[11] | 2014 | 182 | 416 | 269 | 954 | 780 | 189 | 516 | 330 | 1176 | 894 |
| Zhang et al[19] | 2011 | 340 | 496 | 199 | 894 | 1176 | 407 | 451 | 138 | 727 | 1265 |
| La Manna et al[18] | 2010 | 48 | 80 | 68 | 216 | 176 | 126 | 288 | 188 | 664 | 540 |
| Vogiatzi et al[20] | 2010 | 37 | 127 | 37 | 201 | 201 | 40 | 77 | 30 | 137 | 157 |
| Vogiatzi et al[10] | 2008 | 73 | 127 | 41 | 209 | 273 | 53 | 76 | 28 | 132 | 182 |

**Table 3**

**Stratified meta-analysis of the effect of −251A/T polymorphism of IL-8 gene on risk for CAD.**

| | | TA vs TT | | AA vs TT | | TA + AA vs TT (dominant) | | AA vs TA + TT (recessive) | | A vs T | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study group | n[a] | OR (95% CI)[c] | $P^b$ | OR (95% CI)[c] | $P^b$ | OR (95% CI)[c] | $P^b$ | OR (95% CI)[c] | $P^b$ | OR (95% CI)[c] | $P^b$ |
| Total | 9 | 1.16 (0.98–1.38) | .020 | 1.26 (1.01–1.56) | .009 | 1.20 (1.01–1.43) | .006 | 1.15 (1.03–1.27) | .190 | 1.14 (1.02–1.27) | .008 |
| Ethnicities | | | | | | | | | | | |
| East Asian | 5 | 1.29 (1.13–1.48) | .846 | 1.51 (1.28–1.78) | .305 | 1.36 (1.20–1.54) | .585 | 1.30 (1.13–1.50) | .455 | 1.25 (1.15–1.36) | .346 |
| Caucasian | 4 | 1.03 (0.73–1.45) | .027 | 0.93 (0.76–1.13) | .602 | 1.02 (0.76–1.36) | .065 | 0.99 (0.85–1.16) | .747 | 0.98 (0.89–1.08) | .581 |

[a] Number of comparison.

[b] *P* value of *Q* test for heterogeneity test.

[c] Random-effects model was used when *P* value for heterogeneity test <.10; otherwise, fixed-effects model was used.

IL-8 levels seen in atherosclerotic vessel walls. Moreover, this cytokine is involved in the inflammatory response during the initiation and progression of atherosclerosis. IL-8 production remains elevated for an extended period during acute inflammation, whereas other inflammatory cytokines are cleared within a few hours.[29,30] Liu et al[31] reported that IL-8 helps recruit T lymphocytes and smooth muscle cells to the subendothelial space and has a major role in the formation of atherosclerotic lesions, whereas Nair et al[32] found that IL-8 expression was a predictor of cardiovascular risk. The −251A/T SNP lies in the promoter region of the *IL-8* gene, and therefore affects its transcriptional activity. Homozygosity of the −251A allele has been associated with increased expression of the *IL-8* gene.[12,13] In fact, all genetic states of the −251A/T SNP may play a role in the pathogenesis of atherosclerosis by influencing the transcriptional activity and the expression of the *IL-8* gene, and thus influence CAD risk.

In this meta-analysis, 9 studies with a total of 3752 cases and 4219 controls on the association between the potentially functional polymorphisms of *IL-8*-251A/T and CAD risk were included. Pooled results of the overall population showed that there was significant association between most genetic states of −251A/T SNP and CAD risk as follows: allele model (A vs T: OR 1.14, 95% CI 1.02–1.27, $P = .02$); dominant model (AA + AT vs

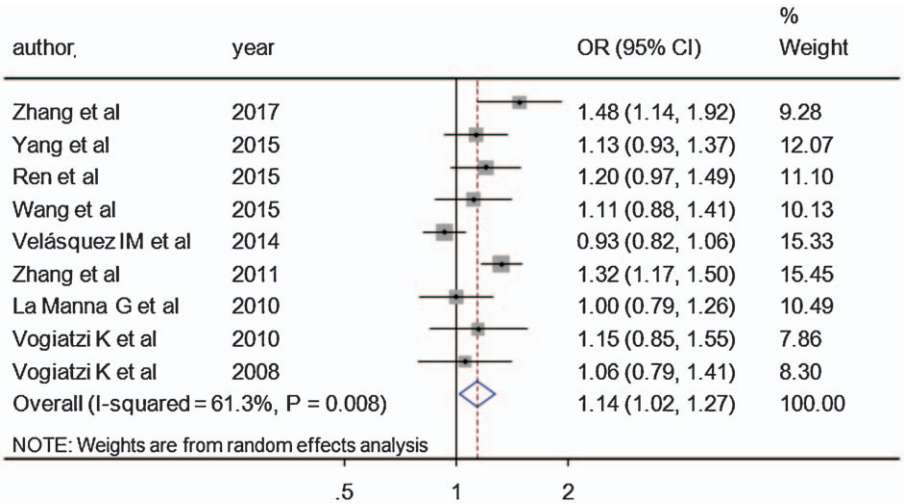


**Figure 2.** Forest plot of published case-control association studies of the −251A/T polymorphism (allele model) used in the overall analysis.

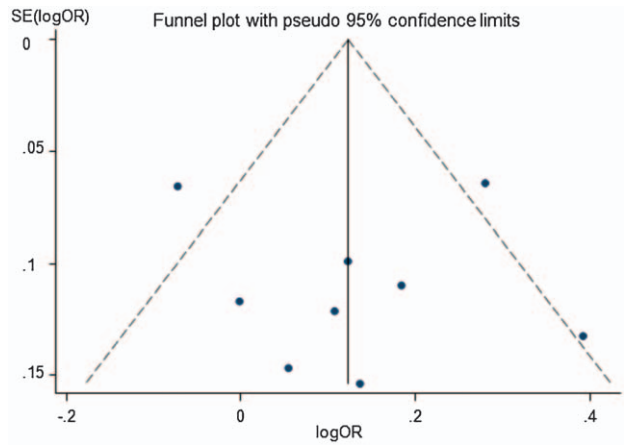


**Figure 3.** Funnel plot assessing evidence of publication bias from 9 studies (A vs T). A versus T = allele model, OR = odds ratio, SE = standard error.

TT: OR 1.20, 95% CI 1.01–1.43, $P = .042$); recessive model (AA vs AT + TT: OR 1.15, 95% CI 1.03–1.27, $P = .01$), and homozygous genetic model (AA vs TT: OR 1.26, 95% CI 1.01–1.56, $P = .037$). In contrast, the heterozygous model (AT vs TT) showed no significant association (OR 1.16, 95% CI 0.98–1.38, $P = .091$). This is the first study to report these findings.

Heterogeneity is a key factor in determining the reliability of meta-analysis results. In the overall population, significant heterogeneity was observed in almost all genetic models: A vs T: $\chi^2 = 20.67$ ($P = .008$), AA + AT vs TT: $\chi^2 = 21.41$ ($P = .006$), AT vs TT: $\chi^2 = 18.14$ ($P = .020$), AA vs TT: $\chi^2 = 20.50$ ($P = .009$). Only the AA vs AT + TT model showed no heterogeneity ($\chi^2 = 11.22$, $P = .190$). To find the source of heterogeneity, we conducted a subgroup analysis by ethnicity. As shown in Table 3, there was a significant association of most genetic models in the East Asian ethnic subgroup, whereas no significant association was found in the Caucasian group. Furthermore, no significant heterogeneity was observed in the East Asian population after subgroup analysis. These results suggest that ethnicity might be the major source of heterogeneity. In addition to ethnicity, sensitivity analysis suggested that the study by Velásquez et al,[11] which focussed on the Caucasian group, was the major contributor of heterogeneity. However, the overall results did not show quantitative changes when excluding any study, thereby underscoring the stability and reliability of this meta-analysis. In addition, publication bias is another important factor in evaluating the reliability of results, and along with the study quality is vital for conducting a meta-analysis. Publication bias was analyzed using Begg funnel plots and Egger test in our study. No significant publication bias was detected, further indicating the reliability of our results.

**Table 4**

**Sensitivity analysis of *IL-8*-251A/T in allele model.**

| Study omitted | OR (95% CI) | *P* for heterogeneity | $I^2$ |
|---|---|---|---|
| Zhang et al[14] | 1.11 (1.00–1.23) | .023 | 57.0% |
| Yang et al[15] | 1.14 (1.01–1.29) | .004 | 66.1% |
| Ren and She[16] | 1.13 (1.00–1.28) | .005 | 65.6% |
| Wang et al[17] | 1.14 (1.01–1.29) | .004 | 66.1% |
| Velásquez et al[11] | 1.21 (1.12–1.30) | .262 | 21.1% |
| Zhang et al[19] | 1.07 (1.00–1.15) | .081 | 44.8% |
| La Manna et al[18] | 1.16 (1.03–1.30) | .007 | 64.0% |
| Vogiatzi et al[20] | 1.14 (1.01–1.28) | .004 | 66.1% |
| Vogiatzi et al[10] | 1.15 (1.02–1.29) | .005 | 65.8% |

CI = confidence interval, OR = odds ratio.

There are some limitations of this meta-analysis. First, selection bias could have influenced the results because the genotypic distribution of this SNP among control subjects deviated from the HWE in 3 studies,[10,15,17] and most of the controls were hospitalized patients who may not be representative of the general population. Second, the studies included in the analysis used different genotyping methods with different quality control issues, which may also influence the results. Third, we only included the published studies in the meta-analysis, and it is possible that we might have missed some related unpublished studies which would have met the inclusion criteria. Apart from that, the addition of some other research, such as the cohort study, can increase the credibility of our meta-analysis results. But, we did not find any other study designs to explore this association of the interleukin-8-251A/T polymorphism and CAD risk by searching for keywords. Finally, the number of cases and controls in the included studies were relatively low (data shown in Table 1), and large-scale multicenter studies are warranted to further validate our results.

## 5. Conclusions

In conclusion, our meta-analysis provides the first unambiguous indication that *IL-8*-251A/T SNP is a risk factor for CAD susceptibility in the overall population, especially in the East Asian ethnic groups. Further large-scale multicenter epidemiological studies are warranted to validate this finding.

## Author contributions

**Data curation:** Ying Wu, Wei Wang, Xiao-yan Li.
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**Methodology:** Ying Wu.
**Project administration:** Ling-ling Qian.
**Software:** Wei Wang, Heng-jian Chen.
**Supervision:** Ling-ling Qian, Ru-xing Wang.
**Validation:** Shi-peng Dang, Xu Tang, Heng-jian Chen.
**Writing – original draft:** Ying Wu.
**Writing – review & editing:** Ru-xing Wang.

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