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Association between interleukin-8 gene −251 A/T polymorphism and the risk of coronary artery disease

A meta-analysis

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Abstract

Background: The association between interleukin-8 (IL-8) gene polymorphism −251 A>T and susceptibility to coronary artery disease (CAD) has been investigated previously; however, results remain controversial. Thus, a meta-analysis was conducted to reassess the effects of this polymorphism on CAD risks.

Methods: The PubMed, Cochrane Library, China National Knowledge Infrastructure, and Wanfang databases were searched for relevant studies published up to December, 2018. The pooled odds ratios (OR) were calculated using STATA 13.0 software for allelic (A vs T) as well as homozygote (AA vs TT), heterozygote (AT vs TT), recessive (AA vs AT + TT), and dominant (AA + AT vs TT) genotype models, respectively.

Results: Ten case-control studies (3744 cases and 3660 controls) were included. Overall, a significant association of IL-8 gene −251 A > T polymorphism with an increased risk of CAD was only observed in the dominant genotype model (OR = 1.48), but not others. In the subgroup analysis, significantly increased risks were also found for Chinese (OR = 1.64), polymerase chain reaction-restriction fragment length polymorphism genotyping (OR = 1.61), acute coronary syndrome (ACS) type (OR = 1.92 for 3 datasets; OR = 1.88 for 4 datasets), high quality (OR = 1.64), and age/gender matching status (OR = 1.55) under the dominant model. Furthermore, significantly increased risks were also found for ACS type under allelic (OR = 1.32 for 3 datasets; OR = 127 for 4 datasets), homozygote (OR = 1.64 for 3 datasets; OR = 1.50 for 4 datasets), heterozygote (OR = 1.32 for 3 datasets; OR = 1.30 for 4 datasets), and recessive (OR = 1.40 for 3 datasets; OR = 1.28 for 4 datasets) models.

Conclusion: This meta-analysis suggests that Chinese patients carrying −251A allele of IL-8 may have an increased risk for the development of CAD, especially ACS.

Abbreviations: ACS = acute coronary syndrome, CAD = coronary artery disease, CI = confidence interval, CVD = cardiovascular disease, HWE = Hardy–Weinberg equilibrium, IHD = ischemic heart disease, IL-8 = interleukin-8, MI = myocardial infarction, NOS = Newcastle–Ottawa scale, OR = odds ratio, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SNP = single nucleotide polymorphism.

Keywords: coronary artery disease, interleukin-8, meta-analysis, polymorphism

1. Introduction

Cardiovascular disease (CVD) is ranked as the first leading cause of death worldwide, with an estimated annual mortality of 23.3 million people by the year 2030.[1] Coronary artery disease (CAD) is the most common form of CVD, accounting for approximately one-third of all deaths.[2] Although diabetes mellitus, hypertension, dyslipidemia, smoking, alcohol

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consumption, and obesity have been demonstrated as main risk factors, several studies suggested that individuals may be genetically predisposed to developing CAD.[3–6] Thus, investigation of key genetic variants underlying CAD may be of significance to develop efficient strategies for predicting, preventing and treating CAD.

There is an increasing amount of evidence to indicate that inflammation plays important roles in the pathogenesis of CAD, specifically in the process of atherosclerosis.[7,8] Progressively increased inflammation may contribute to endothelial dysfunction and then facilitate the deposition of local lipid within the arterial wall, ultimately resulting in plaque formation and vascular stenosis followed by the development of CAD and even sudden death.[9] Interleukin-8 (IL-8) is an important pro-inflammatory mediator produced by macrophages and its level has been reported to be increased in patients with CAD.[10] Elevated IL-8 in plasma was also proved to be an independent predictor for long-term all-cause mortality in patients with acute coronary syndrome (ACS) that include unstable angina and acute myocardial infarction (MI).[11] These findings imply genetic variants that cause the differences in the production of IL-8 levels may be associated with CAD susceptibility. This hypothesis has been implicated in recent studies: Zhang et al found the promoter region of IL-8 had a remarkable single nucleotide polymorphism (SNP) structure (IL-8 −251A/T, rs4073). IL-8 level was the highest among patients carrying the AA genotype, followed by AT and then TT genotype. IL-8 −251 A/T polymorphism was associated with increased susceptibility to ACS (odds ratio [OR] = 1.30, 95% confidence interval [CI]: 1.12–1.53; P = .004).[12] The study of Zhang et al also showed patients with AT (OR = 1.59, 95% CI = 1.01–2.57; P = .04) and AA (OR = 2.06, 95% CI = 1.21–3.52; P = .005) genotypes were at an increased risk for developing CAD compared to those with the TT genotype.[13] However, subsequent research by Kaur et al[14] and Chang et al[15] suggested that the T allele may be a risk factor for CAD, while Yang et al,[16] Ren et al,[17] and Wang et al[18] found no association of IL-8 −251 A/T polymorphism with CAD risks. These controversial conclusions may be partially attributed to small sample size of individual studies. Therefore, we aimed to re-evaluate the effects of IL-8 −251 A/T polymorphism on CAD risks by performing a meta-analysis that can synthesize data from all eligible case-control studies and may achieve a more convincing conclusion. To our knowledge, this related meta-analysis has not been reported previously.

2. Materials and methods

2.1. Search strategy

Articles were identified by an electronic search on PubMed, the Cochrane Library, the China National Knowledge Infrastructure (Chinese), and Wanfang (Chinese) databases using the following keywords interleukin-8 (OR IL-8) AND coronary artery disease (OR CAD OR coronary heart disease OR CHD OR myocardial infarction OR MI OR ischemic heart disease OR IHD OR acute coronary syndrome OR ACS OR angina OR atherosclerosis OR cardiovascular) AND single nucleotide polymorphism (OR SNP OR variation OR variant OR mutation). The searching time was up to December, 2018. Furthermore, additional relevant studies on this topic were identified by a hand search of references cited by retrieved articles. Searches were limited to papers published in the English and Chinese language. This search followed the Guidelines of the preferred reporting items for systematic review and meta-analysis statement.

2.2. Selection criteria

All the articles were eligible if they met the following inclusion criteria:

(1) assessing the association between IL-8 −251A/T polymorphism and CAD;
(2) being human case-control studies;
(3) providing sufficient information on the genotypes or alleles for calculating the OR and its corresponding 95% CI; and
(4) providing the genotype distribution of control groups conformed to the assumptions of the Hardy–Weinberg equilibrium (HWE).

Studies were excluded when they were

(1) duplicated data;
(2) meeting abstracts, case reports/series, review articles, and editorial comment; and
(3) not meeting all of the inclusion criteria.

2.3. Data extraction

The following characteristics were extracted from the eligible studies: author's name, year of publication, country of origin, type of CAD, genotyping method, the source of controls, sex and age matching, HWE test, sample size, genotype and allele frequencies of cases and controls. The quality of included studies was evaluated based on the Newcastle–Ottawa scale (NOS)[18] that assessed 3 aspects:

(1) subject selection (0–4 points),
(2) comparability of subject (0–2 points), and
(3) clinical outcome (0–3 points).

A high-quality study was defined as a score of ≥7. Studies with NOS scores ≥6 were considered to be of high quality. Two authors independently reviewed, extracted, and assessed the quality of the data. All disagreements were discussed and resolved with consensus.

2.4. Statistical analysis

The analyses were conducted using the STATA software (version 13.0; STATA Corporation, College Station, TX). The overall strength of an association between −251 A/T polymorphism and CAD risk was determined by calculating the crude ORs with 95% CIs for allelic (A vs T) model as well as homozygote (AA vs TT), heterozygote (AT vs TT), recessive (AA vs AT + TT), and dominant (AA + AT vs TT) genotype models, respectively. The z-test was used to measure the statistical significance of the pooled OR and $P < .05$ was considered to be statistically significant. Furthermore, the subgroup analysis was also performed according to ethnicity (Chinese or Indian), genotyping method (polymerase chain reaction-restriction fragment length polymorphism [PCR-RFLP] or others), type of CAD (CAD, ACS, or MI), study quality (low quality: quality score <7; high quality: quality score ≥7), and the matching status of age and gender (yes or no).

Heterogeneity among studies was assessed with the Cochran Q (Chi-squared) statistic and the I^2 statistic ($P < .10$ and $I^2 >$ 50% indicated evidence of heterogeneity). A random-effects

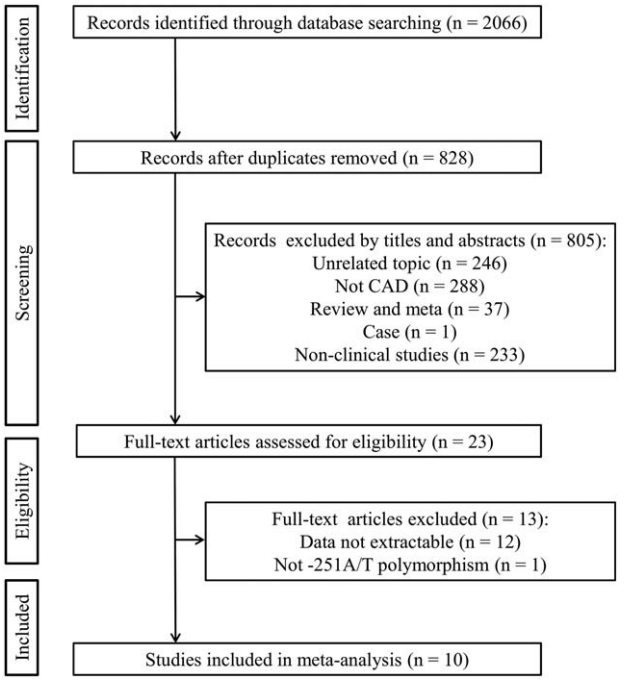

Figure 1. Flow diagram of study identification.

(heterogeneous) or fixed-effects (homogeneous) model was used to calculate pooled effect estimates. The estimate of potential publication bias was evaluated by the Egger regression test ($P < .05$ was set as the significance level) and funnel plots. Sensitivity analysis was performed by omitting each study at a time to find potential outliers.

3. Results

3.1. Characteristics of eligible studies

The flow diagram of study selection is shown in Figure 1. According to the inclusion and exclusion criteria, 10 case–control studies (including 3744 cases and 3660 controls) were eligible for this meta-analysis[12–21] (Table 1). The selected papers were published between 2010 and 2018. Most of the included studies (90%, 9/10) were performed in the Chinese population[12,13,15–21] and only 1 (10%, 1/10) was in Indian.[14] In addition, there were 8 studies conducted by PCR-RFLP,[12,13,15,16,18–21] 1 performed by amplification refractory mutation system-PCR[14] and only 1 used MassARRAY[17] to detect the SNPs. Of these included studies, 6 studies reported about overall CAD (in which 1 was also divided into ACS and non-ACS cases[21]), 1 about ACS (which included 2 datasets)[12] and 1 about MI (which was not reported to be acute or old).[18] Coronary angiography was the mainly used method to diagnose CAD, which was defined as more than 50% or 70% stenosis in at least 1 coronary artery. All of studies provided the distributions of genotype and conformed to HWE. The genotype distribution and allele frequencies in cases and controls are listed in Table 2. According to the NOS criteria, most of the included studies were considered to be of high methodological quality other than one that was performed in Indian[14] (Table 3).

3.2. Meta-analysis

The results of the association between IL-8 −251A/T polymorphism and CAD and the heterogeneity test are displayed in Table 4. Overall, a significant association of IL-8 gene −251 A > T polymorphism with an increased risk of CAD was only observed in the dominant model (AA + AT vs TT: OR = 1.48, 95% CI = 1.08–2.02; $P = .015$) (Fig. 2), but not in the allelic (A vs T: OR = 1.08, 95% CI = 0.87–1.33; $P = .498$), homozygote (AA vs TT: OR = 1.14, 95% CI = 0.77–1.69; $P = .510$), heterozygote (AT vs TT: OR = 1.04, 95% CI = 0.79–1.37; $P = .802$), and recessive (AA vs AT + TT: OR = 1.14, 95% CI = 0.91–1.42; $P = .262$) models.

In the subgroup analysis, significantly increased risks were also found for Chinese (OR = 1.64, 95% CI, = 1.29–2.08; $P < .001$), PCR-RFLP genotyping (OR = 1.61, 95% CI, = 1.24–2.10; $P < .001$), ACS type (OR = 1.92, 95% CI, = 1.63–2.57 for 3 datasets; OR = 1.88, 95% CI, = 1.58–2.24.88 for 4 datasets; both $P < .001$), high quality (OR = 1.64, 95% CI, = 1.29–2.08; $P < .001$), and age/gender matching status (OR = 1.55, 95% CI, = 1.16–2.06; $P = .003$) under the dominant model. Furthermore, significant associations were similarly identified for ACS type under allelic (A vs T: OR = 1.32, 95% CI = 1.17–1.48 for 3 datasets; OR = 1.27, 95% CI = 1.13–1.42 for 4 datasets; both $P < .001$), homozygote (AA vs TT: OR = 1.64, 95% CI = 1.28–2.10, $P < .001$ for 3 datasets; OR = 1.50, 95% CI = 1.28–2.10, $P = .001$ for 4 datasets), heterozygote (AT vs TT: OR = 1.32, 95% CI = 1.10–1.58 for 3 datasets; OR = 1.30, 95% CI = 1.10–1.53 for 4 datasets; both $P = .002$) and recessive (AA vs AT + TT:

Table 1

Characteristics of included studies in the meta-analysis.

Author	Year	Country	Genotype method	Control source	Sample size		Matching	Type	P_{HWE}	Language
					Cases	Controls				
Kaur N	2018	India	ARMS-PCR	PB	500	500	No	CAD	Yes	English
Zhang RJ	2017	China	PCR-RFLP	PB	217	245	Age	CAD	Yes	English
Yang HT	2015	China	PCR-RFLP	PB	410	410	Age	CAD	Yes	English
Ren B	2015	China	MassARRAY	PB	325	342	Age, gender	CAD	Yes	English
Wang S	2015	China	PCR-RFLP	PB	260	285	Age, gender	MI	Yes	English
Zhang X	2011	China	PCR-RFLP	PB	675/360	636/360	Age, gender	ACS	Yes	English
Chang Y	2018	China	PCR-RFLP	PB	349	385	Age, gender	CAD	Yes	Chinese
Zhang BH	2010	China	PCR-RFLP	PB	268	205	Age, gender	CAD	Yes	Chinese
Zheng JH	2015	China	PCR-RFLP	PB	136	122	Age, gender	CAD	Yes	Chinese
Hou HJ	2012	China	PCR-RFLP	PB	244	170	Age, gender	CAD (ACS)	Yes	Chinese

ACS = acute coronary syndrome, ARMS-PCR = amplification refractory mutation system–polymerase chain reaction, CAD = coronary artery disease, HWE = Hardy–Weinberg equilibrium, MI = myocardial infarction, PB = population-based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

Table 2

IL-8 −251A/T polymorphisms genotype and allele distribution in cases and controls.

Author	Sample size (cases/controls)	Genotype of cases (N)			Genotype of control (N)			Allele of cases (N)		Allele of control (N)	
		AA	AT	TT	AA	AT	TT	A	T	A	T
Kaur N	500/500	148	195	157	199	225	76	491	509	623	377
Zhang RJ	217/245	69	101	47	57	108	80	239	195	222	268
Yang HT	410/410	114	178	118	105	171	134	406	414	381	439
Ren B	325/342	93	147	85	85	149	108	333	317	319	365
Wang S	260/285	75	113	72	77	119	89	263	257	273	297
Zhang X	675/636	123	320	232	80	292	264	566	784	452	850
Zhang X	360/360	76	176	108	58	159	143	328	392	275	445
Chang Y	349/385	79	163	107	56	159	170	321	377	271	499
Zhang BH	268/205	43	126	99	39	103	63	212	324	181	229
Zheng JH	136/122	32	49	55	41	60	21	113	159	142	102
Hou HJ	244/170	41	130	73	21	85	64	212	276	127	213

OR = 1.40, 95% CI = 1.12–1.75, $P = .047$ for 3 datasets; OR = 1.28, 95% CI = 1.01–1.63, $P = .040$ for 4 datasets) models.

3.3. Publication bias

The evaluation of publication bias for AA + AT vs TT model using the Egger test indicated that the publication bias was nonsignificant ($P = .370$). Also, no obvious asymmetry was observed in the funnel plot (Fig. 3). These results revealed no evidence of publication bias.

3.4. Sensitivity analyses

As presented in Figure 4, although each study was successively removed, the overall results did not alter obviously, which indicated the high stability of the meta-analysis results.

4. Discussion

On the basis of 10 case–control studies, our meta-analysis revealed IL-8 −251A/T polymorphism was significantly associated with the susceptibility of ACS. Patients with A allele or AA, AT and AA + AT genotypes had a significantly increased risk of developing ACS. Furthermore, the AA + AT genotype was also associated with an increased risk of CAD in overall analysis and this association was consistently significant in subgroups of Chinese, PCR-RFLP genotyping, high quality, and age/gender matching status.

The IL-8 gene, located on chromosome 4q12–21, is composed of 4 exons, 3 introns, and a proximal promoter region.[22] Although several polymorphisms had been reported in these genomic structures of IL-8 gene, including +781C/T, −353A/T, +678T/C, +1633C/T, −251A/T, and +394 T/G,[23–25] only −251A/T[12–21] and +394 T/G[25] polymorphisms were studied to investigate their associations with CAD. Also, −251A/T polymorphism in the promoter region was shown to be related to the expression alteration of IL-8, with AA genotype contributing to a significantly increased level of IL-8 compared with that of the AT or TT genotype.[12,26] Moreover, higher IL-8 mRNA levels were also reported in who presented the TA genotype compared with the TT genotype.[27] Thus, −251A/T polymorphism may be a biomarker associated with a serial of inflammatory diseases, which had been demonstrated in cancer,[28] Alzheimer's disease,[29] and CAD.[12,13,19] In line with these studies, we also found AA + AT genotype was associated with an increased risk of overall CAD and all genetic models including mutant A-251 conferred susceptibility to ACS risk. This finding was also consistent with the fact that the cytokine related immune activity (exhibiting elevated level of IL-8, IL-18, IL-1β, IL-16, etc) was higher in the ACS patients compared with stable angina and normal controls.[30–32]

Table 3

Quality of included studies was evaluated based on the Newcastle–Ottawa Scale (NOS).

Study	Selection (score)				Comparability (score)		Exposure (score)		Total score
	Adequate definition of patient cases	Representativeness of patients cases	Selection of controls	definition of controls	Control for important factor or additional factor	Ascertainment of exposure (blinding)	Same method of ascertainment for participants	Non-response rate	
Kaur N	1	1	1	1	0	0	1	1	6
Zhang RJ	1	1	1	1	1	0	1	1	7
Yang HT	1	1	1	1	1	0	1	1	7
Ren B	1	1	1	1	2	0	1	1	8
Wang S	1	1	1	1	2	0	1	1	8
Zhang X	1	1	1	1	2	0	1	1	8
Chang Y	1	1	1	1	2	0	1	1	8
Zhang BH	1	1	1	1	2	0	1	1	8
Zheng JH	1	1	1	1	2	0	1	1	8
Hou HJ	1	1	1	1	2	0	1	1	8

Table 4

Meta-analysis results.

Comparison	Association			Heterogeneity	
	OR (95% CI)	*P*-value	Model	*P*-value	I^2 (%)
Allelic (A vs T)					
Overall	1.08 (0.87–1.33)	.498	R	.000	90.0
Ethnicity					
China (n = 11)	1.17 (1.00–1.36)	.051	R	.000	78.5
Others (n = 1)	0.58 (0.49 – 0.70)	.000	R	–	–
Genotyping method					
PCR-RFLP (n = 10)	1.16 (0.98–1.38)	.091	R	.000	80.7
Others (n = 2)	0.84 (0.41–1.70)	.619	R	.000	96.1
Type of CAD					
CAD (n = 8)	0.99 (0.82–1.21)	.858	R	.000	92.1
ACS* (n = 3)	1.32 (1.17–1.48)	**.000**	F	.404	0.0
MI (n = 1)	0.88 (0.75–1.04)	.376	R	–	–
ACS† (n = 4)	1.27 (1.13–1.42)	**.000**	F	.342	10.1
Study quality					
Score ≥7 (n = 11)	1.17 (1.00–1.36)	.051	R	.000	78.5
Score <7 (n = 1)	0.58 (0.49–0.70)	.000	R	–	–
Age and gender matching status (yes or no)					
No (n = 3)	0.99 (0.57–1.71)	.961	R	.000	95.2
Yes (n = 9)	1.14 (0.94–1.37)	.181	R	.000	81.7
Homozygote (AA vs TT)					
Overall	1.14 (0.77–1.69)	.510	R	.000	88.7
Ethnicity					
China (n = 11)	1.32 (0.99–1.77)	.060	R	.000	75.7
Others (n = 1)	0.36 (0.26–0.51)	.000	R	–	–
Genotyping method					
PCR-RFLP (n = 10)	1.31 (0.95–1.82)	.105	R	.000	95.9
Others (n = 2)	0.70 (0.19–2.65)	.604	R	.000	78.1
Type of CAD					
CAD (n = 8)	1.06 (0.61–1.85)	.835	R	.000	91.3
ACS* (n = 3)	1.64 (1.28–2.10)	**.000**	F	.332	9.2
MI (n = 1)	1.20 (0.77–1.88)	.413	R	–	–
ACS† (n = 4)	1.50 (1.18–1.92)	**.001**	F	.305	17.2
Study quality					
Score ≥7 (n = 11)	1.32 (0.99–1.77)	.060	R	.000	75.7
Score <7 (n = 1)	0.36 (0.26–0.51)	.000	R	–	–
Age and gender matching status (yes or no)					
No (n = 3)	0.96 (0.35–2.66)	.938	R	.000	94.9
Yes (n = 9)	1.26 (0.88–1.80)	.205	R	.000	79.2
Heterozygote (AT vs TT)					
Overall	1.04 (0.79–1.37)	.802	R	.000	84.3
Ethnicity					
China (n = 11)	1.18 (0.97–1.43)	.107	R	.001	65.1
Others (n = 1)	0.42 (0.30–0.59)	.000	R	–	–
Genotyping method					
PCR-RFLP (n = 10)	1.16 (0.94–1.445)	.554	R	.001	68.6
Others (n = 2)	0.72 (0.25–2.12)	.176	R	.000	94.7
Type of CAD					
CAD (n = 8)	0.94 (0.631.40)	.749	R	.000	87.7
ACS* (n = 3)	1.32 (1.10–1.58)	**.002**	F	.734	0.0
MI (n = 1)	1.17 (0.78–1.76)	.436	R	–	–
ACS† (n = 4)	1.30 (1.10–1.53)	**.002**	F	.826	0.0
Study quality					
Score ≥7 (n = 11)	1.18 (0.97–1.43)	.107	R	.001	65.1
Score <7 (n = 1)	0.42 (0.30–0.59)	.000	R	–	–
Age and gender matching status (yes or no)					
No (n = 3)	0.92 (0.41–2.03)	.830	R		0.000
Yes (n = 9)	1.13 (0.89–1.44)	.313	R		0.001
Recessive (AA vs AT + TT)					
Overall	1.14 (0.91–1.42)	.262	R	.000	73.8
Ethnicity					
China (n = 11)	0.64 (0.49–0.83)	.027	R	.016	54.4
Others (n = 1)	1.23 (1.03–1.48)	.001	R	–	–
Genotyping method					
PCR-RFLP (n = 10)	1.23 (1.00–1.52)	.051	R	.009	58.8
Others (n = 2)	0.87 (0.46–1.64)	.664	R	.003	88.3
Type of CAD					
CAD (n = 8)	1.11 (0.81–1.51)	.515	R	.000	80.3
ACS* (n = 3)	1.40 (1.12–1.75)	**.047**	F	.227	32.5
MI (n = 1)	1.10 (0.75–1.59)	.635	R	–	–
ACS† (n = 4)	1.28 (1.01–1.63)	**.040**	F	.245	27.8
Study quality					
Score ≥7 (n = 11)	0.64 (0.49–0.83)	.027	R	.016	54.4
Score <7 (n = 1)	1.23 (1.03–1.48)	.001	R	–	–
Age and gender matching status (yes or no)					
No (n = 3)	1.01 (0.61–1.69)	.963	R		0.001
Yes (n = 9)	1.21 (0.96–1.52)	.103	R		0.009

(*continued*)

Table 4

(continued).

Comparison	Association			Heterogeneity	
	OR (95% CI)	*P*-value	Model	*P*-value	I^2 (%)
Dominant (AA + AT vs TT)					
Overall	1.48 (1.08–2.02)	.015	R	.000	90.0
Ethnicity					
China (n = 11)	1.64 (1.29–2.08)	**.000**	R	.000	80.2
Others (n = 1)	0.57 (0.42–0.77)	.000	R	–	–
Genotyping method					
PCR-RFLP (n = 10)	1.61 (1.24–2.10)	**0.000**	R	.000	82.2
Others (n = 2)	1.03 (0.32–3.27)	.963	R	.000	96.3
Type of CAD					
CAD (n = 8)	1.33 (0.84–2.09)	.223	R	.000	92.0
ACS* (n = 3)	1.92 (1.63–2.57)	**.000**	F	.169	43.8
MI (n = 1)	1.80 (1.25–2.58)	.001	R	–	–
ACS† (n = 4)	1.88 (1.58–2.24)	**.000**	F	.300	18.2
Study quality					
Score ≥7 (n = 11)	1.64 (1.29–2.08)	**.000**	R	.000	80.2
Score <7 (n = 1)	0.57 (0.42–0.77)	.000	R	–	–
Age and gender matching status (yes or no)					
No (n = 3)	1.34 (0.56–3.17)	.511	R		0.000
Yes (n = 9)	1.55 (1.16–2.06)	**.003**	R		0.000

Bold indicated the *P*-values to be significant by meta-analysis of at least 2 studies.

ACS = acute coronary syndrome, CAD = coronary artery disease, CI = confidence interval, F = fixed-effects model, MI = myocardial infarction, OR = odds ratios, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, R = random-effects model.

* Analysis with 3 datasets, not including the study of Wang et al due to no specific description of it as acute MI.

† Including the study of Wang et al by hypothesis of it as acute MI.

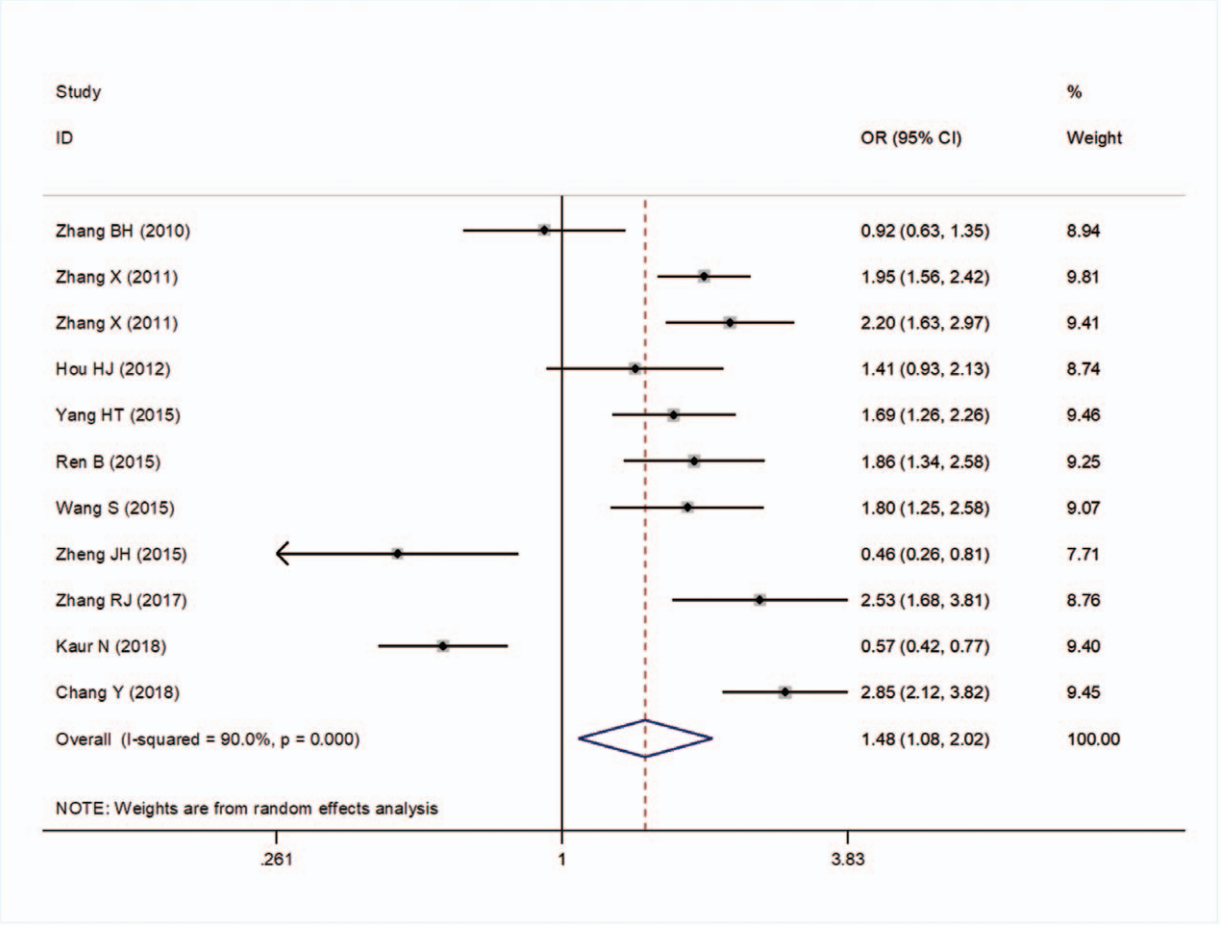

Figure 2. Forest plots of the association of IL-8 gene −251 A > T polymorphism with an increased risk of CAD under the dominant genotype model (AA + AT vs TT). Squares indicate OR; horizontal lines indicate 95% CI; hollow diamond indicates the pooled OR and its 95% CI. CAD = coronary artery disease, CI = confidence intervals, OR = odds ratio.

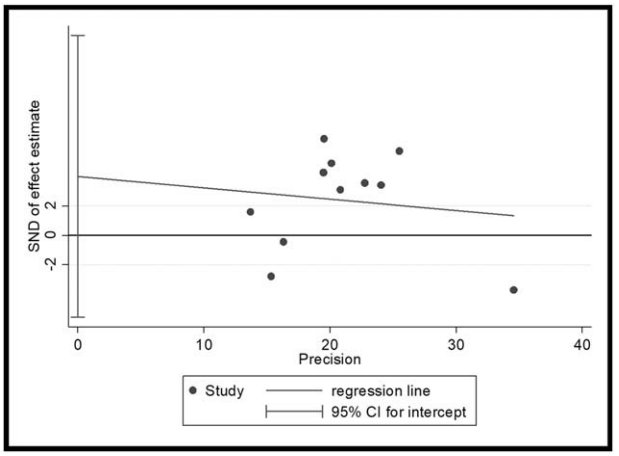

Figure 3. Egger funnel plot of the overall analysis for the assessment of potential publication bias (dominant genotype model). Each circle represents a separate study. CI = confidence intervals, SND = standard normal deviation.

Although the mechanism remains unclear, it is supposed the higher IL-8 may contribute to the development and progression of CAD via the following potential mechanisms:

(1) cholesterol efflux: Chen et al used the human IL-8-neutralizing antibody to demonstrate that IL-8 may inhibit cholesterol efflux and promote lipid accumulation, leading to the development of atherosclerosis[33];
(2) angiogenesis: Kyriakakis et al reported that antigen-activated invariant natural killer T cells could release IL-8 and then up-regulate the expression of surface IL-8 receptors (C-X-C motif chemokine receptor 2 and vascular endothelial growth factor receptor 2) to promote endothelial cell migration and sprouting, influencing the stability of atherosclerotic plaques[34]; and
(3) apoptosis: IL-8 is involved in the initiation and amplification of acute inflammatory reactions and then induces injured apoptosis of endothelial cells.[35]

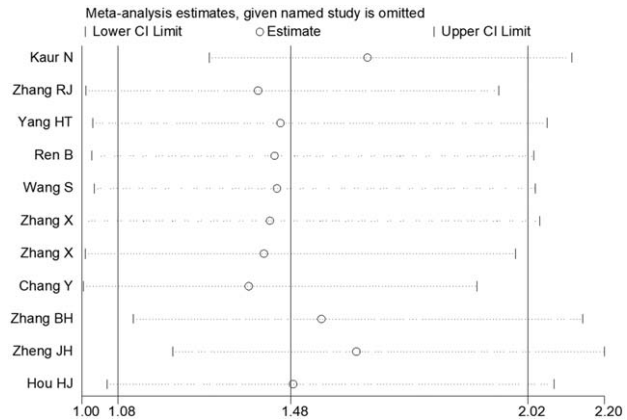

Figure 4. Sensitivity analysis of the overall analysis for the assessment of influence of each study (dominant model). Every hollow round indicates the pooled OR when the left study is omitted in this meta-analysis. The 2 ends of every broken line represent the 95% CI. The horizontal axis is ln (OR). CI = confidence intervals, OR = odds ratio.

There are several limitations in this meta-analysis. First, CAD is a multifactorial disease, which may be influenced by interactions between gene-gene as well as gene-environment. However, unadjusted ORs estimates were only used in this study due to the lack of the link between compounding factors (ie, diabetes mellitus, hypertension, dyslipidemia, smoking, alcohol consumption, and obesity) and genotype distribution in the original data of the eligible studies. Second, the number of cases and controls in some specific subgroups was relatively small, which may not provide sufficient statistical power to estimate the correlation between the IL-8 gene polymorphisms and the susceptibility to CAD. Third, only 2 Asian countries were included in the analysis and most of the data (90%) were from China. Fourth, only English or Chinese published studies were included in this meta-analysis. Non-significant or negative findings in other language may be missed.

In conclusion, this meta-analysis provides robust evidence that Chinese patients carrying -251A allele of IL-8 may have an increased risk for the development of CAD, especially ACS.

Author contributions

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