

# Tumor necrosis factor-alpha G-238A polymorphism and coronary artery disease risk: a meta-analysis of 4,222 patients and 4,832 controls

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**Background:** The aim of the present study was to investigate the association between tumor necrosis factor-alpha (TNF- $\alpha$ ) gene G-238A polymorphism and risk of coronary artery disease (CAD) using a meta-analytical approach.

**Methods:** The PubMed and Embase databases were searched for relevant publications up to January 13, 2015. Four authors (XPH, XDZ, XTZ, and ZJZ) independently selected the studies, extracted, and analyzed the data using the Comprehensive Meta-Analysis software. The sensitivity and subgroups analyses were also performed. Either a fixed effects or a random effects model was used to estimate pooled odds ratios (ORs) and their 95% confidence intervals (CIs).

**Results:** Finally, ten articles including eleven case-control studies involving 4,222 patients and 4,832 controls were yielded. The results indicated no significant association between G-238A polymorphism and CAD risk (A vs G: OR = 1.08, 95% CI = 0.89–1.30; AA vs GG: OR = 1.15, 95% CI = 0.59–2.25; GA vs GG: OR = 1.14, 95% CI = 0.88–1.48; AA vs [GG + GA]: OR = 1.09, 95% CI = 0.56–2.14; (GA + AA) vs GG: OR = 1.11, 95% CI = 0.90–1.38). In the subgroup analyses, similar results were obtained with overall populations. The sensitivity analyses showed that the overall results were robust. No publication bias was detected.

**Conclusion:** Based on current evidence, we can conclude that TNF- $\alpha$  G-238A polymorphism might not be associated with CAD risk.

**Keywords:** tumor necrosis factor-alpha, TNF- $\alpha$ , polymorphism, coronary artery disease, coronary heart disease, meta-analysis

## Introduction

Tumor necrosis factor-alpha (TNF- $\alpha$ ) is an inflammatory mediator that plays important roles in inflammatory and immune responses.<sup>1</sup> Several single-nucleotide polymorphisms (SNPs) have been identified in the TNF- $\alpha$  promoter.<sup>2</sup> Of these SNPs, conversion from guanine (G) to adenine (A) in the promoter at position-308 (rs1800629) and -238 (rs361525) has been intensively studied for these allelic variations showing functional significance.<sup>3,4</sup> Many studies have identified that the TNF- $\alpha$  G-308A and/or G-238A are associated with many human diseases,<sup>5–8</sup> including coronary artery disease (CAD).<sup>9,10</sup> Of these diseases, the association between these two polymorphisms and some diseases were identified via a meta-analytical approach, from which inconsistent results can be pooled from original studies and a more precise results can be provided.<sup>11</sup>

CAD is also named as ischemic heart disease or coronary heart disease, mainly including stable angina pectoris, unstable angina pectoris, and myocardial infarction.<sup>12,13</sup> Serum levels of TNF- $\alpha$  are elevated in patients with CAD and might modify the risk for developing CAD events since it affects endothelial cell hemostatic function.<sup>14</sup> Hence,

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we can hypothesize that TNF- $\alpha$  gene polymorphisms might be involved in the CAD susceptibility. In 1998, Herrmann et al performed a case-control study in France and Northern Ireland population, and the results showed that the TNF- $\alpha$  gene G-308A and G-238A polymorphisms were unlikely to contribute to CAD risk in an important way.<sup>15</sup> Since then, many epidemiological studies have been published and inconsistent results have been revealed. The association between TNF- $\alpha$  G-308A polymorphism and CAD risk has been investigated by three published meta-analyses.<sup>9,10,16</sup> In contrast, there is no meta-analysis on the association between TNF- $\alpha$  gene G-238A polymorphism and CAD risk until now. Therefore, we conducted this meta-analysis to study the overall correlation between the G-238A polymorphism and CAD susceptibility.

## Materials and methods

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>17</sup> As meta-analysis is a secondary analysis, ethical approval is not necessary.

## Eligibility criteria

According to the PICOS<sup>18</sup> approach, the publication was considered eligible if it met all the following criteria: 1) the patient was clearly diagnosed with CAD, coronary heart disease, ischemic heart disease, stable angina pectoris, unstable angina pectoris, myocardial infarction, or other CAD variants; 2) the exposure was the presence of G-238A polymorphism in the TNF- $\alpha$  gene; 3) the control group was healthy population or volunteers without coronary heart disease manifestations, either from hospital or community; 4) the outcome was the incidence of CAD, either fatal or nonfatal; and 5) the study was used a case-control design. Moreover, the information essential for calculating odds ratios (ORs) and relevant 95% confidence intervals (CIs) should be provided. We chose the most comprehensive report if duplicate publication or overlapped information was identified.

## Information sources

The PubMed and Embase databases were searched for relevant publications up to January 13, 2015. Keywords were coronary heart disease, coronary artery disease, ischemic heart disease, angina pectoris, angina, acute coronary syndrome, myocardial infarction, myocardial infarct, polymorphism, and tumor necrosis factor or TNF. References of recent reviews, previous meta-analyses, and eligibility

studies were also manually scanned. Table S1 shows the search strategy used for the PubMed.

## Data collection

Two authors (XPH and ZJZ) independently retrieved and selected studies for inclusion according to the aforementioned eligibility criteria. Then these two authors extracted the following data from the included studies: the last name of first author and publication year, country of origin and ethnicity, endpoints of CAD, polymorphism, sample size of cases and controls, source of controls, genotype distribution of cases and controls, genotyping method, and Hardy–Weinberg equilibrium (HWE) for control. HWE was tested by  $\chi^2$  test at the 50% significance level. Disagreements were resolved by discussion.

## Data analysis

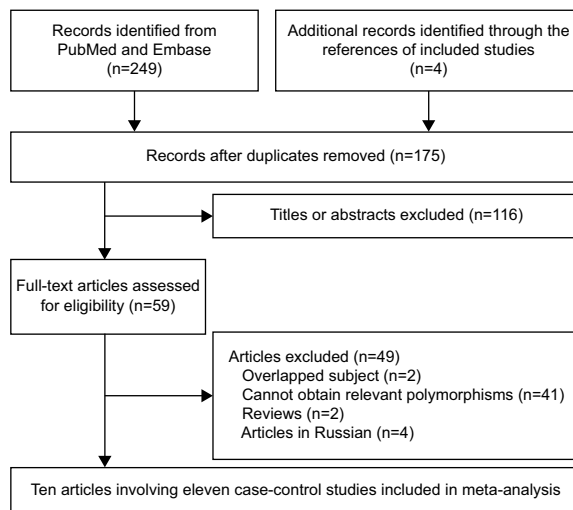
The ORs and corresponding 95% CIs were calculated to summarize the pooled effect sizes for G-238A polymorphism. All possible genetic models, the allelic model (A vs G), dominant model ([AG + AA] vs GG), codominant model (AA vs GG, AG vs GG), and recessive model (AA vs [AG + GG]) were used to estimate the overall relationship.

First, the heterogeneity was quantitatively evaluated using the  $I^2$  statistic.<sup>19</sup> An  $I^2$  value no larger than 25% indicates the absence of heterogeneity, so the fixed effects model was suggested; otherwise, the random effects model was used. The subgroup analysis was performed to investigate the source of heterogeneity and the difference between different ethnicities and HWE. The sensitivity analysis was conducted by sequential omission of individual studies to assess the influence of overall results.<sup>20</sup> The funnel plot and Egger's test were used to detect the publication bias.<sup>21</sup> All the analyses were conducted using the Comprehensive Meta-Analysis software (version 2.2; Biostat, Englewood, NJ, USA).<sup>22,23</sup>

## Results

### Study selection

The flowchart of study selection process is shown in Figure 1. A total of 253 publications were identified initially, and 175 publications were selected for further screening after removing duplicate records. After titles or abstracts were screened, a total of 59 articles preliminarily met the inclusion criteria. Four potential eligible articles were excluded because they were published in Russian and full texts could not be accessed.<sup>24–27</sup> Two case-control studies identified in one article<sup>15</sup> were considered as independent studies. From four articles<sup>28–31</sup> with overlapped population, two articles<sup>28,30</sup>



**Figure 1** Flowchart of study section in the meta-analysis.

presenting more comprehensive information were included. Finally, ten articles with eleven case-control studies were included in this meta-analysis.<sup>15,32–40</sup>

## Study characteristics

Eleven case-control studies involving 4,222 cases and 4,832 controls investigated G-238A polymorphism.<sup>15,32–40</sup> There were five studies based on Caucasian population<sup>15,32,33,35</sup> and six studies concerning Asian population.<sup>34,36–40</sup> Three of these studies were out of HWE.<sup>37–39</sup> All controls were healthy population, eg, healthy visitors of patients, healthy volunteers,

healthy blood donors, or outpatients confirmed negative by cardiac assessment. Table 1 shows the main characteristics of all the included studies.

## Meta-analysis

Of the eligible eleven case-control studies, one study<sup>40</sup> reported significant association; in contrast, the other ten studies demonstrated that the association was nonsignificant (Figure 2). The overall results of five genetic models all identified nonsignificant association between G-238A polymorphism and CAD risk (A vs G: OR =1.08, 95% CI =0.89–1.30,  $I^2=34.33\%$ , Figure 2; AA vs GG: OR =1.15, 95% CI =0.59–2.25,  $I^2=0\%$ ; GA vs GG: OR =1.14, 95% CI =0.88–1.48,  $I^2=54.34\%$ ; AA vs [GG + GA]: OR =1.09, 95% CI =0.56–2.14,  $I^2=0\%$ ; [GA + AA] vs GG: OR =1.11, 95% CI =0.90–1.38,  $I^2=41.92\%$ ).

After being stratified by ethnicity, the results of Asian and Caucasian populations were similar to that of the overall population. The studies in HWE also revealed nonsignificant association. Table 2 shows the overall and subgroup analyses results of G-238A polymorphism and CAD risk. The sensitivity analysis showed that none of the included eleven studies dramatically influenced the pooled results under all the five genetic models (Figure 3).

## Publication bias

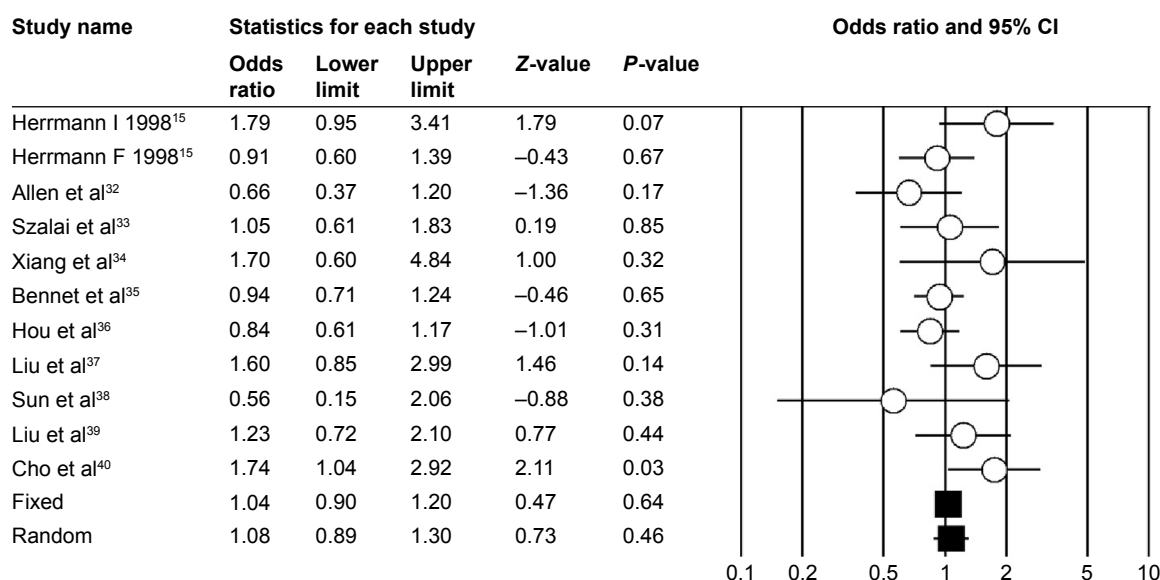
The funnel plots (Figure 4) and Egger's test demonstrated that there was no publication bias in our meta-analysis ( $P=0.28$  for

**Table 1** Characteristics of the included studies

Study	Country (ethnicity)	Disease	Sample (Ca/Co)	Genotype frequency (Ca/Co)			Source of controls	Genotype method	HWE for controls
				GG	GA	AA			
Herrmann I (1998) <sup>15</sup>	Northern Ireland (Caucasian)	MI	196/176	168/161	27/15	1/0	Healthy	PCR-SSCP	Yes
Herrmann F (1998) <sup>15</sup>	France (Caucasian)	MI	446/531	408/481	36/48	2/2	Healthy	PCR-SSCP	Yes
Allen et al <sup>32</sup>	UK (Caucasian)	CAD	180/250	162/220	17/29	1/1	Healthy	PCR-RFLP	Yes
Szalai et al <sup>33</sup>	Hungary (Caucasian)	CAD	318/248	287/225	31/23	0/0	Healthy	PCR-RFLP	Yes
Xiang et al <sup>34</sup>	People's Republic of China (Asian)	CHD	162/182	154/176	7/6	1/0	Healthy	PCR-RFLP	Yes
Bennet et al <sup>35</sup>	Sweden (Caucasian)	MI	1,150/1,468	1,068/1,348	75/119	7/1	Healthy	PCR-RFLP	Yes
Hou et al <sup>36</sup>	People's Republic of China (Asian)	CHD	804/905	740/819	63/86	1/0	Healthy	PCR-RFLP	Yes
Liu et al <sup>37</sup>	People's Republic of China (Asian)	CHD	276/202	248/191	24/7	4/4	Healthy	PCR-RFLP	No
Sun et al <sup>38</sup>	People's Republic of China (Asian)	CHD	73/138	70/129	3/8	0/1	Healthy	PCR-RFLP	No
Liu et al <sup>39</sup>	People's Republic of China (Asian)	CAD	420/328	388/311	28/11	4/6	Healthy	PCR-RFLP	No
Cho et al <sup>40</sup>	South Korea (Asian)	CAD	197/404	169/371	28/32	0/1	Healthy	PCR-RFLP	Yes

**Notes:** Herrmann I 1998, the study conducted in Northern Ireland; Herrmann F 1998, the study conducted in France.

**Abbreviations:** Ca, case group; Co, control group; CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction; HWE, Hardy–Weinberg equilibrium; PCR-SSCP, polymerase chain reaction single-strand conformation polymorphism; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism.



**Figure 2** Forest plot of overall population of TNF- $\alpha$  G-238A polymorphism and CAD risk (A vs G model).

**Notes:** Herrmann I 1998, the study conducted in Northern Ireland; Herrmann F 1998, the study conducted in France.

**Abbreviations:** TNF- $\alpha$ , tumor necrosis factor-alpha; CAD, coronary artery disease; CI, confidence interval.

A vs G;  $P=0.14$  for AA vs GG;  $P=0.06$  for GA vs GG;  $P=0.17$  for AA vs [GG + GA];  $P=0.12$  [GA + AA] vs GG).

## Discussion

CAD remains the major cause of mortality and morbidity worldwide. Smoking, diabetes, hypertension, obesity,

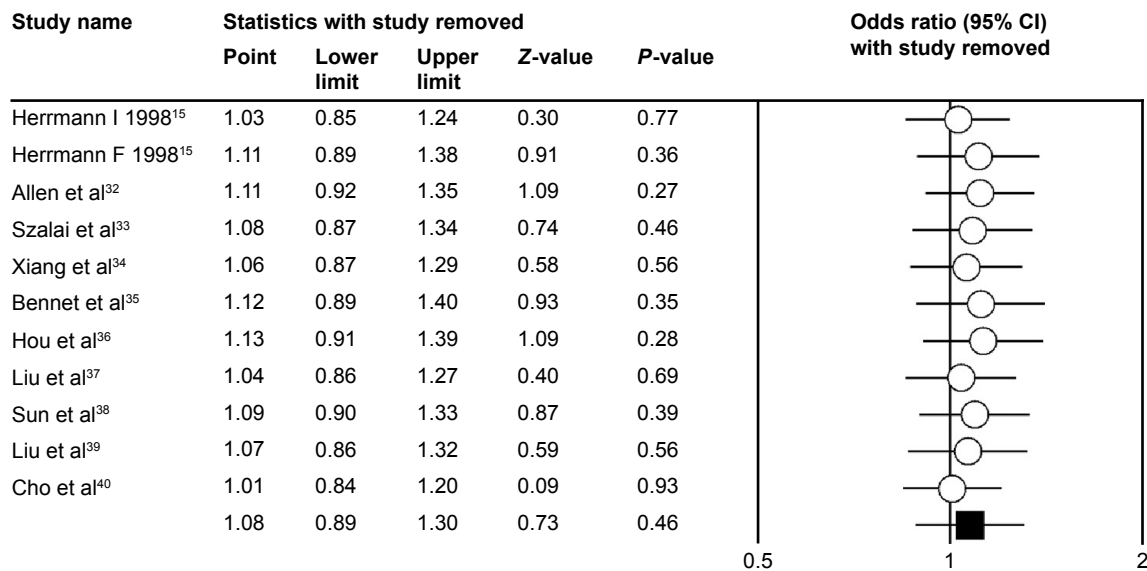
family history, stress, hyperlipidemia, and alcohol abuse were considered the conventional risk factors of CAD; however, these conventional factors can only explain 50% of the total risk factors of CAD cases.<sup>41–47</sup> Genetic factors might contribute to the other half of the total risk factors, and many polymorphisms are considered to be associated with the onset and development of CAD.<sup>12,46,48–51</sup> Our meta-analysis focused on the TNF- $\alpha$  gene promoter G-238A polymorphism and revealed that this polymorphism was not associated with CAD risk. In the subgroup analyses, similar results with overall population were obtained, and the sensitivity analyses showed that the overall results were robust.

There were ten publications with eleven case-control studies focusing on the G-238A polymorphism and CAD risk in our meta-analysis. According to the result of literature search, our meta-analysis is the first meta-analysis on the G-238A polymorphism. Similar to G-308A polymorphism,<sup>9,10,16</sup> our result also revealed a nonsignificant association between G-238A polymorphism and risk of CAD. We also performed subgroup analysis to investigate the effects of ethnicity and HWE. Only Asian and Caucasian populations were adopted. The subgroup analysis revealed no association for Asian population, Caucasian population, and the studies in HWE. Considering the interesting phenomenon of G-308A polymorphism,<sup>9,10,16</sup> the G-238A polymorphism included small number of studies and needs further research. In other words, the current result is not the final result.

**Table 2** Results of overall estimates and subgroup analysis

Genetic model	G-238A polymorphism			
	Studies	OR (95% CI)	Model	P (%)
<b>A vs G</b>				
Overall	11	1.08 (0.89–1.30)	REM	34.33
Asian	6	1.21 (0.88–1.68)	REM	42.46
Caucasian	5	0.98 (0.77–1.24)	REM	25.48
HWE (yes)	8	1.04 (0.84–1.30)	REM	41.47
<b>AA vs GG</b>				
Overall	11	1.15 (0.59–2.25)	FEM	0
Asian	6	0.79 (0.35–1.78)	FEM	0
Caucasian	5	2.60 (0.79–8.48)	FEM	0
HWE (yes)	8	2.42 (0.89–6.55)	FEM	0
<b>AG vs GG</b>				
Overall	11	1.14 (0.88–1.48)	REM	54.34
Asian	6	1.43 (0.88–2.33)	REM	64.4
Caucasian	5	0.91 (0.74–1.11)	FEM	15.9
HWE (yes)	8	1.02 (0.80–1.30)	REM	44.86
<b>AA vs (AG + GG)</b>				
Overall	11	1.09 (0.56–2.14)	FEM	0
Asian	6	0.76 (0.34–1.71)	FEM	0
Caucasian	5	2.38 (0.73–7.77)	FEM	0
HWE (yes)	8	2.26 (0.83–6.12)	FEM	0
<b>(AG + AA) vs GG</b>				
Overall	11	1.11 (0.90–1.38)	REM	41.92
Asian	6	1.31 (0.88–1.94)	REM	53.62
Caucasian	5	0.96 (0.77–1.18)	FEM	8.18
HWE (yes)	8	1.05 (0.83–1.30)	REM	39.85

**Abbreviations:** OR, odds ratio; CI, confidence interval; REM, random effect model; HWE, Hardy–Weinberg equilibrium; FEM, fixed effect model.



**Figure 3** Forest plot of sensitivity analysis by omitting a single study each time of overall population of TNF- $\alpha$  G-238A polymorphism and CAD risk (A vs G model).

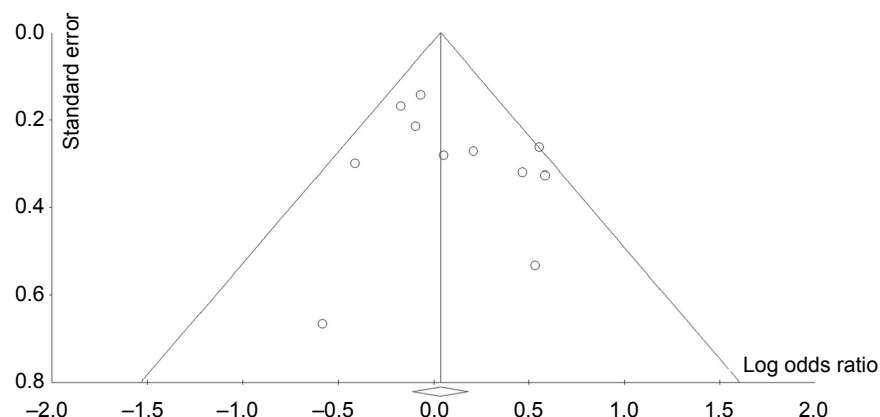
**Notes:** Herrmann I 1998, the study conducted in Northern Ireland; Herrmann F 1998, the study conducted in France.

**Abbreviations:** TNF- $\alpha$ , tumor necrosis factor-alpha; CAD, coronary artery disease; CI, confidence interval.

For this polymorphism, how many new studies should be conducted in the future remains a question. Based on current evidence, we could not judge whether the sample size was sufficient for decisive conclusion. Moreover, whether significant correlation between G-238A polymorphism and risk of CAS exists in other ethnicity, such as Africans or Turks, remains unclear. Also, the polymorphism associated with patients with CAD and concomitant diseases, such as periodontal disease,<sup>52</sup> also needs to be examined in further researches. Moreover, our meta-analysis also provides some clinical implications. We knew that, the personalized drug treatment is involved in the genetic background. Hence, development of a special drug for patients with CAD with G-238A polymorphism is not needed. However, the clinicians should advise their patients with this polymorphism to have peace of mind and not to take this polymorphism as a risk factor in the clinical work.

TNF- $\alpha$  G-238A polymorphism might not be considered for the genetic diagnosis of CAD.

Obviously, heterogeneity was large in three genetic models. Mild heterogeneity detected in certain genetic models and subgroup analyses was only partially explained by ethnicity and HWE (Table 2). The heterogeneity is common in meta-analysis of genetic association studies,<sup>23,53–55</sup> and we should not ignore it since pooled results may be influenced by heterogeneity. Therefore, the substantial heterogeneity was one limitation of our meta-analysis. Second, as all the included studies were limited within Asians or Caucasians, our conclusion may not be reasonably extrapolated for other ethnic groups. Third, the sample size from eligible studies was not enough. The small sample size might influence the result. Although we tried our best to collect all the relevant studies, certain publications published in languages other



**Figure 4** Funnel plot of standard error by log odds ratio for detection publication bias of G-238A polymorphism (A vs G model).



than English or Chinese were excluded because of inaccessibility to the full text and/or impenetrability due to language barriers. Hence, although the test for publication bias revealed no publication bias in our meta-analysis, the bias that originated from publication bias should not be ignored. Fourth, for lacking original data of gene–gene and gene–environmental interactions and adjusted conventional risk factors, we could not further evaluate potential gene–gene and gene–environmental interactions based on adjusted ORs. Finally, for lacking appropriate methodological quality tool,<sup>11</sup> we did not assess the risk of bias of included studies. Hence, current results based on unadjusted data may be confounded to the pooled effect.

## Conclusion

In conclusion, there was no evidence suggesting that TNF- $\alpha$  G-238A polymorphism was associated with the risk of CAD. The nonsignificant results were without ethnic difference. Due to the limitations and implications of current meta-analysis, we suggest that further well-designed studies with large sample size should be conducted to clarify the association between the polymorphisms and CAD risk, among which meta-analysis of genome-wide association studies<sup>56</sup> is the best.

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## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary material

**Table S1** The search strategy of PubMed

No	Query results	Results
14	Search (((((((coronary heart disease[Text Word]) OR ischemic heart disease[Text Word]) OR angina pectori[Text Word]) OR angina[Text Word]) OR acute coronary syndrome[Text Word]) OR myocardial infarction[Text Word]) OR myocardial infarct[Text Word]) OR coronary artery disease[MeSH]) AND ((tumor necrosis factor[Text Word]) OR TNF[Text Word]) AND polymorphism[Text Word]	159
13	Search polymorphism[Text Word]	229,416
12	Search (tumor necrosis factor[Text Word]) OR TNF[Text Word]	167,359
11	Search TNF[Text Word]	113,071
10	Search tumor necrosis factor[Text Word]	136,792
9	Search (((((((coronary heart disease[Text Word]) OR ischemic heart disease[Text Word]) OR angina pectori[Text Word]) OR angina[Text Word]) OR acute coronary syndrome[Text Word]) OR myocardial infarction[Text Word]) OR myocardial infarct[Text Word]) OR coronary artery disease[MeSH]	304,794
8	Search Coronary Artery Disease[MeSH]	37,314
7	Search myocardial infarct[Text Word]	18,735
6	Search myocardial infarction[Text Word]	189,875
5	Search acute coronary syndrome[Text Word]	14,457
4	Search angina[Text Word]	60,634
3	Search angina pectori[Text Word]	0
2	Search ischemic heart disease[Text Word]	20,146
1	Search coronary heart disease[Text Word]	39,801

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