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Contribution of the polymorphism rs1800469 of transforming growth factor β in the development of myocardial infarction: meta-analysis of 5460 cases and 8413 controls (MOOSE-compliant article)

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Abstract

Studies investigating the association between transforming growth factor (TGF-β-509C/T, rs1800469) promoter polymorphism and myocardial infarction (MI) risk reported inconsistent results. The aim of our study was to assess the association between the 509C/T polymorphism of the *TGF-β* gene (rs1800469) and MI risk.

A total of 5460 cases and 8413 controls in 7 case–control studies were incorporated in our current meta-analysis. The original studies were selected through searching the databases of the PubMed and EMBASE. The odds ratio (OR) and 95% confidence interval (95% CI) of TGF-β 509C/T (rs1800469) for MI risk were applied to estimate the strength of the association.

Our results showed that T allele carriers had a 13% increased risk of MI, when compared with the C allele carriers (OR = 1.13, 95% CI: 1.00–1.27). In the subset analysis by the type of MI, significantly elevated risk of MI was associated with the homozygote TT and heterozygote C/T in no-AMI subjects, when compared with the CC homozygote carriers (OR = 1.12, 95% CI:1.02–1.23).

Our meta-analysis shows that the polymorphism with homozygote TT and heterozygote C/T of TGF-β 509C/T (rs1800469) is significantly associated with the increased risk of MI.

Abbreviations: CAD = Coronary artery disease, CI = confidence interval, HCC = hospital-based case-control study, HWE = Hardy-Weinberg equilibrium, MAF = Minor Allele Frequency, MI = myocardial infarction, OR = odds ratio, PCC = population-based case-control study, TGF-β = transforming growth factor-β, VSMCs = vascular smooth muscle cells.

Keywords: cytokine gene polymorphisms, myocardial infarction, transforming growth factor beta

1. Introduction

Coronary artery disease (CAD), including myocardial infarction (MI), is a complex disorder and is one of the leading cause of high

mortality and morbidity worldwide, thus remaining a serious public health burden.[1,2] There are approximately 17.5 million deaths from CAD-related diseases in 2012.[3] Identification of subjects at risk for CAD/MI and gaining insights into the pathogenesis of them remain a tremendous challenge. Therefore, early-phase screening of risk factors can be an effective strategy of primary prevention of the development of CAD and MI. It is widely acknowledged that CAD is a chronic inflammatory disease.[4] The development of CAD and MI is a multistep process involving many factors.[4] Although etiology of CAD and MI requires to be further studied, cumulative evidence indicates that gene-based self-susceptibility and environmental factors may contribute to the development CAD and MI.[5] Interindividual mutations in the genetic and inflammatory mechanisms could elucidate the different degrees of susceptibility to the development of CAD and MI.[6]

Transforming growth factor-β (TGF-β), the most common mutation of 3 isoforms, has been investigated to inhibit the proliferation and migration of vascular smooth muscle cells (VSMCs) in culture.[7,8] TGF-β signaling has been observed to initiate myocardial fibrosis and remodeling in the development of CAD and play an important role in fibrosis in the promotion of CAD and MI. It has been indicated that the serum concentration of active cytokine of TGF-β1 is significantly elevated in patients with CAD and MI than in controls, and the concentration of this TGF-β1 was proportional to the severity of CAD and MI.[8–10] The *TGF-β1* gene is located on chromosome 19q13.2.[11] The occurrence of TGF-β 509C/T (rs1800469) results from a single

nucleotide mutation and has been extensively assessed in different epidemiological studies. A number of studies have attempted to investigate whether naturally occurring polymorphism in the TGF-β (rs1800469) gene change TGF-β1 expression and TGF-β production and whether these polymorphisms are associated with the development of CAD and MI.

Hence, it is suspected that TGF-β-509C/T (rs1800469) correlates with the progression and prognosis of MI. Although there are currently many studies concerning the association between TGF-β-509C/T polymorphism (rs1800469) and MI risk, conclusive results are not yet to be reached. During the last 2 decades, a number of reports have been carried out aiming to clarify the correlation between TGF-β polymorphism (rs1800469) and MI risk in humans.[12–17] However, previous studies have reported inconsistent results. Some studies have showed null association between TGF-β-509C/T (rs1800469) and MI risk,[18] whereas several studies indicate a strong association.[19] These inconsistent findings require further clarification.

To elucidate a more precise conclusion of the effect of TGF-β genotype (rs1800469) and the risk of developing MI, a meta-analysis of all included reports was performed. To the authors' knowledge, this is the first genetic meta-analysis to investigate the relationship between the TGF-β polymorphism (rs1800469) and MI risk.

2. Materials and methods

The review boards of all participating institutions (Chong Gang Iron and Steel General Hospital, Vanderbilt University School of Medicine and Sichuan Provincial People's Hospital) approved the research protocols.

2.1. Literature search

Electronic databases, including PubMed/Medline (US National Library of Medicine) and EMBASE (Elsevier B.V., Amsterdam, Netherlands) were screened for all published reports assessing the association between TGF-β polymorphism and MI risk in humans. The following search keywords were applied: MI, CAD, and TGF-β, in combination with variant, polymorphism, mutation. All languages were incorporated. Studies incorporated in our meta-analysis met the following inclusion criteria: assessment of TGF-β gene (509C/T) polymorphisms (rs1800469) and MI risk; case–control studies; availability of genotype distributions for both controls and cases in human with odds ratio (OR) with 95% confidence interval (CI). Accordingly, the following exclusion criteria were applied: repeat or over-lapping reports/publications; abstracts, letters, reviews and commentaries; and lack of data reporting of genotype frequency.

2.2. Data extraction

Two reviewers (L.D. and H.R.) independently reviewed all potentially eligible publications and then reached a consensus on all of items. The following information were extracted from the published reports for every article: author(s)/name(s); publication year; country or geographical location of study participants; age; sex ratio; age and sex matching; disorder duration and consistency of genotype distributions with the Hardy-Weinberg equilibrium. Allele and genotype frequencies were calculated or extracted from published articles in the eligible studies.

2.3. Statistical analysis

The odds ratios (OR) and 95% confidence intervals (CI) were used as the metrics of effect size for each reports and overall including studies. Two methods were applied to assess between-study heterogeneity across all data comparisons: the ν^2-based Cochran Q statistic and the I^2 metric, which estimate between-study heterogeneity irrespective of the number of reports.[20] Heterogeneity of between-study was considered significant at $P < .10$ using the Q statistic. For the I^2 metric, the following showed cutoff points were applied: $I^2 = 75\%$ to 100%, extreme heterogeneity; $I^2 = 50\%$ to <75%, large heterogeneity; $I^2 = 25\%$ to <50%, moderate heterogeneity; and $I^2 = 0\%$ to <25%, no heterogeneity. Data from all the studies were combined using a fixed-effects model (Mantel-Haenszel method) when heterogeneity was negligible; otherwise, a random-effects model (DerSimonian and Laird method) was used.[21] Forest plots and funnel plots were applied for visualizing the overall effect size and assessment of publication bias, respectively. Analyses were conducted employing Stata version 13.1 (College station, TX). All P values conducted are 2-tailed with a significance level of .05.

3. Results

3.1. Literature search

Figure 1 showed the results of the literature screen and selection criteria. After exclusion of reports that either did not meet the inclusion criteria or were overlapped, it was considered that the remaining 15 articles may be relevant for the current meta-analysis. After evaluating these 15 articles, 8 articles were excluded. Two articles were excluded because of the lack of sufficient information for assessment on MI risk.[12,22] Additional 4 articles were excluded because they did not separately report or calculate the odds risks (ORs) and 95% confidence intervals (CI) for CAD or MI.[9,23–25] Two articles were excluded because the meta-analysis concerned the relationship between TGF-β polymorphism and CAD rather than that of TGF-β polymorphism and the risk of MI.[26,27] In total, the final meta-analysis included 7 independent published studies.

3.2. Study characteristics

A total of 7 articles, which included 5460 MI cases and 8413 controls, were observed to fulfill the inclusion criteria.[11,13–17,28] The 7 studies, including 60 population-based case–control reports and 1 hospital-based case–control studies, were incorporated in our meta-analysis. The studies were from the following countries: 1 study in the Netherlands,[13] 2 studies in France,[11,15] 1 study in Italy,[14] 1 study in Russia,[16] 1 in the UK, [28] and 1 in Greece.[20]

Results of study quality estimate (Newcastle-Ottawa Scale score 0-9) yielded a score of ≥6.5 (high quality) for all reports, with an average score of 7.8. The details of information are showed in Tables 1 and 2.

3.3. Analysis of all studies

As shown in Figure 2, the heterogeneity of TT + CT versus CC for all of 7 studies was analyzed, and the value of $\chi2$ was 9.51 with 6 degrees of freedom and $P = .15$ in a fix-effects model. Additionally, I^2 value was considered as another index of the test of heterogeneity. As shown in Figure 2, the I^2 was 36.9%, suggesting no heterogeneity. Therefore, the fix-effects model to
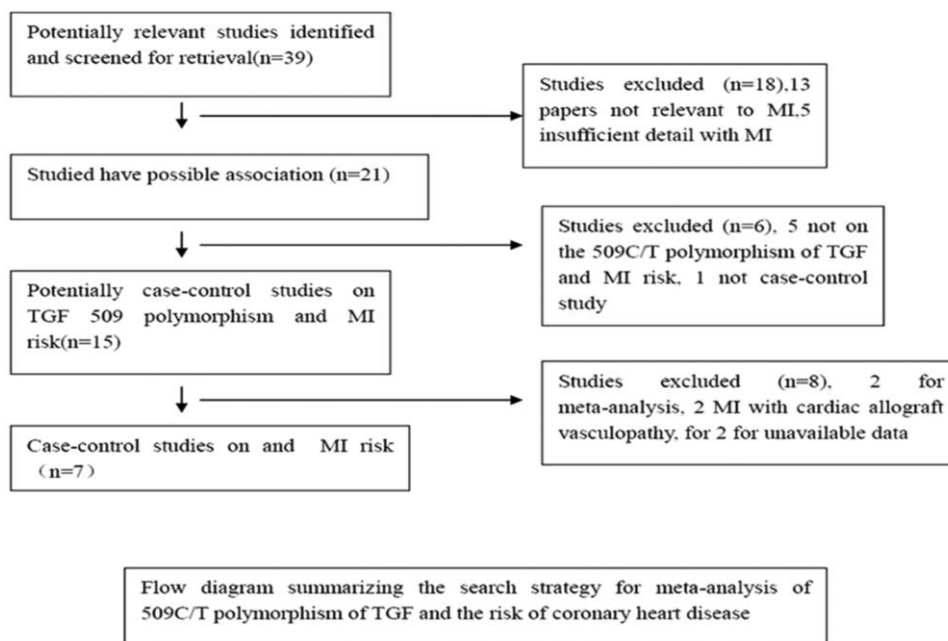
Figure 1. Flow diagram summarizing the search strategy for meta-analysis of 509C/T polymorphism of TGF-β (rs1800469) and the risk of coronary heart disease (CAD).

analyze the data was used. Overall, OR was 1.13 (95% CI= 1.03–1.24), which indicated that individuals who carry the homozygote TT and heterozygote CT may have an increased 13% MI risk compared with the CC homozygote carriers.

When analyzing for sample size, statistical significances were found for synthesize analyses for studies with a sample size <300 (OR [95% CI]: 1.87 [1.27–2.75] for TT vs CC, $P_{\text{heterogeneity}}$=.39; 1.55 [1.10–2.20] for TT vs C carriers, $P_{\text{heterogeneity}}$=.37; 1.50 [1.15–1.95] for T carriers vs CC, $P_{\text{heterogeneity}}$=0.42; 1.39 [1.16–1.67] for T allele vs C allele, $P_{\text{heterogeneity}}$=.61) and middle studies sample size >300 and <600 (OR [95% CI]: 0.97 [0.66–1.44] for TT vs CC, $P_{\text{heterogeneity}}$=.22; 1.45 [0.27–7.72] for TT vs CT, $P_{\text{heterogeneity}}$=.09; 0.94 [0.64–1.36] for TT vs C carriers, $P_{\text{heterogeneity}}$=.14; 1.01 [0.87–1.18] for T carriers vs CC, $P_{\text{heterogeneity}}$=.52; 1.01 [0.86–1.17] for T allele vs C allele,

$P_{\text{heterogeneity}}$=.44) (Figs. 2 and 3). The study with a sample size of >600 was only carried out by Sie et al.[13]

Subgroup analyses according to the age of the MI subjects suggested that homozygous TT in TGF-β 509C/T (rs1800469) was significantly associated with the increased risk of MI in the subjects younger than 60 years (1.35 [1.04–1.75] for TT vs C carriers, $P_{\text{heterogeneity}}$=.20). In contrast, T carriers in TGF-β 509C/T (rs1800469) were associated with the increased MI risk in the subjects older than 60 years (1.01 [0.87–1.18] for T carriers vs CC, $P_{\text{heterogeneity}}$=.52) (Figs. 4 and 5)

Subgroup analyses according to subtype of MI showed that T carrier in TGF-β 509C/T (rs1800469) was significantly associated with the increased risks of no-acute MI (AMI) (1.12 [1.02–1.23] for T carriers vs CC, $P_{\text{heterogeneity}}$=.11) (Fig. 6 and Supplementary Fig. 1, http://links.lww.com/MD/D25).

Table 1

The characteristics of studies included in the meta-analysis.

First author	Year	Design	Source of controls	Age (mean/case, control)	No. of cases	No. of controls	Genotyping methods	Definition of MI	Matching criteria/ adjustment	NOS scores
Sie et al[13]	2006	Netherland	PCC	70.3/69.5	171	3043	Taqman PCR	WHO criteria	Age, sex	7
Koch et al[11]	2006	France and Ireland	Unknown	64.0/60.3	1211	3657	Taqman PCR	Diagnosis based on angiography	Age-matched and sex-matched	7
Crobu et al[14]	2008	Italy	PCC	40/40	67	80	PCR-RELP	WHO criteria	Smoking habits, family history, hypercholesterolemia and hypertension	8
Cambien et al[15]	1996	France	PCC	61.6/61.58	240	263	PCR-SSCP	Unclear	NA	7
Sudomoina et al[16]	2010	Russian	PCC	51.9/53.7	77	90	PCR	Unclear	Age, sex	7
Chen et al[28]	2012	UK	HCC	54.9/49	181	23	PCR-RELP	Conventional criteria	Age, sex	6
Manginas et al[17]	2008	Greece	HCC	60.97/61	16	20	PCR-SSP	ECG change and other criteria	Age, sex	6

HCC = hospital-based case-control study, MI = myocardial infarction, NOS = Newcastle-Ottawa scale, PCC = population-based case-control study, PCR = polymerase chain reaction, RELP = restriction fragment length polymorphism, SSCP = single-strand conformation polymorphism, SSP = sequence specific primer.

Figure 3. Forest plot showing a significant association between TGF-β 509C/T (rs1800469) and risk of MI in small sample size (<300 subjects). Fixed-effect model was used (TT vs C carriers).

Figure 4. Forest plot showing a significant association between TGF-β 509C/T (rs1800469) and risk of MI in sample size 300-600 subjects. Fixed-effect model was used (T carriers vs CC).

Figure 5. Forest plot showing a significant association between TGF-β 509C/T (rs1800469) and risk of MI in subjects aged <60. Fixed-effect model was used (TT vs C carriers).

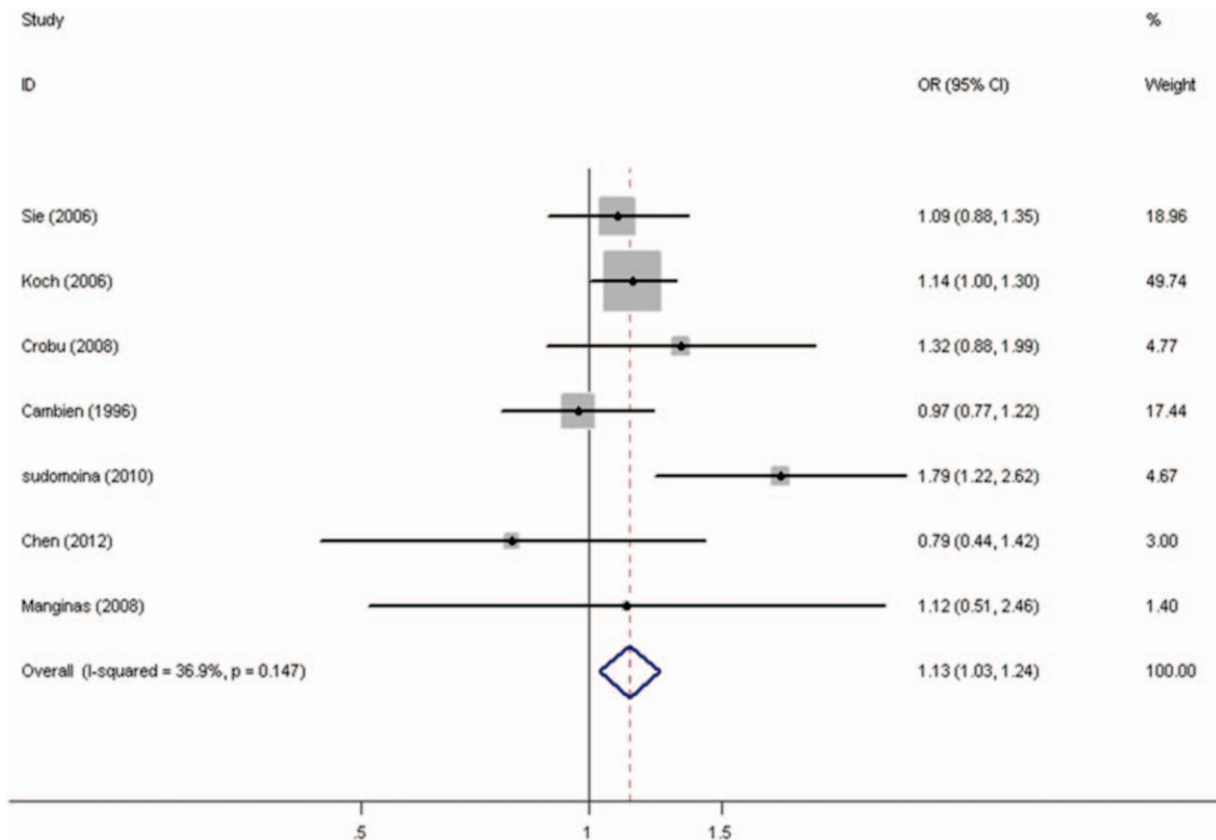**Figure 6.** Forest plot showing a significant association between TGF-β 509C/T (rs1800469) and risk of MI in subjects aged >60. Fixed-effect model was used (T carriers vs CC).
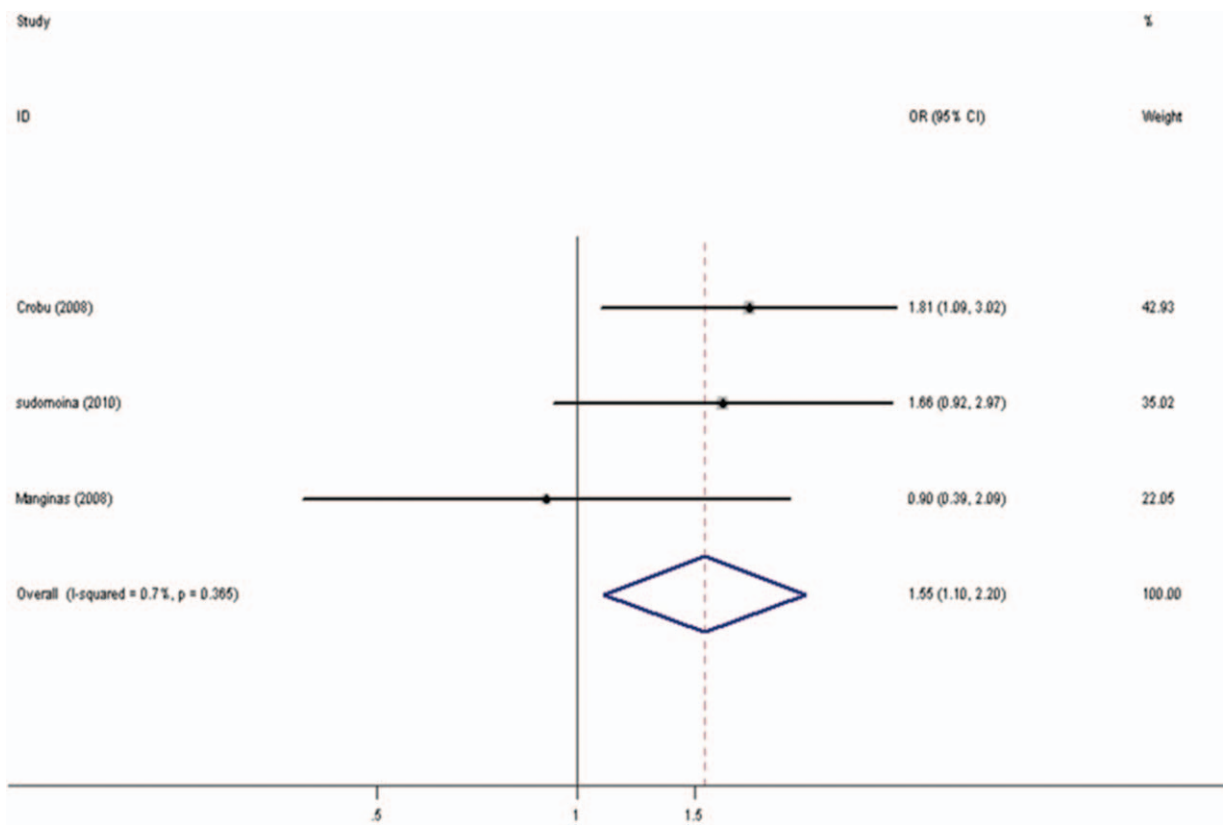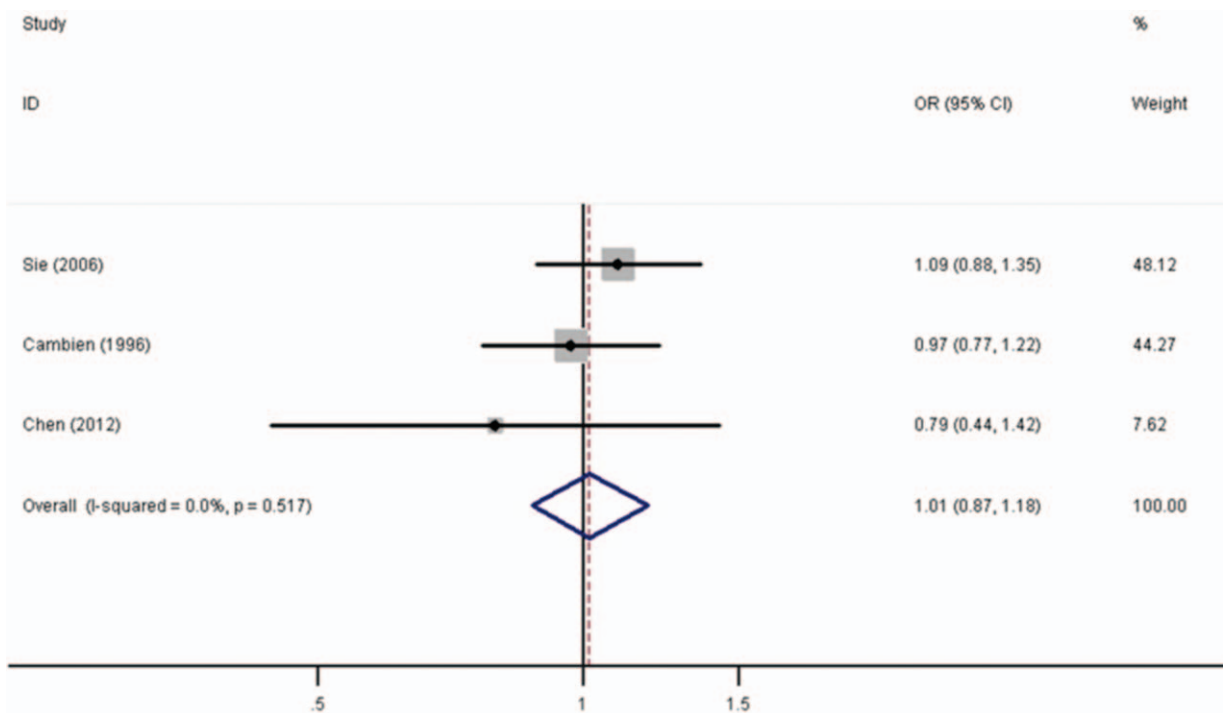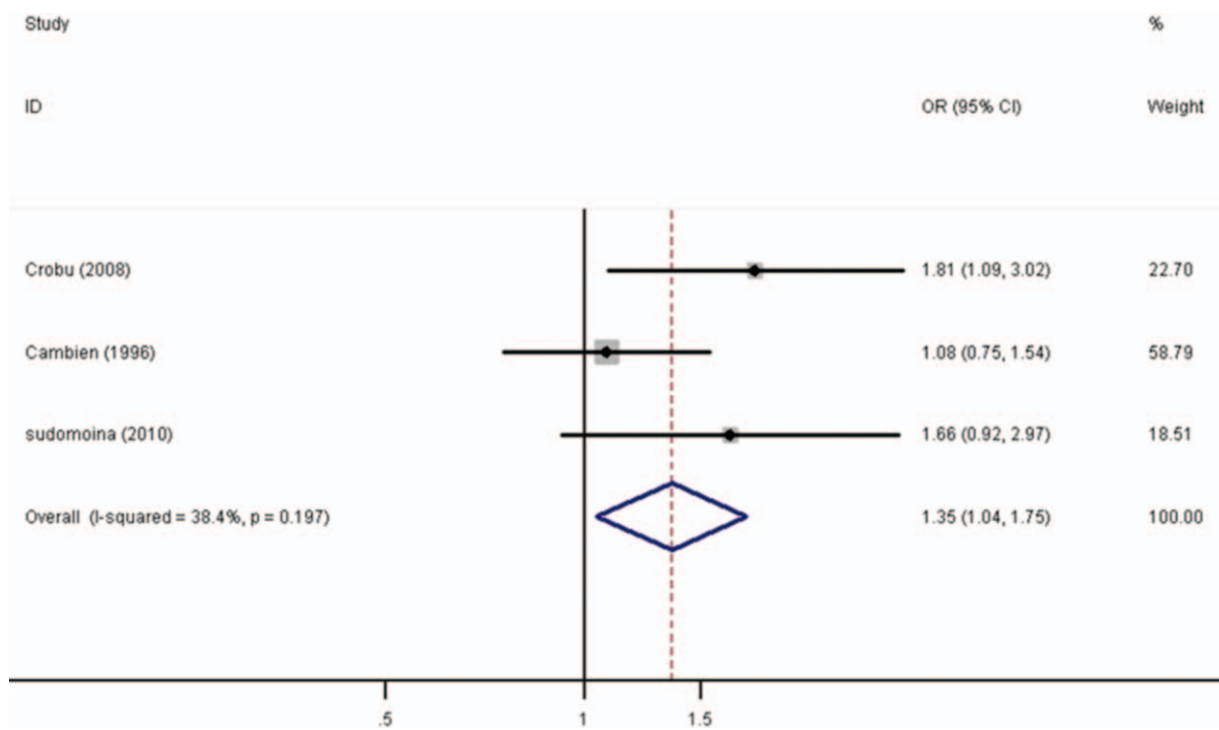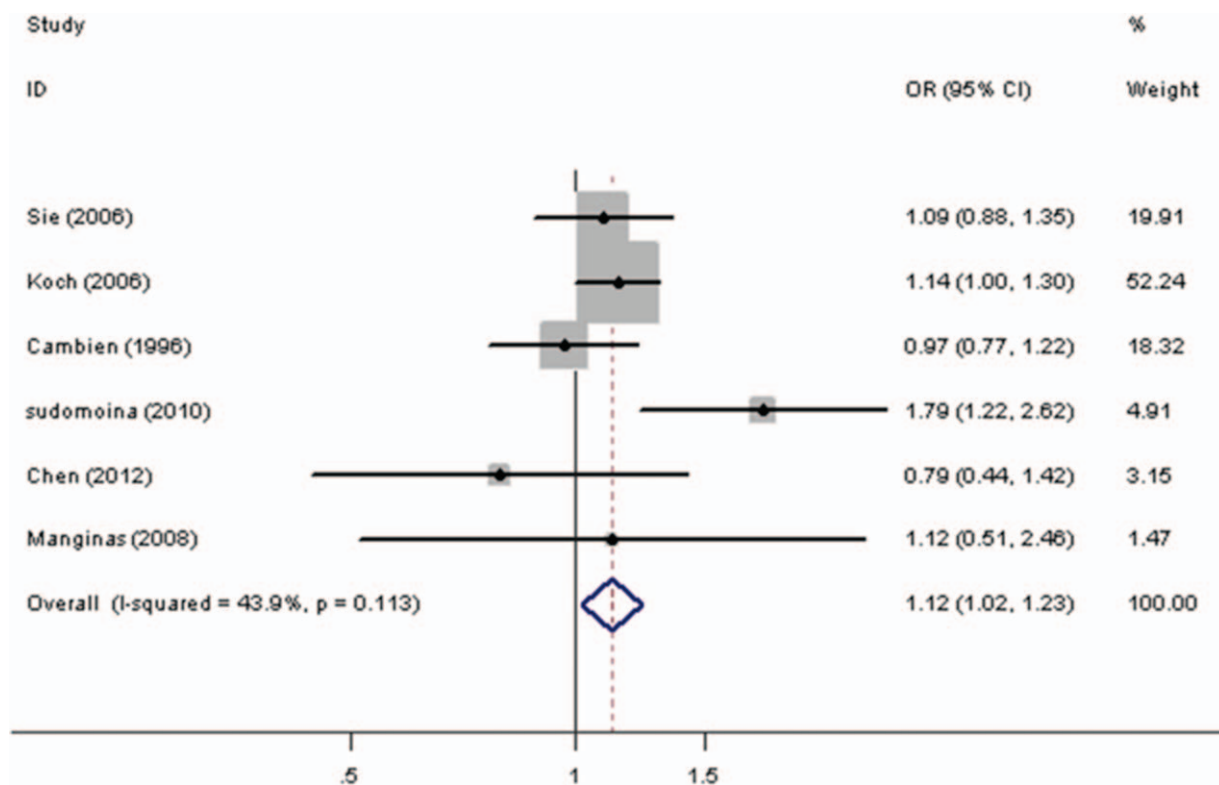
4. Discussion

It is well acknowledged that MI is a multifaceted disorder involving multigene, and gene–environment characteristics.[18] There remains an individual susceptibility to the risk of MI even with comparable exposure to similar risk factors or environments. Thus, in recent years, interest in the genetic susceptibility to the risk of MI has led to increased attention to the investigation of polymorphism or mutation of genes involved in the pathogenesis and development of MI.

In 1998, the identification of the rs1800469 polymorphism in the human *TGF-β* gene promoter region began to generate greater interest which resulted in a serial of reports investigating its application as a genetic biomarker for CAD/MI and other human disorders. The 509C/T polymorphism (rs1800469) in the *TGF-β* gene has been reported to have the correlation with susceptibility to cancers,[29,30] systemic sclerosis[31], pulmonary fibrosis[32], osteoporosis, and atherogenesis[18] with or without CAD. In the "protective cytokine" hypothesis, active cytokine of TGF-β has been proved to be the key inhibitor of atherogenesis, which is an inhibitor of VSMC migration and proliferation thus inhibiting the initiation and development of atherosclerosis. In addition, it is recognized that cytokine of TGF-β maintains endothelium function through suppressing leucocyte adhesion to endothelial cells irrespective of the presence and absence of other inflammatory cytokines. However, the underlying mechanisms remain to be further elucidated in the future.

The current meta-analysis, including 5460 cases and 8413 controls in 7 case–control studies, qualifying the association between the potentially functional polymorphism (rs1800469) in the *TGF-β* gene and the risk of MI. Our present study can obtain enough statistical powers of >95% at the nominal type I error rate of 0.01, to identify the relationship. The results indicated that the T carriers had nearly 13% increased risk of MI. Furthermore, stratification analysis of the subgroup by the type of CAD/MI, and sample size of the subjects was performed. The results suggested a significant association between TGF-β 509C/T (rs1800469) and the risk of MI.

It was reported the GWAS result from CARDIoGRAM-plusC4D shows that among candidate gene studies investigating the susceptibility to CAD and MI only 19 loci showed association at $P< 1 \times 10^{-6}$ in the combined stage 1 and 2 analysis, with 13 of them reaching genome-wide significance, namely IL6R, APOB, VAMP5-VAMP8-GGCX,SLC22A4-SLC22A5, ZEB2-AC074093.1, GUCY1A3, KCNK5, LPL, PLG, TRIB1, ABCG5-ABCG8, FURIN-FES, and FLT1.[33,34] In addition, a population with European ancestry reported that enormous progress has been made in this respect, as exemplified by GUCY1A3, PCSK9, ANGPTL4, and ANGPTL3, that is, genes with genome-wide association to CAD and potential druggability.[33–35] The findings among different studies may be because of different genetic backgrounds, geographical differences, and environmental factors.[34]

Potential limitations and shortages of this meta-analysis should be acknowledged because of the nature of the meta-analysis. Therefore, the conclusion should be interpreted with caution. First, meta-analysis is from retrospective studies and is limited by the qualities of original reports. The number of reports was limited and the total sample size was not relatively large. Second, the current meta-analysis was conducted and based on unadjusted analysis of studies. Third, through the methods of analysis of funnel plots, Beggar test and Egger test, null

publication bias was found. Publication bias may still exist, thus distorting the results and conclusion of this current meta-analysis. In addition, although the total number of cases and controls appear ideal, the number for single cases of CAD was too small to qualify the potential existence of marginal effect size. Finally, all case–control studies were of white ethnicity background. The genetic background of white populations included in our studies may differ from Asian and African populations. Consequently the results and conclusion may be applicable to ethnic white group only. Thus, further studies including white, Asian, and African populations with larger sample sizes and more detailed information of the participants are required in the future.

In conclusion, this meta-analysis suggests that TGF-β 509C/T (rs1800469) is correlated with MI risk. More well-designed studies with diverse populations from different ethnic groups, with larger sample size and additional details information are required to obtain more precise evidence to assess the association and to further validate the conclusion of the current meta-analysis.

Author contributions

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Investigation: Ling Du, Henghua Dai.
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Supervision: Henghua Dai, Tao Gong.
Validation: Minghui Yao, Henghua Dai, Honggang Ren.
Writing – original draft: Ling Du, Tao Gong, Minghui Yao, Honggang Ren.
Writing – review & editing: Honggang Ren, Tao Gong.

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