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Association between the C804A polymorphism in the *TGF-β* gene and the risk of myocardial infarction: a meta-analysis

D.W. Suo, Q. Hu, J. Chen, Q.H. Sun and H. Guo

Department of Emergency, the Fifth Hospital of Zhengzhou University, Zhengzhou, China

Corresponding author: D.W. Suo
E-mail: suodwzd5h@126.com

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ABSTRACT. Tumor necrosis factor-β (TNF-β) is an important mediator of inflammation and may play a role in the pathogenesis of myocardial infarction (MI). While several published studies have investigated the association between the C804A polymorphism in the *TNF-β* gene and MI risk, their results are controversial and ambiguous. In this study, we evaluated the contribution of the *TNF-β* C804A polymorphism to MI risk. A literature search was conducted in the PubMed, Embase, Web of Science, Cochrane Library, and Google Scholar databases to identify eligible studies published before November 1, 2013. We performed a meta-analysis of 9 case-control studies, which included a total of 19,404 MI patients and 13,684 healthy controls. Overall analysis suggested that the *TNF-β* C804A polymorphism was associated with a significantly increased risk of MI. Stratified analysis based on ethnicity revealed a significant association in Asian populations, but not in Caucasian populations. In conclusion, this meta-analysis revealed that the *TNF-β* C804A polymorphism may be associated with an increased risk of MI only in Asian populations. However, additional studies should be

conducted to further confirm the association between *TNF-β* C804A and MI risk.

Key words: Meta-analysis; Myocardial infarction; Polymorphism; TNF-β

INTRODUCTION

Myocardial infarction (MI) is the major clinical complication of coronary atherosclerosis and typically develops from the rupture of an atherosclerotic plaque with thrombus formation and the occlusion of the coronary vessel, resulting in an acute reduction of the blood supply to a portion of the myocardium (Thygesen et al., 2012). Despite the development of new pharmacological approaches, MI remains the principal cause of death in many countries (Yeh et al., 2010). According to data from the American Heart Association, the overall prevalence of MI in the US is 3.6% in adults over the age of 20 years, with rates of 4.7% in men and 2.6% in women (Lloyd-Jones et al., 2010; Schiller et al., 2012). The estimated average number of years of life lost due to MI is 15 (Kung et al., 2008). Although it has been well-established that hypertension, diabetes mellitus, hyperlipidemia, smoking, and obesity are associated with an increased risk of MI, the exact mechanisms leading to MI remain poorly understood (Norhammar et al., 2002; Reynolds et al., 2011). Epidemiological studies have revealed that MI is a complex multifactorial disease influenced by both environmental factors and genetic predisposition. Functionally relevant polymorphisms in genes involved in inflammatory pathways can cause acute thrombus formation over a plaque with abrupt vessel closure, affecting an individual's susceptibility to MI (Helgadottir et al., 2004; Podgoreanu et al., 2006; Bujak and Frangogiannis, 2007).

Tumor necrosis factor-β (TNF-β) is an important mediator of inflammation and may play a role in the pathogenesis of MI. It is likely that functional variations in the gene encoding this protein confer a risk of MI by affecting the degree of inflammation at the lesion. The *TNF-β* gene, which encodes TNF-β on chromosome 6p21, may be associated with MI risk (Clarke et al., 2006). Previous studies have investigated the association between single nucleotide polymorphisms (SNPs) in the *TNF-β* gene, particularly the C804A polymorphism (dbSNP: rs1041981, C>A) in exon 3 of the coding region, and MI risk. However, the results remain controversial and ambiguous. To clarify these inconsistent findings and to evaluate the contribution of the *TNF-β* C804A polymorphism to the risk of MI, we performed a meta-analysis using published data from observational studies.

MATERIAL AND METHODS

Identification of relevant studies

To identify relevant studies that investigated the association between the *TNF-β* C804A polymorphism and the risk of MI, a literature search was conducted of the following electronic databases: PubMed, Embase, Web of Science, Cochrane Library, and Google Scholar. The last search was conducted on November 1, 2013. The following search terms were used: ('tumor necrosis factor beta' or 'TNF-beta' or 'lymphotoxin-alpha' or 'LTA') and ('myocardial infarction' or 'myocardial infarct' or 'MI') and ('genetic polymorphism' or 'single-nucleotide poly-

morphism' or 'SNP'). Search results were restricted to studies examining human populations and articles written in English. All references in eligible articles were extensively reviewed to identify additional published articles.

Inclusion and exclusion criteria

Included studies met the following criteria: 1) case-control studies on the association between the *TNF-β* C804A polymorphism and MI risk; 2) all patients met the diagnostic criteria for MI; and 3) sufficient data were published to calculate odds ratios (ORs) with corresponding 95% confidence intervals (95%CIs). Major exclusion criteria included: 1) not a case-control study; 2) duplicate publications; and 3) no available data reported. For multiple studies that used overlapping cases or controls, the study with the largest sample size was included in the meta-analysis.

Data extraction

Two investigators independently extracted the following data from eligible studies: surname of first author, year of publication, country of origin, ethnicity, number of cases and controls, age, gender ratio, genotyping method, allele and genotype frequencies, etc. In case of disagreement, the investigators achieved consensus through discussion. For data not provided in table form or in the main text, required information was obtained by contacting the corresponding authors when possible.

Quality assessment

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) quality score system was used to evaluate the quality of all eligible studies (da Costa et al., 2011). Forty assessment items with matching quality appraisals were used in this meta-analysis, with scores ranging from 0-40. Studies with a score ≥20 were considered to be of high quality.

Statistical analysis

In this meta-analysis, we assessed the association between *TNF-β* C804A and MI risk using pooled ORs and their corresponding 95%CIs under 5 genetic models, including the allele model (A allele *vs* C allele), the dominant model (CA+AA *vs* CC), the recessive model (AA *vs* CC+CA), the homozygous model (AA *vs* CC), and the heterozygous model (AA *vs* CA). Hardy-Weinberg equilibrium in the controls was tested by comparing the expected and observed genotype frequencies using the Pearson chi-square test for goodness of fit (Teo et al., 2007). Between-study heterogeneity was statistically evaluated using Cochran's *Q*-statistic and the I^2 metric (Higgins and Thompson, 2002; Jackson et al., 2012). When no heterogeneity was found, as indicated by $P > 0.10$ for the *Q*-statistic or $I^2 < 50\%$, a fixed-effect model was applied to estimate the pooled ORs and 95%CIs. Otherwise, a random-effect model was used. In addition to an overall comparison, stratified analyses were performed based on ethnicity (Asian and Caucasian), source of control (population-based and hospital-based), and genotyping method [polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and TaqMan] where applicable. Multivariable regression analyses were also

performed to identify variables that could explain the heterogeneity of associations (van Houwelingen et al., 2002). Sensitivity analyses were conducted by omitting individual studies in turn to reflect the influence of individual datasets on the pooled results (Sacks et al., 1987). Begg's funnel plot and the Egger linear regression test were used to assess potential publication bias (Egger et al., 1997; Peters et al., 2006). All two-tailed $P < 0.05$ were considered to be statistically significant and all analyses were performed using the STATA 12.0 software (Stata Corp., College Station, TX, USA).

RESULTS

Baseline characteristics of studies included

A flow chart of studies retrieved and excluded and their reasons for exclusion is shown in Figure 1. Based on our search strategy, primary screening identified 113 potentially relevant articles. In accordance with the inclusion criteria, 9 case-control studies (Iwanaga et al., 2004; Tobin et al., 2004; Yamada et al., 2004; Ozaki and Tanaka, 2005; Clarke et al., 2006; Tanaka and Ozaki, 2006; Koch et al., 2007; Sedlacek et al., 2007; Wang et al., 2010) were selected for this meta-analysis, which included a total of 19,404 MI patients and 13,684 healthy controls. The publication years of studies included ranged from 2004-2010. The studies included were conducted in 2 major ethnic populations, with 5 in Asian and 4 in Caucasian subjects. The classical PCR-RFLP genotyping method was used in 5 studies, while the other 4 used the TaqMan method. Seven studies used population-based control groups, whereas the other 2 used hospital-based control groups. The genotype frequencies of controls in all studies conformed to Hardy-Weinberg equilibrium. The qualities of all studies included were moderately high, with STROBE scores greater than 20. Table 1 shows the main characteristics of all studies included.

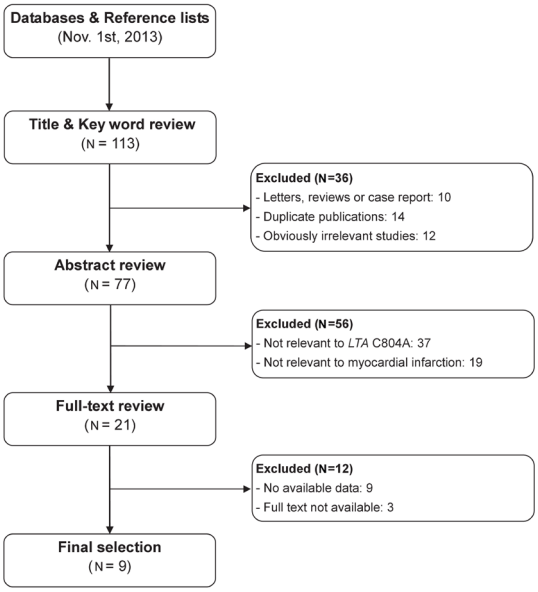

Figure 1. Flow diagram of study selection and specific reasons for excluding studies from the present meta-analysis.

Table 1. Main characteristics of all eligible studies.

First author	Year	Country	Ethnicity	Source of control	Case group		Control group		Male ratio (%) [Case/Control]	Genotyping method	MAF		P value of HWE	STROBE score
					N	Age	N	Age			Case	Control		
Iwanaga et al.	2004	Japan	Asian	PB	477	56.0 ± 8.0	372	59.0 ± 9.0	100%, 100%	TaqMan	0.415	0.343	0.166	27/40
Tobin et al.	2004	UK	Caucasian	PB	547	61.9 ± 9.2	505	58.6 ± 10.7	68%, 62%	PCR-RFLP	0.361	0.344	0.637	26/40
Yamada et al.	2004	Japan	Asian	HB	1891	60.6 ± 10.9	1798	58.6 ± 11.3	78.9%, 55.2%	PCR-RFLP	0.423	0.405	0.542	30/40
Ozaki et al.	2005	Japan	Asian	PB	1133	62.5 ± 11.3	1006	64.3 ± 11.3	NA, NA	PCR-RFLP	0.411	0.371	0.103	28/40
Clarke et al.	2006	UK	Caucasian	PB	6928	54.8 ± 7.3	2712	46.2 ± 9.6	82.3%, 44.6%	TaqMan	0.358	0.358	0.580	29/40
Tanaka et al.	2006	Japan	Asian	PB	2833	NA	3399	NA	NA, NA	PCR-RFLP	0.405	0.368	0.172	25/40
Koch et al.	2007	Germany	Caucasian	PB	3657	64.0 ± 12.0	1211	60.3 ± 11.9	75.8%, 50.0%	TaqMan	0.323	0.304	0.234	31/40
Sedlacek et al.	2007	Germany	Caucasian	PB	1821	58.7 ± 8.6	2572	57.4 ± 9.7	78.0%, 43.2%	TaqMan	0.310	0.307	0.330	26/40
Wang et al.	2010	Taiwan	Asian	HB	117	NA	109	NA	NA, NA	PCR-RFLP	0.352	0.278	0.421	23/40

NA = not available: PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism; MAF = minor allele frequency; HWE = Hardy-Weinberg equilibrium; STROBE = Strengthening the Reporting of Observational Studies in Epidemiology; PB = population-based; HB = hospital-based groups.

Meta-analysis of the association between *TNF-β* C804A and MI risk

Table 2 summarizes the association between the *TNF-β* C804A polymorphism and MI risk. Because between-study heterogeneity clearly existed in the overall analysis (P < 0.10 or I^2 > 50% under all genetic models), the random-effect model was used. The combined results suggested that the *TNF-β* C804A polymorphism was associated with a significantly increased risk of MI (A allele *vs* C allele: OR = 1.10, 95%CI = 1.04-1.16, P = 0.001; CA+AA *vs* CC: OR = 1.08, 95%CI = 1.01-1.16, P = 0.027; AA *vs* CC+CA: OR = 1.24, 95%CI = 1.08-1.41, P = 0.002; AA *vs* CC: OR = 1.27, 95%CI = 1.11-1.45, P < 0.001; AA *vs* CA: OR = 1.21, 95%CI = 1.05-1.40, P = 0.008). Interestingly, in a stratified analysis by ethnicity, we found that this polymorphism played different roles in Asian and Caucasian populations. In Asian populations, subjects harboring the 804A variant were approximately 15% more likely to have MI compared to subjects with the wild-type allele (A allele *vs* C allele: OR = 1.16, 95%CI = 1.09-1.23, P < 0.001; CA+AA *vs* CC: OR = 1.15, 95%CI = 1.04-1.28, P = 0.008; AA *vs* CC+CA: OR = 1.35, 95%CI = 1.10-1.66, P = 0.004; AA *vs* CC: OR = 1.41, 95%CI = 1.20-1.65, P <

Table 2. Meta-analysis of the association between *TNF-β* C804A and MI risk.

Genetic model	Subgroup (case/control)	OR [95%CI]	P_{OR}	P_h	I^2	Effect method
A allele *vs* C allele	Overall (19,404/13,684)	1.10 [1.04-1.16]	0.001	0.015	57.7%	RE
(Allele model)	Asian (6451/6684)	1.16 [1.09-1.23]	<0.001	0.290	19.6%	FE
	Caucasian (12,953/7000)	1.03 [0.98-1.08]	0.234	0.440	0.0%	FE
	PB (17,396/11,777)	1.10 [1.03-1.18]	0.005	0.004	68.2%	RE
	HB (2008/1907)	1.08 [0.99-1.18]	0.090	0.821	0.0%	FE
	PCR-RFLP (6521/6817)	1.14 [1.08-1.19]	<0.001	0.640	0.0%	FE
	TaqMan (13,000/69,767)	1.07 [0.98-1.18]	0.132	0.021	69.1%	RE
CA+AA *vs* CC	Overall (19,404/13,684)	1.08 [1.01-1.16]	0.027	0.069	44.9%	RE
(Dominant model)	Asian (6451/6684)	1.15 [1.04-1.28]	0.008	0.154	40.1%	FE
	Caucasian (12,953/7000)	1.02 [0.95-1.08]	0.628	0.562	0.0%	FE
	PB (17,396/11,777)	1.08 [0.99-1.17]	0.078	0.033	56.4%	RE
	HB (2008/1907)	1.13 [0.99-1.28]	0.076	0.926	0.0%	FE
	PCR-RFLP (6521/6817)	1.11 [1.04-1.19]	0.003	0.939	0.0%	FE
	TaqMan (13,000/69,767)	1.08 [0.95-1.23]	0.255	0.010	73.5%	RE
AA *vs* CC+CA	Overall (19,404/13,684)	1.24 [1.08-1.41]	0.002	0.001	68.4%	RE
(Recessive model)	Asian (6451/6684)	1.35 [1.10-1.66]	0.004	0.014	68.2%	RE
	Caucasian (12,953/7000)	1.11 [0.98-1.26]	0.097	0.229	30.6%	FE
	PB (17,396/11,777)	1.27 [1.09-1.49]	0.003	0.001	73.9%	RE
	HB (2008/1907)	1.07 [0.90-1.26]	0.455	0.999	0.0%	FE
	PCR-RFLP (6521/6817)	1.32 [1.07-1.62]	0.010	0.009	70.2%	RE
	TaqMan (13,000/69,767)	1.14 [0.99-1.30]	0.072	0.165	41.2%	FE
AA *vs* CC	Overall (19,404/13,684)	1.27 [1.11-1.45]	<0.001	0.006	62.5%	RE
(Homozygous model)	Asian (6451/6684)	1.41 [1.20-1.65]	<0.001	0.142	41.9%	FE
	Caucasian (12,953/7000)	1.11 [0.98-1.25]	0.099	0.270	23.5%	FE
	PB (17,396/11,777)	1.29 [1.10-1.52]	0.002	0.002	70.9%	RE
	HB (2008/1907)	1.15 [0.96-1.39]	0.135	0.684	0.0%	FE
	PCR-RFLP (6521/6817)	1.35 [1.16-1.58]	<0.001	0.147	41.1%	FE
	TaqMan (13,000/69,767)	1.18 [0.99-1.42]	0.069	0.056	60.4%	RE
AA *vs* CA	Overall (19,404/13,684)	1.21 [1.05-1.40]	0.008	0.001	69.2%	RE
(Heterozygous model)	Asian (6451/6684)	1.30 [1.02-1.66]	0.032	0.003	75.3%	RE
	Caucasian (12,953/7000)	1.11 [0.98-1.26]	0.113	0.240	28.7%	FE
	PB (17,396/11,777)	1.25 [1.06-1.47]	0.009	0.001	73.4%	RE
	HB (2008/1907)	1.03 [0.86-1.23]	0.756	0.568	0.0%	FE
	PCR-RFLP (6521/6817)	1.30 [1.03-1.65]	0.029	0.003	75.3%	RE
	TaqMan (13,000/69,767)	1.11 [0.97-1.26]	0.120	0.238	29.0%	FE

TNF-β = tumor necrosis factor-beta; MI = myocardial infarction; PB = population-based; HB = hospital-based; OR = odds ratio; CI = confidence interval; P_{OR} = P value of OR; P_h = P value of heterogeneity; RE = random effect; FE = fixed effect.

0.001; AA *vs* CA: OR = 1.30, 95%CI = 1.02-1.66, P = 0.032). However, no significant effects were found for the Caucasian population (P > 0.05 under all genetic models) (Figure 2). After excluding 2 hospital-based studies, the pooled ORs were still significant in the population-based studies (A allele *vs* C allele: OR = 1.10, 95%CI = 1.03-1.18, P = 0.005; AA *vs* CC+CA: OR = 1.27, 95%CI = 1.09-1.49, P = 0.003; AA *vs* CC: OR = 1.29, 95%CI = 1.10-1.52, P = 0.002; AA *vs* CA: OR = 1.25, 95%CI = 1.06-1.47, P = 0.009) (Figure 3). Stratification based on genotyping method revealed a significant association between *TNF-β* C804A and MI risk in the PCR-RFLP subgroup (A allele *vs* C allele: OR = 1.14, 95%CI = 1.08-1.19, P < 0.001; CA+AA *vs* CC: OR = 1.11, 95%CI = 1.04-1.19, P = 0.003; AA *vs* CC+CA: OR = 1.32, 95%CI = 1.07-1.62, P = 0.010; AA *vs* CC: OR = 1.35, 95%CI = 1.16-1.58, P < 0.001; AA *vs* CA: OR = 1.30, 95%CI = 1.03-1.65, P = 0.029), whereas no significant association was found in the TaqMan subgroup (all P > 0.05; Figure 4).

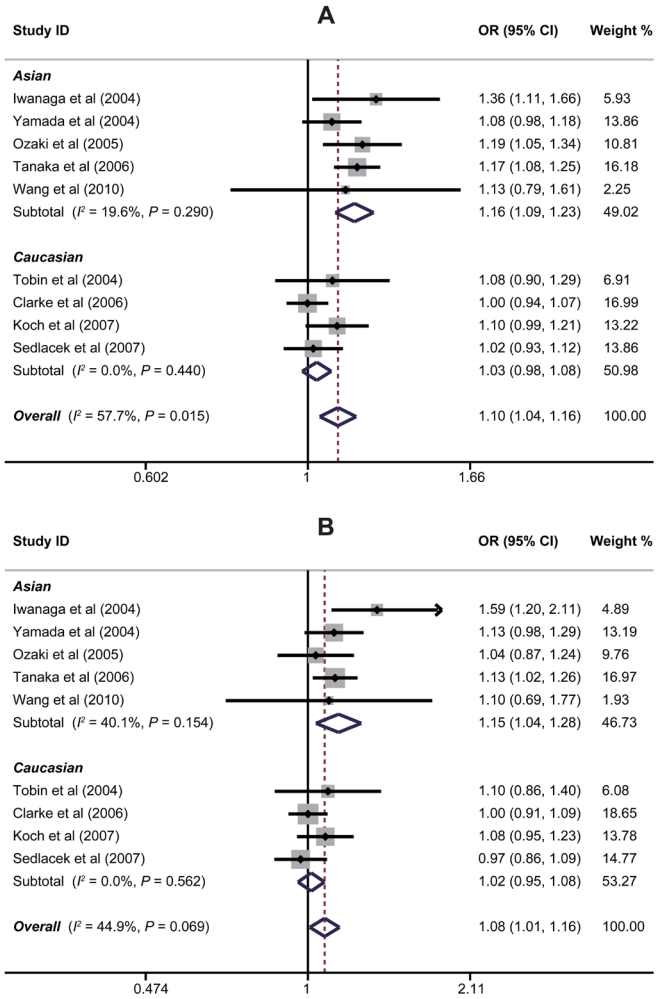

Figure 2. Forest plots of ORs for the association between the *TNF-β* C804A polymorphism and susceptibility to myocardial infarction in subgroup analysis based on ethnicity under the allele model (**A**) and the dominant model (**B**).

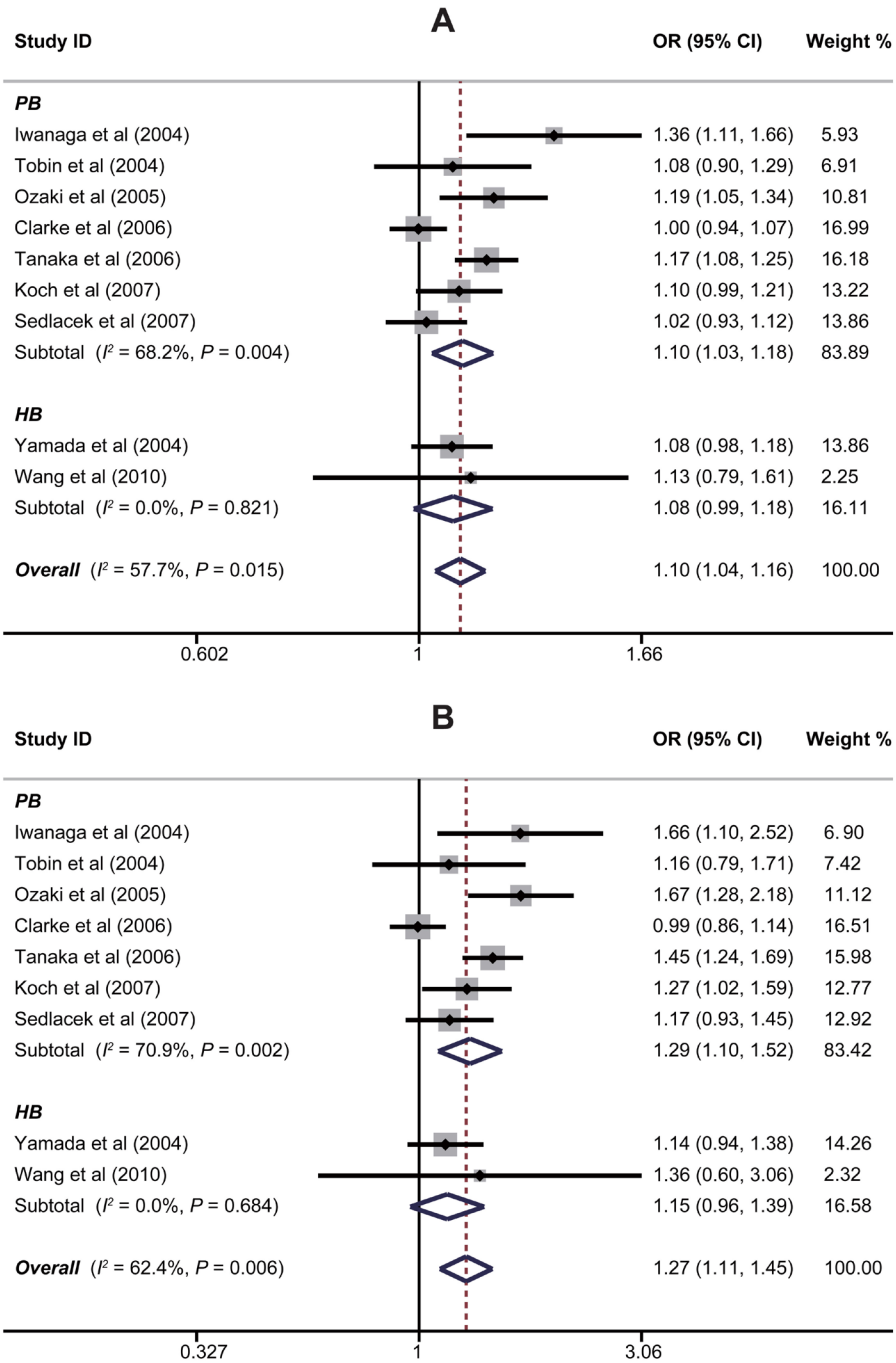

Figure 3. Forest plots of ORs for the association between the *TNF-β* C804A polymorphism and susceptibility to myocardial infarction in subgroup analysis based on source of control under the allele model (**A**) and the homozygous model (**B**).

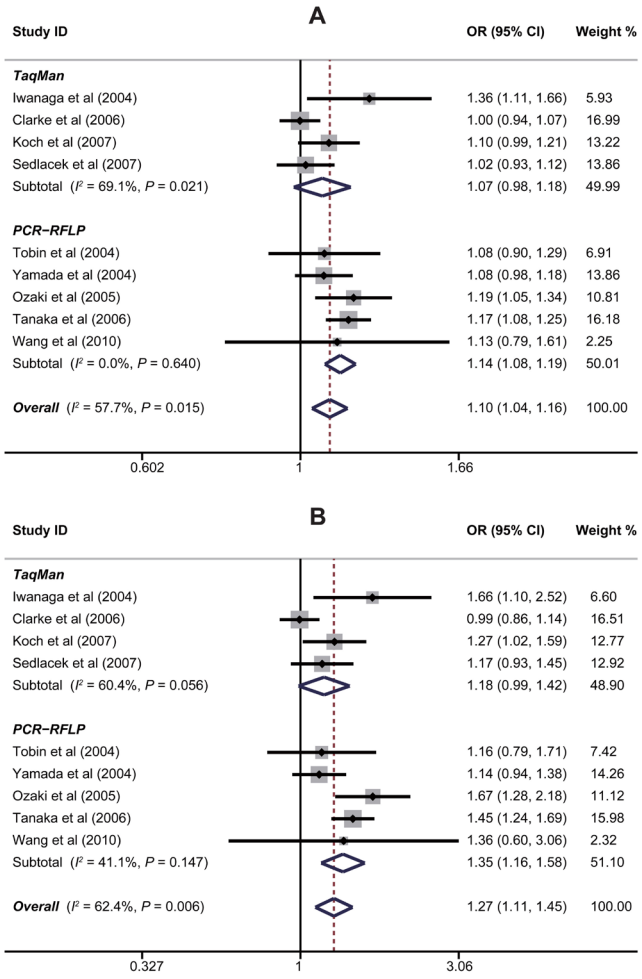

Figure 4. Forest plots of ORs for the association between the *TNF-β* C804A polymorphism and susceptibility to myocardial infarction in subgroup analysis based on genotyping method under the allele model (**A**) and the homozygous model (**B**).

Multivariate meta-regression analyses of potential source of heterogeneity

Potential sources of between-study heterogeneity were also investigated using multivariate meta-regression. Table 3 summarizes the influence of publication year, country of origin, ethnicity, source of controls, and genotyping method on the magnitude of the genetic effect. The results of multivariate meta-regression suggested that publication year (P = 0.156), country of origin (P = 0.175), source of control (P = 0.056), and genotyping method (P = 0.927) could not significantly explain such heterogeneity. In contrast, the influence of ethnicity (P = 0.046) was slightly significant, explaining more than 25% of the heterogeneity. Because between-heterogeneity disappeared in subgroup analysis based on ethnicity as shown in Table 2, ethnicity may be a primary source of between-heterogeneity.

Table 3. Multivariate meta-regression analyses of potential source of heterogeneity.

Heterogeneity factors	Coefficient	Standard error	z	P value	95%CI	
					Lower limit	Upper limit
Publication year	-0.110	0.077	-1.42	0.156	-0.261	0.041
Country of origin	0.264	0.195	1.36	0.175	-0.118	0.646
Ethnicity	-0.265	0.133	-1.99	0.046	-0.527	-0.005
Source of control	-0.502	0.263	-1.91	0.056	-1.017	0.013
Genotyping method	0.008	0.090	0.09	0.927	-0.168	0.185

Sensitivity analysis and publication bias

Sensitivity analysis for *TNF-β* C804A was conducted to determine the influence of individual datasets on pooled ORs by sequentially removing each eligible study. By omitting each study, pooled estimates remained very similar, indicating that no single study heavily influenced summary ORs in our meta-analysis (Figure 5). Begg's funnel plots and the Egger linear regression test were used to assess the potential publication bias of included studies under the allele model. The shapes of the funnel plots did not reveal any evidence of asymmetry (Figure 6). In addition, the Egger test showed no statistical evidence of publication bias (A allele *vs* C allele: $t = 0.10$, P = 0.920; AA *vs* CC: $t = 0.43$, P = 0.681). These results indicate a promising level of robustness and accuracy for the results of the meta-analysis.

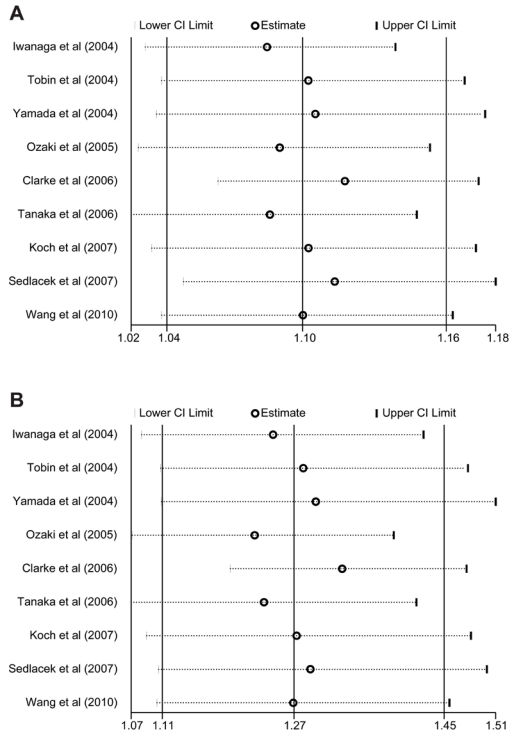

Figure 5. Sensitivity analyses of the association between the *TNF-β* C804A polymorphism and susceptibility to myocardial infarction under the allele model (**A**) and the homozygous model (**B**).

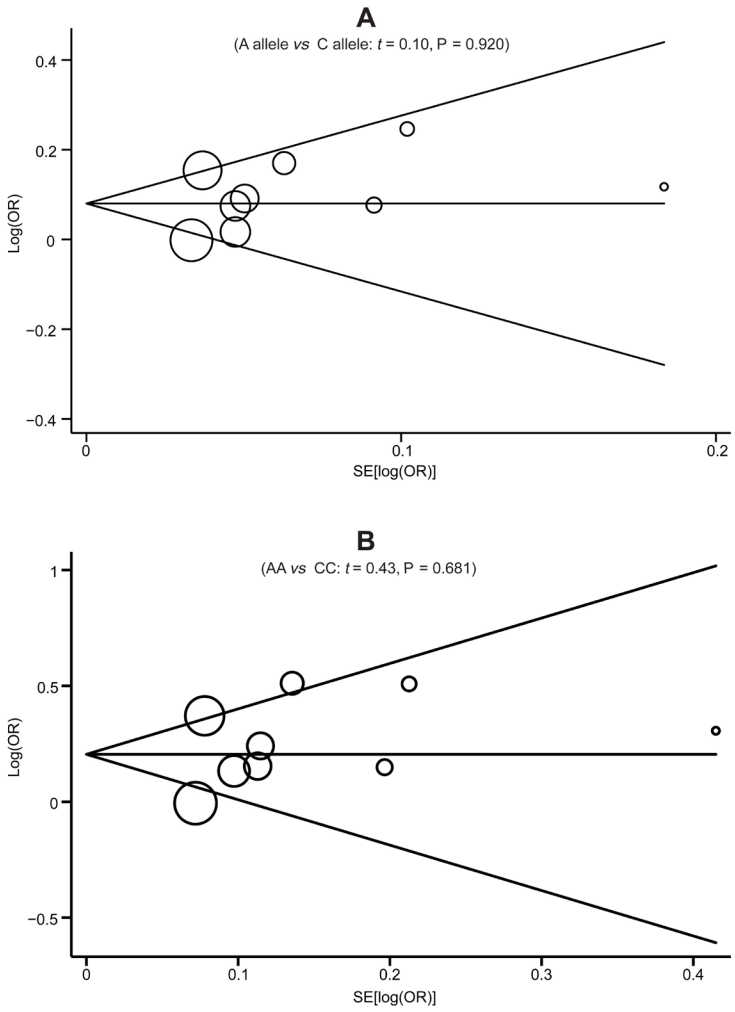

Figure 6. Begg's funnel plots of publication bias for the association between the *TNF-β* C804A polymorphism and susceptibility to myocardial infarction under the allele model (**A**) and the homozygous model (**B**).

DISCUSSION

MI, a multifactorial disease with a complex pathogenesis, is a serious public health problem and threatens the lives of patients (Nawrot et al., 2011). However, the pathogenesis of MI has remained difficult to understand. Over the past several decades, various association studies have been conducted to identify MI-susceptible genes, including *ALOX5AP* (Helgadottir et al., 2004), *TNF-β* (Padovani et al., 2000), *TNF-β* (Ozaki et al., 2002), and *CYP2C* (Collet et al., 2009), among others. Several genetic association studies found that the C804A polymorphism in the *TNF-β* gene was associated with MI risk (Iwanaga et al., 2004; Ozaki and Tanaka, 2005; Tanaka and Ozaki, 2006; Wang et al., 2010). TNF-β is a proinflammatory cytokine with homology to inflammatory cytokine TNF-α and is associated with the

development of atherosclerotic lesions in coronary arteries (Stoll et al., 2004). Variations in the *TNF-β* gene can modify the function of the TNF-β protein both qualitatively and quantitatively, thereby conferring a risk of MI. Iwanaga et al. (2004) first reported a significant association between *TNF-β* C804A and the susceptibility to MI in a Japanese population. Three other studies involving Asian populations also showed significant results (Ozaki and Tanaka, 2005; Tanaka and Ozaki, 2006; Wang et al., 2010). However, 4 subsequent studies of Caucasians failed to demonstrate that *TNF-β* C804A influences the risk of MI (Tobin et al., 2004; Clarke et al., 2006; Koch et al., 2007; Sedlacek et al., 2007). The discrepancies in these results are due in part to their limited sample sizes and insufficient statistical power to demonstrate significant associations. In addition, these studies included different populations and sampling strategies. Thus, in the present study, we performed a meta-analysis to comprehensively assess the relationship between the *TNF-β* C804A polymorphism and the risk of MI.

Meta-analysis has the advantageous ability of synthesizing data from published genetic association studies to obtain greater statistical power for detecting significant associations than possible from an individual study (Munafò and Flint, 2004). A large number of meta-analyses have been conducted to investigate the association between the *TNF-β* gene and various diseases (Schürks et al., 2011; Tiancha et al., 2011; Yang et al., 2012; Zhou et al., 2012; Xu et al., 2013). Our study is the first meta-analysis to describe the association between the *TNF-β* C804A polymorphism and MI risk. This systematic review provides a more comprehensive summary of the currently available evidence regarding the association between the *TNF-β* C804A polymorphism and the risk of MI.

The main finding of this study is that the *TNF-β* C804A polymorphism appears to be associated with an increased risk of MI only in Asian populations. Because heterogeneity is a major limitation when interpreting meta-analysis results, subgroup analysis and multivariate meta-regression were conducted to investigate potential heterogeneity sources. In addition, because individuals of different ethnicities may have diverse genetic backgrounds, and environmental factors could contribute to the same polymorphism playing different roles in different populations, subgroup analysis based on ethnicity was conducted. Interestingly, the *TNF-β* C804A polymorphism significantly increased the risk of MI in Asian populations, whereas no such effect was observed for Caucasian populations. The results of multivariate meta-regression analysis further confirmed that ethnicity may have been a major source of heterogeneity. In addition, the source of controls also contributed to heterogeneity. Because the genotype distribution in population-based controls may be more representative, studies including population-based controls may be more reliable than those including hospital-based controls. This may partially explain why the results of our stratified analysis by source of controls revealed differences between population-based and hospital-based subgroups.

There were some limitations to our study. First, since the number of studies was limited and the total sample size was relatively small, our association estimates may have occurred by chance. Second, as with other complex traits, MI risk may be modulated by other genetic markers in addition to the *TNF-β* gene. Thus, fully elucidating the pathogenesis of MI would require an investigation into the association and combined interactions of many gene variants with MI risk. Third, the included studies only focused on Asian and Caucasian populations, and thus further studies including a broader spectrum of subjects should be carried out to investigate the role of these variants in different ethnicities. Finally, this meta-analysis was based on unadjusted ORs and thus possible effect modifiers, such as hypertension, diabetes mellitus, hyperlipidemia, smoking, and obesity, may have influenced the association estimates.

A calculation of adjusted pooled ORs and further subgroup analyses based on these factors could not be performed because of data limitations. Thus, further well-designed genetic association studies should be conducted to explore these sources of heterogeneity. Despite these limitations, this is the first comprehensive meta-analysis to examine the association between the *TNF-β* C804A polymorphism and MI risk.

In conclusion, the results of our meta-analysis suggest that the *TNF-β* C804A polymorphism is associated with an increased risk of MI only in Asian populations. However, because of the limitations of this study, our results should be interpreted with caution and future large-scale studies are required to confirm their accuracy.

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