



Meta-analysis of angiotensin-converting enzyme insertion/deletion polymorphism and myocardial infarction in Han Chinese

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ABSTRACT. It has been suggested that the angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism is linked to susceptibility to myocardial infarction (MI). In this study, we performed a meta-analysis to assess the relationship between ACE I/D polymorphism and MI in the Chinese Han population. Eight studies including a total of 1609 subjects were selected for inclusion in the analysis. The references were retrieved using the PubMed and China National Knowledge Infrastructure databases. The analyses were performed using the STATA 12.0 software. ORs and 95%CI were assessed after the collected data were pooled for analysis. There was a significant association between ACE I/D polymorphism and MI in the Chinese Han population (II vs DD: OR = 0.40, 95%CI = 0.31-

0.53; II vs DI: OR = 0.72, 95%CI = 0.57-0.91; the dominant model: OR = 1.74, 95%CI = 1.41-2.16; the recessive model: OR = 0.47, 95%CI = 0.38-0.60). The sensitivity analysis further confirmed the result. Publication bias was not observed in this meta-analysis. The ACE I/D polymorphism may be a risk factor for MI in the Chinese Han population. However, larger studies with a stratified case-control population and biological characterization are needed to validate this finding.

Key words: Angiotensin-converting enzyme; Meta-analysis; Insertion/deletion polymorphism; Myocardial infarction

INTRODUCTION

Myocardial infarction (MI) remains one of the major causes of death and disability worldwide, accounting for up to 40% of all deaths (White and Chew, 2008). According to data from the National Health and Nutrition Examination Survey (2003 to 2006) the overall prevalence of MI is 3.6% in US adults over the age of 20, with rates of 4.7% for men and 2.6% for women (Schiller et al., 2012). Despite much investigation, the causes are not yet fully understood. The classic risk factors for MI include hypertension, hypercholesterolemia, diabetes, obesity, and smoking. In addition, genetic factors play an important role in the development of the disorder. It has been estimated that approximately 50% of the major risk factors for coronary artery disease are determined by genetics (Sekuri et al., 2005).

The renin-angiotensin-aldosterone system (RAAS) is essential to cardiovascular hemodynamics and plays an important role in the development of hypertension and cerebrovascular diseases. Angiotensin-converting enzyme (ACE) is an important circulating enzyme in the RAAS. It catalyzes the conversion of angiotensin I to angiotensin II and degrades bradykinin. The human ACE gene has the chromosomal locus 17q23 and many polymorphisms have been identified. The polymorphism rs4646994 is characterized by the presence or absence of a 287-bp Alu repetitive sequence, which results in three genotypes: II, DI, and DD (Haiman et al., 2003). The DD genotype is associated with two-fold higher tissue and plasma concentrations of ACE than the II genotype (Rigat et al., 1990). The ACE insertion/deletion (I/D) polymorphism has therefore been extensively studied in several cardiovascular and cerebrovascular diseases, such as ischemic stroke and coronary artery disease (Gao et al., 2006; Vaisi-Raygani et al., 2010).

In the past decade, a number of epidemiological studies have assessed the association between the ACE I/D polymorphism and MI risk. However, the reported results are controversial. A recent meta-analysis indicated that the ACE I/D polymorphism is related to an increased risk of MI (Chen et al., 2013). However, that meta-analysis included only limited articles with Chinese ancestry; most of the studies performed on Chinese participants were published in Chinese and in Chinese journals. Therefore, it is very important to clarify the relationship between ACE I/D polymorphism and MI risk in Chinese populations. In the present study, we investigated the association between ACE I/D polymorphism and MI risk in a Chinese population by performing a meta-analysis of the data from the literature.

MATERIAL AND METHODS

Selection of studies

Two reviewers searched PubMed and China National Knowledge Infrastructure (CNKI) databases to retrieve papers linking ACE I/D polymorphism and MI risk, which were available from October 2014 and had no language restrictions, using the following key words: “ACE I/D polymorphism”, “myocardial infarction/MI”, “rs4646994”, “single nucleotide polymorphism”, and “genetic polymorphism”. The reference lists of major textbooks, reviews, and included articles were identified through manual searches to find other potentially eligible studies. When more than one study of the same population was identified, we included the study with the largest sample size. When pertinent data were not included, or data presented were unclear, the authors were contacted directly.

Study selection

To be eligible for inclusion in this meta-analysis, the following criteria were stipulated: i) case-control studies must have addressed MI cases and healthy controls; ii) studies must have been about the association between ACE I/D polymorphism and susceptibility to MI; and iii) studies must have included sufficient genotype data for extraction. The exclusion criteria were as follows: i) case-control studies that did not evaluate the association between ACE I/D polymorphism and MI risk; ii) case reports, letters, reviews, meta-analyses, and editorial articles; iii) studies that were based on incomplete raw data and those with no usable data reported; and iv) duplicate data.

Data extraction

Two investigators independently extracted data and reached a consensus on all the items. The following information was recorded for each study: first author, year of publication, country, nationality, number of patients and controls, polymorphisms of gene, and evidence of Hardy-Weinberg equilibrium (HWE). In the case of conflicting evaluations, an agreement was reached following a discussion.

Statistical analysis

Observed genotype frequencies for ACE I/D polymorphism in controls were examined for deviations from HWE using a goodness-of-fit χ^2 -test with one degree of freedom. The strength of the associations between ACE I/D polymorphism and susceptibility to MI was estimated by OR and 95%CI of a homozygote comparison (II vs DD), a heterozygote comparison (II vs DI), a dominant model (DD + DI vs II), and a recessive model (II + DI vs DD) between groups (Lin et al., 2011). The statistical heterogeneity among studies was assessed using I^2 statistics (Higgins et al., 2003). I^2 ranges between 0 and 100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. When $I^2 > 50\%$ indicated heterogeneity across studies, the random-effects model

was used for meta-analysis; otherwise, the fixed-effects model was used. Sensitivity analysis was performed through random-effect model values compared with the fixed effect. We also performed a cumulative meta-analysis to provide a framework for updating the genetic effect from all studies, and to determine how the genetic effect changed as evidence accumulated to ascertain the trend in estimated risk effect (Zintzaras and Lau, 2008). In cumulative meta-analysis, studies were chronologically ordered by publication year, and then the pooled ORs were obtained at the end of each year. The funnel plot asymmetry was assessed by Begg's test to estimate the potential publication bias ($P < 0.05$ was considered to be statistically significant). Meta-analysis was performed using the STATA package version 12.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Study characteristics

A total of 58 potentially relevant publications up to October 2014 were systematically identified through PubMed and CNKI databases. Based on our preliminary search criteria, 50 were excluded because they did not satisfy the inclusion criteria. A total of 828 cases and 781 controls were included in the meta-analysis (Lu et al., 1997; Zheng et al., 1997; Lv et al., 1998; Li et al., 1999; Zhao et al., 2002; Sun et al., 2006; Zhang et al., 2006; Wang et al., 2010). The characteristics of the studies selected are summarized in Figure 1. Genotyping was conducted using polymerase chain reaction/restriction fragment length polymorphism for all studies. All studies were case-control studies that evaluated the association between ACE I/D polymorphism and MI risk. The years of publication of the studies included ranged from 1996 to 2010. The HWE test was conducted on the genotype distribution of the controls in all included studies, and all studies met the HWE requirement except three (Li et al., 1999; Zhao et al., 2002; Sun et al., 2006). The baseline characteristics of all studies included are summarized in Table 1.

Results of meta-analyses

A summary of the meta-analysis findings of the association between ACE I/D polymorphism and MI risk is shown in Table 2 and Figure 2. The meta-analysis indicated that the ACE I/D polymorphism was significantly associated with MI in all the genetic models (II vs DD: OR = 0.40, 95%CI = 0.31-0.53; II vs DI: OR = 0.72, 95%CI = 0.57-0.91; the dominant model: OR = 1.74, 95%CI = 1.41-2.16; the recessive model: OR = 0.47, 95%CI = 0.38-0.60). The cumulative meta-analysis showed an increasing trend in the estimated risk effect during 1996 to 2010, which showed that ACE I/D polymorphism is associated with MI risk, and the results were stable (Figure 3). Furthermore, sensitivity analysis was performed with controls in the HWE and the result was not altered, indicating that the result of meta-analysis was statistically significant (II vs DD: OR = 0.37, 95%CI = 0.25-0.54; II vs DI: OR = 0.80, 95%CI = 0.58-1.11; the dominant model: OR = 1.65, 95%CI = 1.23-2.23; the recessive model: OR = 0.43, 95%CI = 0.31-0.60).

Publication bias

The publication bias of the meta-analysis of the association between ACE I/D poly-

morphism and MI risk was detected by Begg's funnel plot; all graphical funnel plots of the studies included appeared to be symmetrical (Figure 4). The results of the Begg's funnel plot are shown in Table 2. Results showed that there was no publication bias (all $P > 0.05$).

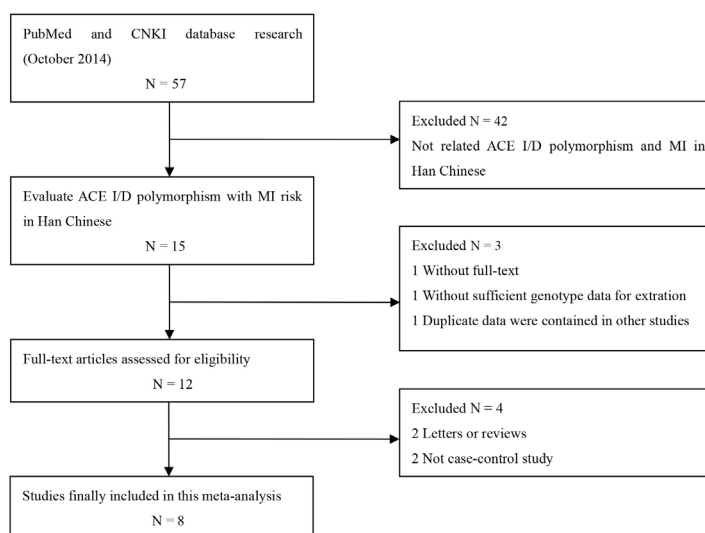


Figure 1. Flow chart showing study selection procedure.

Table 1. Characteristics of the studies included for meta-analysis.

Study included	Year	Area	Cases	Controls	Genotypes for cases			Genotypes for controls			HWE test
					DD	ID	II	DD	ID	II	
Lu et al.	1997	Shanghai	116	103	31	44	41	12	44	47	0.73
Zheng et al.	1997	Beijing	103	96	40	46	17	26	40	30	0.11
Lv et al.	1998	Shandong	58	41	24	18	16	9	17	15	0.33
Li et al.	1999	Beijing	153	150	32	63	58	29	48	73	0.00
Zhao et al.	2002	Heilongjiang	140	57	73	40	27	16	19	22	0.01
Sun et al.	2006	Nanjing	112	128	36	39	37	20	46	62	0.03
Zhang et al.	2006	Guangzhou	93	97	30	41	22	11	43	33	0.60
Wang et al.	2010	Nanchang	53	109	21	17	15	27	49	33	0.31

Table 2. Summary ORs and 95%CI of the studies included for meta-analysis.

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Test of publication bias	
		Case	Control		I ²	P	OR	95% CI	z	P
Overall	II vs DD	828	781	Fixed	1.2%	0.42	0.40	0.31-0.53	0.00	1.00
	II vs DI			Fixed	0.0%	0.70	0.72	0.57-0.91	0.00	1.00
	Dominant model			Fixed	0.0%	0.73	1.74	1.41-2.16	0.00	1.00
	Recessive model			Fixed	18.7%	0.28	0.47	0.38-0.60	0.00	1.00
Consistent with HWE	II vs DD	423	446	Fixed	0.0%	0.72	0.37	0.25-0.54	0.00	1.00
	II vs DI			Fixed	0.0%	0.48	0.80	0.58-1.11	0.00	1.00
	Dominant model			Fixed	0.0%	0.64	1.65	1.23-2.23	0.00	1.00
	Recessive model			Fixed	0.0%	0.70	0.43	0.31-0.60	0.00	1.00

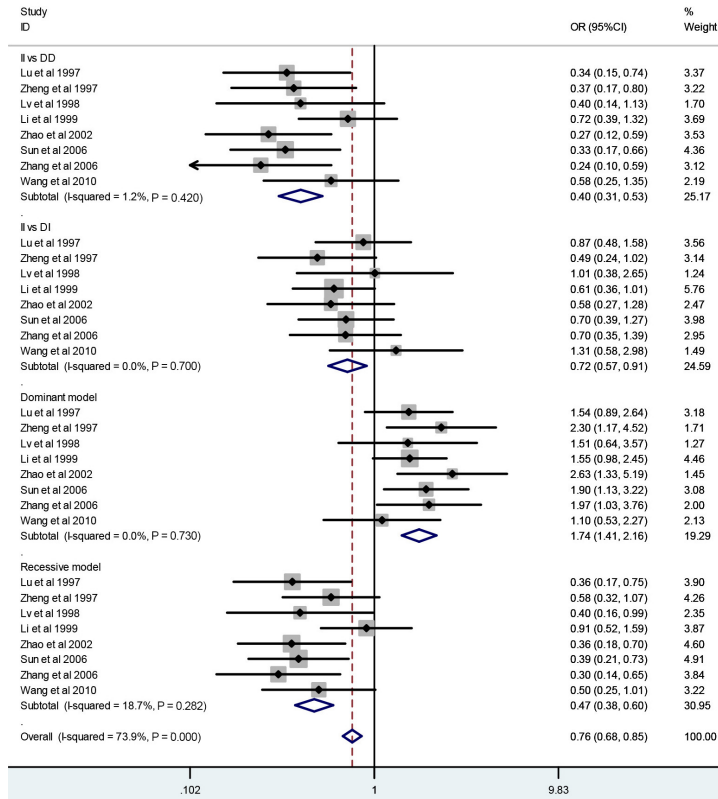


Figure 2. Forest plot of MI risk associated with ACE I/D polymorphism in the Chinese Han population.

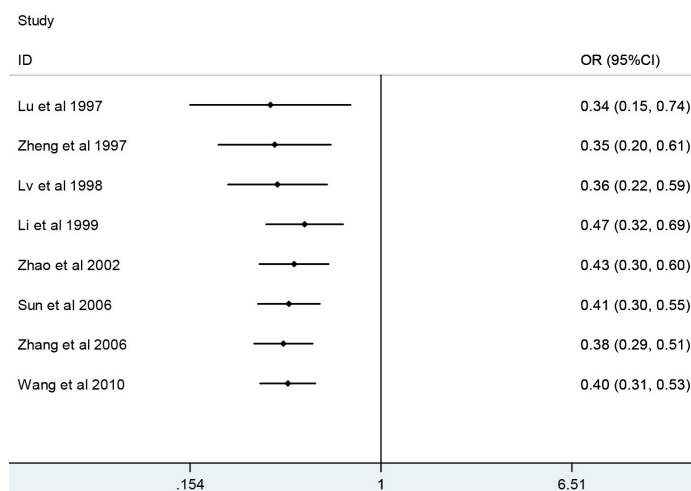


Figure 3. Cumulative meta-analysis for ACE I/D polymorphism in the fixed-effects pooled odds ratios (OR) with the corresponding confidence interval at 95% (95%CI).

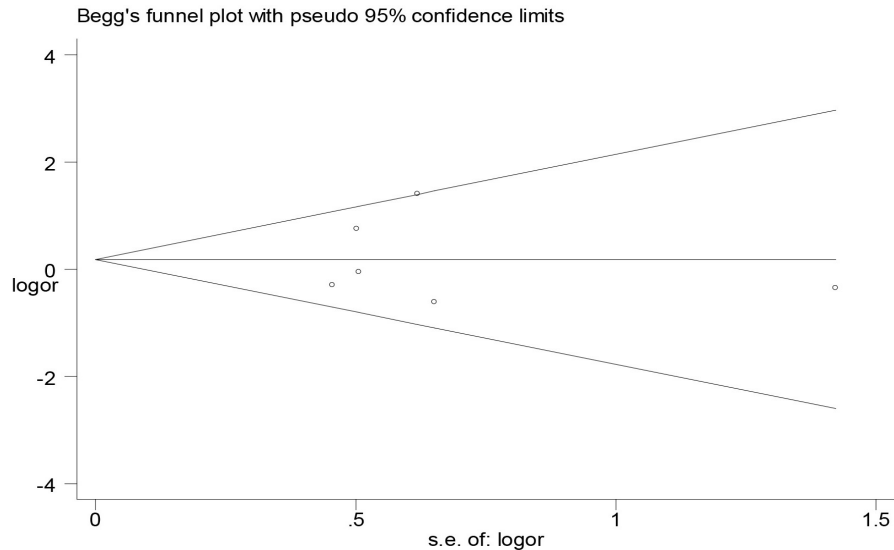


Figure 4. Funnel plot of ACE I/D polymorphism and susceptibility of MI for II vs DD.

DISCUSSION

MI is a multifactorial disease and its pathogenesis is not yet fully understood. Accumulated evidence indicates incontestably that MI is determined by a complex interaction of environmental and genetic factors. The RAAS plays a vital role in the cardiovascular system, and ACE is one of the most important components of the RAAS. Lu et al. (1997) were the first to report that ACE I/D polymorphism was associated with an increased risk of MI in Han Chinese using a case-control study. However, there has been some inconsistency, with some studies supporting this finding and others contradicting it, which suggests that the observed associations between the ACE I/D polymorphism and increased MI risk reflect chance observations rather than true associations. To help resolve these conflicting results, we conducted this meta-analysis to combine the same kinds of study to increase the sample size and statistical power, and thereby achieve a more authentic result.

In this meta-analysis, we extracted data from eight eligible studies comprising a total of 828 MI patients and 781 controls; the population studied was confined to Chinese subjects with homogeneous genetic backgrounds. Our results suggested that ACE I/D polymorphism was significantly associated with MI in the Chinese Han population. The finding was consistent with those from the previous meta-analysis, which indicated that the association was significant among Europeans and East Asians (Chen et al., 2013). Moreover, the existing evidence of the cumulative meta-analyses is sufficient to suggest that there is no statistically significant association between the ACE I/D polymorphism and MI risk. HWE is essential for a sound case-control study. It is probable that studies without HWE in controls have selection bias or genotyping error, which may cause misleading results. In this meta-analysis, we found that the ACE I/D polymorphism was significantly associated with the risk of MI in studies with $P_{\text{HWE}} > 0.05$. The data of the present meta-analysis indicated that the selection biases

hardly affected the results. There was no evidence of publication bias in this meta-analysis for ACE I/D polymorphism. As the number of eligible studies was limited in the meta-analysis, caution should be exercised when considering this conclusion.

Some limitations of this meta-analysis should be acknowledged. Firstly, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Secondly, the small sample size available was not ideal for detecting small genetic effects. Thirdly, the effects of gene-gene and gene-environment interactions were not addressed in this meta-analysis. In addition, the lack of genotype frequency information provided by some published studies did not allow the estimation of the best genetic model of inheritance to follow. Finally, although all cases and controls of each study were well defined with similar inclusion criteria, there may be potential factors that were not taken into account that may have influenced our results.

In conclusion, our results suggest that ACE I/D polymorphism was involved with the susceptibility of MI in the Chinese Han population. Owing to the mentioned limitations, further research should be performed to investigate these associations.

Conflicts of interest

The authors declare no conflict of interest.

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