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Original Article

Association between the insertion/deletion polymorphism of angiotensin converting enzyme gene and rheumatic heart disease: a comprehensive meta-analysis

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Abstract: Objective: Previous reports on the association between the insertion/deletion (I/D) polymorphism of angiotensin converting enzyme (ACE) gene and rheumatic heart disease (RHD), remained conflicting. This study was to further evaluate the association between ACE I/D polymorphism and RHD risk. Methods: Databases including PubMed, EMbase, CNKI and WanFang were retrieved to collect the related case-control studies. After screening studies and extracting data by 2 researchers independently, a meta-analysis was performed by Stata 12.0. Results: A total of 6 articles including 981 RHD patients and 901 controls were included. We found that there was a significant decreased susceptibility to RHD in a heterozygous model (OR=0.76, 95% CI: 0.58-0.99, P=0.040). Further subgroup analysis by age showed that the ACE I/D polymorphism in younger patients, but not in older patients, was significantly associated with RHD (allele model: OR=0.69, 95% CI: 0.52-0.91, P=0.010; homozygous model: OR=0.37, 95% CI: 0.19-0.71, P=0.003; recessive model: OR=0.64, 95% CI: 0.42-0.97, P=0.040). Moreover, there was a direct association between the ACE I/D polymorphism and the risk of mitral valve lesion (MVL) (allele model: OR=0.62, 95% CI: 0.43-0.89, P=0.009; homozygous model: OR=0.27, 95% CI: 0.11-0.64, P=0.003; recessive model: OR=0.57, 95% CI: 0.34-0.95, P=0.030) or combined valve lesion (CVL) (homozygous model: OR=0.47, 95% CI: 0.22-0.99, P=0.048) in younger patients. Conclusion: Taken together, these results suggest that the ACE I/D polymorphism is significantly associated with RHD, and DD genotype increases the risk of RHD.

Keywords: Rheumatic heart disease, angiotensin converting enzyme, polymorphism, genetic, meta-analysis

Introduction

Rheumatic heart disease (RHD) is an inflammatory, autoimmune disease caused by group A hemolytic streptococcus (GAS) repeated infections, rheumatic fever (RF) recurrent episodes, and usually occurs after throat infection [1, 2]. Although rare in developed countries nowadays, RHD is still a severe health issue in other countries [3, 4]. In our country, despite a downward trend, it remains to be one of the major cardiovascular disease (CVD) causing heart failure and death due to a huge population base and a great difference in development among regions. The pathogenesis of RHD, despite incompletely clear, is generally considered to be a consequence of the interaction between genetic and environmental factors. Thus, genetic factors play a role in the pathogenesis. For instance, there is evidence that human leukocyte antigen-II (*HLA-II*), transforming growth factor-beta (*TGF-beta1*), mannose-binding lectin 2 (*MBL2*) gene polymorphisms increased the prevalence of RHD [5-8].

The angiotensin converting enzyme (ACE), a key enzyme in the renin-angiotensin-aldosterone system (RAAS), can convert the Angiotensin I (Ang I) into the biologically active Angiotensin II (Ang II) and inactivate bradykinin [9-11]. *ACE* gene, located on chromosome 17q23, contains 26 exons and 25 inrons [12]. A 287-bp Alu

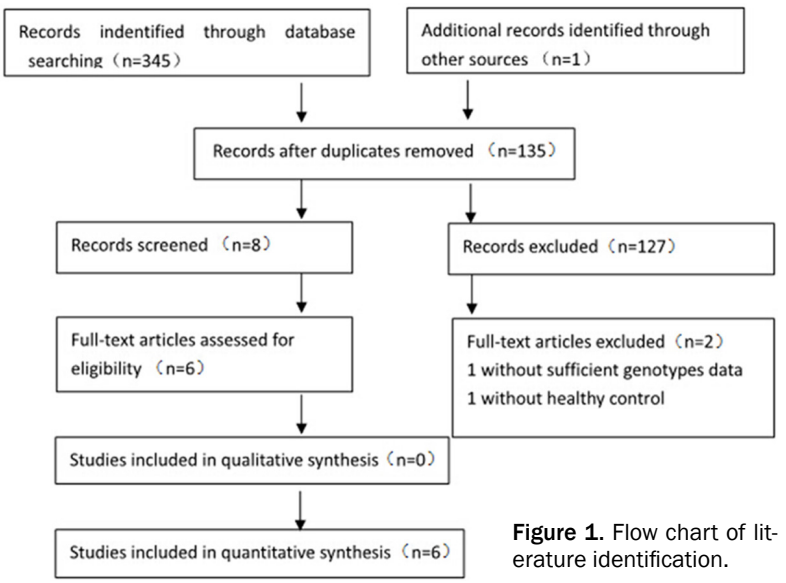


Figure 1. Flow chart of literature identification.

sequence insertion (I) or deletion (D) variant (SNP ID:rs4646994) which is the most studied polymorphism is situated in intron 16 and significantly affects the plasma ACE level [13]. Chain and separation analysis revealed that the level of plasma ACE depends on a single main genetic effect [14]. RAAS plays a crucial role in the occurrence, development and prognosis of CVD. Previous Meta-analysis studies showed the association of *ACE* I/D polymorphism with CVD, such as hypertension, coronary heart disease, cardiomyopathy, etc [15-20].

To date, several studies have reported the association between *ACE* I/D polymorphism and RHD clinical phenotype. However, these results remained inconsistent and conflicting because of sample size and heterogeneity [21-26]. In order to further clarify the distribution frequency of *ACE* gene I/D in RHD patients, a standard meta-analysis was conducted to evaluate the contribution of the genetic polymorphism to RHD risk. Also, this study was to aim at providing proof of evidence-based medicine for prevention and treatment of this disease.

Methods

Literature search and study selection

We performed a comprehensive literature search in the electronic databases PubMed, EMbase, Chinese National Knowledge Infrastructure (CNKI) and Wan-Fang (http://g.wanfangdata.com.cn/) up to May 1, 2015. The following keywords were used as search terms: angiotensin converting enzyme (or *ACE*), rheumatic heart disease (or RHD) and polymorphism (or variant or mutation), with no language restriction. Reference lists were retrieved manually in order to find potential studies and get all standard documents as soon as possible.

The inclusion criteria were as follows: 1) case-control studies (cases with clinically diagnosed RHD and healthy controls); 2) studies on the association between *ACE* I/D polymorphism and RHD; 3) studies with available genotype data for calculating odds ratio (OR) and 95% confidence interval (CI); 4) studies on genotype distribution of controls which was in accordance with the Hardy-Weinberg equilibrium (HWE). The exclusion criteria were as follows: 1) repeated studies; 2) case reports, reviews or meta-analysis; 3) incomplete or unclear data.

Quality evaluation

By using the Newcastle-Ottwa scale, the quality of each study was assessed based on the following eight items: 1) cases with independent validation; 2) obviously representative cases; 3) community controls; 4) controls with no history of RHD; 5) study controls for age; 6) study controls for additional factor(s); 7) ascertainment of exposure; 8) same method of ascertainment for cases and controls; 9) same non-response rate for both groups [27, 28]. The score for each item is 1 and the total score is 9.

Data extraction

Two investigators (Shang and Gong) searched studies, evaluated the quality and extracted the data from the included studies independently. If any discrepancies or contradictions arose, we achieved unanimous decision after discussion or requested assistance from the third reviewer. The same data from different

studies were adopted only once. According to the standard reporting format, the following information extracted from each study was included: the first author's name, publication year, country of study population, ethnicity, average age, sample size, number of genotypes, and HWE status. The information input error was avoided by the double input and validation.

Statistical analysis

HWE was examined using Pearson's chi-square test in the control group. The meta-analysis was performed using STATA 12.0 (Stata Corporation, College Station, TX, USA). The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the association between the *ACE* I/D polymorphism and the risk of RHD in five genetic model: allele model (I vs. D), homozygous model (II vs. DD), heterozygous model (II vs. ID), dominant model (II vs. ID+DD), and recessive model (II+ID vs. DD). Z test was applied to determine the statistical significance of pooled ORs in all genetic models. all *P* values were two sided, and *P* value <0.05 was considered as statistically significant. According to the statistical principle, only the homogeneous data was merged. In contrast, due to a great heterogeneity, the data could not be combined together. The I^2 statistic test was used to evaluate the heterogeneity among studies included without association with the number of literatures [29]. The value of I^2 ranged from 0 to 100%. $I^2 \leq 50\%$ indicated small heterogeneity among studies, and a fixed-effect model was used for meta-analysis. Alternatively, a random-effect model was more appropriate for the meta-analysis ($I^2 > 50\%$) [30, 31]. In addition, the source of the heterogeneity was examined by subgroup analysis according to ethnicity and age, and was validated by meta-regression. The potential confounding factors included ethnicity of patients, average age, sex ratio of study participants, sample size, genotyping method, publication year, etc. Sensitivity analysis was carried out to estimate the stability and reliability of the pooled results by removing each single study sequentially [29]. Begg's funnel plot was applied to assess the potential publication bias of literatures in this meta-analysis. Meanwhile, Egger's test was used to detect the bias quantitatively [32, 33].

Results

Studies selection and characteristics

We performed the meta-analysis according to guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [34]. As shown in **Figure 1**, a total of 346 records were identified through databases and other sources indicated. After excluding 211 repeated studies, 127 irrelevant studies, 1 study without sufficient genotypes data, and 1 study without healthy controls, a total of six studies involving 981 RHD cases and 901 controls finally met our inclusion criteria and were included in this meta-analysis.

The patients from five studies [21, 23-26] were further divided into mitral valve lesion (MVL, n=362) group or combined valve lesion (CVL, n=537) group. Subjects (9-21 years old) from two studies [23, 26] were regarded as the younger group, while subjects from the other four studies [21, 22, 24, 25] were regarded as the older group (35-51 years old). Individuals in control groups were from volunteers, health physical examination, and outpatients without cardiovascular defects. The baseline characteristics in these studies included were shown in **Table 1**.

Meta-analysis results

A significantly decreased susceptibility to RHD was found in a heterozygous genetic model (OR=0.76, 95% CI: 0.58-0.99, P=0.040) (**Figure 2**; **Table 2**), but not in other genetic models (allele model: OR=0.97, 95% CI: 0.72-1.32, P=0.87; homozygous model: OR=0.84, 95% CI: 0.46-1.54, P=0.58; dominant model: OR=1.05, 95% CI: 0.61-1.81, P=0.85; recessive model: OR=0.85, 95% CI: 0.64-1.05, P=0.12) (**Table 2**). Next, subgroup analysis was performed based on age and ethnicity. Age subgroup analysis revealed that the *ACE* I/D polymorphism was significantly associated with RHD in the younger subjects (allele model: OR=0.69, 95% CI: 0.52-0.91, P=0.01; homozygous model: OR=0.37, 95% CI: 0.19-0.71, P=0.003; recessive model: OR=0.64, 95% CI: 0.42-0.97, P=0.04), but not in older subjects. However, we failed to observe a significant association in subgroup analysis according to ethnicity (**Figures 2**, **3**; **Table 2**).

Table 1. Baseline characteristics of included studies

Study	Country	Ethnicity	Quality scores	Sample size (case/control)	RHD			Control			MVL	CVL	Average age		HWE of control
					II	ID	DD	II	ID	DD			RHD	Control	
Chou HT, 2004	China	Asian	7	115/100	55	41	19	30	52	18	53	62	51	50	0.581
Davutoglu V, 2005	Turkey	Caucasian	7	82/154	26	25	31	28	69	57	NA	NA	40	43	0.379
Morsy MM, 2011	Egypt	Caucasian	6	139/79	43	59	37	29	39	11	56	83	10	9	0.713
Gupta U, 2013	India	Asian	6	300/200	101	167	32	92	94	14	158	142	35	37	0.125
Zhang T, 2013	China	Asian	7	246/223	124	97	25	88	109	26	47	199	48	49	0.374
Harbi KM, 2015	Saudi Arabia	Caucasian	7	99/145	4	45	50	19	62	64	48	51	19	21	0.518

RHD: Rheumatic heart disease; MVL: Mitral valve lesion; CVL: Combined valve lesion; HWE: Hardy-Weinberg equilibrium; NA: not available.

Table 2. Pooled ORs and 95% CIs of the association between ACE I/D polymorphism and RHD

	I vs. D			II vs. DD			ID vs. DD			II vs. ID/DD			II/ID vs. DD		
	OR (95% CI)	I^2 (%)	P	OR (95% CI)	I^2 (%)	P	OR (95% CI)	I^2 (%)	P	OR (95% CI)	I^2 (%)	P	OR (95% CI)	I^2 (%)	P
RHD															
Overall	0.97 (0.72-1.32)	79	0.866	0.84 (0.46-1.54)	73	0.578	0.76 (0.58-0.99)	0	0.042	1.05 (0.61-1.81)	84	0.850	0.85 (0.64-1.05)	12	0.122
Ethnicity															
Asian	1.10 (0.68-1.79)	87	0.698	1.06 (0.49-2.33)	74	0.878	0.83 (0.56-1.22)	0	0.334	1.23 (0.58-2.65)	90	0.587	0.94 (0.65-1.35)	8	0.729
Non-Asian	0.85 (0.56-1.30)	71	0.459	0.62 (0.20-1.93)	80	0.412	0.71 (0.50-1.02)	14	0.061	0.83 (0.30-2.28)	82	0.723	0.74 (0.53-1.03)	27	0.077
Age															
Older	1.14 (0.78-1.66)	82	0.489	1.20 (0.66-2.18)	67	0.558	0.78 (0.56-1.08)	0	0.139	1.39 (0.74-2.63)	87	0.310	0.95 (0.70-1.28	0	0.722
Younger	0.69 (0.52-0.91)	0	0.010	0.37 (0.19-0.71)	0	0.003	0.69 (0.34-1.38)	55	0.293	0.52 (0.20-1.38)	61	0.190	0.64 (0.42-0.97)	31	0.036
MVL															
Overall	0.88 (0.64-1.21)	60	0.441	0.70 (0.35-1.40)	64	0.310	0.74 (0.51-1.08)	0	0.115	0.96 (0.56-1.67)	66	0.896	0.73 (0.51-1.04)	0	0.079
Age															
Older	1.08 (0.74-1.56)	58	0.698	1.04 (0.62-1.75)	15	0.881	0.81 (0.48-1.38)	0	0.445	1.24 (0.67-2.28)	71	0.500	0.92 (0.56-1.51)	0	0.734
Younger	0.62 (0.43-0.89)	0	0.009	0.27 (0.11-0.64)	0	0.003	0.62 (0.27-1.48)	55	0.273	0.41 (0.09-1.87)	55	0.249	0.57 (0.34-0.95)	33	0.031
CVL															
Overall	0.92 (0.61-1.38)	82	0.673	0.73 (0.34-1.55)	73	0.413	0.79 (0.56-1.10)	0	0.157	0.92 (0.47-1.81)	85	0.807	0.80 (0.59-1.10)	30	0.176
Age															
Older	1.04 (0.55-1.95)	90	0.911	0.93 (0.31-2.84)	84	0.905	0.81 (0.53-1.25)	0	0.346	1.12 (0.42-2.95)	91	0.821	0.88 (0.48-1.62)	53	0.682
Younger	0.75 (0.54-1.04)	0	0.086	0.47 (0.22-0.99)	0	0.046	0.75 (0.44-1.27)	21	0.281	0.70 (0.40-1.23)	0	0.215	0.68 (0.41-1.12)	0	0.132

OR: odds ratio; CI: confidence interval. *P*-value was for pooled ORs. $I^2 \leq 50\%$ using a fixed-effect model; $I^2 > 50\%$ using random-effect model.

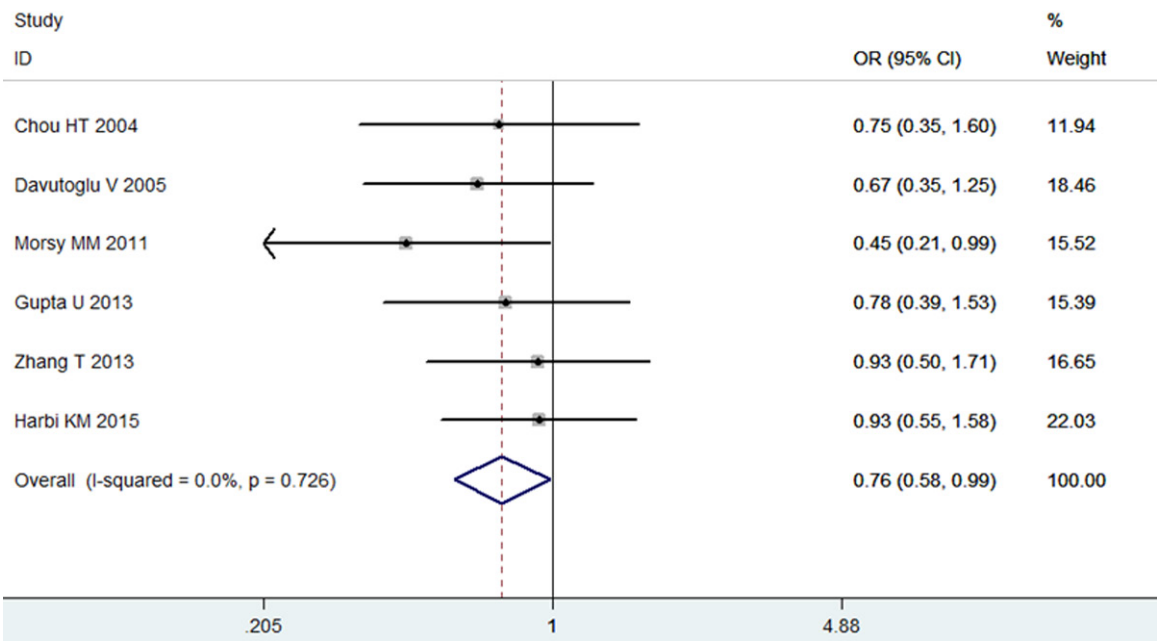


Figure 2. Forest plot of rheumatic heart disease risk associated with ACE I/D polymorphism under a heterozygous genetic model.

No significant association was detected between the *ACE* I/D polymorphism and MVL susceptibility in all genetic model. We also performed MVL subgroup analyses by age. Nonetheless, there was a direct association between the *ACE* I/D polymorphism and MVL risk in younger population (allele model: OR=0.62, 95% CI: 0.43-0.89, P=0.009; homozygous model: OR=0.27, 95% CI: 0.11-0.64, P=0.003; recessive model: OR=0.57, 95% CI: 0.34-0.95, P=0.03) (Details in **Figure 4**; **Table 2**). As seen in **Table 2**, we failed to detect any significant association in older subjects in all genetic models. Similarly, no significant association was obtained between the *ACE* I/D polymorphism and the susceptibility to CVL in all genetic models. But the subgroup analysis by age suggested a direct association between the *ACE* I/D polymorphism and CVL risk in younger subjects (homozygous model: OR= 0.47, 95% CI: 0.22-0.99, P=0.05), but not in older subjects (**Figure 5**; **Table 2**).

It was worth mentioning that significant heterogeneity was detected in the studies included. Therefore, the random-effects model was used when heterogeneous results were merged. Otherwise, the fixed-effect model was adopted for the meta-analysis. All details were shown in **Table 2**. Apparently, in stratification analysis by age, the heterogeneity was markedly reduced in the younger group, consistent with the results of meta-regression (P=0.037 for allele model; P=0.031 for homozygous model).

Sensitivity analysis

Sensitivity analysis was carried out to estimate the effect of individual study on the pooled ORs and 95% CIs by removing single study sequentially. We found that the omission of any single study did not produce significant change in the combined effects in all genetic models, confirming a high stability and reliability of our results (data not shown).

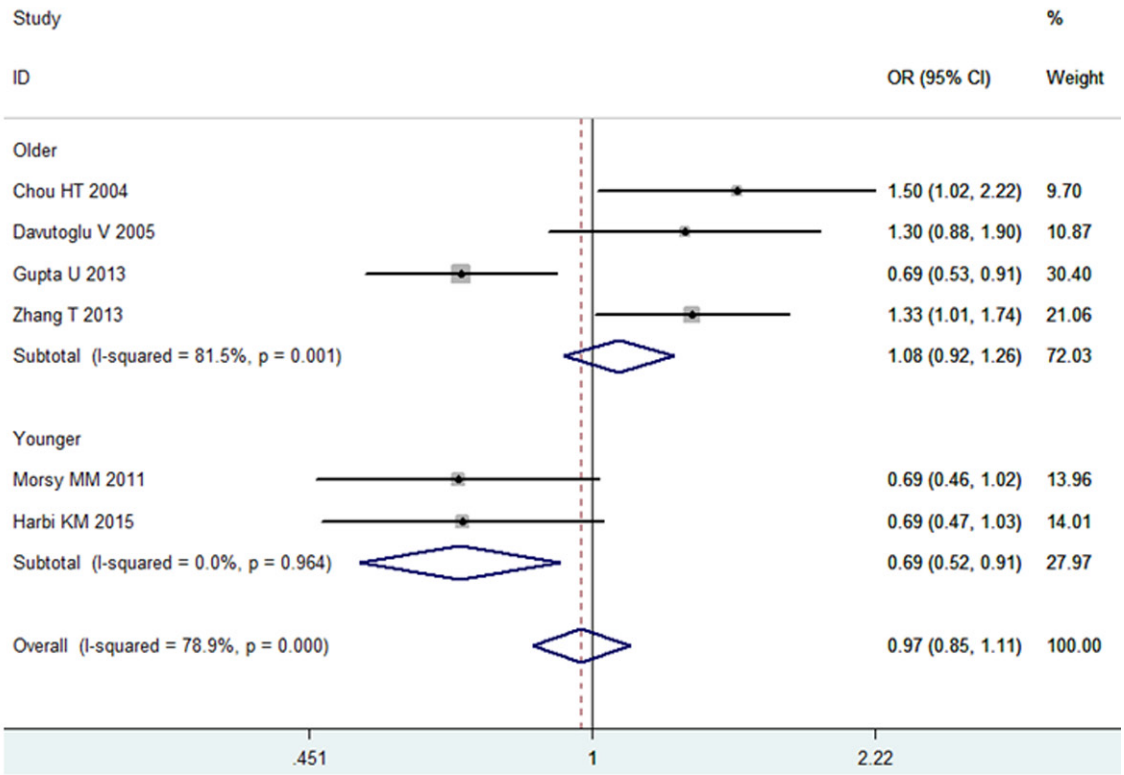
Publication bias

Begg's funnel plot was applied to assess the publication bias of the articles selected. As shown in **Figure 6**, the shape of the funnel plots did not show significant asymmetry, implying absence of publication bias. Moreover, these results were confirmed by Egger's test (allele model: P=0.961; homozygous model: P=0.213; heterozygous model: P=0.077; recessive model: P=0.877; dominant model: P= 0.454).

Discussion

Our results suggested that the *ACE* I/D polymorphism was significantly associated with

A


Study
ID
OR (95% CI)
%
Weight
Older
Chou HT 2004
1.50 (1.02, 2.22)
9.70
Davutoglu V 2005
1.30 (0.88, 1.90)
10.87
Gupta U 2013
0.69 (0.53, 0.91)
30.40
Zhang T 2013
1.33 (1.01, 1.74)
21.06
Subtotal (I-squared = 81.5%, p = 0.001)
1.08 (0.92, 1.26)
72.03
Younger
Morsy MM 2011
0.69 (0.46, 1.02)
13.96
Harbi KM 2015
0.69 (0.47, 1.03)
14.01
Subtotal (I-squared = 0.0%, p = 0.964)
0.69 (0.52, 0.91)
27.97
Overall (I-squared = 78.9%, p = 0.000)
0.97 (0.85, 1.11)
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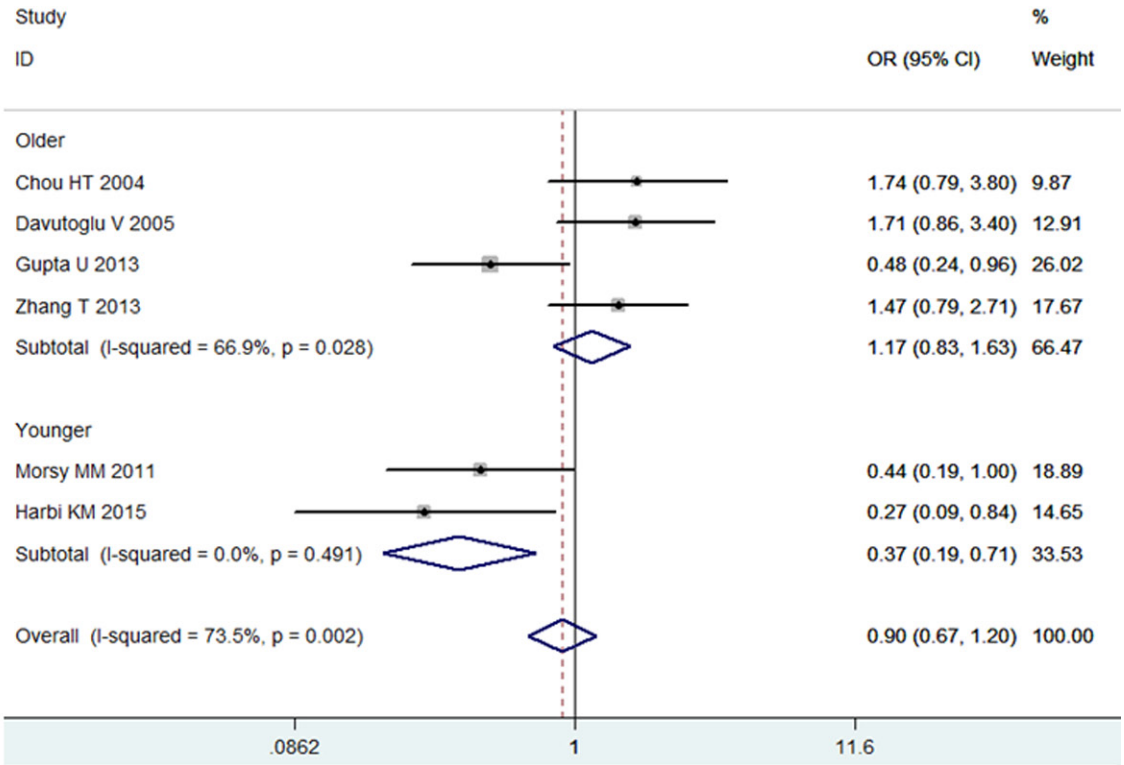
2.22

B


Study
ID
OR (95% CI)
%
Weight
Older
Chou HT 2004
1.74 (0.79, 3.80)
9.87
Davutoglu V 2005
1.71 (0.86, 3.40)
12.91
Gupta U 2013
0.48 (0.24, 0.96)
26.02
Zhang T 2013
1.47 (0.79, 2.71)
17.67
Subtotal (I-squared = 66.9%, p = 0.028)
1.17 (0.83, 1.63)
66.47
Younger
Morsy MM 2011
0.44 (0.19, 1.00)
18.89
Harbi KM 2015
0.27 (0.09, 0.84)
14.65
Subtotal (I-squared = 0.0%, p = 0.491)
0.37 (0.19, 0.71)
33.53
Overall (I-squared = 73.5%, p = 0.002)
0.90 (0.67, 1.20)
100.00
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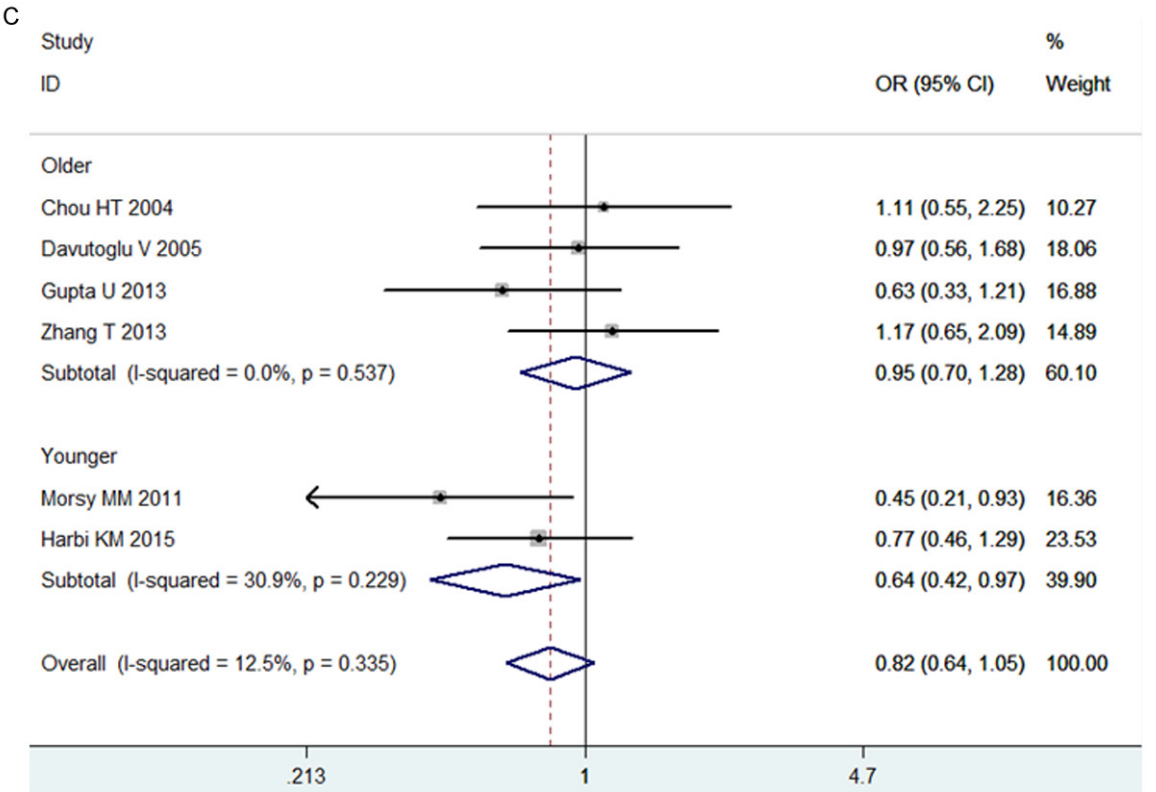
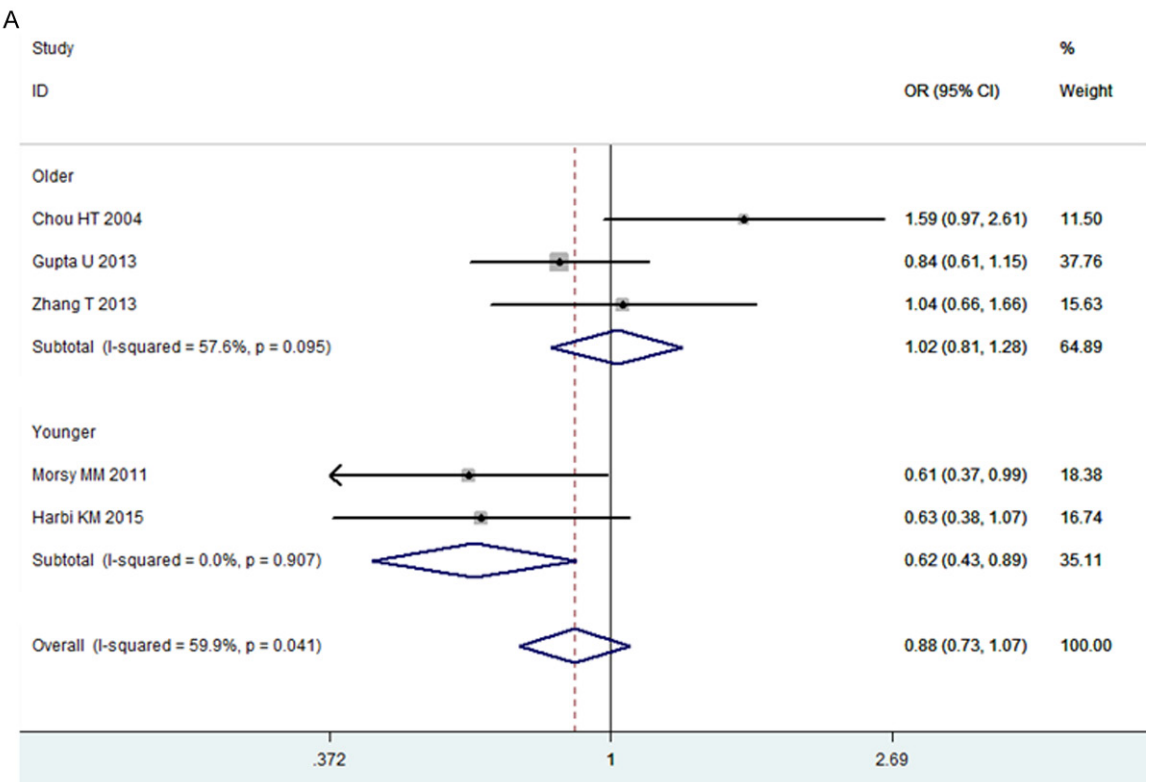


Figure 3. Forest plots of rheumatic heart disease risk associated with ACE I/D polymorphism stratified by age (A: Allele genetic model; B: Homozygous genetic model; C: Recessive genetic model).



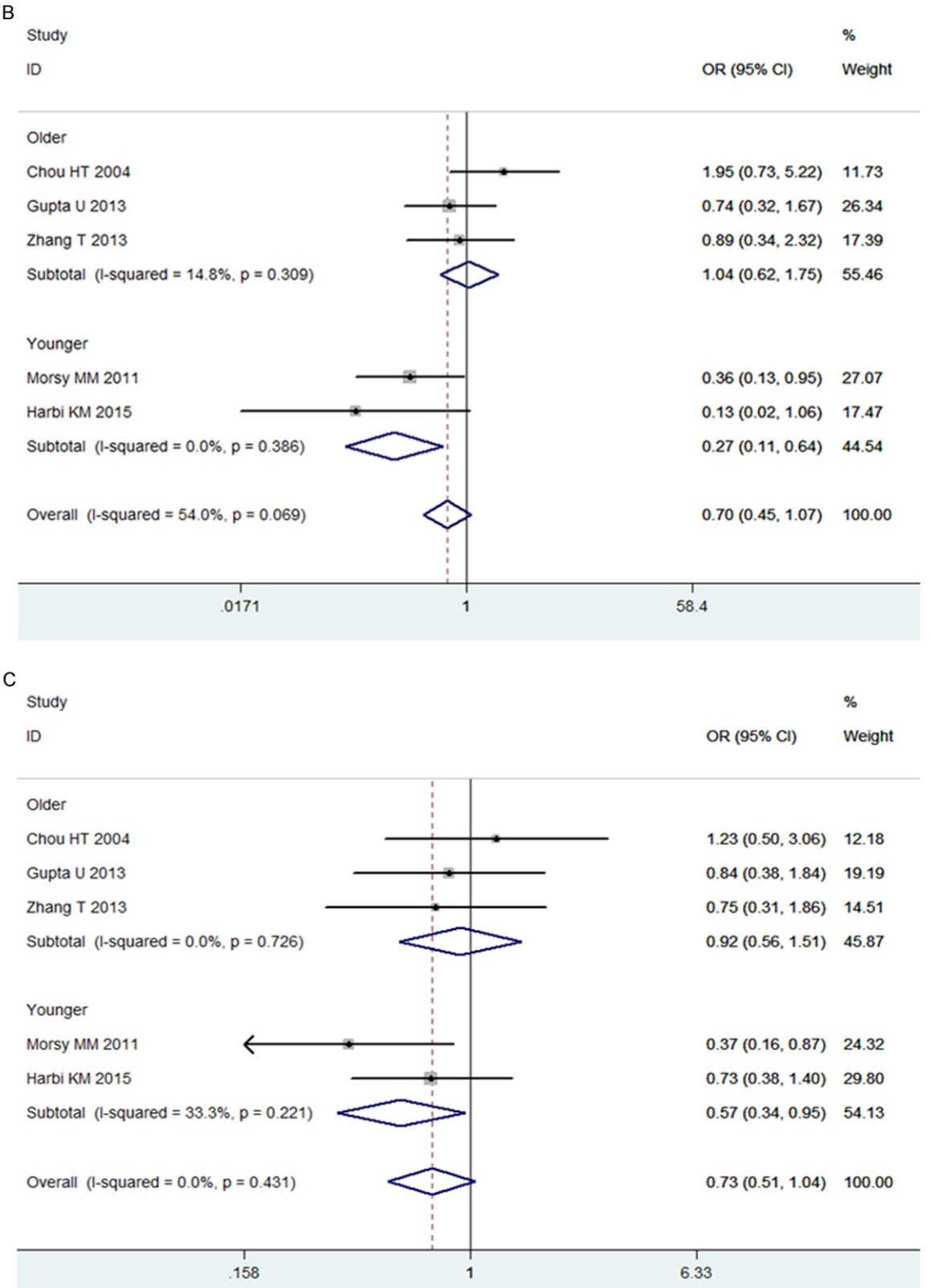


Figure 4. Forest plots of mitral valve lesion risk associated with ACE I/D polymorphism stratified by age (A: Allele genetic model; B: Homozygous genetic model; C: Recessive genetic model).

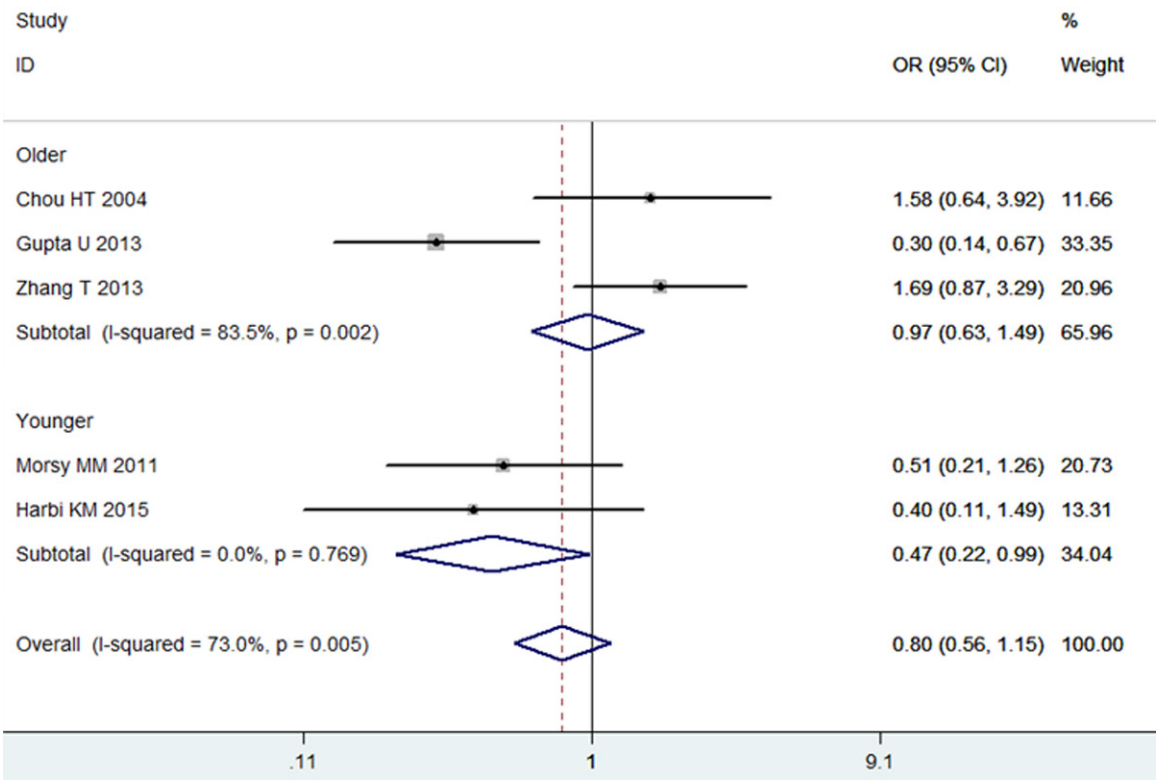


Figure 5. Forest plot of combined valve lesion risk associated with ACE I/D polymorphism under a homozygous genetic model stratified by age.

RHD, and DD genotype increases the risk of RHD. This meta-analysis involving 981 RHD cases and 901 controls revealed that subjects carrying D allele and DD genotype were susceptible to RHD (OR=0.76 for ID vs. DD). Further subgroup analysis suggested that there are significant associations between *ACE* I/D polymorphism and RHD in the younger group (P=0.01 for I vs. D; P=0.003 for II vs. DD; P=0.04 for II/ID vs. DD), but not in the older group in five genetic models (all P>0.05). Also, this association was seen in the younger group of MVL and the CVL. These findings suggest the contributions of *ACE* I/D variants to RHD risk and offer proof of evidence-based medicine for the genetic susceptibility to RHD, as well as provide the basis for the larger scale study across the world.

A number of studies have shown that the *ACE* I/D polymorphism plays a key role in the CVD system, such as myocardial infarction, carotid artery wall thickness, and left ventricular remodeling [35-37]. Evidence from the *in vitro* experiment suggested that plasma *ACE* level was closely related to its genetic variant [38, 39]. And the plasma *ACE* level in DD carriers was almost two fold in II carriers, and was intermediate in ID genotype [13]. In the DD genotype, the lack of a 287-bp Alu sequence may result in the activation of *ACE* gene, and thus causing high expression. Furthermore, the activity of *ACE* is closely related to Ang II level in human [40]. There is evidence that the high level of Ang II contributes to cardiac hypertrophy, interstitial fibrosis and cardiac remodeling. Hence, individuals carrying the DD genotype may have an elevated level of Ang II and are more susceptible to CVD. The present meta-analysis results further support the possibility.

In 2013, Gupta U et al performed a meta-analysis to evaluate the association of *ACE* I/D polymorphism with the RHD risk [24]. In this analysis, the authors only analyzed the allele model, and concluded that *ACE* ID and DD genotypes were associated with an increased risk of RHD. Our meta-analysis involved five kinds of classic genetic models, the sources of heterogeneity and sensitivity analysis, reaching a more comprehensive and detailed conclusion. Subjects from these studies included came from differ-

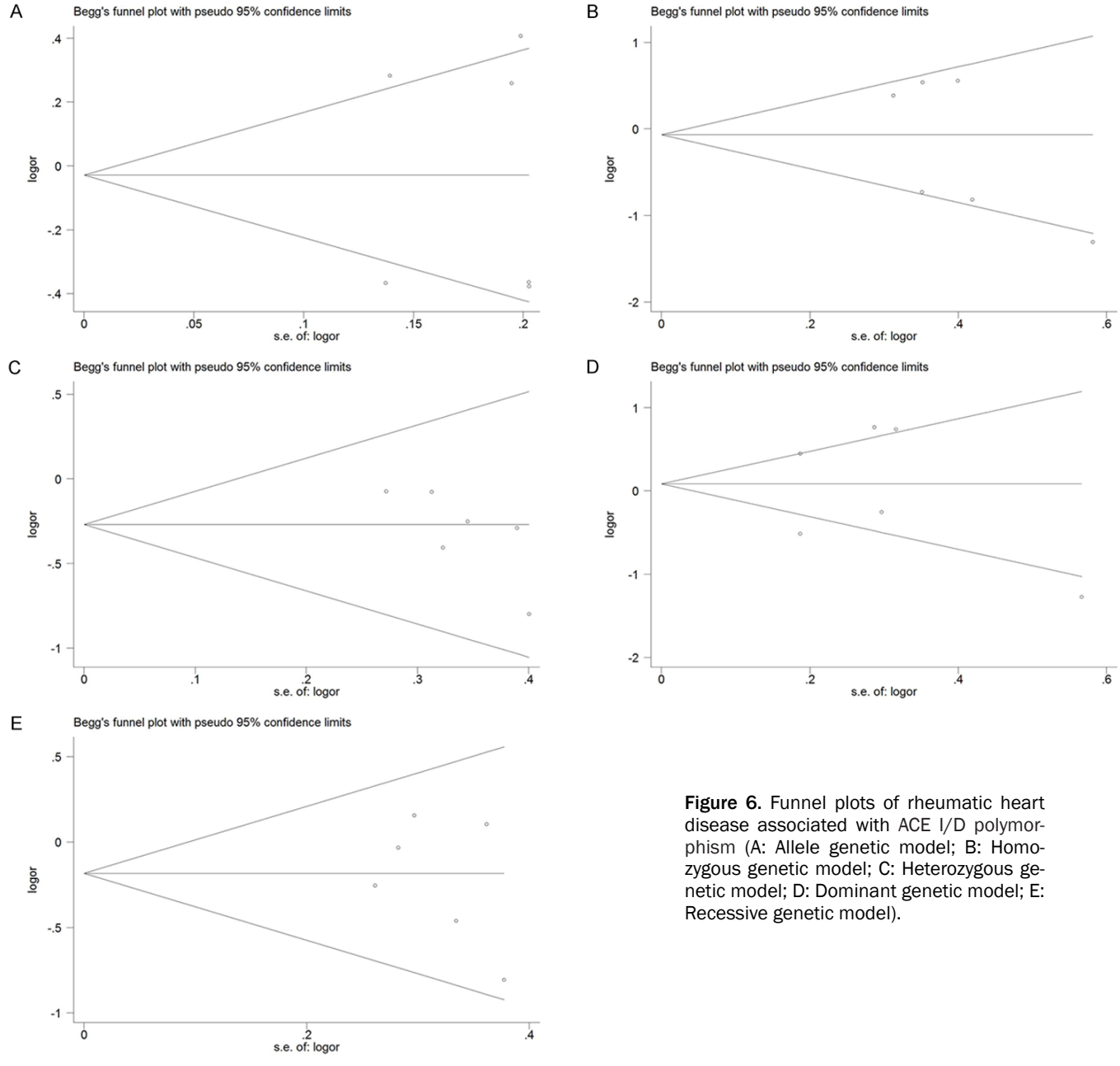


Figure 6. Funnel plots of rheumatic heart disease associated with ACE I/D polymorphism (A: Allele genetic model; B: Homozygous genetic model; C: Heterozygous genetic model; D: Dominant genetic model; E: Recessive genetic model).

ent regions, different countries and ethnicities, thus heterogeneity existed unavoidably. Before an attempt to pool data for meta-analysis, we executed strict and unified inclusion and exclusion criteria. Only the data from the literatures with a same research purpose and high quality were merged, suggesting reliability of our results. In this meta-analysis, there was obvious heterogeneity among the articles included on association between *ACE* I/D polymorphism and RHD susceptibility, thereby we performed subgroup analysis to seek the sources of heterogeneity and verified by meta-regression. We observed that age was attributed to the heterogeneity in the allele, homozygous, heterozygous and recessive models. Additionally, sensitivity analysis and evaluation of publication bias further suggested the reliability of our meta-analysis.

Our analysis has some potential limitations. First, due to less data on genetic epidemiology of RHD, we included only six case-control studies after screening carefully, limiting the statistical power of this meta-analysis. Second, we failed to examine gene-gene and gene-environment interactions because of the absence of original data. Finally, we might need to analyze the multiple loci polymorphisms of *ACE* gene, even build haplotype in order to clarify the relationship.

In conclusion, our data confirm that the *ACE* I/D polymorphism confers susceptibility to RHD, especially in younger population. Further well-designed large studies with different populations and ethnicities are needed to verify the association between the functional polymorphism loci of the *ACE* gene and RHD susceptibility.

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Disclosure of conflict of interest

None.

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