

Original Article

Association between *angiotensin-converting enzyme* gene insertion/deletion polymorphism and osteoarthritis: a meta-analysis

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Received March 30, 2016; Accepted September 2, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: Objective: Osteoarthritis (OA) is a common disease characterized by the degeneration of joint cartilage. Some studies have investigated the association between angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism and OA, but the conclusions were inconsistent. To evaluate the specific relationship, we performed a meta-analysis to clarify the controversies. Methods: We systematically searched the PubMed, Embase, Cochrane Library, CNKI, and Google scholar up to December 20, 2015 to identify all relevant studies. Two reviewers independently selected the studies, extracted the data, and assessed the trials quality. Data extracted from eligible studies were meta-analyzed using RevMan5.3 and Stata12.0 software. Stratification analysis was performed according to the sources of heterogeneity, which was detected from the Meta-regression analysis. Odds ratio (OR) with its 95% confidence interval (CI) was used to assess the strength of the association. Results: Five studies involving 1324 participants were included in the analysis. Meta-analysis showed significant association between ACE I/D polymorphism and OA risk in Caucasians (DD vs. DI + II: OR = 2.10, P < 0.01; DD + DI vs. II: OR = 3.11, P < 0.01; DD vs. II: OR = 3.98, P < 0.01; and D vs. I: OR = 2.10, P < 0.01), but not in overall populations and Asians. Conclusions: Our study indicated that there was no association between ACE I/D gene polymorphism and OA susceptibility in Asians. However, DD genotype and D allele may be risk factors for OA in Caucasians. Due to the limitation of the present studies, further larger studies are needed to confirm our findings.

Keywords: Peptidyl-dipeptidase A, angiotensin converting enzyme, ACE, polymorphism, genetic, gene polymorphism, genetic variation, osteoarthritis, OA, meta-analysis

Introduction

Osteoarthritis (OA) is one of the most common disorders affecting the motor system and characterized by articular cartilage thinning or loss, formation of osteophytes, and/or subchondral sclerosis [1]. It is particularly widespread in the societies where there is a large elderly population, such as China and Turkey [2]. The morbidity of OA increases with age, and it is estimated that 80% of individuals over the age of 75 years are affected [3]. OA causes joint stiffness, pain, and consequently decreases patients' quality of life. Meanwhile, it increases the economic burden on their families and on society [1].

Although the etiology of OA remains unknown, it is widely regarded as a multifactorial disease

involving age, gender, obesity, acute and chronic joint trauma, special occupation. What is more, genetic factors also are considered to be strong determinants of the disease [4]. In the last few years, extensive efforts have led to the identification of a number of OA susceptibility genetic signals in European and Asian populations [5]. Related researches conducted in some areas indicated that angiotensin-converting enzyme (ACE) genetic polymorphism was one of the susceptible factors of OA.

ACE is a key component of the rennin-angiotensin-aldosterone system (RAAS), and plays an important role in the regulation of blood pressure, blood volume, and inflammation [6, 7]. Human ACE gene located on the chromosome 17q23, it spans 21 kb and composes of 26

exons and 25 introns. The most common genetic variation is the insertion/deletion (I/D) of a 287 bp Alu repetitive sequence in intron 16. It possesses two alleles (D and I), and displays three genotypes (DD, DI and II) [8]. ACE I/D polymorphism (Gen Bank accession number: rs1799752) may be associated with serum ACE level and activity, and has been widely studied in cardiovascular [9], neurological [10], and renal [11] diseases.

Some studies have shown that ACE levels in synovial fluid are higher in OA patients than healthy control subjects, which suggests that the ACE I/D polymorphism was associated with OA risk [12, 13]. However, the conclusions were inconsistent. One study showed that the ACE I/D genotype distribution and allele frequencies were similar between patients and healthy controls, while the I allele was a risk factor for early onset (defined as onset age \leq 52 years) and severity of OA [14]. In contrast, it was reported that D allele frequency was higher in OA patients than healthy people, but there was no markedly positive association between ACE I/D gene polymorphism and patients' clinical characteristics [3]. Until now, no meta-analysis or systematic review has been performed to explore the association of ACE I/D gene polymorphism with OA risk. In order to clarify these conflicting findings, we investigated the association between ACE I/D polymorphism and OA susceptibility by using a meta-analysis approach.

Methods

This meta-analysis reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [15].

Inclusion and exclusion criteria

All selected studies met the following criteria: (1) case-control or cohort studies evaluating the association between ACE gene I/D polymorphism and OA risk; (2) patients with OA diagnosed using American College of Radiology (ACR) clinical OA criteria, imaging (e.g., Schneiderman or Kellgren-Lawrence grade system) or total joint replacement due to primary OA; (3) studies with sufficient data (detailed numbers of II, DI, and DD genotypes) for calculating odds ratios (ORs) and their 95% confidence intervals

(CIs); and (4) with two study groups, OA patients and healthy controls. Studies were excluded from consideration if: (1) review articles; (2) editorials/case reports; (3) studies investigating the association between ACE I/D gene polymorphism and other types of arthritis (e.g., rheumatoid, psoriatic, traumatic, etc.); and (4) studies in animals or those using cell lines.

Literature search

We systematically searched the PubMed, Embase, Cochrane Library, and CNKI (China National Knowledge Infrastructure) databases up to December 20, 2015 to identify all relevant studies. The medical subject headings "osteoarthritis", "peptidyl-dipeptidase A", and "polymorphism, genetic", and the free-text words "osteoarthritis", "angiotensin-converting enzyme", and "genetic variation" were combined (the detailed search strategy is described in **File S1**). We widened the search spectrum to "related articles", and manually searched the reference lists of all retrieved studies. We also searched Google scholar to identify additional records, which were not included in those databases. No language restriction was applied to the literature search.

Data extraction

Two investigators independently extracted data in duplicate from all eligible studies into a standard data extraction table. In the case of any conflict, a discussion was initiated to arrive at a consensus. The following information were extracted: first author's name, year of publication, country, source of patients, ethnicity, source of controls, matching criteria for controls, number of cases and controls, genotyping method, OA diagnostic method, genotype distribution of cases and controls, and Hardy-Weinberg equilibrium (HWE) tests in the control group.

Quality assessment

Two investigators independently evaluated the quality of eligible studies using the Newcastle-Ottawa Scale (NOS) [16]. The NOS is constructed by three parts, case and control selection, comparability, and exposure. Each of them respectively comprised 4, 2, and 3 items. We added an item "conform to HWE" to "case and control selection", each item is given 1 point, 10 points in total. If less than 7 scores the study

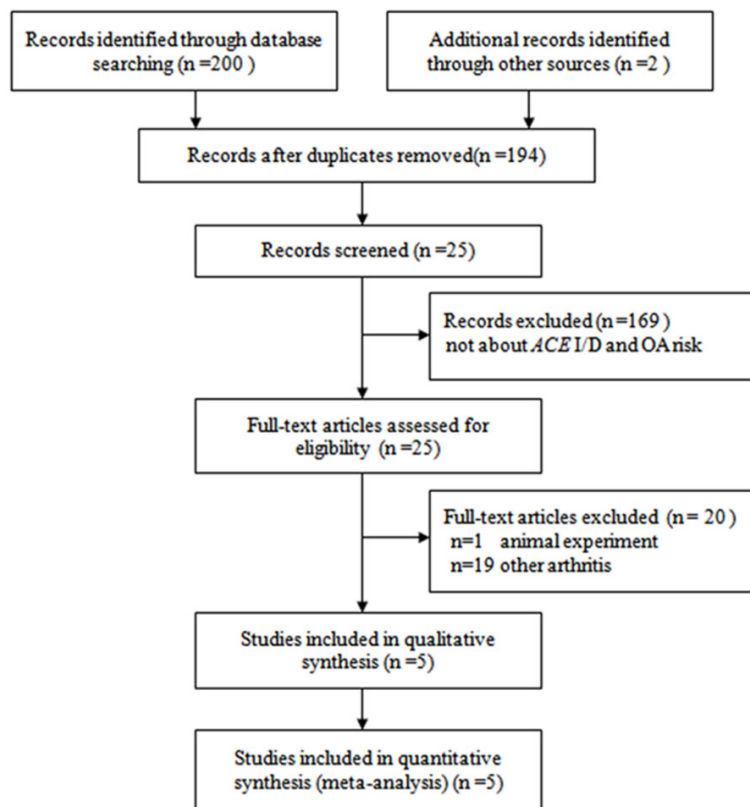


Figure 1. Study selection and exclusion. Flowchart of retrieved and excluded studies, with specification of the reasons. ACE, Angiotensin-converting enzyme; I/D, insertion/deletion.

got, it would be regarded as “low quality”; otherwise, the study would be regarded as “high quality”. Discrepancies were resolved by discussion.

Data synthesis and analysis

The meta-analysis was performed by using Review Manager 5.3 (Cochrane Collaboration, Oxford, United Kingdom) and Stata 12.0 software (Stata Corporation, College Station, TX, USA). The χ^2 test was used to determine whether the genotype distribution of the control group in each study conformed to HWE. Four genetic models were used: DD vs. DI + II, DD + DI vs. II, DD vs. II, and D vs. I. Heterogeneity across studies was measured by I^2 statistics. When $I^2 < 50\%$, the fixed-effects model was used. On the contrary, meta-regression analysis was carried out to detect the source of heterogeneity. Stratification analyses were performed based on the outcome of meta-regression analysis. If the I^2 still $\geq 50\%$, a random-effects model was used. Results are given as ORs with 95% CIs and two-tailed P values, statistical significance

were set at $P < 0.05$. Sensitivity analyses were carried out by omitting each study in turn and by excluding the departure from HWE studies. Funnel plots and Begg’s test were used to assess publication bias.

Results

Study selection

Our search results yielded 202 records (185 from Em-base, 15 from PubMed, 2 from bibliographies, 0 from Cochrane Library and CNKI). After excluding duplications, we screened 194 titles and abstracts. A total of 169 records were deleted, as those did not pertain to the association between ACE I/D and OA risk. Two reviewers independently evaluated 25 potentially relevant studies. After full-text examination, one animal study and 19 studies in which the arthritis was of another type (e.g., rheumatoid, psoriatic, reactive, etc.) were excluded. Thus, five studies [2, 3, 14, 17, 18] were ultimately included in our meta-analysis (**Figure 1**).

Characteristics of included studies

All eligible trials were case-control studies published in English, and involved 1,324 participants, 718 OA patients and 606 healthy controls. Three studies were conducted in Caucasians [2, 3, 17], and two in Asians [14, 18]. The control group’s genotype distribution deviated from HWE in three studies, two in Caucasians [2, 3] and one in Asians [18]. The sample sizes of the investigations varied from 200 [17] to 421 [2]. OA patients in all included studies were recruited based on results of clinical examination and radiographic evidence. Control groups showed no signs or symptoms of OA, and no any other joint disease. Polymerase chain reaction (PCR) was used as a genotyping method in all of the studies. Results of HWE tests and the main features of the included studies are shown in **Table 1**. All studies were of high quality, with a NOS score ≥ 7 (**Table 2**).

ACE I/D polymorphism and OA risk

Table 1. HWE tests and main characteristics of the included studies

Author	Year	Country	OA region	Gender (M/F)		Age (Mean±SD)		Genotype (Case/Control)				HWE Test	
				Case	Control	Case	Control	II	DI	DD	D%	P	Y/N
Hong <i>et al.</i> [14]	2003	Korea	Knee OA	48/94	44/91	58.6±9.4	59.9±8.5	51/44	68/58	23/33	40.1/45.9	0.117	Y
Shehab <i>et al.</i> [18]	2008	Kuwait	Knee OA	13/102	52/59	57.1±9.2	Matched	23/19	22/18	70/74	70.4/74.8	0.000	N
Bayram <i>et al.</i> [3]	2011	Turkey	Unclear [†]	38/102	17/43	54.2±1.2	44.6±2.0	8/16	51/20	81/24	76.1/56.7	0.013	N
Inanir <i>et al.</i> [2]	2013	Turkey	Mixed [†]	60/161	65/135	58.0±10.9	53.0±12.9	37/78	107/77	77/45	59.0/41.8	0.003	N
Poornima <i>et al.</i> [17]	2014	India	Knee OA	32/68	31/69	42.2±8.1	42.2±8.0	18/32	38/46	44/68	63.0/45.0	0.480	Y

OA, Osteoarthritis; M/F: Male/Female; SD, Standard deviation; HWE, Hardy-Weinberg equilibrium; Y: Conform to HWE tests, N: Depart form HWE; [†], Not describe the diseased parts; [‡], Patients containing: Knee OA, Hand OA, Hip OA.

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Table 2. The quality assessment of the included studies (Newcastle-Ottawa quality assessment scale)[†]

Author	Case and control selection				Comparability			Exposure			Score
	Case definition	Case representativeness	Control selection	HWE Test	Control definition	Control for race	Control for others ^Δ	Accuracy	Uniformity	Non-Response	
Hong <i>et al.</i> [14]	1	1	1	1	1	1	1	1	1	1	10
Shehab <i>et al.</i> [18]	1	1	0	0	1	1	0	1	1	1	7
Bayram <i>et al.</i> [3]	1	1	0	0	1	1	0	1	1	1	7
Inanir <i>et al.</i> [2]	1	1	1	0	1	1	1	1	1	1	9
Poornima <i>et al.</i> [17]	1	1	0	1	1	1	0	1	1	1	8

[†], add an item "conform to HWE" in "case and control selection", 10 points in total; ^Δ, Control for other additional factors (e.g., age and gender, etc.).

Table 3. Meta-regression analysis to detect the source of heterogeneity

Variables	Genetic model	Coefficient	95% CI	SE	t-value	P-value
Ethnicity	DD vs. DI + II	1.113	0.292-1.933	0.258	4.32	0.02
	DD + DI vs. II	1.303	0.413-2.192	0.279	4.66	0.02
	DD vs. II	1.769	0.754-2.785	0.319	5.55	0.01
	D vs. I	0.975	0.438-1.512	0.169	5.77	0.01
HWE-status	DD vs. DI + II	0.110	-2.104-2.326	0.696	0.16	0.88
	DD + DI vs. II	0.600	-1.970-3.171	0.809	0.74	0.51
	DD vs. II	0.593	-2.762-3.948	1.054	0.56	0.61
	D vs. I	0.218	-1.587-2.023	0.567	0.38	0.73
NOS score	DD vs. DI + II	-0.169	-1.049-0.712	0.277	-0.61	0.59
	DD + DI vs. II	-0.193	-1.318-0.932	0.353	-0.55	0.62
	DD vs. II	-0.299	-1.680-1.081	0.434	-0.69	0.54
	D vs. I	-0.120	-0.864-0.625	0.234	-0.51	0.65
Sample size	DD vs. DI + II	-0.002	-0.013-0.013	0.004	-0.06	0.95
	DD + DI vs. II	0.001	-0.015-0.017	0.005	0.18	0.87
	DD vs. II	0.001	-0.020-0.021	0.006	0.03	0.98
	D vs. I	0.001	-0.010-0.011	0.003	0.11	0.92

CI, confidence interval; SE, Standard error; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa quality assessment scale.

Heterogeneity test and meta-regression analysis

There was significant heterogeneity across studies. Meta-regression analysis was performed, mainly from four aspects: ethnicity, HWE, sample size, and NOS score, to identify the source of heterogeneity. We found that the heterogeneity was primarily attributable to ethnic variation, not resulting from HWE, sample size, or NOS score (**Table 3**). For example, in DD vs. DI + II genetic model, the meta-regression analysis yielded the following P values: $P_{\text{ethnicity}} = 0.02$, $P_{\text{HWE}} = 0.88$, $P_{\text{NOS}} = 0.59$ and $P_{\text{sample}} = 0.95$, of which only $P_{\text{ethnicity}}$ was < 0.05 . As to stratification analyses were performed by ethnicity. The results shown that all I^2 values decreased to 0% with the exception of the Caucasian group, in which I^2 decreased to 38% in DD + DI vs. II genetic model (**Table 4**).

Results of meta-analysis

Results of the meta-analysis on the association between ACE I/D polymorphism and OA susceptibility are summarized in **Table 4**. Briefly, none of the genetic models had statistical significance in overall populations or Asians. However, In the Caucasians subgroup, all genetic models had significant statistical difference: DD vs. DI + II: OR = 2.10, 95% CI = 1.54-2.85, $P < 0.01$; DD + DI vs. II: OR = 3.11, 95% CI = 2.20-4.39, $P < 0.01$; DD vs. II: OR = 3.98, 95% CI = 2.67-5.95, $P < 0.01$; and D vs. I: OR = 2.10, 95% CI = 1.72-2.58, $P < 0.01$ (**Figure 2**).

Sensitivity analysis

The stability of the results was assessed by sensitivity analyses, which were conducted for all genetic comparisons by using the method

ACE I/D polymorphism and OA risk

Table 4. Meta-analysis results of the association ACE I/D gene polymorphism with OA risk

Genetic model	Group	Studies	Heterogeneity		Begg's test (P)	Effects model	OR (95% CI)	P
			I^2	P				
DD vs. DI + II	Total	5	80%	< 0.01	0.81	Random	1.37 (0.79-2.40)	0.26
	Caucasian	3	0%	0.56	-	Fixed	2.10 (1.54-2.85)	< 0.01
	Asian	2	0%	0.17	-	Fixed	0.69 (0.46-1.03)	0.07
DD + DI vs. II	Total	5	85%	< 0.01	1.00	Random	1.89 (0.94-3.85)	0.07
	Caucasian	3	38%	0.20	-	Fixed	3.11 (2.20-4.39)	< 0.01
	Asian	2	0%	0.92	-	Fixed	0.85 (0.57-1.27)	0.42
DD vs. II	Total	5	88%	< 0.01	0.81	Random	2.50 (0.84-5.02)	0.12
	Caucasian	3	0%	0.51	-	Fixed	3.98 (2.67-5.95)	< 0.01
	Asian	2	0%	0.59	-	Fixed	0.68 (0.42-1.10)	0.12
D vs. I	Total	5	88%	< 0.01	1.00	Random	1.45 (0.90-2.33)	0.13
	Caucasian	3	0%	0.78	-	Fixed	2.10 (1.72-2.58)	< 0.01
	Asian	2	0%	0.95	-	Fixed	0.80 (0.61-1.03)	0.09

ACE, Angiotensin-converting enzyme; I/D, insertion/deletion; OR, odds ratio; CI, confidence interval.

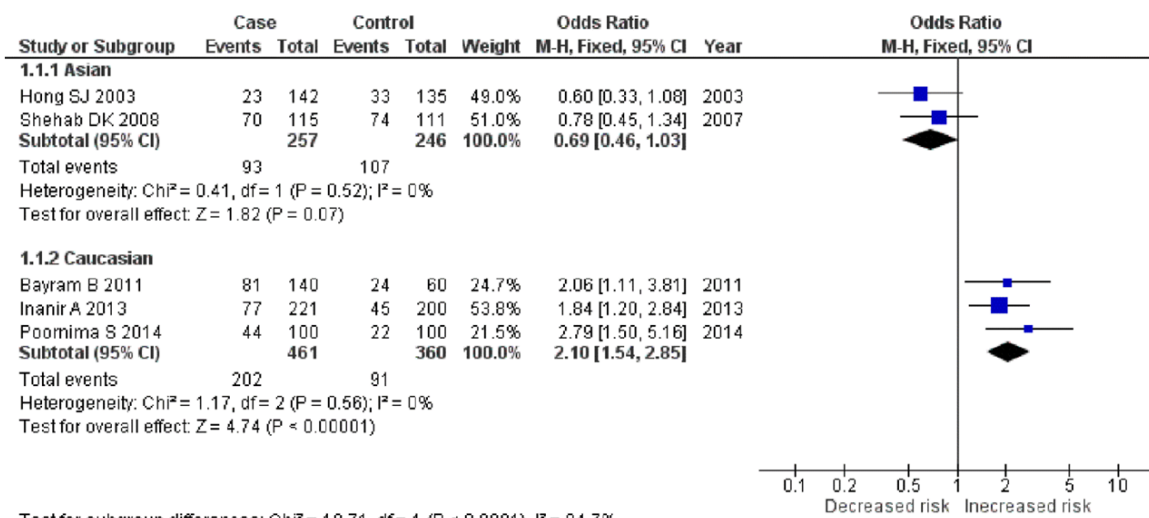


Figure 2. Forest plot for the association between ACE I/D polymorphism and OA risk. (DD vs. DI + II genetic model).

stated above. We found no study having substantial influence on the pooled results in all genetic models (e.g., DD vs. DI + II genetic model for overall populations, **Figure 3**, and for Caucasians subgroup, **Figure 4**). In addition, the results were unaltered by excluding the special studies [2, 3, 18], which the genotype distribution in controls departed from HWE (**Table 5**).

Evaluation of publication bias

Funnel plots were generated and Begg's tests were carried out to evaluate publication bias of the included studies. The shape of plots showed no asymmetry (**Figure 5** displays the

funnel plot of DD vs. DI + II genetic model), and the quantitative results of Begg's tests did not reveal any evidence of publication bias in all genetic models (**Table 3**).

Discussion

To our knowledge, this was the first meta-analysis to investigate the relationship between ACE I/D gene polymorphism and OA susceptibility. Five published studies with 718 OA patients and 606 healthy subjects were included in the analysis. The results revealed that there was no association in the overall populations or Asians. However, the ACE DD genotype and D allele increased the risk of OA in

ACE I/D polymorphism and OA risk

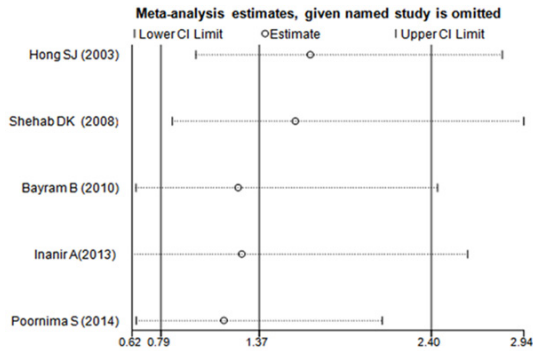


Figure 3. Sensitivity analysis. (omitting each study in turn). The Overall population (DD vs. DI + II genetic model).

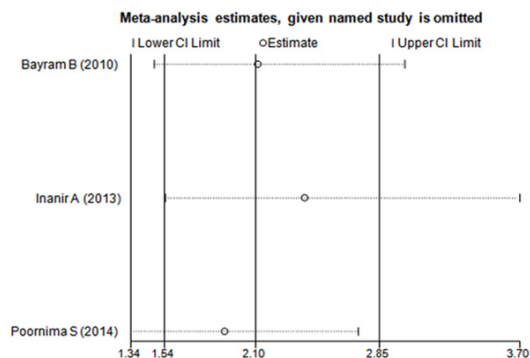


Figure 4. Sensitivity analysis. (omitting each study in turn). The Caucasian subgroup (DD vs. DI + II genetic model).

Caucasians. Three studies were not conforming to HWE, but in the sensitivity analysis, when we excluded those studies, the results had no significant change. It indicated that the departure from HWE's studies did not affect the results of our meta-analysis. Furthermore, the funnel plots shown there were no publication bias in our study. So, our results were robust.

Although the exact pathogenesis of OA remains unclear, genetic factors are considered to be strong determinants of the disease. Twins and family studies have demonstrated that more than 50% of OA cases can be attributed to genetic factors [4]. ACE I/D polymorphism was considered as one of the candidate genes in recent some studies, and indicated that the DD genotype and/or D allele maybe risk factors for OA [2, 3, 17]. While, the exact mechanism underlying the relationship between the polymorphism and OA is still unknown. Previous studies have shown that ACE I/D polymorphism

is associated with serum level and activity of ACE. The DD and II genotypes are associated with the highest and lowest expression levels, respectively. And, the ACE level is two-fold higher in the DD genotype carriers than that in genotype II [19]. ACE acts on the RAAS [20] and kallikrein-kinin system (KKS) [17, 21]. Thus, it plays an important role in the regulation of blood pressure, blood volume, and inflammation [6, 7]. More remarkable, some studies indicated the ACE levels in synovial fluid are higher in OA patients than healthy subjects [2, 13]; and Kallikrein level in synovial fluid and kinin B2 receptor expression in the synovial lining were elevated in OA patients [22]. It implies ACE and kinins are likely to play a role in the pathogenesis of OA [21, 22]. Therefore, there may be a link: ACE I/D-ACE-RAAS/KKS-OA risk, and this might be one of the mechanisms of ACE DD genotype and D allele increased the OA susceptibility. Even so, more animal experiments and clinical trials should be performed to explore the precise pathophysiologic mechanisms of the ACE DD genotype and D allele increasing the OA risk.

However, not all studies support the relevancy [14, 18]. The conclusions of the association between ACE I/D polymorphism and OA risk are usually controversial. Some studies [14, 18] found that there were no significant difference in genotype distribution or allele frequencies between patients and healthy participants. But others [2, 3, 17] shown that the DD genotype and/or D allele were risk factors marker for OA. The conflicting conclusions may be caused by the different ACE allele frequencies in different ethnicity. The average frequency of the D allele among normal Caucasians is 50%-58%, while among Asians is 35%-39% [18, 23, 24]. In our included studies, three Caucasian investigations all considered that the DD genotype and D allele increased the OA risk, while two Asian studies all found no association between ACE I/D polymorphism and OA susceptibility. The diverse distribution of genotypes or alleles of the ACE I/D polymorphism may explain the different associations between the genetic polymorphism and OA risk in Caucasians and Asians.

Although we found ACE DD genotype and D allele increased the risk of OA in Caucasians, it still remain uncertain whether it is related to the onset age, gender, severity and regions of

Table 5. Sensitivity analysis of association between ACE I/D polymorphism and OA susceptibility'

Genetic model	Group	Studies	Heterogeneity test		Effects model	OR (95% CI)	P
			I ²	P			
DD vs. DI + II	Total	2	92%	< 0.01	Random	1.29 (0.28-5.82)	0.74
	Caucasian	1	—	—	Random	2.79 (1.50-5.16)	< 0.01
	Asian	1	—	—	Random	0.60 (0.33-1.08)	0.09
DD + DI vs. II	Total	2	79%	0.03	Random	1.32 (0.54-3.23)	0.54
	Caucasian	1	—	—	Random	2.13 (1.11-4.17)	0.02
	Asian	1	—	—	Random	0.86 (0.52-1.41)	0.56
DD vs. II	Total	2	91%	< 0.01	Random	1.45 (0.25-8.25)	0.68
	Caucasian	1	—	—	Random	3.56 (1.64-7.69)	< 0.01
	Asian	1	—	—	Random	0.60 (0.31-1.17)	0.14
D vs. I	Total	2	92%	< 0.01	Random	1.27 (0.49-3.29)	0.62
	Caucasian	1	—	—	Random	2.08 (1.39-3.10)	< 0.01
	Asian	1	—	—	Random	0.79 (0.56-1.11)	0.17

', exclude departure from HWE studies.

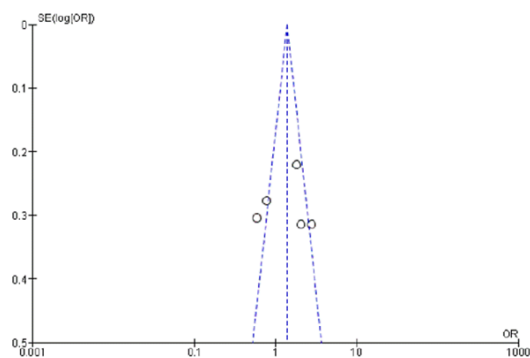


Figure 5. Funnel plot of ACE I/D polymorphism and OA risk. (DD vs. DI + II genetic model).

OA. One Asians' study [14] found that the II genotype and I allele were connected with the early onset age and severe clinical manifestation. While the other [18] reported that ACE I/D polymorphism was not associated with the onset age and OA severity. A Caucasians' study [17] presented the DD genotype and D allele increased the OA risk, but there were no gender difference ($P = 0.75$ and 0.83 , respectively). Limited by study number, especially in the Caucasians, we failed to detect the relation between them. We recommended that future study on the association between ACE I/D polymorphism and OA risk should focus on difference ethnicity, gender, OA grade, diseased region, and so on.

Our study had some limitations. First, although we systematically searched the databases,

extended the search spectrum to "related studies", and manually searched the bibliographies of all retrieved studies, the number of eligible studies was still small, especially the lack of African researches. Second, owing to the limited data, we failed to analysis the association between ACE gene polymorphism and OA onset age and disease severity. Third, we were unable to perform further subgroup analyses such as by gender and categories of body mass index because of lack of sufficient information. Last but not least, we did not assess the potential gene-gene and gene-environment interactions. Undoubtedly, the limitations mentioned above might affect our final conclusions. Despite these limitations, this meta-analysis also had some advantages. First of all, this was the first meta-analysis to investigate the relationship between ACE I/D gene polymorphism and OA susceptibility. Besides, our results are reliable given that heterogeneity was small in intra-subgroup, pooled results were unaltered in sensitivity analyses, and publication bias was inexistent in the included studies. What is more, we found a significant association between ACE I/D polymorphism and OA risk in Caucasians.

The present meta-analysis demonstrated that there was no association between ACE I/D gene polymorphisms and OA susceptibility in overall populations and Asians. However, DD genotype and D allele may be risk factors for OA in Caucasians. Due to the limitation of the present studies, larger studies are needed to confirm our findings.

Disclosure of conflict of interest

None.

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Search strategies (December 20, 2015)

The detailed search strategy in PubMed

#1 Search "Osteoarthritis" [Mesh]

#2 Search (((((((osteoarthritis) OR spine osteoarthritis) OR knee osteoarthritis) OR hip osteoarthritis) OR spine osteoarthritis) OR knee osteoarthritis) OR hip osteoarthritis) OR spine-osteoarthritis) OR knee-osteoarthritis) OR hip-osteoarthritis

#3 Search "Peptidyl-Dipeptidase A" [Mesh]

#4 Search (((Angiotensin) OR Angiotensins) OR "angiotensin converting enzyme") OR ACE

#5 Search "Polymorphism, Genetic" [Mesh]

#6 Search (((("genetic polymorphism") OR polymorphism) OR polymorphisms) OR "genetic variation") OR gene) OR genome

#7 #1 OR #2

#8 #3 OR #4

#9 #5 OR #6

#10 #7 AND #8 AND #9

The detailed search strategy in Cochrane Library

#1 MeSH descriptor: [Osteoarthritis] explode all trees

#2 "osteoarthritis": ti, ab, kw or "spine osteoarthritis" or "hip osteoarthritis" or "knee osteoarthritis" or OA (Word variations have been searched)

#3 MeSH descriptor: [Peptidyl-Dipeptidase A] explode all trees

#4 Angiotensin: ti, ab, kw or Angiotensins: ti, ab, kw or "angiotensin converting enzyme": ti, ab, kw or ACE: ti, ab, kw (Word variations have been searched)

#5 MeSH descriptor: [Polymorphism, Genetic] explode all trees

#6 "Genetic Polymorphism": ti, ab, kw or polymorphism: ti, ab, kw or polymorphisms: ti, ab, kw or "genetic variation": ti, ab, kw or gene: ti, ab, kw (Word variations have been searched)

#7 #1 or #2

#8 #3 or #4

#9 #5 or #6

#10 #7 and #8 and #9

The detailed search strategy in EMBASE

#1 'arthritis'/exp OR 'arthritis'

#2 'osteoarthritis'/exp OR 'osteoarthritis'

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#3 'peptidyl-dipeptidase a'/exp OR 'peptidyl-dipeptidase a'

#4 'angiotensins'

#5 'angiotensins'/exp OR angiotensins

#6 'angiotensin'

#7 'angiotensin'/exp OR angiotensin

#8 'angiotensin converting enzyme'/exp OR 'angiotensin converting enzyme'

#9 ace

#10 'polymorphism genetic'/exp OR 'polymorphism genetic'

#11 'genetic polymorphism'/exp OR 'genetic polymorphism'

#12 polymorphism*

#13 'genetic variation'/exp OR 'genetic variation'

#14 'gene'/exp OR gene

#15 'genome'/exp OR genome

#16 #1 OR #2

#17 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#18 #10 OR #11 OR #12 OR #13 OR #14 OR #15

#19 #16 AND #17 AND #18