Role of *IL-17* gene polymorphisms in osteoarthritis: A meta-analysis based on observational studies

Hao-Yu Yang, Yu-Zhou Liu, Xin-Die Zhou, Yong Huang, Nan-Wei Xu

ORCID number: Hao-Yu Yang (0000-0002-0016-6065); Yu-Zhou Liu (0000-0002-9250-194X); Xin-Die Zhou (0000-0001-6194-6308); Yong Huang (0000-0003-1944-3656); Nan-Wei Xu (0000-0001-6927-3312).

Hao-Yu Yang, Yu-Zhou Liu, Department of Orthopedics, Wuxi 9th People's Hospital affiliated to Soochow University, Wuxi 214000, Jiangsu Province, China

Xin-Die Zhou, Yong Huang, Nan-Wei Xu, Department of Orthopedics, The Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou 213003, Jiangsu Province, China

Corresponding author: Yong Huang, MD, Doctor, Full Professor, Department of Orthopedics, The Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, No. 29 Xinglong Road, Tianning District, Changzhou 213003, Jiangsu Province, China. huangyong@njmu.edu.cn

Abstract

BACKGROUND
Osteoarthritis (OA) is a chronic complex multifactorial joint disease, and a major degenerative form of arthritis. Existing studies on the association between polymorphisms of the *IL-17* gene and the risk of OA in different populations have yielded conflicting findings.

AIM
To investigate the association between polymorphisms of the *IL-17* gene and the risk of OA.

METHODS
We conducted a meta-analysis by systematically searching databases, including PubMed, EMBASE, MEDLINE, Cochrane Library, and Google Scholar to evaluate this association by calculating pooled odds ratios with 95% confidence intervals. Moreover, subgroup analyses stratified by ethnicity and OA type were also conducted.

RESULTS
In a total of 6 citations involving 8 studies (2131 cases and 2299 controls), 4 single nucleotide polymorphisms were identified. Of these 4 polymorphisms, 2 (rs2275913, rs763780) were common in five case-control studies. Together, the pooled results revealed that the A allele and genotype AA/GA of the rs2275913 polymorphism, and the C allele and genotype CC of the rs763780 polymorphism in the *IL-17* gene increased the risk of OA. Furthermore, stratification analyses by ethnicity and OA type showed that the rs2275913 polymorphism increased the risk of OA among Asians and in knee/hip OA, respectively. In addition, stratification analyses also revealed that the rs763780 polymorphism increased OA risk among both Asians and Caucasians in knee/hip OA.

CONCLUSION

The rs763780 polymorphism of the *IL-17F* gene increased the risk of OA, whereas the rs2275913 polymorphism of the *IL-17A* gene increased the risk of OA only among Asians. Due to the limitations of this study, these findings should be validated in future studies.

Key words: Interleukin-17; Polymorphism; Osteoarthritis; Meta-analysis; Odds ratio; Confidence interval

Core tip: Osteoarthritis (OA) is the combined result of complex pathogenic factors, including mechanical, biochemical, environmental, endocrine, metabolic, and genetic factors, which account for nearly 50% of the risk of OA development. Although the pathogenesis and etiology of OA are not known, it is likely that interleukin-17 (IL-17) might play an important role in OA development. Existing studies on the association between polymorphisms of the *IL-17* gene and the risk of OA in different populations have yielded conflicting findings. We meta-analyzed relevant articles to pool available data and investigated whether *IL-17* gene polymorphisms were associated with OA susceptibility.

INTRODUCTION

Osteoarthritis (OA) is a common form of arthritis that can cause progressive loss of joint function[1]. OA is characterized by softening, splitting, and fragmentation of articular cartilage, which is usually accompanied by subchondral bone sclerosis, bone cysts, and bony outgrowths at the joint margins[2]. OA is the combined result of complex pathogenic factors, including mechanical, biochemical, environmental, endocrine, metabolic, and genetic factors, which account for nearly 50% of the risk of OA development[3-6]. Some previous genome-wide association studies[7,8] have suggested that polymorphisms in some genes may affect OA pathogenesis. Genetic markers, in combination with imaging (such as X-ray, magnetic resonance imaging and ultrasound[9,10]) and biochemical markers, have the potential to assist in identifying and diagnosing OA in the early stage[11].

One of the most important family of genes associated with OA is the inflammatory cytokines gene family[12]. Inflammatory cytokines [such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α, matrix metalloprotein-13] and moderate physical activity together play a possible biological role in the development of OA[13,14]. IL-17 involves five confirmed receptors and six members (IL-17A-F)[15,16]. Recent evidence has shown that IL-17 was detectable in serum samples and synovial fluid from OA subjects, and a direct correlation between the IL-17 concentration and the severity of OA was observed[17,18]. IL-17 induces the release of chemokines by chondrocytes and synovial fibroblasts, which contributed to synovial infiltration and cartilage collapse in OA[19]. Although the pathogenesis and etiology of OA are not known, it is likely that IL-17 might play an important role in OA development.

To date, several studies[12,20-24] have explored the relationship between polymorphisms of the *IL-17* gene and OA susceptibility. The association between *IL-17* gene single nucleotide polymorphisms (SNPs) and OA susceptibility may provide novel research directions for OA studies[2]. However, the results of previous studies are inconclusive and conflicting due to clinical heterogeneity, different ethnic populations and small sample sizes. Meta-analysis is a statistical system for assembling results from different studies to produce a single approximate of the major effect with enhanced precision, especially when the results from single case-control studies are incomprehensive and conflicting. Therefore, in the present study we aimed to pool available data and investigated whether *IL-17* gene polymorphisms

were associated with OA susceptibility.

MATERIALS AND METHODS

The current meta-analysis was performed by following the PRISMA statement[25].

Search strategy

We systematically conducted a literature search using the following electronic databases: PubMed, EMBASE, MEDLINE, Cochrane Library, and Google Scholar to identify epidemiological studies published up to September 2019 to retrieve genetic association studies on OA. The terms "Interleukin-17", "IL-17", "SNP", "polymorphism", "variant", "osteoarthritis" and "OA" were used to identify all publications reporting *IL-17* gene polymorphisms and OA risk. No language or other restrictions were placed on the search. Eligible studies were retrieved and cautiously evaluated. Furthermore, the reference lists of all related citations were screened to identify any missing studies.

Inclusion and exclusion criteria

Articles were filtered by two independent reviewers (Yang HY and Liu YZ) to assess the appropriateness of the articles selected using a standardized protocol and data collection form. The inclusion criteria were as follows: (1) Case-control studies on humans; (2) Comparison between OA patients and controls; (3) Studies evaluating the association between *IL-17* gene polymorphisms and OA susceptibility; and (4) Studies with sufficient genetic frequency for extraction. The exclusion criteria were as follows: (1) Studies with lack of information for data extraction; (2) Non-human studies, abstracts only, comments, reviews, editorials or letters, mechanistic studies, and studies missing controls; and (3) Duplicate or overlapping publications. All questionable publications were discussed and addressed by consensus.

Data extraction and quality assessment

From each eligible study, two reviewers (Yang HY and Liu YZ) independently extracted the following data: Authors, publication date, country, ethnicity, sample size, type of OA, source of controls, allele, and genotype frequency distribution. In addition, the two reviewers independently assessed the methodological quality of the included studies according to the Newcastle-Ottawa Scale (NOS)[26]. NOS criteria were scored based on three aspects: (1) Subject selection, 0-4; (2) Comparability of subjects, 0-2; and (3) Exposure, 0-3. The NOS score ranged from 0 (lowest) to 9 (highest). The Hardy-Weinberg equilibrium (HWE) in controls was tested with Pearson's χ^2 test (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl).

Statistical analysis

Quantitative meta-analysis was employed using STATA 11.0 software (STATA Corporation, College Station, TX, United States). To assess the association between *IL-17* gene polymorphisms and the risk of OA, pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Due to a lack of original data (sex and age), crude ORs were calculated, and five genetic models were included. $P < 0.05$ was considered statistically significant. Heterogeneity across studies was assessed by Q statistics with its P value and I^2 statistics[27,28]. If $I^2 > 50\%$ and $P < 0.10$, a random effects model was used in the calculations; otherwise, a fixed effects model was applied. Subgroup analyses were carried based on ethnicity and type of OA. Moreover, the Begg's test and Egger's linear regression analysis were applied to prevent publication bias[29]. To evaluate the precision and consistency of the primary meta-analysis, sensitivity analysis was performed to verify the effects associated with any individual study. Furthermore, false-positive report probability (FPRP) was conducted to evaluate the significant findings and rule out any false associations due to multiple tests[30]. Generally, the FPRP value for a given association between *IL-17* gene polymorphisms and OA risk was calculated with different prior probability. An association with a FPRP value < 0.2 at a prior probability of 0.1 indicated a significant relationship.

RESULTS

Characteristics of the included studies

In this study, the literature search yielded 132 citations, among which 46 duplicates were removed. Then, 78 of the 86 remaining citations were excluded after reviewing

the titles and abstracts. The remaining 8 citations were sent for full text review, which resulted in exclusion of 1 citation due to the lack of detailed genotype data and 1 non-SNP study. Finally, 6 citations (2131 cases and 2299 controls) involving 8 studies and 4 SNPs were included in this study. The year of publication ranged between 2014 and 2019. In four of the included citations[20-22,24], the association between *IL-17* gene polymorphisms in an Asian population were investigated, and in two included citations[12,23] focus was on the Caucasian population. In all 6 citations[12,20-24], the association between rs2275913/rs763780 polymorphisms of the *IL-17* gene and risk of OA were studied. Detailed characteristics of the included citations are shown in Tables 1 and 2. A flowchart of reviews, showing the detailed selection process, is illustrated in Figure 1. The NOS scores ranged from 6 to 7 stars.

Association between rs2275913 polymorphism and OA susceptibility
General analysis showed that the polymorphism rs2275913 of the *IL-17A* gene increased OA risk [OR and 95%CI: 1.26 (1.08, 1.47) in A *vs* G; 1.25 (1.01, 1.55) in AA + GA *vs* GG; 1.53 (1.30, 1.81) in AA *vs* GA + GG; 1.71 (1.42, 2.06) in AA *vs* GG; and 1.15 (1.01, 1.32) in GA *vs* GG, Table 3 and Figure 2]. Stratification analysis by ethnicity showed that the rs2275913 polymorphism increased the risk of OA among Asians [OR and 95%CI: 1.40 (1.18, 1.67) in A *vs* G; 1.44 (1.13, 1.82) in AA + GA *vs* GG; 1.62 (1.34, 1.96) in AA *vs* GA + GG; 1.89 (1.52, 2.34) in AA *vs* GG; and 1.25 (1.06, 1.46) in GA *vs* GG, Table 3 and Figure 3); however, this was not observed in Caucasians. Subgroup analysis by OA type revealed that the rs2275913 polymorphism increased the risk of both knee and hip OA. A change in conclusion was not observed after eliminating a study[24] that did not meet the HWE.

Sensitivity analysis was used to determine the pooled ORs regarding the effects of this SNP on OA risk. Taken together, the results indicated that our data were stable and credible. Neither Egger's nor Begg's tests revealed obvious publication bias for the rs2275913 polymorphism (Figure 4).

Association between rs763780 polymorphisms and OA susceptibility
Results of the pooled analysis on the association between *IL-17F* gene rs763780 polymorphism and OA risk are shown in Table 3 and Figure 5 [OR and 95%CI: 1.32 (1.06, 1.64) in C *vs* T; 1.32 (1.02, 1.72) in CC + TC *vs* TT; 2.08 (1.30, 3.32) in CC *vs* TC + TT; and 2.19 (1.37, 3.51) in CC *vs* TT]. Moreover, subgroup analysis by ethnicity indicated that rs763780 polymorphism increased OA risk among Caucasians in Allele/Dominant/Heterozygote models [OR and 95%CI: 1.75 (1.16, 2.66) in C *vs* T; 1.82 (1.11, 3.00) in CC + TC *vs* TT; and 1.84 (1.06, 3.17) in TC *vs* TT], whereas among Asians in Recessive/Homozygote models [OR and 95%CI: 2.17 (1.32, 3.59) in CC *vs* TC + TT; and 2.28 (1.37, 3.77) in CC *vs* TT]. Stratification analysis by OA type revealed that the rs763780 polymorphism increased the risk of both knee and hip OA. A change in conclusion was not observed after eliminating a study[24] that did not meet the HWE. Both sensitivity analysis and the publication bias test revealed that our data were stable and credible (data not shown).

FPRP analysis result
For all statistically significant results, the FPRP values are summarized in Table 4. For a prior probability of 0.1 and crude ORs, the FPRP analysis indicated that the significant association between IL-17A rs2275913 polymorphism and OA risk was significant for all subjects (allele: FPRP = 0.052, recessive: FPRP = 0.009, and homozygous comparison: FPRP = 0.009), Asians (allele: FPRP = 0.013, dominant: FPRP = 0.048, recessive: FPRP = 0.009, homozygous: FPRP = 0.009, and heterozygous comparison: FPRP = 0.103), and knee OA (recessive comparison: FPRP = 0.010). Similarly, the association of the *IL-17F* rs763780 polymorphism with OA risk also deserved attention in the overall population, especially among Caucasians and individuals with knee/hip OA. In our study, greater values were observed of FPRP > 0.2 for other positive findings between *IL-17* gene polymorphisms and OA risk, which may be attributed to the limited sample size. For future studies, additional validation will be needed using studies with a larger sample size.

DISCUSSION
Although the definite pathogenesis of OA remains unclear, genetic factors are considered to be strong determinants. IL-17 is a cytokine that is mainly synthesized by activated T cells, and its receptors are present in osteoblasts. IL-17 can enhance proinflammatory cytokines, including tumor necrosis factor-α, IL-1 and IL-6, that together play a key role in cartilage degradation and the inhibition of cartilage repair[31,32]. Furthermore, in patients with OA, IL-17 stimulates the release of vascular

Table 1 Characteristics of included studies

Ref.	Yr	Natio-nality	Osteoar-thritis type	Sample size (female / male)		Age (mean)		Study single nucleo-tide polymor-phisms	Geno-type method	Newcastle-Ottawa Scale			Hardy-Wein-berg equili-brium
				Case	Control	Case	Control			I	II	III	
Zhang et al[20]	2019	China	Knee	122 (90/32)	124 (88/36)	66	66	rs2275913	PCR	3	0	3	Yes
								rs763780	PCR	3	0	3	Yes
Zhang et al[20]	2019	China	Knee	76 (52/24)	68 (49/19)	62	61	rs2275913	PCR	3	0	3	Yes
								rs763780	PCR	3	0	3	Yes
Jiang et al[21]	2019	China	NA	410 (271/139)	507 (348/159)	57.35	57.88	rs2275913	PCR-RFLP	3	1	3	Yes
								rs763780	PCR-RFLP	3	1	3	Yes
Bai et al[22]	2019	China	Knee	594 (393/201)	576 (402/174)	59.5	58.3	rs2275913	PCR	3	1	3	Yes
								rs763780	PCR	3	1	3	Yes
Bafrani et al[12]	2019	Iran	Knee	127 (69/58)	127 (73/54)	68.06	66.84	rs2275913	PCR-RFLP	3	1	3	Yes
								rs763780	PCR-RFLP	3	1	3	Yes
								rs2397084	PCR-RFLP	3	1	3	Yes
Vrgoc et al[23]	2018	Croatia	Hip	260 (175/85)	597 (152/445)	67.82	42.64	rs2275913	TaqMan	3	1	3	Yes
								rs763780	TaqMan	3	1	3	Yes
								rs1889570	TaqMan	3	1	3	Yes
Vrgoc et al[23]	2018	Croatia	Knee	240 (174/66)	597 (152/445)	69.74	42.64	rs2275913	TaqMan	3	1	3	Yes
								rs763780	TaqMan	3	1	3	Yes
								rs1889570	TaqMan	3	1	3	Yes
Han et al[24]	2014	SouthKorea	Knee	302 (245/57)	300 (136/164)	60	51	rs2275913	PCR-SSCP	3	0	3	No
								rs763780	PCR-SSCP	3	0	3	No

Newcastle-Ottawa Scale is available from http://www.ohri.ca/programs/clinical epidemiology/oxford.asp. I: Selection; II: Comparability; III: Exposure; NA: Not available; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; SSCP: Single-strand conformation polymorphism.

endothelial growth factor in synovial fibroblasts that was isolated from their joints[19]. Therefore, an increasing number of studies focused on the association between the *IL-17* gene polymorphisms and OA susceptibility.

Han *et al*[24] first examined the alleles and genotypes of *IL-17A* rs2275913 and *IL-17F* rs763780 in a Korean population, and found a significant association between rs2275913 and the susceptibility of knee OA. In addition, Vrgoc *et al*[23] did not observe an association between *IL-17A* rs2275913 and the risk of hip or knee OA in a Croatian population. The C allele of the *IL-17F* gene rs763780 polymorphism increased the risk of hip OA, but not of knee OA. The results of a study by Bafrani *et al*[12] indicated a significant association between rs2275913GA genotype and a decrease in the risk of knee OA. However, the rs763780TC genotype and rs763780C allele were related to an increased risk of knee OA. Zhang *et al*[20] suggested that the genotype AA frequency of *IL-17A* (rs2275913) was significantly different between knee OA patients and the control group in a Chinese Han population, but not in a Tibetan population. Furthermore, Bai *et al*[22] indicated that the *IL-17A* rs2275913 polymorphism had a significant impact on the risk of knee OA. Additionally, the rs763780 C allele was found to be related to a greatly increased risk of developing knee OA. Jiang *et al*[21] suggested a significant association between the increased risk of OA and *IL-17A* rs2275913, but not of *IL-17F* rs763780. The discrepancy in the above-mentioned studies may be due to the following: First, the inclusion criteria differed among studies. For
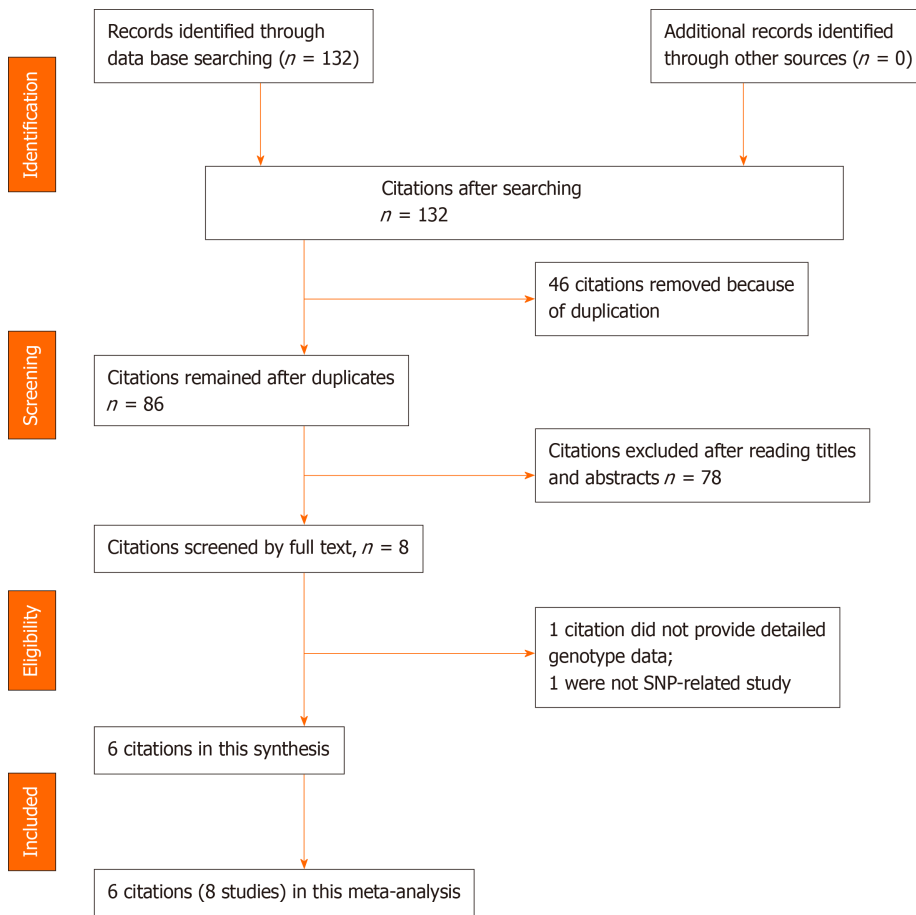
Figure 1 Flowchart of the literature search and selection for this study.

example, Bai *et al*[22] enrolled other types of arthritis or joint diseases, such as inflammatory arthritis, which were excluded by other citations. Moreover, Jiang *et al*[21] used clinical symptoms and radiological evidence of joints, whereas in the Han *et al*[24] study, OA cases who had undergone total knee arthroplasty were enrolled. Second, the allele frequencies of the rs2275913/rs763780 polymorphism in the cases were diverse. Third, the affected joint sites differed. Fourth, the genetic background of OA may vary among races. Finally, the difference in sample sizes may also account for this discrepancy.

Due to the limited sample sizes, previous single studies may have been underpowered and thereby may have presented conflicting findings, especially given the diverse inheritance of the heterogeneous and complex OA etiology, different ethnicities, clinical heterogeneity, and other causes. Therefore, we conducted this meta-analysis.

Our data showed that the rs2275913 and rs763780 polymorphisms increased the risk of OA. Stratification analyses by ethnicity and OA type showed that the rs2275913 polymorphism increased the risk of OA among Asians as well as in knee/hip OA, respectively. Stratification analyses also revealed that the rs763780 polymorphism increased OA risk among both Asians and Caucasians, as well as in knee/hip OA. There may be several possible reasons for the different findings regarding the rs2275913 polymorphism between Asians and Caucasians. First, genetic heterogeneity for OA exists in different populations. Second, these discrepancies may be explained by clinical heterogeneity. Third, the sample sizes of the Caucasian populations were not large enough to support a definitive conclusion. Additionally, different OA types and varying clinical parameters of different populations may also be potential reasons for the inconclusive findings. Furthermore, different characteristics of the OA groups (such as age and sex) and disease severity may also be possible reasons for the discrepancies observed. Finally, varying environmental factors may also have contributed, because the interaction between genetic factors and environmental factors can eventually lead to the development of OA. Gao *et al*[33] and Lee *et al*[34] also conducted meta-analyses to study the association between *IL-17* gene rs2275913/rs763780 polymorphism and OA risk. We consider that our meta-analysis had several additional advantages. First, compared to the work by Lee *et al*[34], our

Table 2 Genotype distributions of *IL-17* gene polymorphisms in the included studies

Ref.	Source of control	Ethnicity	Allele 1	Allele 0	Case 11	Case 10	Case 00	Control 11	Control 10	Control 00	Association with osteoarthritis
rs2275913											
Zhang *et al*[20], 2019	HB	Asian	G	A	42	53	27	49	63	12	AA genotype/A allele increased OA risk
Zhang *et al*[20], 2019	HB	Asian			23	32	21	26	28	14	Not related
Jiang *et al*[21], 2019	HB	Asian			204	170	34	289	194	23	AA genotype/A allele increased OA risk
Bai *et al*[22], 2019	HB	Asian			189	271	134	207	265	104	AA genotype/A allele increased OA risk
Bafrani *et al*[12], 2019	HB	Caucasians			83	35	9	69	51	7	GA genotype decreased OA risk
Vrgoc *et al*[23], 2018	HB	Caucasians			78	71	23	190	172	45	Not related
Vrgoc *et al*[23], 2018	HB	Caucasians			76	85	25	190	172	45	Not related
Han *et al*[24], 2014	HB	Asian			52	109	141	97	106	97	GG genotype decreased OA risk
rs763780											
Zhang *et al*[20], 2019	HB	Asian	T	C	91	30	1	98	24	2	Not related
Zhang *et al*[20], 2019	HB	Asian			59	16	1	54	13	1	Not related
Jiang *et al*[21], 2019	HB	Asian			356	49	4	423	80	2	Not related
Bai *et al*[22], 2019	HB	Asian			380	188	26	411	155	10	CC/TC genotype/C allele increased OA risk
Bafrani *et al*[12], 2019	HB	Caucasians			98	26	3	112	13	2	TC genotype/C allele increased OA risk
Vrgoc *et al*[23], 2018	HB	Caucasians			198	34	0	493	34	1	C allele increased OA risk
Vrgoc *et al*[23], 2018	HB	Caucasians			195	14	1	493	34	1	Not related
Han *et al*[24], 2014	HB	Asian			226	59	17	236	56	8	Not related
rs2397084											
Bafrani *et al*[12], 2019	HB	Caucasians	T	C	111	16	0	109	18	0	Not related
rs1889570											
Vrgoc *et al*[23], 2018	HB	Caucasians	G	A	57	129	58	49	91	46	Not related
Vrgoc *et al*[23], 2018	HB	Caucasians			68	111	51	49	91	46	Not related

HB: Hospital-based; OA: Osteoarthritis.

meta-analysis of the rs3134069 polymorphism included one more case-controlled study[20]. Second, for rs2275913, Gao *et al*[33] regarded the G allele as a minor allele and then analyzed it in 5 genetic models. In fact, according to the dbSNP database, A allele is the true minor allele. Gao *et al*[33] misidentified the minor allele, which led to the wrong choice of genetic model. If the correct genetic model is selected, their results are consistent with our findings. This mistake was also found in the rs763780 polymorphism analysis. Third, FPRP was conducted in our meta-analysis to evaluate the significant findings and rule out any false associations due to multiple tests.

Our study has several limitations that should be considered. First, due to limited data, we were unable to conduct stratification analyses of other potential factors, such as age, sex, and age at OA onset. Second, our results were based on unadjusted estimates of confounding factors, which might have affected the final results. Third, although funnel plots and Egger's tests revealed no publication bias, selection bias could not be fully prevented, because only studies published in the English language were searched. Fourth, we were unable to assess potential gene-gene or gene-environment interactions due to the lack of relevant data. Fifth, in future studies, clinical cases should be investigated to support the analytical results observed in this study. Sixth, we can only infer but cannot conclude that the *IL-17* gene rs2275913/rs763780 polymorphism is a susceptibility locus for other types of OA. Thus, further investigation into more types of OA is warranted. Finally, five genetic models of inheritance were used, thus, type I error may have arisen through lack of correction for multiple testing.

In conclusion, the present meta-analysis demonstrated that the rs763780 polymorphism of the *IL-17F* gene increased the risk of OA, whereas the rs2275913 polymorphism of the *IL-17A* gene only increased the risk of OA among Asians. Given the study limitations, further well-designed prospective studies with large sample sizes should be performed to validate these findings. In the future, it will become feasible to identify and diagnose OA in the early stage, as a result of genetic findings. Furthermore, the biological and functional relevance of these genetic findings is essential to help put the research into a clinical context to benefit people with OA.

Table 3 Meta-analysis of the association between *IL-17* gene polymorphisms and osteoarthritis risk

SNP	Comparison	Category	Category	Studies	Odds ratio (95% confidence interval)	*P* value	*I²*
rs2275913	A *vs* G	Total (random model)		8	1.26 (1.08, 1.47)	0.003	61.6%
	Allele model	Ethnicity	Asian	5	1.40 (1.18, 1.67)	< 0.001	56.1%
			Caucasian	3	1.05 (0.84, 1.31)	0.680	38.8%
		OA type	Knee	6	1.28 (1.04, 1.59)	0.023	69.9%
			Hip	1	1.09 (0.83, 1.42)	0.545	-
	AA + GA *vs* GG	Total (random model)		8	1.25 (1.01, 1.55)	0.039	61.0%
	Dominant model	Ethnicity	Asian	5	1.44 (1.13, 1.82)	0.003	51.4%
			Caucasian	3	0.98 (0.68, 1.41)	0.926	59.8%
		OA type	Knee	6	1.27 (0.93, 1.73)	0.130	70.2%
			Hip	1	1.06 (0.74, 1.51)	0.769	-
	AA *vs* GA + GG	Total (fixed model)		8	1.53 (1.30, 1.81)	< 0.001	0.0%
	Recessive model	Ethnicity	Asian	5	1.62 (1.34, 1.96)	< 0.001	13.3%
			Caucasian	3	1.25 (0.88, 1.78)	0.209	0.0%
		OA type	Knee	6	1.53 (1.27, 1.84)	< 0.001	0.0%
			Hip	1	1.24 (0.73, 2.13)	0.430	-
	AA *vs* GG	Total (fixed model)		8	1.71 (1.42, 2.06)	< 0.001	30.2%
	Homozygote model	Ethnicity	Asian	5	1.89 (1.52, 2.34)	< 0.001	40.8%
			Caucasian	3	1.28 (0.88, 1.86)	0.192	0.0%
		OA type	Knee	6	1.74 (1.41, 2.15)	< 0.001	39.8%
			Hip	1	1.25 (0.71, 2.20)	0.449	-
	GA *vs* GG	Total (fixed model)		8	1.15 (1.01, 1.32)	0.034	47.7%
	Heterozygote model	Ethnicity	Asian	5	1.25 (1.06, 1.46)	0.007	23.7%
			Caucasian	3	0.98 (0.77, 1.24)	0.846	63.1%
		OA type	Knee	6	1.15 (0.98, 1.36)	0.090	60.3%
			Hip	1	1.01 (0.69, 1.47)	0.977	-
rs763780	C *vs* T	Total (random model)		8	1.32 (1.06,1.64)	0.013	51.5%
	Allele model	Ethnicity	Asian	5	1.19 (0.95, 1.48)	0.132	42.6%
			Caucasian	3	1.75 (1.16, 2.66)	0.008	39.3%
		OA type	Knee	6	1.37 (1.17, 1.60)	< 0.001	0.0%
			Hip	1	2.24 (1.38, 3.63)	0.001	-
	CC + TC *vs* TT	Total (random model)		8	1.32 (1.02, 1.72)	0.033	58.4%
	Dominant model	Ethnicity	Asian	5	1.15 (0.90, 1.48)	0.274	44.0%
			Caucasian	3	1.82 (1.11, 3.00)	0.018	51.9%
		OA type	Knee	6	1.35 (1.14, 1.61)	0.001	0.0%
			Hip	1	2.42 (1.47, 3.99)	0.001	-
	CC *vs* TC + TT	Total (fixed model)		8	2.08 (1.30, 3.32)	0.002	0.0%
	Recessive model	Ethnicity	Asian	5	2.17 (1.32, 3.59)	0.002	0.0%
			Caucasian	3	1.48 (0.38, 5.67)	0.570	0.0%
		OA type	Knee	6	2.10 (1.28, 3.45)	0.003	0.0%
			Hip	1	0.76 (0.03, 3.32)	0.864	-
	CC *vs* TT	Total (fixed model)		8	2.19 (1.37, 3.51)	0.001	0.0%
	Homozygote model	Ethnicity	Asian	5	2.28 (1.37, 3.77)	0.001	0.0%
			Caucasian	3	1.62 (0.42, 6.23)	0.481	0.0%
		OA type	Knee	6	2.23 (1.35, 3.67)	0.002	0.0%
			Hip	1	0.83 (0.03, 20.43)	0.909	-
	TC *vs* TT	Total (random model)		8	1.29 (0.97, 1.71)	0.078	62.6%
	Heterozygote model	Ethnicity	Asian	5	1.09 (0.85, 1.40)	0.505	40.5%
			Caucasian	3	1.84 (1.06, 3.17)	0.030	57.6%

OA type	Knee	6	1.28 (1.07, 1.54)	0.008	0.0%
	Hip	1	2.49 (1.51, 4.12)	< 0.001	-

OA: Osteoarthritis; SNP: Single nucleotide polymorphism.

Table 4 False-positive report probability values for associations between *IL-17* gene polymorphisms and risk of osteoarthritis

| Variables	Odds ratio (95%CI)	*P* value	Power	Prior probability				
				0.25	0.1	0.01	0.001	0.0001
rs2275913								
A *vs* G								
All	1.26 (1.08, 1.47)	0.003	0.488	0.018	0.052	0.378	0.860	0.984
Asian	1.40 (1.18, 1.67)	< 0.001	0.673	0.004	0.013	0.128	0.597	0.937
Knee OA	1.28 (1.04, 1.59)	0.023	0.483	0.125	0.300	0.825	0.979	0.998
AA + GA *vs* GG								
All	1.25 (1.01, 1.55)	0.039	0.488	0.194	0.419	0.888	0.988	0.999
Asian	1.44 (1.13, 1.82)	0.003	0.533	0.017	0.048	0.358	0.849	0.983
AA *vs* GA + GG								
All	1.53 (1.30, 1.81)	< 0.001	0.952	0.003	0.009	0.094	0.512	0.913
Asian	1.62 (1.34, 1.96)	< 0.001	0.953	0.003	0.009	0.094	0.512	0.913
Knee OA	1.53 (1.27, 1.84)	< 0.001	0.890	0.003	0.010	0.100	0.529	0.918
AA *vs* GG								
All	1.71 (1.42, 2.06)	< 0.001	0.991	0.003	0.009	0.091	0.502	0.910
Asian	1.89 (1.52, 2.34)	< 0.001	0.995	0.003	0.009	0.091	0.501	0.910
GA *vs* GG								
All	1.15 (1.01, 1.32)	0.034	0.447	0.186	0.406	0.883	0.987	0.999
Asian	1.25 (1.06, 1.46)	0.007	0.548	0.037	0.103	0.559	0.927	0.992
rs763780								
C *vs* T								
All	1.32 (1.06,1.64)	0.013	0.509	0.071	0.187	0.717	0.962	0.996
Caucasian	1.75 (1.16, 2.66)	0.008	0.487	0.047	0.129	0.619	0.943	0.994
Knee OA	1.37 (1.17, 1.60)	< 0.001	0.753	0.004	0.012	0.116	0.570	0.930
Hip OA	2.24 (1.38, 3.63)	0.001	0.006	0.018	0.167	0.669	0.953	0.995
CC + TC *vs* TT								
All	1.32 (1.02, 1.72)	0.033	0.470	0.174	0.387	0.874	0.986	0.999
Caucasian	1.82 (1.11, 3.00)	0.018	0.099	0.247	0.783	0.973	0.973	0.997
Knee OA	1.35 (1.14, 1.61)	0.001	0.520	0.006	0.017	0.160	0.658	0.951
Hip OA	2.42 (1.47, 3.99)	0.001	0.569	0.005	0.016	0.148	0.637	0.946
CC *vs* TC + TT								
All	2.08 (1.30, 3.32)	0.002	0.492	0.012	0.035	0.287	0.802	0.976
Caucasian	2.17 (1.32, 3.59)	0.002	0.471	0.013	0.037	0.296	0.809	0.977
Knee OA	2.10 (1.28, 3.45)	0.003	0.485	0.018	0.053	0.380	0.861	0.984
CC *vs* TT								
All	2.19 (1.37, 3.51)	0.001	0.487	0.006	0.018	0.169	0.672	0.954
Caucasian	2.28 (1.37, 3.77)	0.001	0.469	0.006	0.019	0.174	0.681	0.955
Knee OA	2.23 (1.35, 3.67)	0.002	0.526	0.011	0.033	0.274	0.792	0.974
TC *vs* TT								
Caucasian	1.84 (1.06, 3.17)	0.030	0.511	0.150	0.346	0.853	0.983	0.998
Knee OA	1.28 (1.07, 1.54)	0.008	0.486	0.047	0.129	0.620	0.943	0.994
Hip	2.49 (1.51, 1.71)	< 0.001						

OA: Osteoarthritis.
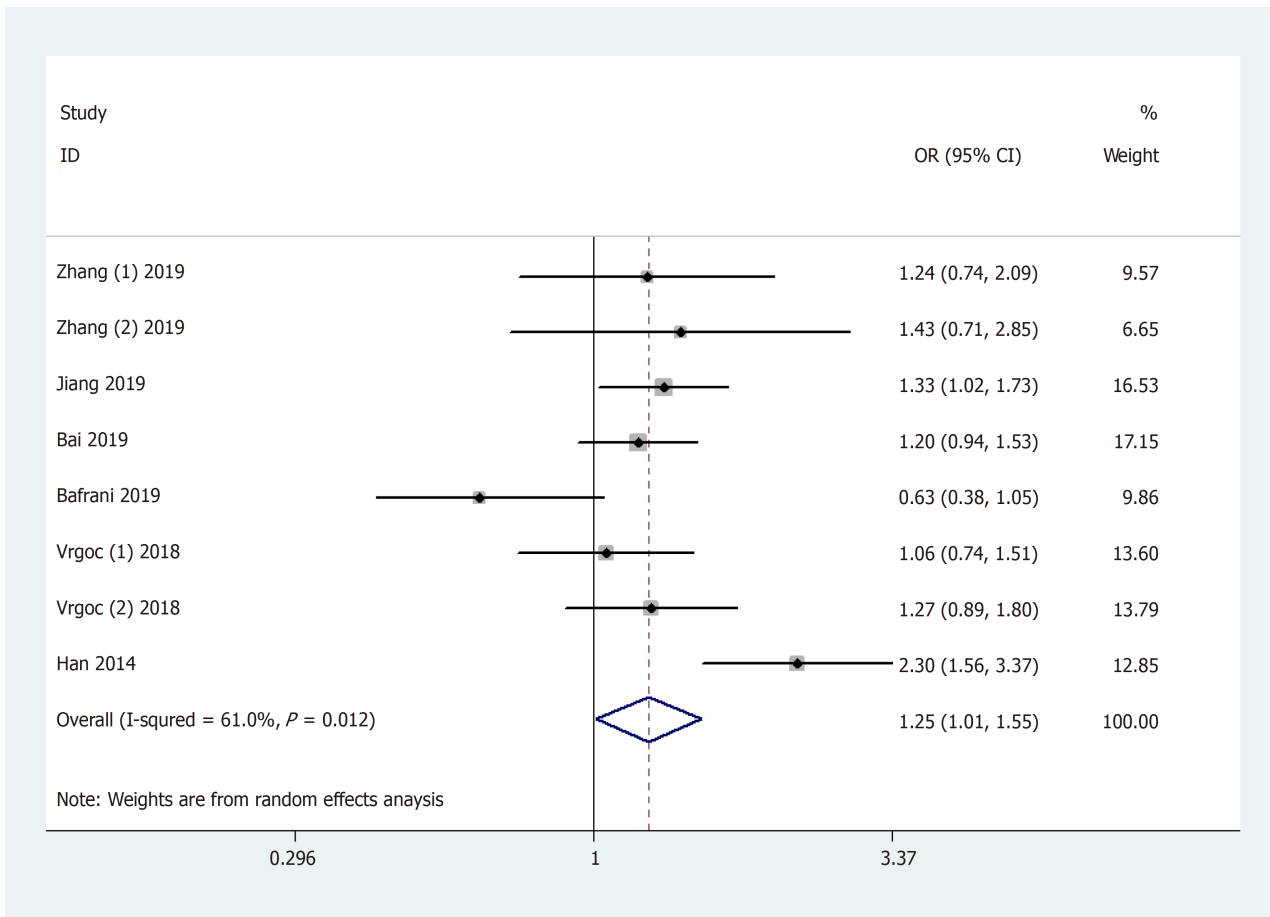
Figure 2 Forest plot shows odds ratios for the associations between rs2275913 polymorphism and osteoarthritis risk (AA + GA *vs* GG).
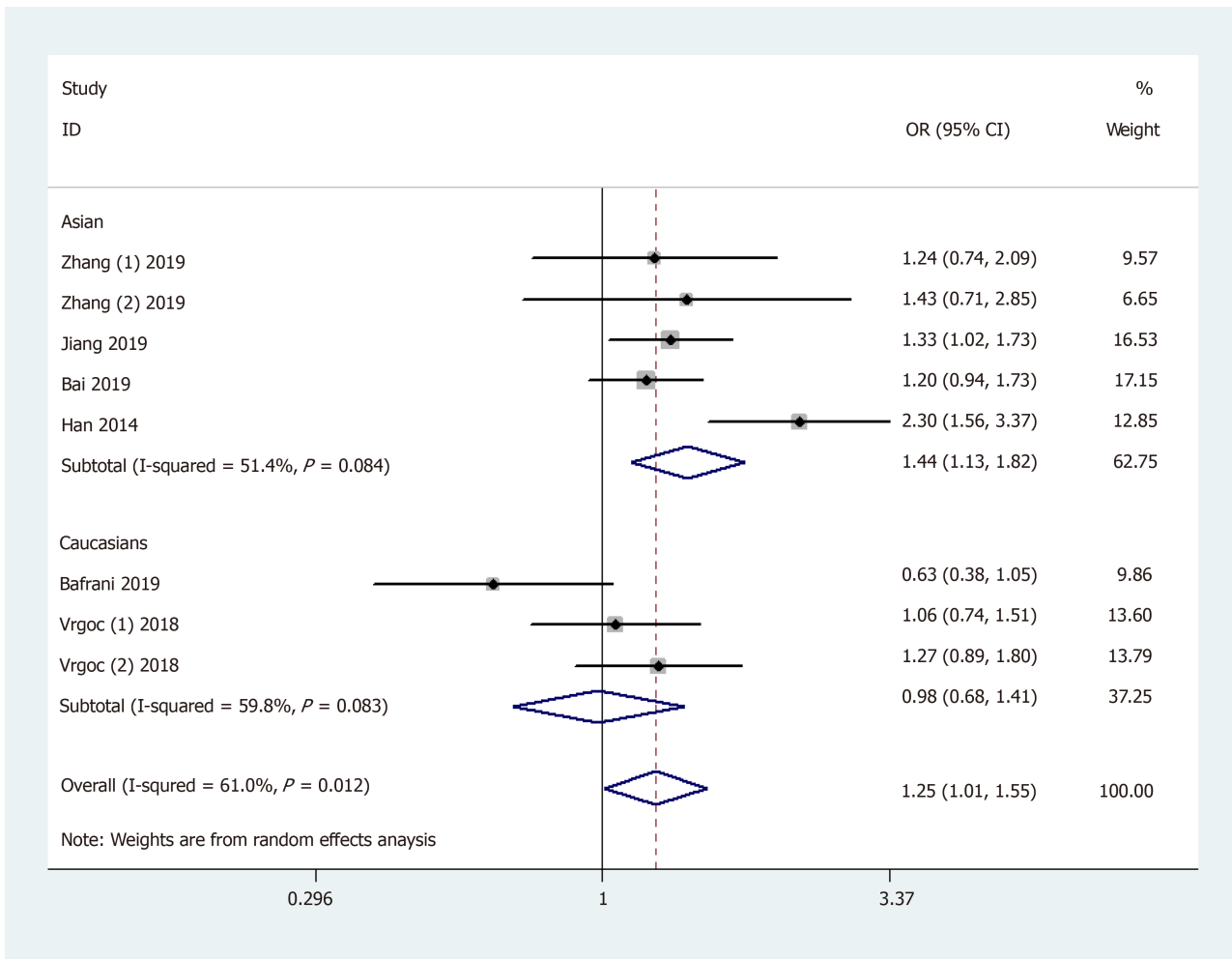
Figure 3 Stratification analysis by ethnicity shows odds ratio for the association between rs2275913 polymorphism and osteoarthritis risk (AA + GA *vs* GG).
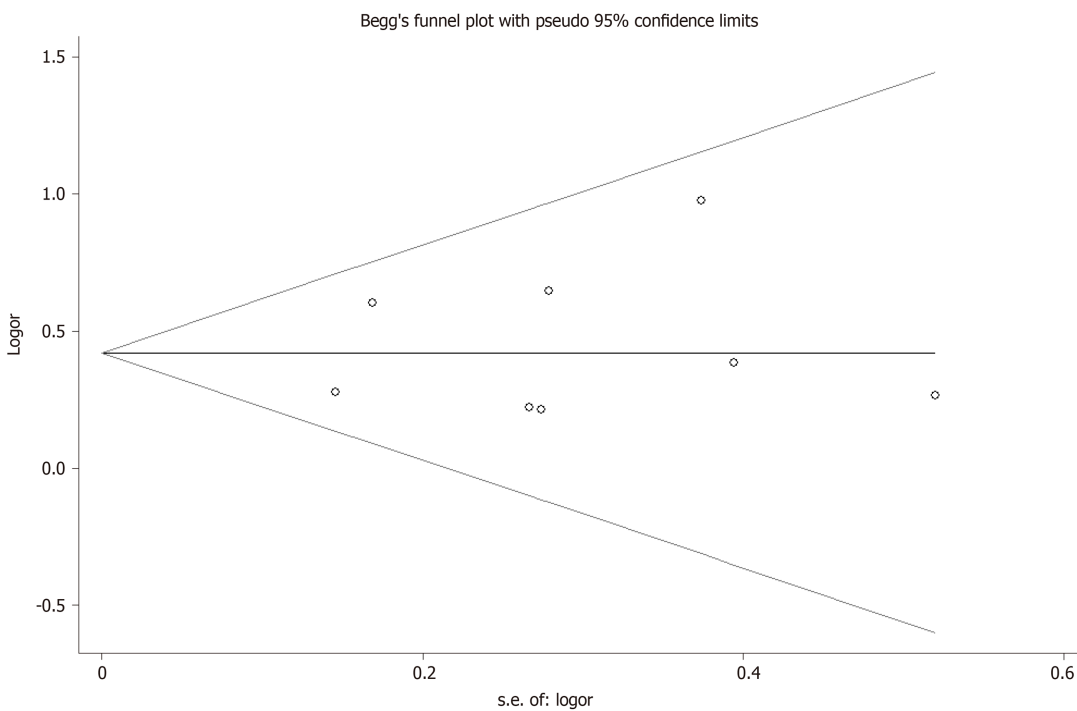

Figure 4 Begg's tests between rs2275913 polymorphism and osteoarthritis (AA *vs* GA + GG).
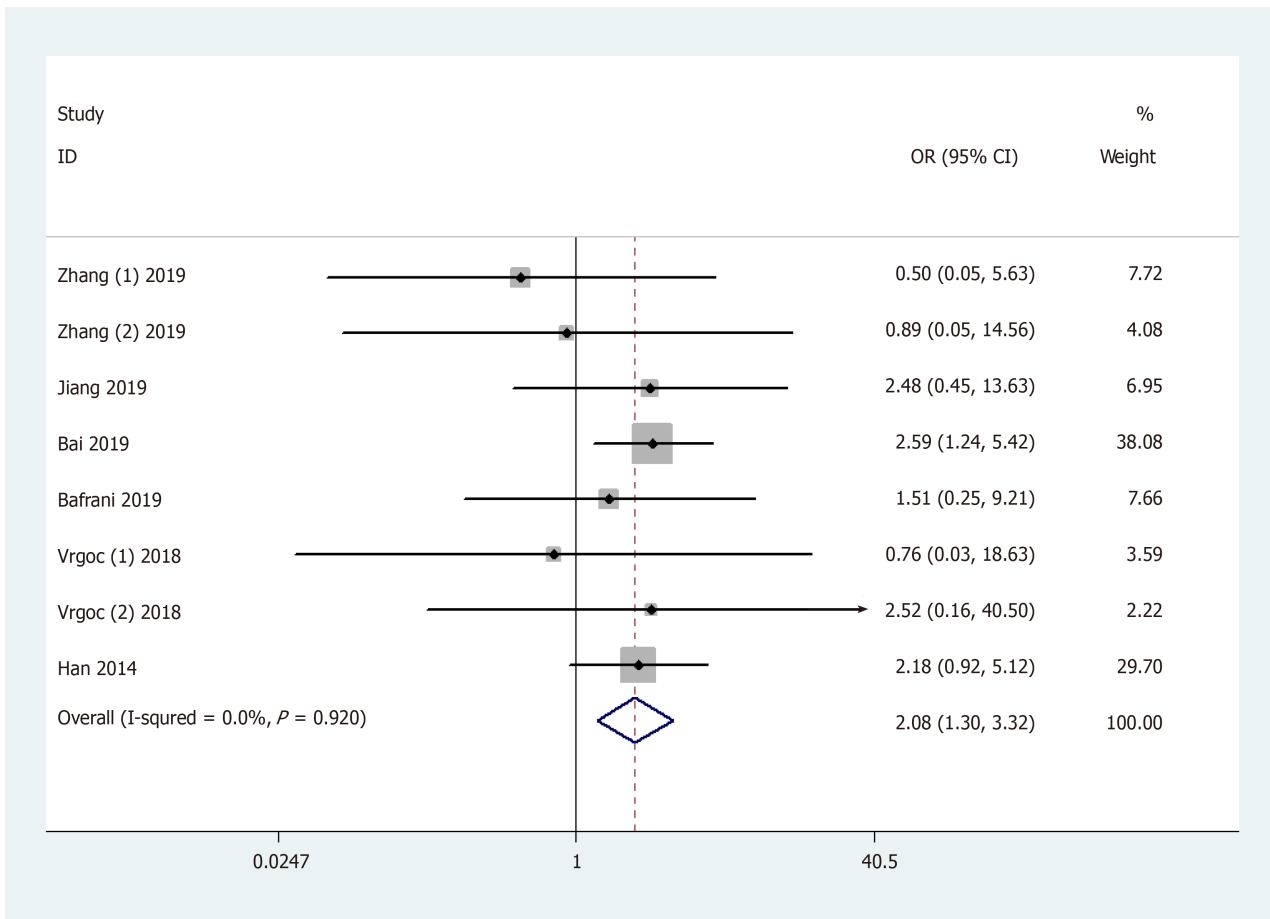
Figure 5 Forest plot shows odds ratios for the associations between rs763780 polymorphism and osteoarthritis risk (CC *vs* TC + TT).

ARTICLE HIGHLIGHTS

Research background

Osteoarthritis (OA) is the combined result of complex pathogenic factors, including mechanical, biochemical, environmental, endocrine, metabolic, and genetic factors, which account for nearly 50% of the risk of OA development. Although the pathogenesis and etiology of OA are not known, it is likely that interleukin-17 (IL-17) might play an important role in OA development.

Research motivation

To date, several studies have explored the relationship between polymorphisms of the *IL-17* gene and OA susceptibility. The association between *IL-17* gene single nucleotide polymorphisms and OA susceptibility may provide novel research directions for OA studies. However, the results of previous studies are inconclusive and conflicting due to clinical heterogeneity, different ethnic populations and small sample sizes.

Research objectives

We meta-analyzed relevant articles regarding the association between the polymorphisms of *IL-17* gene and OA susceptibility.

Research methods

We systematically conducted the literature search using the following electronic databases: PubMed, EMBASE, MEDLINE, Cochrane Library, and Google Scholar to identify epidemiological studies published up to September 2019 to retrieve genetic association studies on OA. Pooled odds ratios with 95% confidence intervals were calculated. Subgroup analyses were carried based on ethnicity and type of OA. Furthermore, false-positive report probability was conducted to evaluate the significant findings and rule out any false associations due to multiple tests.

Research results

In a total of 6 citations involving 8 studies (2131 cases and 2299 controls), 4 single nucleotide polymorphisms were identified. Of these 4 polymorphisms, 2 (rs2275913, rs763780) were common in five case-control studies. Together, the pooled results revealed that the A allele and genotype AA/GA of the rs2275913 polymorphism, and the C allele and genotype CC of the

rs763780 polymorphism in the *IL-17* gene increased the risk of OA. Furthermore, stratification analyses by ethnicity and OA type showed that the rs2275913 polymorphism increased the risk of OA among Asians and in knee/hip OA, respectively. In addition, stratification analyses also revealed that the rs763780 polymorphism increased OA risk among both Asians and Caucasians in knee/hip OA.

Research conclusions

The rs763780 polymorphism of the *IL-17F* gene increased the risk of OA, whereas the rs2275913 polymorphism of the *IL-17A* gene increased the risk of OA only among Asians. Due to the limitations of this study, these findings should be validated in future studies.

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