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Original Article

Assessing the association of IL-17A and IL-17F polymorphisms with osteoarthritis risk: a systematic review and meta-analysis

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Abstract: We conducted a systematic review and meta-analysis to clarify the relationship between these gene polymorphisms and Osteoarthritis (OA) risk. We searched electronic databases and found 736 related reports, five of which were ultimately included in the study. The articles ranged from 2014 to 2019 and included both Asian and Caucasian populations. Genotypes were categorized into TT, TC, and CC across case and control groups. The meta-analysis of interleukin-17A (IL-17A; rs2275913) showed no significant correlation with OA in the overall human population's allele model, codominance model, dominance model, and recessive model (P=0.97, 0.94, 0.77, 0.80, 0.85). Ethnic subgroup analysis showed no association between the Asian or Caucasian populations' IL-17A gene and OA. However, the meta-analysis of interleukin-17F (IL-17F; rs763780) showed that this gene is related to OA in the overall population and each single nucleotide polymorphism (SNP) genetic model (*P*-values: 0.0001, 0.0003, 0.01, 0.01, 0.0008). Ethnic subgroup analysis revealed that the IL-17F gene in the Asian population is related to OA, but only the allele and dominant models of the IL-17F gene in the Caucasian population were related to OA. The IL-17F polymorphism appears to be a risk factor for OA, with Asian populations more susceptible than Caucasians. The IL-17A showed no association with OA.

Keywords: Osteoarthritis, IL-17A gene, IL-17F gene, gene polymorphisms, meta-analysis

Introduction

Osteoarthritis (OA) is a prevalent age-related joint disorder primarily characterized by the degeneration of articular cartilage, often resulting in significant limitations in lower limb function [1, 2]. The hallmark pathological changes include degradation and fragmentation of joint cartilage, subchondral bone sclerosis, and osteophyte formation within the synovium [3, 4].

Despite extensive research, the precise etiology of OA remains unclear. However, recent studies have increasingly emphasized the role of genetic susceptibility in the development of the disease [5]. Among the investigated genetic markers, interleukins (ILs) have emerged as key mediators in the inflammatory processes associated with OA, offering insight into the disease's underlying pathophysiology [6, 7]. The interleukin-17 (IL-17) family-particularly interleukin-17A (IL-17A) and interleukin-17F (IL-17F)-plays a central role in the activation of monocytes and T-helper 17 (Th17) cells, promoting the release of pro-inflammatory mediators and perpetuating joint inflammation [8, 9]. Previous research has established associations between IL-17A and IL-17F gene polymorphisms and various inflammatory conditions, including rheumatoid arthritis and ankylosing spondylitis [10, 11]. Moreover, elevated IL-17 levels observed in the inflamed synovium of OA patients further suggest its role in driving synovitis and disease progression [12].

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Nevertheless, the impact of IL-17A and IL-17F gene polymorphisms on OA susceptibility remains controversial. For example, Bafrani et al. and others have reported inconsistent findings, with some studies suggesting a protective effect of IL-17A polymorphisms against knee OA, while others implicate IL-17F variants in increased disease risk [13]. Geographic and population-based differences further contribute to the variability in results [14, 15].

Given these discrepancies, our study aims to conduct a systematic review and meta-analysis of existing clinical data to evaluate the association between IL-17A (rs2275913) and IL-17F (rs763780) polymorphisms and OA susceptibility. By synthesizing the available evidence across diverse populations and genetic models, we seek to provide a comprehensive and conclusive evaluation of the role of IL-17 gene polymorphisms in OA. Our findings may contribute to a better understanding of OA pathogenesis, inform the development of predictive biomarkers, and potentially support the identification of novel therapeutic targets for this debilitating condition.

Materials and methods

The systematic review and subsequent reporting of results were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. As the data used in this study were obtained solely from previously published literature, the acquisition of informed consent and ethical approval was not required. A comprehensive evaluation of eligible studies was independently performed by two researchers, who assessed study eligibility, extracted data, and appraised methodological quality. Any disagreements were resolved through discussion to reach consensus.

Search strategy

Four electronic databases PubMed, Embase, Web of Science, and Cochrane Library were searched on May 6, 2024, and no time limitation was applied. Vocabulary and syntax were specifically adapted according to the database. The specific search terms of PubMed were: ("osteoarthritis"[MeSH Terms] OR "osteoarthritis"[All Fields]) AND (("interleukin-17"[MeSH Terms] OR "interleukin 17"[All Fields]) OR "IL-17A"[All Fields] OR "IL-17F"[All Fields]) AND ("polymorphism, genetic"[MeSH Terms] OR ("polymorphism"[All Fields] AND "genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "polymorphisms"[All Fields]). No language limitation was applied. Reference lists of relevant articles were also screened manually for any additional possible records.

Inclusion criteria

Studies included in the systematic review needed to meet the following criteria: 1) Studies related to OA and IL-17 gene polymorphisms; 2) Case groups must comply with the diagnostic criteria for osteoarthritis specified in the osteoarthritis treatment guidelines [2]; 3) Studies must include the distribution ratio of the IL-17 gene; 4) Observation indicators: single nucleotide polymorphism (SNP) genetic models: IL-17A: Allelic model (additive model): G vs A; Codominant model: GG vs AA and GG vs GA; Dominant model: AA vs GA+GG; Recessive model: GG vs GA+AA; IL-17F: Allelic model (additive model): C vs T; Codominant model: CC vs CT and CC vs TT; Dominant model: TT vs CT+CC; Recessive model: CC vs CT+TT.

The exclusion criteria were as follows: 1) Repeatedly published literature; 2) Documents with incomplete or unclear analytical data and inconsistent outcome indicators; 3) Studies without gene distribution and diversity data; 4) Case reports, commentaries, expert opinion and narrative reviews.

Data extraction

Literature screening and data extraction were independently conducted by two reviewers to ensure objectivity and minimize bias. Results were cross-checked, and any discrepancies were resolved through discussion. In cases where disagreements persisted, a third reviewer was consulted to reach consensus. The extracted data included the first author's name, year of publication, country of origin, genotyping methods, genotype distribution, and the number of cases and controls in each study. When relevant data were missing from the published articles, we contacted the corresponding authors by email to obtain additional or unpublished information.

Quality assessment

The methodological quality of the included studies was assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS) [17], which evaluates studies based on three domains: selection of study groups, comparability of groups, and ascertainment of outcomes. Each study received a score ranging from 0 to 9. Studies scoring 0-3 were considered low quality, scores of 4-6 indicated moderate quality, and scores of 7-9 represented high quality. This structured quality assessment ensured a rigorous and consistent evaluation of the included studies.

Statistical analyses

We conducted all statistical analyses using Stata version 17 (StataCorp, College Station, TX, USA). For each included SNP, pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated under five genetic models: allele, codominant, dominant, recessive, and over-dominant. Between-study heterogeneity was assessed using the Chi-square-based Q-test and quantified by the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity. Depending on heterogeneity, either a fixed-effects model (Mantel-Haenszel method) or a random-effects model (DerSimonian-Laird method) was applied. Subgroup analyses were performed based on ethnicity (Asian vs. Caucasian). Sensitivity analyses were conducted by sequentially removing individual studies to assess the robustness of the results. Potential publication bias was evaluated using funnel plots and Egger's linear regression test, with $P < 0.05$ considered indicative of significance.

Results

Search results and study selection

The preliminary exploration of the internet databases resulted in the identification of 736 reports in the literature that were pertinent to the topic at hand. After conducting a process of eliminating redundant literature, reviewing titles and abstracts, and applying strict inclusion and exclusion criteria, a total of 23 relevant reports were identified. Subsequently, 18 of these were excluded from further analysis. The inclusion of five studies was ultimately accomplished [13-15, 18, 19]. **Figure 1** illustrates the methodology and outcomes of the literature review.

Study characteristics

The characteristics of studies included in this systematic review are presented in **Tables 1**-**3**. This meta-analysis includes six studies all focusing on the IL-17F rs763780 genotype. They range in publication date from 2014 to 2019. Each study varies in terms of the number of cases and controls, the genotyping method, and ethnicity of the participants. The studies were conducted among both Asian and Caucasian populations, with genotyping methods including polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP), and polymerase chain reaction (PCR). Some studies adhered to the Hardy-Weinberg equilibrium while others did not. The genotypes were categorized into TT, TC, and CC across the case and control groups.

Results of quality assessment

The methodological integrity of each randomized controlled trial (RCT) was assessed using the NOS. Two studies obtained a mean score of 8 points, whereas three studies obtained a mean score of 9 points. The research lacked blinded studies and did not provide any indicators of allocation concealment. There was no evidence of funding bias observed in any of the investigations. No trials included missing outcome data, early termination bias, or baseline imbalances. **Table 4** presents a summary of the biases and their related ratios.

Meta-analysis results of genotype and OA analysis

Relationship between IL-17A and OA: A Meta-analysis including 5 studies shows that there is no significant correlation between the overall human population's IL-17A and each SNP genetic model in terms of allele model (**Figure 2**), codominance model, dominance model (**Figure 3**), and recessive model (**Figure 4**) (P=0.97, 0.94, 0.77, 0.80, 0.85). Ethnic subgroup analysis: there was no association between the Asian population's IL-17A gene and OA (P=0.96,

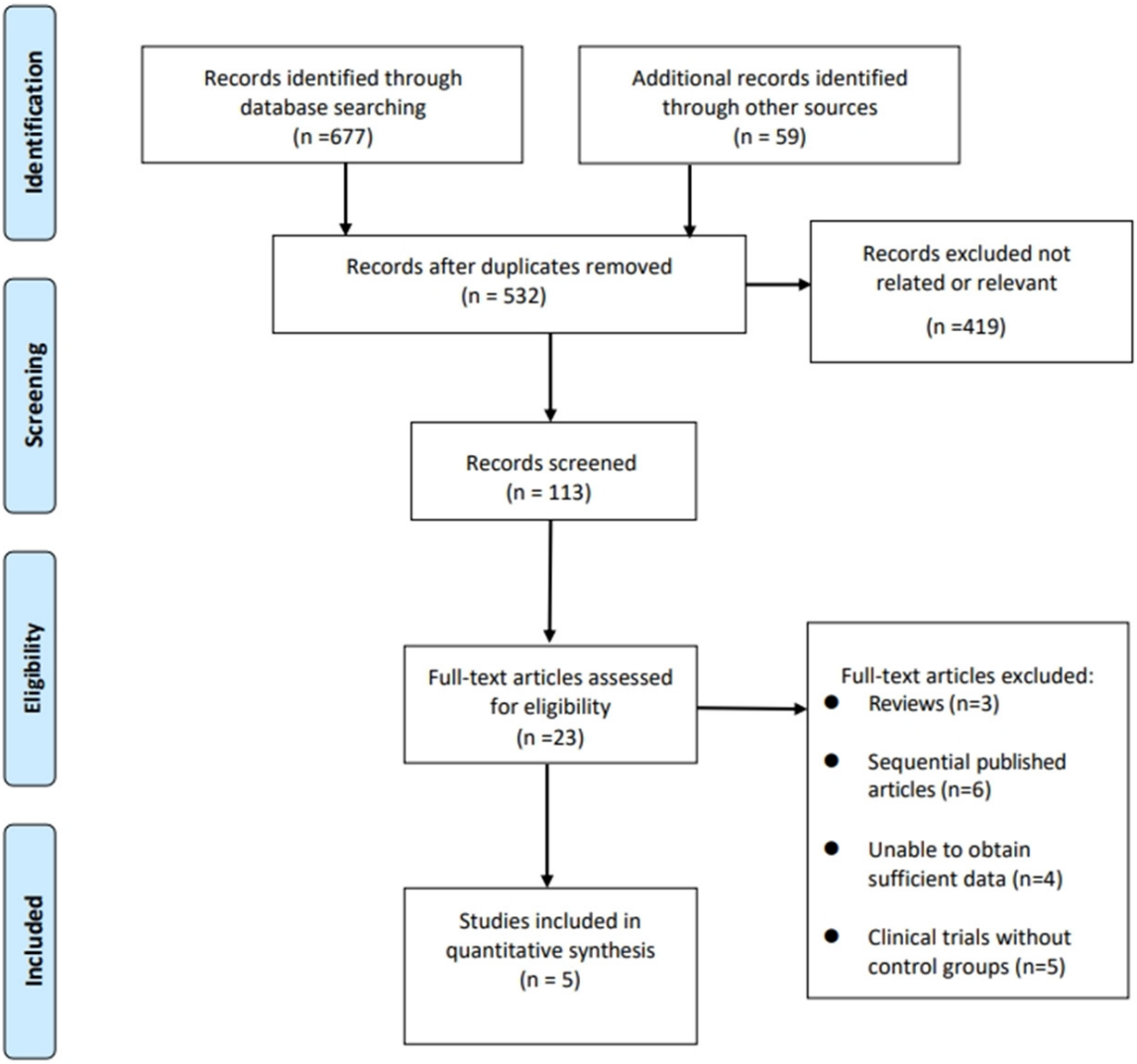

Figure 1. Selection process of included studies.

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

First Author	Year	Country	Ethnicity	Genotyping Method	OA Group (M/F)	Control Group (M/F)	HWE Test
Bafrani HH [13]	2019	Iran	Caucasian	PCR-RFLP	127 (58/69)	127 (54/73)	Yes
Vrgoc G [14]	2017	Croatia	Caucasian	PCR	240 (66/174)	597 (445/152)	Yes
Jiang L [18]	2019	China	Asian	PCR-RFLP	410 (139/271)	507 (159/348)	Yes
Han L [15]	2014	South Korea	Asian	PCR-SSCP	302 (57/245)	300 (164/136)	No
Bai Y [19]	2019	China	Asian	PCR	574 (201/393)	576 (174/402)	Yes

Notes: OA: Osteoarthritis; M/F: Male/Female; HWE: Hardy-Weinberg equilibrium; PCR: Polymerase Chain Reaction; PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; PCR-SSCP: Polymerase Chain Reaction-Single Strand Conformation Polymorphism.

0.95, 1.00, 0.86, 0.98), and the Caucasian population's IL-17A gene model also remained unrelated to OA (P=0.72, 0.24, 0.30, 0.98, 0.26, **Table 5**).

Table 2. Genotype distribution of IL-17A (rs2275913) in osteoarthritis (OA) cases and controls

First Author	Year	IL-17A OA (GG)	IL-17A OA (AG)	IL-17A OA (AA)	IL-17A Control (GG)	IL-17A Control (AG)	IL-17A Control (AA)
Bafrani HH [13]	2019	9	35	83	7	51	69
Vrgoc G [14]	2017	25	85	76	45	172	190
Jiang L [18]	2019	34	170	204	23	194	289
Han L [15]	2014	52	109	141	97	106	97
Bai Y [19]	2019	134	271	189	104	265	207

Notes: OA: Osteoarthritis; IL-17A: Interleukin-17A; GG, AG, AA: Homozygous wild-type, heterozygous, and homozygous variant genotypes, respectively.

Table 3. Genotype distribution of IL-17F (rs763780) in osteoarthritis (OA) cases and controls

First Author	Year	IL-17F OA (CC)	IL-17F OA (CT)	IL-17F OA (TT)	IL-17F Control (CC)	IL-17F Control (CT)	IL-17F Control (TT)
Bafrani HH [13]	2019	3	26	98	2	13	112
Vrgoc G [14]	2017	1	14	195	1	34	493
Jiang L [18]	2019	4	49	356	2	80	423
Han L [15]	2014	17	59	226	8	56	236
Bai Y [19]	2019	26	188	380	10	155	411

Notes: OA: Osteoarthritis; IL-17F: Interleukin-17F; CC, CT, TT: Homozygous wild-type, heterozygous, and homozygous variant genotypes, respectively.

Relationship between IL-17F (rs763780) and OA

A Meta-analysis including 5 studies shows that the IL-17F gene is related to OA in the overall population and each SNP genetic model in terms of allele model (**Figure 5**), codominance model, dominance model (**Figure 6**), and recessive model (**Figure 7**). The *P*-values for each SNP genetic model in the overall human population's IL-17F were 0.0001, 0.0003, 0.01, 0.01, 0.0008, indicating that IL-17F gene is related to OA in the overall population. According to the ethnic subgroup analysis, the IL-17F (rs2275913) gene in the Asian population is related to OA, with each SNP genetic model (P=0.0021, 0.0003, 0.008, 0.01, 0.0006). In the Caucasian population's IL-17F gene, only the allele model P=0.0002, dominant model P=0.01, are related to OA, as shown in **Table 5**.

Publication bias

The funnel plots constructed with the observed study showed symmetry, and no significant publication bias was detected in funnel plots (**Figure 8**).

Discussion

In this systematic review and meta-analysis, we rigorously adhered to the PRISMA guidelines to investigate the association between IL-17A and IL-17F gene polymorphisms and the risk of OA-a prevalent degenerative joint disorder with a multifactorial etiology, including genetic predisposition. Our study provides a comprehensive and updated synthesis of the available evidence, encompassing studies published between 2014 and 2019, and covering both Asian and Caucasian populations. A key strength of our work lies in the inclusion of ethnicity-based subgroup analyses, which offer novel insights into the population-specific genetic risk associated with IL-17 polymorphisms. Our findings reveal that IL-17A polymorphisms are not significantly associated with OA risk in any genetic model or population subgroup. In contrast, IL-17F polymorphisms demonstrate a significant association with increased OA risk, particularly in Asian populations. These results clarify previous inconsistencies in the literature and highlight IL-17F as a potential genetic risk factor for OA, paving the way for improved genetic risk stratification and personalized treatment strategies [20, 21].

Table 4. The quality assessment according to Newcastle-Ottawa Scale of each cohort study

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome Of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough	Adequacy of follow up of cohorts	Total score
Bafrani HH [13]	★	★	★	★	★★	★	★	★	9
Vrgoc G [14]		★	★	★	★★	★	★	★	8
Jiang L [18]	★	★	★	★	★★	★	★	★	9
Han L [15]	★	★	★	★	★★	★		★	8
Bai Y [19]	★	★	★	★	★★	★	★	★	9

Notes: NOS: Newcastle-Ottawa Scale.

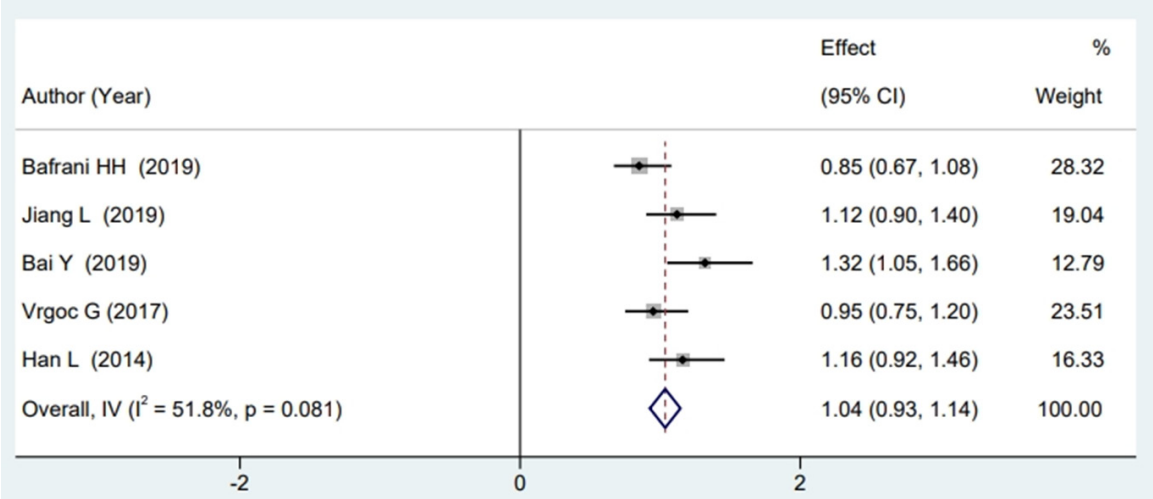

Figure 2. Forest plot of the associations between the interleukin-17A (IL-17A) gene polymorphism and knee osteoarthritis (OA) risk (allele model).

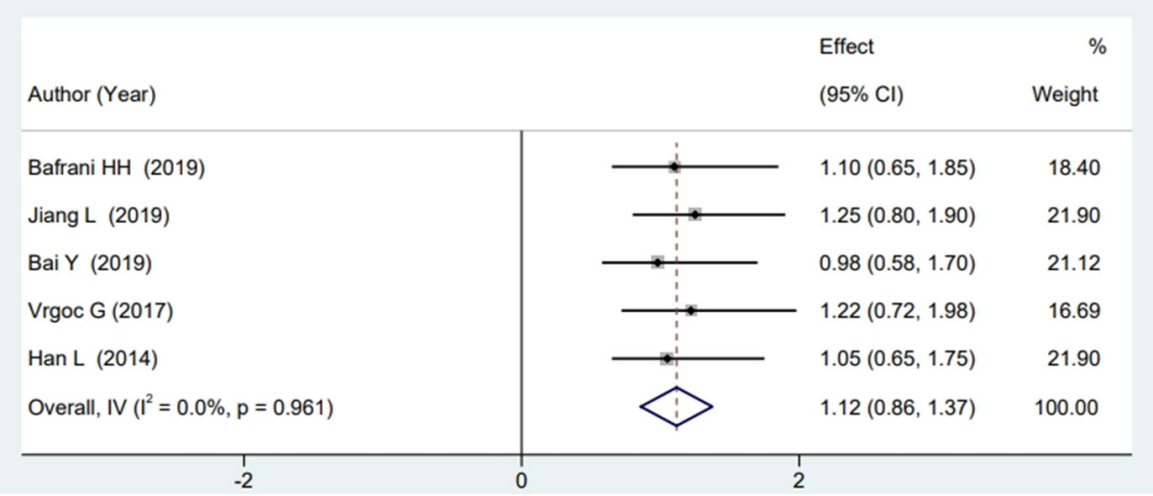

Figure 3. Forest plot of the associations between the interleukin-17A (IL-17A) gene polymorphism and knee osteoarthritis (OA) risk (dominant model).

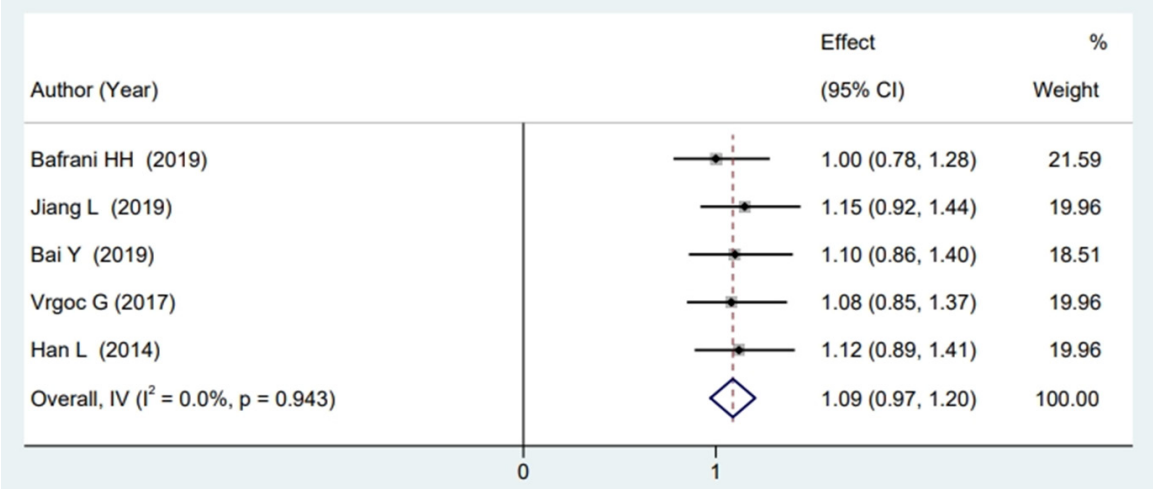

Figure 4. Forest plot of the associations between the interleukin-17A (IL-17A) gene polymorphism and knee osteoarthritis (OA) risk (recessive model).

Table 5. Characteristics of studies included in the meta-analysis

Gene	Population	Genetic Model	Effect Model	Association Test				Heterogeneity Test		
				OR	95% CI	Z	P	Q	P	I^2 (%)
IL-17A	Total	G vs A	R	1.04	0.93-1.14	0.10	0.97	66.39	<0.001	91
IL-17A	Total	GG vs AA	R	1.09	0.64-1.87	0.15	0.94	63.81	<0.001	91
IL-17A	Total	GG vs GA	R	0.98	0.64-1.48	0.37	0.77	37.68	<0.001	82
IL-17A	Total	AA vs GA+AA	R	1.09	0.97-1.20	0.33	0.80	35.96	<0.001	81
IL-17A	Total	GG vs GA+AA	R	1.12	0.86-1.37	0.25	0.85	55.71	<0.001	89
IL-17F	Total	C vs T	F	1.20	1.01-1.45	4.48	0.0001	15.25	0.09	47
IL-17F	Total	CC vs TT	F	2.26	1.47-3.45	3.68	0.0003	2.72	0.99	0
IL-17F	Total	CT vs CC	F	0.61	0.39-0.96	2.52	0.01	4.59	0.85	0
IL-17F	Total	TT vs CT+CC	R	0.79	0.74-0.90	2.53	0.01	17.68	0.04	54
IL-17F	Total	CC vs CT+TT	F	2.14	1.87-2.28	3.45	0.0008	2.75	0.99	0
IL-17A	Asian	G vs A	R	1.02	0.79-1.32	0.11	0.96	65.11	<0.001	90
IL-17A	Asian	GG vs AA	R	1.07	0.63-1.81	0.15	0.95	62.54	<0.001	90
IL-17A	Asian	GG vs GA	R	0.97	0.63-1.47	0.37	1.00	36.54	<0.001	81
IL-17A	Asian	AA vs GA+AA	R	1.07	0.83-1.38	0.34	0.86	34.65	<0.001	80
IL-17A	Asian	GG vs GA+AA	R	1.09	0.68-1.76	0.25	0.98	54.42	<0.001	88
IL-17A	Caucasian	G vs A	R	1.07	0.83-1.38	0.34	0.72	33.12	<0.001	79
IL-17A	Caucasian	GG vs AA	R	1.13	0.66-1.93	0.18	0.24	31.25	<0.001	78
IL-17A	Caucasian	GG vs GA	R	1.02	0.66-1.57	0.39	0.30	28.34	<0.001	77
IL-17A	Caucasian	AA vs GA+AA	R	1.13	0.88-1.46	0.36	0.98	26.42	<0.001	76
IL-17A	Caucasian	GG vs GA+AA	R	1.15	0.71-1.88	0.27	0.26	25.36	<0.001	75
IL-17F	Asian	C vs T	F	1.31	1.14-1.52	3.29	0.0021	7.67	0.26	34
IL-17F	Asian	CC vs TT	F	2.32	1.48-3.64	3.61	0.0003	2.27	0.87	0
IL-17F	Asian	CT vs CC	F	0.56	0.35-0.90	2.73	0.008	2.59	0.86	0
IL-17F	Asian	TT vs CT+CC	R	0.87	0.75-1.02	2.41	0.01	7.76	0.21	33
IL-17F	Asian	CC vs CT+TT	F	2.22	1.42-3.48	3.42	0.0006	2.20	0.89	0
IL-17F	Caucasian	C vs T	F	1.87	1.36-2.56	3.74	0.0002	3.46	0.85	0
IL-17F	Caucasian	CC vs TT	F	1.70	0.44-6.54	0.74	0.46	0.28	0.86	0
IL-17F	Caucasian	CT vs CC	F	1.27	0.31-5.10	0.28	0.83	0.91	0.63	0
IL-17F	Caucasian	TT vs CT+CC	R	0.58	0.35-0.95	2.49	0.01	4.37	0.14	56
IL-17F	Caucasian	CC vs CT+TT	F	1.55	0.40-5.95	0.60	0.60	0.32	0.85	0

Notes: IL-17A: Interleukin-17A; IL-17F: Interleukin-17F; OR: Odds Ratio; CI: Confidence Interval; R: Random-effects model; F: Fixed-effects model.

Our meta-analysis systematically assessed the association between IL-17A and IL-17F gene polymorphisms and susceptibility to OA across multiple genetic models and ethnic groups. The findings highlighted that IL-17F polymorphism is significantly associated with OA, especially in the Asian population, with consistent statistical support across allele, codominant, dominant, and recessive models. In contrast, IL-17A polymorphisms did not show a significant association with OA in any genetic model or population subgroup, suggesting that IL-17A may play a less direct or negligible role in OA susceptibility [22]. Mechanistically, IL-17F, a member of the IL-17 cytokine family, is known to induce pro-inflammatory cytokines and matrix-degrading enzymes, such as matrix metalloproteinases (MMPs), which contribute to cartilage degradation and joint inflammation, key features of OA pathogenesis [23, 24]. The significant association of IL-17F polymorphisms with OA may thus be attributed to their role in enhancing inflam-

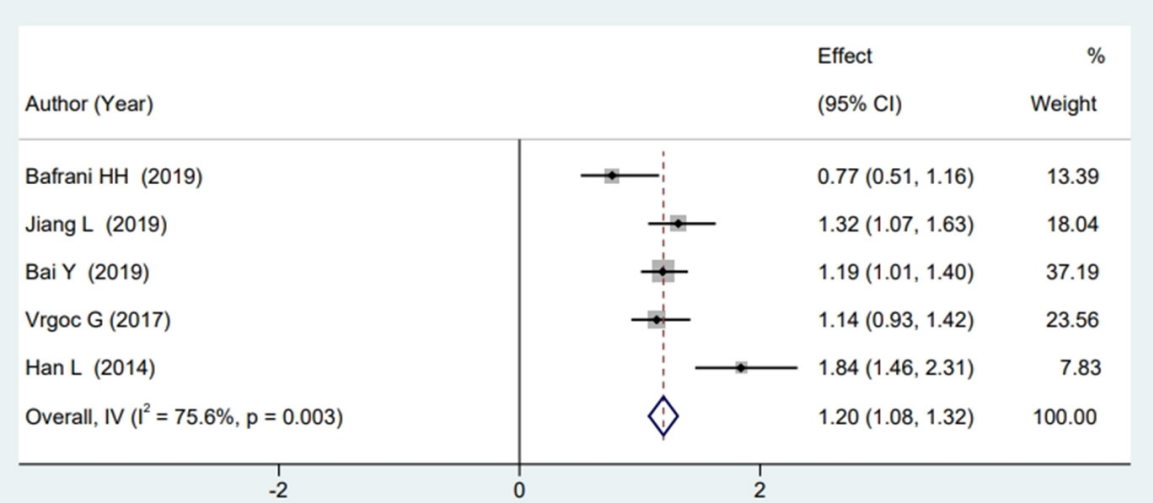

Figure 5. Forest plot of the associations between the interleukin-17F (IL-17F) gene polymorphism and knee osteoarthritis (OA) risk (allele model).

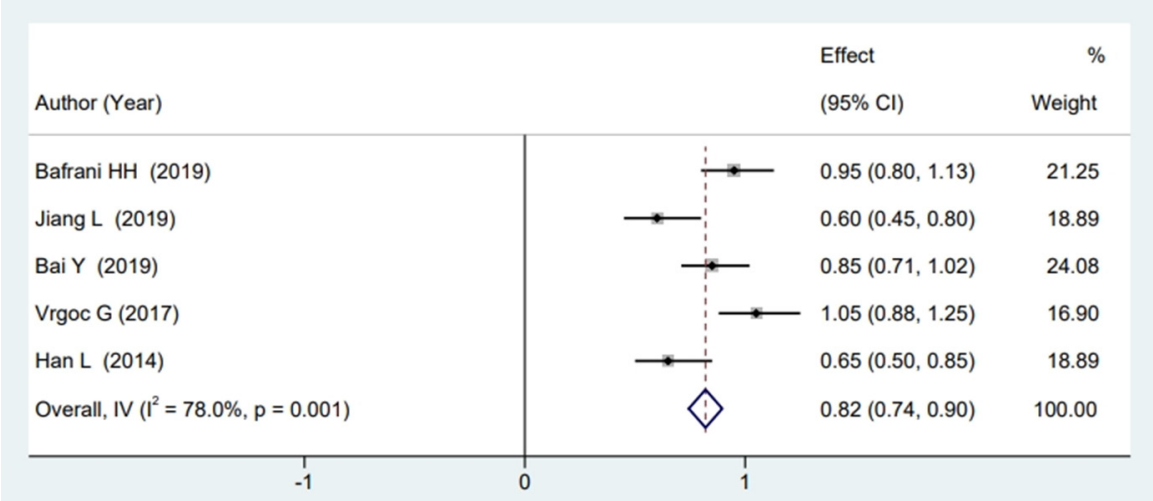

Figure 6. Forest plot of the associations between the interleukin-17F (IL-17F) gene polymorphism and knee osteoarthritis (OA) risk (dominant model).

matory responses [25]. On the other hand, the absence of a significant relationship between IL-17A and OA suggests that its influence may be indirect or modulated by other factors not captured in the current meta-analysis [26]. Additionally, ethnic subgroup analysis indicated a stronger genetic predisposition in Asians compared to Caucasians, possibly reflecting gene-environment or gene-lifestyle interactions that warrant further investigation [27].

Although our meta-analysis revealed significant associations between IL-17F polymorphisms and OA susceptibility, while IL-17A showed no such link, it is important to consider the biological implications of these genetic variations. IL-17A and IL-17F are pro-inflammatory cytokines produced predominantly by Th17 cells, playing pivotal roles in chronic joint inflammation. Specifically, IL-17F is known to stimulate chondrocytes and synovial fibroblasts to produce MMPs, nitric oxide (NO), and pro-inflammatory mediators such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α), all of which are directly involved in cartilage degradation and synovial inflammation-two key pathological features of OA. The rs763780 polymorphism in IL-17F, resulting in a His161Arg amino

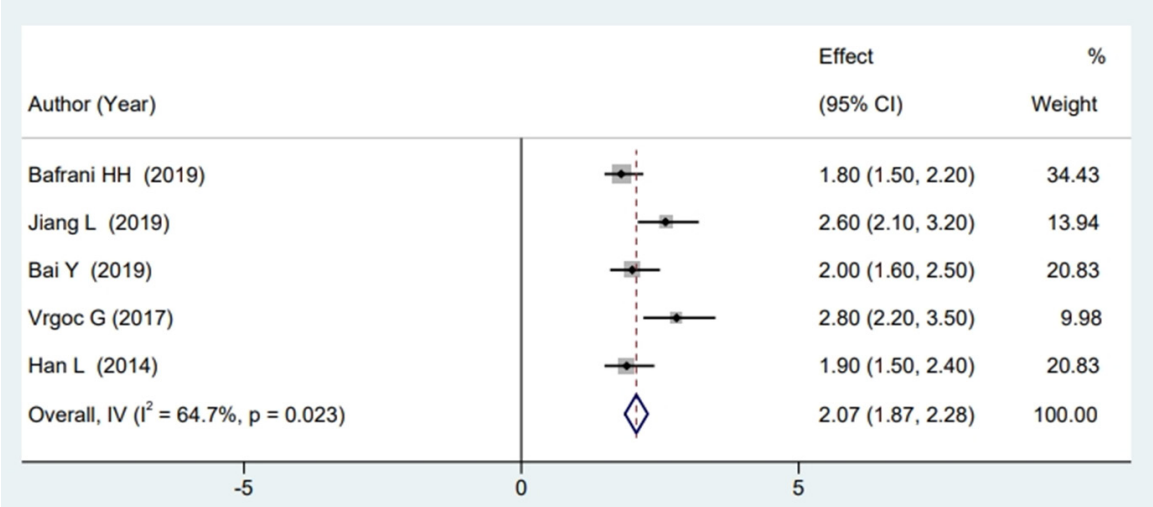

Figure 7. Forest plot of the associations between the interleukin-17F (IL-17F) gene polymorphism and knee osteoarthritis (OA) risk (recessive model).

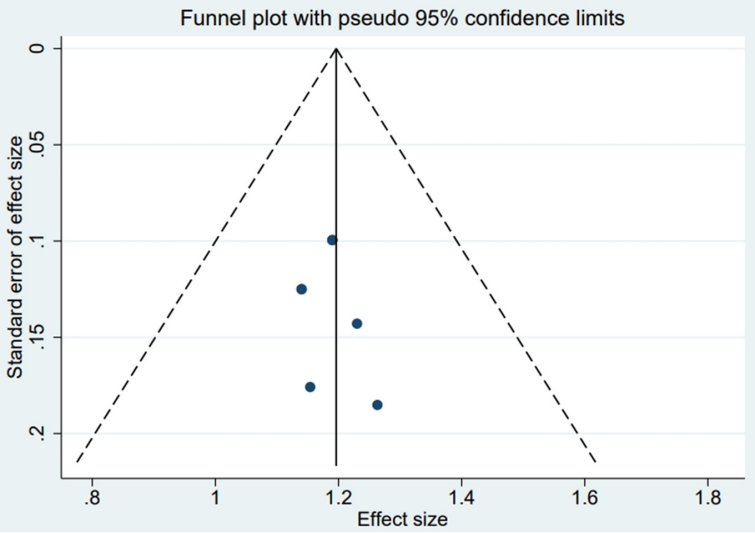

Figure 8. Funnel plot for publication bias in all included studies.

acid substitution, has been shown to alter cytokine bioactivity, potentially enhancing its pro-inflammatory effects and contributing to more rapid cartilage breakdown, increased joint space narrowing, and pain sensitization. Conversely, IL-17A polymorphisms may not significantly impact cytokine function or expression levels in OA-related tissues, which could explain the absence of detectable associations in our study. Therefore, IL-17F polymorphisms may contribute to OA pathogenesis by amplifying inflammatory cascades within the joint microenvironment, accelerating the degradation of extracellular matrix and promoting disease progression, particularly in genetically susceptible individuals. Further functional studies are warranted to delineate how these SNPs influence cytokine signaling, cartilage metabolism, and OA clinical phenotypes.

When comparing IL-17F and IL-17A polymorphisms, IL-17F shows more consistent genetic associations. Although some heterogeneity was observed, particularly in the dominant model of IL-17F, sensitivity analysis identified two studies contributing to data instability. After excluding these studies, the results became markedly more robust, indirectly supporting the reliability of our overall findings. Furthermore, previous research has demonstrated variability in the association between IL-17 polymorphisms and diseases such as cancer and tuberculosis across different ethnic and geographic populations [28]. In our subgroup analysis, significant associations between IL-17F polymorphisms and OA susceptibility were observed in both Asian and Caucasian populations. However, in Caucasians, statistical significance was limited to the allele and dominant models. This suggests that the IL-17F C allele may increase the risk of inflammatory OA in this population, but

with weaker genetic relevance compared to Asians-consistent with findings by Shao et al. [29]. Given the limited number of included studies, particularly among Caucasian cohorts, further research is warranted to validate these results.

Relevant studies examining IL-17A and IL-17F polymorphisms in relation to osteoarthritis provide a broader context for interpreting our findings. Yang et al. [30] concluded that both IL-17A rs2275913 and IL-17F rs763780 polymorphisms are associated with increased OA risk, especially in Asian populations. While their findings align with our results for IL-17F, our study did not find significant associations for IL-17A. Our meta-analysis further refined this relationship through stricter inclusion criteria and updated data. Shao et al. [29] reported that rs2275913 was associated with increased OA risk, while rs763780 conferred risk in Caucasians but not Mongolians. In contrast, our analysis did not support a significant association between IL-17A polymorphisms and OA. Our work contributes to this ongoing debate by applying ethnicity-stratified models and focusing solely on OA. Lu et al. [30] identified rs2275913 as a risk factor for knee OA in Asians, and rs763780 as a risk factor in both Asians and Caucasians. While our findings support the role of rs763780, we did not observe a significant effect for rs2275913. Our analysis offers updated pooled estimates and broader population coverage, enhancing result generalizability.

Our findings underscore the complex genetic architecture of OA and highlight the need for precision medicine approaches that consider inter-individual genetic variability. Future studies should aim to increase sample size, enhance ethnic diversity, explore gene-environment interactions, and elucidate the molecular mechanisms through which IL-17F influences OA pathogenesis. This work contributes to the foundation for developing targeted interventions and novel therapeutics aimed at preventing or slowing OA progression in genetically predisposed individuals. Nevertheless, several limitations should be acknowledged: (1) the overall sample size was relatively small; (2) most of the included studies involved Asian populations, which may limit the generalizability of our conclusions to other ethnic groups; and (3) heterogeneity was present in some analyses, and although sensitivity testing was performed, residual instability may still exist.

Conclusions

IL-17F polymorphism is a risk factor for OA, with Asian populations appearing more susceptible than Caucasians. Further analysis with larger datasets is needed to understand the susceptibility of OA to IL-17A.

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Disclosure of conflict of interest

None.

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