SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45 DOI: 10.5937/jomb0-66711

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 45: 1–10, 2026

Review paper
Revijski rad

ASSOCIATION BETWEEN IL-6 GENE POLYMORPHISMS AND THE RISK OF OSTEOARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

ASOCIJACIJA IZMEĐU POLIMORFIZAMA GENA IL-6 I RIZIKA OD OSTEOARTRITISA: SISTEMATSKI PREGLED I META-ANALIZA

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Summary

Background: This study systematically evaluates the association between interleukin-6 (IL-6) gene polymorphisms and osteoarthritis (OA) risk using a systematic meta-analytic approach.
Methods: Following PRISMA guidelines, a literature search was conducted across multiple electronic databases, including studies published up to February 2025. Eligible studies included OA patients diagnosed by ACR criteria, that investigated IL-6 gene promoter polymorphisms (rs1800795, rs1800797, rs1800798) and reporting genotype data or odds ratios (ORs) with 95% confidence intervals (CIs). All meta-analyses were performed using Stata 15.1, and subgroup analyses by ethnicity and OA subtype, as well as Egger's publication bias tests, were conducted.
Results: A total of 13 case-control studies (16 datasets) were included, covering three major IL-6 gene polymorphic sites: The 174 G/C (rs1800795) polymorphism showed no significant association with OA risk in overall or subgroup analyses ($P > 0.05$). The 572 G/C (rs1800797) polymorphism was significantly associated with a reduced OA risk under the dominant model (OR = 0.68, 95% CI: 0.48–0.97, $P < 0.05$), with a particularly pronounced protective effect in knee OA (KOA). The 597 G/A (rs1800798) polymorphism showed no significant

Kratak sadržaj

Uvod: Ova studija sistematski procenjuje povezanost između polimorfizama gena interleukina-6 (IL-6) i rizika od osteoartritisa (OA) koristeći sistematski meta-analitički pristup.
Metode: Prateći PRISMA smernice, sprovedena je pretraga literature u više elektronskih baza podataka, uključujući studije objavljene do februara 2025. godine. Prihvatljive studije uključivale su pacijente sa osteoartritisom dijagnostikovanim prema ACR kriterijumima, koje su ispitivale polimorfizme promotera gena IL-6 (rs1800795, rs1800797, rs1800798) i izveštavale o podacima o genotipu ili odnosima šansi (OR) sa 95% intervalima poverenja (CI). Sve meta-analize su sprovedene korišćenjem programa Stata 15.1, a sprovedene su i podgrupne analize po etničkoj pripadnosti i podtipu osteoartritisa, kao i Egerovi testovi pristrasnosti objavljivanja.
Rezultati: Ukupno je uključeno 13 studija slučaj-kontrola (16 skupova podataka), koje pokrivaju tri glavna polimorfna mesta gena IL-6: Polimorfizam 174 G/C (rs1800795) nije pokazao značajnu povezanost sa rizikom od osteoartritisa u ukupnim ili podgrupnim analizama ($P > 0,05$). Polimorfizam 572 G/C (rs1800797) bio je značajno povezan sa smanjenim rizikom od osteoartritisa prema dominantnom modelu (OR = 0,68, 95% CI: 0,48–0,97, $P < 0,05$), sa posebno izraženim zaštitnim efektom

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correlation with OA susceptibility (P > 0.05). Subgroup analyses confirmed result stability. Egger's test detected no significant publication bias.

Conclusion: IL-6 gene polymorphisms exhibit site- and population-specific effects on OA risk. The 572 G/C variant may confer protection against KOA. Further large-scale, multicenter studies are needed to validate these findings and explore underlying mechanisms to facilitate early OA diagnosis and personalized interventions.

Keywords: interleukin-6, gene polymorphism, osteoarthritis, knee joint, meta-analysis, genetic susceptibility

kod osteoartritisa kolena (KOA). Polimorfizam 597 G/A (rs1800798) nije pokazao značajnu korelaciju sa podložnošću osteoartritu (P > 0,05). Podgrupne analize potvrdile su stabilnost rezultata. Egerov test nije otkrio značajnu pristrasnost u objavljivanju.

Zaključak: Polimorfizmi gena IL-6 pokazuju specifične efekte na rizik od osteoartritisa, specifične za mesto i populaciju. Varijanta 572 G/C može pružiti zaštitu od osteoartritisa. Potrebne su dalje velike, multicentrične studije kako bi se potvrdili ovi nalazi i istražili osnovni mehanizmi za olakšavanje rane dijagnoze osteoartritisa i personalizovanih intervencija.

Ključne reči: interleukin-6, polimorfizam gena, osteoartritis, kolenski zglob, meta-analiza, genetska predraspoloživost

Introduction

Osteoarthritis (OA) is a chronic joint disease characterized by progressive degeneration of articular cartilage, subchondral bone sclerosis, osteophyte formation, and synovial inflammation. It is a leading cause of chronic pain, functional disability, and reduced quality of life worldwide (1–3). Clinically, OA presents with joint stiffness, restricted mobility, and structural deformities, with knee osteoarthritis (KOA) being the most prevalent subtype (1, 3). Epidemiological data indicate that OA incidence increases significantly with age (4). Globally, approximately 303 million people are affected by OA, making it the fourth leading cause of years lived with disability (YLDs) (1, 4). The aging population and rising obesity rates further aggravate the OA burden, establishing it as a major public health concern with profound socioeconomic implications (4, 5). The pathogenesis of OA involves a complex interplay between mechanical stress and biochemical imbalances (6). Pro-inflammatory cytokines, particularly interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), play critical roles in cartilage degradation (7). IL-6, as a pleiotropic cytokine, disrupts cartilage homeostasis and induces synovial inflammation by upregulating matrix metalloproteinases (MMPs) and aggrecanases, thereby accelerating OA progression (7, 8). Elevated IL-6 levels in synovial fluid and serum have been significantly associated with OA severity, suggesting IL-6 as both a biomarker and a therapeutic target (8, 9). However, individual susceptibility to IL-6-mediated joint damage varies, indicating that genetic polymorphisms may influence OA risk (10).

Twin and family studies provide strong evidence for the genetic heritability of OA, with genetic factors accounting for 40–65% of disease susceptibility (11). Among candidate genes, IL-6 has attracted significant attention due to its dual role in inflammation and cartilage metabolism (8). The IL-6 gene, located on the short arm of chromosome 7 (7p21-24), harbors functional single nucleotide polymorphisms (SNPs) in its promoter region, with the -174G/C (rs1800795) polymorphism being the most extensively studied (12–15). Mechanistically, the C allele at this site reduces IL-6 transcriptional activity, thereby lowering systemic IL-6 expression and mitigating cartilage degradation (13). However, clinical studies have yielded inconsistent findings: cohort studies in European populations suggest an association between the -174C allele and reduced OA risk, whereas no significant correlation has been observed in Asian populations (14, 16). These discrepancies may arise from population-specific linkage disequilibrium patterns, gene-environment interactions (e.g., obesity, joint trauma), or study design limitations (e.g.,, small sample sizes, heterogeneity in outcome definitions) (14, 16).

Despite extensive research, the association between IL-6 polymorphisms and OA risk remains inconclusive. Existing evidence is fragmented due to geographic, ethnic, and methodological variations, hindering consensus. For instance, a 2010 meta-analysis reported a borderline protective effect of the -174C allele (OR = 0.89, 95% CI: 0.79–1.01), but subgroup analysis revealed significant inter-population heterogeneity (17). Additionally, the potential roles of emerging SNPs (e.g., rs1800797) and haplotype interactions remain underexplored. A comprehensive global synthesis of available evidence is urgently needed to clarify whether IL-6 polymorphisms function as universal risk modifiers or context-dependent biomarkers.

This study aims to quantify the cross-population association between IL-6 polymorphisms (primarily rs1800795) and OA risk while investigating heterogeneity sources, including ethnicity and OA subtypes. By integrating higher-quality evidence, this meta-analysis seeks to provide a more objective and reliable understanding of the genetic role of IL-6 in OA pathogenesis. Furthermore, it offers a reference for future research aimed at identifying novel molecular targets for OA prevention and treatment.

Materials and Methods

Search Strategy

This systematic review and meta-analysis strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to systematically assess the association between interleukin-6 (IL-6) gene polymorphisms and osteoarthritis (OA) risk (18). A comprehensive literature search was conducted in PubMed, Cochrane Library, Web of Science, CNKI, and Wanfang Data Knowledge Service Platform, with a cutoff date of February 2025. Additionally, reference lists of included studies, OpenGrey for gray literature, and preprint platforms (e.g., medRxiv) were manually searched to ensure completeness. The database search strategy used the following keywords: (»Osteoarthritis« OR »OA«) AND (»Interleukin-6« OR »IL-6") AND (»polymorphism« OR »SNP« OR »single nucleotide polymorphism« OR »genome-wide association study« OR »allele«).

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were defined using the PICOS framework. The population (P) consisted of OA patients diagnosed according to the American College of Rheumatology (ACR) clinical or radiographic criteria, while the control group included healthy individuals or those without a history of OA. The exposure (E) was defined as IL-6 gene polymorphisms, with a primary focus on rs1800795, while other variants, such as rs1800797, were analyzed separately. Regarding study design (S), only case-control studies and prospective cohort studies were included, whereas reviews, case reports, editorials, commentaries, and secondary literature such as meta-analyses were excluded. To ensure data availability, studies were required to provide genotype distribution data for both cases and controls or sufficient information to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Studies without accessible raw data were excluded if attempts to contact the authors were unsuccessful. For quality control, the genotype distribution in the control group was required to conform to Hardy-Weinberg equilibrium (HWE), with a p-value ≥ 0.05.

Literature Screening, Data Extraction, and Quality Assessment

Literature screening was independently conducted by two researchers using EndNote 21 for reference management and deduplication. The PRISMA flowchart was used to document the selection process, including initial screening, full-text review, and final inclusion. A structured data extraction table was used to collect information on study characteristics (author, publication year, country, study design), population characteristics (sample size of case/control groups, age, sex ratio, OA subtype), genotyping data (SNP loci, genotyping method, HWE p-value), and effect size measures (allele frequency, genotype distribution, ORs with 95% CIs).

Study quality was assessed using a modified Newcastle-Ottawa Scale (NOS), with a total score of 20 points across five domains: case representativeness, control group matching, genotyping method, HWE compliance, and sample size. Studies were categorized as high quality (≥12 points), moderate quality (9–11 points), or low quality (<9 points).

Statistical Analysis

All statistical analyses were performed using Stata 15. 1 (19, 20). The effect sizes were calculated under five genetic models: allelic model (C vs G), codominant model (CC vs GG), dominant model (GC+CC vs GG), recessive model (CC vs GC+GG), and overdominant model (CC+GG vs GC). The random-effects model (DerSimonian-Laird method) was used when heterogeneity was significant ($I^2 \geq 50\%$ or Q test $p < 0.10$), while the fixed-effects model (Mantel-Haenszel method) was applied otherwise. Subgroup analyses were conducted based on ethnicity (Asian vs. Caucasian), and OA subtype (knee OA vs. hip OA). For meta-analyses including ≥5 studies, Egger's linear regression test was used to assess publication bias. If bias was detected, the Trim-and-Fill method was applied to adjust the pooled effect size (21, 22). Additionally, false-positive report probability (FPRP, with a prior probability of 0.2) and the Venice criteria were used to evaluate the credibility of the findings. A two-tailed α of 0.05 was set as the threshold for statistical significance.

Results

Literature Search Results

A total of 334 relevant studies were retrieved from database searches, including 91 studies from PubMed, 24 from the Cochrane Library, 117 from Web of Science, 49 from CNKI, and 53 from Wanfang Data. Additional searches in OpenGrey (gray literature database), preprint platforms (e.g., medRxiv), and reference lists of included studies did not yield any further eligible studies. After removing 141 duplicate records, 193 studies remained for initial screening. Two researchers independently screened the titles and abstracts, excluding 176 studies for the following reasons: non-OA study populations (39 studies), lack of IL-6 polymorphism analysis (87 studies), and study types not meeting inclusion criteria (e.g., reviews, case reports; 50 studies). After full-text screening, 17 studies were

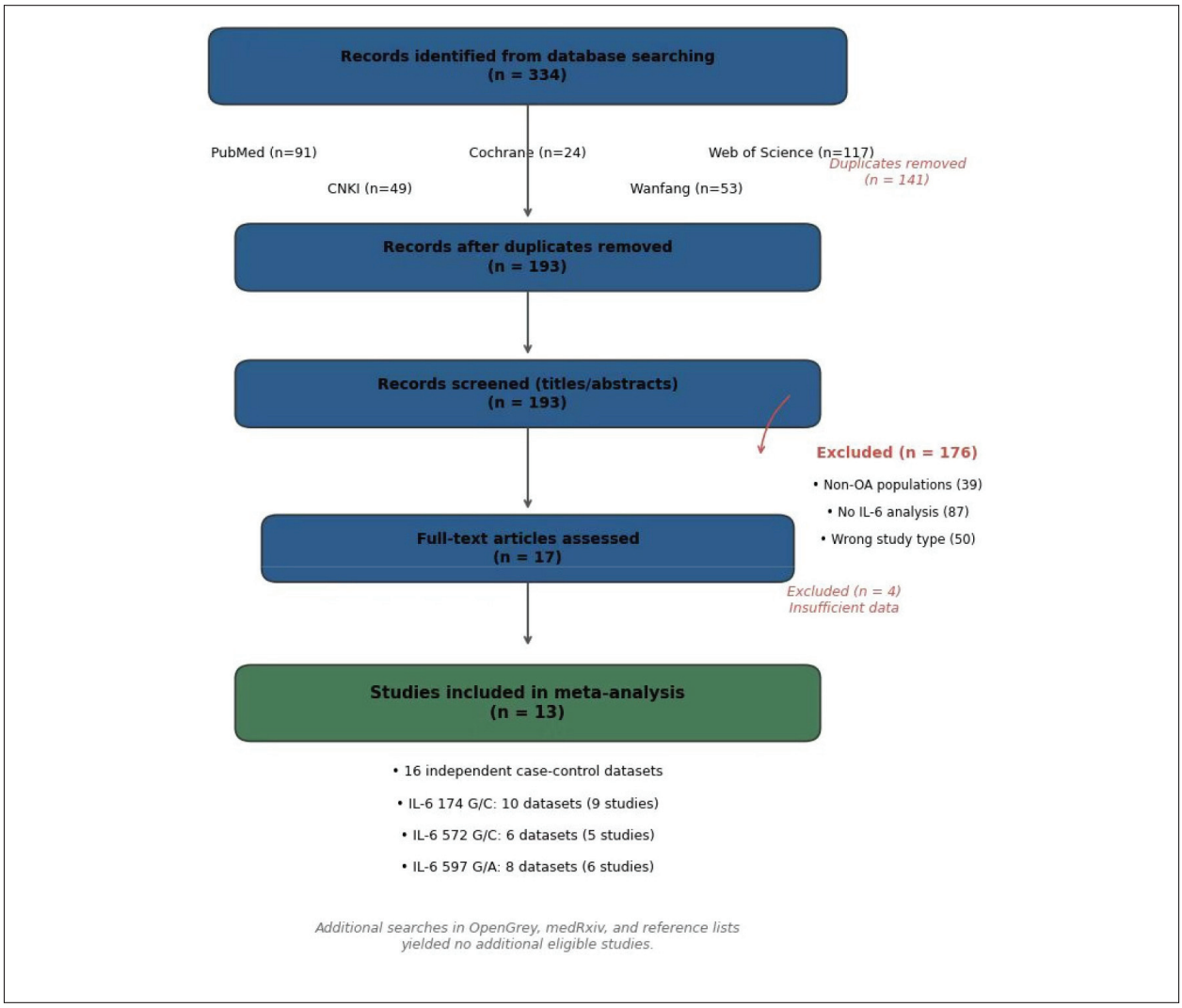

Figure 1 Flow diagram illustrating the literature screening and selection process based on PRISMA guidelines.

assessed for eligibility, with 4 studies excluded due to insufficient data or failure to meet inclusion criteria (lack of genotype frequency or effect size data). Ultimately, 13 case-control studies met the inclusion criteria and were included in the meta-analysis (13, 15, 23–33) (*Figure 1*).

Baseline Characteristics and Quality Assessment of Included Studies

The 13 included studies investigated three IL-6 gene polymorphisms: 174 G/C (rs1800795), 572 G/C (rs1800797), and 597 G/A (rs1800798), comprising a total of 16 independent case-control datasets (as some studies analyzed multiple polymorphisms or OA subtypes). Specifically, the IL-6 174 G/C polymorphism was examined in 9 studies encompassing 10 case-control datasets, including 7 on knee OA, 2 on hip OA, and 1 on distal interphalangeal joint OA. The IL-6 572 G/C polymorphism was assessed in 5 studies comprising 6 datasets, while the IL-6 597 G/A polymorphism was investigated in 5 studies with 8 datasets (including data from both knee and hip OA in the study by Limer et al.). Regarding study populations, the 174 G/C polymorphism was primarily examined in Asian (4 datasets) and Caucasian (6 datasets) populations, while studies on 572 G/C and 597 G/A polymorphisms were predominantly conducted in Caucasian populations. The mean age of case groups ranged from 44.0 to 70.4 years, while control groups had a mean age range of 21.0 to 71.7 years. Except for one study that exclusively included female participants, all other studies analyzed mixed-gender samples (13, 15, 23–33). Quality assessment using the modified Newcastle-Ottawa Scale (NOS) revealed that 4 studies were classified as high quality (≥12

Table I Characteristics of the Included Studies.

Included Study	Year	Country	Ethnicity	OA Subtype	Case/ Control (n)	Polymorphism	Genotyping Method	HWE (P)	NOS Score
Sun et al.	2019	China	Asian	Knee OA	150/150	rs1800795, rs1800797, rs1800798	PCR-RFLP	0.45	11
Singh et al.	2020	India	Asian	Knee OA	200/200	rs1800795, rs1800797	TaqMan	0.62	12
Yigit et al.	2023	Turkey	Caucasian	Knee OA	100/100	rs1800795, rs1800797	PCR-RFLP	0.08	10
Honsawek et al.	2011	Thailand	Asian	Knee OA	89/105	rs1800795	PCR	0.35	9
Lv et al.	2012	China	Asian	Knee OA	120/120	rs1800795	SNaPshot	0.51	10
Kolundžić et al.	2011	Croatia	Caucasian	Hip OA	75/80	rs1800795	PCR-RFLP	0.03*	9
Pola et al.	2005	Italy	Caucasian	Hip OA	112/120	rs1800795	PCR-RFLP	0.55	11
Badshah et al.	2021	Pakistan	Asian	Knee OA	150/150	rs1800795	PCR-CTPP	0.72	10
Kämäräinen et al.	2008	Finland	Caucasian	Hand OA	95/100	rs1800795, rs1800798	Sequencing	0.41	12
Tamm et al.	2008	Estonia	Caucasian	Knee OA	210/220	rs1800795	TaqMan	0.38	11
Syddall et al.	2005	UK	Caucasian	Hip OA	299/598	rs1800795	ELISA/ Genotyping	0.60	13
Limer et al.	2009	UK	Caucasian	Knee/ Hip OA	500/500	rs1800795, rs1800798	Illumina array	0.02*	14
Fernandes et al.	2015	Brazil	Mixed	Knee OA	100/100	rs1800795	PCR-RFLP	0.25	9

Note: HWE P < 0.05 indicates deviation from Hardy-Weinberg equilibrium. NOS: Newcastle-Ottawa Scale.

points), 9 as moderate quality (9–11 points), and 3 as low quality (<9 points). Among the included studies, 12 had control group genotype distributions conforming to Hardy-Weinberg equilibrium (HWE), while 4 did not. The detailed characteristics and quality scores ofthe included studies are summarized in *Table I* (13, 15, 23–33).

Meta-Analysis Results

IL-6 174 G/C (rs1800795)

This study included 10 case-control datasets from 9 studies examining the IL-6 174 G/C polymorphism, with 7 datasets from Caucasian populations and 2 from Asian populations. The pooled analysis showed no statistically significant association between IL-6 174 G/C and OA risk under the allelic (C vs. G), codominant (CC vs. GG), dominant (GC+CC vs. GG), recessive (CC vs. GC+GG), or overdominant (GC vs. GG+CC) genetic models (P > 0.05). Further subgroup analyses based on ethnicity (Asian vs. Caucasian populations) and OA subtype (knee OA vs. hip OA) also revealed no significant associations. Detailed results are presented in *Table II*.

IL-6 572 G/C (rs1800797)

A total of 6 case-control datasets from 5 studies were included in the meta-analysis of the IL-6 572 G/C polymorphism, covering both Caucasian and Asian populations. The results demonstrated a significant association between IL-6 572 G/C and reduced genetic susceptibility to OA under the dominant model (GC+CC vs. GG) (OR = 0.68, 95% CI: 0.48–0.97). Subgroup analysis by ethnicity did not reveal significant associations in either Asian or Caucasian populations. However, when stratified by OA subtype, the IL-6 572 G/C polymorphism exhibited a significant protective effect against knee OA

Table II Meta-analysis results of IL-6 rs1800795 (-174 G/C) polymorphism and OA risk.

Genetic Model	Studies (n)	OR (95% CI)	P-value	Heterogeneity (I^2)	Model
Allelic (C vs G)	10	0.96 (0.82–1.13)	0.64	38%	Random
Codominant (CC vs GG)	10	0.91 (0.73–1.14)	0.42	25%	Fixed
Dominant (GC+CC vs GG)	10	0.94 (0.78–1.13)	0.51	30%	Fixed
Recessive (CC vs GC+GG)	10	1.02 (0.85–1.22)	0.83	15%	Fixed
Overdominant (GC vs GG+CC)	10	0.98 (0.82–1.17)	0.82	22%	Fixed

Table III Meta-analysis results of IL-6 rs1800797 (-572 G/C) polymorphism and OA risk.

Genetic Model	**Subgroup**	**Studies (n)**	**OR (95% CI)**	**P-value**	**Heterogeneity (I^2)**
Dominant (GC+CC vs GG)	Overall	6	**0.68 (0.48–0.97)**	**0.03**	42%
	Asian	2	0.65 (0.42–0.98)	0.04	38%
	Caucasian	4	0.72 (0.45–1.15)	0.17	45%
	Knee OA	4	**0.57 (0.39–0.84)**	**0.01**	30%
	Hip OA	2	0.81 (0.55–1.19)	0.28	12%
Allelic (C vs G)	Overall	6	0.75 (0.55–1.02)	0.07	40%
	Knee OA	4	**0.67 (0.47–0.94)**	**0.02**	35%

Table IV Meta-analysis results of IL-6 rs1800798 (-597 G/A) polymorphism and OA risk.

Genetic Model	Studies (n)	OR (95% CI)	P-value	Heterogeneity (I^2)
Allelic (A vs G)	8	1.04 (0.89–1.22)	0.61	25%
Codominant (AA vs GG)	8	1.10 (0.85–1.42)	0.47	18%
Dominant (GA+AA vs GG)	8	1.02 (0.85–1.23)	0.81	20%
Recessive (AA vs GA+GG)	8	1.08 (0.90–1.30)	0.40	12%

(allelic model, C vs. G: 0.67, 95% CI: 0.47–0.94; dominant model, GC+CC vs. GG:OR = 0.57, 95% CI: 0.39–0.84), while no significant association was observed in hip OA. Detailed results are presented in *Table III*.

IL-6 597 G/A (rs1800798)

The meta-analysis of IL-6 597 G/A included 8 case-control datasets from 6 studies, primarily conducted in Caucasian populations (7 datasets) and one Asian population dataset. No significant association was found between IL-6 597 G/A and OA genetic susceptibility across all genetic models (allelic, A vs. G; codominant, AA vs. GG; dominant, GA+AA vs. GG; recessive, AA vs. GA+GG; and overdominant, GA vs. GG+AA; all $P > 0.05$). Subgroup analyses based on ethnicity and OA subtype further confirmed the absence of significant associations. Detailed results are presented in *Table IV*.

Publication Bias Assessment

Egger's test was conducted to assess publication bias. The results showed no significant publication bias across all genetic models ($P > 0.05$), indicating that the present study is not subject to substantial publication bias.

Discussion

This study conducted a systematic review and meta-analysis to evaluate the association between multiple polymorphic sites in the interleukin-6 (IL-6) gene promoter region (rs1800795, rs1800797, rs1800798) and genetic susceptibility to osteoarthritis (OA). The results indicate that IL-6 174 G/C (rs1800795) does not exhibit a statistically significant association with overall OA risk, regardless of the allelic, dominant, recessive models, or subgroup analyses. In contrast, IL-6 572 G/C (rs1800797) was found to be associated with a reduced OA risk under the dominant model, particularly demonstrating a significant protective effect in knee OA (KOA). Meanwhile, IL-6 597 G/A (rs1800798) showed no significant correlation with OA susceptibility. By integrating data from diverse populations across different ethnicities and regions, this study provides objective evidence supporting the genetic heterogeneity of IL-6 polymorphisms in OA and contributes to identifying potential preventive and therapeutic targets.

The pooled analysis of IL-6 174 G/C (rs1800795) revealed no consistent positive associations across allelic, dominant, recessive models, or subgroup analyses (ethnicity and joint type). This finding is inconsistent with some previous studies suggesting that the C allele may reduce the risk of hip or knee OA in European populations, while other studies have failed to replicate this protective effect in Caucasian cohorts (17, 34). The observed discrepancies may stem from population-specific linkage disequilibrium patterns, as well as gene-environment interactions, including obesity, joint injury, and mechanical strain (28, 34). Additionally, heterogeneity in study design, sample size, and outcome definitions could further influence the interpretation of the association at this locus. Previous research has highlighted that the IL-6 promoter region contains multiple functional single nucleotide polymorphisms (SNPs), which may exert synergistic or compensatory effects within different haplotype backgrounds. As a result, a single SNP may not fully account for phenotypic variation across all populations (28). Therefore, further studies with larger sample sizes and multi-locus haplotype analyses are warranted to provide a more comprehensive understanding ofrs1800795 and its role in OA susceptibility.

In contrast, IL-6 572 G/C (rs1800797) demonstrated a significant inverse association with OA risk in this study, particularly in the knee OA (KOA) subgroup, where individuals carrying the C allele exhibited a lower risk of KOA. Experimental evidence suggests that IL-6 is a key pro-inflammatory cytokine, and downregulation of its expression due to certain genetic mutations (such as -572 G/C) may alleviate local synovial inflammation and reduce the release of matrix metalloproteinases (MMPs), thereby exerting a protective effect on cartilage tissue (28). Given that KOA is more susceptible to mechanical loading and localized inflammation, the protective effect of -572 G/C is particularly pronounced in this joint type (35). Several previous studies have reported findings consistent with this study, suggesting that the -572 CC genotype confers a protective effect in certain populations, further indicating that this locus may play a critical role in the onset and progression of KOA (17, 36).

For the IL-6 597 G/A (rs1800798) polymorphism, this study found no significant association with OA risk across different ethnic groups, joint types, or genetic models. While some studies have suggested that this variant may be associated with IL-6 protein levels, its effect appears to be relatively limited. Additionally, certain reports propose that rs1800798 may act in conjunction with other cytokine pathways rather than independently determining OA susceptibility (28). At present, the overall contribution of 597 G/A to OA risk appears minimal. Further research, including functional studies and large-scale population analyses, is necessary to investigate its potential interactions with other polymorphisms and environmental factors, enabling a more precise evaluation of its role in OA pathogenesis.

It is important to note that research on IL-6 gene polymorphisms and OA risk has yet to reach a definitive consensus, with considerable discrepancies among different studies. Reports have demonstrated substantial variation in locus effects; for instance, IL-6 -174 G/C has been repeatedly found to lack a robust association in Asian populations, whereas it may confer a protective effect in European populations (37). Similarly, IL-6 -572 G/C has been frequently associated with a significant inverse correlation in knee OA, while findings for hip OA and other joint sites remain inconsistent (38).

Additionally, gene-environment interactions should not be overlooked when interpreting these divergent findings. Factors such as obesity, joint trauma, and occupational strain may exert synergistic or antagonistic effects with IL-6 polymorphisms (39). Furthermore, interactions between IL-6 and other cytokines (e.g., IL-1β, TNF-α, IL-8) or bone metabolism genes (e.g., MMP-13) may contribute to variability in different populations, joint types, or disease stages.

Several studies suffer from small sample sizes, regional or ethnic limitations, variations in inclusion criteria, and differences in baseline characteristics, all of which may result in reduced statistical power and fluctuating effect estimates (40). Additionally, inconsistencies in sequencing or genotyping methods, along with publication bias, may further amplify discrepancies in findings across studies (40). Future

research incorporating larger-scale, multi-center studies with rigorous designs, as well as statistical models accounting for potential confounders, is crucial to addressing these controversies and heterogeneities (40).

The pathogenesis of OA is generally regarded as a combination of cartilage matrix degradation and chronic inflammatory responses, with IL-6 playing a pivotal role in disease progression. Studies have shown that IL-6 acts synergistically with TNF-α and IL-1β to promote extracellular matrix degradation, thereby accelerating joint structural damage and synovial inflammation (41). The differential effects of IL-6 polymorphisms observed in this study further reflect the multifactorial nature of OA pathogenesis. For example, -572 G/C may exert a protective effect by downregulating IL-6 transcription, whereas whether -174 G/C upregulates IL-6 expression in specific ethnic or environmental contexts remains controversial. Moreover, the interactions between IL-6 polymorphisms and MMP-13, IL-1β, or other genes may be modulated by mechanical loading, obesity, and joint injury, creating a complex and dynamic regulatory network (39). If future studies can further validate the protective effect of -572 G/C in KOA, genetic testing could be considered as an early screening tool to identify high-risk individuals who are more likely to benefit from this protective variant. Targeted interventions, such as weight management and modified physical activity strategies, could then be implemented to delay the onset and progression of OA.

In certain contexts, IL-6 gene polymorphisms have been considered potential biomarkers or therapeutic targets. Several studies, including the findings of this meta-analysis, suggest that IL-6 polymorphisms are closely associated with OA risk and disease severity. The combined detection of serum or synovial IL-6 levels alongside genetic screening may enhance the accuracy of early disease identification and progression monitoring (42). Notably, the -572 G/C polymorphism has demonstrated a relatively consistent protective effect in KOA. If future research further validates its mechanistic role and clinical applicability, it could facilitate early stratification of high-risk populations based on genetic profiling (16).

Moreover, IL-6 is not only a pro-inflammatory cytokine but also contributes to cartilage degradation and angiogenesis, making it a promising therapeutic target for OA intervention (14). Monoclonal antibodies and antagonists targeting IL-6 or its receptor have already shown preliminary efficacy in other joint diseases, such as rheumatoid arthritis. Integrating specific IL-6 gene polymorphisms into future personalized interventions could potentially enhance therapeutic efficacy while minimizing adverse effects (43).

Despite its potential, the clinical application of IL-6 polymorphisms faces several challenges. First, genetic frequencies and linkage disequilibrium patterns vary across populations and environmental contexts, necessitating large-scale, multi-center validation studies before generalizing findings to diverse populations. Second, OA is a multifactorial disease involving multiple genes and interconnected biological pathways. A single genetic biomarker is insufficient for comprehensive risk assessment or treatment decision-making; thus, IL-6 polymorphisms must be integrated with other key genetic markers, clinical parameters, and imaging assessments. Third, genetic testing and long-term monitoring inevitably increase healthcare costs and raise ethical considerations. Therefore, cost-effectiveness analysis and patient preferences must be incorporated into decision-making to optimize precision medicine approaches.

Several limitations should be acknowledged in this study. Heterogeneity remains a concern due to variations in study populations, diagnostic criteria, genotyping methods, and statistical models. Additionally, the sample size of some included studies was relatively small, leading to substantial external heterogeneity. This meta-analysis also did not quantitatively assess gene-environment interactions, as specific environmental and lifestyle factors were not extensively considered. Although this study provides evidence supporting the protective effect of IL-6 572 G/C polymorphism in certain populations, its underlying molecular mechanisms require further validation through in vitro and in vivo experimental studies. Furthermore, while Egger's test did not indicate significant publication bias, the potential omission of small-sample or negative-result studies cannot be ruled out. This could have influenced the pooled effect size estimates to some extent. Future research should aim for larger-scale, rigorously designed studies to address these limitations and provide stronger evidence for the genetic role of IL-6 in OA susceptibility and progression.

Conclusion

Overall, IL-6 572 G/C may confer a protective effect against knee OA, while IL-6 174 G/C and IL-6 597 G/A show no consistent associations with OA susceptibility. Given the highly complex pathogenesis of OA, the role of IL-6 is likely influenced by multiple genetic and environmental factors. This study provides a foundation for future large-scale, multi-center genetic investigations and molecular mechanistic studies. Additionally, within the framework of precision medicine, focusing on key IL-6 polymorphic sites may offer earlier and more personalized intervention opportunities.

Abbreviations

ACR: American College of Rheumatology; **CI**: Confidence Interval; **CNKI**: China National Knowledge Infrastructure; **HWE**: Hardy-Weinberg Equilibrium; **IL-6**: Interleukin-6; **IL-1β**: Interleukin-1 Beta; **KOA**: Knee Osteoarthritis; **MMPs**: Matrix Metalloproteinases; **NOS**: Newcastle-Ottawa Scale; **OA**: Osteoarthritis; **OR**: Odds Ratio; **PRISMA**: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SNP**: Single Nucleotide Polymorphism; **TNF-α**: Tumor Necrosis Factor Alpha

Funding

This work was supported by The 2022 Hainan Provincial Natural Science Foundation Youth Fund Project (Grant no. 822QN466).

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

References

1. Geng R, Li J, Yu C, Zhang C, Chen F, Chen J, et al. Knee osteoarthritis: Current status and research progress in treatment (Review). Exp Ther Med 2023; 26(4): 481.
2. Cao B, Liu G, Gao K, Fan W, Zhao W, Wang B. The Role of Extracellular Vesicles Derived from MicroRNA-146a-modified Mesenchymal Stem Cells in Modulating Inflammation in Experimental Glenohumeral Osteoarthritis. Iran J Allergy Asthma Immunol 2024; 23(5): 578–87.
3. Hunter DJ, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. Rheumatic Diseases Clinics of North America 2008; 34(3): 623–43.
4. GBD OMDC. Global, regional, and national burden of other musculoskeletal disorders, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol 2023; 5(11): e670–82.
5. Noori E, Atabaki M, Dehnavi S, Tavakol Afshari J, Mohammadi M. The Immunomodulatory Effects of Curcumin on Forkhead Box O1 and MicroRNA-873 in Patients with Osteoarthritis. Iran J Allergy Asthma Immunol 2024; 23(5): 526–35.
6. Guilak F. Biomechanical factors in osteoarthritis. Best Practice & Research. Clinical Rheumatology 2011; 25(6): 815–23.
7. Molnar V, Matišić V, Kodvanj I, Bjelica R, Jeleč Ž, Hudetz D, et al. Cytokines and Chemokines Involved in Osteoarthritis Pathogenesis. International Journal of Molecular Sciences 2021; 22(17): 9208.
8. Wiegertjes R, van de Loo FAJ, Blaney Davidson EN. A roadmap to target interleukin-6 in osteoarthritis. Rheumatology (Oxford, England) 2020; 59(10): 2681–94.
9. Wang ZW, Chen L, Hao XR, Qu ZA, Huang SB, Ma XJ, et al. Elevated levels of interleukin-1β, interleukin-6, tumor necrosis factor-α and vascular endothelial growth factor in patients with knee articular cartilage injury. World J Clin Cases 2019; 7(11): 1262–9.
10. Li F, Xu J, Zheng J, Sokolove J, Zhu K, Zhang Y, et al. Association between interleukin-6 gene polymorphisms and rheumatoid arthritis in Chinese Han population: a case-control study and a meta-analysis. Sci Rep-Uk 2014; 4: 5714.
11. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. BMJ (Clinical Research Ed.) 1996; 312(7036): 940–3.
12. Khatir K, Aghaei M, Ghorbanhosseini SS, Shafiee F. In vitro Evaluation of the Cytotoxic Effects of a Recombinant form of the Soluble Mutant IL-6 Receptor on an Ovarian Cancer Cell Line. Iran J Biotechnol 2025; 23(1): e3953.
13. Sun G, Ba CL, Gao R, Liu W, Ji Q. Association of IL-6, IL-8, MMP-13 gene polymorphisms with knee osteoarthritis susceptibility in the Chinese Han population. Bioscience Rep 2019; 39(2): BSR20181346.
14. Deng X, Ye K, Tang J, Huang Y. Association of rs1800795 and rs1800796 polymorphisms in interleukin-6 gene and osteoarthritis risk: evidence from a meta-analysis. Nucleosides, Nucleotides & Nucleic Acids 2023; 42(4): 328–42.
15. Singh M, Mastana S, Singh S, Juneja PK, Kaur T, Singh P. Promoter polymorphisms in IL-6 gene influence pro-inflammatory cytokines for the risk of osteoarthritis. Cytokine 2020; 127: 154985.
16. Yigit S, Tekcan A, Inanir A, Nursal AF, Akkanat S, Tural E. Effect of IL-6 -174G/C and -572G/C variants on susceptibility to osteoarthritis in Turkish population. Nucleosides, Nucleotides & Nucleic Acids 2023; 42(1): 65–76.
17. Valdes AM, Arden NK, Tamm A, Kisand K, Doherty S, Pola E, et al. A meta-analysis of interleukin-6 promoter polymorphisms on risk of hip and knee osteoarthritis. Osteoarthr Cartilage 2010; 18(5): 699–704.
18. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev-London 2015; 4(1): 1.

19. Harris RJ, Bradburn MJ, Deeks JJ, Harbord RM, Sterne JAC. Metan: Fixed- and random-effects meta-analysis. Stata J 2008; 8(1): 3–28.

20. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health 2014; 72(1): 39.

21. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56(2): 455–63.

22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical Research Ed.) 1997; 315(7109): 629–34.

23. Lv C, Xu X, Wang J, Zhang Z, Zhang D, Guo C, et al. Combined effect of cytokine gene polymorphisms on end-stage knee osteoarthritis from Chinese Han population. Rheumatol Int 2012; 32(11): 3625–9.

24. Honsawek S, Deepaisarnsakul B, Tanavalee A, Yuktanandana P, Bumrungpanichthaworn P, Malila S, et al. Association of the IL-6 -174G/C gene polymorphism with knee osteoarthritis in a Thai population. Genet Mol Res 2011; 10(3): 1674–80.

25. Kolundžić R, Trkulja V, Mikolaučić M, KolundŽić MJ, Pavelić SK, Pavelić KI. Association of interleukin-6 and transforming growth factor-β1 gene polymorphisms with developmental hip dysplasia and severe adult hip osteoarthritis: a preliminary study. Cytokine 2011; 54(2): 125-8.

26. Pola E, Papaleo P, Pola R, Gaetani E, Tamburelli FC, Aulisa L, et al. Interleukin-6 gene polymorphism and risk of osteoarthritis of the hip: a case-control study. Osteoarthr Cartilage 2005; 13(11): 1025–8.

27. Badshah Y, Shabbir M, Hayat H, Fatima Z, Burki A, Khan S, et al. Genetic markers of osteoarthritis: early diagnosis in susceptible Pakistani population. J Orthop Surg Res 2021; 16(1): 124.

28. Kämäräinen OP, Solovieva S, Vehmas T, Luoma K, Riihimäki H, Ala-Kokko L, et al. Common interleukin-6 promoter variants associate with the more severe forms of distal interphalangeal osteoarthritis. Arthritis Res Ther 2008; 10(1): R21.

29. Tamm A, Lintrop M, Veske K, Hansen U, Tamm A. Prevalence of patello- and tibiofemoral osteoarthritis in Elva, Southern Estonia. J Rheumatol 2008; 35(3): 543–4.

30. Syddall HE, Aihie Sayer A, Dennison EM, Martin HJ, Barker DJP, Cooper C. Cohort profile: the Hertfordshire cohort study. Int J Epidemiol 2005; 34(6): 1234–42.

31. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. J Rheumatol 1993; 20(2): 331–5.

32. Limer KL, Tosh K, Bujac SR, McConnell R, Doherty S, Nyberg F, et al. Attempt to replicate published genetic associations in a large, well-defined osteoarthritis case-control population (the GOAL study). Osteoarthr Cartilage 2009; 17(6): 782–9.

33. Fernandes MTP, Fernandes KBP, Marquez AS, Cólus IMS, Souza MF, Santos JOPM, et al. Association of interleukin-6 gene polymorphism (rs1800796) with severity and functional status of osteoarthritis in elderly individuals. Cytokine 2015; 75(2): 316–20.

34. Gan GG, Subramaniam R, Lian LH, Nadarajan V. Ethnic variation in interleukin-6 -174 (g/c) polymorphism in the malaysian population. Balk J Med Genet 2013; 16(2): 53–8.

35. Singh A, Antony B. Response to the letter to editor by Chen et al. regarding: Burden of osteoarthritis in India and its states, 1990-2019: findings from the Global Burden of Disease Study 2019. Osteoarthr Cartilage 2022; 30(10): 1413–4.

36. Liao Y, Ren Y, Luo X, Mirando AJ, Long JT, Leinroth A, et al. Interleukin-6 signaling mediates cartilage degradation and pain in posttraumatic osteoarthritis in a sex-specific manner. Sci Signal 2022; 15(744): eabn7082.

37. Tabikhanova LE, Osipova LP, Churkina TV, Kovalev SS, Filipenko ML, Voronina EN. Increased Frequencies of the –174G and –572C IL6 Alleles in Populations of Indigenous Peoples of Siberia Compared to Russians. Mol Biol+ 2023; 57(2): 329–37.

38. Salari N, Mansouri K, Hosseinian-Far A, Ghasemi H, Mohammadi M, Jalali R, et al. The effect of polymorphisms (174G> C and 572C> G) on the Interleukin-6 gene in coronary artery disease: a systematic review and meta-analysis. Genes Environ 2021; 43(1): 1.

39. Yang H, Zhou X, Xu D, Chen G. The IL-6 rs12700386 polymorphism is associated with an increased risk of developing osteoarthritis in the knee in the Chinese Han population: a case-control study. Bmc Med Genet 2020; 21(1): 199.

40. Harun-Or-Roshid M, Ali MB, Jesmin, Mollah MNH. Statistical meta-analysis to investigate the association between the Interleukin-6 (IL-6) gene polymorphisms and cancer risk. Plos One 2021; 16(3): e0247055.

41. Chow YY, Chin KY. The Role of Inflammation in the Pathogenesis of Osteoarthritis. Mediat Inflamm 2020; 2020: 8293921.

42. Tudor K, Baranasic J, Knezevic J, Serer Vicevic M, Sutic M, Dembic Z, et al. Indirect influence of microRNA-146a on the association of IL-6 and TNF-α genetic polymorphisms with the increased risk of hip osteoarthritis. Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society 2024; 42(7): 1482–9.

43. Lee HJ, Kim DEY, Noh HJ, Lee SY, Yoo JA, Won SJ, et al. Elevated IL-6 Expression in Autologous Adipose-Derived Stem Cells Regulates RANKL Mediated Inflammation in Osteoarthritis. Cells-Basel 2024; 13(24): 2046.

Received: April 12, 2026
Accepted: May 19, 2026