Associations between circulating interleukin-17 levels and Behçet's disease and between IL-17 gene polymorphisms and disease susceptibility: a meta-analysis

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Abstract

Objective

To systematically investigate the relationship between circulating interleukin-17 (IL-17) levels and Behçet's disease (BD) and the associations between polymorphisms in IL17 *genes and BD susceptibility.*

Method

We searched the Medline, Embase, and Cochrane databases for relevant articles. We performed a meta-analysis of serum/plasma IL-17 levels in BD patients and controls and evaluated the associations between IL17A *rs4711998, rs8193036, and rs2275913 and* IL17F *rs763780 and rs2397084 polymorphisms and the risk of BD.*

Results

Twelve studies, involving 901 patients with BD and 1,131 controls, were included. Our meta-analysis revealed that circulating IL-17 levels were significantly higher in the BD group than in the control group (SMD=1.422, 95% confidence interval [CI]=0.689–2.155, p<0.001). Subgroup analysis by data type indicated higher IL-17 levels in the BD group in both the original and calculated data populations. Stratification by publication year revealed significantly lower vitamin D levels in the SSc group in both recent and older publication years. No significant differences in IL-17 levels were observed between the active and inactive disease groups. We found no evidence of associations between BD and IL17A *rs2275913, L17F rs763780, or rs2397084 polymorphisms. However, a significant association was found between BD and* IL17A *rs4711998 and rs8193036 polymorphisms in the pooled cohort of affected individuals compared to that in pooled controls (odds ratio [OR]=1.347, 95% CI=1.043–1.741, p<0.001; OR=0.691, 95% CI=0.542–0.880, p=0.003).*

Conclusion

This meta-analysis revealed significantly higher circulating IL-17 levels in BD patients and showed evidence of associations between IL17A *rs4711998 and rs8193036 polymorphisms and BD.*

Key words

Behçet's disease, IL-17, polymorphism

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Introductin

Behçet disease (BD) is a chronic inflammatory disorder characterised by recurrent oral and genital ulcers, skin lesions, and ocular inflammation (1). Although the pathogenesis of BD is not fully understood, it is thought to be related to abnormal immune responses triggered by environmental factors in genetically susceptible individuals. Among the various cytokines involved in the pathogenesis of BD, interleukin (IL)-17 has gained increasing attention in recent years.

IL-17 is a proinflammatory cytokine secreted by Th17 and other immune cells, including Tc17, γδ T, and innate lymphoid cells (2). IL-17 has been shown to promote neutrophil recruitment and activation, stimulate the production of other proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, and induce the expression of adhesion molecules and chemokines on endothelial cells, leading to the recruitment of immune cells to the site of inflammation (3).

Several studies have reported increased levels of IL-17 in the serum and tissues of patients with BD, suggesting that IL-17 plays a crucial role in the pathogenesis of BD. IL-17 levels are positively correlated with disease activity and severity in BD, and the expression of IL-17 and its receptors is increased in lesions of patients with BD (4-11). In addition to circulating IL-17 levels, genetic variations in *IL17A* and *IL17F* genes have been investigated in relation to BD susceptibility (12-15). *IL17A* and *IL17F* encode IL-17A and IL-17F, respectively. Polymorphisms in these genes may affect their function or expression, potentially altering the Th17 immune response and increasing the risk of BD development (16).

However, studies investigating circulating IL-17 levels in patients with BD and testing polymorphisms in different IL17-encoding genes have yielded mixed results (4-15). This disparity may be attributed to small sample sizes, low statistical power, and/or clinical heterogeneity (17-19). Thus, we performed a meta-analysis to overcome the limitations of individual studies and resolve the inconsistencies in their findings. The aim of our meta-analysis was to systematically review the available evidence on serum/plasma IL-17 levels in patients with BD compared to those found in controls and to determine whether polymorphisms in IL17-encoding genes are associated with BD susceptibility.

Methods

Identification of eligible studies and data extraction

We performed a literature search for studies that examined IL-17 levels in patients with BD and healthy controls, evaluated the relationship between circulating (serum or plasma) IL-17 levels, and tested for associations between polymorphisms in IL17 genes and BD. The Medline, Embase, and Cochrane databases were searched to identify all available articles (From inception to March 2023). The following key words and terms were used in the search: "interleukin-17," "serum OR plasma OR circulating," "polymorphism," and "Behçet's disease." In addition, all cited references were reviewed to identify additional studies not included in the abovementioned electronic databases. Studies were considered eligible based on the following inclusion criteria: (1) case-control, cohort, or cross-sectional studies; (2) provided data on circulating IL-17 levels in both the affected and control groups; and (3) tested IL17 gene polymorphisms in BD and control groups. Studies were excluded if (i) they contained overlapping or insufficient data or (ii) they were reviews or case reports. Data on methods and results were extracted from the original studies by two independent reviewers. Discrepancies between the reviewers were resolved through consensus. The following information was extracted from each study: primary author, year of publication, country, ethnicity, adjustments for age and sex, number of participants, mean and standard deviation (SD) of IL-17 levels, and allele and genotype frequencies of polymorphisms in IL17 genes. When data were presented as medians, interquartile ranges or ranges were used, and when data were presented as means, SD were derived using previously described formulas (20, 21). The Newcastle-Ottawa

Scale was used to assess the quality of each study (22). We performed the meta-analysis in accordance with the PRISMA guidelines (23).

Evaluation of statistical associations

We performed a meta-analysis to examine the relationship between IL-17 levels and BD and evaluate the allelic effect of the minor allele versus the major allele of different polymorphisms in IL17 genes. For data continuity, the results were presented as standardised mean differences (SMDs) and 95% confidence intervals (CIs). Odds ratios (ORs) and 95% CIs were calculated for the dichotomous data. Within-study and between-study variations and heterogeneity were assessed using the Cochran's statistics (24). A heterogeneity test was used to assess the null hypothesis that all studies evaluated the same effect. When the Q-statistic was significant (p<0.10), indicating heterogeneity across studies, a random-effects model was used for the meta-analysis; otherwise, a fixed-effects model was used (25). All studies estimated the same underlying effect and specifically considered within-study variations (24). We quantified the effect of heterogeneity using I^2=100% x (Q-df)/Q (26), where I^2 is a measure of the degree of inconsistency between studies and determines whether the percentage of total variation across studies was due to heterogeneity. I^2 ranged from 0% to 100%. I^2 values of 25%, 50%, and 75% referred to low, moderate, and high estimates, respectively (26). Statistical analyses were performed using the Comprehensive Meta-Analysis Programme (BioStat, Englewood, NJ, USA).

Evaluation of heterogeneity, sensitivity test and publication bias

To examine the potential sources of heterogeneity observed in the meta-analysis, a meta-regression analysis was performed using the following variables: ethnicity, adjustment for age and/or sex, publication year, sample size, and data type. A sensitivity test was performed to assess the influence of each study on the pooled effect size by omitting each study individually. Although funnel plots are often used to detect publication bias, they require diverse study types with varying sample sizes, and their interpretation involves subjective judgment. Therefore, we assessed publication bias using the Egger's linear regression test (27), which measures funnel plot asymmetry using a natural logarithmic scale of effect size.

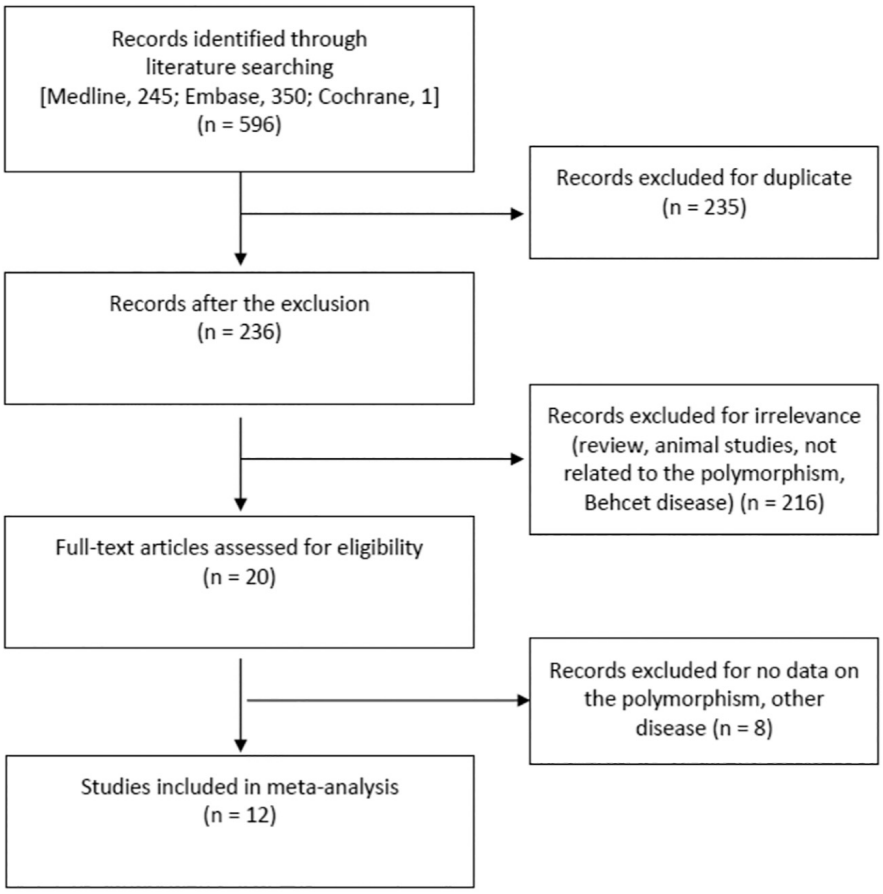

Fig. 1. Flow diagram of the study selection process.

Results

Studies included in the meta-analysis

We identified 596 studies using electronic and manual search methods, of which 20 were selected for full-text review based on the title and abstract, and 8 were excluded because they either lacked data or provided duplicate data. Therefore, 12 articles met the inclusion criteria (4-15) (Fig. 1). The included studies had 901 patients with BD and 1,131 controls (Table I). Eight studies examined IL-17 levels in the affected and control groups, and four studies evaluated polymorphisms in *IL17* genes in both the BD and control groups (Table I). A meta-analysis of *IL17*-related polymorphisms was performed if there were at least two comparisons. Due to the limited number of candidate gene association studies, four types of meta-analyses were performed: rs4711998, rs8193036, and rs2275913 in *IL17A* and rs763780 and rs2397084 in *IL17F*. Each study received a score between 5 and 7 on the quality rating scale. The characteristic features of the studies included in this meta-analysis are summarised in Table I.

Meta-analysis of circulating IL-17 levels in patients with BD compared to those in controls

Using meta-analysis, we found that circulating IL-17 levels were significantly higher in the BD group than in the control group (SMD=1.422, 95% CI=0.689–2.155, p<0.001) (Table II, Fig. 2). Stratification based on ethnicity revealed higher IL-17 levels in the BD group among Asians but not in Arab and European populations (Table II). Subgroup analysis by data type indicated higher IL-17 levels in patients

Table I. Individual study characteristics analysed in the meta-analysis.

A. Circulating IL-17 level

Authors	Country	Ethnicity	Number			Result	
			Case	Control	SMD	Magnitude*	*p*-value
Jadideslam, 2020 (4)	Iran	Arab	46	70	0.683	Medium	<0.001
Talaat, 2019 (5)	Egypt	Arab	44	20	0.086	Small	0.750
Choi, 2017 (6)	Korea	Asian	13	19	0.897	Large	0.017
Gholijani, 2017 (7)	Iran	Arab	44	44	2.486	Large	<0.001
Zou, 2016 (8)	China	Asian	10	10	2.204	Large	<0.001
Mesquida, 2014 (9)	Spain	European	13	20	3.851	Large	<0.001
Ozyurt, 2014 (10)	Turkey	European	30	20	0.625	Medium	0.034
Na, 2013 (11)	Korea	Asian	11	10	1.167	Large	0.014

SMD: standardised mean difference. * Magnitude of Cohen's d effect size: 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥0.8, large effect.

B. IL-17 polymorphisms

Authors	Country	Ethnicity	Number		IL-17 gene and polymorphism tested			Statistical findings (*p*-value)		
			Case	Control						
Arikan, 2023 (12)	Turkey	European	88	133	IL-17A rs2275913,	rs4711998, IL-17F	rs8193036, rs76370,	rs8193036, rs2397084	rs2397084	(*p*<0.05), others (NS)
Kim, 2012 (13)	Korea	Asian	141	259	IL-17A	rs4711998,	rs8193036,	rs2275913	rs8193036	(*p*<0.05), others (NS)
Shu, 2010 (14)	China	Asian	362	412	IL-17A	rs763780		NS		
Jang, 2008 (15)	Korea	Asian	99	114	IL-17F r	s2397084,	rs763780	rs2397084	(*p*<0/05),	other (NS)

NS: not significant.

Table II. Meta-analysis of the association between IL-17 levels and Behçet's disease.

Groups	Population	No. of studies	Test of association			Test of heterogeneity		
			SMD*	95% CI	*p*-value	Model	*p*-value	I^2
All	Overall	8	1.422	0.689-2.155	< 0.001	R	< 0.001	90.0
Ethnicity	Asian	3	1.258	0.745-1.770	< 0.001	F	0.154	46.4
	Arab	3	1.078	-0.196-2.352	0.097	R	< 0.001	95.1
	European	2	2.197	-1.963-5.357	0.173	R	< 0.001	95.7
Data type	Original	6	1.309	0.614-2.005	< 0.001	R	< 0.001	85.6
	Calculated	2	1.931	-1.757-5.620	0.305	R	< 0.001	97.0
Publication year	Recent (≥ 2017)	4	1.034	0.048-2.002	0.040	R	< 0.001	92.7
	Old (≤ 2016)	4	1.901	-0.558-3.244	0.006	R	< 0.001	88.5
Disease activity	Active vs. inactive	5	0.461	-0.070-0.992	0.089	R	0.017	66.8

SMD: standardised mean difference; F: fixed effects model; R: random effects model; NA: not available.
*magnitude of Cohen's d effect size (SMD): 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥0.8, large effect.

with BD in the original and calculated data populations (Table II). No significant differences in the IL-17 levels were observed between the active and inactive disease groups (Table II).

Meta-analysis of IL17A rs4711998, rs8193036, and rs2275913 and IL17F rs763780 and rs2397084 polymorphisms and BD susceptibility

This meta-analysis showed a significant association between BD and *IL17A* rs4711998 and rs8193036 polymorphisms in a pooled cohort of affected individuals compared with those found in pooled controls (OR=1.347, 95% CI=1.043–1.741, *p*<0.001; OR=0.691, 95% CI=0.542–0.880, *p*=0.003, respectively) (Table III, Fig. 3). However, the meta-analysis revealed no evidence of an association between the *IL17A* rs2275913, *L17F* rs763780, and rs2397084 polymorphisms and BD susceptibility (Table III, Fig. 3).

Heterogeneity and publication bias

Between-study heterogeneity was identified in the meta-analysis of IL-17 levels in patients with BD (Table II). Meta-regression analysis showed that data type, sample size, and publication year affected heterogeneity in our meta-analysis of IL-17 levels in patients with BD. Sensitivity analysis showed that no individual study significantly affected the pooled SMD, indicating that the results of this meta-analysis were robust. No heterogeneity was found in the meta-analyses of polymorphisms in *IL17* genes, except for rs2397084 in *IL17F* (Table III). Publication bias results from a disproportionate number of positive studies and poses a problem for meta-analyses. However, we found no evidence of publication bias for any

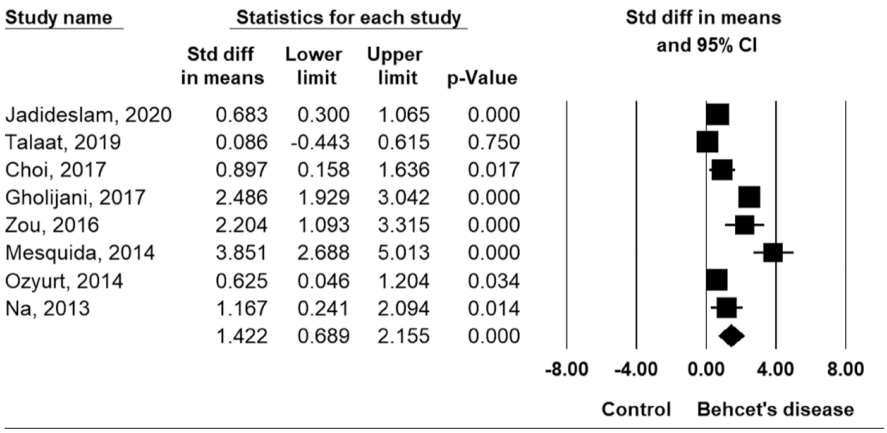

Fig. 2. Meta-analysis of the relationship between circulating IL-17 levels and BD.

of the study participants (*i.e.* the funnel plot showed no evidence of asymmetry, and the Egger's regression test showed all $p>0.05$).

Discussion

The findings from the meta-analysis of circulating IL-17 levels in patients with BD compared with those in controls are interesting. Notably, the results showed significantly higher IL-17 levels in the BD group than in the control group. Subgroup analysis according to ethnicity showed that this difference was more pronounced in Asian populations. The meta-analysis revealed no significant difference in IL-17 levels between patients with active and inactive diseases. In contrast, a meta-analysis of *IL17A* and *IL17F* polymorphisms in BD susceptibility showed a significant association between BD and *IL17A* rs4711998 and rs8193036 polymorphisms. However, no evidence of an association was found between the *IL17A* rs2275913, *IL17F* rs763780, and rs2397084 polymorphisms and BD susceptibility. These findings suggest that genetic variations in *IL17A* are involved in the development of BD, consistent with the role of IL-17 in the pathogenesis of this disease.

The IL-17 signalling pathway plays a critical role in immune responses and inflammation. It involves a complex network of genes and molecules, including IL-23, IL-17 receptors, and intracellular signalling pathways (2). IL-23 is a cytokine that belongs to the IL-12 family and consists of two subunits: p19 (IL-23A) and p40 (shared with IL-12). It is primarily produced by antigen-presenting cells such as dendritic cells, macrophages, and monocytes (3). IL-23 acts as a critical upstream regulator of the IL-17 signalling pathway by stimulating the production of IL-17. IL-17 cytokines bind to a heteromeric receptor complex known as the IL-17 receptor (IL-17R). IL-17R subunits are expressed on a variety of cells, including epithelial cells, fibroblasts, endothelial cells, and immune cells. IL-17A and IL-17F are the two major members of the IL-17 cytokine family. They are secreted by T-helper 17 (Th17) cells, γδ T cells, natural killer (NK) cells, and other immune cells. IL-17A and IL-17F bind to the IL-17 receptor complex, primarily engaging IL-17RA and IL-17RC subunits. The binding of IL-17A or IL-17F to the IL-17 receptor leads to the activation of downstream signalling pathways. The IL-17 signalling pathway activates several intracellular signalling pathways that regulate immune responses and inflammation. The key signalling pathways involved are NF-κB pathway, MAPK pathway, and C/EBP and AP-1 pathways.

The mechanism underlying the higher circulating IL-17 levels in patients with BD may involve dysregulation of the Th17 immune response. There are some factors to consider in exploring the genetic influences on IL-17 levels among different ethnic populations. Genetic polymorphisms in genes involved in the IL-17 signalling pathway can potentially contribute to variations in IL-17 levels. Single nucleotide polymorphisms or other genetic variations in these genes may affect their expression or function, leading to altered IL-17 production. The haplotype diversity across IL-17-related genes within different ethnic populations can provide insights into potential genetic variations associated with IL-17 levels. Genetic differences in IL-17-related genes may interact with environmental factors, such as diet, lifestyle, and exposure to pathogens or environmental toxins. Gene-environment interactions may differently influence IL-17 levels across various ethnic backgrounds.

IL-17 is a cytokine produced by the Th17 cells and plays a role in the regulation of immune responses and inflammation. Th17 cells are a subset of T-helper cells that produce IL-17 and other proinflammatory cytokines and play a critical role in the pathogenesis of autoimmune diseases, including BD

Table III. Meta-analysis of tests of association between polymorphisms in *IL17* genes and Behçet's disease.

Polymorphism		Population	No. of studies	Test of association			Test of heterogeneity		
				OR	95% CI	*p*-value	Model	*p*-value	I^2
IL-17A rs4711998	G *vs.* A	Pooled	3	1.347	1.043-1.741	0.047	F	0.828	0
IL-17A rs8193036	C *vs.* T	Pooled	2	0.961	0.542-0.880	0.003	F	0.311	2.65
IL-17A rs2275913	A *vs.* G	Pooled	2	0.832	0.633-1.093	0.186	F	0.941	0
IL-17F rs763780	C *vs.* T	Pooled	2	0.998	0.782-1.273	0.986	F	0.795	0
IL-17F rs2397084	C *vs.* T	Pooled		0.527	0.002-137.4	0.822	R	0.001	91.7

OR: odds ratio; CI: confidence interval; F: fixed effect model; R: random effect model.

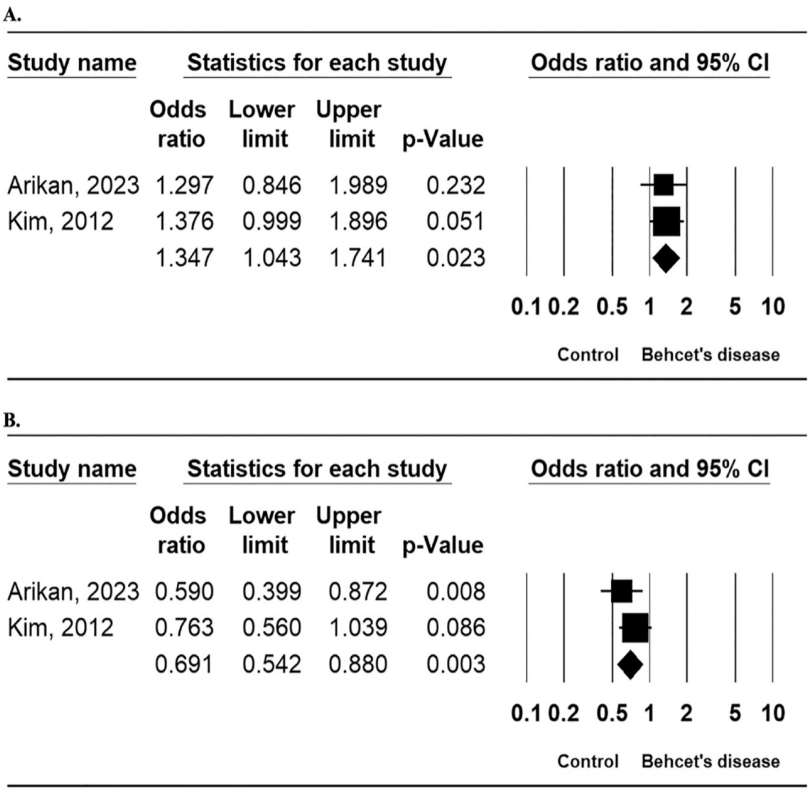

Fig. 3. Odds ratios and 95% confidence intervals of studies and pooled data for allelic association between *IL17A* rs4711998 (**A**) and *IL17F* rs8193036 (**B**) polymorphisms and BD.

(3). In BD, dysregulation of the Th17 immune response leads to overproduction of IL-17 and other proinflammatory cytokines. This overproduction of IL-17 may contribute to chronic inflammation and tissue damage observed in BD. Specifically, IL-17 can activate and recruit immune cells, such as neutrophils, macrophages, and dendritic cells, to the site of inflammation, leading to the release of more proinflammatory cytokines and perpetuating the inflammatory response (28).

The pathogenic roles of IL-17 in BD appear to be different among its clinical subtypes. Increased IL-17 production and Th17 cell infiltration in the lesions of patients with mucocutaneous involvement (29). Dysregulated IL-17 responses and excessive Th17 cell activity may also contribute to the ocular inflammation seen in BD (30). Dysregulated IL-17 responses and Th17 cell activation have been observed in other vasculitis conditions, suggesting that IL-17 may contribute to vascular inflammation in BD as well. Treatment with secukinumab is effective for some tissues affected by BD but not others (31).

Regarding the genetic associations found in the meta-analysis, *IL17A* encodes IL-17A, and genetic variations in this gene may alter the function or expression of this cytokine (2). These alterations may affect the Th17 immune response and lead to the dysregulation of IL-17 production and downstream inflammatory effects, which could increase the risk of developing BD (32). Overall, dysregulation of the Th17 immune response and IL-17 production, potentially caused by genetic variations, is a possible mechanism underlying the findings of meta-analyses of circulating IL-17 levels and *IL17A* and *IL17F* polymorphisms in BD susceptibility. The prevalence of polymorphisms in IL17A rs4711998 and rs8193036 varies among different ethnic groups. In BD, the rs4711998 G allele has been associated with increased susceptibility in Turkish, Japanese, and Chinese populations (12, 13). However, studies conducted in other populations, such as Iranian and Korean, have reported different findings. The prevalence of polymorphisms in rs8193036 was 20% in Europeans, 51.3%–71.3% in Asians, and 85.6%–94% in Arabs (33). The G allele of rs4711998 has been associated with increased IL17A gene expression compared to the A allele (34). This increased gene expression can lead to higher IL-17A cytokine production, potentially contributing to enhanced immune responses and inflammation. The G allele of rs4711998 has been associated with increased susceptibility to BD (12, 13). The C allele of rs8193036 has been associated with decreased mRNA stability and lower IL-17A cytokine production compared to the T allele (34). Association between the rs8193036 C allele and decreased susceptibility to BD has been reported (13).

It is essential to note that meta-analyses have some limitations. One limitation of our study was the potential for publication bias. Although we made efforts to include all relevant studies in our meta-analysis, it is possible that some studies were not published because of nonsignificant results or other reasons. Another limitation was the high degree of heterogeneity observed across the subgroups, which might have affected the accuracy of the overall effect size estimate. Additionally, the number of studies included in some subgroups was relatively small, which might have affected the statistical power of the analyses. A major strength of our study was the comprehensive nature of our meta-analysis. We included several studies and subgroups to examine the association between IL-17 levels and BD across different populations, data types, publication years, and disease activity levels. Finally, our examination of the *IL17* gene polymorphisms provides additional insights into the genetic basis of BD.

In conclusion, our meta-analysis demonstrated that circulating IL-17 levels were significantly higher in patients with BD than in controls, and that the *IL17A* rs4711998 and rs8193036 polymorphisms were associated with BD susceptibility. Based on these findings, we conclude that IL-17 plays an important role in the pathogenesis of BD. However, further studies are warranted to determine whether IL-17 directly contributes to the development of BD.

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