Associations between circulating IL-17 levels and rheumatoid arthritis and between IL-17 gene polymorphisms and disease susceptibility: a meta-analysis

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ABSTRACT

Objectives To systematically review evidence regarding the relationship between circulating interleukin-17 (IL-17) levels and rheumatoid arthritis (RA), and associations between polymorphisms in IL-17 genes and RA susceptibility.

Method We performed a meta-analysis of serum/plasma IL-17 levels in patients with RA and controls, and evaluated evidence of associations between the rs2275913, rs3819024, rs4711998 and rs8193036 polymorphisms in *IL-17A* and the rs763780 and rs2397084 polymorphisms in *IL-17F* and risk for RA.

Results Fourteen studies including 3118 patients with RA and 2725 controls were included. Our meta-analysis revealed that IL-17 levels were significantly higher in the RA group than in the control group ($p=3.1\times10^{-6}$). Subgroup analysis using sample size showed increased IL-17 levels in samples from both small ($n\leq100$) and large ($n>100$) RA groups ($p=1.1\times10^{-4}$ and $p=0.008$, respectively). We found evidence of associations between RA and alleles from the *IL-17A* rs2275913 and *IL-17F* rs763780 polymorphisms in Caucasians ($p=0.003$ and $p=0.037$, respectively). In addition, we found an association between RA and alleles of the *IL-17A* rs3819024 polymorphism in the pooled RA cohort compared with matched controls ($p=0.033$). However, no evidence of association was found between the *IL-17F* rs2397084, *IL-17A* rs4711998 and *IL-17A* rs8193036 polymorphisms and RA susceptibility.

Conclusions Our meta-analysis revealed significantly higher circulating IL-17 levels in patients with RA, and found evidence of associations between the *IL-17A* rs2275913, *IL-17F* rs763780 and *IL-17A* rs3819024 polymorphisms and pathogenesis of RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that predominantly affects synovial joints, and it is characterised by infiltration of the synovium with neutrophils, macrophages, T cells, B cells, plasma cells, dendritic cells and tissue damage.[1 2] Hyperplasia of synovial cells and formation of new blood vessels within the synovial membrane result in the overgrowth of a fibrovascular granulation tissue, known as pannus, and its invasion into the cartilage and subchondral bone causes bone erosion and joint deformation.[3] Although its aetiology is not fully understood, it has been established that genetic and environmental factors contribute to the pathogenesis of RA.

A subtype of T cells, Th17 cells, secrete interleukin-17 (IL-17), which is also produced by other cell types including CD8+ T cells and γδ T cells.[4] IL-17 is a proinflammatory cytokine subclass that participates in tissue inflammation and destruction by inducing the expression of matrix metalloproteases and other proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α), IL-1β and IL-6, which recruits neutrophils, macrophages and lymphocytes to the synovium.[5] Studies on IL-17-deficient mice and mice treated with anti-IL-17 found that IL-17 is crucial in the development of collagen-induced arthritis by enhancing synovial inflammation and joint destruction.[6] In addition, IL-17 cells were reported to be increased in blood of patients with RA compared with healthy controls, and that high levels of IL-17 were found in the synovial fluid of patients with RA.[7] IL-17 consists of six protein members (IL-17A, IL-17B, IL17-C, IL-17D, IL-17E (IL-25) and IL-17F), of which IL-17A and IL-17F are responsible for the activity of Th17 cells in the induction of other cytokines and chemokines, and have been the most frequently studied.[8] *IL-17A* and *IL-17F* are both located on chromosome 6p12, which is a genomic region linked to RA.[9] In addition to the ability of IL-17 to regulate inflammatory reactions and immune responses, and because of their chromosomal location, these genes are considered potential candidate genes for RA.

Studies investigating circulating IL-17 levels in patients with RA compared with healthy controls, and testing polymorphisms in different IL-17-encoding genes, have found associations with RA susceptibility in some, but not all, studies.[10–23] In this study, we performed a meta-analysis to overcome the limitations of individual studies and to resolve inconsistencies in their findings.[24–26] The aim of our meta-analysis was to review systematically available evidence on serum/plasma IL-17 levels in patients with RA compared with those found in controls and to determine whether polymorphisms in IL-17-encoding genes are associated with RA susceptibility.

MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed a literature search for studies that examined IL-17 levels in patients with RA and controls, evaluated the relationship between circulating (serum or plasma) IL-17 levels or tested for

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associations between polymorphisms in IL-17 genes and RA. PUBMED, EMBASE and Cochrane databases were searched to identify all available articles (up to September 2016). The following key words and terms were used in the search: 'IL-17', 'level OR serum OR plasma', 'polymorphism', 'rheumatoid arthritis' and 'RA'. In addition, all references cited were reviewed to identify additional studies that were not included in the above-mentioned electronic databases. Studies were considered eligible based on the following inclusion criteria: (1) they were case-control, cohort or cross-sectional studies; (2) they provided data on IL-17 levels in both affected and control groups; (3) they included at least 10 patients with RA; and (4) they tested IL-17 gene polymorphisms in RA and control groups. No language or race restrictions were applied. Studies were excluded if (1) they contained overlapping or insufficient data, or (2) they were reviews or case reports. Data on the methods and results were extracted from original studies by two independent reviewers. Discrepancies between the reviewers were resolved by consensus. We performed out meta-analysis in accordance with PRISMA guidelines.[27] 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 SD of IL-17 levels, and the allele and genotype frequencies of polymorphisms in IL-17 genes. When data were presented as medians, IQRs or ranges, mean and SD values were derived using previously described formulae.[28 29]

Evaluation of statistical associations

We performed a meta-analysis to examine the relationship between IL-17 levels and RA, and to evaluate the allelic effect of the minor allele[2] versus the major allele[1] of different polymorphisms in IL-17 genes. For continuity of data, results were presented as standardised mean differences (SMDs) and 95% CIs. ORs and 95% CIs were calculated for dichotomous data. We assessed within-study and between-study variations and heterogeneities using Cochran's Q-statistics.[30] The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When the Q-statistic was significant ($p<0.10$), which indicated heterogeneity across studies, a random effects model was used for the meta-analysis, otherwise a fixed effects model was applied.[31] It was assumed that all studies estimated the same underlying effect, and specifically considered within-study variation.[30] We quantified the effect of heterogeneity using $I^2=100\%\times(Q-df)/Q$,[32] where I^2 is a measure of the degree of inconsistency between studies and determines whether the percentage total variation across studies was because of heterogeneity and not because of chance. I^2 ranges from 0% to 100%; I^2 values of 25%, 50% and 75% were referred to as low, moderate and high estimates, respectively.[32] Statistical determinations were performed using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, New Jersey, USA).

Evaluation of heterogeneity and publication bias

To examine potential sources of heterogeneity observed in the meta-analysis, meta-regression analysis was performed using the following variables: ethnicity, adjustment, publication year, sample size and data type. Although funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes, and their interpretation involves subjective judgement. Therefore, we assessed publication bias using Egger's linear regression test,[33] which measures funnel plot asymmetry using a natural logarithm scale of the ORs.

RESULTS

Studies included in the meta-analysis

We identified 1092 studies using electronic and manual search methods, of which 21 were selected for full-text review based on the title and abstract, and 7 were excluded because they either lacked data on the control group or provided other cytokine data. Therefore, 14 articles met our inclusion criteria[10–23] (figure 1). One of the eligible studies contained data on two different groups,[14] which were treated independently. Fifteen comparisons were examined in the meta-analysis, which consisted of 3118 patients with RA and 2725 controls (table 1). Nine comparative studies from eight articles examined IL-17 levels in affected and control groups, and six studies evaluated polymorphisms in IL-17 genes in both the RA and control groups (table 1). Meta-analysis of IL-17-related polymorphisms was performed if there were at least two comparisons. Because of the limited number of candidate-gene association studies, six types of meta-analyses were performed: rs2275913, rs3819024, rs4711998 and rs8193036 in *IL-17A*, and rs763780 and rs2397084 in *IL-17F*. Characteristic features of the studies included in the meta-analysis are summarised in table 1.

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

We found using meta-analysis that IL-17 levels were significantly higher in the RA group than in the control group (SMD=1.421, 95% CI 0.824 to 2.019, $p=3.1\times10^{-6}$) (table 2, figure 2). In addition, subgroup analysis using sample size showed significantly higher IL-17 levels for small ($n\leq100$) and large ($n>100$) sample groups in the RA group compared with those found in the control group (SMD=1.471, 95% CI 0.724 to 2.217, $p=1.1\times10^{-4}$; SMD=1.362, 95% CI 0.362 to 2.362, p=0.008, respectively) (table 2, figure 3).

Meta-analysis of *IL-17A* rs2275913, *IL-17F* rs763780 and *IL-17A* rs3819024 polymorphisms and RA susceptibility

Our meta-analysis identified a significant association between RA and the two alleles of the *IL-17A* rs2275913 polymorphism

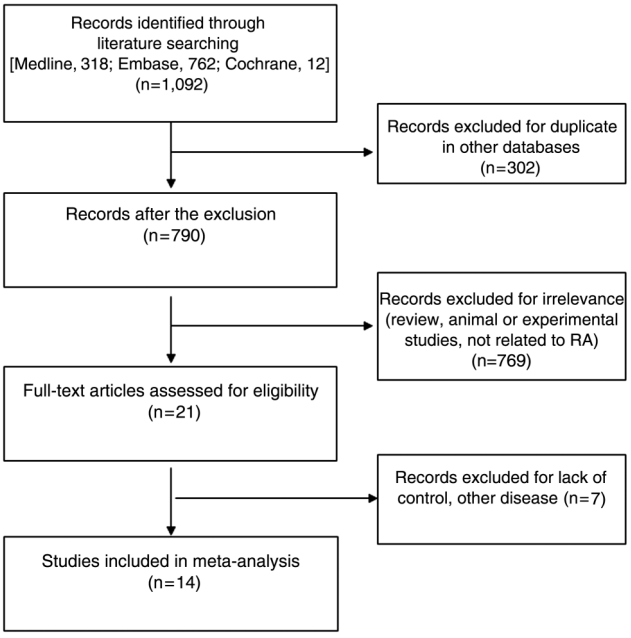


Figure 1 Flow chart for the study selection. RA, rheumatoid arthritis.

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

(A) IL-17 level

Author	Country	Ethnicity	Cohort size (n)		IL-17 level (pg/mL)		Statistical findings		
			Cases	Controls	Cases	Controls	SMD	Magnitude*	p Value
Yang, 2015[10]	China	Asian	152	100	97.50	25.00	1.855	Large	$<1.0\times10^{-8}$
Hong, 2014[11]	China	Asian	130	80	21.27	9.53	1.205	Large	$<1.0\times10^{-8}$
Liu, 2014[17]	China	Asian	90	30	21.95	6.21	2.595	Large	$<1.0\times10^{-8}$
Pavlovic, 2014[12]	Serbia	Caucasian	31	29	14.72	13.01	0.231	Small	0.373
Gullick, 2013[13]	UK	Caucasian	38	30	84.85	18.75	1.392	Large	3.0×10^{-7}
Niu-1, 2012[14]	China	Asian	36	20	3.11	1.60	2.357	Large	$<1.0\times10^{-8}$
Niu-2, 2012[14]	China	Asian	30	20	2.85	1.60	1.479	Large	5.1×10^{-6}
Chen, 2011[15]	Taiwan	Asian	48	12	40.60	6.88	2.015	Large	5.0×10^{-8}
de Paz, 2010[16]	Spain	Caucasian	196	29	1.44	1.68	−0.173	Small	0.384

(B) IL-17 genes and polymorphisms

Author	Country	Ethnicity	Cohort size (n)		IL-17 gene and polymorphism tested	Statistical findings (p value)
			Cases	Controls		
Pawlik, 2016[18]	Poland	Caucasian	417	337	rs2275193, rs763780, rs11465557, rs2397084	NS
Carvalho, 2016[19]	Brazil	Latin American	100	75	rs2275193, rs763780	NS
Shen, 2015[20]	China	Asian	604	832	rs2275193, rs3819024, rs4711998, rs8193036	rs2275193 (p=0.043), rs3819024 (p=0.048), rs4711998 (NS), rs8193036 (p=0.010)
Bogunia, 2015[21]	Poland	Caucasian	88	125	rs2275193, rs763780	rs2275193 (NS), rs763780 (p=0.0002)
Paradowska-Gorycka, 2010[22]	Poland	Caucasian	220	106	rs763780, rs2397084	NS
Nordang, 2009[23]	Norway	Caucasian	938	920	rs2275193, rs3819024, rs4711998, rs8193036	rs2275193 (p=0.002), all others (NS)

*Magnitude of Cohen's d effect size where 0.2 to 0.5 is a small effect, 0.5 to 0.8 is a medium effect and ≥0.8 is a large effect.
SMD, standard mean difference.
NS, not significant.

Table 2 Meta-analysis of the association between circulating IL-17 levels and RA

Groups	Population	Studies (n)	Test of association			Test of heterogeneity		
			SMD	95% CI	p Value	Model	p Value	I^2
All	Pooled	9	1.421	0.824 to 2.019	3.1×10^{-6}	R	0.000	93.4
Ethnicity	Asian	6	1.887	1.437 to 2.376	$<1.0\times10^{-8}$	R	0.000	81.4
	Caucasian	3	0.470	−0.434 to 1.374	0.308	R	0.000	90.8
Sample size	n≤100*	5	1.471	0.724 to 2.217	1.1×10^{-4}	R	0.000	86.6
	n>100	4	1.362	0.362 to 2.362	0.008	R	0.000	96.7

*Number of patients with RA.
R, random effects model; RA, rheumatoid arthritis; SMD, standard mean difference.

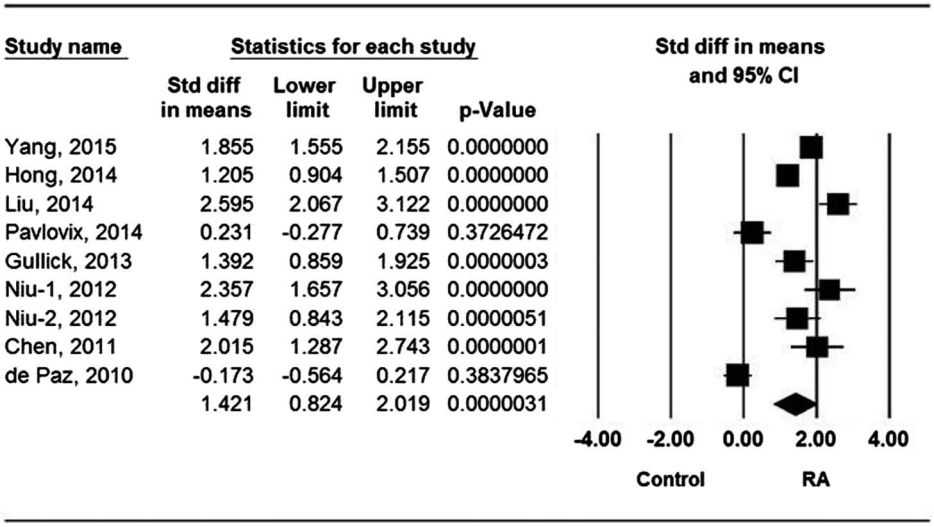
in a pooled cohort of affected individuals compared with that found in pooled controls (OR=0.866, 95% CI 0.794 to 0.944, p=0.001) (table 3, figure 4). Furthermore, stratification by ethnicity found an association between this polymorphism and Caucasian patients with RA compared with that found in matched controls (OR=0.847, 95% CI 0.760 to 0.944, p=0.003) (table 3, figure 4). We found a significant association between RA and the two alleles of the *IL-17F* rs763780 polymorphism in both pooled and Caucasian populations compared with those found in matched controls (OR=2.039, 95% CI 1.103 to 3.701, p=0.023; OR=2.295, 95% CI 1.050 to 5.013, p=0.037, respectively) (table 3, figure 5). In addition, our meta-analysis found an association between RA and the two alleles of the *IL-17A* rs3819024 polymorphism in the combined cohort compared with that found in controls (OR=0.898, 95% CI 0.813 to 0.982, p=0.033) (table 3, figure 6).

Meta-analysis of *IL-17F* rs2397084, *IL-17A* rs4711998 and *IL-17A* rs8193036 polymorphisms and RA susceptibility

No evidence of an association was found between the *IL-17F* rs2397084, *IL-17A* rs4711998 and *IL-17A* rs8193036 polymorphisms and RA susceptibility by meta-analysis (OR=1.126, 95% CI 0.854 to 1.486, p=0.150; OR=1.000, 95% CI 0.815 to 1.118, p=0.997; OR=1.087, 95% CI 0.833 to 1.417, p=0.539, respectively) (table 2).

Heterogeneity and publication bias

Interstudy heterogeneity was identified during the meta-analyses of IL-17 levels in patients with RA (table 2). We found using meta-regression analysis that ethnicity (p<0.001) and publication year (p<0.001), but not data type, sample size and adjustment (all p>0.05), had an effect on heterogeneity in our meta-analysis of IL-17 levels in patients with RA. No



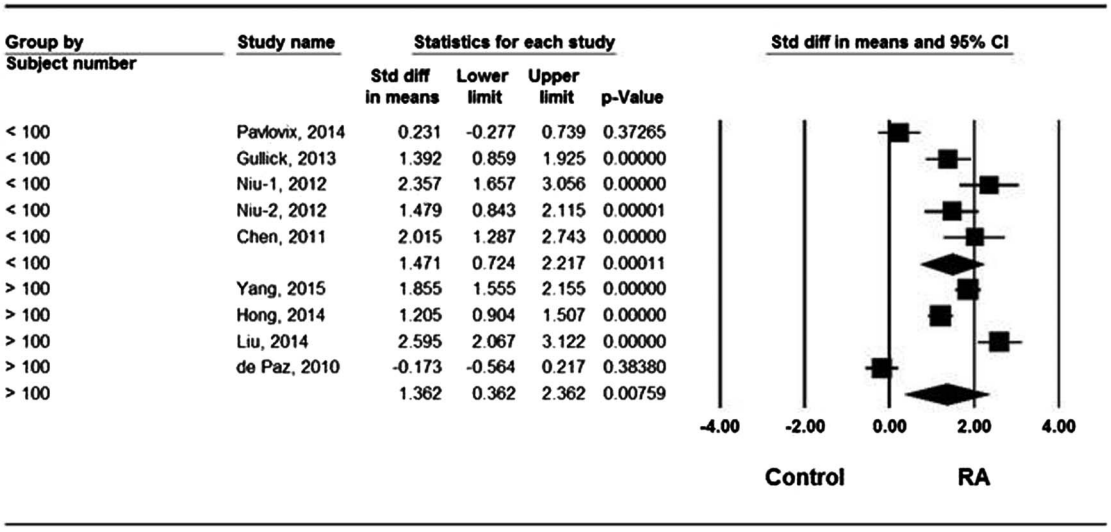


Figure 2 Meta-analysis of the relationship between circulating IL-17 levels and RA for all patients. IL-17, interleukin-17; RA, rheumatoid arthritis.

Figure 3 Meta-analysis of the relationship between circulating IL-17 levels and RA by the number of patients. IL-17, interleukin-17; RA, rheumatoid arthritis.

Table 3 Meta-analysis of tests of association between polymorphisms in IL-17 genes and RA

			Test of association			Test of heterogeneity		
Polymorphism	Population	Studies (n)	OR	95% CI	p Value	Model	p Value	I^2
rs 2275913	Pooled	5	0.866	0.794 to 0.944	0.001	F	0.713	0
A vs G	Caucasian	3	0.847	0.760 to 0.944	0.003	F	0.951	0
rs 763780	Pooled	4	2.039	1.103 to 3.701	0.023	R	0.031	66.1
C vs T	Caucasian	3	2.295	1.050 to 5.013	0.037	R	0.019	74.6
rs 2397084 C vs T	Pooled	2	1.126	0.854 to 1.486	0.399	F	0.498	0
rs 3819024 G vs A	Pooled	2	0.898	0.813 to 0.982	0.033	F	0.716	0
rs4711998 G vs A	Pooled	2	1.000	0.815 to 1.118	0.997	F	0.235	29.0
rs8193036 T vs C	Pooled	2	1.087	0.833 to 1.417	0.539	R	0.016	82.0

F, fixed effects model; R, random effects model; RA, rheumatoid arthritis.

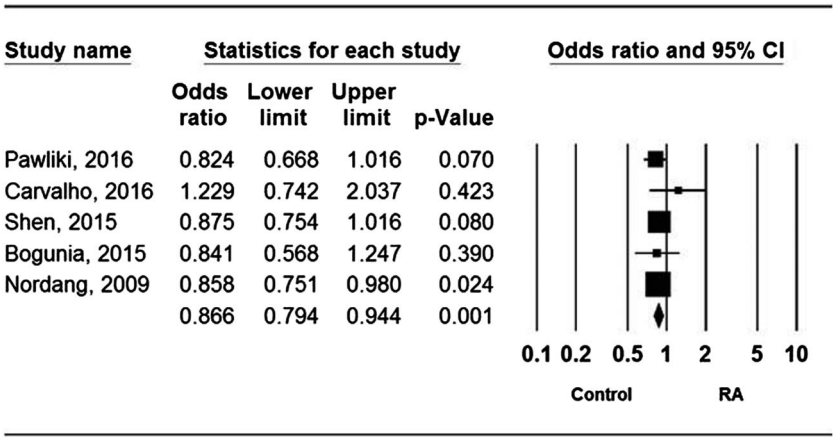


Figure 4 ORs and 95% CIs of individual studies and pooled data for tests of association between *IL-17A* rs2275913 polymorphism and RA. IL-17, interleukin-17; RA, rheumatoid arthritis.

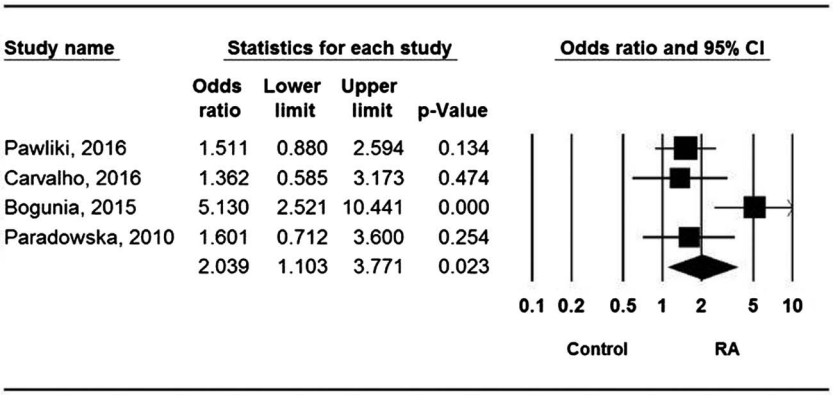


Figure 5 ORs and 95% CIs of individual studies and pooled data for tests of association between *IL-17F* rs763780 polymorphism and RA. IL-17, interleukin-17; RA, rheumatoid arthritis.

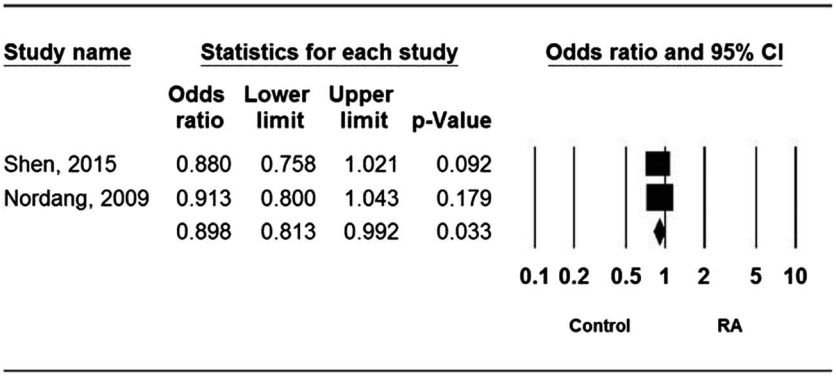


Figure 6 ORs and 95% CIs of individual studies and pooled data for tests of association between *IL-17F* rs3819024 polymorphism and RA. IL-17, interleukin-17; RA, rheumatoid arthritis.

heterogeneity was found in the meta-analyses of polymorphisms in IL-17 genes, with the exception of rs763780 in *IL-17F* and rs8193036 in *IL-17A*. However, the studies included in the meta-analysis for rs763780 showed the same directionality of the effect sizes (figure 2). 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 of the study subjects (ie, the funnel plot showed no evidence of asymmetry, and from Egger's regression test all $p>0.05$).

DISCUSSION

In this meta-analysis, evidence for circulating IL-17 levels in RA and for association between polymorphisms in IL-17 genes and RA susceptibility was evaluated. Our meta-analysis of 14 studies, which included 3118 patients with RA and 2725 controls, showed that circulating IL-17 levels were significantly higher in the RA group compared with that found in the control group. In addition, we identified associations between the *IL-17A* rs2275913, *IL-17F* rs763780 and *IL-17A* rs3819024 polymorphisms and RA susceptibility. These findings indicate that an increased IL-17 level is associated with RA, and that polymorphisms from IL-17-encoding genes are associated with RA risk. Our meta-analysis provides evidence that higher IL-17 levels are strongly correlated with pathogenesis of RA, and therefore, supports the involvement of Th17 cells in RA.

RA is characterised by infiltration of macrophages and T cells into joints, which results in synovial inflammation, pannus formation, cartilage destruction and bone erosion.[1 2] IL-17 is a proinflammatory cytokine subclass that contributes to increased

angiogenesis by stimulating fibroblast-like synoviocytes to produce vascular endothelial growth factor, and is also a potent inducer of TNF-α, IL-1-β, IL-6, IL-8 and granulocyte-colony stimulating factor (G-CSF), all of which enhance inflammation with joint damage.[5] Our findings that IL-17 levels are increased in the blood of patients with RA support a role of IL-17 in the pathophysiology of RA. Nevertheless, further studies are required to better understand the role of IL-17 and to determine whether drugs that block IL-17 are a viable treatment strategy for RA.

Given the potential link between IL-17 and autoimmune or inflammatory diseases, polymorphisms in IL-17 genes, which may affect IL-17 expression, have been studied as potential causes of autoimmune or inflammatory diseases.[34] Our meta-analysis found that the minor alleles of rs2275913 G/A and rs3819024 A/G in *IL-17A* are associated with decreased risk of RA, whereas the minor allele of rs763780 T/C in *IL-17F* is associated with an increased risk of RA. These findings are concordant with those of functional studies of these polymorphisms in *IL-17A* and *IL-17F*. *IL-17A* rs22759133 is located at position −197 in close proximity to two nuclear factors of activated T-cell binding motifs, and it promotes increased production of IL-17.[35] The *IL-17F* rs763780 polymorphism causes a histidine to arginine (His-to-Arg) substitution at amino acid 161, and that IL-17F expression or activity may be affected in carriers with the minor allele of *IL-17F* rs763780.[36] In contrast, the functional significance of *IL-17A* rs3819024 is unclear. However, the association between *IL-17A* rs3819024 and RA may reflect linkage disequilibrium with another potentially functional variant or closely linked susceptibility gene. Based on these findings, and that the *IL-17A* rs2275913, *IL-17F* rs763780 and *IL-17A* rs3819024 polymorphisms are associated with both altered expression of IL-17 and elevated IL-17 levels, we propose a link between these variants and the development of RA.

This meta-analysis had a few limitations. First, most of the recruited studies had small sample sizes, and a limited number of studies tested for evidence of an association between different polymorphisms in IL-17 genes and RA. Therefore, our meta-analysis may be underpowered. Second, the studies examined were heterogeneous in regard to both demographic characteristics and clinical features. Heterogeneity, confounding factors and limited clinical information in these study populations may confound the results. Third, publication bias may adversely affect our analysis because studies with negative findings may not be published or identified in our search. Although we used Egger's regression test, the possibility of bias cannot be eliminated. Nevertheless, this meta-analysis also has its strengths. To the best of our knowledge, our meta-analysis is the first study that provides two parallel lines of evidence examining both IL-17 levels and polymorphisms in IL-17-encoding genes in patients with RA. While individual studies had a limited cohort size ranging from 30 to 938 participants, our pooled analysis had 3118 patients. In addition, compared with individual studies, our study was capable of providing data that are accurate by increasing the statistical power and resolution of our analysis through pooling the results of these independent analyses.

In conclusion, our meta-analysis demonstrated that circulating IL-17 levels were significantly higher in patients with RA compared with that found in controls, and that the *IL-17A* rs2275913, *IL-17F* rs763780 and *IL-17A* rs3819024 polymorphisms are associated with RA susceptibility. Based on these findings, we conclude that IL-17 has an important role in the pathogenesis of RA. However, further studies are warranted to determine whether IL-17 levels directly contribute to the development of RA.

Main messages

- Circulating interleukin-17 (IL-17) levels were significantly higher in the rheumatoid arthritis (RA) group than in the control group.
- *IL-17A* rs2275913 and *IL-17F* rs763780 polymorphisms are associated with RA susceptibility in Caucasians.
- *IL-17A* rs3819024 polymorphism is associated with RA susceptibility.

Current research questions

- Further studies are warranted to determine whether circulating IL-17 levels directly contribute to the development and pathogenesis of RA.
- Further researches are needed to determine whether *IL-17A* rs2275913, *IL-17F* rs763780 and *IL-17A* rs3819024 polymorphisms confer susceptibility to RA in various ethnic groups.
- It is required to determine whether increased IL-17 level is the cause or the consequence of RA.

Contributors YHL designed the study. S-CB and YH-L collected data, performed the statistical analysis, drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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