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Elevated circulating IL-17 level is associated with inflammatory arthritis and disease activity: A meta-analysis

Xu Zhang[a,b,c,1], Yaping Yuan[a,c,1], Zhipeng Pan[d], Yubo Ma[a,c], Meng Wu[a,c], Jiajia Yang[a,c], Renfang Han[a,c], Mengya Chen[a,c], Xingxing Hu[a,c], Rui Liu[a,c], Napoleon Bellua Sam[a,c,f], Shengqian Xu[e], Faming Pan[a,b,c,*]

[a] Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui 230032, China
[b] Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS 7000, Australia
[c] The Key Laboratory of Major Autoimmune Diseases, Anhui Medical University, 81 Meishan Road, Hefei, Anhui 230032, China
[d] Department of Medical Oncology, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230022, China
[e] Department of Rheumatism and Immunity, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230022, China
[f] University for Development Studies, Ghana Students Information Systems Unit, University of Ghana, P.O Box 143, Korle-Bu, Accra, Ghana

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ABSTRACT

Objectives: Previous studies found that the interleukin (IL)-17 level was elevated in inflammatory arthritis, but results were inconsistent. This meta-analysis aimed to investigate the association of IL-17 cytokine with osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA).
Methods: Relevant studies were searched using databases. Standardized mean difference (SMD) was calculated. Correlation coefficient was utilized to evaluate the relationship between IL-17 and disease activity of AS and RA. Subgroup analysis, sensitivity analysis and meta-regression were applied to explore the sources of heterogeneity.
Results: 83 records were enrolled. The IL-17 level was elevated in AS (SMD = 2.348, $P < .001$), RA (SMD = 1.502, $P < .001$), PsA (SMD = 1.710, $P < .001$) and OA (SMD = 1.192, $P = .016$), and similar results occurred in subgroup analysis. Furthermore, the IL-17 level was positively associated with disease activity of AS and RA.
Conclusion: Circulating IL-17 level is significantly elevated in inflammatory arthritis and is related to the disease activity of AS and RA, suggesting that it plays an important role in the pathogenesis and progression of inflammatory arthritis (especially in AS and RA).

1. Introduction

Inflammatory arthritis is a cluster of inflammatory and immune diseases that including osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). In particular, inflammatory arthritis occurs in approximately 80–100 per 100, 000 adults per year [1] These diseases share many common characteristics and have same pathogenesis and pathways [2,3]. In recent years, the role of cytokines in the mechanisms of inflammatory arthritis have been investigated [4–6]. In addition, cytokines play an important role in anti-inflammatory and pro-inflammatory properties and serve as soluble mediators that induce specific immune responses [7]. However, the exact cause of inflammatory arthritis remains unclear.

In the regulatory network of immune cells, T helper-17 cells and their related-cytokines are associated with inflammatory autoimmune diseases [8]. Interleukin-17 (IL-17), a subset of pro-inflammatory cytokine, is secreted by Th17 cells, CD8+ T cells and γδ T cells and involves in inflammatory responses by inducing the production of matrix

Abbreviation: AS, Ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; COR, Correlation coefficient; CRP, C-reactive protein; CNKI, Chinese National Knowledge Infrastructure; CBM, Chinese Biomedical Database; CI, Confidence interval; DAS28, Disease Activity Score for 28 joints; ESR, Erythrocyte sedimentation rate; ELISA, Enzyme-linked-immunosorbent serologic assay; HC, Health control; NOS, Newcastle-Ottawa Scale; OA, Osteoarthritis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PsA, Psoriatic arthritis; RA, Rheumatoid arthritis; SMD, Standardized mean difference; SE, Standard error

* Corresponding author at: Department of Epidemiology & Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui 230032, China.
E-mail address: famingpan@ahmu.edu.cn (F. Pan).
[1] Xu Zhang and Yaping Yuan contributed equally to this work.

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metalloproteases and cytokines [9,10]. IL-17 was firstly discovered in 1993 [11] and proved to be a cause of joint destruction in RA models in the early 21st century [12,13]. Subsequently, increasing studies have focused on the role of IL-17 cytokine in other inflammatory arthritis. For example, previous studies have shown that the IL-17 level in patients with RA [14–16], AS [17,18] and OA [19,20] was significantly higher than that in healthy controls (HCs), but others failed to reach the conclusions [21–25]. In addition, the correlations between IL-17 level and disease activity have been investigated, but results were also contradictory [16,20,24,26–28]. Therefore, the role of IL-17 in the pathogenesis of inflammatory arthritis is suspected, and the clinical value of IL-17 circulating level and its significance in the etiology and progression of inflammatory arthritis remains heatedly debated.

To assess the conflicting results, the purpose of this meta-analysis was to review the available evidence of the IL-17 level in inflammatory arthritis and to determine whether the IL-17 level is associated with disease activity.

2. Materials and methods

2.1. Literature search

This paper follows the criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) with relevant studies searched up to August 2018 from databases of the Web of Science, the PubMed, Chinese National Knowledge Infrastructure (CNKI) and CBM (Chinese Biomedical Database). Keywords are “Interleukin-17” or “Interleukin 17” or “IL-17” or “IL 17”, “Rheumatoid Arthritis” or “RA” or “osteoarthritis” or “OA” or “Ankylosing spondylitis” or “AS” or “Spinal arthritis” or “SpA” or “Reactive arthritis” or “ReA” or “Gouty arthritis” or “Psoriatic arthritis” or “PsA” or “Rheumatic arthritis” or “Inflammatory arthritis”. All eligible studies were retrieved and evaluated without language restrictions, and the bibliographies were checked.

2.2. Selection criteria

Studies were enrolled based on the following criteria: (a) exploring the association of IL-17 circulating levels with inflammatory arthritis; (b) cross-sectional, case-control or cohort designs in human; (c) data on the IL-17 level and/or disease activity in patients and controls must be provided; (d) the control group must be HC. Studies were excluded: (a) not meeting the inclusion criteria; (b) irrelevant or duplicated studies; (c) reviews, meta-analysis or comments; (d) animal studies; (e) dissertations or conference papers.

2.3. Data extraction and quality assessment

Relevant studies were evaluated carefully and independently by two authors (Xu Zhang) and (Yaping Yuan), and discussions with the corresponding author (Faming Pan) were engaged when there were disagreements. The relevant data were extracted: first author's name, publication year, country, ethnicity, sample size, source of specimen, the IL-17 level and its assay approaches, kit manufacturers. Total allowable error for IL-17 in different manufacturers are around 30%. In addition, correlation coefficients (CORs) between IL-17 level and disease activity including Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were extracted for AS patients, and CORs between IL-17 level and ESR, CRP and Disease Activity Score for 28 joints (DAS28) for RA. All studies were assessed using the Newcastle-Ottawa Scale (NOS) assessment scale.

2.4. Statistical analysis

Differences of the circulating IL-17 level between inflammatory arthritis and HCs were calculated by standardized mean differences (SMDs) with 95% confidence intervals (CIs). An approximation method was applied to calculate the mean and standard deviation ($\overline{X} \pm S$) when some studies reported results using the median with first and third quartiles (M (P_{25}, P_{75})) [29]: $\overline{X} \approx \frac{P25 + M + P75}{3}$, $S = \frac{P75 - P25}{1.35}$. The standard errors (SEs) and CORs were used to calculate the pooled-CORs [30]: $SE = \sqrt{\frac{1-r^2}{n-1}}$. Q-statistic ($P < .05$) and I^2 tests ($I^2 > 50\%$) were applied to determine heterogeneity. The random-effects model was performed to calculate the SMD when there was a significant heterogeneity, otherwise, a fixed-effects model was used. Different subgroup analysis and meta-regression analysis were utilized to explore potential sources of heterogeneity. First, subgroup analyses of sample size (Large: sample size ≥100 vs. Small: sample size <100) and ELISA kits manufacturers were performed for inflammatory arthritis, subgroup analysis of ethnicity (Caucasians vs. Asians vs. Africans) was for AS and RA, and subgroup analysis of country (Chinese vs. Korean) was for OA. Secondly, publication year, country, ethnicity, sample size, assay approaches, specimen source and NOS score were used for meta-regression analysis. Sensitivity analysis was to assess the influence of one or more studies in the overall outcomes by sequential omission of individual study. Publication bias was evaluated by Egger's linear regression and Begg's rank correlation tests, and the trim and fill method was used if there was a potential publication bias. Statistical analysis was performed using STATA 11.0 software (Stata Corp, College Station, TX, USA), and $P < .05$ was considered as statistically significant.

3. Results

3.1. Characteristics of eligible studies

The literature selection flow was shown in the Supplementary Fig. 1, 5755 articles were retrieved and four records were identified by searching the references. After screening, 83 records were included. Of these, 26 articles included 1374 AS patients and 1002 HCs, 44 included 2819 RA patients and 1589 HCs, 10 included 633 OA patients and 544 HCs and 5 included 196 PsA patients and 135 HCs. Moreover, one article was performed for AS and RA [31], and another for RA and OA [32]. AS and RA patients were from Caucasians, Asians and Africans, OA from Asians (Chinese and Korean) and PsA from the Chinese population. All studies have a high quality, and characteristics of eligible studies were shown in Supplementary Table 1–4.

3.2. Pooled results and sensitivity analysis

The circulating IL-17 level was significantly higher in inflammatory arthritis than that in HCs (AS: SMD = 2.433, 95% CI = 1.749–3.116, $P < .001$; RA: SMD = 1.502, 95% CI = 1.425–1.579, $P < .001$; PsA: SMD = 1.710, 95% CI = 0.998–2.423, $P < .001$; OA: SMD = 1.192, 95% CI = 0.221–2.163, $P = .016$). Sensitivity analysis showed that the pooled SMDs were not significantly alter (Supplementary Figs. 2–5), suggesting that our results were stable. When one original study was omitted [33], the heterogeneity in PsA patients was absence ($I^2 = 0\%$ and $P = .713$) and the results were changed (SMD = 1.254, 95% CI = 0.983–1.524, $P < .001$) (Table 1, Figs. 1–2).

3.3. Subgroup analysis

Stratified for ethnicity, the IL-17 level was increased in Asians (SMD = 2.794, 95% CI = 2.006–3.582, $P < .001$) and Caucasians (SMD = 0.667, 95% CI = 0.032–1.302, $P = .040$) for AS patients. Meanwhile, the IL-17 level was also elevated in Asians (SMD = 1.674, 95% CI = 1.591–1.758, $P < .001$), Caucasians (SMD = 0.357, 95% CI = 0.156–0.558, $P = .001$) and Africans (SMD = 21.483, 95% CI = 19.052–23.915, $P < .001$) for RA, and the significant difference was detected in Chinese (SMD = 1.321, 95% CI = 0.227–2.366,

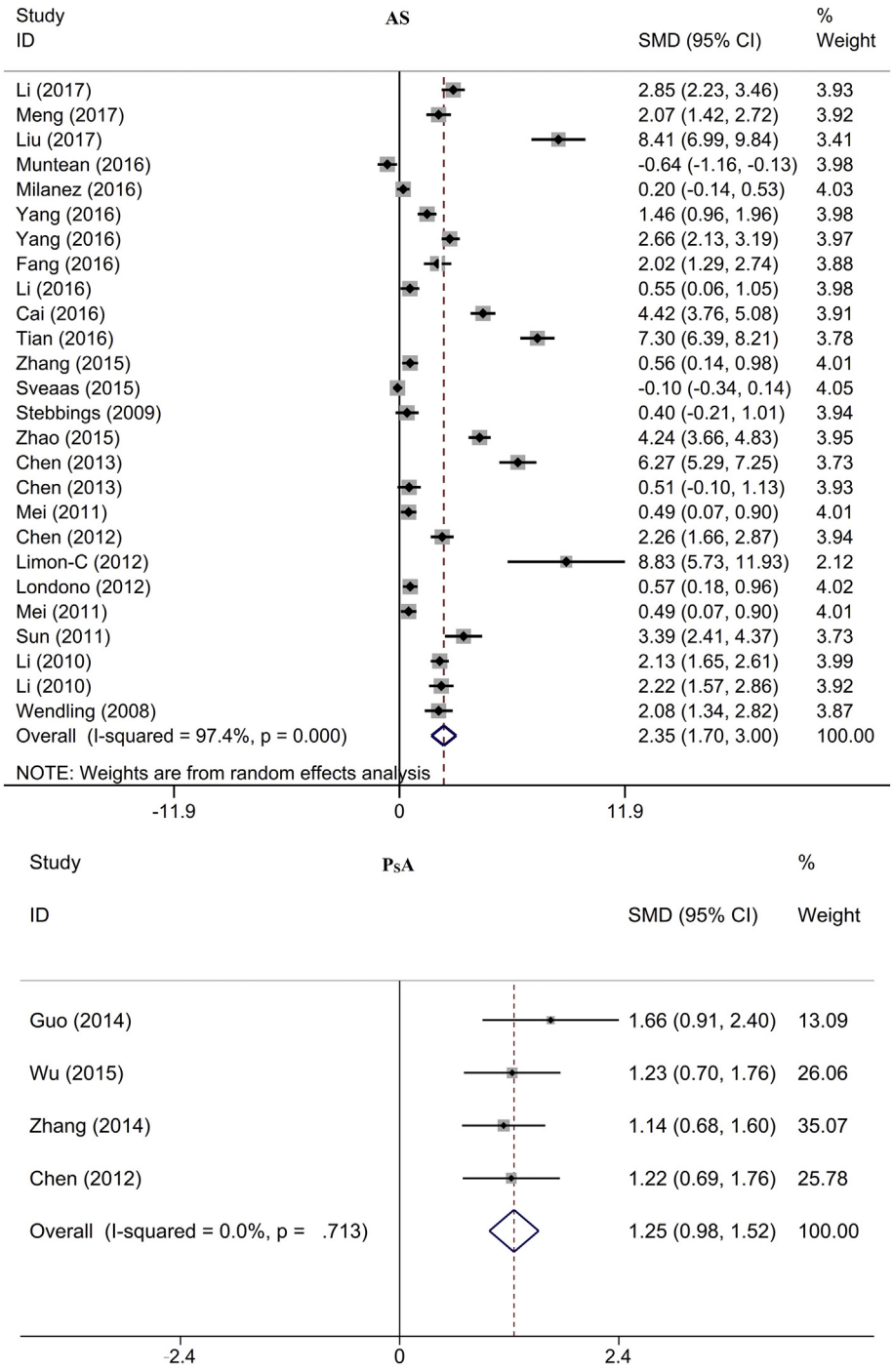

Fig. 1. Forest plots for SMDs of circulating IL-17 levels with AS and PsA (IL-17, interleukin-17; AS, ankylosing spondylitis; PsA, psoriatic arthritis; SMDs, standardized mean differences).

$P = .023$) for OA (Table 2).

Stratified for sample size, the circulating IL-17 level was elevated in both large sample size (AS: SMD = 2.644, 95% CI = 1.254–4.034, $P < .001$; RA: SMD = 1.354, 95% CI = 1.251–1.457, $P < .001$; PsA: SMD = 1.315, 95% CI = 0.980–1.651, $P < .001$) and small sample size (AS: SMD = 2.181, 95% CI = 1.472–2.889, $P < .001$; RA: SMD = 1.689, 95% CI = 1.573–1.805, $P < .001$; PsA: SMD = 1.140, 95% CI = 0.684–1.597, $P < .001$) for AS, RA and PsA patients. Furthermore, the significant difference was shown in the small sample size (SMD = 1.742, 95% CI = 0.881–2.603, $P < .001$) for OA patients (Table 2).

Stratified for kits manufacturers, the circulating level of IL-17 was elevated in different inflammatory arthritis using R&D systems kit (All $P < .05$, Table 2). In addition, the difference also occurred in RA patients using MARKETING (SMD = 1.903, 95% CI = 1.662–2.144, $P < .001$) and Boatman (SMD = 1.680, 95% CI = 0.862–2.498, $P < .001$) and in PsA patients using Biosource (SMD = 1.101, 95% CI = 0.751–1.451, $P < .001$).

3.4. Meta-regression

Meta-regression analysis was used to identify additional sources of heterogeneity and our results found that publication year, country, ethnicity, sample size, test method, specimen source and NOS score did

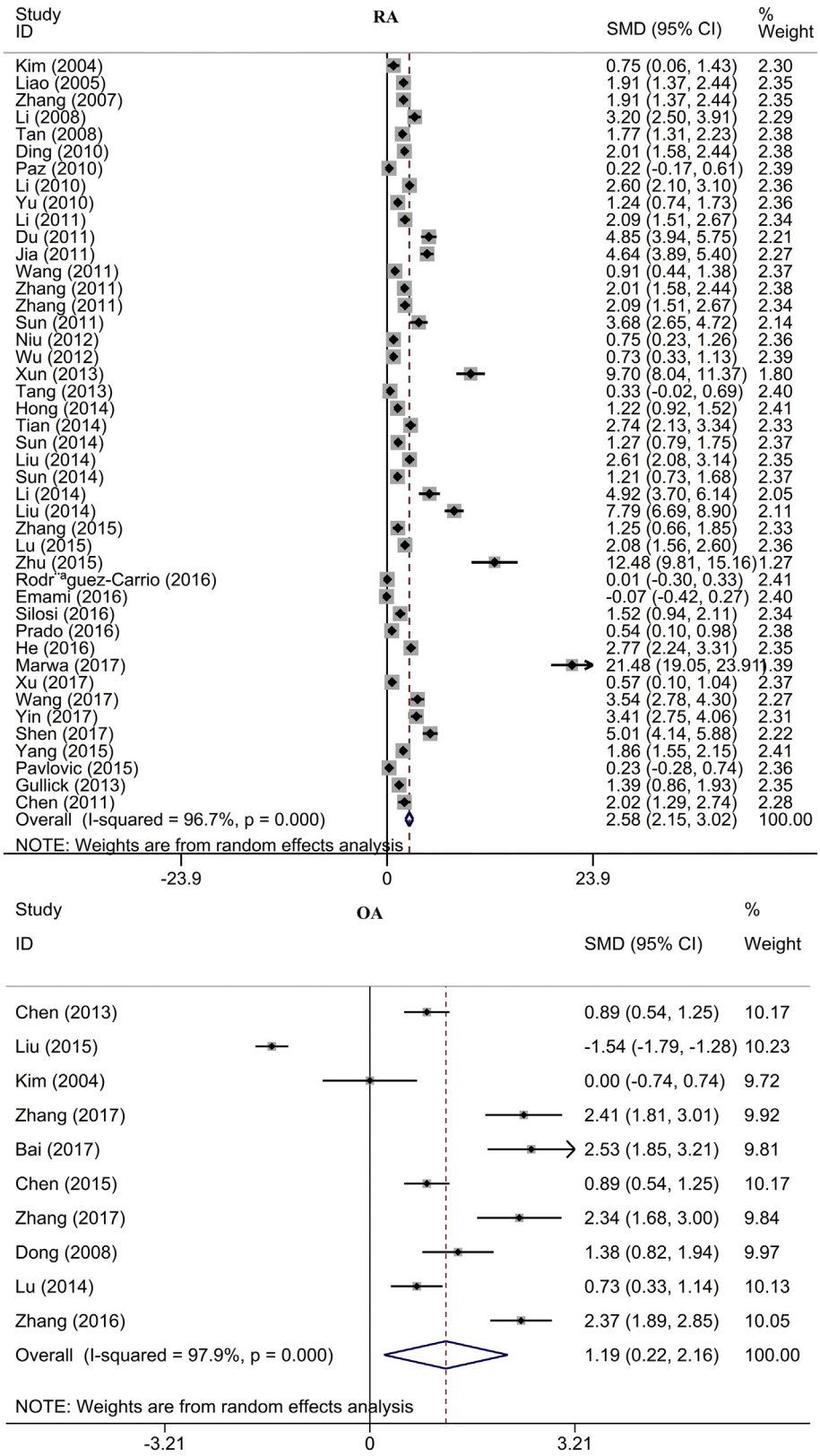

Fig. 2. Forest plots for SMDs of circulating IL-17 levels with RA and OA (IL-17, interleukin-17; RA, rheumatoid arthritis; OA, osteoarthritis; SMDs, standardized mean differences).

Table 1
Pooled results of inflammatory arthritis.

Disease	NO.	SMD	95CI	Z	*P*	Heterogeneity		Publication bias		Model
			(LCI, UCI)			I^2(%)	*P*	P_E	P_B	
AS	26	2.348	(1.696, 3.001)	7.05	< 0.001	97.4	< 0.001	< 0.001	< 0.001	R
RA	44	1.502	(1.425, 1.579)	38.21	< 0.001	96.7	< 0.001	< 0.001	< 0.001	R
OA	10	1.192	(0.221, 2.163)	2.41	0.016	97.9	< 0.001	0.011	0.325	R
PsA	4	1.254	(0.983, 1.524)	9.09	< 0.001	0	0.713	0.01	0.308	F
PsA▽	5	1.710	(0.998, 2.423)	4.70	< 0.001	86.2	< 0.001	0.076	0.086	R

AS, Ankylosing spondylitis; RA, Rheumatoid arthritis; PsA, Psoriatic arthritis; OA, Osteoarthritis; NO., Number of studies; SMD, Standardized mean differences; LCI, Lower confidence interval; UCI, Upper confidence interval; E, *P*-value for egger; B, P-value for Begg; R, Random model; F, Fixed model; ▽, One single study was omitted during the sensitivity analysis.

Table 2
Subgroup analysis results.

Disease	Subgroup	NO.	SMD (95% CI)	Z	P	Heterogeneity	
						I^2 (%)	P
AS	Ethnicity						
	Asians	19	2.794 (2.006, 3.582)	6.95	< 0.001	97.1	< 0.001
	Caucasians	7	0.667 (0.032, 1.302)	2.06	0.040	91.9	< 0.001
	Sample size						
	Large	8	2.644 (1.254, 4.034)	3.73	< 0.001	98.8	< 0.001
	Small	18	2.181 (1.472, 2.889)	6.03	< 0.001	95.8	< 0.001
	Kit Manufacturer						
	R&D Systems	7	1.52 (0.831, 2.210)	4.32	< 0.001	92.3	< 0.001
	Bio-Rad	2	3.456 (−2.662, 9.574)	1.11	0.268	95.8	< 0.001
	Overall	25	2.433 (1.749, 3.116)	6.97	< 0.001	97.5	< 0.001
RA	Ethnicity						
	Asians	37	1.723 (1.637, 1.808)	39.42	< 0.001	95.8	< 0.001
	Caucasians	6	0.455 (0.279, 0.632)	5.05	< 0.001	85.5	< 0.001
	Africans	1	21.483(19.052, 23.915)	17.32	< 0.001	–	–
	Sample size						
	Large	17	1.354 (1.251, 1.457)	25.77	< 0.001	98.0	< 0.001
	Small	28	1.689 (1.573, 1.805)	28.53	< 0.001	94.8	< 0.001
	Kit Manufacturer						
	R&D	11	4.882 (3.302, 6.462)	6.06	< 0.001	98.4	< 0.001
	MARKETINC	4	1.903 (1.662, 2.144)	15.47	< 0.001	0.0	0.908
	Boatman	3	1.680 (0.862, 2.498)	4.03	< 0.001	85.3	0.001
	eBioscience	2	1.092 (−0.662, 2.846)	1.22	0.220	94.5	< 0.001
	CBA	2	0.253 (−0.262, 0.768)	0.96	0.335	72.5	0.056
	Overall	45	1.465 (1.389, 1.540)	37.9	< 0.001	96.7	< 0.001
OA	Country						
	Chinese	9	1.321 (0.277, 2.366)	2.48	0.023	98.1	< 0.001
	Korean	1	0 (−0.741, 0.741)	0.00	1.000	–	–
	Sample size						
	Large	5	0.664 (−0.693, 2.020)	0.96	0.338	98.6	< 0.001
	Small	5	1.742 (0.881, 2.603)	3.96	< 0.001	88.8	< 0.001
	Kit Manufacturer						
	R&D	2	0.433 (0.081, 0.785)	2.41	0.016	41.0	0.193
	Bender	3	0.963 (−0.011, 1.937)	1.94	0.053	94.9	< 0.001
	Overall	10	1.192 (0.221, 2.163)	2.41	0.016	97.9	< 0.001
PSA	Sample size						
	Large	3	1.315 (0.980, 1.651)	7.68	< 0.001	0.0	0.606
	Small	1	1.14 (0.684, 1.597)	4.90	< 0.001	–	–
	Kit Manufacturer						
	R&D	2	0.832 (0.474, 1.191)	4.55	< 0.001	0.0	0.982
	Biosource	2	1.101 (0.751, 1.451)	6.17	< 0.001	53.5	0.142
	Overall	4	1.254 (0.983, 1.524)	9.09	< 0.001	0.0	0.713

AS, Ankylosing spondylitis; RA, Rheumatoid arthritis; PsA, psoriatic arthritis; OA, Osteoarthritis; NO., Number of studies; SMD, Standard mean differences; LCI, Lower confidence interval; UCI, Upper confidence interval.

not affect the overall effects (All $P > .05$, Table 3), but ethnicity may be an influencing factor for RA patients ($P = .013$, Table 3).

3.5. Publication analysis

The Begg's test found that OA and PsA patients lacked publication bias, while the Egger's test showed that there may be publication bias (Table 1). However, the results did not change when the trim and fill method was applied, indicating that our results are steady (Data not shown).

3.6. Correlation of IL-17 level and disease activity

Of the eligible studies, 8 records investigated the CORs between IL-17 level and disease activity for AS and RA patients. The IL-17 level was positively associated with CRP levels (COR = 0.347, 95%

Table 3
Results of meta regression analysis.

Disease	Heterogeneity factors	Coefficient	SE	t	*P*	95% CI (LCI, UCI)
AS	Publication year	0.081	0.199	0.41	0.689	(−0.330, 0.491)
	Country	−0.134	0.248	−0.54	0.593	(−0.646, 0.377)
	Ethnicity	−1.541	1.101	−1.40	0.174	(−3.813, 0.731)
	Sample size	0.334	1.089	0.31	0.762	(−1.913, 2.580)
	Test method	−0.706	0.683	−1.03	0.313	(−2.114, 0.703)
	NOS score	−0.55	0.555	−0.99	0.331	(−1.694, 0.595)
	Specimen source	−1.62	0.983	−1.65	0.112	(−3.650, 0.409)
RA	Publication year	0.264	0.173	1.52	0.135	(−0.086, 0.613)
	Country	0.739	0.403	1.83	0.074	(−0.074, 1.551)
	Ethnicity	3.45	1.324	2.60	0.013	(0.777–6.123)
	Sample size	0.227	1.243	0.18	0.856	(−2.289, 2.743)
	Test method	−2.531	3.861	−0.66	0.516	(−10.348, 5.285)
	NOS score	0.352	0.803	0.44	0.663	(−1.268, 1.972)
	Specimen source	−1.05	1.019	−1.03	0.309	(−3.114, 1.013)
OA	Publication year	0.126	0.099	1.27	0.241	(−0.103, 0.356)
	Country	−1.315	1.422	−0.92	0.382	(−4.593, 1.964)
	Sample size	−1.079	0.792	−1.36	0.211	(−2.906, 0.749)
	NOS score	−0.872	0.448	−1.95	0.087	(−1.905, 0.161)
	Specimen source	−0.058	0.386	−0.15	0.884	(−0.949, 0.832)
PsA	Publication year	0.008	0.125	0.07	0.953	(−0.528, 0.544)
	Sample size	−0.006	0.006	−0.96	0.438	(−0.035, −0.022)
	NOS score	−0.115	0.161	−0.72	0.548	(−0.806, 0.576)

AS, Ankylosing spondylitis; RA, Rheumatoid arthritis; PsA, psoriatic arthritis; OA, Osteoarthritis; SE, standard error; LCI, Lower confidence interval; UCI, Upper confidence interval.

Table 4
Correlation of IL-17 levels and disease activity in AS and RA patients.

Disease	Variable	NO.	COR	95% CI (LCI, UCI)	Z	P	Model
AS							
	CRP	6	0.347	(0.163, 0.530)	3.7	< 0.001	R
	ESR	6	0.163	(−0.136, 0.462)	1.07	0.285	R
	BASDAI	7	0.409	(0.138, 0.680)	2.95	0.003	R
RA							
	CRP	7	0.496	(0.032, 0.660)	5.92	< 0.001	R
	ESR	7	0.343	(0.033, 0.652)	2.17	0.030	R
	DAS28	7	0.335	(0.173, 0.496)	4.05	< 0.001	R

AS, Ankylosing spondylitis; RA, Rheumatoid arthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; COR, Correlation coefficient; DAS28, Disease Activity Score for 28 joints; ESR, Erythrocyte sedimentation rate; NO., Number of studies; LCI, Lower confidence interval; UCI, Upper confidence interval; R, Random model.

CI = 0.163–0.530, $P < .001$) and BASDAI scores (COR = 0.409, 95% CI = 0.138–0.680, $P = .003$) for AS. Also, the IL-17 were positively correlated with CRP levels (COR = 0.496, 95% CI = 0.032–0.660, $P < .001$), ESR levels (COR = 0.343, 95% CI = 0.033–0.652, $P = .030$) and DAS28 scores (COR = 0.335, 95% CI = 0.173–0.496, $P < .001$) for RA (Table 4).

4. Discussion

In this meta-analysis, we first reviewed the literature on the association between circulating IL-17 level and inflammatory arthritis including patients with AS, RA, OA and PsA. As expected, our results provided extremely consistent evidence that the IL-17 level was significantly elevated in inflammatory arthritis. In addition, the IL-17 level was associated with disease activity of AS and RA.

AS is a cytokine-associated arthritis that primarily affects the spine and sacroiliac joint, and RA is an inflammatory disease of synovial inflammation. We found that the IL-17 level was elevated in AS and RA patients in the pooled and stratified analysis, and the IL-17 level was related to disease activity of AS and RA. Previous meta-analysis suggested that the IL17 level was not increased in Caucasian RA patients [34]. The discrepancy may due to the sample size of the previous study is smaller than that in ours. OA is an inflammatory degenerative joint disease and PsA is an inflammatory arthritis associated with psoriasis disease. Compared with previous meta-analysis [34], we firstly explored the association of IL-17 level with OA and PsA, and found that the IL-17 level was higher in overall populations for OA and PsA patients. Taken together, these findings suggested that the IL-17 cytokine plays an important role in the pathogenesis of inflammatory arthritis. Increasing studies have shown that cytokines are essential in the pathogenesis of inflammatory arthritis. Furthermore, Th17 cells are implicated in tissue inflammation and IL-17 plays an important role in the recruitment of other cytokines at the inflammatory sites [35,36]. In osseous tissue, IL-17 induces bone resorption, aggravates bone loss and generates bone destruction [37,38], and another study suggested that the IL-17 causes articular cartilage destruction [39].

Moreover, in the visual inspection of the forest plots of AS and RA results identify studies “outliers” (Figs. 1–2), but sensitivity analysis showed that the overall results were not affected by them (Supplementary Figs. 2 & 4), suggesting that our results with a higher degree of certainty. Second, although the SMD values of some studies were higher, their weights were similar to others, indicating that the effect of these anomalies on the overall results is limited. One explanation of these phenomena stems from the different cytokine kits used in the different studies. In addition, in these studies, patients have high inflammatory cytokine level because they may be at the stage of progression of the disease. In the PsA, a significant heterogeneity ($I^2 = 86.2\%$, $P < .001$) was changed into non-heterogeneity ($I^2 = 0\%$, $P = .713$) when one original study was omitted [33]. The reason may be that the author did not match the gender and age between PsA patients and HCs [33]. This reminds us that it is imorpant to control potential confounding factors in conducting research. In our study, OA patients were from Asians including Chinese and Korean populations, while PsA patients were Chinese individuals. Therefore, subgroup analysis of OA and PsA patients were stratified for patients' country and sample size. The IL-17 level was significantly elevated in the large and small sample size for PsA patients. Furthermore, the IL-17 level was increased in the Chinese OA patients and in the small sample subgroup.

There are several explanations: First, ethnic discrepancy and hereditary factor between Chinese and Korean. Second, source of the specimen may be a contributing factor. The IL-17 production was measured from serum/plasma or synovial fluid in Chinese OA patients, while it was from peripheral blood mononuclear cell (PBMC) in Korean. The circulating level of IL-17 was elevated in inflammatory arthritis using R&D systems, and in RA patients using MARKETINC and Boatman as well as in PsA patients using Biosource. However, the heterogeneities were not significantly altered when stratified for ELISA kits manufacturers. Although the kits used in different studies are different, the concentrations were calculated by interpolation with a standard curve that can partially eliminate the effects of different kits on the overall results. Potential heterogeneity sources are needed to explore in further researches. To deeply identify the reason of heterogeneity, a meta-regression was performed on the publication year, country, ethnicity, sample size, test method, specimen source and NOS score. We found that ethnicity may be a factor influencing the pooled effect size in RA patients. Possible explanation as follows: First, the number of studies is different. For example, thirty-nine studies are from Asians, four studies from Caucasians and one single study from Africans in our analysis. Therefore, it is necessary to conduct more researches on the association of the IL1–7 level with inflammatory arthritis in other ethnicities. Secondly, genetic variation is a significant role. The IL-17 gene polymorphisms have been regarded as underlying reasons of inflammatory autoimmune diseases by affecting the IL-17 cytokine activation and pro-inflammatory functions [40,41]. Previous study suggested that the trim and fill method allows to perform in the presence of publication bias [42]. The results did not change when the test was carried out, suggesting that our results are robust and the influence of publication bias is limited. Therefore, scholars believe that the method is used as a form of sensitivity analysis [42].

Serological indicators of CRP and ESR are non-specific inflammatory markers that contribute to assessment of systemic inflammation status and the diagnostic value of these markers has been demonstrated in inflammatory arthritis [30,43]. BASDAI is a comprehensive self-administered instrument for evaluating disease activity of AS [30] and DAS28 is a quantitative indicator for monitoring disease activity of RA [16,44]. Therefore, this study explored the relationship between IL-17 level and disease activity of AS and RA. We found that the CRP levels were positively associated with IL-17 in AS and RA patients, and the ESR levels were not correlated with IL-17 in AS patients but associated with IL-17 in RA patients. Furthermore, BASDAI and DAS28 were positively related to the IL-17 level in AS and RA patients, respectively. These results were novel findings compared with previous study [34] and suggested that the combined detection of IL-17 cytokine and inflammatory markers is helpful for assessing the occurrence and progression of inflammatory arthritis. Moreover, total allowable error for IL-L17 are around 30% that allow practical application of the results.

Some limitations should be considered. First, sample size of the original studies is limited, so our results may be underpowered and larger sample size should be expected in different populations. Second, heterogeneity, publication bias and other confounding factors may confound our findings, although the results of subgroup analysis, meta-regression, and trim and fill method did not detect them. Finally, OA and PsA patients are from Asians and Chinese, so our conclusion cannot be extrapolated to other populations.

In conclusion, the circulating IL-17 level is significantly elevated in inflammatory arthritis, especially in AS and RA patients who are from Caucasians and Asians. The IL-17 is positively correlated with disease activity of AS and RA. These results suggest that the IL-17 plays an important role in the pathogenesis and progression of inflammatory arthritis, and further studies are warranted to validate our findings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2019.06.026.

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Declaration of Competing Interest

All authors declare they have no conflicts of interest.

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