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Serum Levels of IL-6 and TNF-α May Correlate with Activity and Severity of Rheumatoid Arthritis

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: We aimed to investigate the association of rheumatoid arthritis (RA) with interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) through a meta-analysis.

Material/Methods: The case-control studies that investigated the association between RA and serum levels of IL-6 and TNF-α were retrieved strictly according to the inclusion and exclusion criteria. The statistical analysis was performed using STATA statistical software (Version 12.0, Stata Corporation, College Station, TX, USA).

Results: Fourteen studies were enrolled in our meta-analysis, with a total of 890 patients with RA and 441 healthy people as the controls. The results of this meta-analysis revealed that the serum IL-6 and TNF-α levels of RA patients were significantly higher than in the controls, and this difference was statistically significant (IL-6: SMD=2.40, 95% CI=1.57~3.24, *P*<0.001; TNF-α: SMD=1.93, 95% CI=1.23~2.64, *P*<0.001). According to ethnic subgroup analysis, the serum IL-6 and TNF-α levels of RA patients were also significantly higher compared with the controls in Asians and Caucasians (IL-6: Asians: SMD=3.64, 95% CI=2.16~5.12, *P*<0.001; Caucasians: SMD=0.75, 95% CI=0.47~1.02, *P*<0.001; TNF-α: Asians: SMD=2.74, 95%CI=1.58~3.91, *P*<0.001; Caucasians: SMD=0.81, 95% CI=0.50~1.11, *P*<0.001).

Conclusions: IL-6 and TNF-α may play crucial roles in the activity and severity of RA.

MeSH Keywords: Arthritis, Juvenile • Interleukin-6 • Meta-Analysis

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Background

Rheumatoid arthritis (RA), a chronic inflammatory autoimmune disease, is characterized by consistent synovitis and aggravating cartilage and bones destruction, which deforms multiple joints [1]. RA is also characterized by autoantibody production (antibody of anti-citrullinated protein and rheumatoid factor), hyperplasia and synovial inflammation, and systemic features (e.g., pulmonary, cardiovascular, psychological, and skeletal disorders). Chronic inflammation and bone erosion are the central characteristics of RA [2,3]. RA impacts approximately 0.5~1% of the adult population in developed regions [4]. Even though some patients have mild self-limited disease, many of them have experienced joint destruction, severe physical disability, and multiple co-morbidities [5–7]. Unfortunately, patients with RA may develop various systemic symptoms such as fatigue, fever, anemia, weight loss, anorexia, muscle weakness, and osteoporosis [1,8,9]. Death rates are more than twice as high in RA patients as in the general population, and this gap seems to be widening [4,10]. The specific cause of RA is unknown, but it has been suspected that a complex interplay among environmental factors, genotype, and chance contributes to the occurrence of RA [2,11].

Unrestrained cytokine production has been correlated with various diseases, including RA. In RA, a complicated cytokine network regulates the chronic inflammation and joint destruction [12]. Chronic inflammation in RA is induced by the imbalance between cytokines of pro- and anti-inflammation and the induction of autoimmunity [13]. Potential triggers of RA include autoantibodies such as anti-citrullinated peptides antibodies and rheumatoid triggers, and pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) [13,14]. Cytokines modulate a large range of inflammatory processes correlated with the pathogenesis of RA, and appear abundantly in the serum and the arthritic synovial fluid of patients with RA [15,16]. After synovitis or synovial inflammation develops from autoimmunity in RA, additional triggers, including the production of pro-inflammatory cytokines (e.g., TNF-α and IL-6), further develop bone erosion and osteoclastogenesis, which relates to the regression of bone-resorbing osteoclasts [17,18]. TNF-α, secreted by activated macrophages and T-cells, exerts pro-inflammatory effects through binding to one of its receptors, p55 (TNF-RI) or p75 (TNF-RII), and plays a vital role in production of other cytokines and the induction of chronic inflammation [19,20]. IL-6, as another pro-inflammatory cytokine, drives the activation of local synovial leukocyte and antibody production [21,22]. Evidence from previous studies suggest that TNF-α and IL-6 play a significant role in the occurrence and development of RA due to their pro-inflammatory effects [8,23]. However, studies have also indicated that IL-6 and TNF-α can have anti-inflammatory functions under some circumstances [24,25]. Consequently, the purpose of our meta-analysis was to investigate the association between RA and serum levels of IL-6 and TNF-α via a meta-analysis.

Material and Methods

Search strategy

Electronic databases – EBSCO, PubMed, Ovid, SpringerLink, Web of Science, Wiley, Wanfang Data, and China National Knowledge Infrastructure (CNKI)—were searched to collect all relevant published studies (last updated search in October, 2014). The following key words and subject terms were used in the searches: RA, IL-6, and TNF-α. We also selected ("tumor necrosis factor-alpha" or "cachectin tumor necrosis factor" or "TNF-alpha" or "tumor necrosis factor" or "TNF"), ("Interleukin-6" or "IL-6" or "differentiation factor-2, B-Cell" or "B Cell stimulatory factor-2"), ("arthritis, rheumatoid" or "rheumatoid arthritis" or "RA") in the search strategy. We also further examined the relevant articles manually to discover any additional relevant studies.

Inclusion and exclusion criteria

Studies were qualified for inclusion if they met the following criteria: (1) the study type was case-control; (2) the research topic mentioned the association between RA and serum levels of IL-6 and TNF-α; (3) all subjects were patients clinically diagnosed with RA; (4) the detection method was enzyme-linked immunosorbent assay (ELISA); and (5) complete data was supplied in included studies. When the extracted studies were published by the same authors, only the complete or latest study was included. Studies were excluded if: (1) data were incomplete; (2) the differences in baseline characteristics between the case group and the control group were too great; (3) the article was published repeatedly; or (4) the diagnostic criteria for study subjects were ambiguous.

Data extraction and quality evaluation

Relevant data eligible for the final analyses in retrieved papers were extracted by 2 investigators separately on the basis of the inclusion criteria, including surname of first author, country of origin, publication year, ethnicity, language, disease, detection method, age, sex, study design, and sample size. Review reports from the 2 investigators were compared to identify inconsistency, and disputes were settled through further discussion and reexaminations among all investigators. The methodological quality of the included cases was evaluated by more than 2 investigators under the Methodological Index for Non-Randomized Studies (MINORS) criteria [26]. MINORS is an effective scoring tool, with a 12-item assessment, and each item can be scored from 0 to 2, with an ideal score of 16 for non-comparative studies and a score of 24 for comparative studies. The details of 12 criteria were displayed: the aim was clearly stated (MINORS 01), consecutive inclusion of patients or not (MINORS 02), collection of prospective data or not (MINORS 03), the

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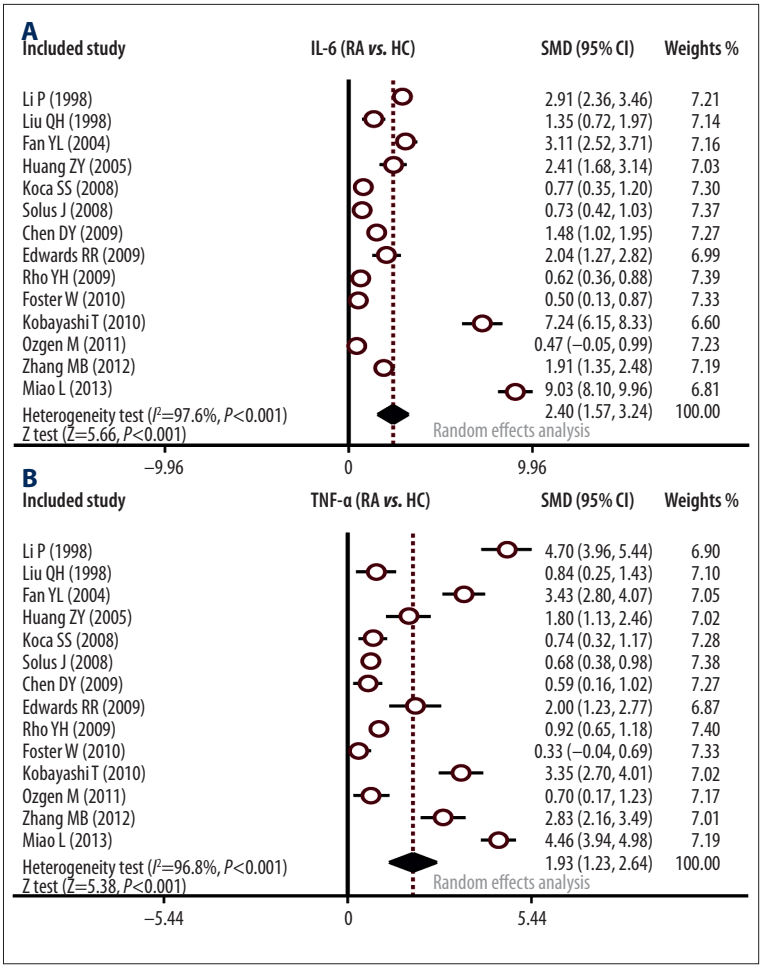

Figure 1. Forest plots of the differences of serum levels of IL-6 and TNF-α between patients with rheumatoid arthritis and the controls (IL-6 – interleukin 6; TNF-α – tumor necrosis factor-α).

endpoints were appropriate for the aim of the study (MINORS 04), unbiased assessment of endpoint or not (MINORS 05), appropriate follow-up period or not (MINORS 06), less than 5% loss of follow-up or not (MINORS 07), prospectively calculated study size or not (MINORS 08), adequate control group or not (MINORS 09), contemporary groups or not (MINORS 10), equivalent baseline of groups or not (MINORS 11), and adequate statistical analyses or not (MINORS 12).

Statistical analysis

STATA 12.0 software (Stata Corp, College Station, TX, USA) was used for statistical analyses. The differences of serum levels of inflammatory cytokines (IL-6 and TNF-α) between the case and control groups were estimated by the standardized mean difference (SMDs) with 95% confidence interval (CI). The significance of pooled SMDs was determined by the z test. Cochran's Q statistic ($P<0.05$ was considered significant) and the I^2 test (0%, no heterogeneity; 100%, maximal heterogeneity) were also used to reflect the heterogeneity among studies [27]. There was great heterogeneity among studies at $P<0.05$ or I^2 >50%; therefore, a random-effects model was used; otherwise, a fixed-effects model was used [28,29]. Univariate and multiple meta-regression analyses were conducted to evaluate the potential source of heterogeneity, and Monte Carlo simulation (MCS) was used to correct and verify the result [30]. Sensitivity analysis was achieved by deleting each included study one at a time to assess the effect of each study on the overall outcome. A funnel plot was constructed to evaluate publication bias that might influence the reliability of the results. The symmetry of the funnel plot was evaluated by Egger's linear regression test [31]. All statistical tests were 2-sided, and *P* values<0.05 were considered statistically significant.

Results

The baseline characteristics of included studies

A total of 849 studies were chosen from the 8 databases via screening both title and key words. Followed by removing reviews, letters, meta-analyses (n=5), duplicates (n=21), non-human studies (n=14), and studies not relevant to the research topics (n=760), the remaining studies (n=49) were checked

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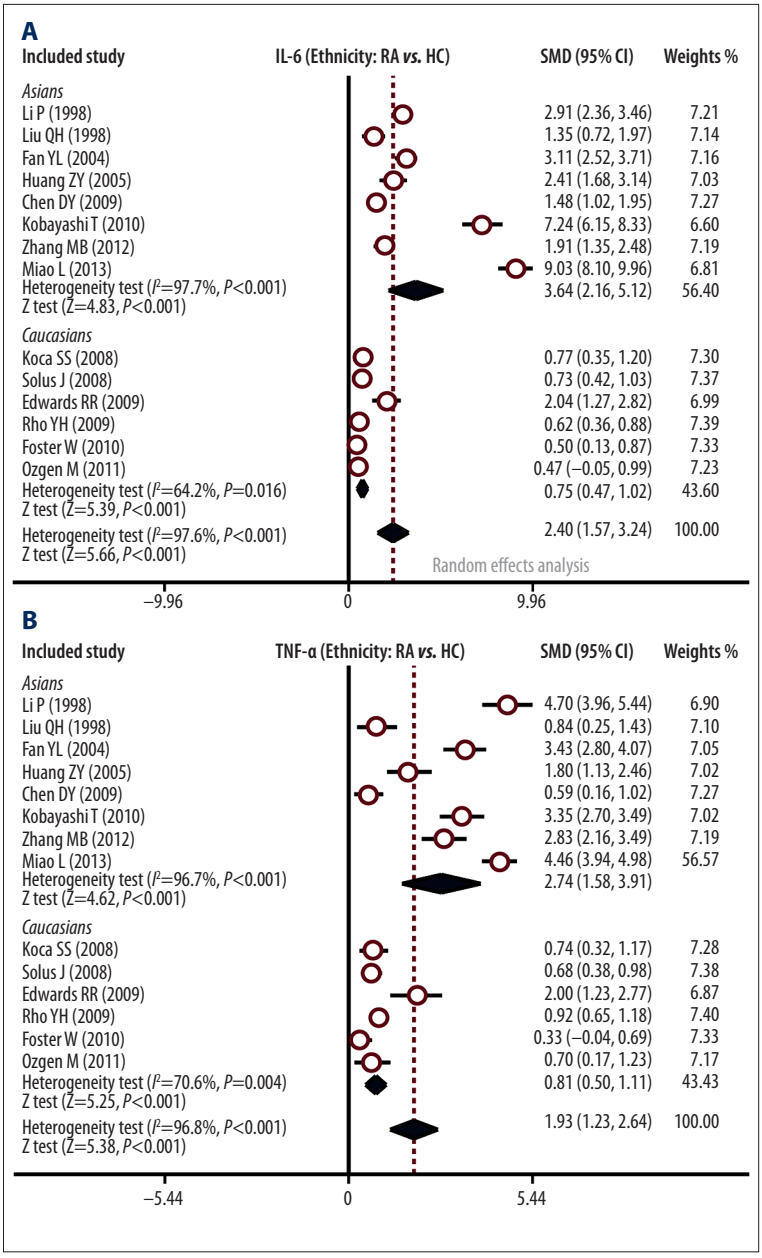

Figure 2. Subgroup analysis of ethnicity and difference in serum levels IL-6 and TNF-α between patients with rheumatoid arthritis and the controls (IL-6 – interleukin 6; TNF-α – tumor necrosis factor-α).

and an additional 31 studies were excluded because they were not case-control or cohort studies (n=7), not related to TNF-α (n=12), or not relevant to IL-6 (n=12). After the remaining 18 studies were further reviewed, 14 studies [23,32–44] were enrolled in the analysis. During the final selection process, the major reason for exclusion was insufficient information (n=4). There were 890 patients with RA in the case group and 441 controls in this meta-analysis. The included studies were all published between 1998 and 2014. The subjects in studies were Asian (n=8) and Caucasian (n=6).

Differences in serum levels of IL-6

Heterogeneity was found among included studies according to the heterogeneity test (I^2=97.6%, P<0.001); thus, a random-effects model was used. The results of this meta-analysis indicated that the serum IL-6 level of RA patients was evidently higher than in the controls, suggesting a statistically significant difference between the case and control groups (SMD=2.40, 95% CI=1.57~3.24, P<0.001) (Figure 1A). In ethnic subgroups, the serum IL-6 level of patients with RA was also significantly higher compared with the controls in Asians and Caucasians (Asians: SMD=3.64, 95% CI=2.16~5.12, P<0.001; Caucasians: SMD=0.75, 95% CI=0.47~1.02, P<0.001) (Figure 2A). The result

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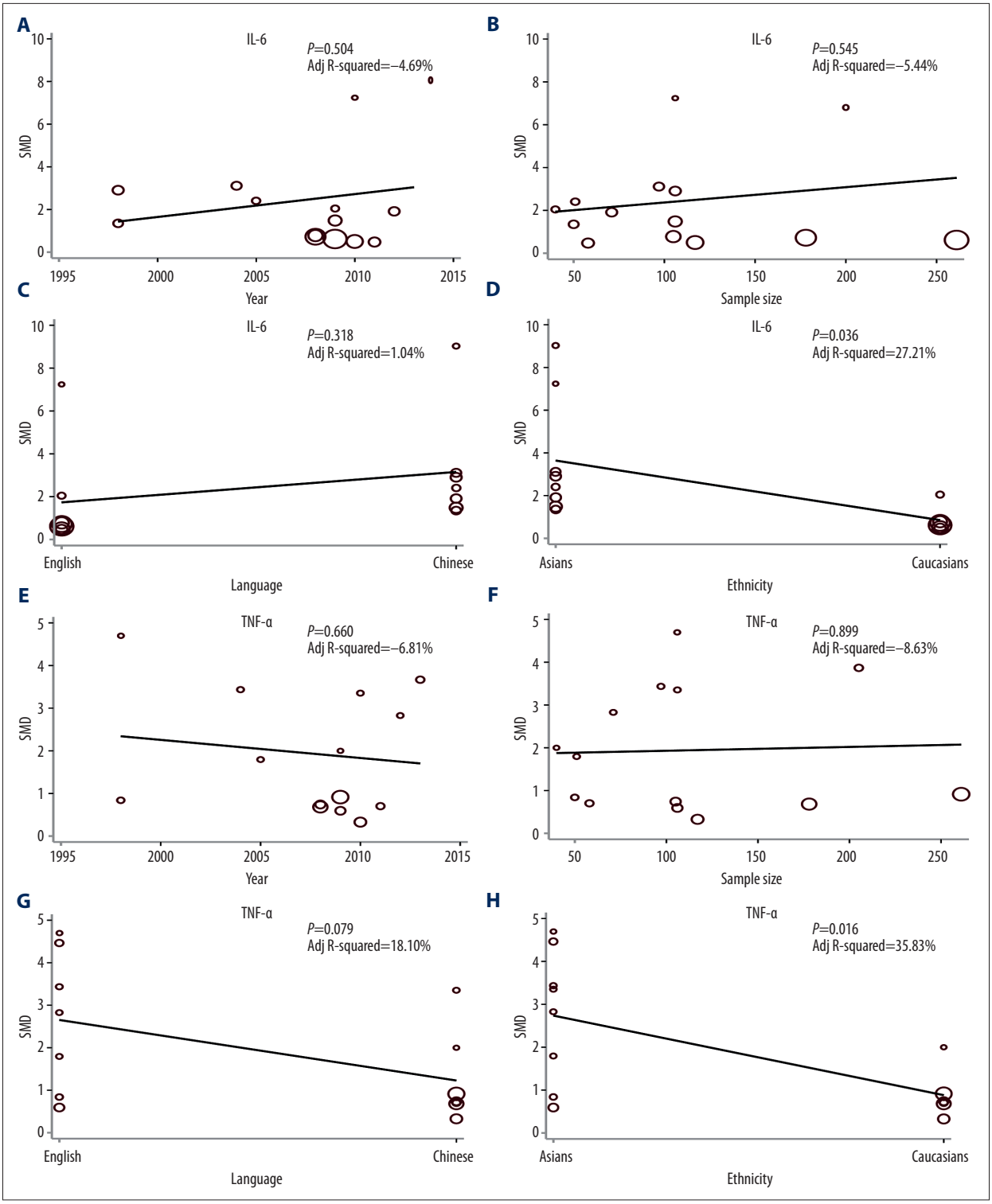

Figure 3. Univariate meta-regression analysis of serum levels IL-6 and TNF-α in patients with rheumatoid arthritis and the controls (IL-6 – interleukin 6; TNF-α – tumor necrosis factor-α).

of univariate meta-regression analysis suggests that ethnicity might be the source of heterogeneity (*P*=0.036), but the year of publication, language, and sample size were not associated with the heterogeneity (year of publication: *P*=0.504; language: *P*=0.318; sample size: *P*=0.545) as presented in Figure 3A–3D. Nevertheless, in multiple meta-regression analysis, ethnicity,

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Table 1. Meta-regression analysis of potential sources of heterogeneity in serum level of interleukin-6.

Heterogeneity factors	Coefficient	SE	t	P (Adjusted)	95% CI	
					LL	UL
Year	0.156	0.0158	1.26	0.462	–0.125	0.436
Ethnicity	–6.474	0.0091	–3.16	0.092	–11.111	–1.836
Language	–3.315	0.0147	–1.59	0.319	–8.045	1.415
Sample Size	0.010	0.0158	1.18	0.509	–0.009	0.029

SE – standard error; LL – lower limit; UL – upper limit.

Table 2. Meta-regression analysis of potential sources of heterogeneity in serum level of tumor necrosis factor-α.

Heterogeneity factors	Coefficient	SE	t	P (Adjusted)	95% CI	
					LL	UL
Year	0.0058	0.801	0.06	1.000	–0.204	0.215
Ethnicity	–2.563	1.567	–1.71	0.336	–5.951	0.825
Language	0.638	1.639	0.42	0.992	–2.817	4.093
Sample Size	0.0045	0.805	0.71	0.943	–0.010	0.019

SE – standard error; LL – lower limit; UL – upper limit.

year of publication, sample size, and language were not potential sources of heterogeneity (Table 1).

Differences in serum levels of TNF-α

A random-effects model was used due to heterogeneity among included studies (I^2=96.8%, P<0.001) according to the heterogeneity test. As presented in Figure 1B, the results indicated that the serum TNF-α level of patients with RA was clearly higher than in the controls, and there was a statistically significant difference between the case and control groups (SMD=1.93, 95% CI=1.23~2.64, P<0.001). On the basis of analyses of the ethnic subgroups, the serum TNF-α level of RA patients was also significantly higher compared with the controls in Asians and Caucasians (Asians: SMD=2.74, 95% CI=1.58~3.91, P<0.001; Caucasians: SMD=0.81, 95% CI=0.50~1.11, P<0.001) (Figure 2B). The univariate meta-regression analysis suggested that the main source of heterogeneity might be ethnicity (P=0.016), but not the year of publication, language, or sample size (year of publication: P=0.660; language: P=0.079; sample size: P=0.899) as shown in Figure 3E–3H. Additionally, in multiple meta-regression analysis, ethnicity, year of publication, language, and sample size were not sources of heterogeneity (Table 2).

Sensitiveness analysis and publication bias

The sensitivity analysis suggests that all included studies had no evident influence on the pooled SMDs of serum IL-6 and TNF-α level in RA patients and the controls, and the shapes of funnel plots of the differences in serum level of IL-6 and TNF-α showed asymmetry (Figure 4). Thus, Egger's test was used to further provide statistical evidence of funnel plot asymmetry, and also showed publication bias among included studies (IL-6: P<0.001; TNF-α: P=0.007).

Discussion

One of the characteristics of RA was consistent chronic inflammation resulting in damage to synovial tissue, which led to irreversible tissue or joint damage [45]. It has been reported that the high level of inflammation *in vivo* is correlated with serious joint damage and the poor prognosis of RA [46]. IL-6 and TNF-α are 2 well-known inflammatory cytokines with critical roles in modulating tissue inflammation; moreover, the plasma concentrations of IL-6 and TNF-α can reflect the severity of inflammation *in vivo* [46,47]. We investigated the association between RA and the serum levels of IL-6 and TNF-α on the basis of previous studies. We found that compared with the controls, the serum levels of IL-6 and TNF-α were significantly higher in patients with RA, suggesting that IL-6 and

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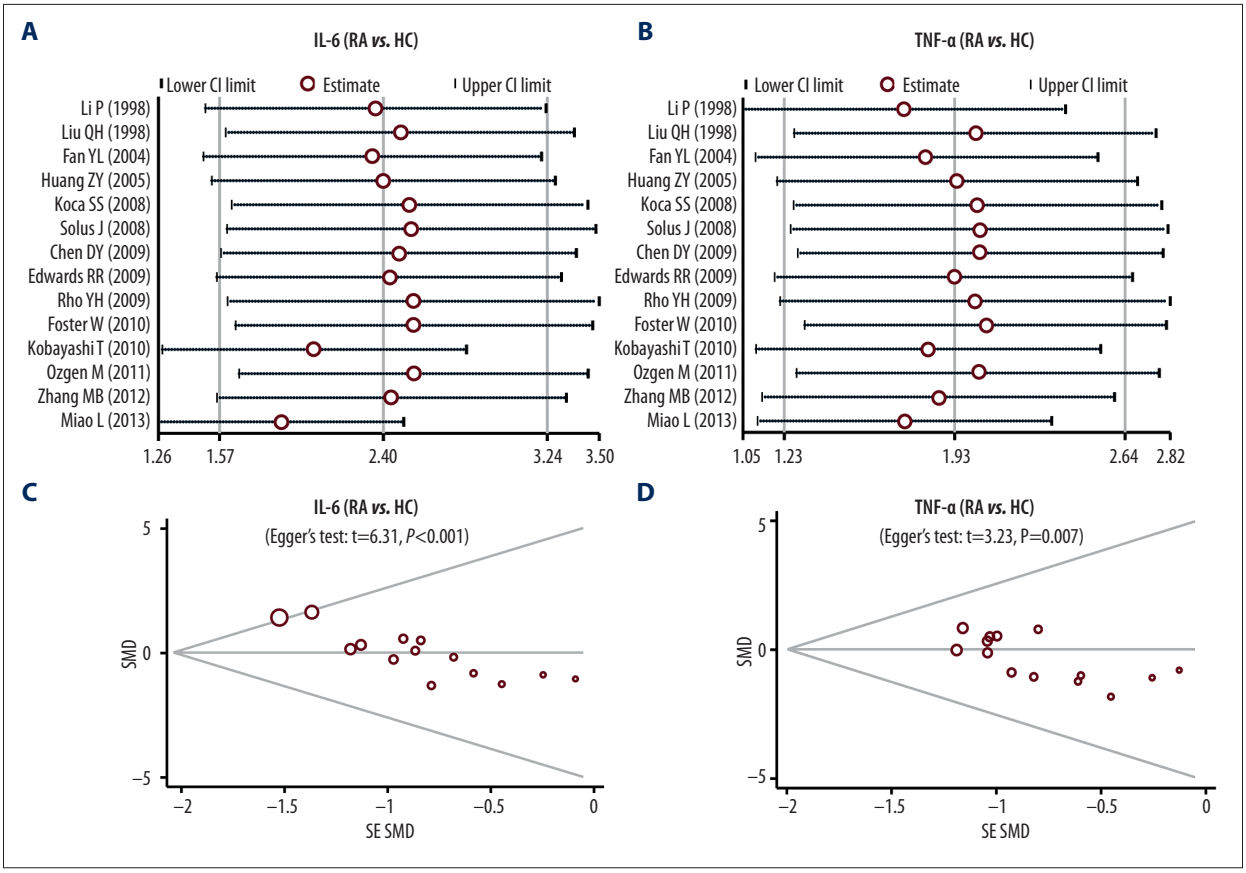

Figure 4. Sensitivity analysis and publication bias evaluation of the differences of serum levels IL-6 and TNF-α between patients with rheumatoid arthritis and the controls (IL-6 – interleukin 6; TNF-α – tumor necrosis factor-α).

TNF-α might play important roles in the pathogenesis of RA. In RA, TNF-α is secreted by various cell types, predominantly by macrophages and dendritic cells in reaction to the interactions between pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) and pattern-recognition receptors (PRRs) or to the cytokine environment [48]. IL-6 is a multifunctional cytokine with biological activities that include the modulation of inflammation, immune response, and hematopoiesis [8]. Varieties of innate effector cells, such as mast cells, macrophages, and natural killer cells, are discovered in the synovial membrane, but neutrophils reside mostly in synovial fluid [2]. Granulocyte colony-stimulating factor, macrophage colony-stimulating factor, and granulocyte–macrophage colony-stimulating factor (GM-CSF) promote the maturation of the above innate effector cells, trafficking to the synovium, and their efflux from the bone marrow [49,50]. Importantly, macrophages act as central effectors of synovitis and are effective biologic agents that could reduce macrophage infiltration consistently in the synovium [51,52]. Macrophages act via release of cytokines, for instance, TNF-α and IL-1, -6, -12, -15, -18, and -23, with TNF-α and IL-6 being the most predominant mediators, eventually resulting in the breakdown of extracellular matrix of bone and cartilage [53].

As the pathology of RA was unclear, most studies speculated that synovial hyperplasia and progressive joint destruction was involved in the possible mechanism of the immune system attacking the joints [54]. The inflammatory reaction involved in the synovial hyperplasia and joint destruction could be enhanced by IL-6, which amplifies the inflammatory cell infiltration [55]. Moreover, the synovial fibroblastic cells secreted IL-6 once it was stimulated by inflammatory cytokines such as IL-1 and TNF-α and, in turn, IL-6 enhanced the proliferation of synovial fibroblastic cells in the presence of soluble IL-6 receptor [8]. The explanation could be that IL-6 and TNF-α affect the progression in synovial hyperplasia, resulting in development and progression of RA. Therefore, it was reasonable to think that the serum levels of IL-6 and TNF-α in RA patients were evidently higher compared with the controls, which is consistent with some previous studies that revealed that IL-6 and TNF-α may contribute to the development of RA due to their pro-inflammatory effects [56,57].

Although RA was characterized by persistent synovitis and continuous joint destruction, anemia was the most common symptom during the early stage of the disease [58]. Research evidence shows that IL-6 injection contribute to induce of

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anemia, and vice versa, suggesting that IL-6, but not TNF-α, plays a crucial role in anemia in monkey collagen-induced arthritis, whose pathogenesis was similar with RA, by inhibiting the IL-6-induced hepcidin production [59,60]. A study by Godfrin-Valnet et al. identified a positive trend of IL-6 and the serum C-terminal cross-linking telopeptide of type I collagen (CTX) levels in patients with osteoporosis, revealing that increased level of IL-6 was correlated with accelerated bone resorption from increased osteoclastogenesis and reduced bone formation [61]. Moreover, elevated vascular endothelial growth factor (VEGF) level was found in RA patients, suggesting that VEGF is involved in RA pathogenesis [62]. Release of TNF-α and IL-6 from synovial tissue modifies the function of distant tissue, including vascular endothelial tissue, which could lead to insulin resistance, abnormal blood fats, and endothelial dysfunction [4].

To avoid the influence of other factors on the overall results, we selected ethnic subgroups analyses to further validate our results. We found that the serum IL-6 and TNF-α levels of RA patients were also significantly higher than in the controls in Asians and Caucasians, indicating that ethnicity did not affect our final results. Additionally, ethnicity, year of publication, language, and sample size also did not affect the results of this meta-analysis.

There were also some limitations in the present meta-analysis. For instance, because the inclusion process was performed manually, there might be some deviation that could impact the results; data on gender and age were lost in several included studies, which might be correlated with the serum levels of IL-6 and TNF-α and thereby might influence the result of this meta-analysis. In addition, according to the baseline characteristics of included studies, the sample size was too small to make firm conclusions about the correlation between RA and serum levels of IL-6 and TNF-α.

Conclusions

IL-6 and TNF-α, as 2 inflammatory cytokines, might play a vital role in the pathogenesis of RA through their pro-inflammatory effects.

Competing interests

No competing interests exist according to the declaration of the author.

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