Title: Effect of curcumin on proinflammatory cytokines: a meta-analysis of randomized controlled trials

Running title: Curcumin and proinflammatory cytokines

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Abstract

It has been suggested that curcumin has the potential for lowering inflammation. In the current meta-analysis, we attempted to clarify the efficacy of curcumin/turmeric supplementation in reducing concentrations of interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α in patients with an inflammatory background. The main databases were searched to identify eligible trials evaluating the effect of curcumin in reducing IL-1, IL-6, IL-8, and TNF-α in serum up to March 2021. The effect sizes for weighted mean difference (WMD) and 95% confidence intervals (CI) were calculated. Overall, 32 randomized controlled trials (RCTs) were included. There was a significant decrease in the serum levels of IL-1 (WMD= -2.33 pg/ml, 95% CI= -3.33 to -1.34, *P*<0.001) and TNF-α (WMD= -1.61 pg/ml, 95% CI= -2.72, -0.51, *P*< 0.001) compared to the placebo group following treatment. Nonetheless, curcumin/turmeric supplementation was non-significantly associated with levels of IL-6 (WMD = -0.33 pg/ml, 95% CI = -0.99-0.34, *P*=0.33) and non-significantly increased levels of IL-8 (WMD= 0.52 pg/ml, 95% CI= -1.13-2.17, *P*= 0.53). The dose-responses analysis indicated that curcumin/turmeric supplementation resulted in IL-1 and IL-8 alteration in a non-linear model. Subgroup analysis according to duration and dose of treatment and target population revealed diverse outcomes. Curcumin could have a beneficial effect in reducing the proinflammatory cytokines IL-1 and TNF-α, but not IL-6 and IL-8 levels.

Keywords: Curcumin; Inflammation; Randomized controlled trials; Interleukin; TNF

1. Introduction

Chronic inflammation has been linked to the etiopathogenesis of several disorders, including cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal, and endocrine systems. Additionally, chronic inflammation increases the risk of various malignancies [1-5]. Cytokines are molecules with a glycoprotein or protein structure [6]. They are produced by stimulated immune cells that function as molecular signals among immune-competent cells [7]. The proinflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α are the primary molecular contributors of chronic inflammation [8]. These proinflammatory cytokines could also induce the expression of adhesion molecules, resulting in vascular dysfunction [9].

The blockers of these cytokines, such as monoclonal antibodies (mAb) and their circulating receptors, could be potential therapeutic targets in the therapy of various inflammatory disorders [10]. However, these antibodies are expensive and have adverse side effects [11, 12]. Accordingly, there is a need for reliable, cost-effective, safe and easily accessible agents. Curcumin is a polyphenolic compound and bioactive dietary polyphenol obtained from the rhizomes of turmeric (*Curcuma Longa*) that has been attributed with antiinflammatory properties [13-15]. Due to low toxicity, extensive pharmacological properties like antiinflammatory, antioxidant, and anti-carcinogenic effects, curcumin is potentially useful in several diseases, such as osteoarthritis, rheumatoid arthritis, metabolic syndrome, diabetes, obesity, anxiety and depression [16, 17]. Curcumin may reduce proinflammatory cytokines by inhibiting IκB kinase and nuclear factor kappa B (NF-κB) signaling pathways [18, 19]. The

purpose of this meta-analysis was to assess the efficacy of curcumin supplementation on the circulatory concentrations of proinflammatory cytokines in randomized controlled trials (RCTs).

2. Methods

This study was performed in a stepwise process following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [20]. There was no need for ethical approval in our meta-analysis.

2.1. Search strategy

An exhaustive systematic search was conducted through PubMed/MEDLINE, ISI web of science, Scopus and Cochrane Library databases with no time limitation up to March 2021. The combination of keywords and Medical subject headings (MeSH) were as follows: ("curcumin" OR "curcuminoid" OR "Curcuma" OR "Curcuma longa" OR "turmeric") AND ("Interleukin 6" OR "IL-6" OR "Interleukin 1" OR "IL-1" OR "Interleukin 8" OR "IL-8" OR "tumor necrosis factor-α" OR "TNF-α"). No restriction filter was imposed on search strategy. Moreover, cross-references within both eligible and review articles were checked for additional publications.

2.2. Inclusion and exclusion criteria

All studies evaluating the effect of curcumin on proinflammatory cytokines meeting the following criteria were considered: i) studies with RCT design. ii) studies on the effect of

curcumin on the blood level (serum / plasma) of proinflammatory biomarkers. iii) studies with sufficient data regarding the mean changes of the IL-1, IL-6, IL-8, and TNF-a along with standard deviation (SD) for both intervention and placebo groups. However, duplicates, non-RCTs studies, studies without a placebo group, letters to the editor, animal studies, case reports, narrative reviews, studies which investigated the effect of other interventions along with curcumin in cases but not in the placebo group and studies with insufficient data were excluded.

2.3. Data extraction

Two authors independently screened the literature and extracted the data according to a predesigned extraction form. The following data were extracted: the first author's name, journal, year of publication, ethnicity, country of origin, study design, mean or range of age, the dosage of curcumin supplements (mg/day), duration of intervention, sample size, the mean and SD of the proinflammatory cytokines before and after curcumin supplementation.

2.4. Quality assessment

The quality of eligible studies was assessed based on the Jadad score [21]. The following criteria were used: randomization (2 points), blinding (2 points), and dropout rate (one point). If the total score were ≤2 points, the study considered low quality, and if it were ≥3 points, the study considered high quality.

2.5. Statistical analyses

Weighted mean difference (WMD) and their 95% confidence intervals (CI) for the effect of curcumin on serum IL-1, IL-6, IL-8, and TNF-α levels were used to estimate the overall effect size in the intervention and placebo groups. For studies not reporting the SD of the mean difference, it was calculated by SD^2= [(SD baseline^2+SD final^2) -(2×0.8×SD baseline× SD final)]. Cochrane's Q test and the I^2 test were explored to evaluate potential heterogeneity among included RCTs [22, 23]. According to these tests, Q with a *P* value less than 0.1 and I^2 exceed 50% are signe of significant heterogeneity. To find the effect of intervention duration and dosage of curcumin on presence of heterogeneity, meta-regression analysis was applied. Subgroup analyses were performed to evaluate whether results were effected by intervention duration (< 10 and ≥10 weeks), the dose of curcumin (< 1000 and ≥1000 mg/day), and target population. Moreover, the influence of individual study on the overall effect size was estimated via sensitivity analysis using the leave-one-out method. Begg's regression test and visual examination of the funnel plot were applied to measure publication bias [24, 25]. The statistical tests were performed using Stata statistical software (version 14.0; Stata Corporation, College Station, TX, USA) and SPSS (version 23.0; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study characteristic

The search and screening process of the literature based on the PRISMA statement is depicted in **Figure 1**. A total of 5422 articles were retrieved during the initial search. Application of

inclusion/exclusion criteria resulted in the exclusion of 5405 articles through title and abstract / full text. Eventually, 17 qualified publications were included in the analysis. Of them, four studies (three publications) were on IL-1 [26-28], thirteen studies (twelve publications) were on IL-6 [26, 28-38], five studies (four publications) were on IL-8 [26, 30, 31, 39], and thirteen studies (twelve publications) were on TNF-α [26, 28, 29, 31-33, 35, 38-42]. All of the included studies were published between 2008 to 2019. The detailed information, including sample size, mean or range of age in the intervention and placebo groups, intervention duration, the dosage of curcumin, and the Jadad score are summarized in **Table 1**.

3.2. Meta-analyses of curcumin's effect on the serum level of IL-1

3.2.1. Overall and subgroup analyses

We included four studies concerning the effect of curcumin on the serum level of IL-1. Overall, these four studies were conducted on 151 patients in the intervention group and 156 individuals in the placebo group. The results showed a significant decrease in the serum level of IL-1 compared to placebo group (WMD= -2.33 pg/ml, 95% CI= -3.33 to -1.34, P<0.001). Additionally, the subgroup analysis did not show any significant association between serum level of IL-1 with intervention duration (<10 and ≥10 weeks) and dosage of curcumin (<1000 and ≥ 1000 mg/day) (**Table 2**).

3.2.2. Dose-response effect of curcumin on serum level of IL-1

To find the non-linear dose-response relationship between curcumin consumption and IL-1 serum level, we carried out dose-response analyses using fractional polynomial modeling. The results revealed that curcumin decrease IL-1 in a non-linear fashion ($P_{\text{non-linearity}}$=0.003).

3.3. Meta-analyses of curcumin's effect on the serum level of IL-6

3.3.1. Overall and subgroup analyses

A total of 13 studies with 403 individuals in the intervention group and 405 individuals in the placebo group met the inclusion criteria and included in the analysis. The combined results from the random-effects model showed no significant decrease in IL-6 serum level following curcumin consumption (WMD = -0.33 pg/ml, 95% CI = -0.99 to 0.34, *P*=0.33; **Figure 2**).

For subgroup analysis, we stratified studies based on curcumin dosage (<1000 and ≥ 1000 mg/day), intervention duration (<10 and ≥10 weeks) and target population [overweight participant *vs*. participants with non-alcoholic fatty liver disease (NAFLD)]. We found that curcumin decreased the serum level of IL-6 in <1000 mg/day (WMD = -1.79 pg/ml, 95% CI = -3.22 to -0.36, *P*=0.01) (**Figure3**). However, IL-6 concentration was not affected by duration of curcumin consumption. Finally, stratification based on target populations also rejected influence of curcumin on IL-6 level in the overweight participants (WMD = 0.28 pg/ml, 95% CI = -0.60 to 1.16, *P*=0.53).

3.3.2. Dose–response effect of curcumin on serum level of IL-6

Following dose-response evaluation, there was no evidence for non-linear dose-response relations between consumption of curcumin and IL-6 level ($P_{non\text{-}linearity}$= 0.11; **Figure 4**).

3.4. Meta-analyses of curcumin's effect on the serum level of IL-8

3.4.1. Overall and subgroup analyses

The analysis of five studies containing 120 patients in the intervention group and 120 healthy individuals in the placebo group did not show any statistically significant association between curcumin consumption and serum level of IL-8 (WMD= 0.52 pg/ml, 95% CI= -1.13 to 2.17, *P*= 0.53). Since the intervention duration of all included studies was <10 weeks, and the curcumin dosage was ≥1000 mg/day, the subgroup analysis was not applicable (**Table 2**).

3.4.2. Dose–response effect of curcumin on IL-8 concentration

We found a non-linear dose-response relation between curcumin consumption and IL-8 levels ($P_{non\text{-}linearity}$= 0.02).

3.5. Meta-analyses of curcumin's effect on the serum level of TNF-α

3.5.1. Overall analysis and subgroup analyses

Thirteen eligible studies involving 380 individuals in the intervention group and 380 healthy individuals in the placebo group were included for quantitative analysis. In **Figure 2**, the serum TNF-α level in the intervention and placebo groups are compared over 13 studies. Our findings demonstrated that the TNF-α level in the intervention group was significantly lower than that in

the placebo group after consumption of curcumin (WMD= -1.61 pg/ml, 95% CI= -2.72, -0.51, *P*< 0.001). Furthermore, subgroup analyses was performed based on dose of curcumin (<1000 and ≥1000 mg/day), duration of intervention (<10 and ≥10 weeks), and target populations (overweight and NAFLD). In this regard, we observed a significant effect of curcumin on TNF-α serum level in dose <1000 mg/day (WMD= -1.99 pg/ml, 95% CI= -3.58 to -0.39, *P*= 0.01) compared to dose ≥1000. TNF-α concentration was just significantly decreased in ≥10 weeks intervention period (WMD= -1.65 pg/ml, 95% CI= -3.04 to -0.26, *P*= 0.02) compared to the placebo group. Furthermore, stratification based on target populations showed that curcumin increased level of TNF-α in the overweight participant (WMD= 0.37 pg/ml, 95% CI= 0.14 to 0.59, *P*= 0.001) and no significant effect was found in NAFLD cases.

3.5.2. Dose-response effect of curcumin on serum level of TNF-α

Following dose-response evaluation, no evidence was observed for non-linear dose response relations between consumption of curcumin and IL-6 concentration ($P_{non\text{-}linearity}$= 0.87; **Figure 4**).

3.6. Meta-regression analyses

Meta-regression analyses were performed to explore potential sources of heterogeneity among studies (**Table 3**). The analyses indicated that none of the expected parameters was the source of heterogeneity (**Figure 5**).

3.7. Publication bias

In this study, we used Begg's weighted regression test and visual examination of the funnel plot to measure publication bias. Overall, no significant publication bias was detected (**Figure 6)**.

3.8. Sensitivity analysis

The effect of individual study on the overall WMD was evaluated by sequential omission of each study. Based on that, we found that the pooled results from this meta-analysis were statistically robust and did not influence by result of single studies (**Figure 7).**

4. Discussion

In humans, a wide level of RCTs has addressed the efficacy, safety, and pharmacokinetics of curcumin supplementation in patients with different inflammatory conditions. Nevertheless, the results are not concordant, and contradictive conclusions have been achieved. Meta-analysis benefits from pooling the data from every single study to provide a more precise estimate of the effect of a particular treatment or other outcomes [43]. As a result, here in the current assessment, a meta-regression and meta-analyses of RCTs were carried out to gain a valid approximation of the effect of curcumin supplementation on the proinflammatory mediators in the context of inflammatory disorders such as type 2 diabetes mellitus and NAFLD. After performing a systematic literature search and going through rigorous inclusion and exclusion criteria, 32 qualified studies were included in the quantitative analysis. Four studies were on IL-1 (151 cases in the intervention group and 156 individuals in the placebo group), thirteen studies on IL-6 (403 cases in the intervention group and 405 individuals in the placebo group), five studies on IL-8 (120 cases in the intervention group and 120 individuals in the placebo

group), and thirteen studies (380 cases in the intervention group and 380 individuals in the placebo group) on TNF-α. Overall pooled analysis indicated that curcumin supplementation had a significant association with reduced levels of all proinflammatory cytokines evaluated, namely TNF-α, IL-1, IL-6 and IL-8.

The antiinflammatory and anti-oxidant characteristics of curcumin and corresponding compounds have been observed in the animal as well as in vitro studies [44], proposing a therapeutic potential in the treatment of several autoimmune and autoinflammatory disorders [45, 46]. However, several reports have testified otherwise. For example, curcuminoids supplementation was reported to be ineffective in the improvement of inflammatory manifestations in hyperlipidemic subjects [34]. Concerning the mechanism of action, curcumin is thought to be involved in alleviating the inflammation through interfering with the signaling pathways of NF-κB and IκB kinase [47].

Previously, several meta-analyses have been conducted to assess the effect of the curcumin/turmeric on inflammation. In 2014, Sahebkar et al. conducted the first analysis on the effect of curcumin supplementation on the C-reactive protein (CRP) level in inflammatory disorders. This study reported that curcuminoids were significantly associated with a lowering in the CRP levels [48]. Following this, the same group performed an RCT and updated meta-analysis in 2015, indicating that there was a significant reduction in serum CRP levels after curcumin supplementation [49]. On the other hand, concerning cytokines, Derosa *et al*. in 2016 included nine RCTs (involving 10 intervention/placebo comparisons, containing 305 intervention subjects and 304 placebo subjects). They found a significant decrease of IL-6 serum levels following curcuminoids supplementation (WMD: -0.60 pg/mL). However, meta-regression did

not show any significant association between the serum IL-6 lowering effects of curcuminoids with either dose or duration of treatment [50]. In 2018, Tabrizi *et al*. conducted an updated meta-analysis to investigate the effects of curcumin supplementation on the inflammatory factors and oxidative stress. In that study, 15 RCTs were included, and it was observed that curcumin supplementation significantly reduced IL-6, high-sensitivity CRP (hs-CRP), and malondialdehyde (MDA) concentrations. Nonetheless, curcumin supplementation did not have a significant impact on TNF-α concentration in serum [51]. White *et al*. performed the latest meta-analysis and included 19 RCTs (two for IL-1β, eight for IL-6, and eight for TNF-α). The analysis indicated that curcumin/turmeric did not significantly decrease levels of IL-1β, IL-6, and TNF-α. The study considered curcumin and turmeric separately and reported no differences between turmeric and curcumin interventions. However, high heterogeneity of effects was detected for IL-1, IL-6, and TNF-α across studies [52]. This meta-analysis revealed that curcumin/turmeric supplementation did not decrease the IL-1, IL-6, and TNF-α levels in patients with inflammatory conditions.

In the current most up-to-date meta-analysis of RCTs with respect to effect curcumin/turmeric supplementation on the serum levels of proinflammatory cytokine, 32 qualified studies were included. Separately for each cytokine, we included four studies were on IL-1 (intervention/placebo; 151 *vs*. 156), thirteen studies on IL-6 (intervention/placebo; 403 *vs*. 405), five studies on IL-8 (intervention/placebo; 120 *vs*. 120), and thirteen studies (intervention/placebo; 380 *vs*. 380) on TNF-α, which included significantly stronger sample size in comparison to previous analyses concerning several studies as well as the frequency of the individuals. The analysis revealed a significant decrease in the serum level of IL-1 compared to

the placebo group (WMD= -2.33 pg/ml). Nonetheless, the subgroup analysis did not show any significant association between the serum level of IL-1 and duration and dose of treatment. Applying the fractional polynomial modeling, the dose-response analysis indicated that curcumin/turmeric supplementation resulted in IL-1 reduction in a nonlinear model. Interestingly, the pooled analysis indicated that curcumin/turmeric supplementation does not influence IL-6 serum level (WMD = -0.33 pg/ml). The subgroup analysis indicated that curcumin/turmeric supplementation decreased the serum level of IL-6 in <1000 mg/day (WMD = -1.79 pg/ml). Besides, no evidence for non-linear dose-response relation was detected between curcumin/turmeric supplementation and IL-6 levels. Although an increased level of IL-8 was detected following curcumin/turmeric supplementation, the difference was not statistically significant. However, for all five studies included, the intervention duration was <10 weeks, and the treatment dose was ≥1000 mg/day. Interestingly, the non-linear dose-response relation between curcumin consumption and serum level of IL-8 was statistically significant. Finally, the pooled analysis indicated that curcumin/turmeric supplementation was effective in the reduction of TNF-α level in the intervention group (WMD= -1.61 pg/ml). A significant effect of curcumin/turmeric supplementation on TNF-α concentration was detected in doses <1000 mg/day compared to doses ≥1000. The other interesting finding in subgroup analyses was the duration of intervention. TNF-α concentration was significantly decreased only in ≥10-weeks intervention period. Furthermore, stratification based on target populations showed that curcumin increased level of TNF-α in the overweight participants and no significant effect was detected in the NAFLD subjects.

The results of the current meta-analysis were partially in contradiction; However, curcumin/turmeric supplementation decreased the levels of IL-1, and TNF-α levels, increased levels of IL-8 (statistically non-significant) were detected. These findings put doubt on the efficacy of curcumin/turmeric supplementation on the reduction of inflammation in patients. That notwithstanding, we did not evaluate the effects of curcumin/turmeric supplementation on the clinical outcomes, and only the proinflammatory cytokines were assessed individually. However, it was not the purpose of this study to determine the effect of curcumin/turmeric supplementation on clinical outcomes. Nonetheless, the findings of this meta-analysis are still worthy and provide a basis for further studies in large scales since meta-analyses are in the top of the hierarchy of evidence [43]. Additionally, it should be noted that increased or non-altered levels of proinflammatory cytokines upon curcumin/turmeric supplementation does not necessarily suggest that it would not be beneficial at reducing clinical events, since curcumin/turmeric might function via lipoxygenase, cyclo-oxygenase, or other pathways [53], but not just through NF-κB and IκB kinase signaling pathways [52, 53].

In comparison to the previous meta-analysis, in which a significant heterogenicity was detected, we performed several statistical analyses to search for the source of heterogenicity and publication bias in the current meta-analysis. We found no substantial statistical and methodological heterogeneity across RCTs. First, the subgroup analysis was conducted based on the duration of intervention, treatment dose, and target population. Second, meta-regression analyses showed that none of the expected heterogeneity parameters was the source of heterogeneity. Third, we used Egger's weighted regression test and visual examination of the funnel plot to determine the publication bias, resulting in no significant publication bias. Fourth,

the impact of each study on the overall WMD was determined through sequential omission of individual study. The analyses revealed that no individual study significantly impressed the overall WMD.

Our meta-analysis has several limitations and caveats. First, we did not evaluate several other inflammatory markers, such as CRP, hs-CRP and other cytokines lacking enough data, such as IL-17 and IL-22. Second, although we did not analyze the effect of curcumin/turmeric supplementation on the clinical inflammatory manifestations, currently there are no ongoing RCT determining the impact of curcumin/turmeric supplementation on the clinical outcomes of patients with chronic inflammatory conditions.

Conclusion

The current meta-analysis was the most up-to-date study that contained a significantly higher frequency of studies and individuals in the intervention/placebo groups and indicated beneficial effects of curcumin/turmeric supplementation in reducing the levels of proinflammatory cytokines such as IL-1 and TNF-α. Nonetheless, the analyses revealed no significantly decreased IL-6 serum concentration upon curcumin/turmeric therapy. However, no publication bias, as well as substantial statistical and methodological heterogeneity, were recognized across RCTs. Even though curcumin or curcuminoid seems to be potentially promising compounds in decreasing systemic inflammation in cases with inflammatory settings, currently there is no consensus on the decisive antiinflammatory properties of it. To empower the findings of current

meta-analysis and reach a conclusion of the antiinflammatory characteristics of the curcumin/turmeric supplementation, additional RCTs are still mandatory.

Abbreviations

RCTs, randomized controlled trials; IL, interleukin; TNF, tumor necrosis factor; mAb, monoclonal antibodies; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; NOS, Newcastle-Ottawa Scale; HWE, Hardy–Weinberg equilibrium.

Declarations:

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Disclosure of conflict of interest

None

References

[1] P. Hunter, The inflammation theory of disease, EMBO reports 13(11) (2012) 968-970.
[2] B.K. Martinez, C.M. White, The emerging role of inflammation in cardiovascular disease, Annals of Pharmacotherapy 52(8) (2018) 801-809.
[3] R.H. Straub, Interaction of the endocrine system with inflammation: a function of energy and volume regulation, Arthritis research & therapy 16(1) (2014) 203.
[4] C. Caruntu, M. Mitran, C. Mitran, I. Sarbu, L.-C. Rusu, C. Matei, C. Constantin, M. Neagu, S.-R. Georgescu, Markers of oral lichen planus malignant transformation, Disease markers 2018 (2018).
[5] M. Sanjadi, Z. Rezvanie Sichanie, H. Totonchi, J. Karami, R. Rezaei, S. Aslani, Atherosclerosis and autoimmunity: a growing relationship, International journal of rheumatic diseases 21(5) (2018) 908-921.
[6] C. Fernandez, M. Buyse, M. German-Fattal, F. Gimenez, Influence of the pro-inflammatory cytokines on P-glycoprotein expression and functionality, J Pharm Pharm Sci 7(3) (2004) 359-71.
[7] B. Burkholder, R.-Y. Huang, R. Burgess, S. Luo, V.S. Jones, W. Zhang, Z.-Q. Lv, C.-Y. Gao, B.-L. Wang, Y.-M. Zhang, Tumor-induced perturbations of cytokines and immune cell networks, Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1845(2) (2014) 182-201.
[8] K. Kaneyama, N. Segami, W. Sun, J. Sato, K. Fujimura, Analysis of tumor necrosis factor-α, interleukin-6, interleukin-1β, soluble tumor necrosis factor receptors I and II, interleukin-6 soluble receptor, interleukin-1 soluble receptor type II, interleukin-1 receptor antagonist, and protein in the synovial fluid of patients with temporomandibular joint disorders, Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 99(3) (2005) 276-284.
[9] C. Zhang, The role of inflammatory cytokines in endothelial dysfunction, Basic research in cardiology 103(5) (2008) 398-406.
[10] F. Breedveld, Therapeutic monoclonal antibodies, The Lancet 355(9205) (2000) 735-740.
[11] J. Descotes, Immunotoxicity of monoclonal antibodies, MAbs, Taylor & Francis, 2009, pp. 104-111.
[12] A.F. Shaughnessy, Monoclonal antibodies: magic bullets with a hefty price tag, Bmj 345 (2012) e8346.
[13] B. Kocaadam, N. Şanlier, Curcumin, an active component of turmeric (Curcuma longa), and its effects on health, Critical reviews in food science and nutrition 57(13) (2017) 2889-2895.
[14] M. Ghandadi, A. Sahebkar, Curcumin: An Effective Inhibitor of Interleukin-6, Curr Pharm Des 23(6) (2017) 921-931.
[15] H. Mollazadeh, A.F.G. Cicero, C.N. Blesso, M. Pirro, M. Majeed, A. Sahebkar, Immune modulation by curcumin: The role of interleukin-10, Crit Rev Food Sci Nutr 59(1) (2019) 89-101.
[16] A. Noorafshan, S. Ashkani-Esfahani, A review of therapeutic effects of curcumin, Current pharmaceutical design 19(11) (2013) 2032-2046.
[17] D. Bukvicki, D. Gottardi, S. Prasad, A.K. Tyagi, The healing effects of spices in chronic diseases, Current medicinal chemistry (2019).
[18] I.A. Leclercq, G.C. Farrell, C. Sempoux, A. dela Peña, Y. Horsmans, Curcumin inhibits NF-κB activation and reduces the severity of experimental steatohepatitis in mice, Journal of hepatology 41(6) (2004) 926-934.
[19] C. Buhrmann, A. Mobasheri, F. Busch, C. Aldinger, R. Stahlmann, A. Montaseri, M. Shakibaei, Curcumin modulates nuclear factor κB (nf-κB)-mediated inflammation in human tenocytes in vitro: role of the phosphatidylinositol 3-kinase/Akt pathway, Journal of Biological Chemistry 286(32) (2011) 28556-28566.
[20] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Annals of internal medicine 151(4) (2009) 264-269.

[21] A.R. Jadad, R.A. Moore, D. Carroll, C. Jenkinson, D.J.M. Reynolds, D.J. Gavaghan, H.J. McQuay, Assessing the quality of reports of randomized clinical trials: is blinding necessary?, Controlled clinical trials 17(1) (1996) 1-12.
[22] R. DerSimonian, N. Laird, Meta-analysis in clinical trials, Controlled clinical trials 7(3) (1986) 177-188.
[23] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Statistics in medicine 21(11) (2002) 1539-1558.
[24] C.B. Begg, M. Mazumdar, Operating characteristics of a rank correlation test for publication bias, Biometrics (1994) 1088-1101.
[25] M. Egger, G.D. Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, Bmj 315(7109) (1997) 629-634.
[26] S. Ganjali, A. Sahebkar, E. Mahdipour, K. Jamialahmadi, S. Torabi, S. Akhlaghi, G. Ferns, S.M.R. Parizadeh, M. Ghayour-Mobarhan, Investigation of the effects of curcumin on serum cytokines in obese individuals: a randomized controlled trial, The Scientific World Journal 2014 (2014).
[27] S. Srivastava, A.K. Saksena, S. Khattri, S. Kumar, R.S. Dagur, Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial, Inflammopharmacology 24(6) (2016) 377-388.
[28] R. Uchio, K. Muroyama, C. Okuda-Hanafusa, K. Kawasaki, Y. Yamamoto, S. Murosaki, Hot Water Extract of Curcuma longa L. Improves Serum Inflammatory Markers and General Health in Subjects with Overweight or Prehypertension/Mild Hypertension: A Randomized, Double-Blind, Placebo-Controlled Trial, Nutrients 11(8) (2019) 1822.
[29] P. Usharani, A. Mateen, M. Naidu, Y. Raju, N. Chandra, Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus, Drugs in R & D 9(4) (2008) 243-250.
[30] Y. Panahi, A. Sahebkar, S. Parvin, A. Saadat, A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications, Annals of clinical biochemistry 49(6) (2012) 580-588.
[31] D.C. Nieman, L. Cialdella-Kam, A.M. Knab, R.A. Shanely, Influence of red pepper spice and turmeric on inflammation and oxidative stress biomarkers in overweight females: a metabolomics approach, Plant foods for human nutrition 67(4) (2012) 415-421.
[32] Y. Panahi, M.S. Hosseini, N. Khalili, E. Naimi, L.E. Simental-Mendía, M. Majeed, A. Sahebkar, Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial, Biomedicine & pharmacotherapy 82 (2016) 578-582.
[33] A.-R. Rahimnia, Y. Panahi, G. Alishiri, M. Sharafi, A. Sahebkar, Impact of supplementation with curcuminoids on systemic inflammation in patients with knee osteoarthritis: findings from a randomized double-blind placebo-controlled trial, Drug research 65(10) (2015) 521-525.
[34] A. Kocher, L. Bohnert, C. Schiborr, J. Frank, Highly bioavailable micellar curcuminoids accumulate in blood, are safe and do not reduce blood lipids and inflammation markers in moderately hyperlipidemic individuals, Molecular nutrition & food research 60(7) (2016) 1555-1563.
[35] F. Samadian, N. Dalili, F.P.-r. Gholi, M. Fattah, N. Malih, M. Nafar, A. Firoozan, P. Ahmadpoor, S. Samavat, S. Ziaie, Evaluation of Curcumin's effect on inflammation in hemodialysis patients, Clinical nutrition ESPEN 22 (2017) 19-23.
[36] M. Abdolahi, P. Sarraf, M.H. Javanbakht, N.M. Honarvar, M. Hatami, N. Soveyd, A. Tafakhori, M. Sedighiyan, M. Djalali, A. Jafarieh, A novel combination of ω-3 fatty acids and nano-curcumin modulates interleukin-6 gene expression and high sensitivity C-reactive protein serum levels in patients with migraine: a randomized clinical trial study, CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders) 17(6) (2018) 430-438.

[37] S. Saraf-Bank, A. Ahmadi, Z. Paknahad, M. Maracy, M. Nourian, Effects of curcumin supplementation on markers of inflammation and oxidative stress among healthy overweight and obese girl adolescents: A randomized placebo-controlled clinical trial, Phytotherapy Research 33(8) (2019) 2015-2022.
[38] S.A. Jazayeri-Tehrani, S.M. Rezayat, S. Mansouri, M. Qorbani, S.M. Alavian, M. Daneshi-Maskooni, M.-J. Hosseinzadeh-Attar, Nano-curcumin improves glucose indices, lipids, inflammation, and Nesfatin in overweight and obese patients with non-alcoholic fatty liver disease (NAFLD): a double-blind randomized placebo-controlled clinical trial, Nutrition & metabolism 16(1) (2019) 8.
[39] P. Khajehdehi, M. Pakfetrat, K. Javidnia, F. Azad, L. Malekmakan, M.H. Nasab, G. Dehghanzadeh, Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study, Scandinavian journal of urology and nephrology 45(5) (2011) 365-370.
[40] F. Alizadeh, M. Javadi, A.A. Karami, F. Gholaminejad, M. Kavianpour, H.K. Haghighian, Curcumin nanomicelle improves semen parameters, oxidative stress, inflammatory biomarkers, and reproductive hormones in infertile men: A randomized clinical trial, Phytotherapy Research 32(3) (2018) 514-521.
[41] S. Saadati, A. Sadeghi, A. Mansour, Z. Yari, H. Poustchi, M. Hedayati, B. Hatami, A. Hekmatdoost, Curcumin and inflammation in non-alcoholic fatty liver disease: a randomized, placebo controlled clinical trial, BMC gastroenterology 19(1) (2019) 133.
[42] N. Sadeghi, A. Mansoori, A. Shayesteh, S.J. Hashemi, The effect of curcumin supplementation on clinical outcomes and inflammatory markers in patients with ulcerative colitis, Phytotherapy Research 34(5) (2020) 1123-1133.
[43] A.-B. Haidich, Meta-analysis in medical research, Hippokratia 14(Suppl 1) (2010) 29.
[44] S. Ghosh, S. Banerjee, P.C. Sil, The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update, Food and Chemical Toxicology 83 (2015) 111-124.
[45] Y. Katanasaka, Y. Sunagawa, K. Hasegawa, T. Morimoto, Application of curcumin to heart failure therapy by targeting transcriptional pathway in cardiomyocytes, Biological and Pharmaceutical Bulletin 36(1) (2013) 13-17.
[46] N.P. Wang, Z.F. Wang, S. Tootle, T. Philip, Z.Q. Zhao, Curcumin promotes cardiac repair and ameliorates cardiac dysfunction following myocardial infarction, British journal of pharmacology 167(7) (2012) 1550-1562.
[47] S. Shishodia, H.M. Amin, R. Lai, B.B. Aggarwal, Curcumin (diferuloylmethane) inhibits constitutive NF-κB activation, induces G1/S arrest, suppresses proliferation, and induces apoptosis in mantle cell lymphoma, Biochemical pharmacology 70(5) (2005) 700-713.
[48] A. Sahebkar, Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis, Phytotherapy research 28(5) (2014) 633-642.
[49] Y. Panahi, M.S. Hosseini, N. Khalili, E. Naimi, M. Majeed, A. Sahebkar, Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis, Clinical nutrition 34(6) (2015) 1101-1108.
[50] G. Derosa, P. Maffioli, L.E. Simental-Mendia, S. Bo, A. Sahebkar, Effect of curcumin on circulating interleukin-6 concentrations: a systematic review and meta-analysis of randomized controlled trials, Pharmacological research 111 (2016) 394-404.
[51] R. Tabrizi, S. Vakili, M. Akbari, N. Mirhosseini, K.B. Lankarani, M. Rahimi, M. Mobini, S. Jafarnejad, Z. Vahedpoor, Z. Asemi, The effects of curcumin-containing supplements on biomarkers of inflammation and oxidative stress: A systematic review and meta-analysis of randomized controlled trials, Phytotherapy research 33(2) (2019) 253-262.
[52] C.M. White, V. Pasupuleti, Y.M. Roman, Y. Li, A.V. Hernandez, Oral turmeric/curcumin effects on inflammatory markers in chronic inflammatory diseases: a systematic review and meta-analysis of randomized controlled trials, Pharmacological research (2019) 104280.

[53] S. Prasad, S.C. Gupta, A.K. Tyagi, B.B. Aggarwal, Curcumin, a component of golden spice: from bedside to bench and back, Biotechnology advances 32(6) (2014) 1053-1064.

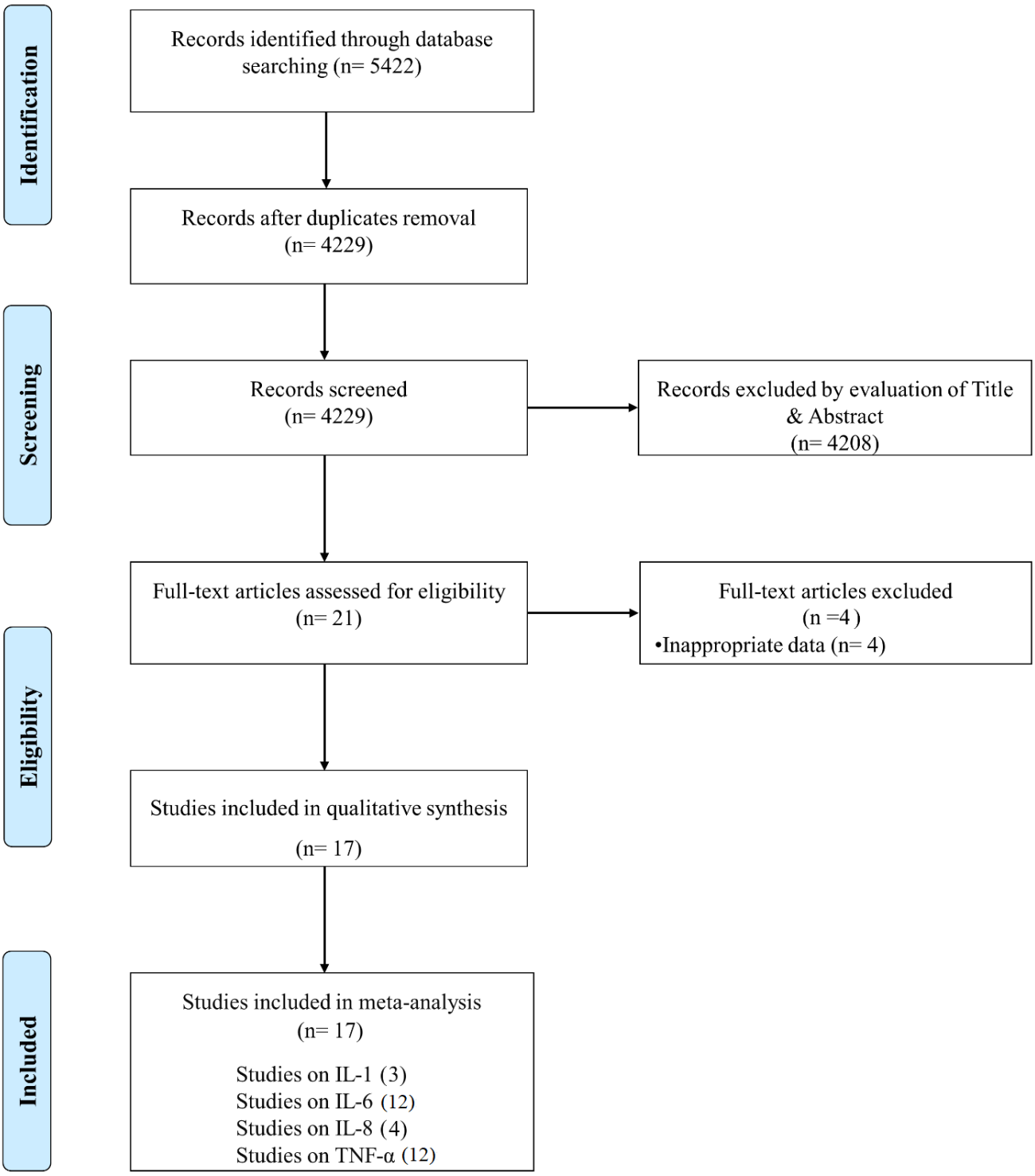
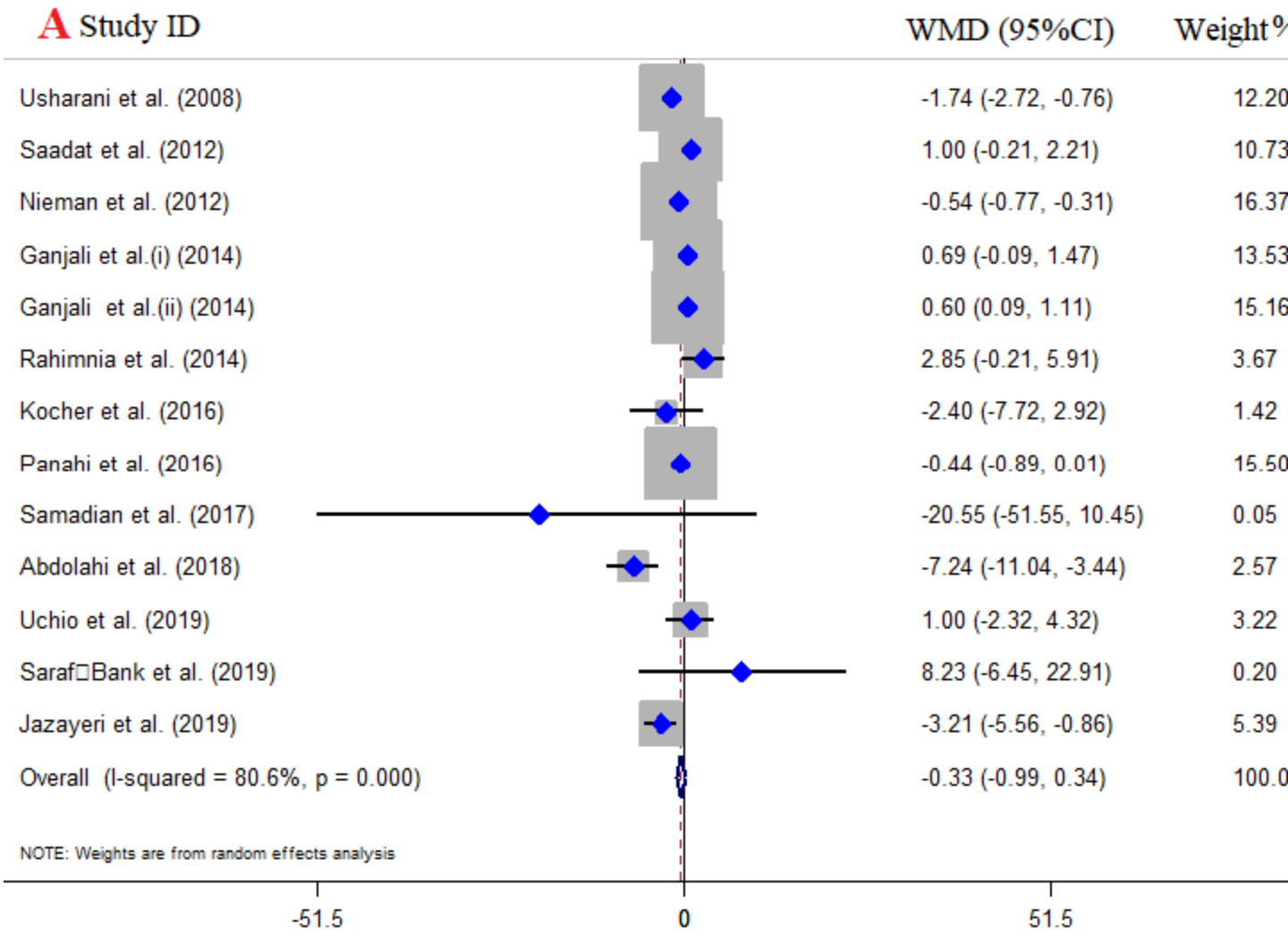


Figure 1. Flow diagram of the study selection process.


A Study ID
WMD (95%CI)
Weight%
Usharani et al. (2008)
-1.74 (-2.72, -0.76)
12.20
Saadat et al. (2012)
1.00 (-0.21, 2.21)
10.73
Nieman et al. (2012)
-0.54 (-0.77, -0.31)
16.37
Ganjali et al.(i) (2014)
0.69 (-0.09, 1.47)
13.53
Ganjali et al.(ii) (2014)
0.60 (0.09, 1.11)
15.16
Rahimnia et al. (2014)
2.85 (-0.21, 5.91)
3.67
Kocher et al. (2016)
-2.40 (-7.72, 2.92)
1.42
Panahi et al. (2016)
-0.44 (-0.89, 0.01)
15.50
Samadian et al. (2017)
-20.55 (-51.55, 10.45)
0.05
Abdolahi et al. (2018)
-7.24 (-11.04, -3.44)
2.57
Uchio et al. (2019)
1.00 (-2.32, 4.32)
3.22
Saraf□Bank et al. (2019)
8.23 (-6.45, 22.91)
0.20
Jazayeri et al. (2019)
-3.21 (-5.56, -0.86)
5.39
Overall (I-squared = 80.6%, p = 0.000)
-0.33 (-0.99, 0.34)
100.0
NOTE: Weights are from random effects analysis
-51.5
0
51.5

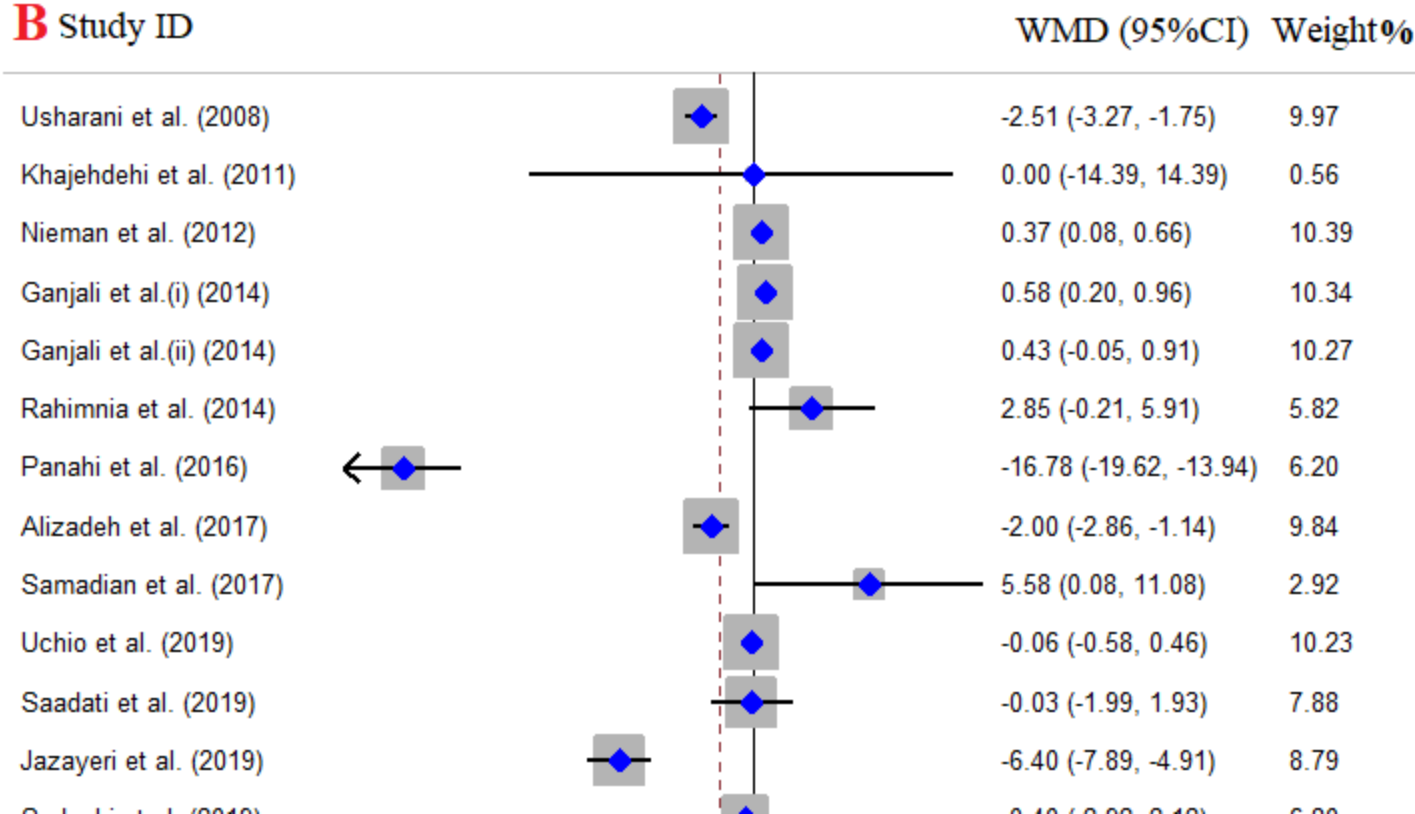
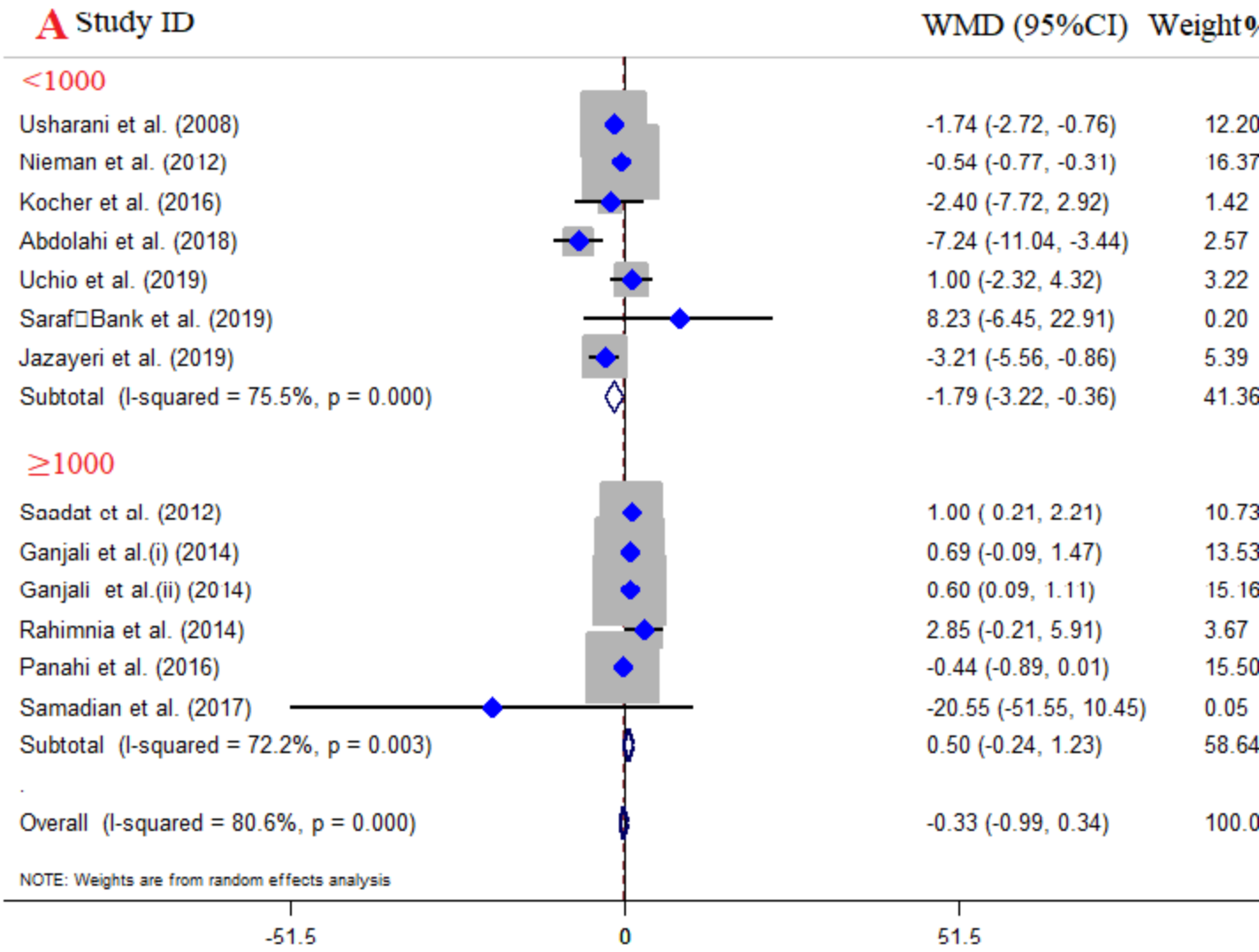

B Study ID
WMD (95%CI)
Weight%
Usharani et al. (2008)
-2.51 (-3.27, -1.75)
9.97
Khajehdehi et al. (2011)
0.00 (-14.39, 14.39)
0.56
Nieman et al. (2012)
0.37 (0.08, 0.66)
10.39
Ganjali et al.(i) (2014)
0.58 (0.20, 0.96)
10.34
Ganjali et al.(ii) (2014)
0.43 (-0.05, 0.91)
10.27
Rahimnia et al. (2014)
2.85 (-0.21, 5.91)
5.82
Panahi et al. (2016)
-16.78 (-19.62, -13.94)
6.20
Alizadeh et al. (2017)
-2.00 (-2.86, -1.14)
9.84
Samadian et al. (2017)
5.58 (0.08, 11.08)
2.92
Uchio et al. (2019)
-0.06 (-0.58, 0.46)
10.23
Saadati et al. (2019)
-0.03 (-1.99, 1.93)
7.88
Jazayeri et al. (2019)
-6.40 (-7.89, -4.91)
8.79

Figure 2. Forest plot presenting WMD and 95% CI for the effect of curcumin on IL-6 and TNF-α serum level in overall population for IL-6 (A) and TNF-α (B).


A Study ID
WMD (95%CI)
Weight%
<1000
Usharani et al. (2008)
-1.74 (-2.72, -0.76)
12.20
Nieman et al. (2012)
-0.54 (-0.77, -0.31)
16.37
Kocher et al. (2016)
-2.40 (-7.72, 2.92)
1.42
Abdolahi et al. (2018)
-7.24 (-11.04, -3.44)
2.57
Uchio et al. (2019)
1.00 (-2.32, 4.32)
3.22
Saraf□Bank et al. (2019)
8.23 (-6.45, 22.91)
0.20
Jazayeri et al. (2019)
-3.21 (-5.56, -0.86)
5.39
Subtotal (I-squared = 75.5%, p = 0.000)
-1.79 (-3.22, -0.36)
41.36
≥1000
Saadat et al. (2012)
1.00 (0.21, 2.21)
10.73
Ganjali et al.(i) (2014)
0.69 (-0.09, 1.47)
13.53
Ganjali et al.(ii) (2014)
0.60 (0.09, 1.11)
15.16
Rahimnia et al. (2014)
2.85 (-0.21, 5.91)
3.67
Panahi et al. (2016)
-0.44 (-0.89, 0.01)
15.50
Samadian et al. (2017)
-20.55 (-51.55, 10.45)
0.05
Subtotal (I-squared = 72.2%, p = 0.003)
0.50 (-0.24, 1.23)
58.64
Overall (I-squared = 80.6%, p = 0.000)
-0.33 (-0.99, 0.34)
100.0
NOTE: Weights are from random effects analysis
-51.5
0
51.5

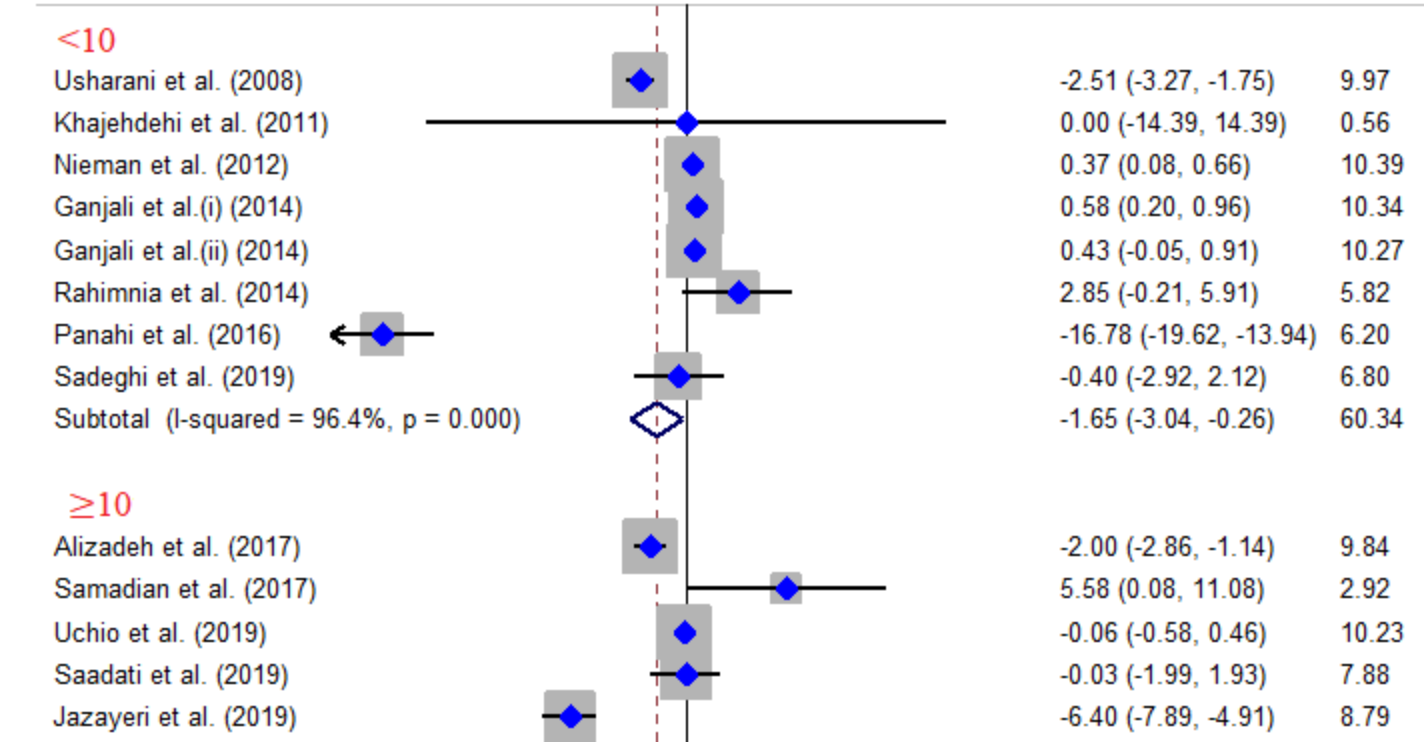
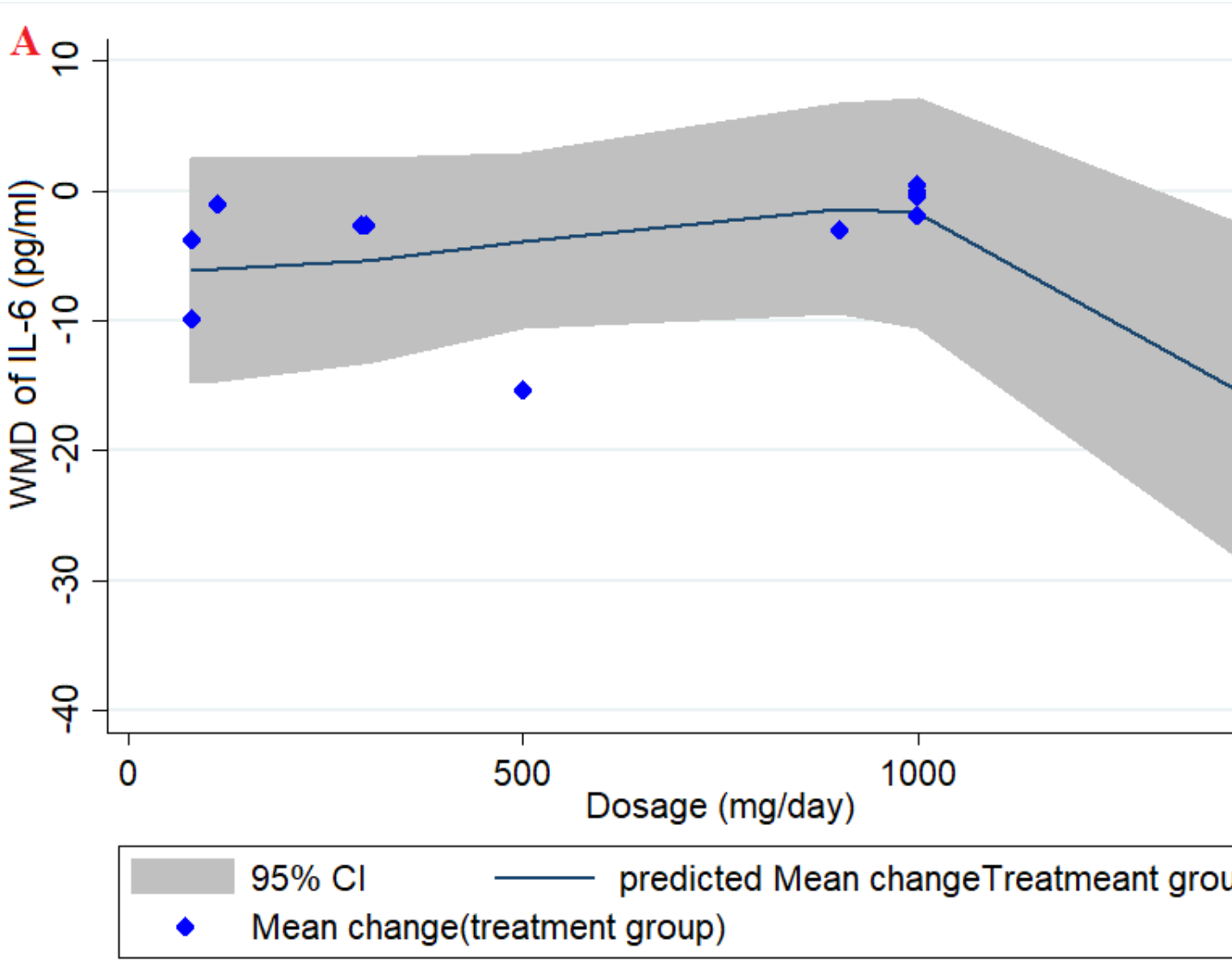

B Study ID
WMD (95%CI)
Weight
<10
Usharani et al. (2008)
-2.51 (-3.27, -1.75)
9.97
Khajehdehi et al. (2011)
0.00 (-14.39, 14.39)
0.56
Nieman et al. (2012)
0.37 (0.08, 0.66)
10.39
Ganjali et al.(i) (2014)
0.58 (0.20, 0.96)
10.34
Ganjali et al.(ii) (2014)
0.43 (-0.05, 0.91)
10.27
Rahimnia et al. (2014)
2.85 (-0.21, 5.91)
5.82
Panahi et al. (2016)
-16.78 (-19.62, -13.94)
6.20
Sadeghi et al. (2019)
-0.40 (-2.92, 2.12)
6.80
Subtotal (I-squared = 96.4%, p = 0.000)
-1.65 (-3.04, -0.26)
60.34
≥10
Alizadeh et al. (2017)
-2.00 (-2.86, -1.14)
9.84
Samadian et al. (2017)
5.58 (0.08, 11.08)
2.92
Uchio et al. (2019)
-0.06 (-0.58, 0.46)
10.23
Saadati et al. (2019)
-0.03 (-1.99, 1.93)
7.88
Jazayeri et al. (2019)
-6.40 (-7.89, -4.91)
8.79

Figure 3. Forest plot presenting WMD and 95% CI for the effect of curcumin on IL-6 and TNF-α serum level in subgroups; A: IL-6 based on dosage (mg/day), B: TNF-α based on intervention duration (week).


A
WMD of IL-6 (pg/ml)
10
0
-10
-20
-30
-40
0
500
1000
Dosage (mg/day)
95% CI
predicted Mean changeTreatmeant grou
Mean change(treatment group)

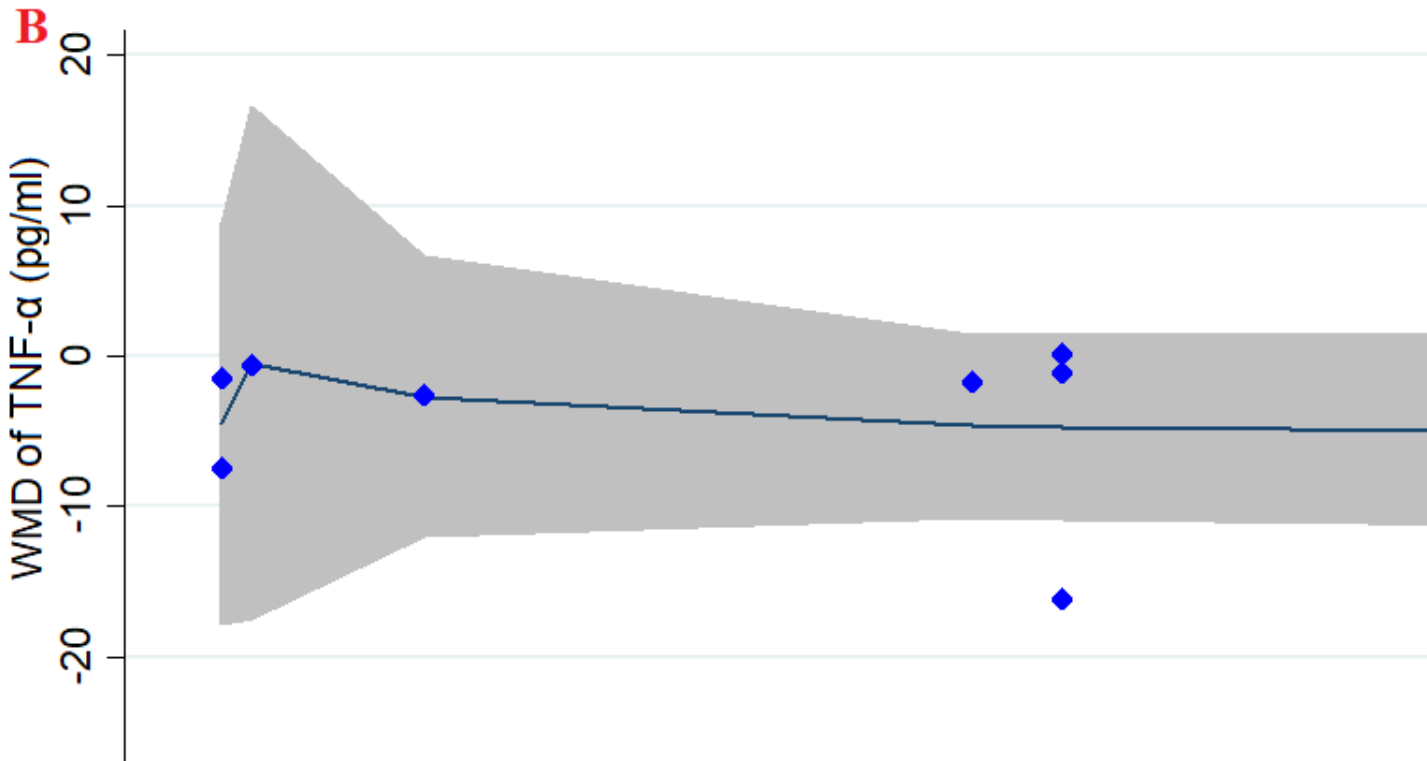
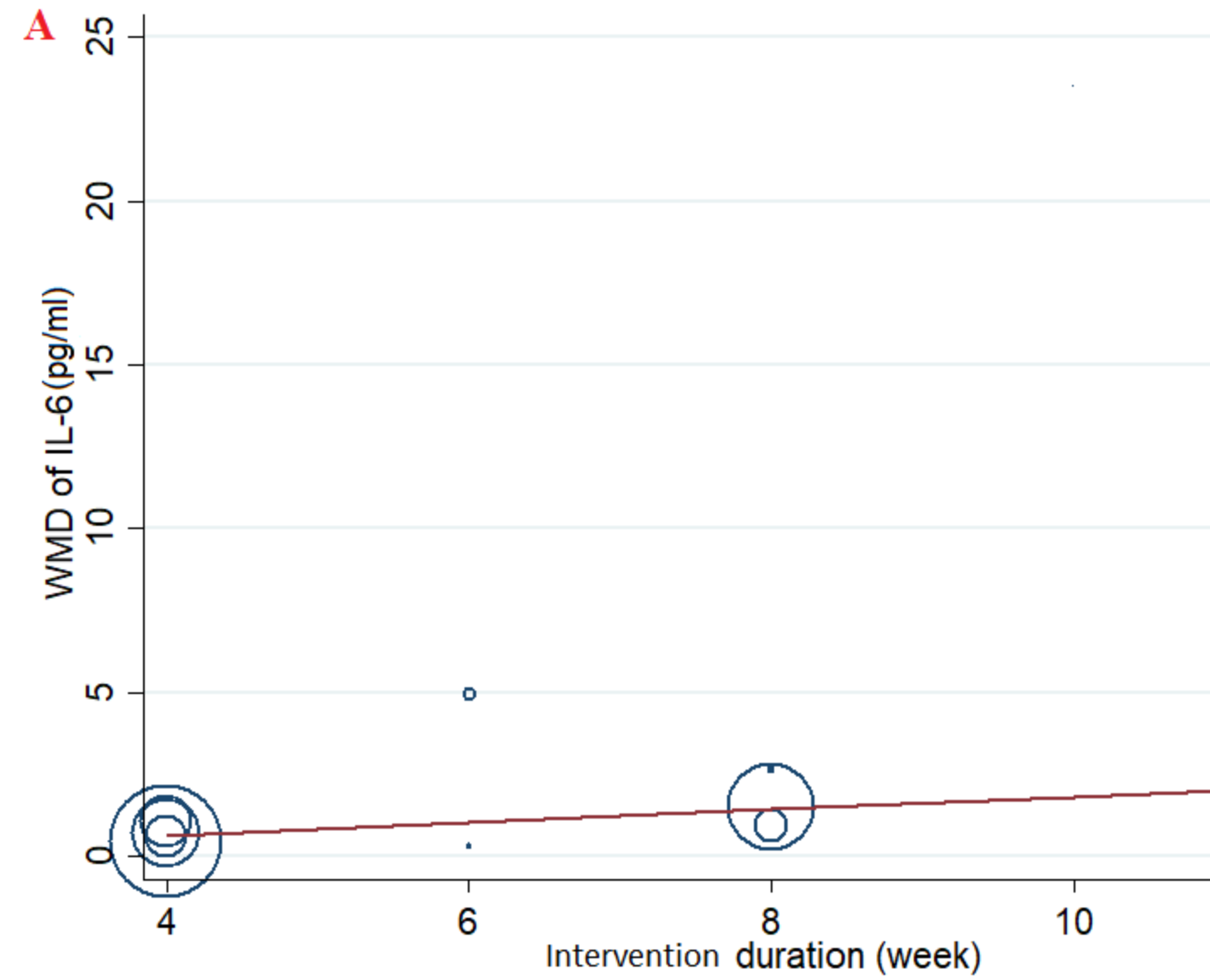

B
WMD of TNF-α (pg/ml)
20
10
0
-10
-20

Figure 4. Fracpoly regress for the effect of curcum on serum level of IL-6 (A) and TNF-α (B).


A
WMD of IL-6(pg/ml)
25
20
15
10
5
0
4
6
8
10
Intervention duration (week)

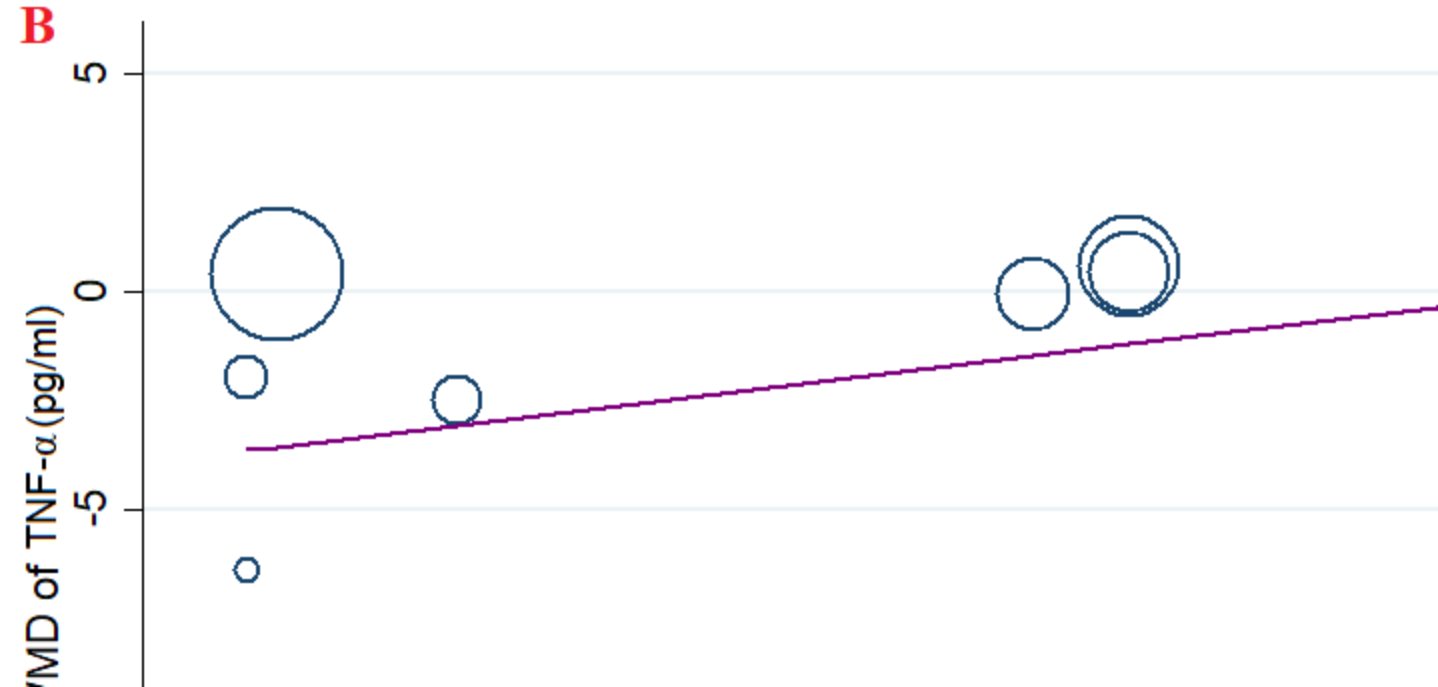
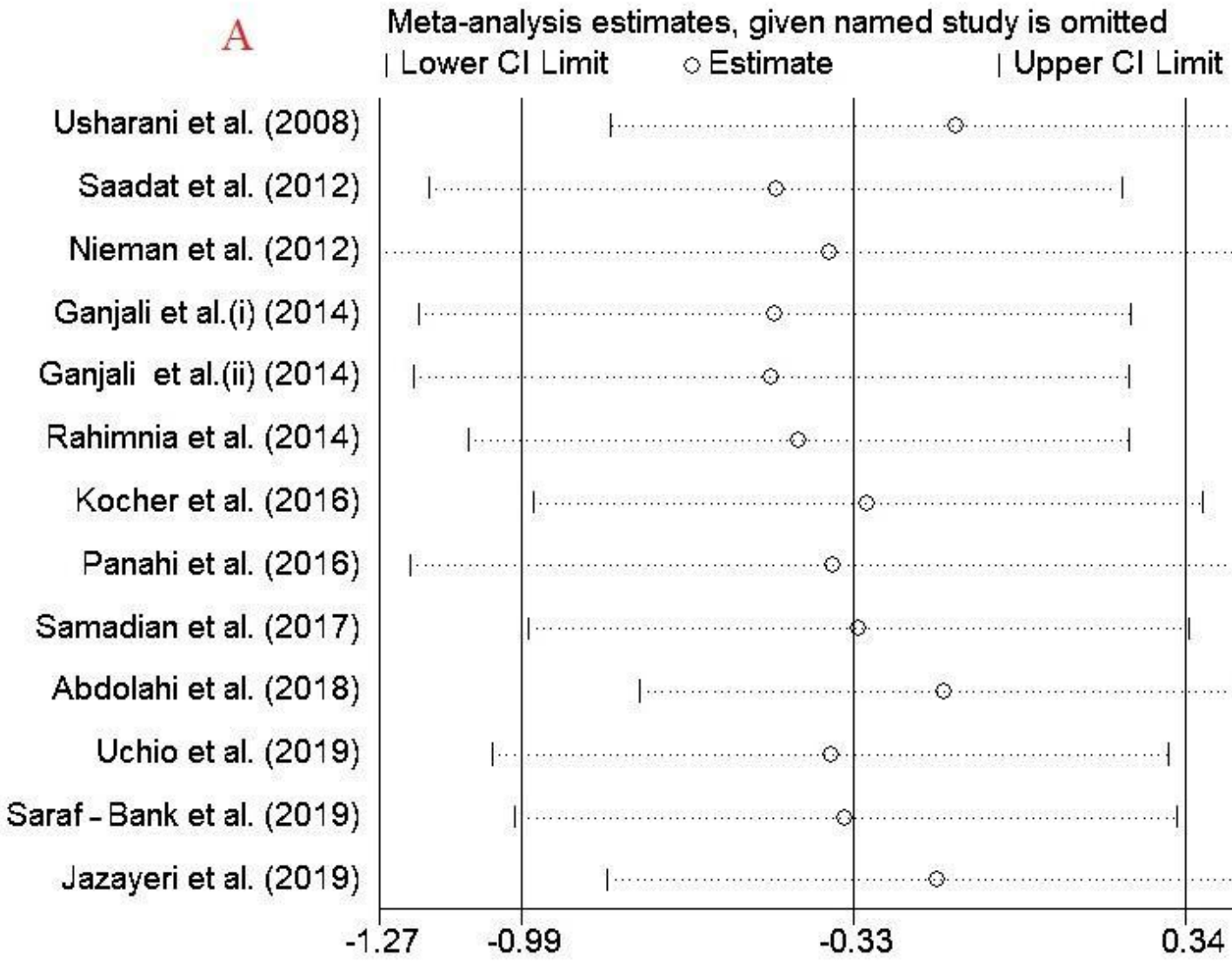

B
WMD of TNF-α(pg/ml)
5
0
-5

Figure 5. Random-effects meta-regression plots of the association between WMD of IL-6 and TNF-α and curcumin supplementation based on A:intervention duration (IL-6) and B: dosage (TNF-α).

Figure 6: Funnel plots detailing publication bias in studies included in the meta-analysis of the effect of curcumin on IL-6 (A), TNF-α (B).


A
Meta-analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Usharani et al. (2008)
Saadat et al. (2012)
Nieman et al. (2012)
Ganjali et al.(i) (2014)
Ganjali et al.(ii) (2014)
Rahimnia et al. (2014)
Kocher et al. (2016)
Panahi et al. (2016)
Samadian et al. (2017)
Abdolahi et al. (2018)
Uchio et al. (2019)
Saraf-Bank et al. (2019)
Jazayeri et al. (2019)
-1.27
-0.99
-0.33
0.34

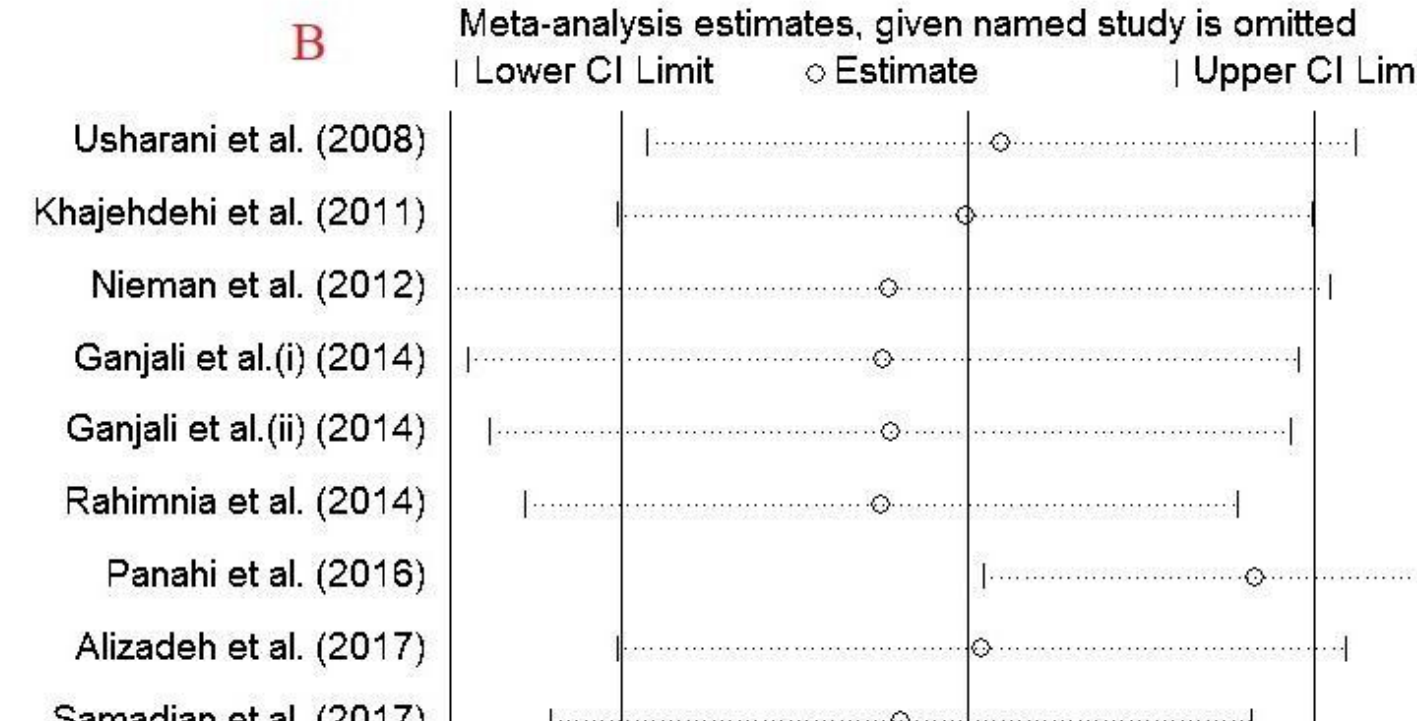

B
Meta-analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Lim
Usharani et al. (2008)
Khajehdehi et al. (2011)
Nieman et al. (2012)
Ganjali et al.(i) (2014)
Ganjali et al.(ii) (2014)
Rahimnia et al. (2014)
Panahi et al. (2016)
Alizadeh et al. (2017)

Figure 7. Leave-one-out sensitivity analyses of the impact of curcumin consumption on the serum levels of IL-6 (A), and TNF-α (B).

Table 1. Demographic characteristics of the included studies.

Year	Country	Intervention / Control (Sample size)	Mean age (Intervention / Control)	Intervention Duration (Week)	Target population	Dosage (mg/day)	Interver
2014	Iran	15 / 15	18-65 / 18-65	4	Overweight	1000	Curcu
2014	Iran	15 /15	18-65 / 18-65	4	Overweight	1000	Curcu
2016	India	78 / 82	50.23 ± 8/ 50.27 ± 8	16	Knee Osteoarthritis	500	Curcu
2019	Japan	43 / 44	58.8± 5.3 / 58.5 ± 5.3	12	Overweight	900	Curcu
2008	India	23 / 21	55.52 ± 10 /49.75 ± 8.18	8	T2DM	300	curcu
2012	Iran	40 / 40	47.5 ± 10 /48.3 ± 8.5	4	Chronic cutaneous	1000	curcu
2012	USA	30 / 30	55.7±1.4 / 57.7±1.7	4	Overweight	112	Tur
2014	Iran	15 / 15	18-65 / 18-65	4	Overweight	1000	Curcu
2014	Iran	15 / 15	18-65 / 18-65	4	Overweight	1000	Curcu
2014	Iran	19 / 21	57.32±8 / 57.57±9	6	Knee Osteoarthritis	1500	curcu
2016	Germany	42 / 42	NR / NR	6	Hyperlipidemic	294	Curcu
2016	Iran	50 / 50	44.80 ± 8 /43.46 ± 9.7	8	Mts	1000	Cur
2017	Iran	35 / 36	49.6 ± 16 /NR	12	ESRD	1500	Tur
2018	Iran	19 / 19	37.36±1.9 /43.46 ± 9.70	8	Migraine	80	Nano-
2019	Japan	43 / 44	58.8± 5.3 / 58.5 ± 5.5	12	Overweight	900	Curcu
2019	Iran	30 / 30	16.03 ± 1.5 / 15.98 ± 1	10	Overweight	500	Cur
2019	Iran	42 / 42	41.86 ± 5.6 /42.5 ± 6.2	12	NAFLD	80	Nano-
2011	Iran	20 / 20	52.9 ± 9.2 / 52.6 ± 9.7	8	Diabetic nephropathy	1500	Tur
2012	Iran	40 / 40	47.5 ± 10.7 / 48.3 ± 8.5	4	Chronic cutaneous	1000	curcu
2012	USA	30 / 30	55.7±1.4 / 57.7±1.7	4	Overweight	112	Turmer
2014	Iran	15 / 15	18-65 / 18-65	4	Overweight	1000	Curcu

2014	Iran	15 / 15	18-65 / 18-65	4	Overweight	1000	Curcu
2008	India	23 / 21	55.52 ± 10 / 49.75 ± 8.1	8	T2DM	300	curcu
2011	Iran	20 / 20	52.9 ± 9.2 / 52.6 ± 9.7	8	Diabetic nephropathy	1500	Tur
2012	USA	30 / 30	55.7±1.4 / 57.7±1.7	4	Overweight	112	Tur
2014	Iran	15 / 15	18-65 / 18-65	4	Overweight	1000	Curcu
2014	Iran	15 / 15	18-65 / 18-65	4	Overweight	1000	Curcu
2014	Iran	19 / 21	57.32±8.7 / 57.57±9.05	6	Knee Osteoarthritis	1500	curcu
2016	Iran	50 / 50	44.80 ± 8.6 / 43.46 ± 9.7	8	Mts	1000	Curcu
2017	Iran	28 / 28	30.54 ± 4 / 30 ± 3.96	10	Infertility	80	Cur
2017	Iran	35 / 36	49.6 ± 16.8 / NA	12	ESRD	1500	Tur
2019	Japan	43 / 44	58.8± 5.3 / 58.5 ± 5.5	12	Overweight	900	Cu
2019	Iran	25 / 23	11.5 ± 46.1 / 10.9 ± 45.1	12	NAFLD	1500	Cur
2019	Iran	42 / 42	41.86 ± 5.6 / 42.5 ± 6.2	12	NAFLD	80	Nano-
2019	Iran	35/ 35	40.1 ± 13.2 / 40.6 ± 12.4	8	Ulcerative colitis	1500	Cur

IL; Interleukin, TNF-α; Tumor necrosis factor-α, NR; Not reported, Mts; Metabolic syndrome, T2DM; Type 2 diabetes mellitus, NAFLD; Non-alcoholic fatty liver disease, ESRD; End-Stage Renal Disease.

Table 2. The effects of curcumin consumption on inflammatory biomarkers in overall population and subgroup analyses.

Parameter		Number of trials	Weighted mean difference	95%CI (*P* value)	T
IL-1					
Overall		4	**-2.33**	**-3.33 to -1.34 (<0.001)**	
Subgroup					
Dosage (mg/day)	<1000	2	-0.02	-0.17 to 0.12 (0.73)	

	≥1000	2	-7.32	-21.76 to 7.11 (0.32)
Intervention duration (week)	< 10	2	-0.02	-0.17 to 0.12 (0.73)
	≥10	2	-7.32	-21.76 to 7.11 (0.32)
IL-6				
Overall		13	-0.33	-0.99 to 0.34 (0.33)
Subgroup				
Dosage (mg/day)	<1000	7	**1.79-**	**-3.22 to -0.36 (0.01)**
	≥1000	6	0.50	-0.24 to 1.23 (0.18)
Intervention duration (week)	< 10	9	-0.21	-0.88 to 0.46 (0.54)
	≥10	4	-0.89	-5.22, 3.43 (0.68)
Target population	Overweight	5	0.28	-0.60 to 1.16 (0.53)
IL-8				
Overall		5	0.52	-1.13 to 2.17 (0.53)
TNF-α				
Overall		13	**-1.61**	**-2.72 to -0.51 (<0.001)**
Subgroup				
Dosage (mg/day)	<1000	5	**-1.99**	**-3.58 to -0.39 (0.01)**
	≥1000	8	-1.31	-3.29 to 0.68 (0.19)
Intervention duration (week)	< 10	8	**-1.65**	**-3.04 to -0.26 (0.02)**
	≥10	5	-1.31	-3.66 to 1.04 (0.27)
Target population	Overweight	4	**0.37**	**0.14 to 0.59 (<0.001)**
	NAFLD	2	-3.25	-9.49 to 2.99 (0.30)

IL; Interleukin, CI; Confidence interval, TNF-α; Tumor necrosis factor-α, NAFLD; Non-alcoholic fatty liver disease

Table 3. Findings from meta-regression on the effects of curcumin consumption on inflammatory biomarkers.

Parameter	Coefficient	Standard Error	95%CI
IL-1			
Dosage	0.03	0.04	-0.009, 0.050
Intervention Duration	-0.94	0.54	-3.29, 1.40
IL-6			
Dosage	0.002	0.002	-0.0032, 0.0085
Intervention Duration	0.19	0.079	-0.02, 0.37
IL-8			
Dosage	-0.003	0.003	-0.012, 0.011
Intervention Duration	-1.82	5.61	-19.69, 16.03
TNF			
Dosage	0.002	0.002	-0.003, 0.005
Intervention Duration	-0.15	0.50	-1.26, 0.94

IL; Interleukin, TNF-α; Tumor necrosis factor-α