# Effect of tomato consumption on inflammatory markers in health and disease status: A systematic review and meta-analysis of clinical trials

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# Effect of tomato consumption on inflammatory markers in health and disease status: A systematic review and meta-analysis of clinical trials

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SUMMARY

*Background and aims:* Inflammation is a major cause of chronic diseases. Several studies have investigated the effects of tomato intake on inflammatory biomarkers; however, the results are equivocal. Therefore, the present study aimed to systematically review and analyses randomized clinical trials (RCTs) assessing the effects of tomato intake on inflammatory biomarkers in adults.

*Methods:* A systematic search was performed in PubMed, Scopus, ISI Web of Science, and Cochrane Library databases to find RCTs related to the effect of tomato intake on inflammatory markers, including C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α), up to November 2021. Meta-analyses were performed using the random-effects model.

*Results:* A total of 465 subjects sourced from seven eligible RCTs (8 treatment arms) were entered into the analysis. Pooled effect size of articles indicated that tomato intake was not significantly effective on CRP (WMD: 0.13 mg/dL, 95% CI: −0.09 to 0.36; P = 0.23, $I^2$: 83.9%) and IL-6 (Hedges' g = −0.12; 95% CI -0.36, 0.13; P = 0.34, $I^2$: 0.0%) levels compared to the control group. But it can significantly reduce TNF-α (Hedges' g = −0.45; 95% CI -0.76, −0.13; P = 0.005, $I^2$: 0.0%) levels.

*Conclusion:* Generally, the present study showed that tomato intake has no significant effect on serum CRP, and IL-6 concentrations, but can reduce serum TNF-α levels significantly. However, additional well-designed studies that include more diverse populations and longer duration are warranted.



## 1. Introduction

Inflammatory responses are protective biological processes to eliminate detrimental stimuli by coordination of pro and anti-inflammatory endogenous mediators [1]. Inflammation can be both acute and chronic [2]. Chronic inflammation, which is

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reflected by the enhancement of cytokines, markers of endothelial activation, and acute-phase proteinsis, is recognized as a major contributor to the development of non-communicable diseases, including cardiovascular diseases (CVDs), type 2 diabetes (T2DM), neurological disorders, pulmonary diseases, autoimmune disorders and most types of cancers [3–7]. C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α) are the most important inflammatory mediators concerning health status which are secreted by adipocytes and are increasingly considered indicators of chronic inflammation [8,9]. The concentration of these inflammatory mediators can be influenced by various factors such as disease development, age, smoking, and specific nutrients [10,11]. Different therapeutic strategies such as medication and lifestyle modifications have been applied to reduce inflammatory responses [12,13]. Recent studies have reported that the administration of anti-inflammatory drugs has adverse effects ranging from minor symptoms such as digestive problems to serious disorders like liver-kidney disorders [14,15]. So recently researchers have focused on dietary interventions, as a cheap strategy with few side effects, to reduce inflammation in humans.

Evidence suggests that greater consumption of fruit and vegetables can effectively reduce inflammation and oxidative stress [16,17]. Tomato, otherwise referred to as *Solanum lycopersicum*, is ubiquitous in most dietary patterns across the world and its contribution to health has been reported in scientific research [18]. It can be consumed as fresh or processed products such as sauce, paste, or juice. Tomato is a rich source of many substances including carotenoids (lycopene, carotenes, lutein, and phytoene), flavonoids, vitamins, amino acids, and other nutrients [19,20]. Previous studies have assessed the beneficial effects of tomato and their results have indicated a lot of useful properties such as antioxidant, anticancer, antimicrobial, anti-mutagenic, anti-inflammatory, anti-neurodegeneration, antiplatelet, and cardio-protective [21–23]. Most of the health benefits of tomato might be due to its anti-inflammatory and antioxidant properties [18]. Therefore, several randomized controlled trials (RCTs) have evaluated the effects of tomato intake on inflammatory mediators [24–30]. Although some investigations demonstrated that the consumption of tomato is associated with decreased levels of inflammatory mediators, others found unchanged levels of inflammatory markers [25,26,28–30]. Discrepancies among current evidence might be related to the differences in study design, different characteristics of studies populations, duration of supplementation, as well as different amounts of tomato used. In the systematic review and meta-analysis article, we included all published RCTs assessing the effect of tomato intake on CRP, IL-6, and TNF-α.

## 2. Methods

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement [31].

### 2.1. Search strategy

In this systematic review and meta-analysis, two investigators searched independently PubMed, Scopus, ISI Web of Science, and Cochrane Library for studies listed from database inception to November 2021. The following MeSH and non-MeSH terms were used in our search strategy ("Inflammation" OR "C Reactive Protein" OR "CRP" OR "Tumor Necrosis Factor-alpha" OR "TNF alpha" OR "Tumor Necrosis Factor-α" OR "Tumor Necrosis Factor" OR "TNF-α" OR "Interleukin 6" OR "IL6") AND ("Lycopersicon esculentum" OR "tomato"). The search was not restricted to publication time, study design, and language. In order not to miss any relevant publications, we also analyzed reference lists of relevant articles.

### 2.2. Study selection

The search results were imported into a bibliographic database and duplicates were removed automatically for accelerating the process of screening citations (EndNote X6; Thomson Reuters, New York). After removing duplicate citations, two independent individuals screened titles and abstracts to identify articles of interest. Subsequently, full texts of related articles were obtained and reviewed. Articles were included if they met all of the following criteria: (a) designed as RCTs (parallel or cross-over); (b) performed on adults (aged ≥18 years); (c) included participants randomized to tomato or control group; (d) circulating CRP, IL-6, and TNF-α levels were reported; and (e) data reporting regarding the changes of mentioned outcomes from baseline. Articles were excluded if they had a concomitant intervention for which effects could not be separated; or were of less than 1 weeks' duration, or studies on patients with inflammatory diseases such as hepatitis C, inflammatory bowel disease, and arthritis. Articles published in languages other than English were also excluded. If duplicate publications from the same study were identified, the publication with the largest number of cases from the study was included. In addition, when the articles reported insufficient data, the authors of that article were contacted by e-mail to request missing information. Any disagreement was resolved by discussion, consensus, or arbitration by a third senior investigator.

### 2.3. Data extraction

Two authors performed literature searches independently, and they resolved discrepancies by consensus or discussion with a third author. Data abstracted from the eligible articles were the last name of the first author, publication year, location of the study, total sample size, individuals' characteristics (e.g., mean age, sex, and body mass index [BMI]), type of study population, duration of the intervention, and dose of intervention.

### 2.4. Quality assessment

The quality of qualified studies was measured by two independent investigators by using the Cochrane Collaboration modified risk of bias tool [32], in which the risk of bias in RCTs is assessed in seven domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each trial is considered "high risk" if it contained methodological flaws that may have affected the results, "low risk" if the flaw was deemed inconsequential, and "unclear risk" if the information was insufficient to determine. In the event of a discrepancy, it was resolved by consensus or discussion.

### 2.5. Statistical analysis

We used Stata software (version 12.0; Stata Corporation, College Station, TX, USA) to perform the meta-analysis and statistical analysis. Mean change and standard deviation (SD) of outcomes were used for calculating pooled weighted mean difference (WMD). Also, Hedges' g [33] was used to calculate pooled effect size for TNF-α and IL-6. In the event of no reported SD of the mean difference, it was calculated as follows: SD = square root [(SD pre-treatment) $^2$ + (SD post-treatment) $^2$ − (2 × R × SD pretreatment × SD post-treatment)]. For trials that only reported standard error of the mean (SEM), SD was obtained using the following formula:

SD = SEM $\sqrt{n}$, where "n" is the number of subjects in each group. Since included RCTs were carried out in different settings, random-effect models were used to conduct all meta-analyses. The heterogeneity was assessed by using the $I^2$ statistic with a value of <25%, 26–50%, and >50% were considered as low, moderate, and high degrees of heterogeneity, respectively. To identify whether differences in study characteristics were potential contributors to heterogeneity, we performed subgroup analyses based on participants' mean age, health status, gender, and study duration. Rather, sensitivity analyses were performed, to explore the extent to which inferences might depend on a particular study or group of studies. We also assessed publication bias by Egger's regression asymmetry test. A *P value* ‘0.05 was accepted as statistically significant unless otherwise specified.

## 3. Results

Our search yielded 785 articles for an initial review. Following the removal of duplicates, 467 were retained. We excluded 455 irrelevant references by reading titles and abstracts. In the next step, 5 papers were excluded based on the full-text review. These exclusions were due to the following reasons: administered tomato in combination with other components (n = 4), and study with an intervention period of less than one week (n = 1). As a result, a total of seven articles were identified as eligible for the present meta-analysis. The flow chart of studies is presented in Fig. 1.

### 3.1. Study characteristics

Details characteristics of the included trials are outlined in Table 1. In total, 465 participants were enrolled in selected articles. These studies were published between 2000 and 2020 and were carried out in Iran [30], New Zealand [26], Germany [27], Israel [29], Scotland [25], the Czech Republic [28], and Taiwan [24]. The mean age of the participants ranged from 23 to 62 years old. Four studies [25,26,28,29] included both male and female participants, two studies enrolled female subjects [24,30], and one study included only male participants [27]. The follow-up period ranged from 2 to 12 weeks. Included studies were carried out in various populations, including T2DM patients [26], patients with hypertension [28], overweight or obesity subjects [30], post-menopausal women [24], middle-aged subjects [25], and healthy participants [27,29].

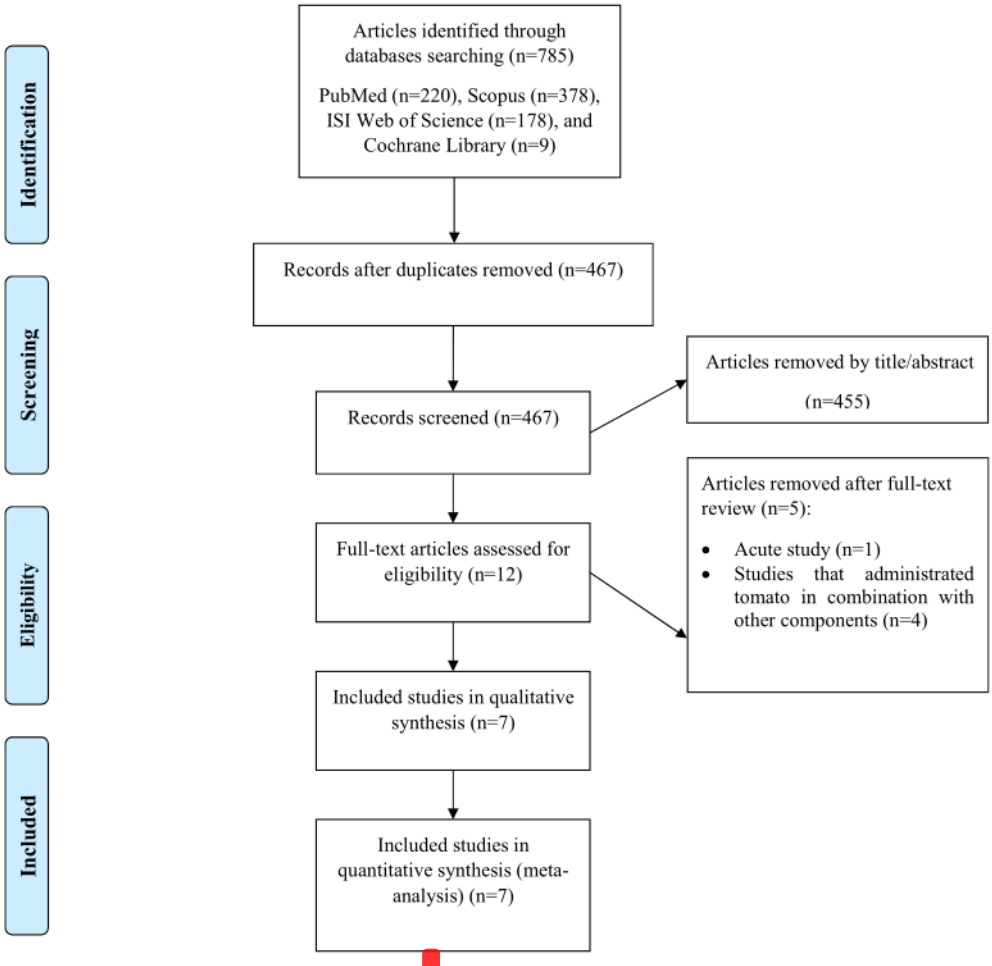


**Fig. 1.** Flow diagram of literature selection process for the systematic review of randomized controlled trials investigating the effect of tomato intake on inflammatory biomarkers in adults.

**Table 1**
Summary characteristics of 7 randomized controlled trials identified in the current systematic review and meta-analysis assessing the effect of tomato intake on inflammatory biomarkers in adults.

| First author (year) | Country | Sample size | Gender | Mean age (years) | Mean BMI (kg/m$^2$) | Duration (weeks) | Participant's health status | Intervention | Control | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|
| Upritchard et al. (2000) | New Zealand | 28 | Both | 62 | 30 | 4 | T2DM | 500 ml/d of tomato juice | Placebo | CRP |
| Briviba et al. (2004) a | Germany | 25 | Male | 34 | NR | 2 | Healthy smokers | Tomato oleoresin extract capsules | Placebo | TNF-α |
| Briviba et al. (2004) b | Germany | 30 | Male | 33 | NR | 2 | Healthy non-smokers | Tomato oleoresin extract capsules | Placebo | TNF-α |
| Blum et al. (2007) | Israel | 63 | Both | 45 | 29 | 4 | Healthy volunteers | 300 g/day tomatoes | Usual diet with tomatoes prohibited | CRP |
| Thies et al. (2012) | Scotland | 157 | Both | 51 | 26 | 12 | Middle-aged | High-tomato-based diet | Low in tomato-based foods | CRP, IL-6 |
| Ghavipour et al. (2013) | Iran | 104 | Female | 23 | 28 | 3 | Overweight and obese | 330 ml/d of tomato juice | Water | CRP, TNF-α, IL-6 |
| Michalickova et al. (2019) | Czech Republic | 26 | Both | 47 | 26 | 4 | Hypertension | 200 g/day of tomato fruit juice enriched with 1 g of ethanolic extract of whole tomato fruit | 200 g/day tomato fruit juice | CRP |
| Yang et al. (2020) | Taiwan | 32 | Female | 59 | 26 | 8 | Post-menopausal | 250 g/day of beefsteak tomatoes | Normal diet | CRP |

BMI, body mass index; T2DM, type 2 diabetes mellitus; NR, not reported; CRP, c-reactive protein; TNF-α, tumor necrosis factor-α; IL-6, interleukin 6.

### 3.2. Quality assessment

The Cochrane risk of bias checklist showed that most of the studies had high methodological quality. The details of quality assessment in individual studies are provided in Table 2.

### 3.3. Effect of tomato on C-reactive protein

Overall, six studies [24–26,28–30] evaluated the effect of tomato intake on CRP levels. Pooled effect size of articles indicated that tomato was not significantly effective on CRP (WMD: 0.13 mg/dL, 95% CI: −0.09 to 0.36; P = 0.23, $I^2$: 83.9%) (Fig. 2). To find sources of heterogeneity, subgroup analysis revealed that participants' gender ($I^2$ = 0.0%, P = 0.71) and health status ($I^2$ = 0.0%, P = 0.55) were the potential sources of heterogeneity. However, subgroup analysis based on gender, participants' mean age, health status, and study duration showed that the effect is not statistically significant in all subgroups (Table 3). In addition, findings from sensitivity analysis showed that none of the studies significantly influenced the overall effect.

### 3.4. Effect of tomato on tumor necrosis factor-α

Combining effect sizes from 2 trials [27,30] (3 treatment arms), we showed that tomato intake significantly decreases TNF-α (Hedges' g = −0.45; 95% CI -0.76, −0.13; P = 0.005) levels. No evidence of heterogeneity was detected among the trials based on $I^2$ index (0.0%) (Fig. 3). We could not perform subgroup analysis due to a lack of sufficient study. Excluding individual studies did not result in a significant change in the overall meta-analysis results.

### 3.5. Effect of tomato on interleukin 6

The effect of tomato intake on IL-6 was examined in 2 clinical trials [25,30]. Meta-analysis could not show any beneficial effect of tomato on IL-6 (Hedges' g = −0.12; 95% CI -0.36, 0.13; P = 0.34, $I^2$: 0.0%) (Fig. 4). We could not perform subgroup analysis due to a lack of sufficient study.

### 3.6. Publication bias

According to the Egger's regression asymmetry test, no effect of publication bias was observed for CRP (P = 0.34), TNF-α (P = 0.17), and IL-6 (P = 0.21).

## 4. Discussion

The present meta-analysis is an effort towards evaluating the importance of tomato intake in improving inflammation. The key findings of this study were that tomato intake had no significant

**Table 2**
Quality of included randomized controlled trials assessing the effect of tomato intake on inflammatory biomarkers in adults using the Cochrane risk of bias tool.

| First author (year) | Random sequence generation | Allocation concealment | Blinding of participants, personnel | Blinding of outcome assessment | Incomplete outcome data | Selective outcome reporting | Other sources of bias |
|---|---|---|---|---|---|---|---|
| Upritchard et al. (2000) | L | U | H | H | L | L | U |
| Briviba et al. (2004) | L | H | L | H | L | L | L |
| Blum et al. (2007) | L | H | H | U | L | L | U |
| Thies et al. (2012) | L | L | L | U | L | L | L |
| Ghavipour et al. (2013) | L | L | L | U | L | L | U |
| Michalickova et al. (2019) | L | L | L | L | L | L | U |
| Yang et al. (2020) | L | H | H | U | L | L | U |

U, unclear risk of bias; L, low risk of bias; H, high risk of bias.

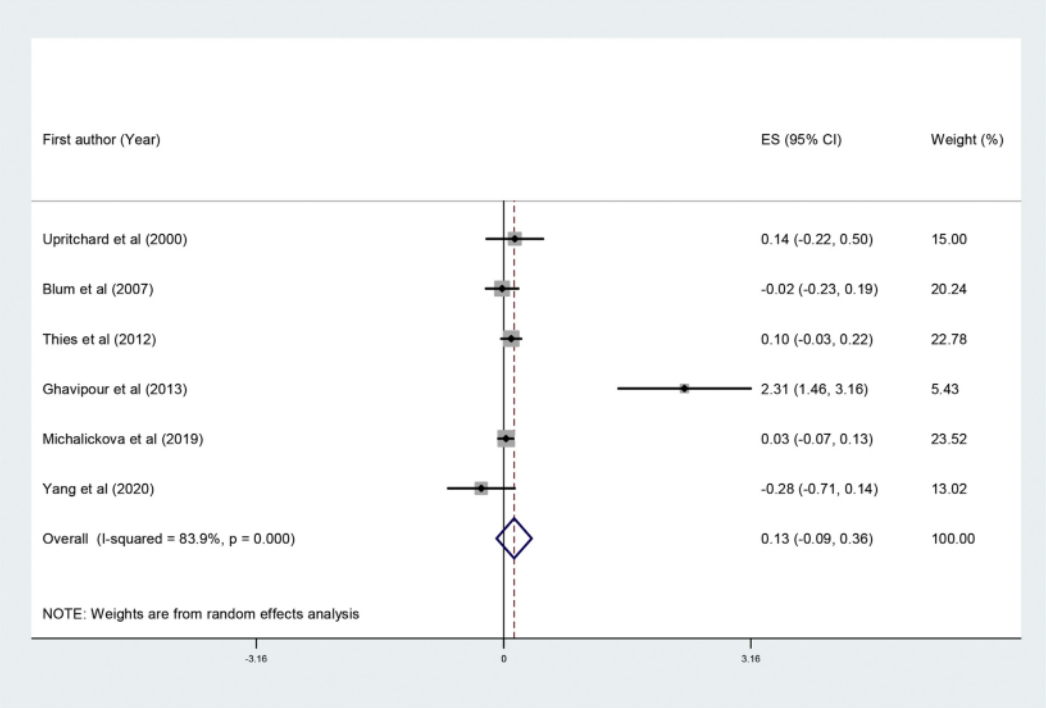


**Fig. 2.** Forest plot showing non-significant effect of tomato intake on C-reactive protein levels in adults. Values are weighted mean differences with 95% CIs determined with the use of random-effects models. The heterogeneity was assessed by using the I2 statistic, and values > 50% were considered as substantial heterogeneity between studies.

**Table 3**
Subgroup analyses to assess the effect of tomato intake on serum CRP concentrations.

| Sub-grouped by | No. of trials | Effect size[a] | 95% CI | $I^2$ (%) | P for heterogeneity |
|---|---|---|---|---|---|
| Participant's mea age | | | | | |
| <50 years | 3 | 0.46 | −0.06 to 0.98 | 92.8 | <0.001 |
| >50 years | 3 | 0.04 | −0.15 to 0.23 | 32.9 | 0.22 |
| Duration | | | | | |
| ≥8 weeks | 2 | −0.04 | −0.32 to 0.39 | 64.6 | 0.09 |
| <8 weeks | 4 | 0.34 | −0.06 to 0.74 | 89.4 | <0.001 |
| Gender | | | | | |
| Both | 4 | 0.05 | −0.02 to 0.12 | 0.0 | 0.71 |
| Female | 2 | 0.99 | −1.56 to 3.53 | 96.5 | <0.001 |
| Health status | | | | | |
| Healthy | 4 | 0.30 | −0.15 to 0.74 | 90.1 | <0.001 |
| Non-healthy | 2 | 0.04 | −0.06 to 0.13 | 0.0 | 0.55 |

The heterogeneity was assessed by using the I2 statistic, a value of <25%, 26–50%, and >50% were considered as low, moderate, and high degrees of heterogeneity, respectively.
[a] Calculated by Random-effects model.

effect on IL-6 and CRP, but did yield significant reductions in TNF-α. Results of subgroup analysis regarding CRP revealed that subgroup analysis based on participant's mean age, gender, health status, and intervention duration could not change these results.

The calculated CI for the effect of tomato intake on CRP was very close to the significant increase threshold. Indeed, it may be because tomato is usually consumed in sauces and tomato paste forms. These products are usually processed. Moreover, the anti-inflammatory effects of tomato are usually due to its antioxidant compounds, which may be due to high processing, the antioxidant content of these products is reduced [34–36]. In addition, the lack of significant benefit of tomato intake on CRP and IL-6 was likely due to limited power, with only 6, and 2 studies for CRP and IL-6, respectively. Indeed, the power of a meta-analysis strongly depends on the number of included studies. Another reason for the non-significant effect might be due to the short duration of studies.

Our results showed that tomato intake leads to a reduction in serum TNF-α concentrations compared with control. We did not conduct any sub-group analysis for TNF-α due to limited RCTs. Our results are in line with the previous trial. Ghavipour et al. [30] found that there was a significant decrease in the level of TNF-α in the group given tomato juice when a comparison was made with that of the control group. In addition, Kirkil et al. [37] have reported that lycopene supplementation can significantly lower TNF-α levels in patients with chronic obstructive lung disease. Furthermore, RISO et al. [38] have reported the beneficial effects of tomato drink on

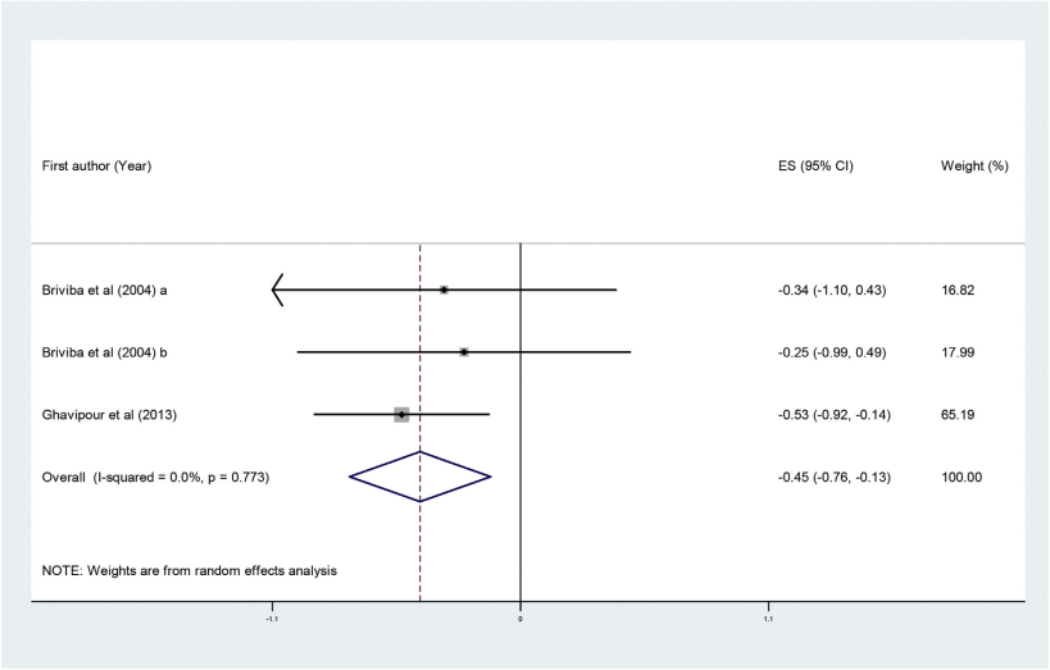


**Fig. 3.** Forest plot showing significant effect of tomato intake on tumor necrosis factor-α levels in adults. Values are Hedges' g with 95% CIs determined with the use of random-effects models.

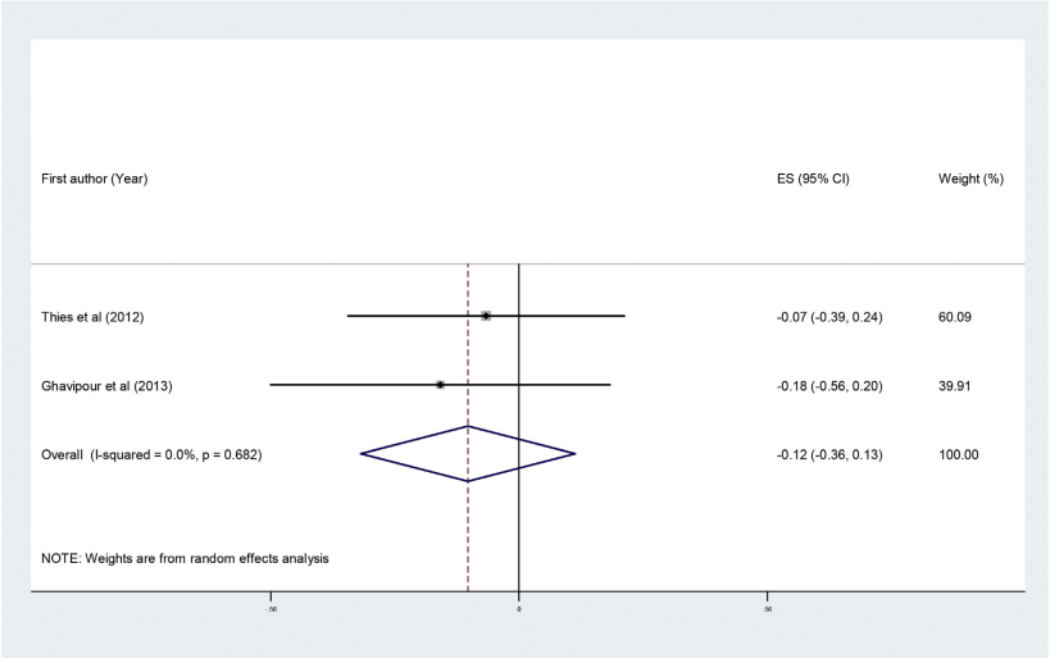


**Fig. 4.** Forest plot showing non-significant effect of tomato intake on interleukin 6 levels in adults. Values are Hedges' g with 95% CIs determined with the use of random-effects models.

the production of inflammatory mediators such as TNF-α in young healthy volunteers. In another study, TNF-α was reduced during treatment with tomato juice in people who had recently been diagnosed with metabolic syndrome [39]. This result supports the hypothesis behind the anti-oxidative and anti-inflammatory efficacy of tomato and indicates that tomato intake can be a promising adjuvant agent that can be used along with conventional medicine for mitigating inflammation [36,40]. However, this result was derived from a low number of studies and should be interpreted with caution. Hence, more studies are needed to confirm the above statement.

The exact mechanism for improving TNF-α levels is not yet clear; however, there are numerous beneficial nutrients in tomato that have antioxidant and anti-inflammatory properties, such as lycopene, carotenes, lutein, flavonoids, and vitamins [36,41]. Studies have shown that lycopene decreases the translocation of nuclear factor kappa B (NF-kB), which leads to a decreased expression of TNF-α [30,42,43]. Tomato also contains other important nutrients including the antioxidants b-carotene and vitamin C. These nutrients have been shown to decrease inflammation via their probable redox-based effect on the inactivation of NF-kB [30,44]. In addition, lycopene can improve serum TNF-α levels, by increasing the NO/cGMP levels, as well as decreasing the generation of reactive oxygen species and nitrotyrosine [45].

Although generally tomato is known as a safe vegetable without any serious adverse effects, several undesired side effects have been related to tomato and tomato-based products consumption. Some of the side effects reported in this area include allergic reactions, gastrointestinal problems, and diarrhea [44]. In addition, tomato, especially the sauce, has a strong flavor and can make its way into breast milk. This can make the baby uncomfortable and irritable [44,46].

Some limitations should be considered when interpreting our findings. The main limitations of this systematic review and meta-analysis include a limited number of studies, a small sample size, and study duration. Due to the small number of studies, we were unable to perform dose response analysis. Another limitation that might be considered is that only studies involving humans were included in this study. Furthermore, the included studies were heterogeneous concerning the study design and characteristics of patients. The results of most included studies were also not adjusted for confounding factors. In addition, specific differences in tomato type and genus were not assessed. Finally, we did not register the protocol of the current study on PROSPERO registry system due to the delay in processing the submitted protocols for studies outside the UK. This lack of registration might be a source of bias for this review. However, this meta-analysis was designed and performed according to the Cochrane guidelines.

## 5. Conclusions

Generally, the present meta-analysis showed that tomato intake has no significant effect on serum levels of CRP, and IL-6, but can reduce TNF-α significantly. The authors advocate that further, well-controlled, studies should be conducted to clarify the safety and efficacy of tomato intake on inflammatory biomarkers.

## Author contribution

G.W and M.J.A carried out the concept, design, and drafting of this study. M.R AND M.S searched databases, screened articles and extracted data. G.W performed the acquisition, analysis, and interpretation of data. M.J.A critically revised the manuscript. All authors approved the final version of the manuscript. G.W and M.J.A are the guarantors of this study.

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## Declaration of Competing Interest

The authors have no conflict of interest to report.

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