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## Review and Meta-analysis

## Systematic review and meta-analysis of randomized, controlled trials on the effects of soy and soy products supplementation on serum adiponectin levels



Trias Mahmudiono <sup>a</sup>, Nodirjon Kadirovich Khaydarov <sup>b</sup>, Saade Abdalkareem Jasim <sup>c</sup>,  
 Ali Thaeer Hammid <sup>d</sup>, Virgilio E. Failoc-Rojas <sup>e</sup>, Mohammed Nader Shalaby <sup>f</sup>,  
 Behrooz Jannat <sup>g</sup>, Mehran Nouri <sup>h, i, \*</sup>, Abdulmnannan Fadel <sup>j</sup>

<sup>a</sup> Department of Nutrition, Faculty of Public Health, Universitas Airlangga, Indonesia

<sup>b</sup> Tashkent State Dental Institute, Makhtumkuli Street 103, Tashkent, 100047, Uzbekistan

<sup>c</sup> Al-maarif University College, Medical Laboratory Techniques Department, Al-anbar-Ramadi, Iraq

<sup>d</sup> Computer Engineering Techniques Department, Faculty of Information Technology, Imam Ja'afar Al-Sadiq University, Baghdad, Iraq

<sup>e</sup> Medicina basada en la evidencia, Universidad Privada Norbert Wiener, Lima, Peru

<sup>f</sup> Biological Sciences and Sports Health Department, Faculty of Physical Education, Suez Canal University, Egypt

<sup>g</sup> Halal Research Center of IRI, Food and Drug Administration, Ministry of Health and Medical Education, Tehran, Iran

<sup>h</sup> Department of Community Nutrition, School of Nutrition and Food Science, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>i</sup> Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>j</sup> School of Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK

## ARTICLE INFO

## Article history:

Received 31 December 2021

Received in revised form

23 June 2022

Accepted 24 June 2022

## Keywords:

Soy

Adipokines

Adiponectin

Systematic review

Meta-analysis

## ABSTRACT

**Background and aims:** Our aim in this meta-analysis was to determine the effect of soy and soy product supplementation on serum adiponectin levels.

**Method:** A systematic search was conducted using Medline (PubMed and Web of Science), Scopus, and Cochrane Library for eligible trials up to August 2020. A random-effects model was used to pool calculated effect sizes.

**Results:** Seven trials were included in the overall analysis. Our analysis showed that soy and soy product supplementation did not significantly affect adiponectin concentrations (WMD =  $-0.77$   $\mu\text{g/ml}$ , 95% CI:  $-0.61$ ,  $2.15$ ,  $P = 0.27$ ) in comparison with a placebo. The between-study heterogeneity was high ( $I^2$ : 68.2%,  $P = 0.004$ ). Subgroup analysis, based on participants' health status and duration of the supplementation, could not detect the potential source of the observed heterogeneity. In addition, subgroup analysis showed that the effect was not statistically significant in all subgroups.

**Conclusion:** Overall, soy and soy product supplementation did not change the circulatory adiponectin levels. In addition, the results were not affected by the participant's health status and duration of supplementation. However, further studies are needed to confirm the present results.

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## 1. Introduction

Soy is a popular legume of Asian origin [1]. This functional food can be used to supply calories, because of its high content of fiber, protein, minerals, vitamins, phytochemicals, antioxidants, and unsaturated fatty acids [2]. The effects of soy protein consumption on cardiovascular risk factors and other endpoints have been studied

in a large number of clinical trials [3–5]. Likewise, meta-analyses have documented that soy protein and soy isoflavones improve lipid profile, glycemic status, blood pressure and inflammatory markers, modestly [6–9]. In recent years, the beneficial effects of soy products on adiponectin concentrations has aroused the interest of scientists.

Adipose tissue produces several hormone-like proteins and cytokines termed adipokines [10–12]. Adiponectin is an adipokine that plays a role in several regulatory actions in human metabolism [13]. This fat-derived hormone acts as a protective protein with anti-inflammatory, anti-atherogenic, and anti-diabetic properties

\* Corresponding author.

E-mail address: [mehran\\_nouri71@yahoo.com](mailto:mehran_nouri71@yahoo.com) (M. Nouri).

[13–17]. Decreased levels of adiponectin (hypoadiponectinemia) have been reported in most chronic diseases, including cardiovascular diseases, metabolic syndrome, non-alcoholic fatty liver disease, hypertension, and type 2 diabetes mellitus [10,14,15,18,19]. In addition, adiponectin levels are negatively correlated with overall obesity parameters [20]. Given the positive role of adiponectin in moderating many metabolic processes [13], improving the level of this hormone-like protein is the focus of many researchers.

Lifestyle modification, particularly dietary management in combination with moderate physical activity and pharmacological intervention, have been reported to increase plasma adiponectin levels [21,22]. Recently, herbal medicines have received more attention as complementary medicine because many have phytochemicals that may improve the levels of adipokines. Previous studies have reported that supplementation with curcumin [23], resveratrol [24] and green tea [25] can increase adiponectin concentrations.

Previous information regarding soy and soy product supplementation and adipokines among adults are far from conclusive [26–31]. Some studies support the effectiveness of soy food consumption in increasing adiponectin levels [26,31], while others do not [28,30].

Since the exact effects of soy and soy product supplementation on serum adiponectin concentrations are still inconclusive, a systematic review and meta-analysis of available randomized controlled trials (RCTs) seemed appropriate to summarize the current data to assess their overall effect. Therefore, we conducted a meta-analysis of available RCTs to resolve this inconsistency.

## 2. Methods

The current systematic review and meta-analysis were conducted in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [32].

### 2.1. Searches

In this systematic review and meta-analysis, two investigators searched Medline (PubMed and Web of Science), Scopus, and Cochrane Library for studies listed from the database inception to August 1, 2020. The following search terms were used in the current study: (“Soy Foods,” OR “Soy,” OR “Soya,” OR “Tofu,” OR “Natto,” OR “Soybeans,” OR “Soy Products,” OR “Isoflavones,”) AND (“adipokines,” OR “adipocytokines,” OR “adiponectin”). Language restrictions were not applied to all search sections. Searches of potential articles were also done by analyzing the list of references of eligible studies. Discrepancies were resolved through discussion between reviewers until consensus was reached. After loading retrieved records into EndNote, duplicates were removed.

### 2.2. Inclusion and exclusion criteria

Two independent reviewers screened the titles and abstracts of all retrieved articles in the initial literature search, and a third author resolved disagreements. After applying inclusion and exclusion criteria, the full texts of relevant articles were further evaluated. The inclusion criteria for this meta-analysis were the PICOS (Participants, Intervention, Comparison, Outcome, Study types) framework as follows: 1) population: healthy and unhealthy adults (>18 years); 2) intervention: natural or commercial soy products; 3) comparison: control group; 4) outcome: reporting the baseline and follow-up levels of the serum concentrations of adiponectin in the intervention group or the comparison group, and 5) study design: RCTs (parallel design).

The exclusion criteria included 1) non-English articles, 2)

studies without a clear control arm, 3) study duration <2 weeks, 4) studies in which participants took other food or drug supplements besides soy and soy products, and 5) the articles reporting no information on the serum concentration of adiponectin at baseline or after intervention and gave no information with which to compute it.

### 2.3. Data extraction and quality assessment

Data extraction was conducted independently by two reviewers. Data was extracted after the perfect match with the full manuscript reading. Conflicts over data extraction were resolved by consensus. The following information was extracted: last-named author; study location; date; the number of participants; the characteristics of the target population, such as age, sex, health status, body mass index (BMI); intervention features (including dose, type, and duration of exposure); and mean and standard deviation (SD) of the adiponectin at baseline and end of the intervention.

The RCTs were assessed for risk of bias using the Cochrane tool [30], and the quality of each article was studied by two authors. Any discrepancy was addressed through re-evaluation and consensus among the authors. This tool contains seven domains, which are random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias, and other sources of bias. A judgment of “adequate” (L) indicated a low risk of bias, whereas “inadequate” (H) indicated a high risk of bias, taking into account the recommendations of the Cochrane Handbook. We labeled uncertain or unknown risk of bias as “U”.

### 2.4. Statistical analysis and data synthesis

All analyses were conducted using STATA statistical software (version 13.0; STATA Corporation LP, College Station, TX) using a DerSimonian-Laird random-effects model to account for heterogeneity between studies [33]. The change in means and SD of adiponectin levels between intervention and control groups was used to calculate effect sizes (weighted mean differences, WMD) with 95% confidence intervals (CI) to compare reported outcomes across studies by a meta-analysis. Heterogeneity among the studies was estimated through the use of the  $I^2$  statistic, with values of 0–25%, 26–75%, or 76–100% representing a low, moderate, or high degree of heterogeneity, respectively [34]. Subgroup analyses were conducted based on the duration of follow up and health status to explore potential sources of heterogeneity. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-one-out method (i.e. removing one study at a time and repeating the analysis). A two-sided p-value < 0.05 was considered statistically significant.

## 3. Results

### 3.1. Literature search

The study selection process and the number of studies at each review stage are shown in a PRISMA flow diagram (Fig. 1). The initial search identified 603 articles for screening. We identified 162 duplication records. After removing duplicates, 441 relevant articles were screened by title and abstract. After screening by title and abstract 419 papers were excluded, which 22 papers were retained for full-text review; of these articles, 15 were excluded due to the lack of our inclusion criteria. Finally, a total of 7 papers [26,28–31,35,36] met the objectives and were included in the current meta-analysis.

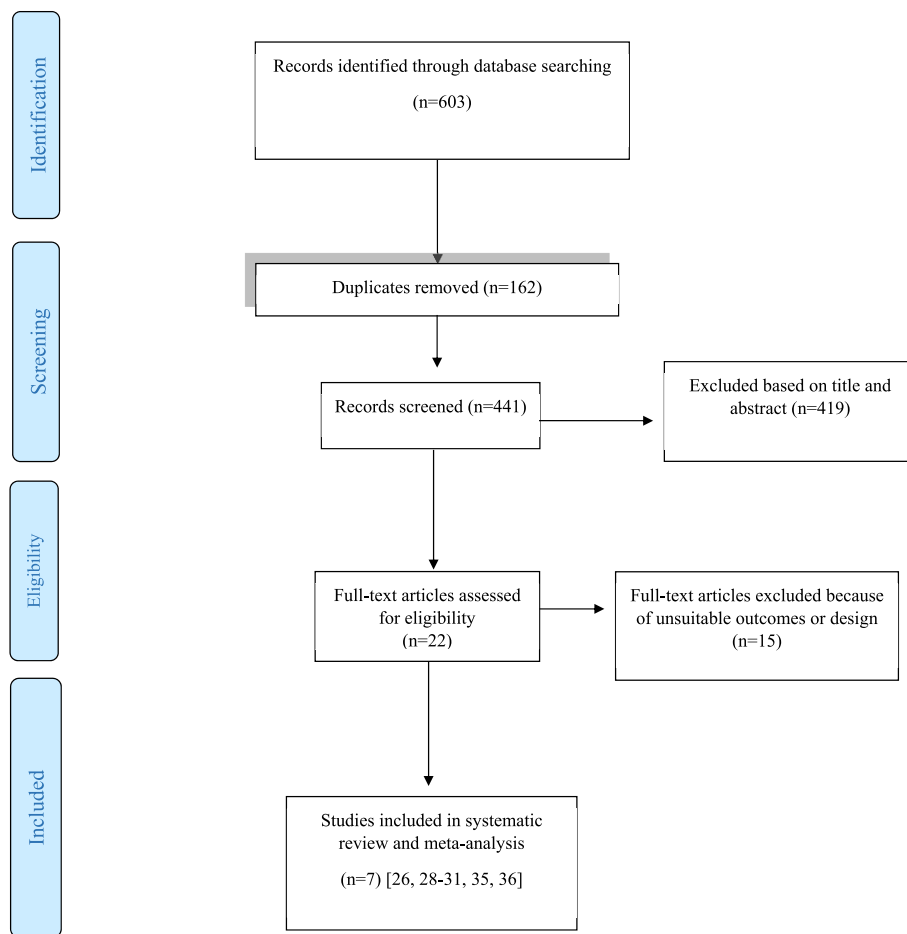


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process.

### 3.2. Study characteristics

Table 1 lists the characteristics of the included studies. There were 500 participants included in these RCTs dated between 2009 and 2016. Four of the included trials were performed in the USA and the remaining studies were done in Spain, Canada, and Brazil. The RCTs' lengths ranged from between 8 and 96 weeks, with sample sizes ranging from 30 to 183 participants. The mean age of

participants ranged from 43 to 69 years. Soy was used in different forms including soy protein, soybean, soy isoflavones, and soy products. All articles except one study [29] were performed on female participants. Participants were healthy, postmenopausal women [26,28,31,36], patients with metabolic syndrome [35], and prostate cancer [29]. Quality assessment characteristics of the studies are provided in Table 2.

Table 1

Summary characteristics of 7 randomized controlled trials identified in the current systematic review and meta-analysis assessing the effect of soy and soy product supplementation on adiponectin levels in adults.

Study (publication year)	Location	Sample size	Gender	Mean age (year)	Mean BMI (kg/m <sup>2</sup> )	Duration (weeks)	Health status	Intervention	Comparator
Nadadur et al. (2016) [28]	USA	37	Female	58	NR	8	Healthy postmenopausal women	Soy protein	Control diet
Lozovoy et al. (2012) [35]	Brazil	30	Female	47	35	12	Metabolic syndrome	Soybean	Usual diet
Llaneza et al. (2011) [31]	Spain	87	Female	56	34	24	Healthy obese postmenopausal women	Diet + exercise + soy isoflavones extract	Diet + exercise
Riesco et al. (2012) [36]	Canada	55	Female	58	28	24	Healthy postmenopausal women	Exercise + soy extract	Placebo + exercise
Napora et al. (2011) [29]	USA	33	Male	69	29	12	Prostate Cancer	Soy protein	Whole milk protein
Charles et al. (2009) [26]	USA	75	Female	56	25	12	Healthy postmenopausal women	Soy protein powder	Placebo powder
Maskarinec et al. (2009) [30]	USA	183	Female	43	26	96	Healthy postmenopausal women	Soy products	Regular diet

BMI, body mass index.

**Table 2**  
Quality of included randomized controlled trials assessing the effect of soy and soy product supplementation on adiponectin levels in adults using the Cochrane risk of bias tool.

Study (publication year)	Random Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Nadadur et al. (2016) [28]	L	U	L	L	U	L	U
Lozovoy et al. (2012) [35]	U	U	H	U	L	L	U
Llaneza et al. (2011) [31]	L	H	L	L	L	L	U
Riesco et al. (2012) [36]	U	L	L	U	U	U	U
Napora et al. (2011) [29]	L	U	L	U	L	U	U
Charles et al. (2009) [26]	L	L	L	U	L	L	U
Maskarinec et al. (2009) [30]	U	U	U	L	L	U	U

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

### 3.3. Effects of soy and soy products supplementation on serum adiponectin concentrations

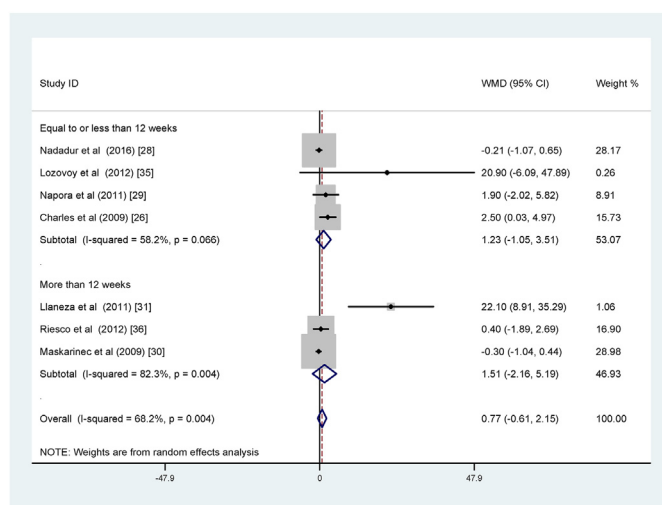
Seven trials [26,28–31,35,36] with 500 subjects provided information on changes of adiponectin levels following soy and soy product supplementation. As shown in Fig. 2, the results showed no significant increase in adiponectin levels after soy and soy product supplementation, compared with control groups (WMD = -0.77 µg/ml, 95% CI: -0.61, 2.15, P = 0.27), and the between-study heterogeneity was high (I<sup>2</sup>: 68.2%, P = 0.004). Subgroup analysis based on participants' health status and duration of the intervention could not detect the potential source of the observed heterogeneity. In addition, subgroup analysis showed that the effect was not statistically significant in all subgroups (Figs. 3 and 4).

### 3.4. Sensitivity analysis

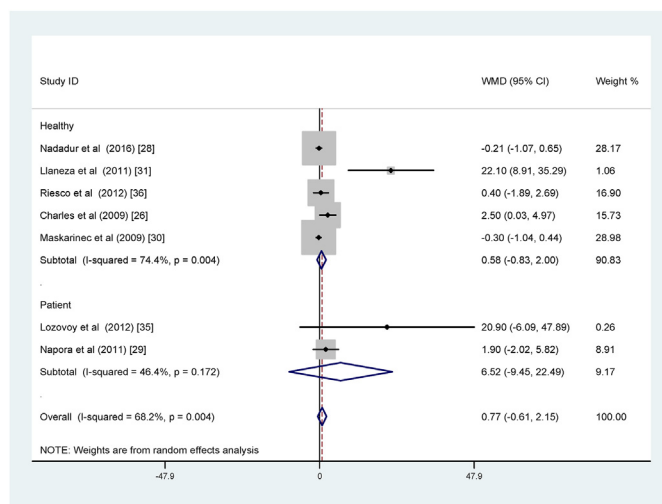
We tested the robustness of our findings by sensitivity analysis. Results showed that overall estimates were not affected by the elimination of any study.

## 4. Discussion

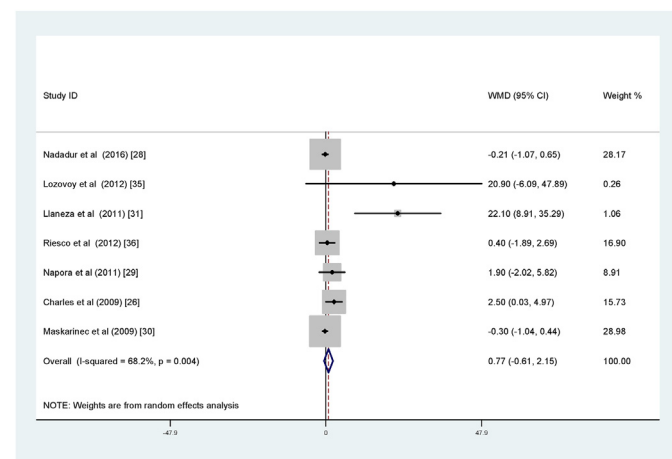
The current meta-analysis showed that soy and soy product supplementation had no significant effect on serum adiponectin



**Fig. 3.** Forest plot showing pooled WMDs with 95% CI for the effect of soy and soy product supplementation on adiponectin levels with subgroup analysis stratified by the duration of intervention.



**Fig. 4.** Forest plot showing pooled WMDs with 95% CI for the effect of soy and soy product supplementation on adiponectin levels with subgroup analysis stratified by the participant's health status.



**Fig. 2.** Forest plot showing pooled WMDs with 95% CI for the effect of soy and soy product supplementation on adiponectin (µg/ml) in adults.

concentrations in adults. Statistical analysis also revealed that the heterogeneity between the seven studies was significant and the overall effects were stable in the sensitivity analysis. In addition, the results were not varied by participant's health status or duration of supplementation.

The present systematic review is not consistent with the suggestion made by a recent meta-analysis [37] which claimed that there were beneficial effects of soy isoflavone supplementation on adiponectin levels in postmenopausal women. Post menopause is associated with changes in several metabolic risk factors including decreased adiponectin [38]. Therefore, it is possible that soy and its products have a better effect on people with lower levels of adiponectin. This discrepancy is probably attributed to the difference in the method of calculating the effect size. In addition, given the high heterogeneity and the low number of studies in our analysis, these results should be interpreted with caution.

The exact mechanisms by which soy products may influence adiponectin secretion are still unclear. However, previous studies have reported that adiponectin secretion from adipocytes is reduced by oxidative stress and inflammation [39,40]. Therefore, antioxidant factor-like soy products might increase adiponectin secretion from adipose tissue [41,42]. Another mechanism that could be associated with the adiponectin increase is the nitric oxide (NO) pathway. Previous studies have reported that soy and its products can increase the production of NO in endothelial cells, resulting in increased secretion of adiponectin [43,44].

Our meta-analysis had several limitations that must be kept in mind. The main limitations of this systematic review and meta-analysis include a limited number of studies, a small sample size, and study duration. In addition, there was a notable heterogeneity between studies, resulting from differences between participants' characteristics, and the soy dosage used in the included studies. Regarding the aforementioned limitations, more investigations must be conducted to have a better understanding of the precise effect of soy products on adiponectin levels. Furthermore, we did not register the protocol of the current study on the 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.

## 5. Conclusion

In conclusion, we found that soy and its products could not increase adiponectin levels, but we still need more RCTs with longer intervention duration, higher doses, and studies in different countries. Furthermore, the confounding effect of diet should be adjusted.

## Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of competing interest

The authors declare no conflict of interest.

## Acknowledgments

None.

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