



The effects of dietary selenium supplementation on inflammatory markers among patients with metabolic diseases: a systematic review and meta-analysis of randomized controlled trials

Shirin Djalalinia^{1,2} · Motahareh Hasani³ · Hamid Asayesh⁴ · Hanieh-Sadat Ejtahed^{5,6} · Hanieh Malmir⁵ · Amir Kasaeian^{7,8} · Maryam Zarei⁹ · Fereshteh Baygi¹⁰ · Hadith Rastad^{11,12} · Armita Mahdavi Gorabi¹³ · Mostafa Qorbani¹²

Received: 28 January 2021 / Accepted: 23 May 2021 / Published online: 9 June 2021
© Springer Nature Switzerland AG 2021

Abstract

Purpose Selenium (Se) is a trace element having significant effects on human metabolism. Recent studies suggest that Se supplementation have a pivotal effect on the inflammatory markers. Therefore, the aim of this study was to assess the effect of Se supplementation on plasma inflammatory markers including C-reactive protein (CRP) and high-sensitivity C-reactive protein (hs-CRP) and nitric oxide (NO) as a stress oxidative index, among patients with metabolic diseases.

Methods To assess the effects of Se on the inflammatory markers, following the PRISMA-P guidelines, we systematically searched ISI/WOS, PubMed/MEDLINE, and Scopus for studies that assessed the effect of Se supplementation on the inflammatory markers. Data extraction was performed by two independent investigators. Using the random effects or fixed-effects model depending on the results of heterogeneity tests was used to estimate the pooled standardized mean difference (SMD). Heterogeneity between studies was assessed using Cochran's Q test and I² index.

Results The initial search revealed 3,320 papers. After screening process and considering inclusion criteria, 7 publications were eligible for inclusion in the meta-analysis. The meta-analysis results showed that Se supplementation did not significantly affect CRP and hs-CRP concentrations (mean difference (MD) = -0.15; 95% CI: -0.55- 0.23; P = 0.43). Subgroup analysis of CRP type showed that Se supplementation significantly decreased hs-CRP level (pooled SMD = -0.44; 95% CI: -0.67–0.21). Moreover, no significant change was observed in NO level by continuing to take Se supplementation, (pooled SMD: 0.003, 95%CI: -0.26, 0.26).

Conclusions This study revealed that Se supplementation would have desirable effects on cardio-metabolic indicators through affecting the levels of inflammatory markers. Given the importance of concerns, more attention should be given to more prospective studies with longer follow-up.

Keywords Selenium · Supplementation · Inflammatory markers · Inflammation · Systematic review

Background

The trace mineral selenium (Se) is an essential micronutrient and plays important biological roles in human body [1, 2]. This essential mineral must be obtained through nutritional diet. In this regard, evidence reveal that, low Se level may be related to increased risk of adverse health outcomes, such as cancer and cardiovascular disease (CVD) [3]. Evidence

shows that Se is also essential for optimal functioning of the CVD system [4].

Selenium can affect the inflammatory processes; it is one of the most interesting research fields. Se also regulates the progression of many infectious diseases [4]. The antioxidant nature of some selenoproteins like glutathione peroxidase, is discussed as predisposing factors for many morbidities and mortalities such as carcinogenesis and heart diseases [5–7].

Previous studies have suggested that the Se supplementation through inhibiting the production of advanced glycation end products and decreasing the free radical production and lipid hydroperoxide could affect inflammatory mechanisms, glucose homeostasis, and oxidative stress [8]. In many cases,

✉ Mostafa Qorbani
mqorbani1379@yahoo.com

Extended author information available on the last page of the article

increasing serum levels of Se and the correction of required prescribed doses might be accompanied by interested results in reducing the risk of many diseases [6, 9, 10]. Metabolic diseases, such as diabetes, metabolic syndrome, obesity, and cardiovascular diseases are associated with increased inflammation in the body, leading to increasing inflammatory markers like C-reactive protein (CRP), nitric oxide (NO) and high-sensitivity C-reactive protein (hs-CRP). In this case, some evidence has shown that Se can reduce inflammation and decrease the rate of metabolic diseases [11–18].

Despite the importance of Se effects on related complications of metabolic disorders, such as the significant disability, increased dependency, reduced quality of life and increased economic burden of health care costs, there is still an evident gap among the related scientific literature, practical experiences and proposed plans [19–23]. Therefore, present paper provides the comprehensive systematic review on the probable effects of Se supplementation on inflammatory and stress oxidative markers among patients with metabolic diseases.

Methods

To assess the effect of Se on inflammatory markers, following the PRISMA-P guide-lines, we developed a systematic review which aggregated and analyzed all related evidence. The details of the study protocol have previously been published [16].

The review question

Considering the main question of the effect of Se on inflammatory and stress oxidative markers, this review investigated the effect of Se supplementation on the inflammatory and stress oxidative markers including CRP, NO, and hs-CRP.

PICOS: we considered adults and adolescents with metabolic diseases as population (P); Se supplementation as intervention (I); patients with metabolic diseases and taking placebo as comparator (C); plasma inflammatory markers including CRP and hs-CRP and NO as a stress oxidative index as outcome (O), and clinical trial as study design (S).

Inclusion and exclusion criteria

Studies that met the following criteria were included in the meta-analysis: [1] clinical trials in which control group received the placebo, [2] studies assessing the effect of se supplements or Se-enriched yeast on inflammatory markers in subjects with metabolic disorders; and [3] Se could be used as mono therapy or even in combination therapy. Duplicate publications and irrelevant papers considering other inflammatory markers or dietary Se instead of Se

supplementation or studies conducted on other diseases were excluded from the study.

Search strategy and locate studies

We systematically searched the databases of PubMed, EMBASE, MEDLINE, Cochrane Library, ISI/WOS, and Scopus for relevant papers. The search terms developed based on the topics of research question. The search strategy included: "inflammation"[Mesh] OR "inflammatory factors"[Title/Abstract] OR "C-reactive protein"[Title/Abstract] OR CRP[Title/Abstract] OR "nitric oxide"[Title/Abstract] OR NO[Title/Abstract] OR "high-sensitivity C-reactive protein" [Title/Abstract] OR hs-CRP[Title/Abstract] combined with "Se"[Mesh] OR "se"[Title/Abstract] OR selenium[Title/Abstract] combined with "metabolic syndrome"[Title/Abstract] OR "cardiovascular diseases"[Title/Abstract] OR diabetes[Title/Abstract] OR GDM[Title/Abstract] OR PCOS[Title/Abstract] OR obesity[Title/Abstract], restricted to "human subject". The same process followed in other databases.

All of the relevant review articles and meta-analysis were checked for their references. If there were more than one paper from a specific study, the one with more complete data was considered. There was no limitation for language. Searches were done on March 2021. As other resources, all publications' references were checked.

Select studies

To establish the inter-rater reliability (IRR), a comprehensive list of abstracts was retrieved and reviewed by two independent investigators. Possible disagreements and controversies were resolved by discussion and consensus or even third investigator. Relevant eligible papers obtained were reviewed in full.

Assess study quality

Using comprehensive recommended guidelines of the Consolidated Standards of Reporting Trials (CONSORT) 2010, 25-items checklist [24], study quality was assessed by two independent research experts.

Data extraction

Using a data extraction form, according to the study groups, the information was extracted from each study for citation, type of study, study subjects, publication year, sample size, dose of supplementation, intervention group, control group, mean age of participant, outcome, intervention duration, follow up duration, measurement interval, result, effect size.

Statistical analysis

The mean change (endpoint from baseline) and standard deviation (SD) in inflammatory markers for both intervention and placebo groups were used to calculate the standardized mean difference (SMD) as effect size. We calculated the SMD using the means and SD of the two groups using a previously described method [18].

Meta-analysis was performed to estimate the pooled SMD with the 95% confidence interval (CI) of the effect of Se supplementation on the inflammatory markers. The Cochran's Q test and the I^2 statistic were used to assess the heterogeneity between studies. The result of Q test was considered as statistically significant at 0.1. Either a fixed-effects or, in

the presence of heterogeneity, a random-effect model was used to calculate pooled SMD [25]. The I^2 statistic also was used to quantify the degree of heterogeneity between studies, which I^2 values of 25%, 50%, and 75% were considered to correspond to low, medium, and high levels of heterogeneity, respectively [26]. Subgroup analysis was performed based on CRP types and dose of Se supplementation. We performed sensitivity analysis to evaluate the extent to which the pooled SMD depending on excluding studies with low quality score. Publication bias was estimated visually and statistically using Begg's funnel plots and Egger's test, respectively and results of Egger's test was considered as statistically significant at 0.1 [27]. The statistical analysis was performed using STATA version 10.

Fig. 1 Flow chart of the articles selected for meta-analysis

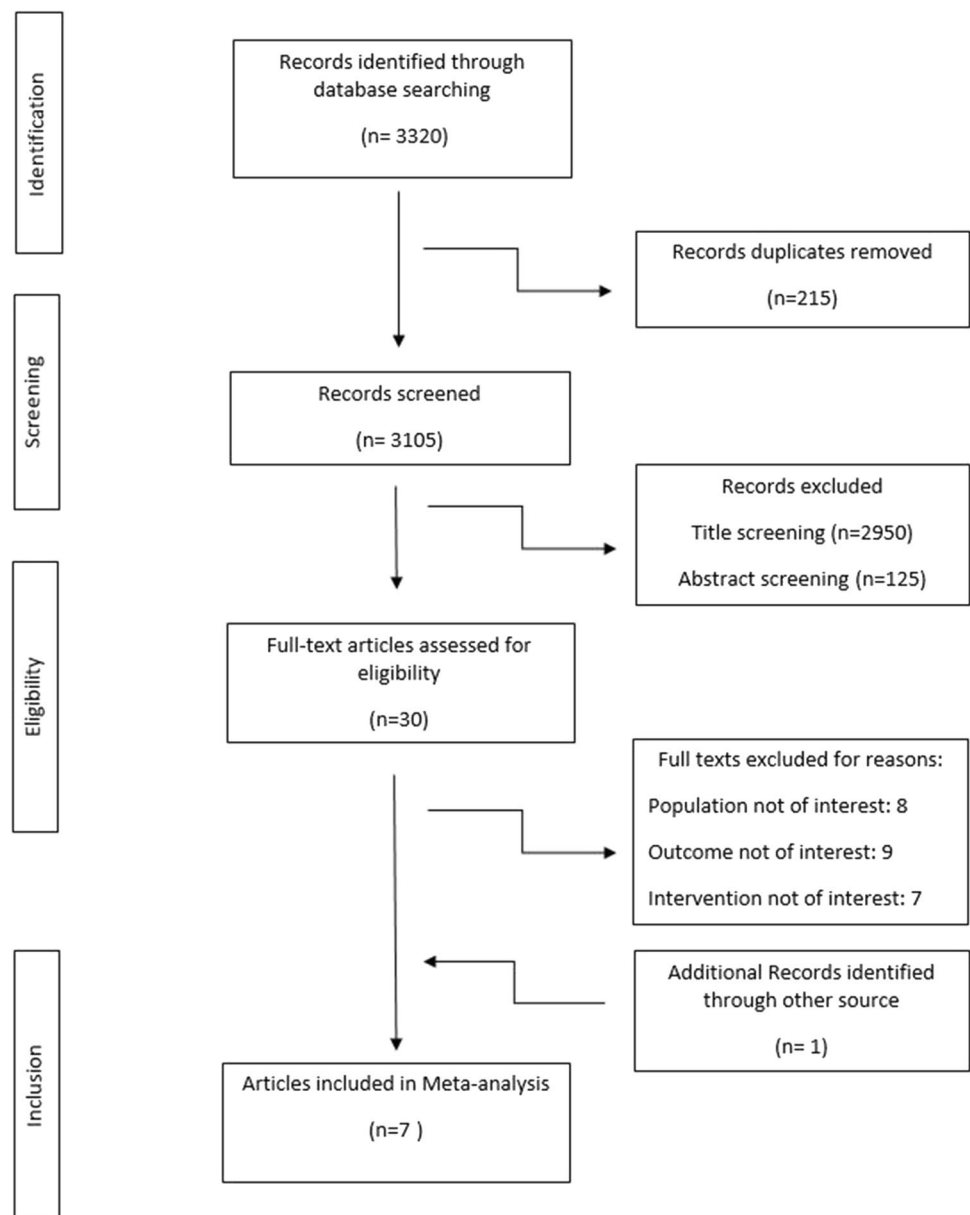


Table 1 Characteristics of the included studies in the systematic review

Author, year	Country	Type of study	Study subject	Sample size	Dose of supplementation	Intervention group	Control group	Mean age or age range(Y)	Outcome	Intervention duration	Measurement interval
1 Asemi, 2015	Iran	RCT	GDM Women	I=35 C=35	200 µg/d	MT	placebo	28.6±4.6	hs-CRP (ng/mL)NO (mmol/L)	6 weeks from weeks 24 to 28 of gestation	Baseline and end of study
2 Shargorodsky, 2010	Israel	RCT	Patient with >2 CVD RFs	I=36 C=34	100 µg/d	CT	placebo	62.17 ± 6.21	hs-CRP(mg/dl) Homocysteine(µmol/l) Ur cathacholamines(mg/24 h)	6 months	Base line and end of study
3 Ravn-Haren, 2007	Denmark	R cross over	Diabetic Men	I=20 C=20	300 µg/d	CT	placebo	26-8	CRP	1 week	Baseline and after 1 week and end of study
4 Alizadeh, 2012	Iran	RCT	Premenopausal women with central obesity	I=17 C=17	200 µg/d	CT	placebo	33.9±8.5	hs-CRP, mg/l NOx, µmol/l	2 weeks run-in period 6 weeks intervention period	Baseline and after 3, and 6 weeks
5 Muret, 2014	Switzerland	RCT	Obese children and adolescents	I=23 C=21	50 µg/d	CT	placebo	12.7 ± 1.5	CRP,2 mg/L serum	4 months	Baseline and after 4 months
6 Razavi, 2016	Iran	RCT	PCOS patients	I=32 C=32	200 µg/d	MT	placebo	18–40	hs-CRP (ng/ml) NO (µmol/l)	8 weeks	Baseline and after 2 months
7 Farrokhanian, 2016	Iran	RCT	Patients with type 2 diabetes & CVD	I=30 C=30	200 µg/d	MT	placebo	40–85	hs-CRP (ng/ml) NO (µmol/l)	8 weeks	Baseline and after 2 months

Results

Search result & characteristics of included studies

Figure 1 shows the detailed processes of the search and study selection. A total of 7 trials [6 randomized controlled trials and 1 crossover trial] were included in this study (Table 1). The initial search revealed 3,320 papers. After excluding the duplicate studies, 3105 publications were screened based on title and abstract. Totally, 30 publications were assessed for eligibility based on the study inclusion and exclusion criteria. Finally, 7 articles were included in the meta-analysis. Other studies were excluded based on different types of population, outcome, and intervention (Fig. 1).

Overall, 193 participants were included in the Se supplementation group and 189 participants in the placebo group. The age of the patients ranged from 10 to 85 years. Four trials recruited both men and women and in other three studies only female subjects were enrolled [10, 28, 29]. Four trials used Se combined with other vitamins or minerals [3, 9, 10, 30] and 3 trials used Se alone as oral supplement. The daily dose of Se were 200 mg/day in four trials [10, 12, 28, 29], one trial used 300 mg/day

[3], one RCT used 50 mg/day [12] and one study used 100 mg/day [9]. Four trials were conducted in Iran and 3 in Europe. All RCTs were placebo-controlled, and all were double-blinded. Duration of treatment ranged from 42 [28] to 168 days [9]. The effect of Se supplementation on the inflammatory markers in included studies is presented in Table 2. The effect of Se supplementation on inflammatory markers was statistically significant in four studies.

Meta-analysis and sub group analysis

Overall, five trials involving 298 participants in Se or placebo groups reported the effect of Se supplementation on hs-CRP level and 2 studies assessed the effect of Se supplementation on the CRP. Four studies reported level of NO as an outcome at baseline and follow-up (Table 3).

The overall effect of Se supplementation on the level of inflammatory markers is shown in Table 3. The results of the random effect meta-analysis showed that Se supplementation led to a significant reduction in hs-CRP levels [SMD = -0.44; 95% CI: (-0.67,-0.21); P < 0.001] in subjects with metabolic diseases with no obvious

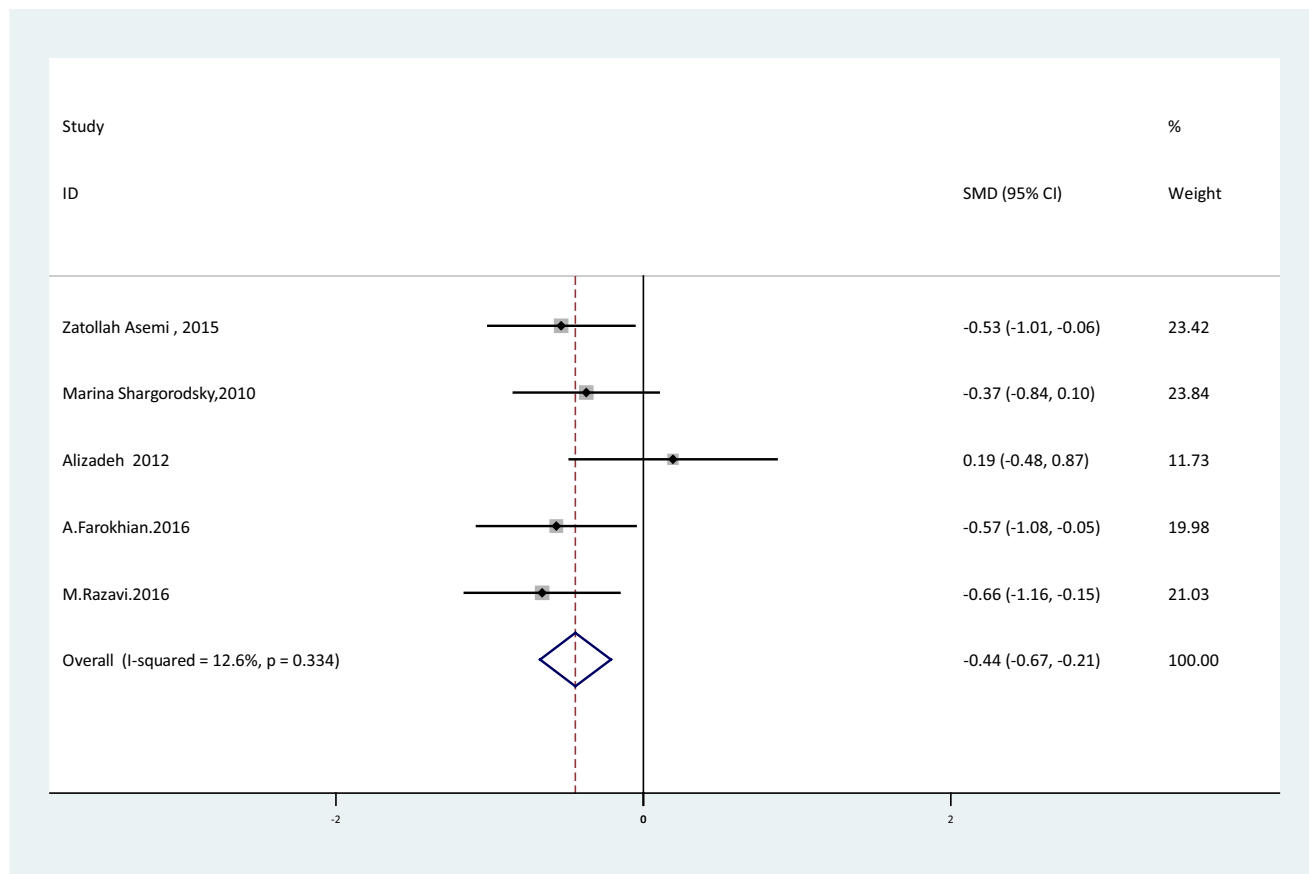


Fig. 2 Forest plot of randomized controlled trials to investigate the effect of Selenium supplementation on levels of hs-CRP

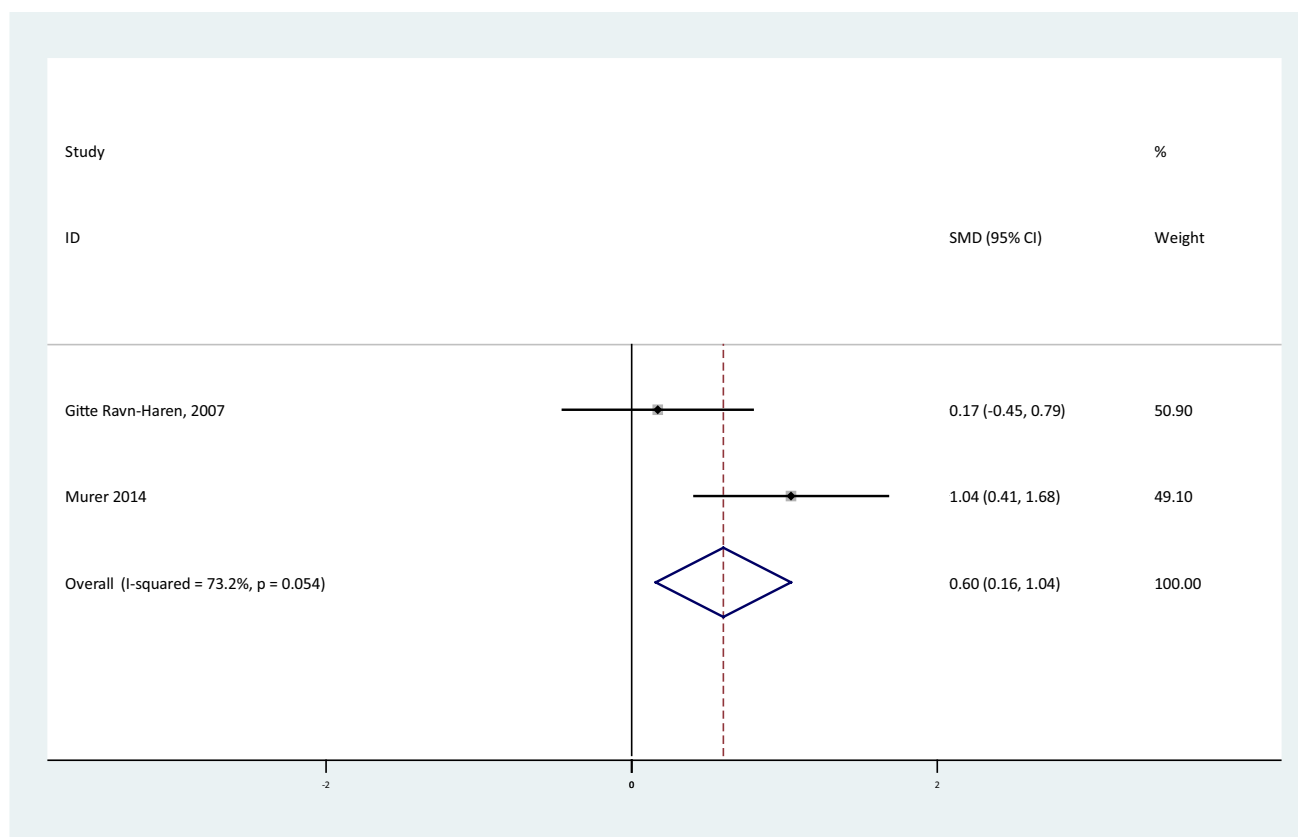


Fig. 3 Forest plot of randomized controlled trials to investigate the effect of Selenium supplementation on levels of CRP

heterogeneity between studies [I^2 :12.6%, Q test: 4.58; P: 0.33] (Fig. 2). CRP level was significantly increased, but it should be considered that combining two effect size was not reliable [SMD = 0.6; 95% CI: (0.16, 1.04); P < 0.001] (Fig. 3).

The results of fixed effect meta-analysis showed that there were no significant improvement in NO levels [SMD: 0.003, 95%CI: (-0.26, 0.26); P = 0.98] with no obvious heterogeneity between studies [I^2 :28.4%, Q test: 4.19; P: 0.24] following Se supplementation (Fig. 4).

In subgroup analysis, according to dose of Se supplementation (< 200 $\mu\text{g}/\text{d}$ and \geq 200 $\mu\text{g}/\text{d}$), the effect of Se supplementation on all inflammatory markers (CRP, hs-CRP and NO) did not change significantly. Unfortunately, due to both the lack of studies in this field and a lack of the available data, it was not possible for us to perform subgroup analysis based on other effective factors.

Quality assessment

Table 4 shows the quality of included studies. Three studies were classified as high quality, with CONSORT score higher than 30 [10, 12, 28], 3 as medium quality, with

CONSORT score in range of 25–29 [9, 29, 30], and 1 as low quality, with CONSORT score lower than 25 [3]. Randomization as a prerequisite for inclusion in this meta-analysis was conducted in 7 studies. All 6 RCTs were double-blind, but only two studies was described as blinding [12, 29].

Sensitivity analysis

Sensitivity analysis was performed according to the quality assessment score. Based on this analysis, the effect of Se supplementation on the level of inflammatory factors was evaluated by excluding low quality score studies including the Ravn-Haren et al. [3]. Results showed that the effect of Se supplementation on hs-CRP levels did not change significantly without this study in metabolic diseases.

Publication bias

Publication bias was estimated by the Egger's test. No evidence of publication bias was observed in the inflammatory markers after Se supplementation (coefficient = 4.9, P = 0.18). Figure 5 shows the funnel plot of the effect of Se supplementation on the level of inflammatory markers confirming that no publication bias exist between studies.

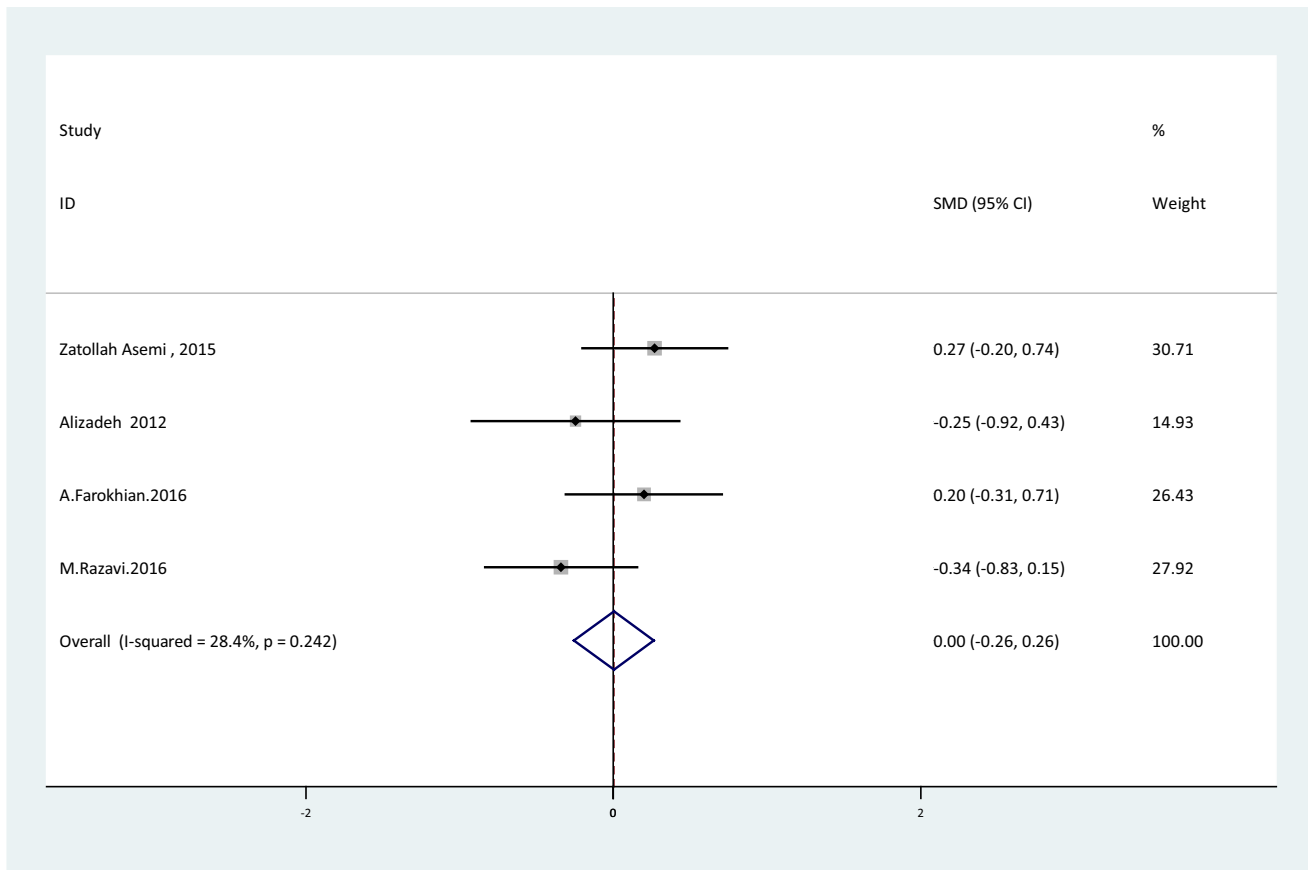


Fig. 4 Forest plot of randomized controlled trials to investigate the effect of Selenium supplementation on levels of NO

Fig. 5 Funnel plot of randomized controlled trials to investigate the effect of Selenium supplementation on inflammatory markers

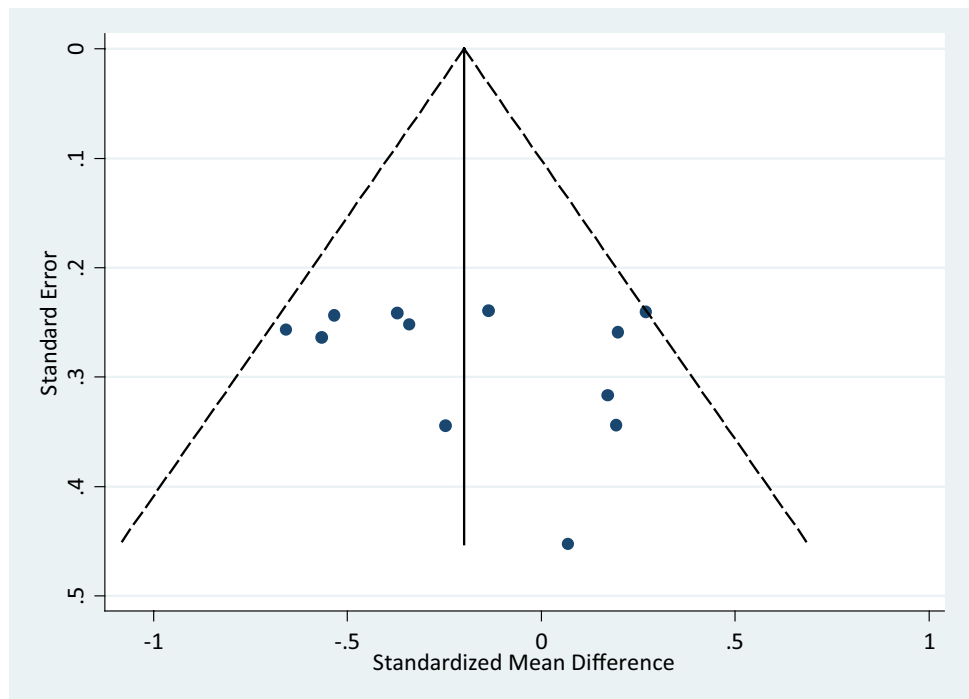


Table 2 Effect of selenium supplementation on inflammatory markers in included studies

	Author, year	Outcome	Results		
			Group	Mean change \pm SD	significance
1	Asemi, 2015	hs-CRP (ng/mL)	I: -791.88 \pm 2271.84 P: 500.55 \pm 2563.34	Yes	-0.53
		NO (mmol/L)	I: 20.91 \pm 65.32 P: 5.03 \pm 51.68	No	0.26
2	Shargorodsky, 2010	hs-CRP(mg/dl)	I: -1.32 \pm 2.8 P: -0.49 \pm 1.4	No	-0.37
		Homocysteine(μ mol/l)	I: -0.05 \pm 2.83 P: 0.36 \pm 3.2	No	-0.13
		Ur cathacholamines (mg/24 h)	I: 3.76 \pm 20 P: 2.46 \pm 18	No	0.07
3	Ravn-Haren, 2007	CRP	I: 0.08 \pm 1.15 P: -0.08 \pm 0.65	No	0.17
4	Alizadeh, 2012	hs-CRP, mg/l	I: 0 \pm 1.45 P: -0.3 \pm 1.64	No	0.19
		NOx, μ mol/l	I: -8 \pm 58.6 P: 3.7 \pm 32.5	Yes	-0.24
5	Murer, 2014	CRP,2 mg/L serum	I: 5.52 \pm 8.3 P: -1.9 \pm 4.5	No	1.11
6	Razavi, 2016	hs-CRP (ng/ml)	I: -711.3 \pm 1959.3 P: 193.5 \pm 1117.4	Yes	-0.56
		NO (μ mol/l)	I: 3.85 \pm 13.37 P: 0.07 \pm 23.38	No	0.19
7	Farrokhian, 2016	hs-CRP (ng/ml)	I: -1 372.3 \pm 2 318.8 P: -99.8 \pm 1 453.6	Yes	-0.76
		NO (μ mol/l)	I: -8.9 \pm 16.7 P: -4.3 \pm 9.3	No	-0.34

I Intervention group, C Control group, *hs-CRP*, high-sensitivity C-reactive protein, *CRP* C-reactive protein, *NO* nitric oxide, *SMD* standardized mean difference

Discussion

Despite of studies conducted, the probable effects of Se supplementation on inflammatory markers remained a question. This is the first systematic review to date to assess association between Se supplementation and the inflammatory markers. Of total 3320 searched papers after screening, 7 studies were eligible for final analysis. The findings provide

evidence-based document for health practitioners and policy makers.

Based on the included data of Se supplementation, it is revealed that the Se supplementation significantly decreased the hs-CRP levels. On the other hand, there was no significant improvement in level of NO as an oxidative stress marker with obvious heterogeneity by Se supplementation.

Table 3 Meta-analysis of effect of selenium supplementation on inflammatory profile

Inflammatory variables	Group (Number) ^a	Number of study	Pooled SMD (95% CI)	Model	Heterogeneity assessment		
					I ²	Q test	P-value
NO	I= 114 P= 114	4	0.003 (-0.26, 0.26)	Fixed	28.4%	4.19	0.24
hs-CRP	I= 150 P= 148	5	-0.44 (-0.67,-0.21)*	Fixed	12.6%	4.58	0.33
CRP	I= 43 P= 41	2	0.6(0.16, 1.04)*	Random	73.2%	3.73	<0.001

I Intervention group, C Control group, *hs-CRP*, high-sensitivity C-reactive protein, *NO*, nitric oxide, I² I-square index, Q Cochran's Q test

*Statistically significant

Table 4 Quality assessment of included studies according to the CONSORT checklist

	Zatollah Asemi, 2015	Marina Shargorodsky, 2010	lizadeh 2012	Gitte Ravn-Haren, 2007	Murer 2014	M. Razavi, 2016	A. Farrokhan, 2016
1a	Yes	No	Yes	Not applicable	Yes	No	Yes
1b	Yes	Yes	Yes	Yes	No	Yes	Yes
2a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2b	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3b	No	No	No	No	No	No	No
4a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4b	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6b	No	No	No	No	No	No	No
7a	Yes	Yes	Yes	No	Yes	Yes	Yes
7b	Yes	Yes	Yes	No	Yes	Yes	Yes
8a	Yes	No	Yes	Not applicable	Yes	Yes	Yes
8b	No	No	Yes	Not applicable	Yes	Yes	Yes
9	Yes	No	Yes	Not applicable	Yes	Yes	Yes
10	Yes	No	No	Not applicable	No	Yes	Yes
11a	No	No	No	Not applicable	No	Yes	Yes
11b	No	No	No	No	No	No	No
12a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12b	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13b	Yes	Yes	Yes	No	Yes	Yes	Yes
14a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14b	No	No	No	No	No	No	No
15	Yes	Yes	Yes	No	Yes	Yes	Yes
16	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17b	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Yes	Yes	Yes	No	Yes	No	Yes
20	Yes	Yes	Yes	Yes	Yes	No	Yes
21	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23	Yes	No	Yes	Not applicable	Yes	No	Yes
24	No	No	No	No	No	No	No
25	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total	30	25	30	20	29	28	32

Table 4 (continued)

Zatollah Asemi, 2015	Marina Shargorodsky, 2010	lizadeh 2012	Gitte Ravn-Haren, 2007	Murer 2014	M. Razavi, 2016	A. Farrokhian, 2016
(1a) Identification as a randomized trial in the title						
(1b) Structured summary of trial design, methods, results, and conclusions						
(2a) Scientific background and explanation of rationale						
(2b) Specific objectives or hypotheses						
(3a) Description of trial design (such as parallel, factorial) including allocation ratio						
(3b) Important changes to methods after trial commencement (such as eligibility criteria), with reasons						
(4a) Eligibility criteria for participants						
(4b) Settings and locations where the data were collected						
(5) The interventions for each group with sufficient details to allow replication, including how and when they were actually administered						
(6a) Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed						
(6b) Any changes to trial outcomes after the trial commenced, with reasons						
(7a) How sample size was determined						
(7b) When applicable, explanation of any interim analyses and stopping guidelines						
(8a) Method used to generate the random allocation sequence						
(8b) Type of randomization; details of any restriction (such as blocking and block size)						
(9) Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned						
(10) Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions						
(11a) If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how						
(11b) If relevant, description of the similarity of interventions						
(12a) Statistical methods used to compare groups for primary and secondary outcomes						
(12b) Methods for additional analyses, such as subgroup analyses and adjusted analyses						
(13a) For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome						
(13b) For each group, losses and exclusions after randomization, together with reasons						
(14a) Dates defining the periods of recruitment and follow-up						
(14b) Why the trial ended or was stopped						
(15) A table showing baseline demographic and clinical characteristics for each group						
(16) For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups						
17a) For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)						
17b) For binary outcomes, presentation of both absolute and relative effect sizes is recommended						
(18) Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory						
(19) All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)						
(20) Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses						
(21) Generalizability (external validity, applicability) of the trial findings						
(22) Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence						
23) Registration number and name of trial registry						
(24) Where the full trial protocol can be accessed, if available						
(25) Sources of funding and other support (such as supply of drugs), role of funders						

Considering the related literature, another trial showed the effect of the Se supplementation on reproductive outcomes, biomarkers of inflammation, and oxidative stress among women with polycystic ovary syndrome (PCOS) [29].

In a study, supplementation of Se in daily dietary programs of pregnant women with Gestational Diabetes (GDM) resulted in better glucose homeostasis, reduced inflammation, and improved oxidative stress [28]. Considering the probable mechanisms, these beneficial effects on improvement of glucose homeostasis may be rooted from its effect on the inhibition of inflammatory cytokines, such as tumor necrosis factor (TNF)- α and interleukin (IL)-1 [31]. In patients with type 2 Diabetes mellitus (T2DM) and coronary heart disease (CHD), effects of Se supplementation on metabolic status were evaluated through prescription of a

200 $\mu\text{g/day}$ Se supplementation. This approach resulted in a significant decrease in insulin, HOMA-IR, HOMA-B, serum hs-CRP, QUICKI score and TAC concentrations [12].

The findings of studies conducted provide desirable effects of Se supplementation on cardiovascular risk factors, such as oxidative stress and insulin resistance [10].

Researcher confirmed that, regular administration of antioxidant supplements including vitamin C, vitamin E, coenzyme and Se could significantly increase the large and small artery elasticity in patients with multiple cardiovascular risk factors. Glucose and lipid metabolism and hypertension were also improved by these supplementations [9].

As a practical point for achieving the desired responses, the duration of intervention was discussed in many studies [3]. A group of researchers reported that according to their

studies, short-term Se supplementation could not seem to be effective in blood lipid markers. This uses also in expression and activity of selected enzymes and a transcription factor involved in processes of glutathione-mediated detoxification and anti-oxidation [3]. In a practical trial, antioxidant supplementation with antioxidant and Se for four months significantly led to improvement of liver function tests as well as antioxidant-oxidant balance; however, it had no significant effects on the systemic inflammatory markers [30].

As the main strength, the present study is the first comprehensive systematic review of the effects of Se supplementation on the inflammatory markers. Using standard comprehensive systematic search approaches, we found and assessed all available related sources of data. The limitation of this study was the limited measured outcome variables conducted in scattered studies. Therefore, we faced with challenges for the appropriate comparison of available data. Also, it should be considered that different methodological designs (randomized controlled trials and cross over) of included studies can influence our findings.

Conclusions

The results of present study demonstrated that Se supplementation significantly decreased hs-CRP levels, but there was no significant improvement in the level of NO. As a practical application in the field of policy-related research, further studies on different mechanisms, different patterns of Se supplementation and various biochemical outcomes are recommended.

Abbreviations SMD: Standardized mean difference; CI: Confidence interval; Se: Mineral selenium; CRP: C-reactive protein; IL: Interleukins; TNF α : Tumor necrosis factor- α ; RCTs: Randomized control trials; PCOS: Polycystic ovary syndrome; GDM: Gestational Diabetes; CHD: Coronary heart disease

Acknowledgements The authors are thankful of the team working on this study and all participants who made this experience.

Authors' contributions The concept of this study was proposed by S.D., M.Q., This study was designed S.D., M.Q., M.H., Data extraction was done by H.A., H.-S.E., A.K., M.Z., F.B., H.R., A.M.G., Analysis or interpretation was performed by M.Q., S.D. Literature search was done by S.D. This study was written by S.D., M.Q. All authors read and approved the final manuscript.

Funding This study was funded by the Alborz University of Medical Sciences.

Data availability The dataset supporting the conclusions of this article is included within the article.

Declarations

Conflict of Interest The authors declare no conflicts of interest.


References

1. Rayman MP. The importance of selenium to human health. *The Lancet*. 2000;356(9225):233–41.
2. Faghihi T, Radfar M, Barmal M, Amini P, Qorbani M, Abdollahi M, et al. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. *Am J Ther*. 2014;21(6):491–5.
3. Ravn-Haren G, Bügel S, Krath B, Hoac T, Stagsted J, Jørgensen K, et al. A short-term intervention trial with selenate, selenium-enriched yeast and selenium-enriched milk: effects on oxidative defence regulation. *Br J Nutr*. 2008;99(4):883.
4. Sun W, Wang Q, Guo Y, Zhao Y, Wang X, Zhang Z, et al. Selenium suppresses inflammation by inducing microRNA-146a in *Staphylococcus aureus*-infected mouse mastitis model. *Oncotarget*. 2017;8(67):110949.
5. El-Bayoumy K, Sinha R, Richie JP Jr. Forms of selenium in cancer prevention. *Diversity of Selenium Functions in Health and Disease*. 2015;38:137.
6. Nicastro HL, Dunn BK. The Selenium and Vitamin E Cancer Prevention Trial (SELECT): prevention of prostate cancer using selenium and/or vitamin E in the SELECT cancer prevention trial. *Selenium2015*. p. 428–57.
7. Benstoem C, Goetzenich A, Kraemer S, Borosch S, Manzanares W, Hardy G, et al. Selenium and Its Supplementation in Cardiovascular Disease—What do We Know? *Nutrients*. 2015;7(5):3094.
8. Alissa E, Bahijri S, Ferns G. The controversy surrounding selenium and cardiovascular disease: a review of the evidence. *Medical science monitor: international medical journal of experimental and clinical research*. 2003;9(1):RA9.
9. Shargorodsky M, Debby O, Matas Z, Zimlichman R. Effect of long-term treatment with antioxidants (vitamin C, vitamin E, coenzyme Q10 and selenium) on arterial compliance, humoral factors and inflammatory markers in patients with multiple cardiovascular risk factors. *Nutr Metab*. 2010;7:55.
10. Alizadeh M, Safaeiyan A, Ostadrahimi A, Estakhri R, Daneghian S, Ghaffari A, et al. Effect of L-arginine and selenium added to a hypocaloric diet enriched with legumes on cardiovascular disease risk factors in women with central obesity: a randomized, double-blind, placebo-controlled trial. *Ann Nutr Metab*. 2012;60(2):157.
11. Abramson SB. Nitric oxide in inflammation and pain associated with osteoarthritis. *Arthritis Res Ther*. 2008;10(2):S2.
12. Farrokhiyan A, Bahmani F, Taghizadeh M, Mirhashemi S, Aarabi M, Raygan F, et al. Selenium supplementation affects insulin resistance and serum hs-CRP in patients with type 2 diabetes and coronary heart disease. *Hormone and metabolic research= Hormon-und Stoffwechselforschung= Hormones et métabolisme*. 2016;48(4):263.
13. Kamath DY, Xavier D, Sigamani A, Pais P. High sensitivity C-reactive protein (hsCRP) & cardiovascular disease: An Indian perspective. *Indian J Med Res*. 2015;142(3):261–8.
14. Luan Y-y, Yao Y-m. The clinical significance and potential role of C-reactive protein in chronic inflammatory and neurodegenerative diseases. *Frontiers in Immunology*. 2018;9(1302).
15. Morrow DA, Ridker PM. C-reactive protein, inflammation, and coronary risk. *The Medical clinics of North America*. 2000;84(1):149–61, ix.
16. Djalalinia S, Khosravi M, Hasani M, Moghaddam SS, Atoofi MK, Mahdavi-Gorabi A, Noroozi M, Qorbani M, Asayesh H, Soleimani A. Effects of selenium supplementation on cardiometabolic risk factors, inflammatory, and antioxidant markers: A systematic review and meta-analysis protocol. *International Journal of Preventive Medicine*. 2019;10.
17. Razban MM, Eslami M, Bagherzadeh A. The relationship between serum levels of hs-CRP and coronary lesion severity. *Clujul Med*. 2016;89(3):322–6.

18. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Frontiers in immunology*. 2018;9:754-.
19. Wei J, Zeng C, Gong Q-y, Yang H-b, Li X-x, Lei G-h, et al. The association between dietary selenium intake and diabetes: a cross-sectional study among middle-aged and older adults. *Nutrition Journal*. 2015;14.
20. Lu C-W, Chang H-H, Yang K-C, Kuo C-S, Lee L-T, Huang K-C. High serum selenium levels are associated with increased risk for diabetes mellitus independent of central obesity and insulin resistance. *BMJ Open Diabetes Research & Care*. 2016;4(1).
21. Heinrich CJ. Evidence-based policy and performance management: Challenges and prospects in two parallel movements. *The American Review of Public Administration*. 2007;37(3):255–77.
22. Djalalinia S, Ramezani-Tehrani F, Malekafzali H, Hejazi F, Peykari N. Development and evaluation of a nutritional health program for adolescents. *Iran J Nurs Midwifery Res*. 2013;18(5):425.
23. Peykari N, Tehrani F, Eftekhari M, Malekafzali H, Dejman M, Neot R, et al. A peer-based study on adolescence nutritional health: a lesson learned from Iran. *JPMA The Journal of the Pakistan Medical Association*. 2011;61(6):549.
24. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8(1):18.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–88.
26. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ: British Medical Journal*. 2003;327(7414):557.
27. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–34.
28. Asemi Z, Jamilian M, Mesdaghinia E, Esmailzadeh A. Effects of selenium supplementation on glucose homeostasis, inflammation, and oxidative stress in gestational diabetes: Randomized, double-blind, placebo-controlled trial. *Nutrition (Burbank, Los Angeles County, Calif)*. 2015;31(10):1235.
29. Razavi M, Jamilian M, Kashan Z, Heidar Z, Mohseni M, Ghandi Y, et al. Selenium supplementation and the effects on reproductive outcomes, biomarkers of inflammation, and oxidative stress in women with polycystic ovary syndrome. *Hormone and metabolic research= Hormon-und Stoffwechselforschung= Hormones et metabolisme*. 2016;48(3):185.
30. Murer S, Aeberli I, Braegger C, Gittermann M, Hersberger M, Leonard S, et al. Antioxidant supplements reduced oxidative stress and stabilized liver function tests but did not reduce inflammation in a randomized controlled trial in obese children and adolescents. *J Nutr*. 2014;144(2):193.
31. Brigelius-Flohe R, Banning A, Kny M, Böhl G-F. Redox events in interleukin-1 signaling. *Archives of biochemistry and biophysics*. 2004;423(1):66–73.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Shirin Djalalinia^{1,2} · Motahareh Hasani³ · Hamid Asayesh⁴ · Hanieh-Sadat Ejtahed^{5,6} · Hanieh Malmir⁵ · Amir Kasaeian^{7,8} · Maryam Zarei⁹ · Fereshteh Baygi¹⁰ · Hadith Rastad^{11,12} · Armita Mahdavi Gorabi¹³ · Mostafa Qorbani¹² 

¹ Development of Research & Technology Center, Deputy of Research and Technology, Ministry of Health and Medical Education, Tehran, Iran

² Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

³ School of Public Health, Iran University of Medical Sciences, Tehran, Iran

⁴ Department of Medical Emergencies, Qom University of Medical Sciences, Qom, Iran

⁵ Obesity and Eating Habits Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

⁶ Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

⁷ Hematology-Oncology and Stem Cell Transplantation Research Center, Research Institute for Oncology, Hematology and Cell Therapy, Tehran University of Medical Sciences, Tehran, Iran

⁸ Digestive Diseases Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran

⁹ Department of Nutrition and Dietetics Faculty of Medicine and Health Sciences, University Putra Malaysia, Selangor, Serdang, Malaysia

¹⁰ Centre of Maritime Health and Society, Department of Public Health, University of Southern Denmark, Esbjerg, Denmark

¹¹ Cardiovascular Research Center, Alborz University of Medical Sciences, Karaj, Iran

¹² Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

¹³ Social Determinants of Health Research Center Alborz, University of Medical Sciences, Karaj, Iran