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ORIGINAL ARTICLE

Effect of selenium supplementation on antioxidant markers: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Aim The aim of this study is the systematic review and meta-analysis of controlled trial studies to assess the antioxidant effects of selenium (Se) supplementation.

Methods The systematic review and meta-analysis were performed according to the previously published protocol. The PubMed, Web of Sciences, and Scopus databases were meticulously searched for relevant data, without time or language restriction, up to June 1, 2017. All clinical trials which assessed the effect of Se supplementation on antioxidant markers, including oxidative stress index (OSI), antioxidant potency composite (APC) index, plasma malonaldehyde (MDA), total antioxidant capacity (TAC), antioxidant enzymes (superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT)), and total antioxidant plasma (TAP), were included. The effect of Se supplementation on antioxidant markers was assessed using standardized mean difference (SMD) and 95% confidence interval (CI). The random-effect meta-analysis method was used to estimate the pooled SMD.

Results In total, 13 studies which assessed the effect of Se supplementation on antioxidant markers were included. The random-effect meta-analysis method showed that Se supplementation significantly increased GPX (SMD = 0.54; 95% CI = 0.21–0.87) and TAC (SMD = 0.39, 95% CI = 0.13, 0.66) levels and decreased MDA levels (SMD = − 0.54, 95% CI = − 0.78, − 0.30). The effect of Se supplementation on other antioxidant markers was not statistically significant ($P > 0.05$).

Conclusion The findings showed that Se supplementation might reduce oxidative stress by increasing TAC and GPX levels and decreasing serum MDA, both of which are crucial factors for reduction of oxidative stress.

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Keywords Selenium · Supplementation · Antioxidant

Introduction

Selenium (Se) is an essential micronutrient for human health. It plays a key role in regulation of selenoprotein synthesis, selenoproteins being the means by which Se exerts its biological functions throughout the body [1, 2]. The selenoproteins, including glutathione peroxidase (GPX), iodothyronine deiodinases (IDD), and thioredoxin reductase (TrxR), participate in antioxidant defense and prevent oxidative stress damage [3, 4]. Se is hence a critical factor for optimal functioning of the immune system, as well as of cellular processes and metabolic cycling [5–7].

Oxidative stress, which is a disturbance in the balance between antioxidant defense and reactive oxidant species can cause toxic effects and damage cellular function and biomolecules (e.g., lipids), lipoproteins, DNA, and proteins [5, 8, 9]. Oxidative stress has thus been implicated in initiation and development of such diseases as insulin resistance, diabetes mellitus, cardiometabolic diseases, cancer, and neurodegenerative diseases [8–11].

A number of studies have shown that low Se status, and hence selenoprotein insufficiency, is associated with suboptimal health while also causing several diseases [5, 12]. More specifically, Se deficiency impairs immune function and selenoprotein synthesis, which results in immune cells being unable to protect against oxidative stress [13, 14]. Furthermore, animal studies have demonstrated that low levels of selenoproteins are related to hyperglycemia and insulin resistance [15].

Previous studies have demonstrated that Se supplementation may have beneficial effects in reducing the risk of chronic metabolic disorders, hyperglycemia, hyperlipidemia, and cancer [16–18]. Meanwhile, there is scientific evidence that dietary Se intake is inversely associated with all-cause mortality [18]. There is also an inverse relationship between the onset of cardiovascular diseases and blood Se levels [19, 20]. An increase of Se intake in Beijing, China, led to a reduction in the cardiovascular disease mortality rate from 1984 to 1990 [1]. Given the critical role of selenoproteins in antioxidant defense and regulation of circulating lipoproteins, vascular endothelial cells, and cardiac function, it is hypothesized that Se supplementation may be protective against cardiometabolic disease [5, 21].

Due to the numerous controversies surrounding Se and its impact on both health and disease, it is clear that further studies are required to provide solid evidence which may be used by both clinicians and policymakers for the setting up of relevant health programs and nutritional interventions [22, 23].

Although several controlled trials have investigated the effects of Se supplementation on antioxidant markers, its pooled effect on antioxidant markers is as yet unclear and controversial. The aim of this systematic review and meta-analysis was therefore to assess the effects of Se supplementation on antioxidant markers.

Methods

This systematic review followed the PRISMA guidelines [24], while the meta-analysis was performed according to a previously published protocol [23].

Data sources and search strategy

The PubMed, ISI/WOS, and Scopus databases were analyzed meticulously for relevant data, without time or language restriction, up to June 1, 2017 (Fig. 1). The reference lists of the retrieved reviews and meta-analyses were also screened to identify pertinent data. We excluded non-relevant articles and those with duplicate citation.

Study selection and data extraction

We included randomized controlled trials (RCTs) and quasi-RCT crossover studies, in which the control group received a placebo. Studies were considered regardless of dosage or duration of administration of antioxidants. Regarding the crossover studies, data from the first period were recorded and analyzed.

With regard to the RCTs, all studies among the different target groups of diabetic patients, polycystic ovarian syndrome (PCOS) patients, obese participants, and healthy subjects were included. Studies in which Se was applied as a single therapy or even combination therapy were considered as acceptable.

All clinical trials assessing the effect of Se supplementation on antioxidant markers, including oxidative stress index (OSI), antioxidant potency composite (APC) index, plasma malonaldehyde (MDA), total antioxidant capacity (TAC), antioxidant enzymes (superoxide dismutase (SOD), GPX, thiobarbituric acid-reactive substances (TBARS), catalase (CAT)), and total antioxidant plasma (TAP), were included.

Studies were excluded if they were (1) non-relevant; (2) a duplicate citation; (3) more than one paper from a specific study; (4) case reports, reviews, editorials, and studies performed on children (age < 18); and (5) concerned specific sub-group populations.

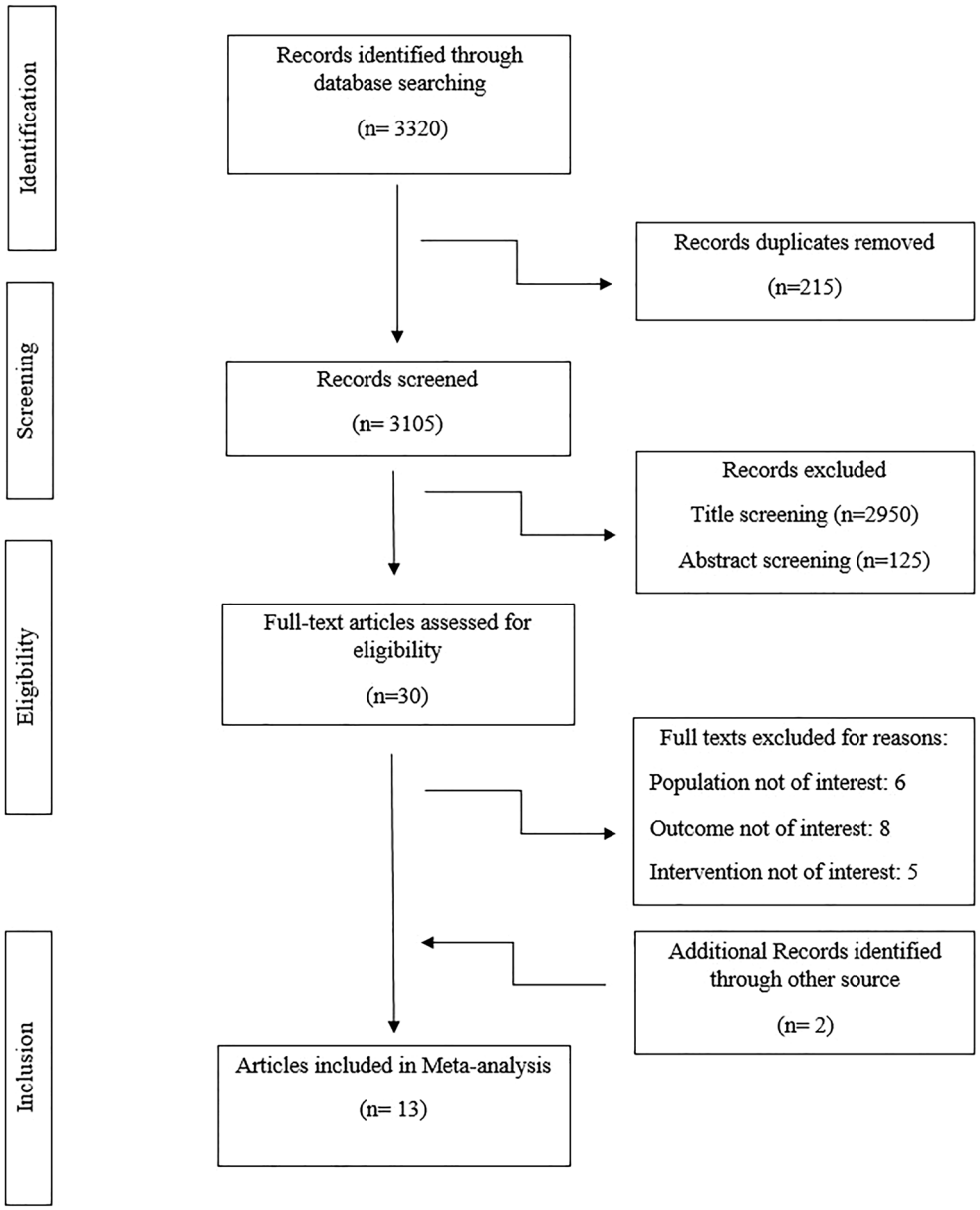

Fig. 1. Flowchart of the number of studies selected for the meta-analysis

To establish inter-rater reliability, titles and abstracts were screened by two experts independently. Possible discrepancies were resolved by the main researcher. After assessment of relevancy, based on the inclusion/exclusion criteria, the full-text review determined the eligibility of papers.

The comprehensive recommended guidelines of the Consolidated Standards of Reporting Trials (CONSORT) 2010 25-item checklist [25], quality assessment, and data extraction and analysis were used, followed by two independent experts.

The main fields of relevant data were citation, type of study, study subjects, publication year, sample size, dose of supplementation, intervention group, control group, mean age of participants, outcome, intervention duration, follow-up duration, measurement interval, results, and effect size.

Data analysis

A meta-analysis was conducted for relevant antioxidant markers on which data were available from more than two individual studies. The mean change from baseline in antioxidant marker concentrations and standard deviation for both intervention and control groups was used to calculate the effect size. The effect size is presented as standardized mean difference (SMD). To pool the data, we used the random-effect model based on the result of heterogeneity among studies. A random-effect model was used if the Q-statistic for heterogeneity was significant at the level of 0.1 [26]. In other cases, the fixed-effect model was used [27]. The degree of heterogeneity was quantified, using I^2 statistics, which is the estimation of the total variation across studies due to

heterogeneity [28]. Possible sources of heterogeneity (such as quality assessment score, duration of intervention, study subjects, mean age of participants, dose of Se supplementation, type of study subjects, subjects with metabolic diseases, and healthy subjects) and sex ratio were explored by random-effect meta-regression analysis. Subgroup analyses were performed according to type of study population (type of disease) to identify between-study heterogeneity. Subgroup heterogeneity was evaluated using the fixed-effect model. A forest plot was used to present the results of the meta-analysis schematically. Publication bias was evaluated by visual inspection of the funnel plot and the Egger's regression test. In addition, sensitivity analysis was conducted according to the study quality to test the robustness of the results.

The statistical analysis was carried out using Stata software, version 10 [25]. P value ≤ 0.05 was considered statistically significant.

Results

Search results and characteristics of included studies

From 3320 searched documents, following the refinement processing according to the inclusion/exclusion criteria, in total, 13 RCTs were included. These publications were dated from 2004 to 2016. Figure 1 shows the selection process of the articles included.

The meta-analysis included 13 studies (12 randomized controlled trials and 1 crossover). All studies had assigned a total of 2790 participants randomly to intervention and control groups. The age of the patients was from 10 to 85 years. Nine trials had recruited both men and women, while, in four other studies, only female subjects were enrolled [29–32]. Four trials used Se combined with other vitamins or minerals [10, 30, 33, 34] and nine trials used Se only as an oral supplement. The daily Se dose was 200 m/day in seven trials [29, 30, 32, 34–37]; one trial used 300 mg/day [33]; one RCT used 50 mg/day [10], and one study used 60 and 960 mg/day [31, 38]. In two studies, three different groups were given three different doses (100, 200, 300 mg/day); hence, they were considered as separate studies [15, 39]. Six trials were conducted in Iran, six in Europe, and one in the USA. All trials were placebo-controlled and all were double-blinded. The length of the intervention periods ranged from 42 days [25] to 180 days [15, 39] (Table 1).

Meta-analysis

Four trials involving 228 participants in the Se or placebo groups reported the effect of Se supplementation on TAC. Three studies reported GSH (glutathione), five studies MDA, 10 Se, three GPX, two TBARS, and four adiponectin as outcome at baseline and follow-up (Table 2).

The effect of Se supplementation on antioxidant levels is shown in Table 2. The pooled results indicated that Se supplementation significantly increased GPX levels (SMD = 0.54; 95% CI = 0.21–0.87). There was no significant heterogeneity between the three included trials (Q = 5.74, I^2 = 65.2%, P = 0.057).

There was a significant improvement of antioxidant profile such as TAC [(SMD) = 0.39, 95% CI = (0.13, 0.66)] with obvious heterogeneity (Q = 10.27; P = 0,016; I^2 = 70.8%), Se [(SMD) = 3.24, 95% CI = (3.1, 3.4)] with obvious heterogeneity (Q = 358.82; P = 0.0; I^2 = 97.5%), and MDA [(SMD) = − 0.54, 95% CI = (− 0.78, − 0.30)] without significant heterogeneity (Q = 7.50; P = 0.11; I^2 = 46.6%) through Se supplementation.

According to the meta-analysis, the intake of Se compared with placebo resulted in no significant improvement in GSH [(SMD) = 0.16, 95% CI = (− 0.12, 0.45)] and significant heterogeneity (Q = 10.94; P = 0.004; I^2 = 81.7%), TBARS [(SMD) = − 0.12, 95% CI = (− 0.50, 0.25)], and adiponectin [(SMD) = 0.04, 95% CI = (− 0.09, 0.18)]. There was no significant evidence of heterogeneity for TBARS (Q = 0.14; P = 0.71; I^2 = 0%) and adiponectin (Q = 0.40; P = 0.94; I^2 = 0%), respectively. The pooled effect of Se supplementation on each antioxidant marker is depicted in Fig. 2.

Quality assessment

Table 3 shows the quality of the included studies. Six studies were classified as high quality, with the CONSORT score higher than 30 [15, 29, 30, 36, 37, 39]; four studies were classified as medium quality, with the CONSORT score in the range of 25–29 [10, 31, 32, 35]; and three studies were classified as low quality, with the CONSORT score lower than 25 [33, 34, 38]. Randomization as a prerequisite for inclusion in this meta-analysis was conducted in 13 studies.

All 12 RTCs were double-blind, but only four studies were described as blinding [15, 32, 37, 39].

Meta-regression and subgroup analysis

The effect of influencing factors was analyzed using a random-effect meta-regression. There was no effect of influencing factors, such as duration, mean age, study subjects, dose, antioxidant profile, and female ration on heterogeneity (P > 0.05). The results of meta-regression showed that the quality score was also non-significant (coefficient = 0.12, P = 0.2). To determine the source of heterogeneity, the subgroup analyses were divided according to study subjects (subjects with metabolic diseases and healthy subjects). Subgroup analysis showed that the effect of Se supplementation on antioxidant markers did not change according to study subjects.

Table 1. Characteristics of the included studies in the meta-analysis

	Author , year	Country	Type of study	Study subject	Sample size	Dose of supplementation	Intervention group	Control group	Mean age of participant	Out come	Intervention duration
1	Zatollah Asemi, 2015	Iran	RCT	GDM women	I = 35 C = 35	200 μg	MT	Placebo	28.6 ± 4.6 years	TAC (mmol/L)	6 wks from weeks 24 to 28 of gestation
1	Zatollah Asemi, 2015	Iran	RCT	GDM women	I = 35 C = 35	200 μg	MT	Placebo	28.6 ± 4.6 years	GSH (mmol/L)	6 wks from weeks 24 to 28 of gestation
1	Zatollah Asemi, 2015	Iran	RCT	GDM women	I = 35 C = 35	200 μg	MT	Placebo	28.6 ± 4.6 years	MDA (mmol/L)	6 wks from weeks 24 to 28 of gestation
2	Rayman, 2012	USA	RCT	Elderly adults	I1 = 120 I2 = 124 I3 = 117 C = 100	100 μg 200 μg 300 μg	MT	Placebo	67.5 years	Plasma Se	Six months
2	Rayman, 2012	USA	RCT	Elderly adults	I1 = 120 I2 = 124 I3 = 117 C = 100	100 μg 200 μg 300 μg	MT	Placebo	67.5 years	Adiponectin levels marker of insulin resistance	Six months
3	Gitte Ravn-Haren, 2007	Denmark	R cross over	Healthy	N = 20	300 μg	CT	Placebo	26.8 years	Plasma Se	1 week
3	Gitte Ravn-Haren, 2007	Denmark	R cross over	Healthy	N = 20	300 μg	CT	Placebo	26.8 years	GR	1 week
3	Gitte Ravn-Haren, 2007	Denmark	R cross over	Healthy	N = 20	300 μg	CT	Placebo	26.8 years	GPX	1 week
3	Gitte Ravn-Haren, 2007	Denmark	R cross over	Healthy	N = 20	300 μg	CT	Placebo	26.8 years	LOX	1 week
4	Alizadeh, 2012	Iran	RCT	Subjects with central obesity	I = 17 C = 17	200 μg/d	CT	Placebo	33.9 ± 8.5 years	TAC, _mol/l	2 weeks run-in period 6 weeks intervention period
4	Alizadeh, 2012	Iran	RCT	Subjects with central obesity	I = 17 C = 17	200 μg/d	CT	Placebo	33.9 ± 8.5 years	MDA, nmol/ml	2 weeks run-in period 6 weeks intervention period
5	Murer, 2014	Switzerland	RCT	Obese children	I = 23 C = 21	50 μg	CT	Placebo	12.7 ± 1.5 years	Plasma Se	4 months
5	Murer, 2014	Switzerland	RCT	Obese children	I = 23 C = 21	50 μg	CT	Placebo	12.7 ± 1.5 years	MDA,2 mmol/L plasma	4 months
85	Murer, 2014	Switzerland	RCT	Obese children	I = 23 C = 21	50 μg	CT	Placebo	12.7 ± 1.5 years	a-Tocopherol, mmol/L plasma	4 months
5	Murer, 2014	Switzerland	RCT	Obese children	I = 23 C = 21	50 μg	CT	Placebo	12.7 ± 1.5 years	8-iso-PGF2a	4 months
6	Guertin, 2016	Ithaca	RCT	Healthy	I = 66 C = 81	200 μg/d	CT	Placebo	63.1 ± (6.1) years	8-iso-PGF2α	38 months
7	Mao, 2015	UK	RCT	Primiparous women	I = 104 C = 106	60 μg	MT	Placebo		Adiponectin level marker of insulin resistance	From 12 weeks of gestation until delivery
8	Faghihi, 2014	Iran	RCT	Type 2 diabetes	I = 33 C = 27	200 μg/d	MT	Placebo	53.54 ± (7.52) years	TBARS (mmol/L)	3 months
8	Faghihi, 2014	Iran	RCT	Type 2 diabetes	I = 33 C = 27	200 μg/d	MT	Placebo	53.54 ± (7.52) years	FRAP (mmol/L)	3 months
8	Faghihi, 2014	Iran	RCT	Type 2 diabetes	I = 33 C = 27	200 μg/d	MT	Placebo	53.54 ± (7.52) years	Plasma Se	3 months
9	P. Faure, 2004	France	RCT	Type 2 diabetes	I = 27 P = 21 C = 10	960 μg/d	MT	Placebo	49 to 58 years	Plasma Se	3 months
9	P. Faure, 2004	France	RCT	Type 2 diabetes	I = 27 P = 21 C = 10	960 μg/d	MT	Placebo	49 to 58 years	GSH Px	3 months

Table 1. (continued)

9	P. Faure, 2004	France	RCT	Type 2 diabetes	I = 27 P = 21 C = 10	960 μg/d	MT	Placebo	49 to 58 years	SOD	3 months
9	P. Faure, 2004	France	RCT	Type 2 diabetes	I = 27 P = 21 C = 10	960 μg/d	MT	Placebo	49 to 58 years	Plasma TBARS (μMol)	3 months
10	M. Razavi, 2016	Iran	RCT	PCOS patients	I = 32 C = 32	200 μg/d	MT	Placebo	18–40 years	TAC (mmol/l)	8 weeks
10	M. Razavi, 2016	Iran	RCT	PCOS patients	I = 32 C = 32	200 μg/d	MT	Placebo	18–40 years	GSH (μmol/l)	8 weeks
10	M. Razavi, 2016	Iran	RCT	PCOS patients	I = 32 C = 32	200 μg/d	MT	Placebo	18–40 years	MDA (μmol/l)	8 weeks
11	A. Farrokhian, 2016	Iran	RCT	Type 2 diabetes & CHD	I = 30 C = 30	200 μg/d	MT	Placebo	40–85 years	TAC (mmol/l)	8 weeks
11	A. Farrokhian, 2016	Iran	RCT	Type 2 diabetes & CHD	I = 30 C = 30	200 μg/d	MT	Placebo	40–85 years	GSH (μmol/l)	8 weeks
11	A. Farrokhian, 2016	Iran	RCT	Type 2 diabetes & CHD	I = 30 C = 30	200 μg/d	MT	Placebo	40–85 years	MDA (μmol/l)	8 weeks
12	F.Bahmani, 2015	Iran	RCT	Diabetic nephropathy	I = 30 C = 30	200 μg/d	MT	Placebo	45–85 years	GPx	12 weeks
	Frederik Cold, 2015	Denmark	RCT	Elderly population	I1 = 124 I2 = 122 I3 = 119 C = 126	100 μg 200 μg 300 μg	MT	Placebo	66.3 years	Plasma Se	6 months

	Follow-up duration	Measurement interval	Result (means ± SD)			Effect size	
				Mean change	Significancy	*r*	*d*
1	–	Baseline and end of study	I P	62.98 ± 118.44 17.45 ± 117.33	No	0.18	0.38
1	–	Baseline and end of study	I P	52.14 ± 58.31 − 39.93 ± 153.52	Yes	0.37	0.79
1	–	Baseline and end of study	I P	− 0.01 ± 0.36 0.67 ± 1.90	Yes	− 0.24	− 0.50
2		Baseline and after six months	I1 I2 I3 P	57.8 ± 23.5 100.3 ± 38.7 136.4 ± 47.3 2.1 ± 25.4	Yes No	0.75 0.83 .87	2.27 3.00 3.53
2		Baseline and after six months	I1 I2 I3 P	− 0.02 ± 2.15 − 0.02 ± 1.81 0.07 ± 1.85 − 0.1 ± 1.94	No No	0.01 0.02 0.04	0.03 0.04 0.08
3	3 week washout	Baseline and 1 week and end of study	I P	2.8 ± 12.2 − 3 ± 12.8	No No	0.22	0.46
3	3 week washout	Baseline and 1 week and end of study	I P	− 0.01 ± 0.08 0.01 ± 0.08	No No	− 0.12	− 0.25
3	3 week washout	Baseline and 1 week and end of study	I P	0.41 ± 2.15 0.27 ± 2.1	No No	0.03	0.06
3	3 week washout	Baseline and 1 week and end of study	I P	2 ± 25.7 2 ± 26.9	No No	0	0
4	8 week	Baseline and after 3, 6 weeks	I P	0.012 ± 0.13 0.005 ± 0.17	No	0.02	0.04
4	8 week	Baseline and after 3, 6 weeks	I P	0 ± 0.82 0.1 ± 0.82	No	− 0.06	− 0.12
5	–	Baseline and after 4 months	I P	0.09 ± 0.13 0.02 ± 0.15	Yes	0.24	0.50

Table 1. (continued)

5	–	Baseline and after 4 months	I	− 0.14 ± 0.29	No	− 0.52	− 1.21
			P	0.2 ± 0.27			
85	–	Baseline and after 4 months	I	22.9 ± 9.8	Yes	0.83	2.99
			P	-0.9 ± 5.5			
5	–	Baseline and after 4 months	I	− 0.07 ± 0.27	Yes	0	0
			P	− 0.07 ± 0.28			
6	–	Baseline and after 38 months	I	641.1 ± 424	No	0.007	0.014
			P	636 ± 281			
7		Baseline and after 12, 20 and 35 weeks	I	− 3.05 ± 5.45	No	− 0.01	− 0.02
			P	− 2.91 ± 5.1			
8		Baseline and after 3 months	I	− 3.98 ± 15.6	No	− 0.03	− 0.06
			P	− 3.15 ± 11.5			
8		Baseline and after 3 months	I	− 26.8 ± 81.7	No	0.07	0.15
			P	− 38.74 ± 71.3			
8		Baseline and after 3 months	I	29.29 ± 40.8	Yes	0.33	0.71
			P	− 1.73 ± 45.5			
9		Baseline and after 3 months	I	0.23 ± 0.17	Yes	0.68	1.87
			P	− 0.08 ± 0.16			
9		Baseline and after 3 months	I	3.1 ± 7.8	Yes	0.17	0.35
			P	− 0.07 ± 9.9			
9		Baseline and after 3 months	I	− 0.01 ± 0.11	No	− 0.07	− 0.15
			P	0.01 ± 0.15			
9		Baseline and after 3 months	I	− 0.07 ± 0.33	No	− 0.1	− 0.2
			P	0.01 ± 0.45			
10		Baseline and after 2 months	I	− 19.54 ± 135.00	No	− 0.04	− 0.09
			P	− 4.32 ± 200.88			
10		Baseline and after 2 months	I	− 16.72 ± 132.53	No	− 0.17	− 0.34
			P	35.05 ± 168.55			
10		Baseline and after 2 months	I	− 0.13 ± 1.03	Yes	− 0.31	− 0.66
			P	1.40 ± 3.11			
11		Baseline and after 2 months	I	301.3 ± 400.6	Yes	0.45	1.03
			P	− 127.2 ± 428.0			
11		Baseline and after 2 months	I	− 30.4 ± 172.2	No	− 002	− 005
			P	− 21.7 ± 145.2			
11		Baseline and after 2 months	I	− 0.4 ± 1.5	No	− 0.1	− 0.2
			P	− 0.1 ± 1.2			
12		Baseline and after 3 months	I	2.3 ± 21.7	Yes	0.45	1.02
			P	− 27.7 ± 35.2			
		Baseline and after 6 months	I1	− 64.8 ± 21.5	Yes	0.9	3.5
			I2	− 120.9 ± 36.7		0.9	4.3
			I3	169.8 ± 48.1		0.9	4.8
			P	− 0.9 ± 14.9			

RCT, randomized controlled trial; CT, combination therapy; MT, monotherapy; I, intervention group; C, control group; GSH, glutathione; MDA, malondialdehyde; TAC, total antioxidant capacity; TBARS, thiobarbituric acid-reactive substances; FRAP, ferric-reducing ability of plasma; GPX, glutathione peroxidase; SOD, superoxide dismutase; GR, glutathione reductase; LOX, lipid resistance to oxidation

Table 2 Meta-analysis of effect of selenium supplementation on antioxidant profile

Antioxidant profile	Group (number)[a]	Number of studies	Pooled SMD (95% CI)	Model	Heterogeneity assessment		
					I^2 (%)	Q test	P value
TAC	$I = 114$ $P = 114$	4	0.39 (0.13, 0.66)*	Random	70.8	10.27	0.016
GSH	$I = 97$ $P = 97$	3	0.16 (− 0.12, 0.45)	Random	81.7	10.94	0.004
MDA	$I = 137$ $P = 135$	5	− 0.54 (− 0.78, − 0.30)*	Fixed	46.6	7.50	0.112
Se	$I = 829$ $P = 767$	10[a]	3.24 (3.1, 3.4)*	Random	97.5	358.82	< 0.001
GPX	$I = 77$ $P = 71$	3	0.54 (0.21, 0.87)*	Random	65.2	5.74	0.057
TBARS	$I = 60$ $P = 48$	2	− 0.12 (− 0.50, 0.25)	Fixed	0	0.14	0.71
Adiponectin	$I = 465$ $P = 406$	4[a]	0.04 (− 0.09, 0.18)	Fixed	0	0.40	0.94

GSH, glutathione; MDA, malondialdehyde; TAC, total antioxidant capacity; TBARS, thiobarbituric acid-reactive substances; GPx, glutathione peroxidase; Se, selenium

* Statistically significant

[a] In one study, three different doses of adiponectin were used, and we considered it as three studies. In total, 38 antioxidants have been assessed in 13 studies (each study assessed more than one antioxidant)

Publication bias

Publication bias was estimated by Egger's test. The results of Egger's test did not support the existence of publication bias by Se supplementation on antioxidant profile (coefficient = 2.2, $P = 0.5$) (Fig. 3).

Sensitivity analysis

To test the robustness of the results, we conducted sensitivity analysis according to the study quality. After the exclusion of three low-quality studies, a total of 10 trials were analyzed. There was no significant difference

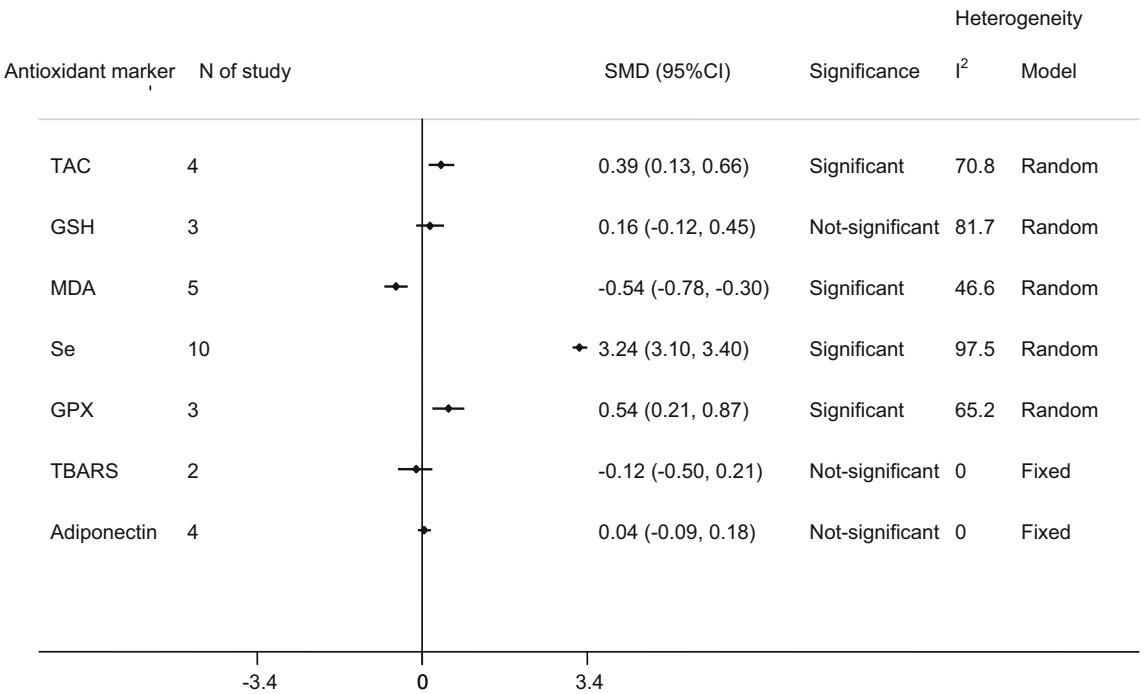

Fig. 2. Forest plot of the effect of Se supplementation on antioxidant markers

Table 3. Quality assessment of included studies according to the CONSORT checklist

	Zatollah Asemi (2015)	Mao (2004)	Alizadeh (2012)	Rayman (2012)	Gitte Ravn-Haren (2007) crossover	Murer (2014)	Razavi (2016)	Faghihi (2014)	Farrokhian (2016)	Bahmani (2015)	Faure (2004)	Guertin (2016)	Frederik Cold (2015)
1a	Yes	No	Yes	Yes	Not applicable	Yes	No	Yes	Yes	No	No	No	Yes
1b	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
2a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3b	No	No	No	No	No	No	No	No	No	No	No	No	No
4a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6b	No	No	No	No	No	No	No	No	No	No	No	No	No
7a	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Yes
7b	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8a	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	No	No	Yes
8b	No	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	No	No	Yes
9	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	No	Yes	Yes	No	No	Yes
10	Yes	No	No	Yes	Not applicable	No	Yes	No	Yes	Yes	No	No	No
11a	No	No	No	Yes	Not applicable	No	Yes	No	Yes	Yes	No	No	No
11b	No	No	No	No	No	No	No	No	No	No	No	No	No
12a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13b	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14b	No	Yes	No	No	No	No	No	No	No	No	No	No	No
15	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
16	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
17b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
20	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
21	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
22	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23	Yes	Yes	Yes	Yes	Not applicable	Yes	No	No	Yes	Yes	No	Yes	Yes
24	No	No	No	Yes	No	No	No	No	No	No	No	No	No
25	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total	30	29	30	33	20	29	28	26	32	31	23	24	30

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

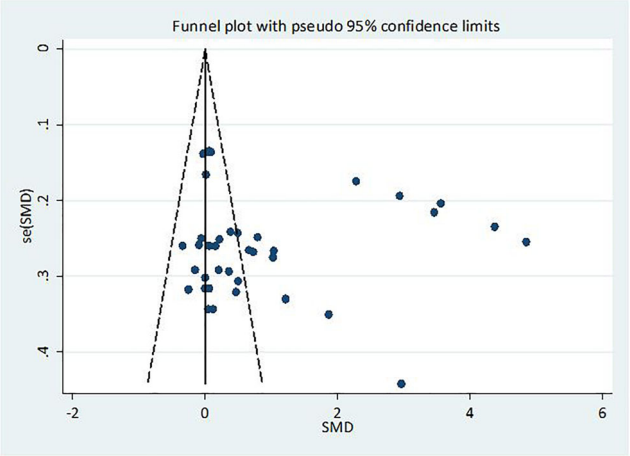

Fig. 3. Funnel plot detailing publication bias in the studies reporting the impact of Se supplementation on Overall antioxidant profile.

in the results of the effect of Se supplementation on the level of plasma Se [(SMD) = 3.36, 95% CI = (3.2, 3.5)] and overall effect [(SMD) = 1.09, 95% CI = (0.5, 1.6)] by sensitivity analysis.

Discussion

The meta-analysis of this study was carried out on the basis of pooled data from 13 RCTs to assess the effect of Se supplementation on antioxidant factors. The results of analysis showed that Se supplementation increased GPX and Se levels and the total antioxidant capacity decreased MDA levels, whereas it had no significant effect on GSH, TBARS, and adiponectin levels.

According to the study analysis, Se intake increased Se and GPX levels increased considerably. Epidemiological studies have shown that Se intervention increases GSH-PX activity in plasma and erythrocytes [40, 41].

Various published reports support the fact that Se supplementation increases TAC and reduces MDA levels. A randomized, double-blind, placebo-controlled trial in 2016 reported that high Se-yeast supplement is effective in increasing TAC and decreasing MDA levels [42]. Several trials have shown that Se supplementation can reduce MDA levels [43, 44] and improve TAC and GSH levels [44]. Mahmoodpoor et al. [45] conducted a randomized, placebo-controlled trial in 2018 to investigate the effect of high-dose Se on antioxidant reserve of the lungs and ventilator-associated pneumonia (VAP) in critically ill patients. They demonstrated that serum Se and GPX-3 activity levels increased steadily in the treatment group within 10 days (P b 0.025), while they remained unchanged in the placebo group. They also stated that despite increasing antioxidant activity, Se supplementation did not affect the incidence of VAP in critically ill patients.

The results of one meta-analysis in 2017 on the effect of Se supplementation on coronary heart disease demonstrated that Se supplementation decreased serum CRP and increased GSH-PX levels, suggesting a positive effect on reducing oxidative stress and inflammation in CHD [46].

In an animal study carried out in 2017 by Mansour on the effect of Se yeast supplementation on growth, antioxidant status in meagre, it was shown that catalase and superoxide dismutase activity, as well as total antioxidant status, significantly increased, while thiobarbituric-reactive substances in liver homogenate significantly decreased with Se supplementation [47].

In another study, Se supplementation in 1-day-old male broilers resulted in amelioration of GPX activity, total antioxidant capacity, and malondialdehyde formation ($P < 0.05$) [48].

Significant heterogeneity was observed regarding the impact of Se supplementation on TAC, Se, and GPX levels. A random-effect model was subsequently applied. Meta-regression was performed to identify the source of heterogeneity. According to the meta-regression analysis, influencing factors, such as duration, mean age, dose, and female ratio had no effect on heterogeneity. However, there was a significant association between the type of antioxidant factors and heterogeneity ($P = 0.008$). We therefore conducted subgroup analyses based on antioxidant factors to determine the effect of Se supplementation on each factor.

The meta-analysis of the study has some limitations. In many investigations, Se has been used in combination with other vitamins or minerals, which makes it impossible to isolate the specific effects of Se or of different Se forms in these trials. In addition, the included studies were heterogeneous in type of patients, species of Se, and duration of treatment, as well as Se content of the soil in the various environments. These factors could well have affected the results of the studies. As other challenges assessed the complementary required data through the time-consuming process, we contacted the corresponding authors.

In the future, carefully designed double-blind clinical trials with large sample sizes with stratified participants based on the initial Se levels are recommended.

Conclusion

The study findings indicated that Se supplementation might be effective in reducing oxidative stress and inflammation through increasing TAC and GPX levels and decreasing serum MDA, both of which are crucial influencing factors for reduction of oxidative stress. However, the results also showed that Se supplementation is not sufficient to reduce TBARS or affect adiponectin and GSH levels. There was no evidence of adverse events. To the best of our knowledge, this

study is the first published meta-analysis assessing the effect of Se supplementation on oxidative stress markers.

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Authors' contributions MQ and RH participated in the study design and drafted the manuscript. SD and MQ participated in the study design and statistical analysis and drafted the manuscript. MH and HA contributed to the protocol development and drafted the manuscript. MK, AM, and MZ contributed to the data acquisition. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

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