Meta-Analysis

Effects of Selenium Administration on Blood Lipids: A Systematic Review and Dose–Response Meta-Analysis of Experimental Human Studies

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Context: *Overexposure to the essential trace element selenium has been associated with adverse metabolic and cardiovascular outcomes, hypertension, and diabetes. However, dose–response meta-analyses analyzing the effects of selenium administration on the lipid profile in experimental human studies are lacking.*

Objective: *Through a restricted cubic spline regression meta-analysis, the dose–response relation between the dose of selenium administered or blood selenium concentrations at the end of the trials and changes over time in blood lipids, ie, total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides was assessed.*

Data Sources: *Searches were performed on PubMed, Web of Science, Embase, and the Cochrane Library from inception up to January 11, 2025 to identify randomized controlled trials (RCTs) investigating the impact of selenium supplementation on blood lipid profiles among adults.*

Data Extraction: *A total of 27 eligible RCTs that enrolled healthy individuals, pregnant individuals, and participants with specific health conditions were identified and the relevant data was extracted.*

Data Analysis: *Dose–response analysis indicated that selenium administration at and above 200 μg/day decreased HDL and LDL cholesterol and increased triglyceride levels. Blood selenium concentrations at the end of the trial above approximately 150 μg/L were positively associated with triglyceride and LDL cholesterol concentrations, and inversely associated with HDL cholesterol. Inorganic selenium supplementation showed stronger associations than organic selenium. At the lowest levels of baseline intake, selenium supplementation appeared instead to have beneficial effects on the lipid profile, with an overall indication of U-shaped curves, apart from HDL-cholesterol. The adverse effects of selenium were stronger in studies involving healthy participants as compared with unhealthy participants and pregnant females, in those having a longer duration of the intervention, particularly more than 3 months, and in European populations at selenium intake levels of above 300 μg/day.*

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Conclusions: *In this dose–response meta-analysis of experimental human studies, an adverse effect of selenium administration on blood lipids at levels around or above the current upper level of intake was observed.*
Systematic Review Registration: *PROSPERO registration No. CRD42022380432.*
Key words: blood lipids, cholesterol, meta-analysis, selenium, systematic review, triglycerides.

INTRODUCTION

Selenium is a trace element with nutritional and toxicological properties, depending on its dose and chemical species.[1–3] The main source of selenium in humans is diet, largely determined by the amount of this element in the soil.[4] Seafood and fish, meats, cereals, mushrooms, and Brazilian nuts are foods rich in selenium.[5,6] The recommended dietary intake of selenium ranges from 34 to 70 µg/day, depending on the criteria used for such an assessment.[7,8] The physiological functions of selenium are mediated by selenoproteins such as selenoprotein P (SEPP1) and glutathione peroxidase (GPx), with transport and antioxidant properties.[9] Conversely, toxic properties are ascribed to selenoproteins themselves, to various inorganic and organic selenium species, and to selenocompounds, at high levels of exposure.[8,10]

Some investigators suggested during the 1970s that selenium may contribute to the prevention of cancer, cardiovascular diseases, and other chronic diseases, at both nutritional and supranutritional exposure levels, on the basis of some observational evidence, biological plausibility, and the first randomized controlled trial (RCT) carried out with selenium.[7,11–18] However, large and methodologically stronger RCTs have recently failed to confirm any beneficial effect of selenium for cancer and cardiovascular diseases.[19,20] These experimental human studies also raised concerns about selenium toxicity, including an increased risk of metabolic and high-grade prostate cancer.[20] Such effects add to the symptoms and signs of acute and chronic selenium intoxication, such as vomiting, diarrhea, pain, nausea, a garlic-like odor on the breath, nail abnormalities, alopecia, and dermatitis.[4,21] Adverse metabolic effects of chronic low-dose selenium overexposure may contribute to obesity, hypertension, dyslipidemia, non-alcoholic fatty liver disease, and type 2 diabetes in particular, as supported by some experimental and nonexperimental studies among humans.[21–29] However, the extent to which these adverse effects are mediated or accompanied by an adverse effect on lipids is not well defined. Selenium, in fact, is known to regulate progenitor cell proliferation, adipocyte differentiation and maturation, as well as lipolysis.[22] Previous animal experiments have reported increased activity of LDL-receptor, the expression of mRNA, and lipid accumulation after selenium supplementation.[30] A recent meta-analysis showed that selenium increases levels of low-density lipoprotein (LDL) cholesterol and systolic blood pressure.[31] However, to our knowledge, no dose–response meta-analysis has been carried out to assess the pattern of association between the entire range of selenium exposure and lipid profile, with particular reference to the possibility of nonlinear relations.

Within the context of active investigation into the effects of selenium on the lipid profile in the human, a meta-analysis aiming to assess the dose–response effect of selenium administration on lipid profiles in RCTs was conducted. To do that, a newly developed statistical methodology was used, ie, the one-stage approach[32] based on restricted cubic spline models, which enables the use of results from all studies when at least 2 levels of exposure are available.[33]

METHODS

This systematic review was conducted following the PRISMA recommendations.[34] The protocol for this study has been registered on PROSPERO (No. CRD42022380432). The GRADE approach with 5 domains (imprecision, inconsistency, indirectness, risk of bias, and publication bias) was used to rate the certainty of the evidence.[35]

Literature Search

Searches for the relevant literature in PubMed, Web of Science, Embase, and the Cochrane Library, with no language restrictions, from inception up to January 11, 2025 were performed. The search terms "selenium", "lipid profile", "LDL", "very-low-density lipoprotein cholesterol (VLDL)", "high-density lipoprotein (HDL) cholesterol", "cholesterol", "triglycerides", and "randomized clinical trials" were used, by setting the research question according to the PICOS statement (Population, Intervention, Comparator(s), Outcomes, and Study design) (Table 1). Detailed search strategies are provided in Figure 1. The gray literature was also retrieved, according to the EUnetHTA guidelines.[36] In this review, only experimental studies with randomized and controlled designs in adults were considered, encompassing oral or parenteral administration of

Table 1. PICOS Criteria for Inclusion of Studies

Parameter	Criteria
Participant	Adults (≥18 years), any condition
Intervention	Selenium supplementation
Comparison	Control groups not supplemented with selenium
Outcome	Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides
Study design	Randomized controlled trials

selenium through dietary supplements, and whenever possible including the evaluation of internal exposure using blood biomarkers, ie, serum or plasma levels.[37] The end point of interest was the lipid profile: Cholesterol, HDL, LDL, and triglycerides.

Retrieved articles were imported into the Rayyan QCRI online application and duplicates were removed. Two authors (T.U. and G.F.) independently screened publication titles and abstracts and evaluated full-text publications for inclusion in the review. Full-text articles were included when both reviewers agreed that the inclusion criteria were met. Agreement between the authors who screened the articles was higher than 90% (Kohen's $\kappa > 0.90$). In cases of disagreement, both authors performed a second review of the full text to determine eligibility for inclusion through a consensus-based discussion. If the 2 authors still disagreed, a third author (T.F.) was sought to resolve the disagreement. Table S1 provides a fully detailed list of the full-text articles excluded, with related reasons for exclusion.

Data Extraction

Two authors (T.U. and G.F.), with the help of a third author (T.F.), extracted the following data from each eligible study: (1) first author name; (2) publication year; (3) country; (4) dose and duration of selenium supplements, selenium concentrations before and after the intervention (when these data were available), and the difference between the intervention and control groups at the end of the intervention; (5) type of population; (6) outcome of interest (levels of cholesterol, HDL, LDL, triglycerides) before and after the intervention; (7) number of participants; (8) duration of the study; (9) blood levels of selenium before and after intervention; and (10) sample type (serum or plasma). For 1 study,[38] the dose of selenium supplementation was converted to the effective dose of Na-selenite administered per day ($100\ \mu g\ selenium : 333\ \mu g\ Na - selenite = 500\ \mu g\ selenium : x$). For 5 studies,[38–42] cholesterol and triglyceride levels were converted from mmol/L to mg/dL, using as conversion factors 38.67 and 88.57, respectively.[43] Two studies[44,45] provided conversion factors. Mean or median values along with standard deviation (SD), standard error (SE), or interquartile range (IQR) were extracted. For data conversion from SD to IQR, the formula proposed by Cochrane was used, ie, IQR/1.35.[46] If not already reported, the mean difference of the change in selenium plasma levels was calculated as Mt—Mc, were Mt is the mean in the selenium treatment group and Mc is the mean in the control/placebo group. To impute the SD of the change from baseline for the experimental intervention, the following formula according to Cochrane methodology[47] was used:

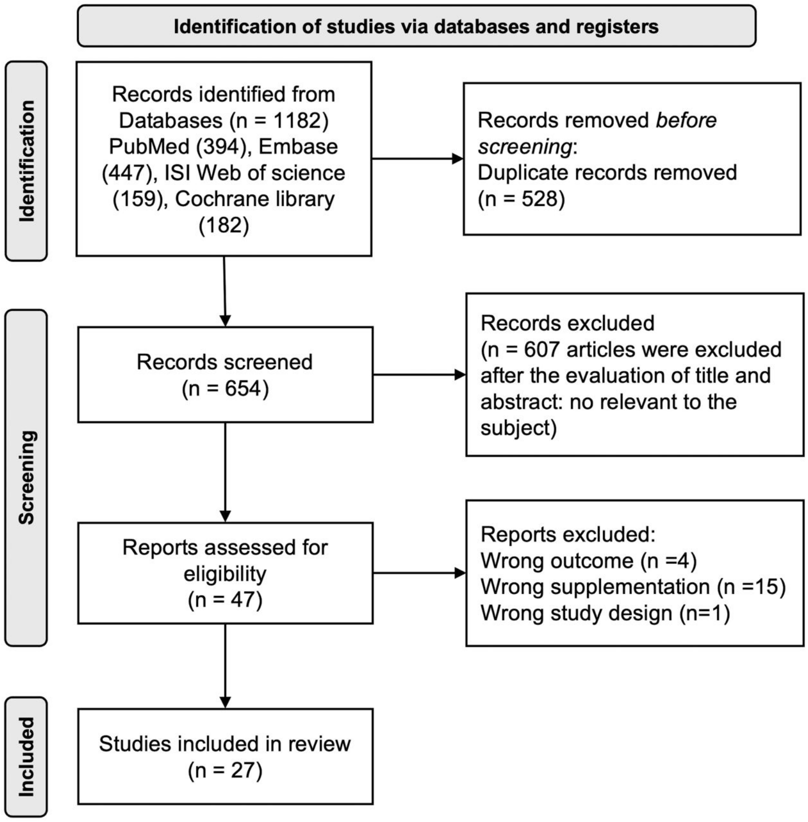
$$SD_{change} = \sqrt{SD^2_{baseline} + SD^2{}_{final} - (2 \times 0.5 \times SD_{baseline} \times SD_{final})}$$

Risk of Bias

Two authors (T.F. and T.U.) independently assessed the risk of bias of the included studies using the specific tool for randomized trials, RoB 2.0 (Table S2).[48] Disagreement was resolved with the help of a third author (M.V.). Five domains, with each of them rated as having a low, moderate, or high risk of bias, were analyzed, as follows: (1) "bias arising from the randomization process", assessing both allocation concealment and random allocation; (2) "bias due to deviations from intended interventions", assessing blinding of participants and personnel, and reporting of selenium levels before and after the intervention; (3) "bias due to missing outcome data", assessing whether authors did not report the results anticipated in the trial protocol or methods; (4) "bias in the measurement of outcome", assessing the modality of the lipid profile evaluation; and (5) "bias in selection of reported results", based on information on the trial registration to avoid selection of the results produced. If 2 domains were considered to have some concerns, the overall judgment resulted in "some concerns." Otherwise, the studies were considered to be at low risk of bias.

Data Analysis

In our meta-analysis, a first comparison of the blood lipids in the intervention groups, ie, the selenium-supplemented participants, with the blood lipids of participants receiving the placebo (or the lowest amount of selenium, if a placebo was not available). Forest plots were used via a random-effects model in order to consider possible heterogeneity of the results of the included studies.[47] A dose–response meta-analysis was then performed, by assessing changes in blood lipids during the follow-up, according to the dose of selenium administered or to the circulating selenium



Database	Search strategy
PubMed	(selenium OR selenite OR selenate) AND (dyslipidemia[Tiab] OR dyslipidemic[Tiab] OR hypercholesterolemia[Tiab] OR hypercholesterolemic[Tiab] OR hypocholesterolemic[Tiab] OR TG[Tiab] OR Triglyceride[Tiab] OR TC[Tiab] OR "Total cholesterol"[Tiab] OR cholesterol[Tiab] OR "low-density lipoprotein"[Tiab] OR "high-density lipoprotein"[Tiab] OR HDL[Tiab] OR LDL[Tiab] OR hypertriglyceridemia[Tiab] OR hypotriglyceridemic [Tiab]) AND ('clinical trial' OR 'randomized' OR 'randomized controlled trial' OR 'RCT' OR 'randomized-controlled trial' OR 'TRIALS' OR 'intervention' OR 'experimental study' OR 'interventional study') AND (humans[MH])
Embase	('selenium'/exp OR selenium OR 'selenite'/exp OR selenite OR 'selenate'/exp OR selenate) AND ('triacylglycerol'/exp OR triacylglycerol OR 'low density lipoprotein'/exp OR 'low density lipoprotein' OR 'high density lipoprotein'/exp OR 'high density lipoprotein' OR 'cholesterol'/exp OR cholesterol OR 'triglycerides'/exp OR triglycerides) AND ('clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'intervention study'/exp OR 'intervention study') AND ('human'/exp OR 'human')
Cochrane library	(selenium OR selenite OR selenate) AND ('lipid profile' OR LDL OR VLDL OR HDL OR TG OR Cholesterol OR triglycerides OR LDL-C OR HDL-C) AND ('clinical trial' OR 'randomized' OR 'randomized clinical trial' OR 'RCT' OR 'ranzomized-clinical trial' OR 'TRIALS' OR 'intervention' OR 'experimental study' OR 'interventional study') AND (HUMAN)
Web of Science	ALL=((selenium OR selenite OR selenate) AND ('lipid profile' OR LDL OR VLDL OR HDL OR TG OR Cholesterol OR LDL-C OR HDL-C OR Triglycerides) AND ('clinical trial' OR 'randomized' OR 'randomized controlled trial' OR 'RCT' OR 'ranzomized-controlled trial' OR 'TRIALS' OR 'intervention' OR 'experimental study' OR 'interventional study') AND (HUMAN))

Figure 1. Flow Chart for Study Identification in Online Databases of 27 Randomized Controlled Trials (RCTs) Included in the Dose–Response Meta-Analysis.

concentration achieved at the end of the intervention. The weighted mean difference (MD) and 95% confidence interval (CI) of 4 categories of blood lipids was estimated, due to homogeneity in the units of measurements of the outcomes. Meta-analysis was performed when at least 2 studies were available for each end point. For the dose–response meta-analysis, a restricted cubic spline model based on the 1-stage methodology (an approach for dose–response meta-analysis based on a weighted mixed-effects model that enables use of the results from all studies when at least 2 levels of exposure are available) was used.[49–52] The estimation method was based on the restricted maximum-likelihood random-effects model.[32,53] The restricted cubic spline model was generated using 3 knots at fixed percentiles (10th, 50th, and 90th) of blood selenium concentrations. For each analysis, different reference doses were used. For selenium supplementation, the reference value was set to 0 µg/day, since the control group did not receive any selenium supplementation. For modeling the relationship between circulating selenium concentrations at the end of the trial and lipid end points, a reference point of 105 µg/L of blood selenium was used, corresponding to an intake of approximately 70 µg/day.[54] Whenever possible, stratified analyses according to population characteristics (ie, sex and health status), country region (Europe vs Asia), type of selenium compounds ("organic" vs "inorganic"), and study duration (≤12 weeks vs >12 weeks) were performed. The dose–response meta-analysis was only computed when 3 or more studies were available. Meta regression analyses using the trial duration as an independent variable were also performed. For all data analyses, the results were reported and interpreted based on an evaluation of the magnitude, direction, and precision of the effect estimates, rather than binary significance testing.[55–57]

Egger's test to assess potential publication bias via contour-enhanced funnel plot asymmetry were used.[58] The presence of heterogeneity between the effect sizes was assessed using I^2 and τ^2 tests,[59] and sensitivity analyses were performed assessing study-specific curves.[35] Leave-one-out sensitivity analyses were then performed to quantify the impact of potential study outliers on the estimation of the overall effect size.

All analyses were carried out using the "*drmeta*," "*meta*," "*mkspline*" routines of Stata software (StataMP 18.0, StataCorp LLC, College Station, TX, 2023).

Certainty of the Evidence

The overall certainty of the evidence was assessed using the GRADE approach.[60] Taking into account the PICOS question, the certainty was assessed for changes in MDs in lipid profile levels due to selenium supplementation yielded by the dose–response analysis in all studies. The GRADEPro GDT (https://gradepro.org) was used to present the certainty assessment and to summarize the findings in tabular form.

RESULTS

In Figure 1, the flow chart presents the stages of study retrieval and the assessment of eligibility. After the removal of 528 duplicate publications, 654 potentially eligible publications were identified from the literature search, from which 607 publications were further excluded based on title/abstract screening. After full-text evaluation, 47 studies were evaluated for inclusion in the final analysis. Of these, 20 studies were excluded for the following reasons: Wrong supplementation if the study used other drugs/supplements in addition to selenium; wrong outcome, if not evaluating blood lipid profile or not evaluating their levels both before and after treatment; and if not a RCT. The numbers of publications excluded after the full-text evaluations, with reasons for the exclusions, are reported in Table S1.

The main characteristics of the 27 studies included in the meta-analysis are presented in Table 2. Most trials ($N = 21$) were carried out in Iran,[40,42,61–79] while the remaining 6 trials were carried out in Europe, namely 2 in Denmark,[39,41] and 1 each in Finland,[44] Germany,[80] the United Kingdom,[45] and the Czech Republic.[38] Overall, the trials included 2958 participants (1830 in the selenium treatment groups and 1128 in the control groups). Nine studies recruited only female participants,[40,61,62,68,71,72,74,78,79] and 1 included only male healthy subjects.[41] The other 16 studies enrolled male and female participants, but none performed sex-stratified analysis. The duration of the trials ranged from 2 to 24 weeks (median = 12 weeks). Selenium supplementation occurred in the inorganic form using sodium selenite in 4 trials, while organic selenium was administered in the form of selenium-enriched yeast in 20 studies. In 3 trials, selenium was administered in both inorganic and organic forms.[41,69]

For intervention with the inorganic selenium, the most common supplemented dose was 200 µg/day, ranging from 96 µg/day[44] to 480 µg/day.[41] For selenized-yeast, the administered dose ranged from 100 to 300 µg/day. One study did not specify the dose administered.[73] Blood selenium concentrations (reported as either plasma or serum concentrations) at the beginning and end of the trial were available in 10 studies, showing an increase in selenium concentrations after the intervention in every trial.[38,39,41,44,45,64,66,73,78,80]

Four studies were conducted on generally healthy populations,[39,41,44,45] and 3 trials among pregnant

Table 2. Main Characteristics of the Included Studies

Reference	Country	Population	Sample size	Trial duration (weeks), and blindness	Intervention	Plasma/serum Se levels (μg/L)	Outcomes	Results
Alizadeh et al (2012)[61]	Iran	Females with central obesity	C: 17 I: 17	6 (DB)	C: Placebo tablets with starch and lactose I: 200 μg selenium yeast	ND	Total cholesterol, HDL, LDL, TG	After 6 weeks, L-arginine had significantly reduced WC. Se had lowered fasting concentrations of serum insulin and the homeostasis model assessment of insulin resistance index. The interaction between L-arginine and Se reduced the fasting concentration of nitric oxides (NO_x), and HDEL lowered TG and WC and significantly increased the fasting concentration of NO_x
Asemi et al (2015)[62]	Iran	Gestational diabetes patients	C: 35 I: 35	6 (DB)	C: Placebo capsules (not specified) I: 200 μg selenium supplements as Se yeast	ND	Total cholesterol, HDL, LDL, TG	A significant effect of Se supplements was observed on HOMA B-cell function, lipid profiles, plasma nitric oxide, or total antioxidant capacity concentrations
Assarzadeh et al (2022)[63]	Iran	Hemodialysis patients	C: 30 I: 29	12 (DB)	C: Placebo capsules (not specified) I: 200 μg of selenium yeast	ND	Total cholesterol, HDL, LDL, TG	The changes in cholesterol, triglyceride, and LDL were not significant in either group; however, HDL substantially increased in the intervention group
Atapour et al (2022)[64]	Iran	End-stage renal disease in hemodialysis	C: 38 I: 40	12 (DB)	C: Placebo tablets containing glucose I: Selenium 400 μg tablets as Se yeast	C-Pre: 45.0 C-Post: 42.9 I-Pre: 40.1 I-Post: 66.6	Total cholesterol, TG	Weight, physical activity, total cholesterol, and TG did not change significantly after the interventions in either the intervention or control groups
Bahmani et al (2016)[65]	Iran	Diabetic nephropathy patients	C: 30 I: 30	12 (DB)	C: Placebo tablets (not specified) I: 200 μg selenium supplements as selenium yeast	ND	Total cholesterol, HDL, LDL, TG	Taking selenium supplements had no significant effects on FPG, the quantitative insulin sensitivity check index (QUICKI) or lipid profiles compared with the placebo

(continued)

Table 2. Continued

Reference	Country	Population	Sample size	Trial duration (weeks), and blindness	Intervention	Plasma/serum Se levels (μg/L)	Outcomes	Results
Cold et al (2015)[39]	Denmark	Healthy	C: 126 I1: 124 I2: 122 I3: 119	24 (DB)	C: 250 mg of yeast placebo, 80 mg of cellulose, 65 mg of dicalcium phosphate and ≤5 mg of other inactive ingredients I1: Se-enriched yeast 100 μg I2: Se-enriched yeast 200 μg I3: Se-enriched yeast 300 μg	C-Pre : 88.2 C-Post : 87.4 I1-Pre: 89.7 I1-Post: 156.2 I2-Pre: 90.5 I2-Post: 214.3 I3-Pre: 85.9 I3-Post: 260.0	HDL, total cholesterol, non-HDL cholesterol	Total cholesterol decreased significantly both in the intervention groups and in the placebo group after 6 months and 5 years, with small and nonsignificant differences in changes in plasma concentration of total cholesterol, HDL cholesterol, non-HDL cholesterol, and the total:HDL cholesterol ratio between the intervention and placebo groups
Faghihi et al (2014)[66]	Iran	Diabetes type 2 patients	C: 27 I: 33	12 (DB)	C: Placebo tablets (not specified) I: 200 μg sodium selenite	C-Pre: 47.1 C-Post: 45.4 I-Pre: 42.7 I-Post: 72.0	Total cholesterol, HDL, LDL, TG	Between-group comparison showed that fasting plasma glucose, glycosylated hemoglobin A1c, and HDL cholesterol were statistically significantly higher in the selenium recipient arm
Farrokhian et al (2016)[67]	Iran	Diabetes type 2 and coronary heart disease	C: 30 I: 30	8 (DB)	C: Placebo cellulose I: 200 μg/day selenium tablets as Se yeast	ND	Total cholesterol, HDL, LDL, TG	No significant changes occurred in FPG, lipid concentrations, plasma NO, GSH, or MDA
Gargari et al (2015)[68]	Iran	Females with central obesity	C: 17 I: 17	8 (DB)	C: Placebo tablets with starch and lactose I: Hypocaloric diet + Se-yeast 200 μg	ND	HDL, TG	Se supplementation significantly lowered fasting concentrations of serum insulin, HOMA-IR, and ALT in females with central obesity; L-arginine significantly reduced WC, whereas HCD significantly lowered SBP, TG, and WC

(continued)

Table 2. Continued

Reference	Country	Population	Sample size	Trial duration (weeks), and blindness	Intervention	Plasma/serum Se levels (μg/L)	Outcomes	Results
Ghazi et al (2021)[69]	Iran	Patients with atherosclerosis	C: 17 I1: 16 I2: 16	8 (DB)	C: Starch capsules that contain cellulose, silicon dioxide, and starch I1: 200 µg selenium-enriched yeast I2: 200 µg sodium selenite	ND	Total cholesterol, HDL, LDL, TG	There were no significant within- or among-group changes in the blood pressure, lipid, or glucose profiles throughout the study. Only the LDL levels significantly differed significantly between groups. The LDL level was lower in the yeast group in comparison with the placebo group. The after-intervention LDL levels were 61.87 ± 16.89 mg/dL, 77.37 ± 36.28 mg/dL, and 82.88 ± 21.79 mg/dL in selenium-enriched, sodium selenite and the placebo group, respectively
Jamilian et al (2015)[40]	Iran	Polycystic ovary syndrome	C: 35 I: 35	8 (DB)	C: Placebo cellulose I: 200 µg selenium supplements as Se yeast	ND	Total cholesterol, HDL, LDL, TG, VLDL	Se supplementation resulted in a significant reduction in serum TG and VLDL cholesterol concentrations compared with the placebo
Kamali et al (2019)[70]	Iran	Undergoing for coronary artery bypass grafting surgery	C: 16 I: 17	4 (DB)	C: Placebo capsules (not specified) I: 200 µg of Se yeast	ND	Total cholesterol, HDL, LDL, TG	After the 4-week intervention, Se supplementation significantly decreased FPG, insulin, the homeostasis model of assessment-estimated insulin resistance (HOMA-IR), and total:HDL cholesterol ratio, and significantly increased HDL cholesterol levels compared with the placebo
Karamali et al (2015)[71]	Iran	Cervical intraepithelial neoplasia	C: 28 I: 28	24 (DB)	C: Placebo tablets (starch) I: 200 selenium yeast	ND	Total cholesterol, HDL, LDL, TG	In addition, patients who received Se supplements had significantly decreased serum TG and increased HDL cholesterol levels

(continued)

Table 2. Continued

Reference	Country	Population	Sample size	Trial duration (weeks), and blindness	Intervention	Plasma/serum Se levels (μg/L)	Outcomes	Results
Luoma et al (1985)[44]	Finland	Healthy	C: 13 I: 10	2 (DB)	C: Placebo yeast tablets (not specified) I: 96 µg selenium yeast	C-Pre: 75.1 C-Post: 72.5 I-Pre: 72.6 I-Post: 88.2	Total cholesterol, HDL, LDL, TG	Se supplementation increased the serum selenium level, GSH-Px activity, and the HDL: TG ratio, but it did not affect HDL or TG concentrations
Mesdaghinia et al (2017)[72]	Iran	Pregnant females at risk for IUGR	C: 30 I: 30	10 (DB)	C: Placebo capsules with starch I: 100 µg selenium yeast	ND	Total cholesterol, HDL, LDL, TG	Se supplementation in pregnant women at risk for IUGR resulted in improved PI, TAC, GSH, hs-CRP, and markers of insulin metabolism and HDL levels, but it did not affect MDA, NO, FPG, or other lipid profiles
Omrani et al (2016)[73]	Iran	Hemodialysis patients	C: 38 I: 36	12 (DB)	C: Placebo capsules with starch I: Selenium tablets (not specified)	C-Pre: 44.1 C-Post: 53.6 I-Pre: 34.3 I-Post: 181.0	Total cholesterol, HDL, LDL, TG	The mean serum LDL level significantly increased in the experimental group from 85.66 to 109.12 mg/dL. In the control group, serum LDL significantly increased from 80.55 to 97.05 mg/dL. However, with control of the LDL effect before and after the study, it was revealed that the LDL change was not statistically significant. Neither total cholesterol nor triglyceride levels showed significant changes from before to after the study in any group
Rashidi et al (2020)[74]	Iran	Females diagnosed with PCOS	C: 32 I: 34	12 (DB)	C: Rice flour I: 200 µg of Se yeast	ND	Total cholesterol, HDL, LDL, TG	Serum levels of TG, total cholesterol, LDL cholesterol, HDL cholesterol, and Apo-B100 had not changed significantly within or between the study groups by the end of the study

(continued)

Table 2. Continued

Reference	Country	Population	Sample size	Trial duration (weeks), and blindness	Intervention	Plasma/serum Se levels (μg/L)	Outcomes	Results
Ravn-Haren et al (2008)[41]	Denmark	Healthy	C: 20 I1: 20 I2: 20 I3: 20	4 (DB)	C: Placebo tablets (not specified) I1: Se-enriched milk (480 μg) I2: Selenate (300 μg) I3: Se-enriched yeast (300 μg)	C-Pre: 113.2 C-Post: 110.2 I1-Pre 107.1 I1-Post: 127.6 I2-Pre: 107.8 I2-Post: 110.6 I3-Pre: 114.5 I3-Post: 125.0	Total cholesterol, HDL, LDL, TG	Short-term Se supplementation does not seem to affect blood lipid markers. After 1 week's supplementation, only total and LDL cholesterol were positively correlated with serum selenium levels
Raygan et al (2018)[42]	Iran	Congestive heart failure	C: 27 I: 26	12 (DB)	C: Placebo capsules (not specified) I: 200 µg of Se yeast	ND	Total cholesterol, HDL, LDL, TG	Se supplementation significantly decreased LDL cholesterol and the total:HDL cholesterol ratio, and significantly increased HDL cholesterol levels compared with the placebo
Rayman et al (2011)[45]	United Kingdom	Healthy	C: 107 I1: 123 I2: 124 I3: 120	24 (DB)	C: Placebo yeast (comprising 250 mg of yeast placebo, 80 mg of cellulose, 65 mg of dicalcium phosphate, and 5 mg of other inactive ingredients) I1: 100 µg selenium yeast I2: 200 µg selenium yeast I3: 300 µg selenium yeast	C-Pre: 91.0 C-Post: 93.4 I1: Pre: 90.5 Post: 147.5 I2: Pre: 90.3 Post: 192.8 I3: Pre: 92.4 Post: 231.0	HDL, total cholesterol, Non-HDL cholesterol	At baseline, increasing plasma Se was associated with increasing total and HDL cholesterol levels and with a decreasing total:HDL cholesterol ratio Increasing plasma Se concentrations from baseline to 6 months were associated with decreasing total cholesterol levels, non-HDL cholesterol levels, and the ratio of total:HDL cholesterol, and with increasing HDL cholesterol levels
Salehi et al (2013)[75]	Iran	Hemodialysis patients	C: 40 I: 40	12 (DB)	C: Placebo capsules (not specified) I: 200 selenium yeast	ND	Total cholesterol, HDL, LDL, TG	Selenium supplementation also hindered an increase in IL-6 levels compared with the placebo group. Changes in other parameters were not significantly different between the 2 groups

(continued)

Table 2. Continued

Reference	Country	Population	Sample size	Trial duration (weeks), and blindness	Intervention	Plasma/serum Se levels (μg/L)	Outcomes	Results
Salimian et al (2022)[76]	Iran	Diabetic hemodialysis patients	C: 27 I: 26	24 (DB)	C: Starch capsules I: Selenium 200 μg as Se yeast	C-Pre:/ C-Post: 56.0 I-Pre:/ I-Post: 60.7	Total cholesterol, HDL, LDL, TG	After Se supplements, a significant reduction in serum insulin levels, insulin resistance, total cholesterol, LDL cholesterol, and CRP, and a significant increase in insulin sensitivity, HDL cholesterol, and total glutathione was observed compared with the placebo
Schnabel et al (2008)[80]	Germany	Coronary heart disease	C: 144 I1: 148 I2: 141	12 (DB)	C: Placebo (not specified) I1: 200 μg sodium selenite I2: 500 μg sodium selenite	C-Pre: 93.4 C-Post: 95.9 I1-Pre: 97.4 I1-Post: 122.9 I2-Pre: 99 I2-Post: 141	Total cholesterol, HDL, LDL, TG	Sodium selenite supplementation induced an increase in the activity of GPx-1, an antioxidant selenoprotein involved in cardiovascular protection. However, no significant modification emerged on the lipid profile after 12 weeks of selenium supplementation
Tamtaji et al (2018)[77]	Iran	Alzheimer's disease	C: 26 I: 26	12 (DB)	C: Placebo capsules with starch I: Selenium 200 μg as Se yeast	ND	Total cholesterol, HDL, LDL, TG	Se supplementation, compared with the placebo, significantly reduced serum hs-CRP, insulin, homeostasis model of assessment insulin resistance (HOMA-IR), LDL cholesterol, and the total:HDL cholesterol ratio, and significantly increased total glutathione and the quantitative insulin sensitivity check index (QUICKI)
Tara et al (2010)[78]	Iran	Pre-eclampsia in pregnant females	C: 83 I: 83	24 (DB)	C: Placebo yeast tablets (not specified) I: 100 μg of selenium yeast	C-Pre: 122.9 C-Post: 119.4 I-Pre: 122.5 I-Post: 168.6	Total cholesterol, HDL, LDL, TG	At the end of the trial, there were significant increases in total cholesterol, TG, LDL, and HDL cholesterol in both the Se group and the control group

(continued)

Table 2. Continued

Reference	Country	Population	Sample size	Trial duration (weeks), and blindness	Intervention	Plasma/serum Se levels (μg/L)	Outcomes	Results
Valenta et al (2011)[38]	Czech Republic	Patients with Systemic Inflammatory Response Syndrome/sepsis	C: 75 I: 75	2 (O)	C: Na-selenite in parental nutrition with no extra selenium I: Na-selenite in parental nutrition + Se supplementation: 1000 µg on day 1, 500 µg/day on days 2-14	C-Pre: 30.0 C-Post: 33.9 I-Pre: 33.2 I-Post: 105.0	Total cholesterol	Plasma Se and GPx activity were increased in the Se group from day 1 onwards. Negative correlations were demonstrated between plasma Se, CRP, PCT, and SOFA at admission but not on days 7 or 14. Prealbumin and cholesterol increased in the Se group versus the respective baselines
Zadeh Modarres et al (2022)[79]	Iran	Females diagnosed with PCOS undergoing IVF	C: 20 I: 20	8 (DB)	C: Starch capsules I: 200 µg of Se yeast	ND	Total cholesterol, HDL, LDL, TG	Selenium supplementation resulted in a significant decrease in FPG, HOMA-IR, and insulin levels, and enhanced QUICKI. In addition, Se administration was significantly linked to a decrease in MDA levels. Se supplementation did not affect lipid profiles, TAC, or GSH levels.

Abbreviations: ALT, alanine aminotransferase; C, control group; CRP, C-reactive protein; DB, double-blind; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GPx-1, glutathione peroxidase 1; GSH, glutathione; HCD, hypocaloric control diet; HDEL, hypocaloric diet enriched in legumes; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; I, intervention group; IUGR, intrauterine growth restriction; IVF, in vitro fertilization; LDL, low-density lipoprotein; MDA, malondialdehyde; ND, selenium serum/plasma levels not available; NO x, Nitric oxides; O, open; PCOS, polycystic ovary syndrome; PI, pulsatility index; PCT, procalcitonin; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; Se, selenium; SOFA, sequential organ failure assessment; TAC, total antioxidant capacity; TG, triglycerides; VLDL, very-low-density lipoprotein; WC, waist circumference.

females,[62,72,78] whereas the majority of trials ($N = 19$) were carried out in patients with chronic diseases. Three trials recruited participants diagnosed with polycystic ovary syndrome,[40,74,79] 5 trials enrolled hemodialysis patients,[63,64,73,75,76] 5 articles engaged patients affected by cardiovascular disease,[42,67,69,70,80] 2 studies involved women with central obesity,[61,68] 1 study was conducted on patients affected by Systemic Inflammatory Response Syndrome (SIRS)/sepsis,[38] 2 studies involved diabetic patients,[65,66] 1 study focused on patients with cervical intraepithelial neoplasia,[71] and 1 trial was conducted in patients with Alzheimer's dementia.[77] Regarding the end points, the majority of studies reported blood concentrations of total cholesterol ($N = 25$), HDL cholesterol ($N = 24$), LDL cholesterol ($N = 21$), and triglycerides ($N = 23$). Two trials reported blood concentrations of non-HDL cholesterol.[39,45]

Almost all studies were deemed to be at low risk of bias; 5 were considered to have moderate risk of bias,[38,44,74,78,80] while none were considered at high risk of bias (Table S2). Bias in the domain "Effect of assignment to intervention" was the most common, generally due to a missing measurement/reporting of blood selenium concentrations before and after supplementation, in both the placebo and treatment groups.

In the forest plot, comprising the 27 studies and comparing the highest vs lowest exposure category in each study, selenium supplementation was associated with an overall reduction in total cholesterol (MD: −2.06; 95% CI −4.71, 0.58). A smaller but very imprecise decrease was observed for triglycerides (MD: −0.96; 95% CI −5.96, 4.04). No substantial effect was observed for LDL (MD: −0.52; 95% CI −3.23, 2.18) and HDL cholesterol (MD: 0.26; 95% CI −0.86, 1.37) (Figures S1-S4).

Figure 2 shows the dose–response meta-analysis evaluating the effects of selenium supplementation on lipid profiles. Selenium supplementation above 200 µg/day was associated with increased levels of total cholesterol ($N = 25$) and triglycerides ($N = 23$) and decreased levels of LDL ($N = 21$) and HDL ($N = 24$) cholesterol. Specifically, for total cholesterol, there was a U-shaped association, with lower total cholesterol levels observed for selenium concentrations between 100 and 200 µg/day, after which their levels slightly and linearly increased. Conversely, selenium supplementation showed an almost linear inverse association with LDL cholesterol above 100 µg/day of intervention. The association with HDL cholesterol was slightly inversely U-shaped, with higher HDL levels at selenium supplementation of approximately 100 µg/day (Figure 2).

When evaluating blood selenium concentrations achieved by the end of the study in the 10 trials reporting this measure, there was a positive association with total ($N = 10$) and LDL cholesterol ($N = 9$) and triglyceride ($N = 8$) levels, although with different patterns of association. For total and LDL cholesterol, the association was U-shaped, with an inflection point of the curve at approximately 125 µg/L. For triglycerides, the association was J-shaped, the inflection point being located at approximately 100 µg/L. HDL cholesterol was slightly linearly inversely associated with selenium levels ($N = 9$) (Figure 3).

In analyses stratified according to participant characteristics, negative effects and increased MDs of total cholesterol (MD: 3.14; 95% CI −8.56, 14.85), LDL (MD: 2.89; 95% CI −6.96, 12.73), and triglycerides (MD: 9.89; 95% CI −8.70, 28.49) were observed only among pregnant females compared with healthy/unhealthy subjects. Among unhealthy subjects and pregnant females, selenium supplementation was associated with increased HDL cholesterol levels, while detrimental effects were observed in the healthy subject category (MD: −2.13; 95% CI −3.72, −0.54) (Figures S5-S8). With regards to sex, evidence for a detrimental effect of selenium administration was observed on total cholesterol (MD: 0.45; 95% CI −5.97, 6.87) and LDL cholesterol (MD: 1.63; 95% CI −4.01, 7.27) among females, and on HDL cholesterol (MD: −3.11; 95% CI −8.18, 1.96) among males. No sex differences were noted on triglyceride concentrations (Figures S9-S12). When analyses were stratified by type of selenium supplementation (organic vs inorganic), inorganic selenium generally showed the most detrimental effects on total (MD: 21.39; 95% CI −22.00, 64.79) and LDL cholesterol levels (MD: −2.32; 95% CI −2.34, 6.98), though the number of studies based on inorganic forms ($N = 4$) was much lower than the number of trials administering organic selenium species ($N = 20$) (Figures S13-S16). When stratifying by geographic region, some differences emerged between studies conducted in Asia and Europe (Figures S17-S20). Opposite and slightly adverse effects were observed for HDL and LDL cholesterol levels in European (MD: −1.80; 95% CI −3.24, −0.36 and MD: 1.55; 95% CI −3.00, 6.11, respectively) compared with Asian populations (MD: 1.42; 95% CI 0.12, 2.72 and MD: −1.37; 95% CI −4.58, 1.85, respectively). Trial duration also seemed to affect the end point, since less favorable effects emerged in particular for LDL (MD: 3.01; 95% CI −10.20, 16.22) and HDL cholesterol (MD: −0.50; 95% CI −2.68, 1.67) and triglyceride concentrations (MD: 0.53; 95% CI −28.85, 29.90) with a longer period of intervention, ie, more than 3 months of selenium supplementation (Figures S21-S24). Further assessment of the role of trial duration using meta-regression analysis confirmed such an association (Figure S25).

When feasible, dose–response meta-analyses stratified by population characteristics (healthy/unhealthy/pregnancy status and sex), type of selenium

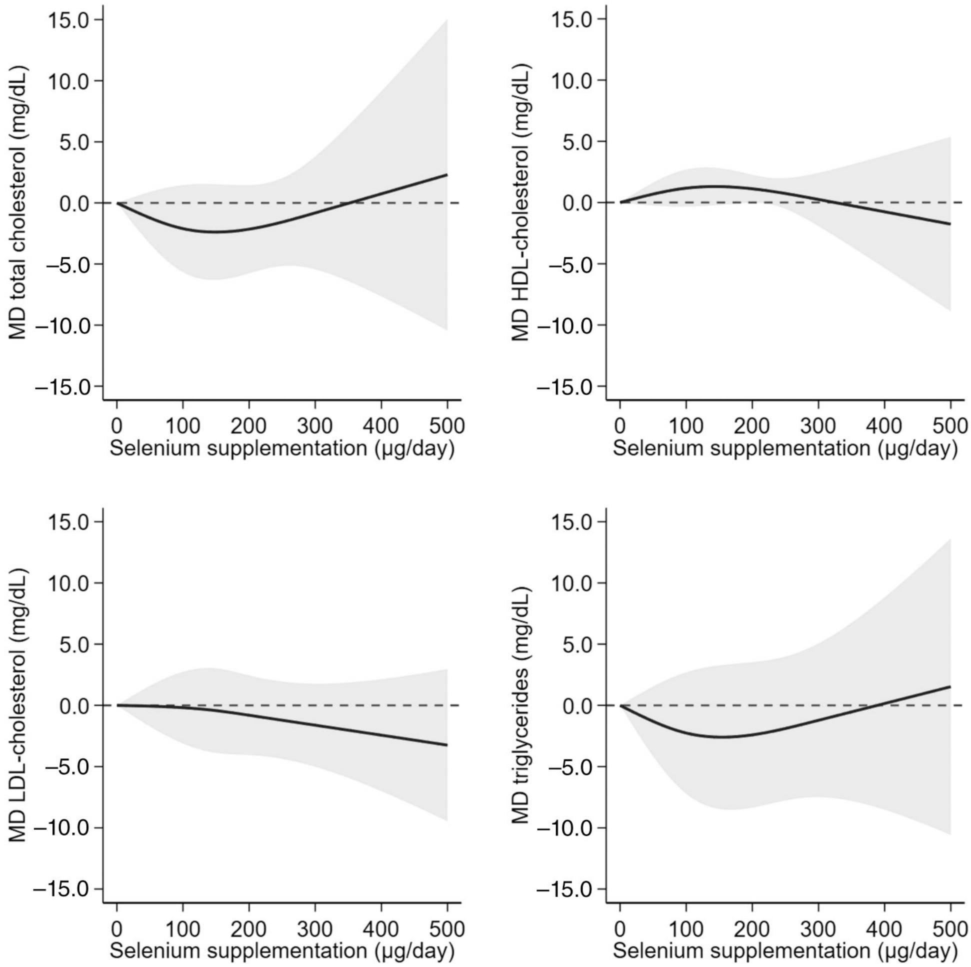


Figure 2. Dose–Response Meta-Analysis of Changes in Total ($N = 23$), High-Density Lipoprotein (HDL) ($N = 24$), Low-Density Lipoprotein (LDL) Cholesterol ($N = 20$), and Triglyceride ($N = 23$) Levels According to the Dose of Selenium Administered (μg/day), All Studies and Length of Follow-Up. The solid black line represents the effect with a variation of weighted mean difference (MD) (y-axis) according to the plasma selenium levels (x-axis). The gray area represents the 95% confidence interval (CI). The short-dashed line represents the null effect, $MD = 0$. Selenium supplementation above 200 µg/day was positively associated with total cholesterol and triglycerides. It was also associated with decreased levels of LDL and HDL cholesterol. Specifically, for total cholesterol, there was a U-shaped association. The association for HDL cholesterol was substantially null and, if anything, slightly inversely U-shaped.

administration (supplementation with organic or inorganic selenium), and country were also performed. Summary estimates were generally imprecise. Among healthy subjects, selenium supplementation showed a similar effect on total cholesterol compared with the overall population, while the impact on HDL cholesterol levels seemed to be detrimental and inverse. In unhealthy subjects, the association with total and HDL cholesterol were flat compared with the overall population, showing no substantial effects, while it had an inverted U-shape for LDL cholesterol with decreasing concentrations above 200 µg/day, and an inverse relation for triglycerides. The associations appeared almost null for pregnant females (Figure S26).

The highest dosages of selenium supplementation had slightly detrimental effects on total and HDL cholesterol and triglyceride in studies including both males and females, while demonstrating no adverse effects on LDL cholesterol levels. Studies including only females showed inverted U-shaped relations with all examined lipid measures (Figure S27).

Dose–response meta-analysis according to the specific selenium form administered was feasible only for studies using organic supplementation ($N = 22$). Exclusion of studies using only inorganic supplementation ($N = 4$) showed a pattern of U-shaped association for total cholesterol and an inverse U-shaped association for triglycerides and LDL cholesterol. Conversely, HDL cholesterol showed a slight increase due to supplementation with organic selenium (Figure S28).

Finally, stratified analysis by region showed a marginal effect of selenium supplementation in Asian populations ($N = 20$) and detrimental effects at >300 µg/day in European populations ($N = 5$), when considering

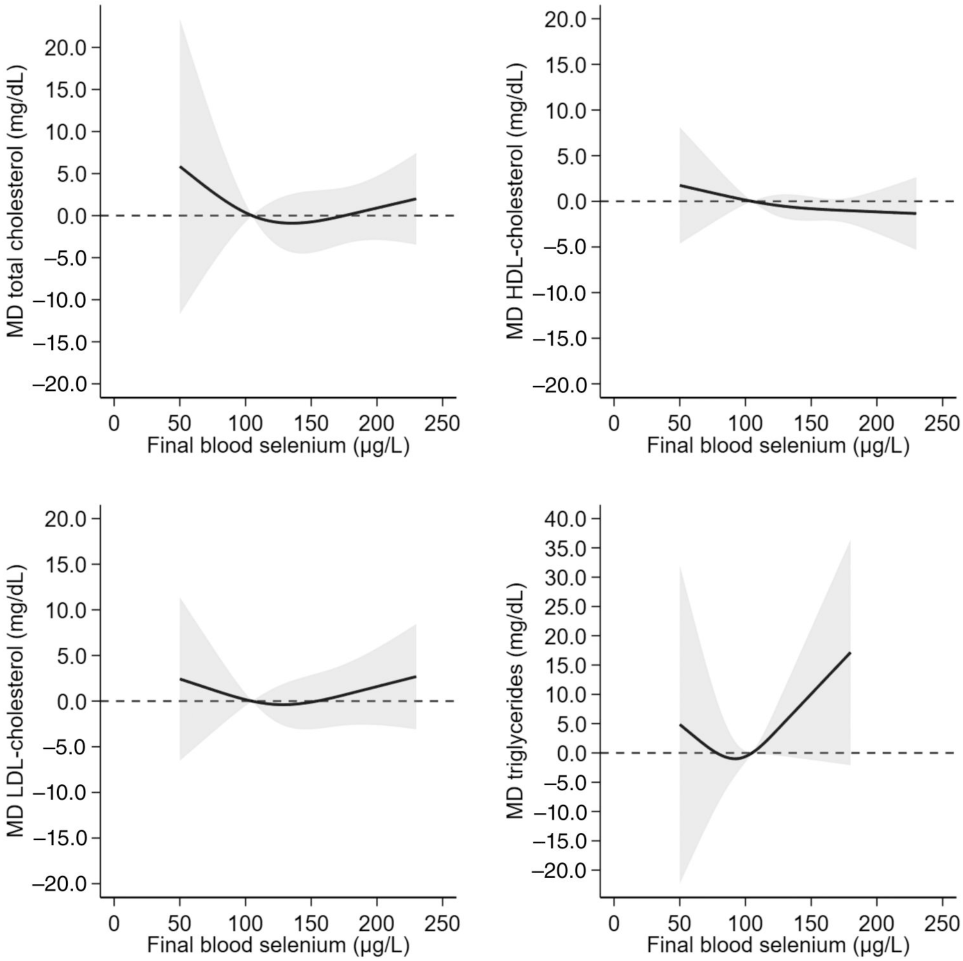


Figure 3. Changes in Total ($N = 10$), High-Density Lipoprotein (HDL) ($N = 9$), Low-Density Lipoprotein (LDL) Cholesterol ($N = 9$), and Triglyceride ($N = 8$) Levels during the Follow-Up According to Blood Selenium Concentrations (μg/L) at the End of the Trial, All Studies. The solid black line represents the effect with a variation of weighted mean difference (MD) (*y*-axis) according to the plasma selenium levels (*x*-axis). The gray area represents the 95% confidence interval (CI). The short-dashed line represents the null effect, MD = 0. Blood selenium concentrations achieved at the end of the study were positively and nonlinearly associated with total and LDL cholesterol and triglyceride levels. HDL cholesterol was slightly and almost linearly inversely associated with selenium levels.

total cholesterol and triglycerides as an outcome, although the maximum intake in Asia was lower than in Europe. A slight positive association was observed with HDL cholesterol, while an inverted U-shaped association was observed with LDL cholesterol (Figure S29).

Sensitivity analysis assessing study-specific curves for selenium supplementation showed very high variation for HDL cholesterol (Figures S30-S31). Leave-one-out analysis showed substantial homogeneity of the results, with some exceptions, including a lower MD for LDL cholesterol and triglycerides when excluding 1 group for Schnabel et al (2008)[80] and Tara et al (2010),[78] respectively (Figures S32-S35). Similarly, exclusion of the single study not administering selenium through the oral route[38] did not affect the overall estimate (Figure S32).

Counter-enhanced funnel plots for publication bias are shown in Figures S36-S39, indicating some evidence of asymmetric distribution for LDL cholesterol, suggesting possible occurrence of some publication bias for this end point.

Finally, GRADE assessment showed generally a low certainty of the evidence (since not all studies were carried out in the general population) and very serious imprecision, although the presence of dose–response increased the level of certainty (Table S3).

DISCUSSION

This dose–response meta-analysis, the first so far carried out to the best of our knowledge, gave an indication that selenium supplementation can adversely affect lipid profiles, particularly HDL cholesterol and triglycerides, and partially LDL cholesterol. These results agree with those of some observational studies, in which circulating selenium concentrations were positively associated with cholesterol (total and LDL) and triglycerides concentrations, and with the risk of dyslipidemia.[28,30,81] The results of this meta-analysis suggested a threshold for a detrimental effect of selenium on total and HDL cholesterol and triglycerides at approximately 200 µg/day, while opposite and inconsistent results emerged for LDL cholesterol. It is noteworthy that, for this end point, trials with the longest duration of intervention indicated an adverse effect of selenium supplementation. In addition, no such inconsistency was noted when blood selenium concentrations were used to assess actual exposure status in the trial participants, since all the investigated end points consistently indicated adverse effects of circulating selenium levels at approximately 100 µg/L and above, corresponding to approximately 70 µg of daily selenium intake.[54] For HDL cholesterol, adverse effects occurred starting at 50 µg/Se/L. This would imply that the upper level of selenium, lowered in 2023 to 255 µg/day by the European Food Safety Authority,[21] may still be inadequate to protect against the adverse effects of selenium administration. Conversely, these results are consistent with the WHO recommended dietary intake of 26 and 34 µg/selenium/day among females and males, respectively.[82]

In general, the results obtained based on achieved blood selenium concentrations at the end of the trial appear to be more reliable than those based on doses of selenium administered in these trials. In fact, the former results took into account compliance with the assigned treatment (selenium supplementation), and individual differences in absorption, excretion, and metabolism of the metalloid. However, when examining differences between achieved blood selenium concentrations and selenium supplementation, we found similar patterns of associations with blood lipid MDs. The only exception was the relationship with LDL cholesterol, for which an opposite effect was observed when considering supplementation doses. Some differences emerged across geographic region, though most of the studies were conducted in Iran, thus limiting the generalizability of our results.

Dose–response analysis based on blood selenium concentrations suggested for 3 lipid end points, though not for HDL cholesterol, a potential increase at very low exposure levels (approximately 50–80 µg/L, ie, 30–50 µg/selenium/day of intake), suggesting there could also be a deleterious effect of selenium deficiency on lipid profile. For HDL cholesterol, however, no such relationship emerged, since the inverse relationship between selenium status and this end point emerged at blood concentrations as low as 50 µg/L.

Observational studies, particularly cross-sectional studies, appear to support the results of our meta-analysis of the experimental data. In fact, positive associations between selenium and metabolic syndrome, higher triglycerides, and LDL cholesterol, as well as with lower HDL cholesterol have previously been reported in the National Health and Nutrition Examination Surveys (NHANES) and other studies.[28,83–90] However, increased serum selenium levels were inversely associated with the average changes in total and LDL cholesterol in a few studies.[91] Similarly, selenium levels demonstrated modestly beneficial effects on blood lipid levels in populations with relatively low selenium status, where low selenium concentrations showed adverse effects, especially on the HDL profile.[92,93]

These results are also consistent with the findings from several experimental and nonexperimental human studies indicating adverse metabolic effects of selenium exposure. RCTs have consistently shown that selenium administration is associated with an increased risk of type 2 diabetes mellitus.[21,24,26,94] There is also evidence from observational studies of a detrimental effect of selenium on non-alcoholic fatty acid liver disease,[27] on the risk of obesity,[22] and on both diastolic and systolic blood pressure levels.[25,31]

There is some biological plausibility for an adverse effect of selenium on the lipid profile. High doses of selenium may alter lipid metabolism in laboratory animals by modifying hepatic fatty acid metabolism, protein synthesis, and energy metabolism, and causing increases in body mass.[95–97] In such studies, nutritional levels of selenium also increased triglyceride and total cholesterol levels, with transcriptomic analyses revealing that lipid metabolism was the main pathway altered by dietary selenium treatment. These observations suggest that nutritionally adequate levels of selenium may increase liver lipid contents by activating fatty acid biosynthesis and elongation and unsaturated fatty acid biosynthesis pathways.[95,98] Alteration of redox homeostasis and pro-oxidant features of selenium and selected selenium compounds might represent other pathways involved in such processes.[12,95,99–101] Finally, too high levels of selenoprotein P, whose excess and adverse effects on glucose metabolism have been involved in the etiology of type 2 diabetes, could also be detrimental to the lipid profile.[29,102]

Recent studies indicate that selenium supplementation among individuals with adequate selenium intake could lead to altered energy regulation and cause liver and cardiovascular dysfunction.[95,103] It is feasible that U-shaped associations characterize the relationship between a nutrient such as selenium and the lipid profile, similarly to what has been observed for other outcomes[25,27,104–108] and in the current meta-analysis. Therefore, selenium deficiency might be linked to inadequate selenoprotein synthesis, potentially leading to disturbances in the redox balance, changes in protein function, and abnormalities in crucial cardiovascular lipid signaling pathways. However, elevated blood selenium concentrations could also be associated with selenoprotein upregulation as a compensatory reaction against the pro-oxidant effects of selenium, thereby having unfavorable effects on certain lipid signaling pathways.[3,8,12,102]

RCTs are experimental studies representing the gold standard and can provide the highest quality evidence in scientific research, mainly due to avoidance of confounding via randomization, better exposure assessment, and clarification of temporality. However, most trials conducted so far recruited participants with heterogeneous health status and background selenium concentrations, and administered different amounts of daily selenium supplements. This indicates potential for bias of meta-analyses based on forest plots comparing the highest vs lowest amounts of exposure, given the possibility of U-shaped and J-shaped relationships and the different population characteristics, thus undermining the reliability of both the individual and summary estimates, as shown for other outcomes.[109,110] Therefore, only a dose–response meta-analysis of results, like the one presented in this study, across the entire range of exposure from all trials allows for a comprehensive analysis of the effects of selenium administration on lipid profiles. These aspects should also be taken into account when comparing the results obtained in European populations with those in Asian populations, which could be attributed to underlying differences in selenium status or a specific selenium species. On the other hand, RCTs carried out in Asian populations used a narrower range of selenium supplementation compared with those carried out in European populations, thus limiting their comparability. It is also possible that different confounders, effect mediators, may explain the differences we observed between studies carried out in Asian populations compared with Western populations.

Some limitations of our study must be acknowledged. First, some stratified analyses (eg, by age group) could not be performed, since the trials included did not report MDs according to subgroups, and those that we could carry out yielded imprecise estimates, due to small numbers of studies or study heterogeneity. In addition, none of the studies performed speciation analyses to address the effects on different blood selenium compound concentrations, and few documented the exact chemical forms used for the intervention. Therefore, the extent to which effects differed according to specific selenium species, with reference both to added selenium and to the background status could not be assessed. Sample overlapping (double-counting) for studies combining more than 2 groups is another potential source of bias, but only in forest plots. Finally, many of the included studies were performed among participants with chronic disease and Asian populations, as well as among pregnant females, thus also limiting the generalizability of our results to other populations, though giving on the other hand more reliable evidence for the populations investigated.

CONCLUSIONS

The results of this first dose–response meta-analysis on the association between selenium and lipid profile suggest that selenium levels are associated with adverse effects on lipid profiles, with a nonlinear, generally U-shaped, association, as expected for a substance with both nutritional and toxicological properties. Specifically, selenium doses exceeding 200 µg/day or blood selenium concentrations exceeding 150 µg/L seem to induce adverse effects on the different lipid end points, suggesting that current upper levels of the element may still not be cautious enough, despite their recent updates.[3,21,111] A too-low selenium intake could also be detrimental to lipid metabolism and should be avoided. Overall, these results should be taken into account when considering selenium supplementation for individuals already meeting the nutritional requirements for this element.

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Author Contributions. T.U.: Data curation, Formal analysis, Investigation, Writing—original draft, and Writing—reviewing and editing. G.F.: Data curation, Formal analysis, Writing—original draft, and Writing—reviewing and editing. L.A.W.: Supervision, Writing—original draft, and Writing—reviewing and editing. M. V.: Conceptualization, Supervision, Writing—original draft, and Writing—reviewing and editing. T.F.: Conceptualization, Methodology, Software, Supervision, Validation, Writing—original draft, and Writing—reviewing and editing. All authors have read and approved the final manuscript.

Supplementary Material

Supplementary Material is available at *Nutrition Reviews* online.

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Conflicts of Interest

L.A.W. receives in-kind donations from Kindara.com (fertility apps) and Swiss Precision Diagnostics (home pregnancy tests). She also serves as a consultant for the Gates Foundation and AbbVie, Inc. All of these relationships are for work unrelated to this manuscript. The remaining authors have no relevant interests to declare.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon reasonable request, pending application to and approval by the corresponding author.

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