



March 27, 2023

Re: Vitalité: Curated Blend and Cellular Absorption Technology Clinical Dossier

Here at THREE, we provide curated proactive wellness solutions using our proprietary Cellular Absorption Technology, proven to help you live a life of greater health and purpose.

This dossier contains peer-reviewed clinical studies both on the curated blend and the Cellular Absorption Technologies used in Vitalité that validates its ability to do the following:

- Provide a vast portfolio of vitamins, minerals, and nutrients vital for proper health.
- Promote heart, brain, and eye health.
- Support health of the gut microbiome.
- Promote cellular energy.

One thing that you can expect from us here at THREE is that we are always in the process of running clinical studies in elucidating new mechanisms of action by which our products work along with discovering additional areas in which our products can promote human health. We have several exciting clinical studies in the pipeline and will announce these when they are completed.

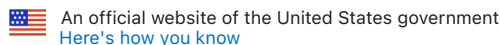
The clinical studies contained herein, and others that will follow, explain why our products provide the powerful health benefits our customers from all around the world experience every time they use a THREE product.

Thank you for joining us on this journey and for trusting us with your proactive wellness needs.

Be well,

A handwritten signature in black ink, appearing to read "Dr. Dan Gubler".

Dr. Dan Gubler  
Chief Scientific Officer  
Three International



FULL TEXT LINKS

Meta-Analysis [BMC Musculoskelet Disord.](#) 2020 Oct 31;21(1):711.

doi: 10.1186/s12891-020-03733-0.

# Effects of $\beta$ -carotene intake on the risk of fracture: a Bayesian meta-analysis

Tesfaye Getachew Charkos <sup>1</sup>, Yawen Liu <sup>1</sup>, Kemal Sherefa Oumer <sup>1</sup>, Ann M Vuong <sup>2</sup>, Shuman Yang <sup>3</sup>

Affiliations

PMID: 33129293 PMID: [PMC7603770](#) DOI: [10.1186/s12891-020-03733-0](#)[Free PMC article](#)

## Abstract

**Background:** Epidemiological studies examining the association between  $\beta$ -carotene intake and risk of fracture have reported inconsistent findings. We conducted a meta-analysis to investigate the association between  $\beta$ -carotene intake and risk of fracture.

**Methods:** We systematically searched PubMed, EMBASE and Cochrane library databases for relevant articles that were published until December 2019. We also identified studies from reference lists of articles identified from the clinical databases. The frequentist and Bayesian random-effects model was used to synthesize data.

**Results:** Nine studies with a total of 190,545 men and women, with an average age of 59.8 years, were included in this meta-analysis. For  $\beta$ -carotene intake (1.76-14.30 mg/day), the pooled risk ratio (RR) of any fracture was 0.67 (95% Credible Interval (CrI): 0.51-0.82; heterogeneity:  $P = 0.66$ ,  $I^2 = 0.00\%$ ) and 0.63 (95%CrI: 0.44-0.82) for hip fracture. By study design, the pooled RRs were 0.55 (95% CrI: 0.14-0.96) for case-control studies and 0.82 (95% CrI: 0.58-0.99) for cohort studies. By geographic region, the pooled RRs were 0.58 (95% CrI: 0.28-0.89), 0.86 (95% CrI: 0.35-0.1.37), and 0.91(95% CrI: 0.75-1.00) for studies conducted in China, the United States, and Europe, respectively. By sex, the pooled RRs were 0.88 (95% CrI: 0.73-0.99) for males and 0.76 (95% CrI, 0.44-1.07) for females. There was a 95% probability that  $\beta$ -carotene intake reduces risk of hip fracture and any type of fracture by more than 20%.

**Conclusions:** The present meta-analysis suggests that  $\beta$ -carotene intake was inversely associated with fracture risk, which was consistently observed for case-control and cohort studies. Randomized controlled trials are warranted to confirm this relationship.

**Keywords:** Bayesian; Fracture; Meta-analysis; Osteoporosis; Vitamin a;  $\beta$ -Carotene.

## Figures

## FULL TEXT LINKS



Meta-Analysis    [Nutrients](#). 2021 Jul 9;13(7):2355. doi: 10.3390/nu13072355.

# Folic Acid Supplementation Improves Glycemic Control for Diabetes Prevention and Management: A Systematic Review and Dose-Response Meta-Analysis of Randomized Controlled Trials

Omid Asbaghi <sup>1</sup>, Damoon Ashtary-Larky <sup>2</sup>, Reza Bagheri <sup>3</sup>, Seyedeh Parisa Moosavian <sup>4</sup>, Hadi Pourmirzaei Olyaei <sup>5</sup>, Behzad Nazarian <sup>6</sup>, Mahnaz Rezaei Kelishadi <sup>7</sup>, Alexei Wong <sup>8</sup>, Darren G Candow <sup>9</sup>, Frédéric Dutheil <sup>10</sup>, Katsuhiko Suzuki <sup>11</sup>, Amirmansour Alavi Naeini <sup>7</sup>

## Affiliations

PMID: 34371867    PMCID: [PMC8308657](#)    DOI: [10.3390/nu13072355](#)

[Free PMC article](#)

## Abstract

**Background:** There is a growing interest in the considerable benefits of dietary supplementations, such as folic acid, on the glycemic profile. We aimed to investigate the effects of folic acid supplementation on glycemic control markers in adults.

**Methods:** Randomized controlled trials examining the effects of folic acid supplementation on glycemic control markers published up to March 2021 were detected by searching online databases, including Scopus, PubMed, Embase, and ISI web of science, using a combination of related keywords. Mean change and standard deviation (SD) of the outcome measures were used to estimate the mean difference between the intervention and control groups at follow-up. Meta-regression and non-linear dose-response analysis were conducted to evaluate the association between pooled effect size and folic acid dosage (mg/day) and duration of the intervention (week). From 1814 detected studies, twenty-four studies reported fasting blood glucose (FBG), fasting insulin, hemoglobin A1C (HbA1C), and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) as an outcome measure.

**Results:** Results revealed significant reductions in FBG (weighted mean difference (WMD): -2.17 mg/dL, 95% CI: -3.69, -0.65,  $p = 0.005$ ), fasting insulin (WMD: -1.63 pmol/L, 95% CI: -2.53, -0.73,  $p < 0.001$ ), and HOMA-IR (WMD: -0.40, 95% CI: -0.70, -0.09,  $p = 0.011$ ) following folic acid supplementation. No significant effect was detected for HbA1C (WMD: -0.27%, 95% CI: -0.73, 0.18,  $p = 0.246$ ). The dose-response analysis showed that folic acid supplementation significantly changed HOMA-IR ( $r = -1.30$ ,  $p$ -nonlinearity = 0.045) in non-linear fashion. However, meta-regression analysis did not indicate a linear relationship between dose, duration, and absolute changes in FBG, HOMA-IR, and fasting insulin concentrations.

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Meta-Analysis [Crit Rev Food Sci Nutr. 2022;62\(30\):8435-8453.](#)

doi: 10.1080/10408398.2021.1928598. Epub 2021 May 18.

# Beneficial effects of folic acid supplementation on lipid markers in adults: A GRADE-assessed systematic review and dose-response meta-analysis of data from 21,787 participants in 34 randomized controlled trials

Omid Asbaghi <sup>1</sup>, Damoon Ashtary-Larky <sup>2</sup>, Reza Bagheri <sup>3</sup>, Behzad Nazarian <sup>1</sup>, Hadi Pourmirzaei Olyaei <sup>4</sup>, Mahnaz Rezaei Kelishadi <sup>5</sup>, Michael Nordvall <sup>6</sup>, Alexei Wong <sup>6</sup>, Frédéric Dutheil <sup>7</sup>, Amirmansour Alavi Naeini <sup>5</sup>

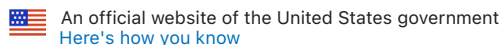
Affiliations

PMID: 34002661 DOI: [10.1080/10408398.2021.1928598](#)

## Abstract

Folic acid supplementation has received considerable attention in the literature, yet there is a large discrepancy in its effects on lipid markers in adults. Therefore, this systematic review and meta-analysis of 34 randomized controlled trials (RCTs) evaluated the effects of folic acid supplementation on triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol concentrations in a cohort of 21,787 participants. A systematic search current as of March 2021 was performed in PubMed/Medline, Scopus, Web of Science, and Embase using relevant keywords to identify eligible studies. A fixed or random-effects model was used to estimate the weighted mean difference (WMD) and 95% confidence intervals (CIs). Thirty-four RCTs were included in this meta-analysis. The pooled analysis revealed that serum TG (WMD: -9.78 mg/dL; 95% CI: -15.5 to -4.00;  $p = 0.001$ ,  $I^2=0.0%$ ,  $p = 0.965$ ) and TC (WMD: -3.96 mg/dL; 95% CI: -6.71 to -1.21;  $p = 0.005$ ,  $I^2=46.9%$ ,  $p = 0.001$ ) concentrations were significantly reduced following folic acid supplementation compared to placebo. However, folic acid supplementation did not affect serum concentrations of LDL (WMD: -0.97 mg/dL; 95% CI: -6.82 to 4.89;  $p = 0.746$ ,  $I^2=60.6%$ ,  $p < 0.001$ ) or HDL cholesterol (WMD: 0.44 mg/dL; 95% CI: -0.53 to 1.41;  $p = 0.378$ ,  $I^2= 0.0%$ ,  $p = 0.831$ ). A significant dose-response relationship was observed between the dose of folic acid supplementation and serum concentrations of HDL cholesterol ( $r = 2.22$ ,  $p = 0.047$ ). Folic acid supplementation reduced serum concentrations of TG and TC without affecting LDL or HDL cholesterol. Future large RCTs on various populations are needed to show further beneficial effects of folic acid supplementation on lipid profile.

**Keywords:** Dyslipidemia; folate; folic acid; lipid profile; meta-analysis.



FULL TEXT LINKS



Meta-Analysis Clin Nutr ESPEN. 2023 Feb;53:206-213. doi: 10.1016/j.clnesp.2022.11.020.

Epub 2022 Dec 6.

# The effect of folic acid supplementation on body weight and body mass index: A systematic review and meta-analysis of randomized controlled trials

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Habib Yarizadeh<sup>5</sup>, Behzad Zamani<sup>5</sup>, Zahra Sohrabi<sup>6</sup>

Affiliations

PMID: 36657915 DOI: [10.1016/j.clnesp.2022.11.020](https://doi.org/10.1016/j.clnesp.2022.11.020)

## Abstract

**Background and objective:** Several trials have evaluated the effects of folate supplementation on obesity indices. However, their results were inconsistent. Therefore, the current meta-analysis was conducted to summarize data from available randomized clinical trials (RCTs) about the impact of folate supplementation on weight and body mass index (BMI).

**Method:** Medline/PubMed, Scopus, Embase, and ISI web of science were searched to identify relevant articles up to December 2020. The effect sizes were expressed as weighted mean difference (WMD) and 95% confidence intervals (CI) using the random-effects model.

**Results:** Pooled data from nine studies showed that folic acid supplementation did not change body weight (WMD: -0.16 kg, 95%CI: -0.47 to 0.16, P = 0.32) and BMI (WMD: -0.23 kg/m<sup>2</sup>, 95%CI: -0.49 to 0.03, P = 0.31), but there was significant heterogeneity between the included studies for BMI (I<sup>2</sup> = 90.1%, P < 0.001). Moreover, subgroup analyses in level of homocysteine and health status indicated significant effect of folic acid supplementation on BMI in those with homocysteine level ≥15 μmol/L (WMD: -0.17 kg/cm<sup>2</sup>, -0.33 to -0.01, p = 0.03) and in women with polycystic ovary syndrome (PCOS) (WMD: -0.30kg/cm<sup>2</sup>, -0.54 to -0.06, p = 0.01).

**Conclusion:** Our outcomes demonstrated that folic acid improves BMI in those with homocysteine levels ≥15 μmol/L and women with PCOS.

**Keywords:** Anthropometric index; Body weight; Folate; Meta-analysis; Supplementation.

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## Related information

[PubChem Compound \(MeSH Keyword\)](#)

FULL TEXT LINKS

Meta-Analysis [Nutr Metab Cardiovasc Dis.](#) 2019 May;29(5):432-439.

doi: 10.1016/j.numecd.2018.11.006. Epub 2018 Dec 6.

# Effects of folic acid supplementation on C-reactive protein: A systematic review and meta-analysis of randomized controlled trials

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Affiliations

PMID: 30940490 DOI: [10.1016/j.numecd.2018.11.006](#)

## Abstract

**Background and aim:** Given the contradictory results of previous randomized controlled trials (RCTs), we performed a systematic review and meta-analysis to quantify and summarize the effects of folic acid supplementation on C-reactive protein (CRP).

**Methods and results:** We performed a systematic search of all available RCTs conducted up to October 2018 in the following databases: PubMed, Scopus, and Cochrane. RCTs that investigated the effect of folate on CRP were included in the present study. Data were combined with the use of generic inverse-variance random-effects models. Statistical heterogeneity between studies was evaluated using Cochran's Q-test. Ten RCTs (1179 subjects) were included in the present meta-analysis. Pooled analysis results showed that folate supplementation significantly lowered the serum CRP level (weighted mean difference (WMD): -0.685 mg/l, 95% CI: -1.053, -0.318,  $p < 0.001$ ). However, heterogeneity was significant ( $I^2 = 96.7\%$ ,  $p = 0.000$ ). Stratified analyses indicated that sex, intervention period, and type of study population were sources of heterogeneity. Following analysis, results revealed that the greatest impact was observed in women (WMD: -0.967 mg/l, 95% CI: -1.101, -0.833,  $p = 0.000$ ), patients with type 2 diabetes mellitus (WMD: -1.764 mg/l, 95% CI: -2.002, -1.526,  $p = 0.000$ ), and intervention period less than 12 weeks (WMD: -0.742 mg/l, 95% CI: -0.834, -0.650,  $p = 0.000$ ).

**Conclusion:** This meta-analysis suggested that folic acid supplementation could significantly lower the serum CRP level. Folic acid leads to greater CRP lowering effect in women, patients with T2DM, and those with less than 12-week intervention.

**Keywords:** C-reactive protein; Folate; Folic acid; Meta-analysis.

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Meta-Analysis Clin Ther. 2021 Dec;43(12):e346-e363. doi: 10.1016/j.clinthera.2021.10.002.

Epub 2021 Nov 29.

# The Effects of Folic Acid Supplementation on Pro-inflammatory Mediators: a Systematic Review and Dose-Response Meta-Analysis of Randomized Controlled Trials

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Affiliations

PMID: 34857394 DOI: [10.1016/j.clinthera.2021.10.002](https://doi.org/10.1016/j.clinthera.2021.10.002)

## Abstract

**Purpose:** Despite extensive research, findings regarding the effects of folic acid supplementation on inflammatory mediators have been controversial and inconclusive. This study therefore aimed to summarize the findings of all available clinical trials regarding the effects of folic acid supplementation on inflammatory biomarkers in adults.


**Methods:** A systematic search was conducted of PubMed/MEDLINE, Scopus, Web of Science, EMBASE, and Google Scholar until April 2020. All randomized controlled trials that examined the influence of folic acid supplementation on C-reactive protein, interleukin 6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were included. Pooled effect sizes were calculated based on the random effects model, and dose-response analysis was modeled by using a fractional polynomial model.

**Findings:** In total, 18 randomized controlled trials involving 2286 participants were analyzed. Folic acid supplementation significantly reduced serum levels of C-reactive protein (mean difference [MD], -0.21 mg/L; 95% CI, -0.41 to -0.01; n = 16), TNF- $\alpha$  (MD, -14.88 pg/mL; 95% CI, -23.68 to -6.09; n = 10), and IL-6 (MD, -0.93 pg/mL; 95% CI, -1.72 to -0.14; n = 11). Subgroup analyses suggested a significant reduction at doses  $\leq$  5 mg/d and studies longer than 12 weeks in duration. A significant nonlinear association was also found between folic acid dosage ( $P_{\text{nonlinearity}} < 0.001$ ) and duration of administration ( $P_{\text{nonlinearity}} < 0.001$ ) with serum TNF- $\alpha$  levels.

**Implications:** This meta-analysis indicates the beneficial effects of folic acid supplementation on pro-inflammatory cytokines. Further studies with a longer duration of administration, higher doses, and larger sample sizes should be performed exclusively on patients with chronic inflammatory disorders to elucidate the favorable role of folate intake on inflammatory biomarkers. International Prospective Register of Systematic Reviews identifier: CRD42021249947.

**Keywords:** cytokine; folate; folic acid; inflammation; meta-analysis.

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Meta-Analysis [Eur J Intern Med.](#) 2019 May;63:34-41. doi: 10.1016/j.ejim.2019.02.009.

Epub 2019 Feb 22.

# Iron supplementation for restless legs syndrome - A systematic review and meta-analysis

[Tomer Avni](#)<sup>1</sup>, [Shelley Reich](#)<sup>2</sup>, [Nirit Lev](#)<sup>3</sup>, [Anat Gafter-Gvili](#)<sup>2</sup>

Affiliations

PMID: 30798983 DOI: [10.1016/j.ejim.2019.02.009](#)

## Abstract

**Background:** Iron supplementation, is recommended for the treatment of restless legs syndrome (RLS). We gathered evidence for the efficacy and safety of iron supplementation for RLS.

**Methods:** A systematic review and meta-analysis of randomized controlled trials that compared iron supplementation versus no iron for patients with RLS was performed. Multiple databases were searched. The primary outcome was the effect of iron on the International Restless Legs Syndrome score (IRLSS) at 4 weeks after treatment. For dichotomous data, risk ratios (RR) with 95% confidence intervals (CIs) were estimated and pooled. For continuous data, weighted mean differences (WMD) were calculated.

**Results:** Ten trials fulfilled the inclusion criteria. Iron therapy was associated with a significant decrease of the IRLSS of -3.55 [95% CI (-5.41) - (-1.68)] points and an increase in the percentage of patients with improvement of the IRLSS score, RR of 2.16 [95% CI 1.56-2.98]. IV FCM was associated with improvement in both the IRLSS (WMD of -2.79 (95% CI (-4.62) - (-0.96)), 4 trials,  $I^2 = 0\%$ ) and on the RLS-QOL by WMD of 8.67 (95% CI 1.68-15). Iron was associated with an increased rate of adverse events RR 2.04 (95% CI 1.46-2.85), which were not severe and not associated with increased rate of treatment discontinuation.

**Conclusion:** Iron supplementation is associated with improvement of the IRLSS score. Our meta-analysis supports the use of iron, oral or IV, as effective therapy for patients with RLS. Further studies should assess subgroups of patients most likely to benefit from iron supplementation.

**Keywords:** Anemia; Ferric carboxymaltose; Iron; Meta-analysis; Restless legs.


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Review [Cochrane Database Syst Rev.](#) 2016 Apr 18;4:CD009747.

doi: 10.1002/14651858.CD009747.pub2.

# Daily iron supplementation for improving anaemia, iron status and health in menstruating women

[Michael Sze Yuan Low](#) <sup>1</sup>, [Joanna Speedy](#), [Claire E Styles](#), [Luz Maria De-Regil](#), [Sant-Rayn Pasricha](#)

Affiliations

PMID: 27087396 DOI: [10.1002/14651858.CD009747.pub2](#)

## Abstract

**Background:** Iron-deficiency anaemia is highly prevalent among non-pregnant women of reproductive age (menstruating women) worldwide, although the prevalence is highest in lower-income settings. Iron-deficiency anaemia has been associated with a range of adverse health outcomes, which restitution of iron stores using iron supplementation has been considered likely to resolve. Although there have been many trials reporting effects of iron in non-pregnant women, these trials have never been synthesised in a systematic review.

**Objectives:** To establish the evidence for effects of daily supplementation with iron on anaemia and iron status, as well as on physical, psychological and neurocognitive health, in menstruating women.

**Search methods:** In November 2015 we searched CENTRAL, Ovid MEDLINE, EMBASE, and nine other databases, as well as four digital thesis repositories. In addition, we searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and reference lists of relevant reviews.

**Selection criteria:** We included randomised controlled trials (RCTs) and quasi-RCTs comparing daily oral iron supplementation with or without a cointervention (folic acid or vitamin C), for at least five days per week at any dose, to control or placebo using either individual- or cluster-randomisation. Inclusion criteria were menstruating women (or women aged 12 to 50 years) reporting on predefined primary (anaemia, haemoglobin concentration, iron deficiency, iron-deficiency anaemia, all-cause mortality, adverse effects, and cognitive function) or secondary (iron status measured by iron indices, physical exercise performance, psychological health, adherence, anthropometric measures, serum/plasma zinc levels, vitamin A status, and red cell folate) outcomes.

**Data collection and analysis:** We used the standard methodological procedures of Cochrane.

**Main results:** The search strategy identified 31,767 records; after screening, 90 full-text reports were assessed for eligibility. We included 67 trials (from 76 reports), recruiting 8506 women; the number of women included in analyses varied greatly between outcomes, with endpoint haemoglobin concentration being the outcome with the largest number of participants analysed

## FULL TEXT LINKS



Meta-Analysis    [Nutrients](#). 2021 Nov 15;13(11):4074. doi: 10.3390/nu13114074.

# Oral Magnesium Supplementation for Treating Glucose Metabolism Parameters in People with or at Risk of Diabetes: A Systematic Review and Meta-Analysis of Double-Blind Randomized Controlled Trials

[Nicola Veronese](#)<sup>1</sup>, [Ligia J Dominguez](#)<sup>1 2</sup>, [Damiano Pizzol](#)<sup>3</sup>, [Jacopo Demurtas](#)<sup>4 5</sup>, [Lee Smith](#)<sup>6</sup>, [Mario Barbagallo](#)<sup>1</sup>

## Affiliations

PMID: 34836329    PMCID: [PMC8619199](#)    DOI: [10.3390/nu13114074](#)


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## Abstract

There is a large and growing body of literature focusing on the use of oral magnesium (Mg) supplementation for improving glucose metabolism in people with or at risk of diabetes. We therefore aimed to investigate the effect of oral Mg supplementation on glucose and insulin-sensitivity parameters in participants with diabetes or at high risk of diabetes, compared with a placebo. Several databases were searched investigating the effect of oral Mg supplementation vs placebo in patients with diabetes or conditions at high risk of diabetes. Data were reported as standardized mean differences (SMDs) with their 95% confidence intervals (CIs) using follow-up data of glucose and insulin-sensitivity parameters. Compared with placebo, Mg supplementation reduced fasting plasma glucose in people with diabetes. In people at high risk of diabetes, Mg supplementation significantly improved plasma glucose per se, and after a 2 h oral glucose tolerance test. Furthermore, Mg supplementation demonstrated an improvement in insulin sensitivity markers. In conclusion, Mg supplementation appears to have a beneficial role and improves glucose parameters in people with diabetes. Moreover, our work indicates that Mg supplementation may improve insulin-sensitivity parameters in those at high risk of diabetes.

**Keywords:** diabetes; glucose; magnesium; meta-analysis.

## Figures

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Meta-Analysis Br J Nutr. 2022 Dec 28;128(12):2363-2372.

doi: 10.1017/S0007114521005201. Epub 2022 Jan 20.

# The effects of oral magnesium supplementation on glycaemic control in patients with type 2 diabetes: a systematic review and dose-response meta-analysis of controlled clinical trials

Omid Asbaghi <sup>1</sup>, Sajjad Moradi <sup>2</sup>, Sara Kashkooli <sup>1</sup>, Mehdi Zobeiri <sup>3</sup>, Shokufeh Nezamoleslami <sup>4</sup>, Mohammad Ali Hojjati Kermani <sup>5</sup>, Anastasia-Viktoria Lazaridi <sup>6</sup>, Maryam Miraghajani <sup>1</sup>

Affiliations

PMID: 35045911 DOI: [10.1017/S0007114521005201](https://doi.org/10.1017/S0007114521005201)

## Abstract

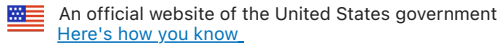
The current systematic review and meta-analysis were conducted to evaluate the effects of oral Mg supplementation on glycaemic control in type 2 diabetes mellitus (T2DM) patients. Related articles were found by searching the PubMed, SCOPUS, Embase and Web of Science databases (from inception to 30 February 2020). A one-stage robust error meta-regression model based on inverse variance weighted least squares regression and cluster robust error variances was used for the dose-response analysis between Mg supplementation and duration of intervention and glycaemic control factors. Eighteen eligible randomised clinical trials were included in our final analysis. The dose-response testing indicated that the estimated mean difference in HbA1c at 500 mg/d was  $-0.73\%$  (95 % CI:  $-1.25, -0.22$ ) suggesting modest improvement in HbA1c with strong evidence ( $P$  value:  $0.004$ ). And in fasting blood sugar (FBS) at 360 mg/d was  $-7.11$  mg/dl (95 % CI:  $-14.03, -0.19$ ) suggesting minimal amelioration in FBS with weak evidence ( $P$  value:  $0.092$ ) against the model hypothesis at this sample size. The estimated mean difference in FBS and HbA1c at 24 weeks was  $-15.58$  mg/dl (95 % CI:  $-24.67, -6.49$ ) and  $-0.48$  (95 % CI:  $-0.77, -0.19$ ), respectively, suggesting modest improvement in FBS ( $P$  value:  $0.034$ ) and HbA1c ( $P$  value:  $0.001$ ) with strong evidence against the model hypothesis at this sample size. Oral Mg supplementation could have an effect on glycaemic control in T2DM patients. However, the clinical trials so far are not sufficient to make guidelines for clinical practice.

**Keywords:** Glycaemic control; Magnesium supplementation; Meta-analysis; Type 2 diabetes.

## Related information

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[PubChem Compound \(MeSH Keyword\)](#)



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Meta-Analysis    [Nutrients](#). 2022 Feb 5;14(3):679. doi: 10.3390/nu14030679.

# Effect of Magnesium Supplementation on Inflammatory Parameters: A Meta-Analysis of Randomized Controlled Trials

[Nicola Veronese](#)<sup>1</sup>, [Damiano Pizzol](#)<sup>2</sup>, [Lee Smith](#)<sup>3</sup>, [Ligia J Dominguez](#)<sup>1 4</sup>, [Mario Barbagallo](#)<sup>1</sup>

Affiliations

PMID: 35277037    PMCID: [PMC8838086](#)    DOI: [10.3390/nu14030679](#)

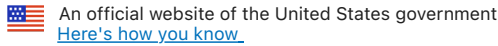
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## Abstract

Magnesium (Mg) may have several beneficial effects on human health outcomes. One hypothesized mechanism eliciting such effects is the action of Mg on serum inflammatory parameters. However, studies on this topic to date have several important limitations. Therefore, the present systematic review and meta-analysis aimed to summarize the current state of the art of all randomized control trials (RCTs) investigating the effects of Mg supplementation versus placebo on serum parameters of inflammation. We searched several databases until 23 November 2021 for RCTs. Eligible studies were RCTs investigating the effect of oral Mg supplementation vs. placebo and having serum inflammatory markers as an outcome. Among 2484 papers initially screened, 17 randomized controlled trials (889 participants; mean age: 46 years; females: 62.5%) were included. Generally, a low risk of bias was present. In meta-analysis, Mg supplementation significantly decreased serum C reactive protein (CRP) and increased nitric oxide (NO) levels. In descriptive findings, Mg supplementation significantly reduced plasma fibrinogen, tartrate-resistant acid phosphatase type 5, tumor necrosis factor-ligand superfamily member 13B, ST2 protein, and IL-1. In conclusion, Mg supplementation may significantly reduce different human inflammatory markers, in particular serum CRP and NO levels.

**Keywords:** C reactive protein; inflammation; magnesium; meta-analysis; randomized controlled trial; tumor necrosis factor.

## Figures



FULL TEXT LINKS

Randomized Controlled Trial [Stress Health](#). 2021 Dec;37(5):1000-1009.

doi: 10.1002/smi.3051. Epub 2021 May 6.

# Effect of magnesium and vitamin B6 supplementation on mental health and quality of life in stressed healthy adults: Post-hoc analysis of a randomised controlled trial

Lionel Noah <sup>1</sup>, Louise Dye <sup>2</sup>, Béatrice Bois De Fer <sup>3</sup>, André Mazur <sup>4</sup>, Gisèle Pickering <sup>5</sup>, Etienne Pouteau <sup>1</sup>

Affiliations

PMID: 33864354 PMID: [PMC9292249](#) DOI: [10.1002/smi.3051](#)[Free PMC article](#)

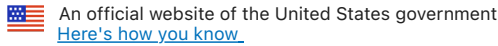
## Abstract

Magnesium status and vitamin B6 intake have been linked to mental health and/or quality of life (QoL). In an 8-week Phase IV randomised controlled study in individuals with low magnesemia and severe/extremely severe stress but who were otherwise healthy, greater stress reduction was achieved with magnesium combined with vitamin B6 than with magnesium alone. We present a previously unreported secondary analysis of the effect of magnesium, with and without vitamin B6, on depression, anxiety, and QoL. Adults with Depression Anxiety Stress Scales (DASS-42) stress subscale score >18 were randomised 1:1 to magnesium + vitamin B6 combination (Magne B6<sup>®</sup>; daily dose 300 and 30 mg, respectively) or magnesium alone (Magnespasmyl<sup>®</sup>; daily dose 300 mg). Outcomes included changes from baseline in DASS-42 depression and anxiety scores, and QoL (Short Form-36 Health Survey). DASS-42 anxiety and depression scores significantly improved from baseline to week 8 with both treatments, particularly during the first 4 weeks. Improvement in QoL continued over 8 weeks. Participants' perceived capacity for physical activity in daily life showed greater improvement with magnesium + vitamin B6 than magnesium alone (Week 4). In conclusion, magnesium supplementation, with or without vitamin B6, could provide a meaningful clinical benefit in daily life for individuals with stress and low magnesemia.

**Keywords:** anxiety; depression; magnesium supplementation; quality of life; stress; vitamin B6 supplementation.

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## Figures



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Meta-Analysis    [Hormones \(Athens\)](#). 2019 Dec;18(4):451-462.

doi: 10.1007/s42000-019-00143-3. Epub 2019 Dec 10.

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

Motahareh Hasani <sup>1</sup>, Shirin Djalalinia <sup>2 3</sup>, Maryam Khazdooz <sup>1</sup>, Hamid Asayesh <sup>4</sup>,  
Maryam Zarei <sup>5</sup>, Armita Mahdavi Gorabi <sup>6</sup>, Hossein Ansari <sup>7</sup>, Mostafa Qorbani <sup>8 9</sup>,  
Ramin Heshmat <sup>10</sup>

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PMID: 31820398    DOI: [10.1007/s42000-019-00143-3](#)

## Erratum in

[Correction to: Effect of selenium supplementation on antioxidant markers: a systematic review and meta-analysis of randomized controlled trials.](#)

Hasani M, Djalalinia S, Khazdooz M, Asayesh H, Zarei M, Gorabi AM, Ansari H, Qorbani M, Heshmat R.

*Hormones (Athens)*. 2020 Sep;19(3):451. doi: [10.1007/s42000-020-00224-8](#).

PMID: 32613535

## 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).

## FULL TEXT LINKS



Review [Nutrients](#). 2022 Aug 5;14(15):3205. doi: 10.3390/nu14153205.

# Effects of Selenium Supplementation in Patients with Mild Cognitive Impairment or Alzheimer's Disease: A Systematic Review and Meta-Analysis

Meire Ellen Pereira <sup>1 2</sup>, Júlia Vicentin Souza <sup>2</sup>, Maria Eduarda Andrade Galiciolli <sup>1 2</sup>,  
Fernanda Sare <sup>2</sup>, Giovanna Scorsin Vieira <sup>2</sup>, Isabeli Lopes Kruk <sup>2</sup>, Cláudia Sirlene Oliveira <sup>1 2</sup>

## Affiliations

PMID: 35956381 PMID: [PMC9370215](#) DOI: [10.3390/nu14153205](#)

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## Abstract

Elevated levels of oxidative stress could cause and aggravate Alzheimer's disease (AD). Selenium (Se) is a trace element with antioxidant and anti-inflammatory activity with neuroprotective effects. To evaluate the effects of Se supplementation in patients with AD or mild cognitive impairment (MCI) through a systematic review and meta-analysis, data were searched and collected from four electronic databases, including clinical trial studies published until December 2020, following the PRISMA guidelines. Statistical analysis was performed by RevMan, and the risk of bias was assessed using the Rob 2 tool. A total of 1350 scientific papers were collected, and following evaluation 11 papers were included in the systematic review and 6 of these were used in the meta-analysis. Studies that evaluated only Se supplementation observed an improvement in Se levels, glutathione peroxidase (GPX) activity, and in some cognitive tests in MCI patients; similarly, improvement in Se levels and mini-mental score was also observed in AD patients. Regarding supplementation of Se plus other nutrients, improvement in cognitive tests was observed in both AD and MCI patients. Therefore, Se supplementation is a good alternative for patients with AD and MCI for improving Se levels and GPX activity. More detailed studies are required to further evaluate the effects of Se on the cognitive deficit and oxidative stress associated with AD and MCI.

**Keywords:** Brazil nut; neurodegenerative disease; oxidative stress; selenium.

## Figures

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Filters applied: Systematic Review, Humans. [Clear all](#)

FULL TEXT LINKS



[Nutrients](#). 2020 Apr 13;12(4):1072. doi: 10.3390/nu12041072.

# Trace Mineral Intake and Deficiencies in Older Adults Living in the Community and Institutions: A Systematic Review

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Affiliations

PMID: 32294896 PMID: [PMC7230219](#) DOI: [10.3390/nu12041072](#)

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## Abstract

The global population is ageing with many older adults suffering from age-related malnutrition, including micronutrient deficiencies. Adequate nutrient intake is vital to enable older adults to continue living independently and delay their institutionalisation, as well as to prevent deterioration of health status in those living in institutions. This systematic review investigated the insufficiency of trace minerals in older adults living independently and in institutions. We examined 28 studies following a cross-sectional or cohort design, including 7203 older adults ( $\geq 60$ ) living independently in 13 Western countries and 2036 living in institutions in seven Western countries. The estimated average requirement (EAR) cut-off point method was used to calculate percentage insufficiency for eight trace minerals using extracted mean and standard deviation values. Zinc deficiency was observed in 31% of community-based women and 49% of men. This was higher for those in institutional care (50% and 66%, respectively). Selenium intakes were similarly compromised with deficiency in 49% women and 37% men in the community and 44% women and 27% men in institutions. We additionally found significant proportions of both populations showing insufficiency for iron, iodine and copper. This paper identifies consistent nutritional insufficiency for selenium, zinc, iodine and copper in older adults.

**Keywords:** Elderly; copper; iodine; iron; micronutrient; mineral; nutrition; selenium; zinc.

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Meta-Analysis Sci Rep. 2022 Nov 19;12(1):19927. doi: 10.1038/s41598-022-24467-0.

# A meta-analysis of effects of vitamin E supplementation alone and in combination with omega-3 or magnesium on polycystic ovary syndrome

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Affiliations

PMID: 36402830 PMID: PMC9675810 DOI: 10.1038/s41598-022-24467-0

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## Abstract

Vitamin E supplementation might have favorable effects on risk factors of polycystic ovary syndrome (PCOS). This systematic review and meta-analysis aimed to summarize the effects of vitamin E supplementation or vitamin E in combination with omega-3 or magnesium on PCOS. PubMed, Scopus, ISI Web of Science, Cochrane, Embase electronic databases, and Google scholar were searched for all available articles up to September 2022. Randomized controlled trials (RCTs) that examined the effect of vitamin E supplementation or vitamin E in combination with omega-3 or magnesium on lipid and glycemic profiles, anthropometric measurements, biomarkers of inflammation and oxidative stress, hormonal profile, and hirsutism score in patients with PCOS were included. Ten RCTs (with 504 participants) fulfilled the eligible criteria. Vitamin E supplementation or vitamin E in combination with omega-3 or magnesium in comparison to placebo could significantly reduce serum levels of TG (weighted mean difference: - 18.27 mg/dL, 95% CI - 34.68 to - 1.87), VLDL (- 5.88 mg/dL, 95% CI - 8.08 to - 3.68), LDL-c (- 12.84 mg/dL, 95% CI - 22.15 to - 3.52), TC (- 16.30 mg/dL, 95% CI - 29.74 to - 2.86), TC/HDL-c ratio (- 0.52, 95% CI - 0.87 to - 0.18), hs-CRP (- 0.60 ng/mL, 95% CI - 0.77 to - 0.44), hirsutism score (- 0.33, 95% CI - 0.65 to - 0.02) and significantly increase nitric oxide levels (2.79  $\mu$ mol/L, 95% CI 0.79-4.79). No significant effect was found on HDL-c, glycemic indices, hormonal profile, anthropometric measurements, and other biomarkers of inflammation or oxidative stress. This meta-analysis highlights the potential anti-hyperlipidemic, anti-oxidant, and anti-inflammatory properties of vitamin E supplementation alone or in combination with omega-3 or magnesium on PCOS patients.

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## Figures

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Meta-Analysis [Curr Rev Clin Exp Pharmacol. 2022;17\(3\):205-215.](#)

doi: 10.2174/2772432817666211230100723.

# Effect of Vitamin C Supplements on Respiratory Tract Infections: A Systematic Review and Meta-Analysis

[Tahmina Afrose Keya](#)<sup>1</sup>, [Anthony Leela](#)<sup>1</sup>, [Kevin Fernandez](#)<sup>1</sup>, [Nasrin Habib](#)<sup>2</sup>, [Mumunur Rashid](#)<sup>3</sup>

Affiliations

PMID: 34967304 DOI: [10.2174/2772432817666211230100723](#)

## Abstract

**Background:** Respiratory tract infections are a primary cause of illness and mortality over the world.

**Objective:** This study was aimed to investigate the effectiveness of vitamin C supplementation in preventing and treating respiratory tract infections.

**Methods:** We used the Cochrane, PubMed, and MEDLINE Ovid databases to conduct our search. The inclusion criteria were placebo-controlled trials. Random effects meta-analyses were performed to measure the pooled effects of vitamin C supplementation on the incidence, severity, and duration of respiratory illness.

**Results:** We found ten studies that met our inclusion criteria out of a total of 2758. The pooled risk ratio (RR) of developing respiratory illness when taking vitamin C regularly across the study period was 0.94 (with a 95% confidence interval of 0.87 to 1.01) which found that supplementing with vitamin C lowers the occurrence of illness. This effect, however, was statistically insignificant ( $P=0.09$ ). This study showed that vitamin C supplementation had no consistent effect on the severity of respiratory illness (SMD 0.14, 95% CI -0.02 to 0.30;  $I^2 = 22%$ ,  $P=0.09$ ). However, our study revealed that vitamin C group had a considerably shorter duration of respiratory infection (SMD -0.36, 95% CI -0.62 to -0.09,  $P = 0.01$ ).


**Conclusion:** Benefits of normal vitamin C supplementation for reducing the duration of respiratory tract illness were supported by our meta-analysis findings. Since few trials have examined the effects of therapeutic supplementation, further research is needed in this area.

**Keywords:** Ascorbic acid; efficacy; immunity; incidence; respiratory illness; severity.

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Review [Br J Nutr.](#) 2015 Apr 28;113(8):1182-94. doi: 10.1017/S0007114515000227.

# Effect of vitamin C and vitamin E supplementation on endothelial function: a systematic review and meta-analysis of randomised controlled trials

[Ammar W Ashor](#)<sup>1</sup>, [Mario Siervo](#)<sup>1</sup>, [Jose Lara](#)<sup>1</sup>, [Clio Oggioni](#)<sup>1</sup>, [Sorena Afshar](#)<sup>1</sup>, [John C Mathers](#)<sup>1</sup>

Affiliations

PMID: 25919436 DOI: [10.1017/S0007114515000227](#)

## Abstract

Randomised controlled trials (RCT) testing the effects of antioxidant supplements on endothelial function (EF) have reported conflicting results. We aimed to investigate the effects of supplementation with antioxidant vitamins C and E on EF and to explore factors that may provide explanations for the inconsistent results. We searched four databases (MEDLINE, Embase, Cochrane Library and Scopus) from inception until May 2014 for RCT involving adult participants aged  $\geq 18$  years who were supplemented with vitamins C and E alone or in combination for more than 2 weeks and reporting changes in EF measured using flow mediated dilation or forearm blood flow. Data were pooled as standardised mean difference (SMD) and analysed using a random-effects model. Significant improvements in EF were observed in trials supplementing with vitamin C alone (500-2000 mg/d) (SMD: 0.25, 95% CI 0.02, 0.49,  $P=0.043$ ) and vitamin E alone (300-1800 IU/d; 1 IU vitamin E=0.67 mg natural vitamin E) (SMD: 0.48, 95% CI 0.23, 0.72,  $P=0.0001$ ), whereas co-administration of both vitamins was ineffective (vitamin C: 500-2000 mg/d; vitamin E: 400-1200 IU/d) (SMD: 0.12, 95% CI -0.18, 0.42,  $P=0.428$ ). The effect of vitamin C supplementation on EF increased significantly with age ( $\beta$  0.023, 95% CI 0.001, 0.05,  $P=0.042$ ). There was a significant negative correlation between baseline plasma vitamin E concentration and the effect of vitamin E supplementation on EF ( $\beta$  -0.03, 95% CI -0.06, -0.001,  $P=0.029$ ). Supplementation with either vitamin C or vitamin E alone improves EF. However, subgroup analysis emphasises the importance of careful characterisation and selection of a population group which may benefit from such supplementation.

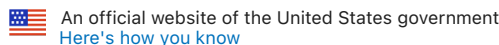
**Keywords:** Cardiovascular risk.

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Review [Nutr Metab Cardiovasc Dis.](#) 2016 Aug;26(8):663-73.

doi: 10.1016/j.numecd.2016.04.011. Epub 2016 Apr 25.

# Effect of vitamin D<sub>3</sub> supplementation on blood pressure in adults: An updated meta-analysis

[M Golzarand](#)<sup>1</sup>, [S Shab-Bidar](#)<sup>2</sup>, [G Koochakpoor](#)<sup>3</sup>, [R Speakman J](#)<sup>4</sup>, [K Djafarian](#)<sup>5</sup>

Affiliations

PMID: 27287826 DOI: [10.1016/j.numecd.2016.04.011](#)

## Abstract

**Background and aims:** Previous randomized clinical trials (RCTs) of the effects of vitamin D<sub>3</sub> supplementation (VD<sub>3</sub>S) on blood pressure have generated inconsistent results. We evaluated the effect of VD<sub>3</sub>S on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a meta-analysis.

**Data synthesis:** Literature searches of PubMed, Scopus, Ovid, and Google scholar for publications in English were conducted up to April 2015. RCTs that assessed the effect of VD<sub>3</sub>S on SBP and DBP were selected.

**Conclusions:** A total of 30 RCTs with 41 arms including 4744 participants were included. The mean duration of the studies was 5.6 ± 4.0 months, and doses of VD<sub>3</sub>S varied between 200 and 12,000 IU/day. VD<sub>3</sub>S had no effect on SBP (-0.68 mmHg, 95%CI: -2.19 to 0.84), and DBP (-0.57 mmHg, 95%CI: -1.36 to 0.22). Subgroup analysis revealed that daily vitamin D<sub>3</sub> therapy at a dose of >800 IU/day for <6 months in subjects ≥50 years old reduced both SBP and DBP (p < 0.001). In addition, VD<sub>3</sub>S showed hypotensive effects in healthy subjects and hypertensive patients, but a hypertensive effect in overweight and obese subjects. However, after excluding overweight and obese subjects, VD<sub>3</sub>S significantly reduced SBP and DBP. VD<sub>3</sub>S in combination with calcium supplementation significantly elevated SBP (3.64 mmHg, 95%CI: 3.15-4.13) and DBP (1.71 mmHg, 95%CI: 1.25-2.18). No evidence of publication bias was found. The effects of VD<sub>3</sub>S on blood pressure depend on dose of supplementation, treatment regimens, trial duration, and population subgroup. Supplementation may be beneficial at daily doses >800 IU/day for <6 months in subjects ≥50 years old.

**Keywords:** Blood pressure; Cholecalciferol; Hypertension; Meta-analysis; Vitamin D<sub>3</sub> supplementation.

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## Related information

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Meta-Analysis    [Sci Rep. 2020 Oct 14;10\(1\):17234. doi: 10.1038/s41598-020-73741-6.](#)

# The effect of vitamin E supplementation on selected inflammatory biomarkers in adults: a systematic review and meta-analysis of randomized clinical trials

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Affiliations

PMID: 33057114    PMID: [PMC7560744](#)    DOI: [10.1038/s41598-020-73741-6](#)[Free PMC article](#)

## Abstract

The previous meta-analysis of clinical trials revealed a beneficial effect of vitamin E supplementation on serum C-reactive protein (CRP) concentrations; however, it is unknown whether this vitamin has the same influence on other inflammatory biomarkers. Also, several clinical trials have been published since the release of earlier meta-analysis. Therefore, we aimed to conduct a comprehensive meta-analysis to summarize current evidence on the effects of vitamin E supplementation on inflammatory biomarkers in adults. We searched the online databases using relevant keywords up to November 2019. Randomized clinical trials (RCTs) investigating the effect of vitamin E, compared with the placebo, on serum concentrations of inflammatory cytokines were included. Overall, we included 33 trials with a total sample size of 2102 individuals, aged from 20 to 70 years. Based on 36 effect sizes from 26 RCTs on serum concentrations of CRP, we found a significant reduction following supplementation with vitamin E (- 0.52, 95% CI - 0.80, - 0.23 mg/L,  $P < 0.001$ ). Although the overall effect of vitamin E supplementation on serum concentrations of interleukin-6 (IL-6) was not significant, a significant reduction in this cytokine was seen in studies that used  $\alpha$ -tocopherol and those trials that included patients with disorders related to insulin resistance. Moreover, we found a significant reducing effect of vitamin E supplementation on tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) concentrations at high dosages of vitamin E; such that based on dose-response analysis, serum TNF- $\alpha$  concentrations were reduced significantly at the dosages of  $\geq 700$  mg/day vitamin E ( $P_{\text{non-linearity}} = 0.001$ ). Considering different chemical forms of vitamin E,  $\alpha$ -tocopherol, unlike other forms, had a reducing effect on serum levels of CRP and IL-6. In conclusion, our findings revealed a beneficial effect of vitamin E supplementation, particularly in the form of  $\alpha$ -tocopherol, on subclinical inflammation in adults. Future high-quality RCTs should be conducted to translate this anti-inflammatory effect of vitamin E to the clinical setting.

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Meta-Analysis [J Hum Hypertens](#). 2019 Jul;33(7):499-507. doi: 10.1038/s41371-019-0192-0.  
Epub 2019 Mar 7.

# Effect of vitamin E supplementation on blood pressure: a systematic review and meta-analysis

Mohammad Reza Emami <sup>1</sup>, Maryam Safabakhsh <sup>1</sup>, Shahab Alizadeh <sup>2</sup>, Omid Asbaghi <sup>3</sup>,  
Mohammad Zeinali Khosroshahi <sup>3</sup>

Affiliations

PMID: 30846828 DOI: [10.1038/s41371-019-0192-0](#)

## Abstract

Although emerging evidence suggests that vitamin E may contribute to blood pressure improvement, the effects of vitamin E on systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) are still controversial. The aim was to evaluate the influence of vitamin E on SBP, DBP, and MAP through meta-analysis. We identified all studies that assessed the effect of vitamin E supplementation on SBP, DBP, and MAP from PubMed/Medline, SCOPUS, and Google scholar up to March 2018. Weighted mean differences (WMD) and 95% confidence interval (CI) were expressed as effect size. Pre-specified subgroup analysis was conducted to evaluate potential sources of heterogeneity. Meta-regression analyses were performed to investigate association between blood pressure-lowering effects of vitamin E and duration of follow-up and dose of treatment. Eighteen trials, comprising 839 participants met the eligibility criteria. Results of this study showed that compared to placebo, SBP decreased significantly in vitamin E group (WMD = -3.4 mmHg, 95% CI = -6.7 to -0.11, P < 0.001), with a high heterogeneity across the studies ( $I^2 = 94.0\%$ , P < 0.001). Overall, there were no significant effects on DBP and MAP. This meta-analysis suggested that vitamin E supplements decreased only SBP and had no favorable effect on DBP and MAP.

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Meta-Analysis    [Nutrients](#). 2022 Apr 12;14(8):1599. doi: 10.3390/nu14081599.

# Can Low-Dose of Dietary Vitamin E Supplementation Reduce Exercise-Induced Muscle Damage and Oxidative Stress? A Meta-Analysis of Randomized Controlled Trials

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Affiliations

PMID: 35458161    PMCID: [PMC9027756](#)    DOI: [10.3390/nu14081599](#)

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## Abstract

Vitamin E plays an important role in attenuating muscle damage caused by oxidative stress and inflammation. Despite of beneficial effects from antioxidant supplementation, effects of antioxidants on exercise-induced muscle damage are still unclear. The aim of this meta-analysis was to investigate the effects of dietary vitamin E supplementation on exercise-induced muscle damage, oxidative stress, and inflammation in randomized controlled trials (RCTs). The literature search was conducted through PubMed, Medline, Science Direct, Scopus, SPORTDiscuss, EBSCO, Google Scholar database up to February 2022. A total of 44 RCTs were selected, quality was assessed according to the Cochrane collaboration risk of bias tool (CCRB), and they were analyzed by Revman 5.3. Dietary vitamin E supplementation had a protective effect on muscle damage represented by creatine kinase (CK; SMD -1.00, 95% CI: -1.95, -0.06) and lactate dehydrogenase (SMD -1.80, 95% CI: -3.21, -0.39). Muscle damage was more reduced when CK was measured immediately after exercise (SMD -1.89, 95% CI: -3.39, -0.39) and subjects were athletes (SMD -5.15, 95% CI: -9.92, -0.39). Especially vitamin E supplementation lower than 500 IU had more beneficial effects on exercise-induced muscle damage as measured by CK (SMD -1.94, 95% CI: -2.99, -0.89). In conclusion, dietary vitamin E supplementation lower than 500 IU could prevent exercise-induced muscle damage and had greater impact on athletes.

**Keywords:** exercise; inflammation; muscle damage; oxidative stress; vitamin E.

## Figures

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Meta-Analysis [Horm Metab Res.](#) 2019 Aug;51(8):503-510. doi: 10.1055/a-0955-6662.

Epub 2019 Aug 13.

# The Effect of Zinc Supplementation on Serum Leptin Levels: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Mohammad Reza Emami <sup>4</sup>, Hamed Kord-Varkaneh <sup>5</sup>, Naheed Aryaeian <sup>6</sup>, Jamal Rahmani <sup>7</sup>,  
Seyed Mohammad Mousavi <sup>8 9</sup>

Affiliations

PMID: 31408896 DOI: [10.1055/a-0955-6662](#)

## Abstract

Recently, obesity has become a common worldwide concern. Leptin, as an adipocytokine, plays a major role in the etiology of obesity. Prior studies have demonstrated that zinc potentially affects serum leptin levels. However, clinical trials carried out in this regard are not consistent. Therefore, current meta-analysis was conducted to ascertain the actual effect of zinc supplementation on serum leptin levels in adults. Databases of PubMed, SCOPUS, and Google Scholar were methodically searched to identify relevant articles up to April 2018. Clinical trials that examined the effect of zinc supplementation on serum leptin concentrations as outcome variables in human adults were included. The mean difference (SD) of leptin changes in the intervention and placebo groups were used to calculate the overall effect size. Totally, 663 articles were identified, of which 6 studies were eligible randomized controlled trials (RCTs) with 7 treatment arms. The analysis suggested that zinc supplementation exerts no significant effect on overall serum leptin (WMD: 0.74 ng/ml; 95% CI: -1.39 to 2.87, p=0.49). Nevertheless, sex and duration of intervention seemed to impact the extent of zinc's influence. In trials with female subjects, zinc consumption led to a significant decrease in serum leptin level (WMD: -1.93 ng/ml; 95% CI: -3.72 to -0.14, p=0.03) as well as trials that lasted for more than 6 weeks (WMD: -1.71 ng/ml; 95% CI: -3.07 to -0.35, p=0.01), in comparison to the control group. Zinc supplementation did not significantly improve leptin concentrations, but it may result in a decreased circulating leptin level in studies with a duration of more than 6 weeks especially among females.


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Review Eur J Nutr. 2020 Aug;59(5):1815-1827. doi: 10.1007/s00394-020-02204-5.

Epub 2020 Feb 24.

# The effect of zinc supplementation on blood pressure: a systematic review and dose-response meta-analysis of randomized-controlled trials

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## Erratum in

[Correction to: The effect of zinc supplementation on blood pressure: a systematic review and dose-response meta-analysis of randomized-controlled trials.](#)

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## Abstract

**Purpose:** Despite previous investigations on the effects of zinc supplementation on blood pressure, inconsistent findings are available in this regard. Therefore, we conducted a systematic review and meta-analysis of randomized clinical trials on the effects of zinc supplementation on blood pressure (BP) in adults.

**Methods:** Relevant studies published up to September 2019 were searched through PubMed/Medline, Scopus, ISI Web of Science, and Google Scholar using suitable keywords. All randomized clinical trials (RCTs) that examined the effect of oral zinc supplementation on systolic blood pressure (SBP) or diastolic blood pressure (DBP) in adults were included.

**Results:** Overall, nine trials were included in our study. Zinc supplementation significantly reduced SBP compared to the control [weighted mean differences (WMD) - 1.49 mmHg; 95% CI - 2.85 to - 0.13; P = 0.03]. However, zinc supplementation had no significant effects on DBP (WMD - 0.88 mmHg; 95% CI - 2.04 to 0.29; P = 0.14). Nonlinear analysis failed to indicate a significant influence of supplementation dosage or duration on both SBP and DBP. Sensitivity analysis showed that no individual study had a significant impact on our final results. In addition, we found no evidence for the presence of small-study effects among studies for both SBP and DBP.

**Conclusion:** We found a significant reduction in SBP following zinc supplementation. However, zinc

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Meta-Analysis J Interferon Cytokine Res. 2021 Mar;41(3):81-101. doi: 10.1089/jir.2020.0209.

# The Effects of Zinc Supplementation on C-Reactive Protein and Inflammatory Cytokines: A Meta-Analysis and Systematical Review

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## Abstract

Zinc is known for anti-inflammatory and antioxidant roles. In this meta-analysis, we aim to evaluate the impact of zinc supplementation on inflammatory markers, acute-phase reactants, and serum zinc level during inflammatory and infectious diseases. PubMed, Scopus, and Web of Science databases were screened systematically with the terms "zinc supplementation" AND "CRP" OR "IL-1 $\beta$ " OR "IL-2" OR "IL-6" OR "IL-10" OR "IL-12" OR "TNF- $\alpha$ " OR "TGF- $\beta$ " OR "IFN- $\gamma$ " OR "WBC (clinical trial)" OR "macrophage (clinical trial)" OR "lymphocyte (clinical trial)" OR "neutrophil (clinical trial)" OR "virus (clinical trial)" OR "antiviral (clinical trial)" for all databases. A total of 2,258 publications were screened, and 73 articles had suitable data for the meta-analysis. Serum zinc level was significantly higher in supplementation group compared with controls [ $P = 0.0006$ , mean difference: 11.35 (4.84, 17.87)] ( $n = 37$ ). Zinc supplementation downregulates acute-phase reactants, especially serum C-reactive protein (CRP) in adults [ $P < 0.00001$ , mean difference: -0.75 (-0.98, -0.52)] ( $n = 22$ ) and pregnant women [FEM  $P < 0.00001$ , mean difference: -1.77 (-2.53, -1.00)] ( $n = 3$ ) but not in children [REM  $P = 0.10$ , mean difference: -0.85 (-1.86, 0.17)] ( $n = 3$ ). In subgroups analysis of chronic inflammatory diseases, serum CRP [REM  $P < 0.00001$ , mean difference: -0.57 (-0.76, -0.38)] were significantly lower in zinc-supplemented patients compared with no intervention group. Zinc supplementation (mg/day) correlated with serum interferon-gamma (IFN- $\gamma$ ) level ( $P = 0.018$ ,  $r = 1,000$ ). In the nonsupplemented group, serum zinc correlated with serum interleukin-6 (IL-6) level ( $P = 0.041$ ,  $r = -0.829$ ) and serum tumor necrosis factor alpha (TNF- $\alpha$ ) level ( $P = 0.063$ ,  $r = 0.730$ ). Zinc intake correlated with serum zinc ( $P = 0.0428$ ,  $r = 0.5115$ ) and TNF- $\alpha$  ( $P = 0.0043$ ,  $r = -0.9461$ ). This meta-analysis shows that zinc supplementation improves CRP levels in adults and pregnant women. It might have modulatory effects on cytokine secretions and blood cells in inflammatory and infectious diseases. For the first time, we investigated the effects of zinc supplementation on inflammatory cytokine.

**Keywords:** C-reactive protein (CRP); cytokine; infection; inflammation; zinc.

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Meta-Analysis [Pharmacol Res.](#) 2020 Nov;161:105166. doi: 10.1016/j.phrs.2020.105166.

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# Clinical effectiveness of zinc supplementation on the biomarkers of oxidative stress: A systematic review and meta-analysis of randomized controlled trials

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## Abstract

**Background:** Oxidative stress plays an important role in the occurrence of chronic diseases. Zinc supplementation is also known to be an antioxidant agent. While, there is no review on the effects of zinc supplementation on oxidative stress, this study aimed to systematically summarize randomized clinical trials (RCTs) which have evaluated the impacts of zinc supplementation on oxidative stress biomarkers.

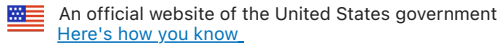
**Methods:** Systematic searches were performed using the PubMed/Medline, Scopus, and Google Scholar databases, up to April 2020. All RCTs assessed the effect of oral zinc supplementation on serum malondialdehyde (MDA), total antioxidant capacity (TAC), glutathione (GSH), and nitric oxide (NO) levels, were included. For each variable, mean differences (MD) and standard deviations (SDs) were combined using the random-effects model, and the fractional polynomial model was used to implement the dose-response analysis.

**Results:** Ten RCTs were included. The pooled analysis of data showed that zinc supplementation significantly reduced MDA levels (MD: -0.42  $\mu\text{mol/L}$ ; 95 % CI: -0.71 to -0.13), increased serum TAC (MD: 225.96  $\text{mmol/L}$ ; 95 % CI: 68.42-383.5) and GSH levels (MD: 49.99  $\mu\text{mol/L}$ ; 95 % CI: 2.25 to 97.73), compared with the placebo group. In contrast, no significant changes were seen in NO levels following zinc supplementation (MD: -1.66  $\mu\text{mol/L}$ ; 95 % CI: -5.89 to 2.57). Dose-response analysis showed a significant non-linear relationship between zinc supplementation dosage and serum levels of MDA ( $p < 0.01$ ), but not other biomarkers.

**Conclusions:** The current study showed that zinc supplementation would significantly decrease MDA and increase TAC and GSH, but not NO levels. Thus, it encourages the use of zinc supplementation in oxidative stress-related diseases.

**Keywords:** Antioxidants; Malondialdehyde; Oxidative stress; Reactive oxygen species; Zinc.

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# Zinc Supplementation and Body Weight: A Systematic Review and Dose-Response Meta-analysis of Randomized Controlled Trials

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## Abstract

The aim of this study was to determine the effect of zinc supplementation on anthropometric measures. In this systematic review and dose-response meta-analysis, we searched PubMed, Scopus, ISI Web of Science, and the Cochrane Library from database inception to August 2018 for relevant randomized controlled trials. Mean differences and SDs for each outcome were pooled using a random-effects model. Furthermore, a dose-response analysis for zinc dosage was performed using a fractional polynomial model. Quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Twenty-seven trials (n = 1438 participants) were included in the meta-analysis. There were no significant changes in anthropometric measures after zinc supplementation in the overall analysis. However, subgroup analyses revealed that zinc supplementation increased body weight in individuals undergoing hemodialysis (HD) [3 trials, n = 154 participants; weighted mean difference (WMD) = 1.02 kg; 95% CI: 0.38, 1.65 kg; P = 0.002; I<sup>2</sup> = 11.4%] and decreased body weight in subjects who are overweight/obese but otherwise healthy (5 trials, n = 245 participants; WMD = -0.55 kg; 95% CI: -1.06, -0.04 kg; P = 0.03; I<sup>2</sup> = 31.5%). Dose-response analyses revealed a significant nonlinear effect of supplementation dosage on BMI (P = 0.001). Our data suggest that zinc supplementation increases body weight in patients undergoing HD and decreases body weight in individuals who are overweight/obese but otherwise healthy, although after normalization for study duration, the association observed in subjects who are overweight/obese disappeared. Although more high-quality studies are needed to reach a definitive conclusion, our study supports the view that zinc may be associated with body weight.

**Keywords:** body mass index; body weight; dose-response; meta-analysis; obesity; zinc.

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Meta-Analysis [Crit Rev Food Sci Nutr.](#) 2022;62(11):3023-3041.

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# Zinc supplementation and immune factors in adults: a systematic review and meta-analysis of randomized clinical trials

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## Abstract

**Purpose:** This systematic review and meta-analysis aimed to investigate the effect of zinc supplementation on immune factors in randomized controlled trials.

**Methods:** A comprehensive search was done in PubMed, Scopus, Web of Science, Embase, and Cochrane databases up to December 2020. We used standard and weighted mean differences and 95% confidence intervals for net changes in selected parameters of immune responses. Subgroup analysis was used to find heterogeneity.

**Result:** Overall, 35 RCTs comprising 1995 participants were eligible for this meta-analysis. There was a significant reduction of circulating CRP (WMD: -32.4; 95% CI: -44.45 to -19.62,  $p < 0.001$ ), hs-CRP (WMD: -0.95; 95% CI: -1.01 to -0.89,  $p < 0.001$ ), Neutrophil levels (SMD: -0.46; 95% CI: -0.90 to -0.01,  $p = 0.043$ ), following zinc supplementation. CD4 level also increased significantly, (WMD: 1.79; 95% CI: 0.57 to 3,  $p = 0.004$ ). Zinc supplementation had no significant effect on WBC (SMD: -0.66; 95% CI: -1.67 to 0.36,  $p = 0.204$ ), lymphocyte (WMD: 1.86; 95% CI: -0.86 to 4.58,  $p = 0.181$ ), monocyte levels (SMD: -0.16; 95% CI: -0.07 to 0.39,  $p = 0.167$ ), CD3 (SMD: 0.37; 95% CI: -0.49 to 1.22,  $p = 0.399$ ).

**Conclusion:** Zinc supplementation decreased the CRP, hs-CRP and TNF- $\alpha$ , IL-6, neutrophil and increased CD3 and CD4 level significantly.

**Keywords:** Zinc; adult; immune system; meta-analysis; systematic review.

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