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REVIEW

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 supplementation had no significant effect on DBP. In addition, no nonlinear association was found between supplementation dosage and duration with changes in both SBP and DBP. Further RCTs using different dosages of zinc in various durations are required to confirm our conclusion.

Keywords Zinc · Blood pressure · Diastolic blood pressure · Meta-analysis · Systolic blood pressure

Introduction

Cardiovascular diseases (CVDs) are the most prevalent causes of death worldwide, accounting for about 33% of all deaths [1]. Hypertension is a major risk factor for CVDs and is correlated to approximately 70% of chronic heart failure, strokes, and heart attacks [2]. Hypertension contributes to 37% of cardiovascular mortalities in Western countries [3, 4]. It is estimated that 33% of healthy adults have high blood pressure [5]. Every 2 mmHg reduction in systolic

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blood pressure (SBP) and 1 mmHg in diastolic blood pressure (DB) are associated with 10% decrease in the risk of CVDs [6]. Thus, the primary prevention of hypertension is a priority to the healthcare system.

Lifestyle and nutritional modifications are identified as substantial parts of primary prevention programs [7]. It has been shown that specific nutrients, as well as dietary patterns, help in lowering blood pressure [8, 9]. Zinc is an essential trace element that is involved in gene expression, enzyme action, cell signaling, cell membrane stabilization, and metabolic reactions [10, 11]. Available systematic reviews and meta-analyses have indicated that zinc supplementation may improve serum levels of LDL cholesterol, triglycerides, total cholesterol, fasting blood sugar, C-reactive protein concentrations, and insulin resistance [12–14]. Zinc controls blood pressure and plays a role in vascular tone modulation by inhibition of nuclear factor kappa-light-chain-enhancer of activated B-cell (NF-κB) transactivation activity, thus regulating activity and expression of inducible nitric oxide synthase (iNOS) [15]. Therefore, zinc deficiency might be associated with elevated blood pressure. Some studies have found an inverse association between serum zinc and blood pressure [16, 17]. Furthermore, it has been indicated that impairment in zinc metabolism is a risk factor for hypertension and that dietary zinc intake is inversely associated with SBP independently from energy intake, sodium intake, and body mass [18, 19].

However, zinc supplementation has been reported to have a conflicting effect on blood pressure. While some clinical trials revealed some beneficial effects of zinc supplementation on blood pressure [20, 21], others failed to find such an influence [22–24]. We, therefore, conducted this systematic review and dose–response meta-analysis of randomized-controlled trials to summarize the effects of zinc supplementation on blood pressure in adults.

Methods

This meta-analysis, addressing the effect of zinc supplementation on blood pressure, was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [25].

Search strategy

A literature search was conducted through defined databases (PubMed/Medline, Scopus, ISI Web of Science, and Google Scholar) to identify relevant studies published until September 2019. Medical Subject Headings (MeSH) and related keywords were used: ("Zinc"[Mesh] OR zinc[Title/Abstract]) AND ("Arterial Pressure"[Mesh] OR "Prehypertension"[Mesh] OR "Hypertension"[Mesh] OR "Blood Pressure"[Mesh] OR "Blood Pressure"[Title/Abstract] OR "Systolic Pressure"[Title/Abstract] OR "Diastolic Pressure"[Title/Abstract] OR Hypertension[Title/Abstract] OR "High Blood Pressure"[Title/Abstract] OR "High Blood Pressures"[Title/Abstract] OR "diastolic blood pressure"[Title/Abstract] OR "systolic blood pressure"[Title/Abstract] OR SBP[Title/Abstract] OR DBP[Title/Abstract] OR Prehypertension[Title/Abstract] OR Pre-Hypertension[Title/Abstract] OR Prehypertensions[Title/Abstract] OR Pre-Hypertensions[Title/Abstract] OR Hypertens*[Title/Abstract] OR "Arterial Pressure"[Title/Abstract] OR "Arterial Tension"[Title/Abstract] OR "Arterial Pressures"[Title/Abstract] OR "Arterial Blood Pressure"[Title/Abstract] OR "Aortic Pressure"[Title/Abstract] OR "Aortic Tension"[Title/Abstract]) AND ("Random Allocation"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Cross-Over Studies"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR RCT[Title/Abstract] OR "Intervention Studies"[Title/Abstract] OR intervention[Title/Abstract] OR "controlled trial"[Title/Abstract] OR randomized[Title/Abstract] OR randomised[Title/Abstract] OR random[Title/Abstract] OR randomly[Title/Abstract] OR placebo[Title/Abstract] OR assignment[Title/Abstract]). There was no time and language limitation. References in all relevant reviews were also checked for additional studies that might be missed in our search. The PubMed's e-mail alert service was also used as a tool to find any new records that may have appeared on this topic after our primary search. We used only the most informative or most recent publication when there were several publications from the same trial.

Inclusion criteria

Studies were included if they: (1) were randomized-controlled trials (RCTs) with either parallel or crossover designs; (2) included populations aged ≥ 18 years; (3) examined the effects of oral zinc supplementation on SBP or DBP as the primary or secondary outcomes with a control group; (4) had a duration of intervention of at least 2 weeks; and (5) reported mean/median and standard deviation (SD) or other available data (95% confidence interval, interquartile range, standard errors, and ranges) on SBP or DBP.

Exclusion criteria

Observational (cohort, case–control, and cross-sectional) studies, reviews, animal studies, in-vitro studies, and those that were conducted on children and adolescents or pregnant and lactating women were not included. Studies without randomized allocation, trials that assessed the effect of zinc in combination with other interventions, studies with insufficient data, citations that did not assess SBP or DBP, articles

that reported the findings of the same trial, and publications in languages other than English were excluded. In addition, book chapters, editorials, grey literature, interviews, conference abstracts, comments, methodological papers, opinion pieces, and letters were not included in this meta-analysis.

Data extraction

Two reviewers (SMM and AM) independently extracted the following data from eligible published papers: first author's name, publication year, study country, study design (parallel or cross-over), participant health status, number of subjects in the zinc and control groups, age, gender and body mass index (BMI) of participants, dosage and duration of intervention, and quantity of SBP or DBP at study baseline and end of trial, as well as changes within each group. To minimize possible errors, data were cross-checked and disagreements were resolved by discussion with the corresponding author (AE). Studies with longer duration of intervention were chosen for inclusion in the meta-analysis over studies with a short duration on the same population.

Risk of bias

The quality of eligible publications was assessed using the Cochrane risk of bias tool for RCTs (Table 1) [26]. Two independent investigators (TM and MDM) completed this checklist for each included paper. Methodological features applied for assessment were: (a) adequate sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessment, (e) incomplete outcome data, (f) selective outcome reporting (reporting bias), and (g) other potential sources of bias. Based on the mentioned items, studies were classified in terms of bias into three groups: low risk, moderate risk, and high risk of bias [26].

Data synthesis and statistical analysis

The effect sizes were reported as weighed mean difference (MD) between the zinc and control groups for SBP or DBP and its standard deviations (SD). Weighed mean differences (WMD) and 95% confidence intervals (CI) were determined using the random-effects model following DerSimonian and Laird method [27]. For studies that did not report mean change (SD), we computed it using this formula: mean change = final values − baseline values; SD = square root [(SD baseline)^2 + (SD final)^2 − (2R × SD baseline × SD final)] [28]. The best correlation coefficient (R) for SBP and DBP was calculated from studies in which mean (SD) changes were reported [28]. If the required values in published studies were reported as median and interquartile range, we used the approach suggested by Hozoet et al. to compute means and SDs [29]. Furthermore, standard errors (SEs) were converted to SDs using the following formula: $SD = SEM \times \sqrt{n}$, where "n" is the number of subjects. In addition, 95% CIs were also converted to SDs, using the formula:

$$SD = \text{sqrt}(n) \times (\text{Upper CI Limit (UL)} - \text{Lower CI Limit (LL)})/3.92.$$

Between-study heterogeneity was assessed using the I^2 index, defined as I^2 values > 50%. Subgroup analyses were conducted based on prespecified factors, including dosage

Table 1 Study quality and risk of bias assessment of included studies according to the Cochrane Collaboration's tool

References	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall quality*
Afkhami-Ardekani [31]	U	H	L	L	L	L	L	Fair
Parham [32]	L	U	L	U	L	L	L	Fair
Tabrizi [34]	U	H	L	L	L	L	L	Fair
Seet [22]	U	U	L	L	L	L	L	Fair
Kim [23]	U	U	L	L	L	L	L	Fair
Ranasinghe [20]	L	L	L	L	L	L	L	Good
Naghizadeh [21]	L	L	L	U	L	L	L	Good
Suliburska [24]	U	L	H	H	L	L	L	Poor
Sadeghi [33]	L	L	H	H	L	L	U	Poor

U unclear risk of bias, *L* low risk of bias, *H* high risk of bias

*Good quality: all criteria met; fair quality: one criterion not met (i.e., high risk of bias for one domain or two criteria unclear); poor quality: two or more criteria listed as high or unclear risk of bias

and type of zinc supplements, study duration, baseline BMI, mean age, participants' health condition, and gender. To explore the influence of each study on the pooled effect size, sensitivity analyses were conducted. The potential for small-study effects was assessed by visual inspection of funnel plots. We did not perform Eggers test to examine small-study effects because of having less than ten papers in the current analysis [30]. In addition, fractional polynomial models (polynomials) were used to explore nonlinear associations between zinc dosage (mg/days) and duration of intervention (weeks). All statistical analyses were done using STATA (Version 14.0, Stata Corp, College Station, TX). $P < 0.05$ was regarded as statistically significant.

Results

Study selection

The primary search identified a total of 976 articles; of these, 186 duplicates were removed. A flowchart of the detailed steps of the selection strategy procedure is shown in Fig. 1. After screening by title/abstract, 761 publications were exclude and 29 records remained for further examination. Of these articles, 22 studies were excluded for the following reasons: particpants were children or pregnant women ($n = 4$), the intervention was done in combination with other components ($n = 4$), the intervention duration was shorter than 2 weeks ($n = 1$), lack of a control group ($n = 2$),

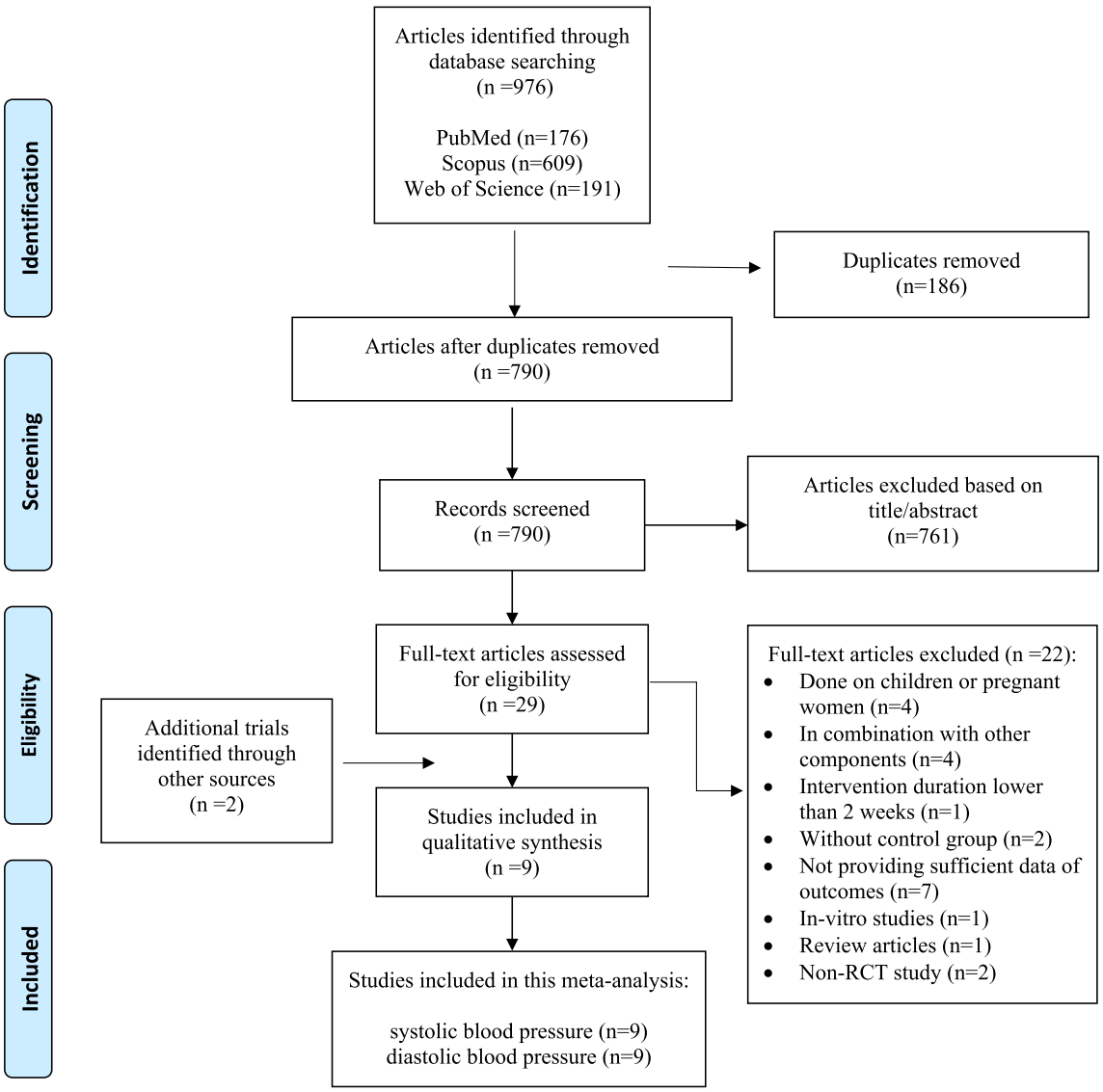

Fig. 1 Flow diagram of the number of literature search and selection strategy

insufficient data reported for the outcomes ($n=7$), an in vitro ($n=1$) or review articles ($n=1$), and non-RCTs ($n=2$). Two additional trials were found through the hand search of the reference lists of related papers. Therefore, overall nine trials were eligible for inclusion in the final quantitative analysis.

Study characteristics

Characteristics of nine included studies are described in Table 2. Selected qualified trials enrolled 544 participants aged from 25 to 56 years old. Six trials included both male and female participants [20, 21, 24, 31–33], whereas two trials had exclusively recruited females [23, 34], and one trial was done on men only [22]. Number of subjects in the intervention and control groups was 277 and 267 in total, respectively. Participants were patients with type-2 diabetes [22, 31, 32], prediabetes [20], individuals with diabetic retinopathy [21], polycystic ovary syndrome [34], hypertension [24], obesity [23], and patients under hemodialysis [33]. Baseline

BMI varied from 25.5 to 33.6 kg/m^2. These trials were published from 2008 to 2019 and performed in Iran [21, 31–34], Singapore [22], Korea [23], Sri Lanka [20], and Poland [24]. All selected studies were parallel RCTs except for one trial with a cross-over design [32]. The elemental dosage of zinc prescribed in these trials varied from 5 to 150 mg/days, and the duration of zinc supplementation ranged from 1 to 12 months.

In terms of findings, three trials indicated that zinc supplementation had a significant reducing effect on SBP x trials failed to reach such a significant effect [22–24, 32–34]. With regards to DBP, one study revealed a significant reduction [20], and others failed to find any favorable effect on DBP after zinc supplementation [21–24, 31–34].

Pooled effect of zinc supplementation on SBP

The effect of zinc supplementation on SBP was examined in nine trials, including a total of 544 participants. Our analysis based on the random-effects model revealed that zinc supplementation resulted in a significant reduction in SBP (WMD − 1.49 mmHg; 95% CI − 2.85 to − 0.13; $P=0.03$), with no evidence of heterogeneity between studies ($I^2=24.2\%$, $P=0.22$) (Fig. 2a).

In our subgroup analyses, a significant reduction in SBP was observed in trials that used the gluconate form (WMD − 2.59 mmHg; 95% CI − 5.18, − 0.06, $P=0.05$), but not in studies that used the sulfate (WMD − 1.16 mmHg; 95% CI − 2.42, 0.10; $P=0.07$) or elemental form of zinc (WMD − 1.55 mmHg; 95% CI − 3.47, 0.37, $P=0.11$). SBP was also decreased in trials that administered zinc supplements at the dose of < 50 mg/days (WMD − 1.90 mmHg; 95% CI − 3.40, − 0.40; $P=0.01$), in studies with a duration of ≥ 3 months (WMD − 2.46 mmHg; 95% CI − 4.11, − 0.80; $P=0.004$), those that were done on overweight subjects ($25 \le$ BMI < 30 kg/m^2) (WMD − 1.41 mmHg; 95% CI − 2.43, − 0.39; $P=0.007$), trials that were performed in subjects with a mean age of ≥ 50 years (WMD − 1.90 mmHg; 95% CI − 3.41, − 0.39; $P=0.01$), those that were performed in patients with insulin resistance-related disorders (WMD − 1.77 mmHg; 95% CI − 2.82, − 0.73; $P=0.001$), studies that were done in both genders (WMD − 1.84 mmHg; 95% CI − 3.39, − 0.28, $P=0.02$), and trials that carried out in Middle-East countries (WMD − 1.60 mmHg; 95% CI − 2.81, − 0.39, $P=0.01$) (Table 3).

Pooled effect of zinc supplementation on DBP

Nine eligible trials, including a total of 544 subjects, examined the effect of zinc supplementation on DBP. Combining their findings based on the random-effects model, there was no significant effect of zinc supplementation on DBP (WMD − 0.88 mmHg; 95% CI − 2.04 to 0.29, $P=0.14$); however, between-study heterogeneity was high ($I^2=60.5\%$, $P=0.009$) (Fig. 2b). Subgroup analysis based on (type of zinc supplements [$I^2=0.0\%$, $P=0.32$], study duration [$I^2=43.0\%$, $P=0.15$], baseline BMI [$I^2=0.0\%$, $P=0.36$], and health status of subjects [$I^2=6.4\%$, $P=0.37$]) explained this heterogeneity. We found a significant reduction in DBP when zinc supplementation was done at the dosage of ≥ 50 mg/days (WMD − 0.70 mmHg; 95% CI − 1.28, − 0.12; $P=0.01$). In addition, the significant effect on DBP was seen in trials that used the sulfate form (WMD − 0.73 mmHg; 95% CI − 1.30, − 0.16; $P=0.01$), those with a duration of < 3 months (WMD − 0.70 mmHg; 95% CI − 1.26, − 0.14; $P=0.01$), those that enrolled overweight subjects ($25 \le$ BMI < 30 kg/m^2) (WMD − 0.65 mmHg; 95% CI − 1.18, − 0.12; $P=0.01$), trials that were performed in subjects with a mean age of ≥ 50 years (WMD − 1.09 mmHg; 95% CI − 2.05, − 0.14; $P=0.02$), those that were performed on patients with insulin-resistance–related disorders (WMD − 0.62 mmHg; 95% CI − 1.15, − 0.10; $P=0.02$), in studies that were done on both genders (WMD − 1.33 mmHg, 95% CI − 2.34, − 0.32, $P=0.009$), and in trials that were performed in Middle-East countries (WMD − 0.83 mmHg; 95% CI − 1.39, − 0.27, $P=0.003$).

Dose–response effect of zinc on blood pressure

Following the dose–response assessment, we find a significant non-linear association between zinc supplementation dosage and SBP ($P_{\text{nonlinearity}}=0.05$), and greater reduction was seen when prescribed at doses under 25 mg/days elemental zinc. A significant non-linear association was also found for DBP ($P_{\text{nonlinearity}}=0.02$), and the greatest reduction was seen at doses higher than 50 mg/days elemental zinc.

Table 2 Demographic characteristics of the included studies

References	Country	Study design	Health status of subjects	Gender	Sample size zinc/placebo	Duration (month)	Mean age (year)	Baseline BMI (kg/m^2)	Intervention		Results
									Treatment group	Control group	
Afkhami-Ardekani [31]	Iran	Randomized, placebo-controlled parallel trial	Type 2 diabetes	Both	20/20	1.5	52.6	27.6	660 mg/day Zinc sulfate (150 mg elemental zinc)	Placebo	Significant reduction in SBP
Parham [32]	Iran	Randomized, double-blind, placebo-controlled, crossover trial	Type 2 diabetic patients	Both	39/39	6	54.9	33.3	132 mg/day zinc sulfate (30 mg elemental zinc)	30 mg of lactose	No significant change
Tabrizi [34]	Iran	Randomized, double-blind, placebo-controlled parallel trial	Women with polycystic ovary syndrome	Females	30/30	2	27.1	29.3	50 mg/day Zinc sulfate (12 mg elemental zinc)	Placebo (corn starch)	No significant change
Seet [22]	Singapore	Randomized, double-blind, placebo-controlled parallel trial	Type 2 Diabetic Patients	Males	20/20	3	55	26	240 mg/day zinc gluconate (35 mg elemental zinc)	Placebo (99% microcrystalline cellulose, 1% magnesium stearate)	No significant change
Kim [23]	Korea	Randomized, placebo-controlled parallel trial	Obese Korean women	Females	20/20	2	25	28.2	30 mg/day tablets of zinc gluconate (5 mg elemental zinc)	Placebo (free zinc starch)	No significant change
Ranasinghe [20]	Sri Lanka	Randomized, double-blind, placebo-controlled parallel trial	Pre-diabetes	Both	73/65	12	51.9	25.5	20 mg/day elemental Zinc	Placebo	Significant reduction in SBP and DBP
Naghizadeh [21]	Iran	Randomized, double-blind, placebo-controlled parallel trial	Diabetic retinopathy	Both	23/22	3	57.4	27.7	50 mg/day Zinc gluconate (7 mg elemental zinc)	Placebo (maltodextrin; 30 mg)	Significant reduction in SBP
Suliburska [24]	Poland	Randomized, placebo-controlled parallel trial	Hypertensive patients	Both	35/30	1	53.6	33.6	15 mg/day elemental Zinc	Placebo	No significant change

Table 2 (continued)

References	Country	Study design	Health status of subjects	Gender	Sample size zinc/placebo	Duration (month)	Mean age (year)	Baseline BMI (kg/m^2)	Intervention		Results
									Treatment group	Control group	
Sadeghi [33]	Iran	Randomized, single-blind, placebo-controlled parallel trial	Patients under Hemodialysis	Both	17/21	2	55.9	< 30	220 mg/day zinc sulfate (50 mg elemental zinc)	220 mg corn starch	No significant change

SBP systolic blood pressure, *DBP* diastolic blood pressure

(Fig. 3). In addition, the duration of zinc administration was not significantly associated with SBP ($P_{\text{nonlinearity}} = 0.76$) and DBP ($P_{\text{nonlinearity}} = 0.59$) (Fig. 4).

Sensitivity analysis and small-study effects

To identify the influence of a single study on the overall, we re-analyzed the data. The pooled results of SBP and DBP were robust in the leave-one-out sensitivity analysis.

Visual inspection of the funnel plots revealed no evidence of asymmetry *i* (Fig. 5). These observations were confirmed by the use of Egger's regression tests for SBP ($P = 0.85$), and DBP ($P = 0.61$), indicating no evidence of small-study effects.

Discussion

In this systematic review and meta-analysis, we summarized data from nine randomized trials, retrieving a total of 544 patients from different geographical settings (Iran, Singapore, Korea, Sri Lanka, and Poland). Although there was some observational studies in our initial search, we restricted the meta-analysis to RCTs only, because the evidence provided by these studies is of high quality. We found that zinc supplementation significantly decreased SBP (WMD − 1.49 mmHg; 95% CI − 2.85 to − 0.13; $P = 0.03$), without any significant effect on DBP (WMD − 0.88 mmHg; 95% CI − 2.04 to 0.29; $P = 0.14$).

Zinc is a fundamental chemical element for humans and is widely involved in physiological processes, such as protein, lipid, nucleic acid metabolism, and gene transcription [35]. The precise relationship between serum zinc concentration and blood pressure regulation is still unclear. However, there have been a few theories related to potential abnormalities caused by zinc deficiency [36]. Several studies reported the relationship between zinc and hypertension. However, the results are controversial. In accordance with other findings, in a Turkish and an Italian study, serum zinc concentration was lower in hypertensive patients compared to normotensive patients [37, 38]. Kim et al. in a cross-sectional study showed that dietary zinc intake was inversely correlated with SBP, but no correlation was seen with DBP, in obese women [18]. In an animal model, Tomat et al. reported that moderate zinc restriction was associated with increased arterial blood pressure in male rats [39]. Taittonen et al. in a 6-year follow up study found that dietary zinc was not linked with blood pressure in healthy children [40]. In another population-based cohort study, it was suggested that dietary zinc intake had no association with incident hypertension in men [41]. As these studies were performed on different subjects with different study designs, direct comparisons of their findings are not possible.

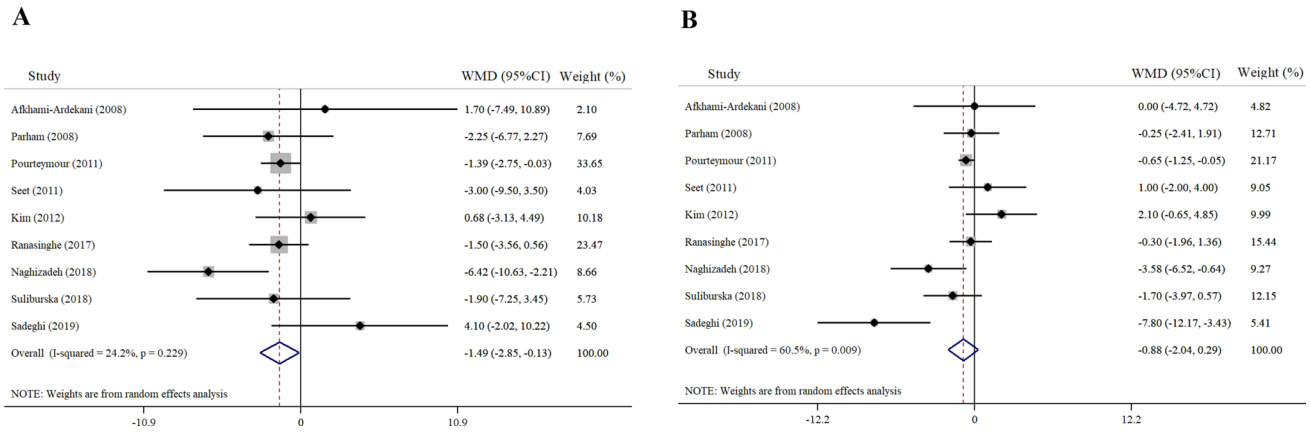

Fig. 2 Forest plot presenting weighted mean difference and 95% confidence intervals (CIs) for the effect of zinc supplementation on **a** SBP and **b** DBP

It is well established that zinc contributes to nitric oxide synthase (NOS) activity, an important generator of nitric oxide (NO) [42]. Thus, in a state of zinc deficiency, decreased NOS activity and a lower artery wall regulation are observed, resulting in endothelial dysfunction and the development of hypertension. Nitric oxide regulates multiple functions in human beings, such as body temperature, neurotransmission, and, most importantly, vascular tone [43, 44]. When NO is endogenously produced by the endothelium, it diffuses into the adjacent smooth muscle, and by binding to the heme moiety of cytosolic guanylate cyclase, it produces increasing intracellular levels of guanosine monophosphate, which ultimately promotes vasodilation [43]. Additionally, cardiovascular peptides (angiotensin converting enzyme and neutral endopeptidases) are zinc-dependent [45]. These enzymes are directly related to blood pressure levels and, during an impaired state, the median blood pressure might alter from normal levels [46]. Finally, zinc concentration has a directly proportional association with superoxide scavenger activity. Superoxide scavengers are bioactive substances that reduce blood pressure [47, 48]. Therefore, sufficient zinc consumption is essential to provide endothelium function and adequate blood pressure levels, due to the unique biochemical properties of zinc.

Most oral supplements have a relative nonlinear dose–response pattern and, as a consequence, an increased dosage is not directly associated with a higher response [49, 50]. In our analysis, we observe a non-linear dose–response relationship between dosage of zinc supplements and SBP or DBP. Additionally, duration of zinc supplementation was not significantly associated in a nonlinear fashion with SBP and DBP. As blood pressure levels are affected by multiple variables such as neuro-endocrine regulation, and the renal-endocrine system [51], lack of a significant non-linear association is not unexpected.

Interestingly, despite the relatively common adverse effects associated with zinc supplementation, we found a limited number of studies that included this aspect. Zinc supplementation can cause gastrointestinal disorders (i.e., indigestion, diarrhea, nausea, and vomiting) and headache [52]. Furthermore, long-term zinc intake can lead to copper deficiency, which is heavily involved in cell oxidation and neural signaling systems [35]. As a consequence, hematological and neurological abnormalities can be the result of inadequate and prolonged zinc supplementation. Regardless of these effects and the international clinical guidelines associated with the assessment of serum zinc level, a few physicians and health professionals request blood analysis for assessment of zinc status [53]. It is crucial to prescribe zinc supplementation only after measurement of the serum zinc levels [36]. Furthermore, zinc supplements have pharmacological interactions with certain antibiotics (especially quinolone and tetracyclines), penicillamine (a rheumatoid arthritis drug), and thiazide diuretics (a blood pressure controller) [54, 55]. Despite these concerns, zinc supplementation has been found to benefit human health.

Our meta-analysis has some advantages. First, to the best of our knowledge, this is the first meta-analysis of RCTs evaluating the impact of zinc supplementation on blood pressure in adults. Second, since our study only involved RCTs, the causal inference of our findings is strong. Third, to explore the effects across different subgroups and detect possible sources of heterogeneity, subgroup analysis was performed. However, limitations of our study include the relatively restricted number of randomized-controlled trials. Moreover, we had some sort of between-study heterogeneity in some of our analyses. Thus, there is a clear need for researchers to conduct high-quality randomized-controlled trials, at different dosages, while also analyzing any adverse effects following zinc supplementation. In addition, the effect of zinc supplementation on blood

Table 3 Meta-analysis displaying the effect of zinc supplementation on blood pressure based on several subgroups

Study group	Trials, *n*	Meta-analysis		Heterogeneity		
		WMD (95% CI), mmHg	*p* values	I^2 (%)	*p*-Within group	*p* for between subgroup heterogeneity
SBP						
Zinc dosage (mg/day)						0.45
< 50	5	− 1.90 (− 3.40, − 0.40)	0.01	37.2	0.17	
≥ 50	4	− 1.14 (− 2.43, 0.14)	0.08	17.3	0.30	
Type of zinc supplement						0.62
Sulfate	4	− 1.16 (− 2.42, 0.10)	0.07	15.3	0.31	
Gluconate	3	− 2.59 (− 5.18, − 0.06)	0.05	66.8	0.05	
Elemental	2	− 1.55 (− 3.47, 0.37)	0.11	0.0	0.89	
Study duration (month)						0.14
< 3	5	− 0.93 (− 2.15, 0.27)	0.13	3.8	0.38	
≥ 3	4	− 2.46 (− 4.11, − 0.80)	0.004	29.8	0.23	
Baseline BMI						0.70
Overweight (25 ≤ BMI < 30)	7	− 1.41 (− 2.43, − 0.39)	0.007	42.3	0.10	
Obese (≥ 30)	2	− 2.10 (− 5.55, 1.34)	0.23	0.0	0.92	
Mean age						0.45
< 50 years	2	− 1.15 (− 2.43, 0.12)	0.07	0.6	0.31	
≥ 50 years	7	− 1.90 (− 3.41, − 0.39)	0.01	33.3	0.17	
Health status of subjects						0.10
Insulin resistance–related disorders[a]	6	− 1.77 (− 2.82, − 0.73)	0.001	13.6	0.32	
Other	3	0.68 (− 2.07, 3.45)	0.62	4.5	0.35	
Gender						0.71
Male	1	− 3.00 (− 9.49, 3.49)	0.36	–	–	
Female	2	− 1.15 (− 2.44, 0.13)	0.08	0.31	0.6	
Both	6	− 1.84 (− 3.39, − 0.28)	0.02	0.11	43.7	
Geographical region						0.90
Middle-east	5	− 1.60 (− 2.81, − 0.39)	0.01	0.06	55.8	
East Asia	3	− 1.15 (− 2.89, 0.60)	0.19	0.52	0.0	
Europe	1	− 1.90 (− 7.24, 3.44)	0.48	–	–	
DBP						
Zinc dosage (mg/day)						0.88
< 50	5	− 0.61 (− 1.60, 0.37)	0.22	54.4	0.06	
≥ 50	4	− 0.70 (− 1.28, − 0.12)	0.01	73.8	0.009	
Type of zinc supplement						0.75
Sulfate	4	− 0.73 (− 1.30, − 0.16)	0.01	71.1	0.01	
Gluconate	3	− 0.07 (− 1.74, 1.59)	0.93	76.0	0.01	
Elemental	2	− 0.78 (− 2.12, 0.55)	0.24	0.0	0.32	
Study duration (month)						0.83
< 3	5	− 0.70 (− 1.26, − 0.14)	0.01	73.2	0.005	
≥ 3	4	− 0.57 (− 1.69, 0.53)	0.31	43.0	0.15	
Baseline BMI						0.73
Overweight (25 < BMI < 30)	7	− 0.65 (− 1.18, − 0.12)	0.01	68.9	0.004	
Obese (≥ 30)	2	− 0.93 (− 2.50, 0.62)	0.24	0.0	0.36	
Mean age						0.31
< 50 years	2	− 0.52 (− 1.11, 0.06)	0.08	72.7	0.05	
≥ 50 years	7	− 1.09 (− 2.05, − 0.14)	0.02	61.5	0.01	
Health status of subjects						0.49
Insulin resistance-related disorders[a]	6	− 0.62 (− 1.15, − 0.10)	0.02	6.4	0.37	

Table 3 (continued)

Study group	Trials, *n*	Meta-analysis		Heterogeneity		
		WMD (95% CI), mmHg	*p* values	I^2 (%)	*p*-Within group	*p* for between subgroup heterogeneity
Other	3	−1.21 (−2.84, 0.41)	0.14	86.2	0.001	
Gender						0.21
Male	1	1.00 (−2.00, 4.00)	0.51	–	–	
Female	2	−0.52 (−1.11, 0.06)	0.08	72.7	0.05	
Both	6	−1.33 (−2.34, −0.32)	0.009	63.0	0.02	
Geographical region						0.12
Middle-east	5	−0.83 (−1.39, −0.27)	0.003	71.5	0.008	
East Asia	3	0.46 (−0.82, 1.74)	0.48	12.8	0.32	
Europe	1	−1.70 (−3.97, 0.57)	0.14	–	–	

SBP systolic blood pressure, *DBP* diastolic blood pressure, *WMD* weighted mean difference

[a]Including polycystic ovarian syndrome, type 2 diabetes mellitus, prediabetes, and diabetic retinopathy

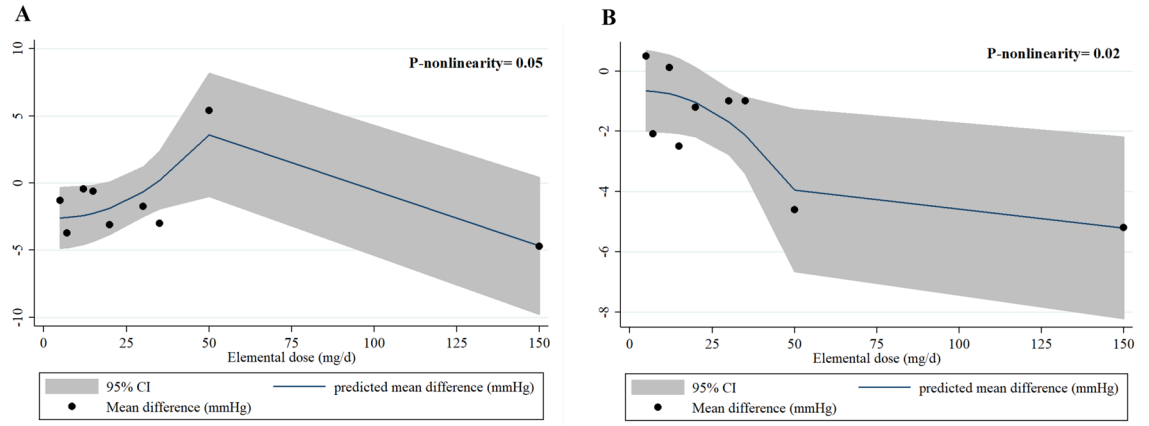

Fig. 3 Non-linear dose–response relations between zinc dosage (g/day) and unstandardized mean difference in **a** SBP and **b** DBP. The 95% CI is revealed in the shaded regions

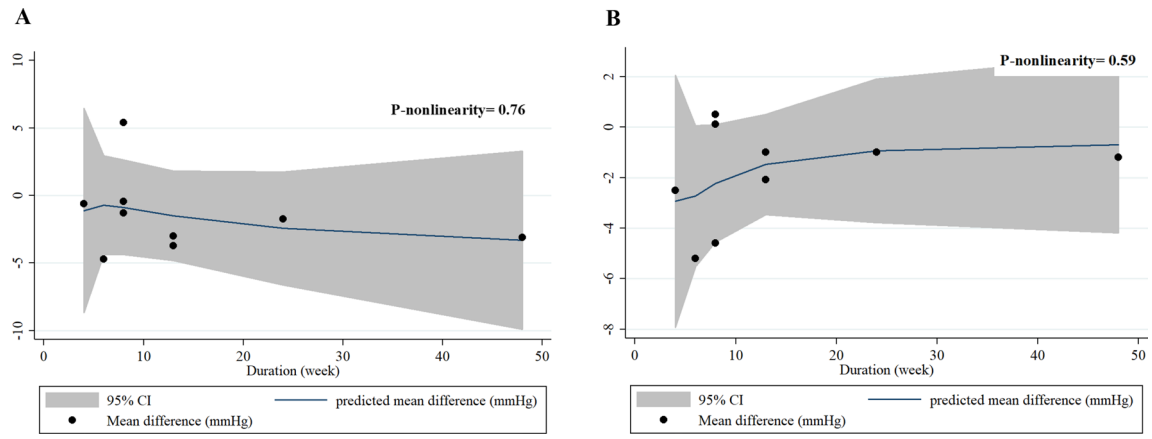

Fig. 4 Non-linear dose–response relations between duration of treatment (weeks) and unstandardized mean difference in **a** SBP and **b** DBP. The 95% CI is revealed in the shaded regions

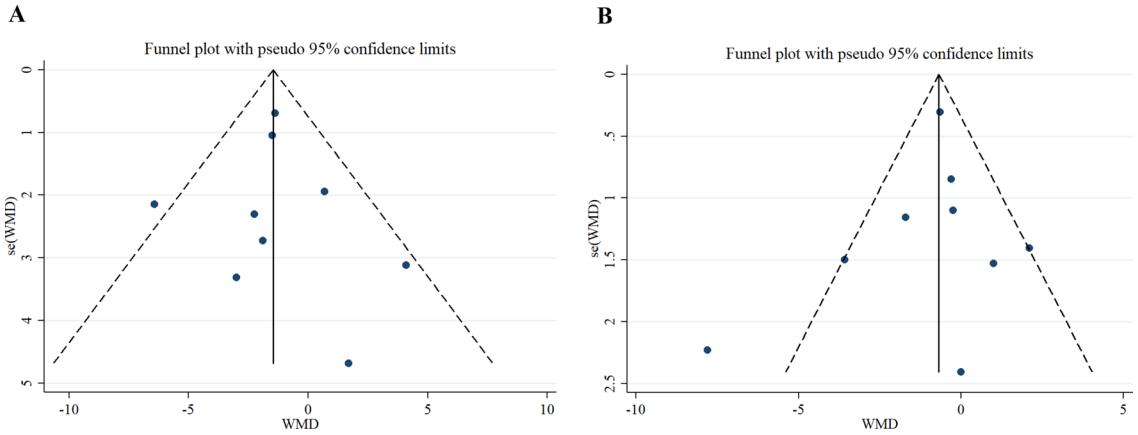

Fig. 5 Funnel plot indicating publication bias in the studies reporting the impact of zinc supplementation on **a** SBP and **b** DBP

pressure may be dependent on the pre-intervention zinc status and change in circulating zinc concentrations from the baseline. The generalizability of our findings is limited due to the fact that all included studies with the exception of one study were performed in the Asian countries.

Conclusion

In conclusion, zinc supplementation might have a favorable effect on SBP, but not on DBP. Our analyses indicated that zinc supplementation in overweight and older subjects with insulin-resistance-related disorders may lower SBP and DBP. However, additional high-quality clinical trials with larger sample sizes and adequate durations are needed to provide definite evidence of the beneficial effects of zinc consumption on blood pressure. Our findings provide further evidence for physicians and medical researchers on the efficacy of alternative treatments for patients with hypertension.

Author contributions SMM and AE conceived the study. TM and AM carried out the literature search and screening articles. MDM and HKV performed data extraction and quality assessment, independently. SMM, JR, and TM analyzed and interpreted data and wrote the manuscript. AE supervised the study. The final version of manuscript has been read and approved by all authors.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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