REVIEW

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; $P = 0.002$; $I^2 = 11.4\%$] 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; $P = 0.03$; $I^2 = 31.5\%$). 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. *Adv Nutr* 2020;11:398–411.

Keywords: zinc, obesity, body weight, body mass index, dose–response, meta-analysis

Introduction

Overweight and obesity are increasing rapidly and affect over one-third of the world's population (1). Obesity increases the risk of chronic diseases such as sleep disorders (2), joint and bone diseases (3, 4), psychiatric disorders (5), type 2 diabetes (6), hypertension (7), cardiovascular disease (8), and some cancers (9, 10). Although obesity is largely preventable, it is difficult to treat given its multifactorial nature (11). Weight management strategies include dietary modification, increased physical activity (12), and medical or surgical management for severe and morbid obesity (13, 14).

Positive energy balance has been established as the most important factor for developing obesity, but micronutrient imbalance may play a contributing role. Despite excessive energy intake, individuals with overweight or obesity have a higher prevalence of micronutrient deficiencies than individuals with normal weight (15–17). In order of increasing prevalence of deficiency, such micronutrients include zinc, vitamin C, selenium, and vitamin D (18, 19).

Zinc plays an important role in enzyme function and metabolic regulation (20), and is a significant modulator of

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Abbreviations used: BF%, body fat percentage; BW, body weight; FFM, fat-free mass; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HC, hip circumference; HD, hemodialysis; MD, mean difference; MUAC, midupper arm circumference; RCT, randomized controlled trial; WC, waist circumference; WHR, waist-to-hip ratio; WMD, weighted mean difference.

appetite and eating behaviors (21, 22). Hypozincemia has been suggested to contribute to insulin resistance and obesity through decreased insulin secretion (23–26). Zinc has important functions in appetite regulation and can decrease food intake, for example, by increasing leptin production and subsequently decreasing hypothalamic neuropeptide Y (27, 28). Zinc can also increase food intake, by activating G-protein coupled receptor 39 (GPR39) in the enteric nervous system and increasing gastrointestinal motility by increasing serotonin and galanin production (29–31). Several studies have shown that individuals with obesity have lower serum zinc concentrations (32, 33). A recent meta-analysis of 23 observational studies found that individuals with obesity had lower concentrations of serum zinc than individuals without obesity (34). Low serum zinc concentrations in individuals with obesity may be due to the presence of chronic oxidative stress, which results in increased glucocorticoid production and decreased zinc transporters (33, 35). In addition, expression of zinc transporters can be induced by cytokines released by adipose tissue, altering the distribution of zinc in the body (36). Although it is tempting to propose that zinc supplementation is a useful intervention to tackle obesity, it is difficult to draw a causal inference from a meta-analysis of observational studies.

Several randomized controlled trials (RCTs) have assessed the effects of zinc supplementation on body composition and anthropometric measures, but with controversial findings (37–39). This prompted us to perform a systematic review and meta-analysis of RCTs to investigate whether zinc supplementation affects body composition and anthropometric outcomes in adults.

Methods

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (40) and was registered in the PROSPERO international prospective register of systematic reviews as CRD42018093235.

Search strategy

A systematic search was conducted in PubMed, Scopus, ISI Web of Science, and the Cochrane Library from database inception to August 2018, without language restrictions. We used a combination of keywords relevant to zinc, body composition, anthropometric and cardiometabolic measures, and study design to identify related publications. Further details about the search strategy are provided in **Supplemental Table 1**. The reference lists of all eligible studies were manually checked to find additional relevant articles.

Inclusion criteria

Titles and abstracts of all retrieved articles were evaluated independently by 2 reviewers (SA and OT, separately). Original RCTs (either parallel or crossover designs) were considered eligible for inclusion in the present meta-analysis if they *1*) were conducted in adult human subjects; *2*) compared the effect of supplementation with zinc or zinc-fortified foods with a control group; and *3*) reported changes in body composition or anthropometric measures including body weight (BW), BMI, hip circumference (HC), waist circumference (WC), waist-to-hip ratio (WHR), body fat percentage (BF%), fat-free mass (FFM), midupper arm circumference (MUAC), or any related measures as the outcome of interest. Studies reporting weight-related measures as primary or secondary outcomes were included in the meta-analysis.

Exclusion criteria

We excluded trials if they *1*) were conducted in subjects under the age of 18 y (children and adolescents) or in pregnant or lactating women; *2*) did not have placebo or untreated control groups; *3*) used supplements as placebo; or *4*) applied any other intervention to only the intervention or control group. Discrepancies were resolved by discussion with the corresponding author (SS).

Data extraction

Two reviewers (SA and OT) extracted the following information from eligible studies: first author's name, year of publication, study location, age of participants, sex of participants, follow-up duration, study design, number of participants in the intervention and control groups, type of zinc supplementation, dose of zinc supplementation, outcome assessment method (measured or self-reported), and means and SDs of body composition and anthropometric measures before and after the intervention or mean differences (MDs) and SDs during the follow-up period. Corresponding authors were contacted to provide missing information (37, 41–43). For trials that evaluated multiple doses of zinc supplementation, we included the highest dose in the analysis (44, 45). Data were cross-checked to minimize potential errors, and disagreements were resolved through discussion with the corresponding author (SS).

Risk of bias

The Cochrane risk of bias tool for RCTs was used to assess each study as having low, high, or unclear risk of bias on 6 criteria: selection bias, performance bias, detection bias, attrition bias, reporting bias, and bias due to problems not covered elsewhere (46). Studies were labelled as good quality if all criteria were met (i.e., low risk of bias for each domain), fair quality if 1 criterion was not met or 2 criteria were unclear, or poor quality if $\geq$2 criteria were listed as high or unclear risk of bias (46).

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of evidence for each outcome based on the following domains: assessed risk of bias, publication bias, imprecision of results, heterogeneity, and indirectness of evidence (47–49). The quality of evidence was categorized as high, moderate, low, and very low.

Statistical analyses

We examined the effect of zinc supplementation/fortification on change in the following outcomes: *1*) BW (kg); *2*) BMI (kg/m^2); *3*) WC (cm); *4*) HC (cm); *5*) WHR; and *6*) BF%. Meta-analysis was only performed for outcomes reported by ≥3 independent studies. The dose of elemental zinc was calculated from the zinc compounds and mineral zinc content used for analysis. The MDs in anthropometric measures between the intervention (zinc supplementation) and placebo or control groups and their 95% CIs were used as the effect sizes in the meta-analysis. Weighted mean differences (WMDs) and their corresponding SDs were estimated using the DerSimonian and Laird random-effects model (50). For studies in which SD changes from baseline were missing, we calculated SEs and then converted them into SDs based on the formula provided in the Cochrane Handbook of Systematic Reviews (51). We used a correlation coefficient of 0.99 for BW (37–39, 42, 44, 45, 52–64), 0.93 for BMI (39, 41, 42, 45, 52–63, 65–69), and 0.5 for other outcomes, as reported in the studies. Because of the high variation in the length of interventions (range: 4–48 wk), an additional meta-analysis was conducted based on the change in the outcomes normalized for study duration (change per week). Furthermore, we explored the potential nonlinear effects of zinc dosage (in milligrams per day) on BW and BMI using fractional polynomial models (70). Data were insufficient to perform dose–response analyses for other outcomes. Statistical heterogeneity was investigated with the Cochran's *Q* test and the I^2 statistic (I^2) (71). Prespecifed subgroup analyses were performed by sex (male, female), duration of intervention (≤8 wk, >8 wk), baseline BMI (nonoverweight defined as BMI ≤18.5 to 24.9 kg/m^2 and overweight or obese defined as BMI >24.9 kg/m^2), type of zinc supplementation (sulfate, gluconate, aminochelate), dosage of zinc supplementation (<40 mg/d, ≥40 mg/d), and health status of subjects [healthy, insulin resistance–related disorders, hemodialysis (HD), and other conditions] to determine potential sources of heterogeneity for BW, BMI, and WC. There was an insufficient number of studies to conduct subgroup analyses for other outcomes. Sensitivity analyses were conducted by excluding 1 study or a group of studies at a time. Publication bias was assessed by visual inspection of funnel plots for outcomes with ≥10 studies, and plot symmetry was assessed statistically using Egger's regression asymmetry and adjusted rank correlation tests (72). When publication bias was present, Duval and Tweedie's trim-and-fill method was used to correct funnel plot asymmetry (73). All statistical analyses were performed using STATA version 11.2 (STATA Corp). Two-sided *P* values <0.05 were considered significant.

Results

The flowchart of the literature search is shown in **Figure 1**. The primary search returned 14,174 articles, of which 190 were assessed in full text for inclusion in the meta-analysis. Thirty trials were eligible for inclusion according to the prespecified criteria. Excluded studies are reported in **Supplemental Table 2**.

Risk of bias and quality of evidence

Seven trials were classified as good quality (i.e., low risk of bias) (38, 45, 59, 60, 65, 68, 69), 20 as fair quality (37, 39, 41–44, 52–58, 61–64, 66, 67, 74), and 3 as poor quality (75–77) (**Supplemental Table 3**). Common biases were related to random sequence generation and allocation concealment. All trials were randomized, although most did not explicitly describe the randomization procedure (16, 37, 39, 41, 43, 44, 52, 54–56, 61, 62, 66, 67, 74–77). Seven trials documented adequate allocation concealment (38, 45, 59, 60, 65, 68, 69), whereas in the remainder this information was absent or unclear. Three studies were not considered double-blinded (75–77) because control groups did not receive a placebo. All studies reported details about missing outcome data and all expected outcomes; therefore, there was a low risk of bias for the "incomplete outcome data" and "selective reporting" domains, respectively.

The quality of evidence was assessed using the GRADE system. The quality of evidence was very low for the effect of zinc supplementation on BW, BMI, and HC, and low for that of zinc supplementation on WC, WHR, and BF% (**Supplemental Table 4**).

Study characteristics

The 3 trials identified as poor quality were excluded from subsequent analyses (75–77). The characteristics of the remaining 27 studies are outlined in **Table 1**. All studies assessed the effects of zinc supplementation on anthropometric and body composition measures, but we did not find any study evaluating the effect of supplementation with zinc-fortified foods. Participants included both men and women in 16 trials (39, 41, 42, 45, 52, 53, 58–60, 62–65, 67–69), whereas 10 trials focused exclusively on women (37, 38, 43, 54–57, 61, 66, 74) and 1 trial was restricted to men (44). The length of interventions ranged from 4 to 48 wk, and elemental zinc supplementation dosage ranged from 10 to 150 mg/d. All but 1 trial (67) employed a parallel design. One trial was conducted in zinc-deficient subjects (63). Anthropometric characteristics were measured by 1 member of the research team in all studies. Four trials were conducted in patients undergoing HD (39, 52, 63, 67), 5 were conducted in patients with prediabetes or type 2 diabetes (41, 53, 58, 60, 69), 4 recruited patients with polycystic ovary syndrome (38, 43, 54, 61), and 6 enrolled healthy subjects (44, 45, 55, 57, 59, 74). The remaining trials included patients with atherosclerosis or ischemic stroke (42, 65), anorexia nervosa (37), postmenopausal osteoporosis (56), pulmonary tuberculosis (68), depressive symptoms (62), hypothyroidism (66), and head and neck cancers (64).

Meta-analysis

BW.

Nineteen trials (967 participants) reported the effect of zinc supplementation on BW (37–39, 42, 44, 45, 52–64). The overall analysis revealed no significant association between zinc supplementation and change in BW; however, between-study heterogeneity was high (WMD = 0.04 kg; 95% CI: −0.36,

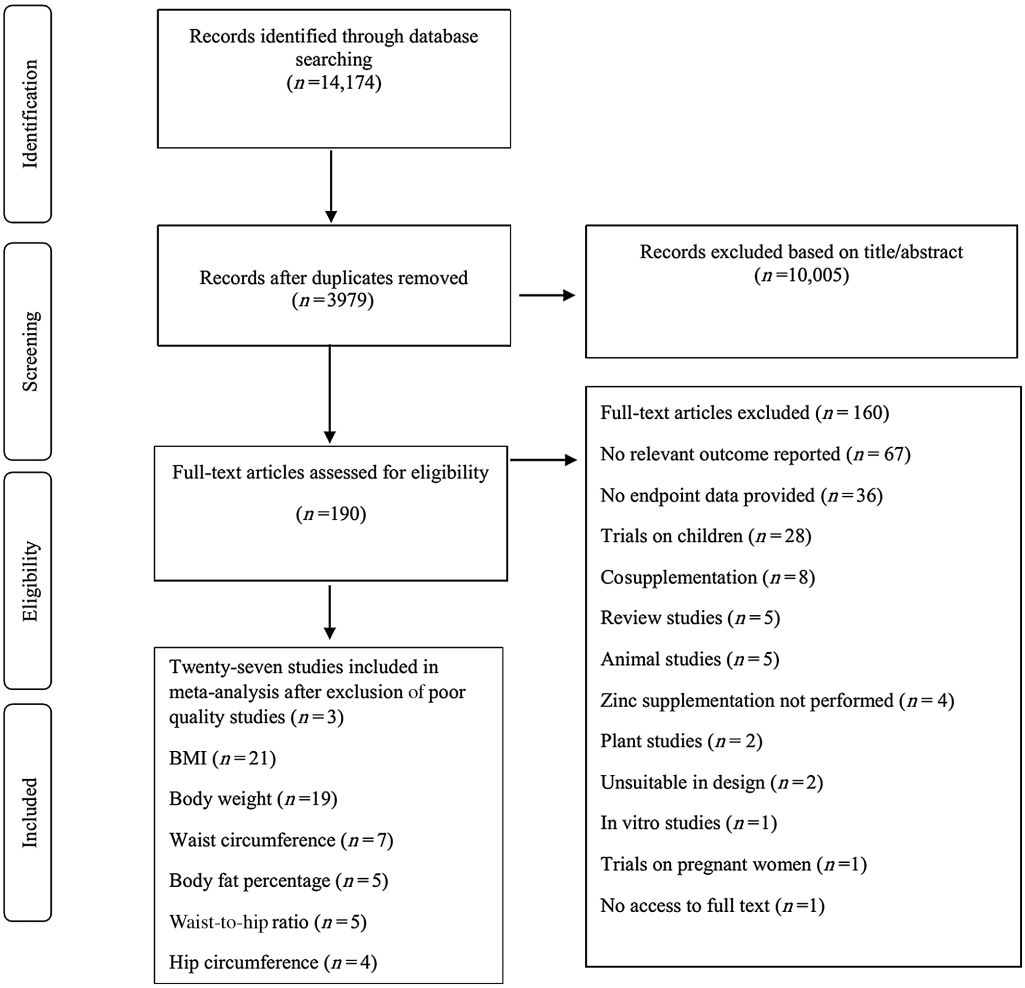

FIGURE 1 Flow diagram of the study selection process.

0.45 kg; $P = 0.83$; $I^2 = 83.6\%$; P-heterogeneity < 0.001) (**Figure 2**). Subgroup analysis based on the health status of subjects considerably reduced the heterogeneity (**Table 2**) and showed that zinc supplementation is associated with an increase in BW in patients undergoing HD compared with controls (WMD = 1.02 kg; 95% CI: 0.38, 1.65 kg; $P = 0.002$; $I^2 = 11.4\%$; P-heterogeneity = 0.32). Furthermore, we found that BW was significantly reduced after zinc supplementation in subjects that are overweight/obese but otherwise healthy (WMD = −0.55 kg; 95% CI: −1.06, −0.04 kg; $P = 0.03$; $I^2 = 31.5\%$; P-heterogeneity = 0.21). The nonlinear dose–response analysis failed to show a significant effect of zinc supplementation dosage on BW (P-nonlinearity = 0.17) (**Supplemental Figure 1**).

BMI.

In total, 21 trials (1230 participants) examined the effect of zinc supplementation on BMI (39, 41, 42, 45, 52–63, 65–69). In the pooled analysis, there was no significant effect of zinc supplementation on BMI, but there was significant between-study heterogeneity (WMD = 0.00 kg/m^2; 95% CI: −0.17, 0.18 kg/m^2; $P = 0.97$; $I^2 = 56.9\%$; P-heterogeneity = 0.001) (**Figure 3**). Subgroup analyses identified the health status of subjects as an important source of heterogeneity (**Table 3**). Nonlinear dose–response meta-analysis revealed a significant effect of zinc supplementation dosage on BMI (P-nonlinearity = 0.001) (**Supplemental Figure 2**).

WC.

Pooling effect sizes from 7 trials (456 participants) (43, 57, 59, 61, 65, 69, 74) revealed no significant effect of zinc supplementation on WC, with no evidence of between-study heterogeneity (WMD = −0.09 cm; 95% CI: −0.66, 0.48 cm; $P = 0.76$; $I^2 = 0.0\%$; P-heterogeneity = 0.97) (**Figure 4** and **Supplemental Table 5**).

HC.

Meta-analysis of 4 trials (286 participants) (43, 61, 69, 74) found that zinc supplementation had no significant effect on HC with no heterogeneity between studies (WMD = 0.05 cm; 95% CI: −0.61, 0.71 cm; $P = 0.87$; $I^2 = 0.0\%$; P-heterogeneity = 0.81) (**Supplemental Figure 3**).

TABLE 1 Characteristics of good- and fair-quality trials that investigated the effect of zinc supplementation on anthropometric and body composition measures in adults and were eligible for inclusion in the meta-analysis[1]

Authors	Participants (*n*), sex	Mean age (y)	Country	Health status of subjects	Zinc deficiency	Outcomes	Zinc type (zinc dosage in mg/d)	Duration (wk)	Results
Afkhami-Ardekani et al. (41)	40, M/F	52.6	Iran	T2DM	NM	BMI	Zinc sulfate (660)	6	No significant change
Aquilani et al. (42)	26, M/F	74 (int) 72 (cont)	Italy	Ischemic strokes	NM	Weight, BMI	Zinc sulfate (10)[2]	4	Significant change in weight
Argani et al. (52)	60, M/F	55.6 (int) 55.6 (cont)	Iran	Hemodialysis	NM	Weight, BMI, BF%, FFM	Zinc sulfate (440)	8	Significant increase in BMI and weight in male
Ashghari et al. (53)	60, M/F	45.8	Iran	T2DM and obese	NM	BMI, weight, WHR	Zinc gluconate (30)	12	No significant change
Birmingham et al. (37)	35, F	20.6 (int) 23.8 (cont)	Colombia	Anorexia nervosa	NM	Weight	Zinc gluconate (100)	6	No significant change
Black et al. (44)	22, M	21.3 (int) 21.1 (int) 22.4 (cont)	United States	Healthy	NM	Weight	Zinc gluconate (373 and 560)	12	No significant change
Dias et al. (65)	54, M/F	62	Brazil	Atherosclerosis	NM	BMI, WC	Zinc bis-glycine (30)[2]	16	Significant reduction in WC in int group
Foroozanfard et al. (38)	52, F	24.7 (int) 25.7 (cont)	Iran	PCOS	NM	Weight	Zinc sulfate (220)	8	No significant change
Ghaemmaghami et al. (39)	39, M/F	58 (int) 52 (cont)	Iran	Hemodialysis	NM	Weight, BMI, BF%, FFM	Zinc sulfate (440)	8	No significant change
Jamilian and Zolfi (54)	52, F	24.7 (int) 25.7 (cont)	Iran	PCOS	NM	Weight, BMI	Zinc sulfate (220)	8	No significant change
Jamilian et al. (43)	48, F	—	Iran	PCOS	NM	Weight, BMI, WC, HC	Zinc sulfate (220)	8	No significant change
Kim and Ahn (55)	40, F	20.8 (int) 20.8 (cont)	South Korea	Obesity	NM	Weight, BMI, BF%	Zinc gluconate (30)[2]	8	Significant increase in BF% in cont group
Kim and Lee (74)	40, F	20.8 (int) 20.8 (cont)	South Korea	Obesity	NM	BMI, weight, WC, HC, WHR	Zinc gluconate (30)[2]	8	No significant change
Lin et al. (64)	97, M/F	50 (int) 51 (cont)	Taiwan	Head and neck cancers	NM	Weight	Zinc gluconate (75)[2]	8	No significant change
Mahdaviroshan et al. (56)	60, F	59.5 (int) 56.6 (cont)	Iran	Postmenopausal osteoporotic	NM	Weight, BMI	Zinc sulfate (220)	8	No significant change
Mahmoodianfard et al. (66)	28, F	44.7 (int) 47.8 (cont)	Iran	Hypothyroid	NM	BMI	Zinc gluconate (30)[2]	12	No significant change
Marreiro et al. (57)	56, F	35.5 (int) 33.9 (cont)	Brazil	Obesity	NM	BMI, weight, WC, WHR, BF%	Zinc aminochelate (30)	4	No significant change
Mazani et al. (67)	65, M/F	52.7	Iran	Hemodialysis	NM	BMI	Zinc sulfate (440)	8	No significant change
Momen-Heravi et al. (58)	60, M/F	58.3 (int) 60 (cont)	Iran	T2DM	NM	Weight, BMI	Zinc sulfate (220)	12	No significant change
Pakasi et al. (68)	140, M/F	30.9 (int) 31.4 (cont)	Indonesia	Pulmonary tuberculosis	NM	BMI, BF%, MUAC	Zinc sulfate (15)[2]	24	Significant increase in anthropometrics measures in int group
Payahoo et al. (59)	60, M/F	31 (int) 33 (cont)	Iran	Obesity	NM	Weight, BMI, WC	Zinc gluconate (30)	4	Significant decrease in body weight, BMI, and WC

(*Continued*)

TABLE 1 (*Continued*)

Authors	Participants (*n*), sex	Mean age (y)	Country	Health status of subjects	Zinc deficiency	Outcomes	Zinc type (zinc dosage in mg/d)	Duration (wk)	Results
Pérez et al. (60)	28, M/F	55 (int) 56 (cont)	Chile	T2DM	NM	Weight, BMI	Zinc sulfate (30)[2]	48	No significant change
Pourteymour Fard Tabrizi et al. (61)	60, F	27.1 (int) 26.9 (cont)	Iran	PCOS	NM	BMI, weight, WC, HC, WHR	Zinc sulfate (50)[2]	8	No significant change
Ranasinghe et al. (69)	138, M/F	51.9 (int) 51.7 (cont)	Sri Lanka	Prediabetes	NM	BMI, WC, HC, WHR	Elemental (20)	48	No significant change
Ranjbar et al. (62)	38, M/F	37 (int) 37.5 (cont)	Iran	Depression	NM	Weight, BMI	Zinc sulfate (25)	12	No significant change
Rashidi et al. (63)	55, M/F	56.4 (int) 59 (cont)	Iran	Hemodialysis	D	Weight, BMI	Zinc sulfate (220)	6	No significant change
Venneria et al. (45)	73, M/F	74.5 (int) 75.1 (int) 74 (cont)	Italy	Healthy	NM	Weight, BMI	Zinc gluconate (15 and 30)[2]	24	Significant decrease in body weight in cont group

[1] BF%, body fat percentage; cont, control group; D, deficient; FFM, fat-free mass; HC, hip circumference; int, intervention group; MUAC, midupper arm circumference; NM, not mentioned; PCOS, polycystic ovarian syndrome; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHR, waist-to-hip ratio.
[2] Elemental zinc.

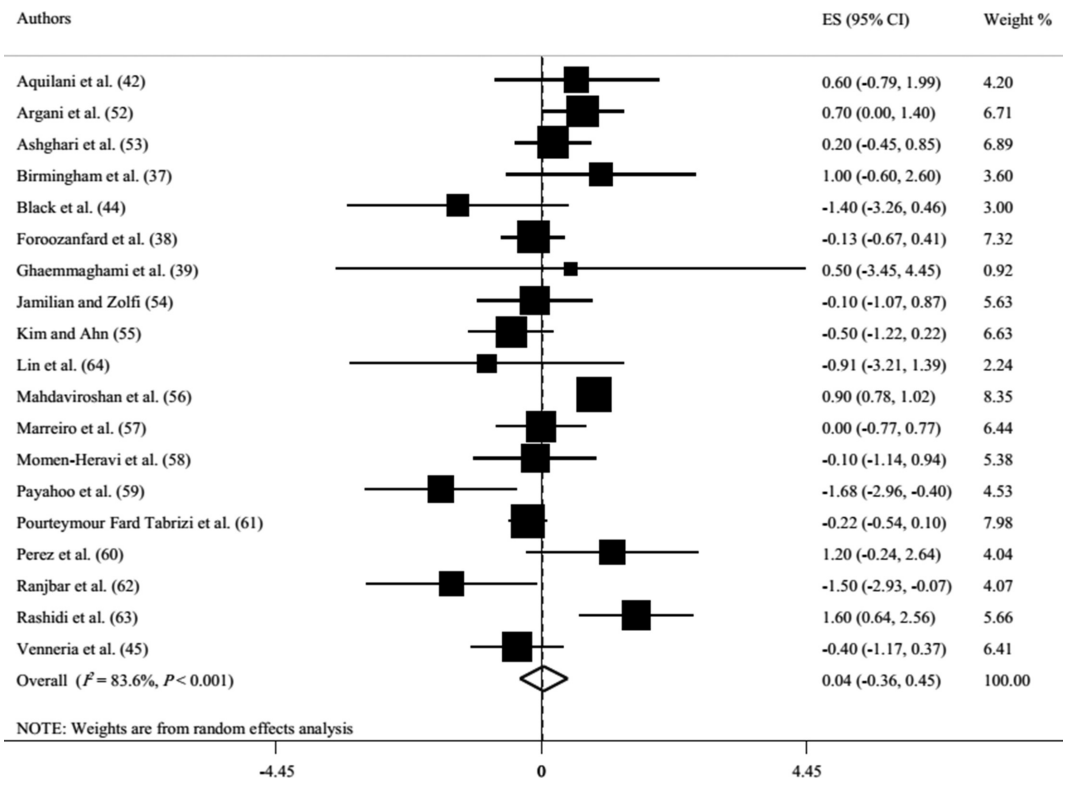

FIGURE 2 Forest plot of randomized controlled trials showing weighted mean differences in weight change (in kilograms) between zinc supplementation and control groups for all eligible studies. Analysis was conducted using a random-effects model. Solid squares depict the weight assigned to the corresponding study; the black diamond represents the summary effect. ES, effect size.

WHR.

We did not find any significant effect of zinc supplementation on WHR in the analysis of 5 trials (354 participants) (53, 57, 61, 69, 74), and there was no evidence of heterogeneity (WMD = −0.00; 95% CI: −0.02, 0.01; $P = 0.61$; $I^2 = 0.0\%$; P-heterogeneity = 0.90) (**Supplemental Figure 4**).

BF%.

Five trials (335 participants) reported data on BF% (39, 52, 55, 57, 68). There was no significant change in BF% and no between-study heterogeneity with zinc supplementation (WMD = −0.30; 95% CI: −1.48, 0.89; $P = 0.62$; $I^2 = 0.0\%$; P-heterogeneity = 0.57) (**Supplemental Figure 5**).

Outcomes not included in the meta-analysis: FFM and MUAC

We found 2 trials on the effect of zinc supplementation on FFM (39, 52) and the results showed no significant effect on FFM. Only 1 eligible trial reported data on MUAC, in which zinc supplementation resulted in a significant improvement in MUAC in malnourished patients with pulmonary tuberculosis (68).

Sensitivity analysis and publication bias

We sequentially excluded 1 study at a time as a sensitivity analysis and found that 1 study (56) had a large impact on the summary estimates of BW and BMI, although this did not affect the significance of the results for BW (WMD = 0.05 kg; 95% CI: −0.36, 0.47 kg; $P = 0.8$; $I^2 = 84.3\%$; P-heterogeneity < 0.001) or BMI (WMD = −0.04 kg/m^2; 95% CI: −0.17, 0.07 kg/m^2; $P = 0.46$; $I^2 = 0.8\%$; P-heterogeneity = 0.44).

Funnel plots revealed some evidence of asymmetry in the meta-analyses of the effect of zinc supplementation on BW (**Supplemental Figure 6**A) and BMI (Supplemental Figure 6B). Tests confirmed these observations for BMI (Begg's test, $P = 0.54$; Egger's test, $P = 0.002$) and BW (Begg's test, $P = 0.48$; Egger's test, $P = 0.007$). However, the trim-and-fill method was applied and the results remained stable.

Additional analyses

We also ran a meta-analysis normalized for the length of interventions. As shown in **Supplemental Tables 6–9**, there was no change in the results, except for the effect of zinc supplementation on change in BW per week in healthy subjects, which became nonsignificant (WMD = −0.06; 95% CI: −0.13, 0.01; $P = 0.1$; $I^2 = 50.7\%$; P-heterogeneity = 0.08).

Discussion

In this systematic review and meta-analysis, we summarized data from 27 RCTs which investigated the effects of zinc supplementation on body composition indexes in adults. The

TABLE 2 Meta-analysis showing the effect of zinc supplementation on body weight (in kilograms) based on several subgroups[1]

		Meta-analysis			Heterogeneity			
Study group	**Studies, *n***	**Participants, *n***	**WMD (95% CI), kg**	***P*-effect**	***Q* statistic**	***P*-within group**	**I^2 (%)**	***P*-between group**
Overall	19	967	0.04 (−0.36, 0.45)	0.83	110.04	<0.001	83.6	—
Sex								0.001
Male	1	18	− 1.40 (−3.26, 0.46)	0.14	0.00	—	—	
Female	7	355	0.09 (−0.50, 0.69)	0.74	67.45	<0.001	91.1	
Both	11	594	0.07 (−0.51, 0.66)	0.80	29.43	0.001	66.0	
Type of zinc supplement								<0.001
Sulfate	11	530	0.31 (−0.18, 0.81)	0.21	68.89	<0.001	85.5	
Gluconate	7	381	− 0.40 (−0.96, 0.15)	0.15	11.21	0.08	46.5	
Aminochelate	1	56	0.00 (−0.76, 0.76)	1.00	0.00	—	—	
Zinc supplemented, mg/d								<0.001
<40	9	416	0.27 (−0.27, 0.81)	0.32	64.20	<0.001	87.5	
≥40	10	551	− 0.19 (−0.67, 0.29)	0.44	18.32	0.03	50.9	
Baseline BMI, kg/m^2								0.63
Nonoverweight (≤24.9)	7	334	0.57 (−0.13, 1.28)	0.11	10.27	0.11	41.6	
Overweight and obese (≥25)	12	633	− 0.14 (−0.63, 0.35)	0.58	99.54	<0.001	88.9	
Study duration, wk								<0.001
Short period (≤8)	13	692	0.16 (−0.31, 0.64)	0.50	85.72	<0.001	86.0	
Long period (>8)	6	275	− 0.22 (−0.84, 0.40)	0.49	10.04	0.07	50.2	
Health status of subjects								<0.001
Healthy overweight/obese	5	245	− 0.55 (−1.06, −0.04)	0.03	5.84	0.21	31.5	
Insulin resistance–related disorders[2]	6	312	− 0.09 (−0.33, 0.14)	0.42	4.48	0.48	0.0	
Hemodialysis	3	154	1.02 (0.38, 1.65)	0.002	2.26	0.32	11.4	
Ischemic strokes	1	26	0.60 (−0.78, 1.98)	0.39	0.00	—	—	
Depression	1	38	− 1.50 (−2.93, −0.07)	0.04	0.00	—	—	
Osteoporosis	1	60	0.90 (0.77, 1.02)	<0.001	0.00	—	—	
Anorexia nervosa	1	35	1.00 (−0.60, 2.60)	0.22	0.00	—	—	
Head and neck cancers	1	97	− 0.91 (−3.21, 1.40)	0.43	0.00	—	—	

[1] All analyses were conducted using a random-effects model. WMD, weighted mean difference.
[2] Including polycystic ovarian syndrome, type 2 diabetes mellitus, and prediabetes.

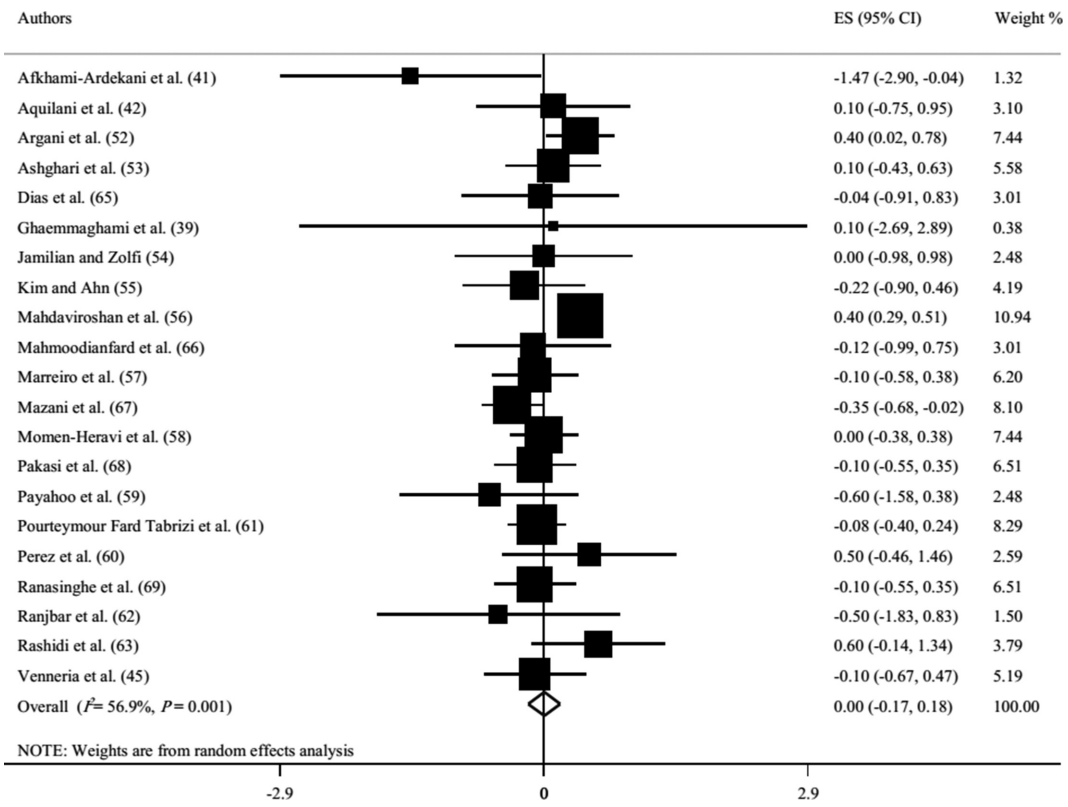

FIGURE 3 Forest plot of randomized controlled trials showing weighted mean differences in BMI change (in kg/m^2) between zinc supplementation and control groups for all eligible studies. Analysis was conducted using a random-effects model. Solid squares depict the weight assigned to the corresponding study; the black diamond represents the summary effect. ES, effect size.

main results of this study showed that zinc supplementation was not associated with a meaningful effect on any weight-related outcome. However, findings from subgroup analyses found that zinc supplementation increased BW by 1.02 kg in subjects undergoing HD and decreased BW by ∼0.5 kg in subjects that are overweight/obese but otherwise healthy when compared with a placebo group. Although, after normalizing for study duration, the result for the effect of zinc supplementation on BW changed to nonsignificant in participants that are overweight/obese but otherwise healthy. The findings of this study provide further support for recommending zinc supplementation for weight management in specific subgroups of the population (e.g., patients undergoing HD or subjects that are overweight/obese but otherwise healthy).

The conclusion that zinc may be a regulator of BW indexes in certain subgroups is supported by the involvement of zinc in the control of appetite and food intake (21, 22). Zinc is involved in the modulation of leptin, a key regulator of energy balance in the central nervous system (29, 78). A recent meta-analysis of 15 observational studies concluded that obese individuals have lower serum zinc concentrations than normal-weight individuals (34). However, this association has only been confirmed in some, not all, clinical trials (37–39).

The present meta-analysis showed that zinc supplementation was associated with a significant reduction in BW in individuals that are overweight/obese but otherwise healthy, and a significant increase in BW in patients undergoing HD. Because the baseline BMI of patients undergoing HD was <25 in all included studies, an explanation for the opposite findings observed in the 2 subgroups may be related to the baseline weight status. However, we did not find any significant association between zinc supplementation and weight change in the subgroup of baseline BMI. Another explanation for the observed results seems to be associated with the health status of participants. Significant between-study heterogeneity was observed in the overall and subgroup analyses, but it decreased obviously when the results were stratified by health status of subjects, suggesting that the effect of zinc supplementation on obesity indexes depends on health status. It should be noted that, after normalization for length of intervention, no significant change in BW was observed. The WMD also was much attenuated. However, there are some limitations to note when interpreting the findings. It seems that weight change pattern is not equal throughout an intervention and it is not reliable when total weight change is divided by the study duration. Moreover, concern arises about the underestimation of treatment effects in long-term studies, when calculating change of BW per

TABLE 3 Meta-analysis showing the effect of zinc supplementation on BMI (in kg/m^2) based on several subgroups[1]

		Meta-analysis			Heterogeneity			
Study group	**Studies, *n***	**Participants, *n***	**WMD (95% CI), kg/m^2**	***P*-effect**	***Q* statistic**	***P*-within group**	**I^2 (%)**	***P*-between group**
Overall	21	1230	0.00 (−0.17, 0.18)	0.97	46.37	0.001	56.9	—
Sex								<0.001
Female	6	296	0.04 (−0.25, 0.35)	0.76	14.62	0.01	65.8	
Both	15	934	− 0.02 (−0.20, 0.16)	0.82	18.68	0.17	25.1	
Type of zinc supplement								0.03
Sulfate	13	723	0.06 (−0.17, 0.30)	0.59	36.07	<0.001	66.7	
Gluconate	5	259	− 0.10 (−0.40, 0.19)	0.47	1.66	0.79	0.0	
Aminochelate	2	110	− 0.08 (−0.50, 0.33)	0.68	0.01	0.90	0.0	
Elemental	1	138	− 0.10 (−0.55, 0.35)	0.66	0.00	—	—	
Zinc supplemented, mg/d								0.001
<40	12	741	− 0.07 (−0.26, 0.10)	0.41	3.69	0.97	0.0	
≥40	9	489	0.07 (−0.21, 0.36)	0.62	32.04	<0.001	75.0	
Baseline BMI, kg/m^2								0.02
Nonoverweight (≤24.9)	5	330	− 0.005 (−0.36, 0.35)	0.97	8.65	0.07	53.7	
Overweight and obese (≥25)	16	900	0.009 (−0.19, 0.20)	0.93	32.47	0.006	53.8	
Study duration, wk								0.009
Short period (≤8)	12	613	0.007 (−0.25, 0.27)	0.96	37.39	<0.001	70.6	
Long period (>8)	9	617	− 0.03 (−0.22, 0.16)	0.74	2.20	0.97	0.0	
Study design								0.001
Parallel	20	1165	0.04 (−0.12, 0.21)	0.59	35.42	0.01	46.4	
Crossover	1	65	− 0.35 (−0.68, −0.17)	0.04	0.00	—	—	
Health status of subjects								<0.001
Healthy overweight/obese	4	227	− 0.17 (−0.47, 0.13)	0.26	0.90	0.82	0.0	
Insulin resistance–related disorders[2]	7	438	− 0.03 (−0.22, 0.15)	0.68	5.49	0.48	0.0	
Hemodialysis	4	219	0.16 (−0.40, 0.72)	0.57	10.94	0.01	72.6	
Cardiovascular events	2	80	0.03 (−0.57, 0.63)	0.91	0.05	0.82	0.0	
Hypothyroidism	1	28	− 0.12 (−0.98, 0.74)	0.78	0.00	—	—	
Depression	1	38	− 0.50 (−1.83, 0.83)	0.46	0.00	—	—	
Osteoporosis	1	60	0.40 (0.28, 0.51)	<0.001	0.00	—	—	
Pulmonary tuberculosis	1	140	− 0.10 (−0.55, 0.35)	0.66	0.00	—	—	

[1] All analyses were conducted using a random-effects model. WMD, weighted mean difference.
[2] Including polycystic ovarian syndrome, type 2 diabetes mellitus, and prediabetes.

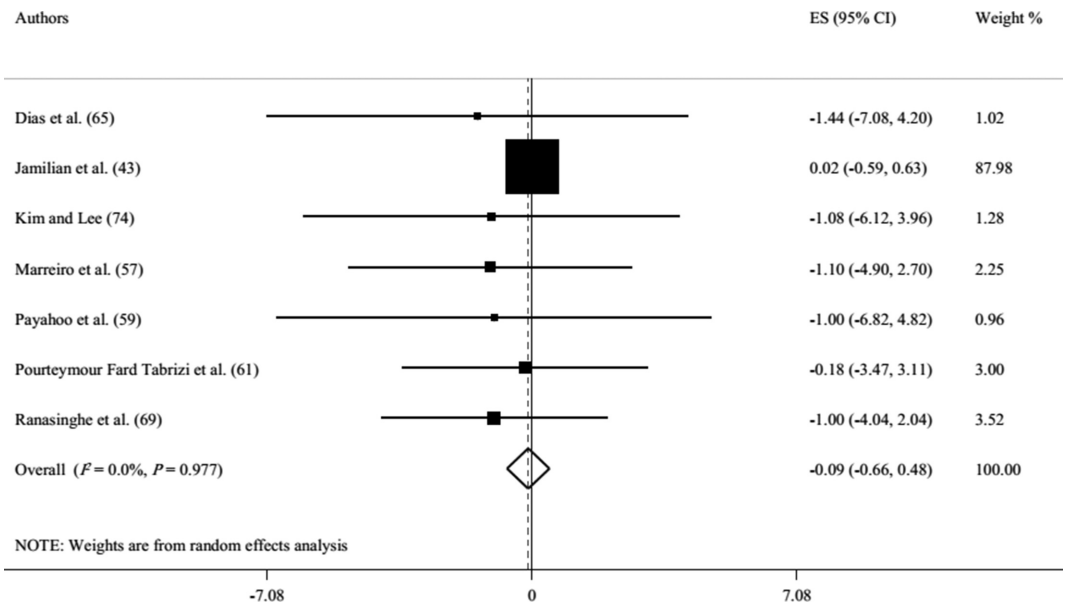

FIGURE 4 Forest plot of randomized controlled trials showing weighted mean differences in waist circumference change (in centimeters) between zinc supplementation and control groups for all eligible studies. Analysis was conducted using a random-effects model. Solid squares depict the weight assigned to the corresponding study; the black diamond represents the summary effect. ES, effect size.

week. Finally, owing to there being few available studies on the effect of zinc supplementation on BW indexes in healthy individuals, further clinical trials are required to reach a firm conclusion in this area.

Zinc supplementation has been proposed to increase leptin synthesis (79) and improve leptin sensitivity (80). Leptin is a key adipokine that regulates energy hemostasis and food intake via central nervous system signaling (78, 81). Zinc directly modulates the sensation of satiety and food intake via critical effects on synthesis of serotonin and dopamine (82). Moreover, zinc transporters regulate adipocyte metabolism. For example, ZIP13 is a zinc transporter required for appropriate beige adipocyte differentiation (83).

Our study showed that supplementation with zinc results in weight gain in patients undergoing HD. A high prevalence of zinc deficiency has been previously shown in this population (84). In patients undergoing HD, imbalanced redox status and unfavorable inflammatory profile (85–87) are well-established factors that reduce food intake and feeding behaviors (e.g., meal frequency, meal size) (88). The antioxidant and anti-inflammatory properties of zinc can improve inflammatory and antioxidant status (89, 90). Abnormal taste perception might be a reason for inadequate dietary intake and subsequent weight loss in patients undergoing HD (91). Some studies have shown an improvement in taste and smell acuity with zinc supplementation, which was accompanied by increased energy intake in patients undergoing dialysis (92, 93).

We found that zinc supplementation had no significant effect on BMI, WC, and body composition measures, which persisted across all subgroups. It should be noted that most included studies reported body composition measures as secondary outcomes. There is a possibility that studies in which changes in body composition measures are reported as secondary outcomes lead to biased estimates of the difference between intervention and placebo or untreated control groups (94). In addition, a longer duration of intervention and a higher dose of supplementation may be required to influence obesity indexes other than BW. Our dose–response analyses showed that a relatively high dosage of zinc supplementation (100 mg/d) led to a significant reduction in BMI.

Our meta-analysis has several strengths. First, to the best of our knowledge, this is the first meta-analysis of RCTs assessing the effect of zinc supplementation on weight and body composition measures in adults. Second, because our analysis only included RCTs, the causal inference of our conclusions is strong. Third, a rigorous methodology was adopted to identify available trials evaluating the effect of zinc supplementation on weight-related indexes. Fourth, we assessed the overall quality of evidence using the GRADE system for each outcome. Fifth, subgroup analyses were performed to test the effects across different subgroups and uncover potential sources of heterogeneity. Sixth, an additional meta-analysis was conducted to normalize for study duration, although the results of the overall analysis did not change. However, the association between zinc supplementation and change in BW per week in healthy subjects became nonsignificant.

However, there are several limitations that need to be considered when interpreting the findings. First, 12 out of 27 trials were of moderate methodological quality, which may

have contributed to the heterogeneous results in the subgroup analyses. Second, we considered some confounding factors such as supplementation dose, type of supplement used, and duration of zinc supplementation in the subgroup analyses. However, in most of the included trials, weight-related indexes were reported as secondary outcomes and several confounding factors, including circulating concentrations of zinc, dietary intake, physical activity, smoking, and the method used to measure body composition, were not taken into account. Third, the effect of zinc supplementation on weight may depend on baseline zinc status and change in circulating concentrations of zinc from baseline. However, neither mean zinc concentrations at baseline nor zinc deficiency status were consistently reported across RCTs. Fourth, there were only 2 RCTs with a length of intervention ~1 y, which might hinder the precision of the estimates of the long-term effects of zinc supplementation on weight-related indexes, although the results remained nonsignificant when study duration was considered in the meta-analysis. Fifth, the small number of trials limited our ability to conduct subgroup and publication bias analyses for HC, WHR, and BF%. Finally, trials recruited participants with a wide range of health statuses, which resulted in high heterogeneity between studies.

In conclusion, our systematic review and meta-analysis shows no significant effect of zinc supplementation on anthropometric indexes in the overall population. However, the results indicate that zinc supplementation increases BW in patients undergoing HD. An ambiguous association between zinc supplementation and decreased BW in individuals that are overweight/obese but otherwise healthy was also observed, but disappeared when normalized for study duration. High-quality, long-term, large-scale studies are needed to evaluate the efficacy and effective dose of zinc supplementation on weight-related indexes.

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