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# Meta-Analysis: Effects of Zinc Supplementation Alone or with Multi-Nutrients, on Glucose Control and Lipid Levels in Patients with Type 2 Diabetes

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**ABSTRACT:** The present study aims to assess the effects of zinc supplementation on metabolic parameters in patients with type 2 diabetes. A literature search was conducted in PubMed™, Google Scholar™, and Scopus™ up to March 2018. Twenty randomized controlled trials met the predefined inclusion criteria and were included in the meta-analysis. Weighted mean difference (WMD) with 95% confidence intervals (CIs) were calculated for net changes in glycemic indices including fasting blood glucose (FBG) and hemoglobin A1c (HbA1c), and in lipid markers including total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), and high density lipoprotein cholesterol (HDL-c). Subgroup analyses were performed based on intervention and study quality. Compared to controls, zinc supplementation significantly reduced the concentrations of both FBG and HbA1c (FBG WMD: −19.66 mg/dL, 95% CI: −33.71, −5.62; HbA1c WMD: −0.43 mg/dL, 95% CI: −0.80, −0.07). The pooled estimate showed a significant decrease in serum TC and LDL-c, and increase in serum HDL-c levels in treatment group compared with the control group (TC WMD: −18.51 mg/dL, 95% CI: −21.36, −15.66; LDL-c WMD: −4.80 mg/dL, 95% CI: −6.07, −3.53; HDL-c WMD: 1.45 mg/dL, 95% CI: 1.40, 1.51). Subgroup analysis of "no co-supplement" intervention demonstrated significant differences for mean changes in HDL-c and FBG levels, whereas subgroup analysis of high quality studies showed significant differences for mean changes of LDL-c, HDL-c, and FBG levels. Results suggested that zinc supplementation reduces FBG, HbA1c and LDL-c levels and increases HDL-C levels; however, these changes were related to intervention and quality of studies.

**Keywords:** zinc supplementation, glycemic status, lipid profile, type 2 diabetes, meta-analysis

## INTRODUCTION

Diabetes mellitus (DM) is a chronic and progressive disease characterized by high blood glucose concentrations resulting from defects in insulin secretion and/or insulin action (1). The global prevalence of diabetes and pre-diabetes is increasing because of population growth, aging, urbanization, lifestyle changes, and the high prevalence of obesity (2). Diabetes has various adverse effects on the cardiovascular system, vision, kidney function, and the nervous system, leading to increased risk of morbidity and mortality (3). The number of people suffering from diabetes has risen from 108 million in 1980 to 422 million in 2014, with high prevalence in middle- and low-income countries (4).

The mechanisms that result in type 2 diabetes mellitus (T2DM) development are complicated. Some studies suggest supplementation with zinc may alter T2DM characteristics, including dyslipidemia, chronic hyperglycemia, and insulin resistance (1). Both hypozincemia and hyperzincuria have been observed in diabetic patients, which may increase the incidence of bacterial attack due to overexpression of various inflammatory factors or may reduce zinc availability to the brain (5). Zinc, as an essential mineral, plays a critical role in various biological processes, including as a cofactor in antioxidant enzymes, and in insulin action and carbohydrate metabolism (6, 7). Zinc is involved in insulin crystallization and insulin

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signaling by inducing activation of the phosphoinositide 3-kinase (PI3K)/Akt cascade, which mediates glucose metabolism (1). Animal and human studies have demonstrated the beneficial effects of zinc supplementation on fasting insulin levels, and fasting glucose and lipid profiles in both type-1 and type-2 diabetic patients; however, may of these results have been contradicted in other studies. A systemic review and meta-analysis of the effect of zinc supplementation on diabetes was performed by Jayawardena et al. (8). The authors observed that zinc exhibits beneficial effect on glycemic control, lipid parameters, and systolic and diastolic blood pressure. However, in another meta-analysis by Foster et al. (9), no beneficial effects of zinc supplementation were observed on lipid profiles in humans.

Currently, there are no up-to-date systemic reviews or meta-analyses examining zinc supplementation on glycemic control and lipid parameters in subjects with T2DM based on intervention and study qualities. The present study aimed to systematically assess the effects of zinc supplementation on markers of glycemic control [glucose, insulin, and hemoglobin A1c (HbA1c)] and lipid profiles [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), and triglycerides (TG)] in humans, and to conduct a meta-analysis of qualified controlled trials to quantify the effect of zinc supplementation.

## MATERIALS AND METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement for interventional research (10).

### Search strategy and study selection

A comprehensive search was conducted from January 1990 to March 2018. The Pubmed™ database, Google Scholar™, and Scopus™ were used to obtain relevant articles based on inclusion criteria. Two groups of medical subject headings (MeSH) and non-MeSH keywords were used as search terms. Group 1: "Zn", "zinc", and "zinc supplementation"; group 2: "glycemic control", and lipid indices ("cholesterol", "plasma lipids", "triglycerides", "HDL-c", "LDL-c", "serum lipids", "FBS", "FBG", "fasting blood glucose", "diabetes", or "T2DM"). Studies were limited to those in human, clinical trials, and those published in English. The titles and abstracts were screened to determine study eligibility. Studies were retrieved if they were human clinical trials that measured the effects of zinc supplementation on at least one of the following outcomes: changes in HDL-c, LDL-c, TC, TG, fasting blood glucose (FBG), and HbA1c.

### Inclusion criteria

We used the following inclusion criteria: 1) controlled trial; 2) studies focusing on the effect of Zn on glycemic control, including HDL-c, LDL-c, TG, TC, FBG, and HbA1c; 3) age of study population ≥18 year; and 4) patients with type 2 diabetes. We additionally assessed the methodology of each trial and used data in this study that related to the outcome measures: glucose concentration, HbA1C, Zn, TG, LDL-c, HDL-c, and TC, at both baseline and post intervention.

### Exclusion criteria

Exclusion criteria were as follows: 1) papers that were not available in English; (2) papers containing insufficient data required for meta-analysis; (3) papers that did not allow access to full texts or relevant data; (4) papers which were not original publications (including reviews, mini-reviews, letters, and comments); and (5) duplications.

### Data extraction and quality assessment

The key data we collected from each of the studies were as follows: year of publication, country where the study was conducted, mean/range subject age, sample size of intervention and control groups, clinical condition of subjects, details of intervention (including the dosage of zinc supplementation in gram per day), type of the diet or intervention in the control group, intervention period, and significant outcomes. In addition, serum levels of FBG, TC, LDL-c, HDL-c, and TG were reported in mg/dL and HbA1c was reported as the percentage of total haemoglobin. For papers containing data in mmol/L, a numerical conversion to mg/dL was calculated based on molecular weight. Serum HbA1c was represented as a percentage.

The Jadad scale was used as a scale to independently assess the methodological quality of the clinical trials. Jadad scoring were applied to each study, which assigns values ranging from 0 to 5 based on three parameters (randomization, blinding, and follow-up) (11). For randomization, each study gets one point if randomization was mentioned, and one additional point if the method of randomization was appropriate. Moreover, one point is subtracted if the method of randomization was inappropriate. With regards to blinding, the study is assigned one point if blinding was mentioned, one additional point if the method of blinding was appropriate and one point for follow-up. One point is subtracted if the method of blinding was described inappropriately (the fate of all the subjects including the number and the cause of the subject's attrition).

### Statistical analysis

The meta-analysis was performed using Review Manager

Software (RevMan 5.3; Cochrane Collaboration, Oxford, England). Changes is metabolic factor from baseline to the final measurement were calculated as mean differences (MD) with the 95% confidence interval (CIs) (12). Cohen's d was used to calculate the effect size comparison using comprehensive meta-analysis software program version 2. According to Cohen's suggestion (13), effect sizes of 0.2 are small, 0.5 are medium, and 0.8 or more are large.

A threshold of $P<0.1$ was set to identify the presence of heterogeneity. Inconsistency between the studies was additionally considered significant when $I^2>50\%$. A fixed effects model was used if $I^2<50\%$ and $P>0.1$. A random effects model was used if $I^2>50\%$ and $P<0.1$.

To identify the influence of confounding factors, subgroup analysis were conducted according to the Cochrane guidelines (14). To determine the source of heterogeneity, we divided two subgroup analyses according to their design: 1) Based on the quality of the articles (those with three points or higher were placed in a low risk group of bias and those with lower than three points were placed in a high risk group); 2) Based on the intervention of zinc supplementation either alone or in combination with other co-supplements.

The potential for publication bias was investigated by visual inspection of a funnel plot. In the test, standard errors were plotted against the effect size for each study. If publication bias exists, the funnel plot demonstrates an asymmetric shape. The Egger regression asymmetry test was used to test the asymmetry of the funnel plot and Egger's weighted regression test was used to statistically examine and verify any potential publication bias.

## RESULTS

### Search results and study selection

A flow chart showing the process of literature search and selection is presented in Fig. 1. During the literature search, we identified 256 relevant articles, of which 155 total abstracts were excluded due to duplications (n=21), non-English studies (n=14), reviews (n=11), and 109 irrelevant articles such as case reports, editorials, and letters. The remaining articles were considered for full-text review. An additional 81 articles were excluded, which included preclinical studies or those containing inadequate characterization of patients, insufficient reporting of data or irrelevant outcomes. Finally, based on our defined inclusion and exclusion criteria, 20 papers were included in the meta-analysis (Fig. 1).

### Study characteristics and quality assessment

Characteristics of the included studies are shown in Table 1. The dates of publication ranged from 1992 to 2016

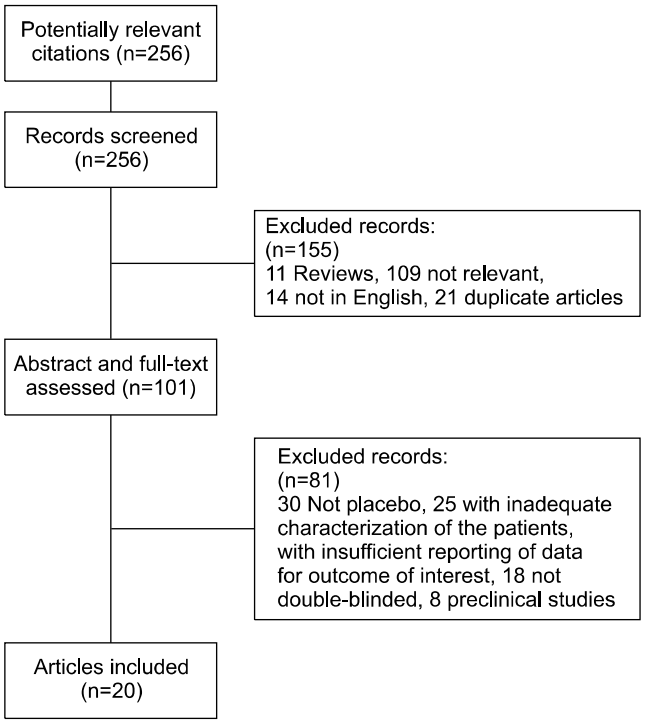


**Fig. 1.** Flow diagram of included and excluded studies.

(15-36). The number of participants per study ranged from 13 to 60, and subject ages ranged from 18 to 73 years old. The studies investigated either the effects of zinc supplementation alone (15,17-19,26-28,31-34,36) or in combination with the other minerals and/or vitamins (16,20-25,29,30,35).

The dosage of zinc used in these trials ranged from 7.5 to 660 mg/d. The zinc compounds used in the trials included zinc sulfate (15,17,19-28,32,33,36,37), zinc chloride (16), zinc glucoronate (31,34), zinc phosphate (28), and zinc acetate (29,30). The length of follow up varied from 3 weeks to 6 months. Based on previous meta-analysis studies, which suggested studies with Jadad scores $\geq$3 are high quality studies (38-40), and according to the quality checklist, six studies (16,19,23,29,32,33) were considered to be of high-quality, while the other fourteen studies (15,17,20-22,24-28,30,31,34,36) were considered to be low-quality (Table 1).

### The effects of zinc on blood glucose and lipid concentration

Since varying units for applied indices (including TG, TC, LDL-c, HDL-c, and FBG) were used in the included studies, all were converted to the same unit (mg/dL) for comparison. The test for overall heterogeneity indicated that zinc significantly effects all the investigated glycemic indices (Fig. 2). Subgroup analyses was therefore performed to identify potential factors that could contribute to the heterogeneity; however, heterogeneity remained. Due to the observed heterogeneity between trials (mean

**Table 1.** Characteristics of included trials

| No. of subjects in case group | No. of controls | Gender | Age (mean±SD) | Follow-up duration | Dosage | Co-supplements | Baseline values (mg/dL) (HbA1c: %) | Significant outcome | Jadad score | Reference no. |
|---|---|---|---|---|---|---|---|---|---|---|
| 20 | 20 | F/M | 52.7±8.6 | 6~12 weeks | $ZnSO_4$; 660 mg/d | None | FBG=156.10±50.30; HbA1c=7.83±1.53; TG=216.92±113.92; TC=170.97±44.29; LDL-c=92.45±34.63; HDL-c=47.92±15.30 | Reduction in TG, TC, LDL, and HbA1c | 2 | 15 |
| 50 | 51 | F/M | 54.6±9.2 | 3 months | $ZnSO_4$; 30 mg/d | None | FBG=190.99±106.30; HbA1c=8.1±1.5 | Reduction in HbA1c | 3 | 17 |
| 30 | 30 | F/M | 30~70 | 8 weeks | $ZnSO_4$; 40 mg/d | None | FBG=172.23±23.83; HbA1c=9.56±0.71; TG=166.08±31.93; TC=203.00±16.36; LDL-c=132.85±14.11; HDL-c=40.62±4.79 | FBG, HbA1c, and lipid profile were significantly reduced | 4 | 19 |
| 50 | 25 | F/M | 52.5±8.2 | 4 months | $ZnSO_4$; 20 mg/d | $Mg^{2+}$, vitamin B1, B2, B6, B12, C, E, folate, biotin | FBG=178.4±40.7; HbA1c=9.4±0.9 | Reduced severity of neuropathy symptoms in patients with mild-moderate neuropathy | 3 | 22 |
| 51 | 18 | F/M | 50.0±9.0 | 3 months | $ZnSO_4$; 30 mg/d | $Mg^{2+}$, vitamin C, E | FBG=171.35±50.45; HbA1c=10.38±2.70; LDL-c=106.94±23.16; HDL-c=40.15±15.83 | Decreasing fasting serum glucose and malondialdehyde concentrations; increasing HDL-c and apolipoprotein A1 in MV group; improvement of glomerular but not tubular renal function | 3 | 21 |
| 51 | 18 | F/M | 50.3±8.2 | 3 months | $ZnSO_4$; 30 mg/d | $Mg^{2+}$, vitamin C, E | TG=167.0±84.5; TC=181.1±33.1 LDL-c=107.4±23.1; HDL-c=40.3±15.5 | mean serum levels of HDL-c and apo A1 increased significantly in the MV group | 3 | 20 |
| 36 | 12 | F | 65.0±7.8 | 3 months | $ZnSO_4$; 40 mg/d | flaxseed oil; 2 g/d | FBG=122.52±9.0; HbA1c=6.6±0.3; TG=97.35±17.7; TC=154.44±11.58; LDL-c=77.22±7.72; HDL-c=61.77±3.86 | No statistically significant effects of zinc supplementation on HbA1c, serum glucose, and insulin concentrations, or HOMA-IR observed | 4 | 23 |
| 60 | 36 | F/M | 53.4±7.2 | 4 months | $ZnSO_4$; 22 mg/d | $Mg^{2+}$, $Cu^{2+}$, $Se^{2}$, and multivitamin | FBG=112.43±16.93; HbA1c=7.50±1.30; LDL-c=100.38±32.43; HDL-c=52.12±8.49 | Reduced HbA1c, FBG, 2-h PPBS, TC, and TC/HDL-c ration | 2 | 24 |
| 60 | 36 | F/M | 54.6±7.0 | 4 months | $ZnSO_4$; 22 mg/d | Multivitamin (vitamin A, D3, and E)/mineral preparation ($Mg^{2+}$, $Mn^{2+}$, $Cu^{2+}$, and $Se^{2+}$) | FBG=112.43±16.93; HbA1c=7.50±1.30; LDL-c=100.38±32.43; HDL-c=52.12±8.49 | Better glycemic control of diabetic patients who had high baseline FBS levels by zinc supplementation with other multi vitamins | 2 | 25 |
| 30 | 20 | F/M | 49.9±11.0 | 6 weeks | $ZnSO_4$; 660 mg/d | None | No data | Reduced FBG and 2 h-PPBS, improved motor nerve conductionvelocity | 3 | 26 |

**Table 1.** Continued

| No. of subjects in case group | No. of controls | Gender | Age (mean±SD) | Follow-up duration | Dosage | Co-supplements | Baseline values (mg/dL) (HbA1c: %) | Significant outcome | Jadad score | Reference no. |
|---|---|---|---|---|---|---|---|---|---|---|
| 40 | 20 | F/M | 50.9±11.1 | 6 weeks | $ZnSO_4$; 660 mg/d | None | FBG=182.34±12.79 | Reduced FBG and 2 h-PPBS, improved motor nerve conductionvelocity | 1 | 27 |
| 28 | 28 | F/M | 26~62 | 3 weeks | $Zn_3(PO_4)_2$; 28 mg/d | None | FBG=233.35±44.75 | Increased serum insulin; reduced FBG and glucagon | 1 | 28 |
| 31 | 15 | F/M | 49.1±6.0 | 3 months | Zn acetate; 50 mg/d | Melatonin | FBG=155.13±10.99; HbA1c=7.60±0.47 | Reduced FBG and 2-h PPBS | 4 | 29 |
| 31 | 15 | F/M | 49.1±6.0 | 3 months | Zn acetate; 50 mg/d | Melatonin; 10 mg | TG=216.81±7.08; TC=206.94±7.72; LDL-c=125.86±4.63; HDL-c=35.90±3.08 | Reduced TC, TG, LDL-c, and microalbuminuria | 1 | 30 |
| 16 | 15 | F/M | 63.4±6.8 | 12 weeks | Zn chloride; 15 mg/d | Chromium; 100 μg | FBG=141.5±37.3; HbA1c=7.3±0.9; TG=192.9±124.1; TC=198.0±45.2; LDL-c=111.8±39.9; HDL-c=53.8±13.8 | No beneficial effects observed | 5 | 16 |
| 72 | 76 | F/M | 54.9±11.05 | 4 weeks | Zn gluconate; 50 mg/d | None | FBG=143.0±47.48; HbA1c=7.62±1.25 | No beneficial effects observed | 1 | 31 |
| 25 | 25 | F/M | 53.2±9.2 | 6 months | $ZnSO_4$; 30 mg/d | None | FBG=167.0±46.0; HbA1c=8.0±1.4; TG=159.0±77.0; TC=183.0±37.0; LDL-c=105.0±34.0; HDL-c=45.0±12.0 | Reduced urinary albumin excretion | 4 | 32 |
| 15 | 15 | M | 51.70±7.13 | 4 months | $ZnSO_4$; 100 mg/d | None | FBG=160.61±62.53; LDL-c=101.03±37.57; HDL-c=41.55±12.90 | Reduced TC and TG; increased HDL-c | 4 | 33 |
| 20 | 20 | M | 56.0±7.5 | 3 months | Zn gluconate; 240 mg/d | None | FBG=149.4±50.4; TG=130.09±46.02; TC=176.06±31.66; LDL-c=106.56±27.79; HDL-c=41.31±10.42 | No beneficial effects observed | 2 | 34 |
| 27 | 27 | M | 56.3±7.6 | 3 months | $ZnSO_4$; 50 mg/d | None | FBG=147.09±39.76; HbA1c=8.35±0.87; TG=155.48±41.03; TC=151.52±19.10; LDL-c=89.96±20.74; HDL-c=30.04±6.41 | the mean FBS, PPBS, and glycosylated HbA1c were decreased significantly | 1 | 36 |

HbA1c, hemoglobin A1c; TG, triglycerides; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; FBG, fasting blood glucose; MV, mineral/vitamin; HOMA-IR, homeostasis model assessment-insulin resistance; PPBS, post-prandial blood glucose; FBS, fasting blood sugar.

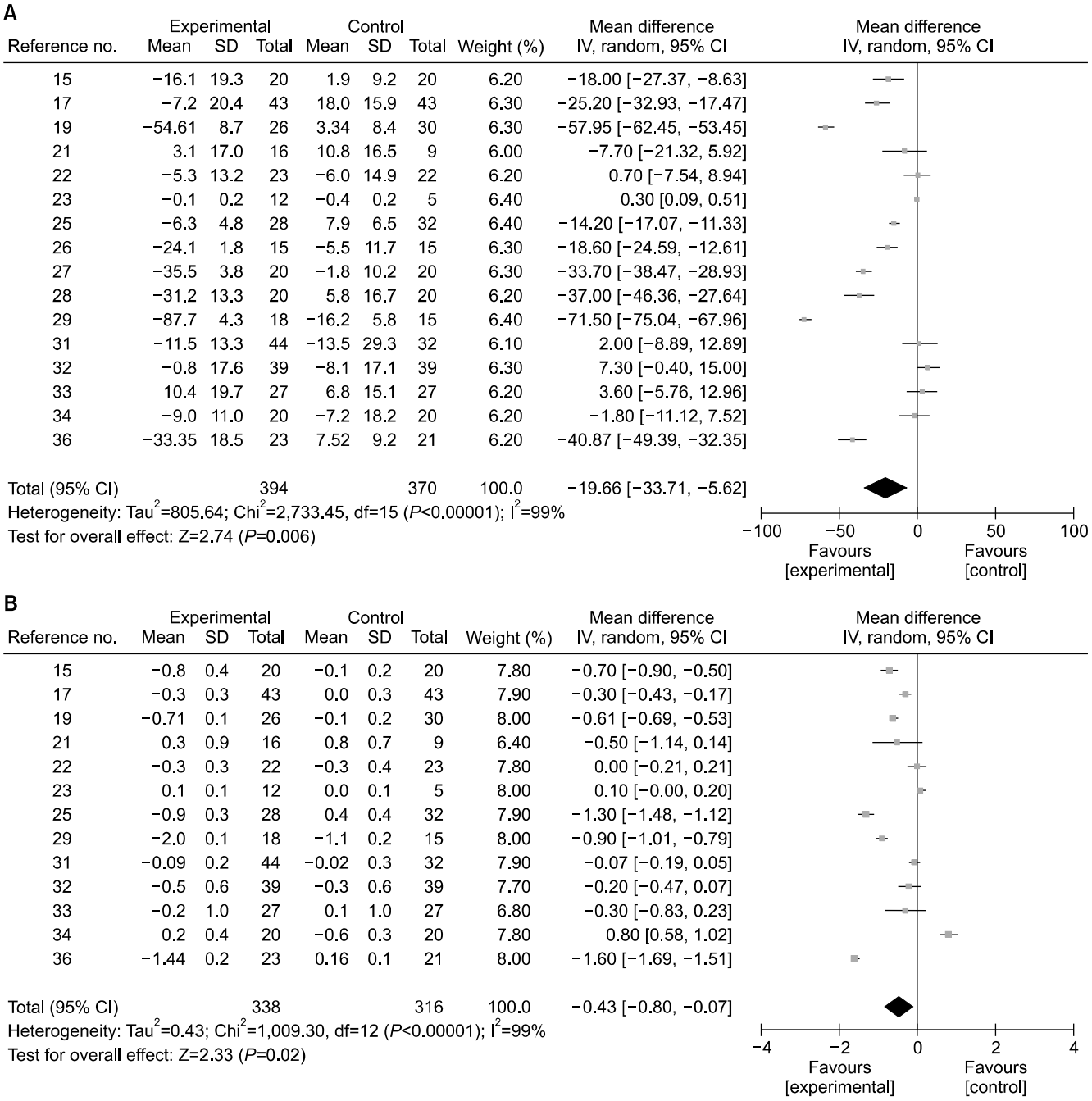


**Fig. 2.** Forest plots showing the association between zinc supplementation and the glycemic indices; (A) fasting blood glucose (FBG) and (B) hemoglobin A1c (HbA1c).

change of almost all the indicators) the random effect model was used to pooling data.

The serum level of FBG was analyzed in sixteen trials of the included studies (15,17,19,21-23,25-29,31-34,36). The pooled estimate showed significant differences between the mean changes of FBG and HbA1c in the treatment group compared with the control group (FBG WMD: −19.66 mg/dL, 95% CI: −33.71, −5.62; *P* for heterogeneity <0.00001, $I^2$=99%) (Fig. 2A). The mean change for HbA1c was calculated in thirteen of the included studies (15,17,19,21-23,25,29,31-34,36). The total mean difference for HbA1c was −0.43 (95% CI: −0.80, −0.07; *P* for heterogeneity <0.00001, $I^2$=99%) (Fig. 2B). The average percent change from baseline for FBG and HbA1c in the treated group were 9.7% and 6.3%, respectively.

The serum level of TG was analyzed in thirteen of the included trials (15,16,19-21,23-25,30,32-34,36). The pooled mean net change of TG in the treatment group was −0.32 compared with the control group and was not statistically significant (95% CI: −1.30, 0.66; *P* for heterogeneity <0.00001, $I^2$=96%) (Fig. 3A). The total se-

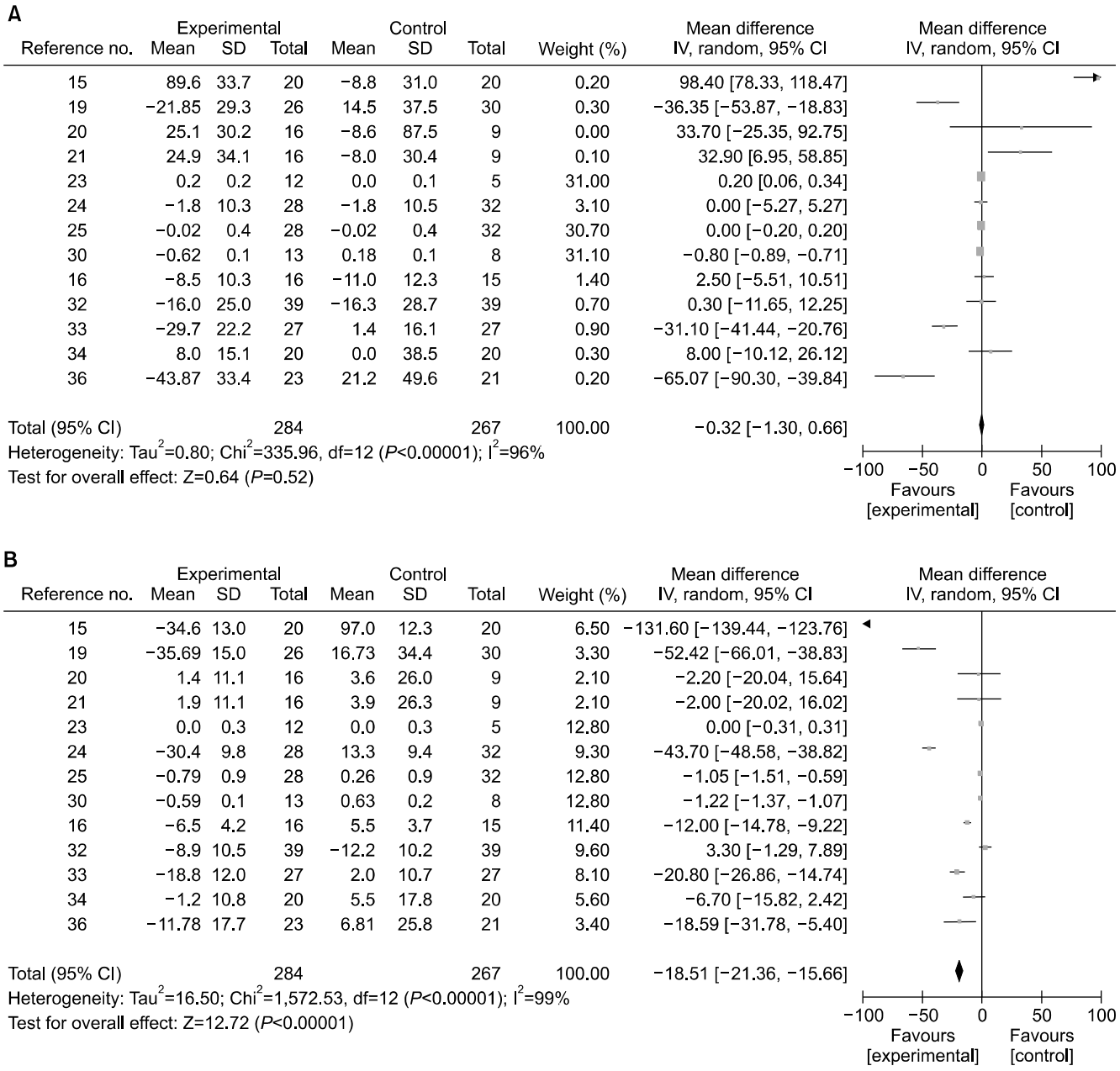


**Fig. 3.** Forest plots showing the association between zinc supplementation and serum lipid indices; (A) triglyceride (TG), (B) total cholesterol (TC), (C) low-density lipoprotein cholesterol (LDL-c), and (D) high-density lipoprotein cholesterol (HDL-c).

rum cholesterol level was measured in thirteen of the included trials (15,16,19-21,23-25,30,32-34,36). The pooled estimate showed a significant decrease in the amount of serum TC in the treatment group compared with the control group (WMD: −18.51 mg/dL; 95% CI: −21.36, −15.66; *P* for heterogeneity <0.00001, $I^2$=99%) (Fig. 3B). In addition, thirteen of the included trials investigated the effects of zinc supplements on the levels of LDL-c and HDL-c (15,16,19-21,23-25,30,32-34,36). The pooled mean net change in serum LDL-c was −4.80 in the treatment group (95% CI: −6.07, −3.53; *P* for heterogeneity <0.00001, $I^2$=97%), which was significantly different from controls (Fig. 3C). The pooled WMD for HDL-c was 1.45 mg/dL (95% CI: 1.40, 1.51; *P* for heterogeneity <0.00001, $I^2$=100%), suggestive of a significant difference in the mean change of HDL-c between the two groups (Fig. 3D). The average percent change from baseline for LDL-c and HDL-c in the treated group were 5.1% and 7.7%, respectively.

### Effect of additional supplements

In addition, we performed a subgroup analysis based on the intervention (with co-supplement vs. no co-supplement), shown in Table 2. Significant differences in the mean change of TC, LDL-c, HDL-c, and FBG levels were observed during subgroup analysis by "with co-supplement" intervention (TC WMD: −2.31 mg/dL, 95% CI: −3.35 to −1.27; LDL-c WMD: −0.53 mg/dL, 95% CI:

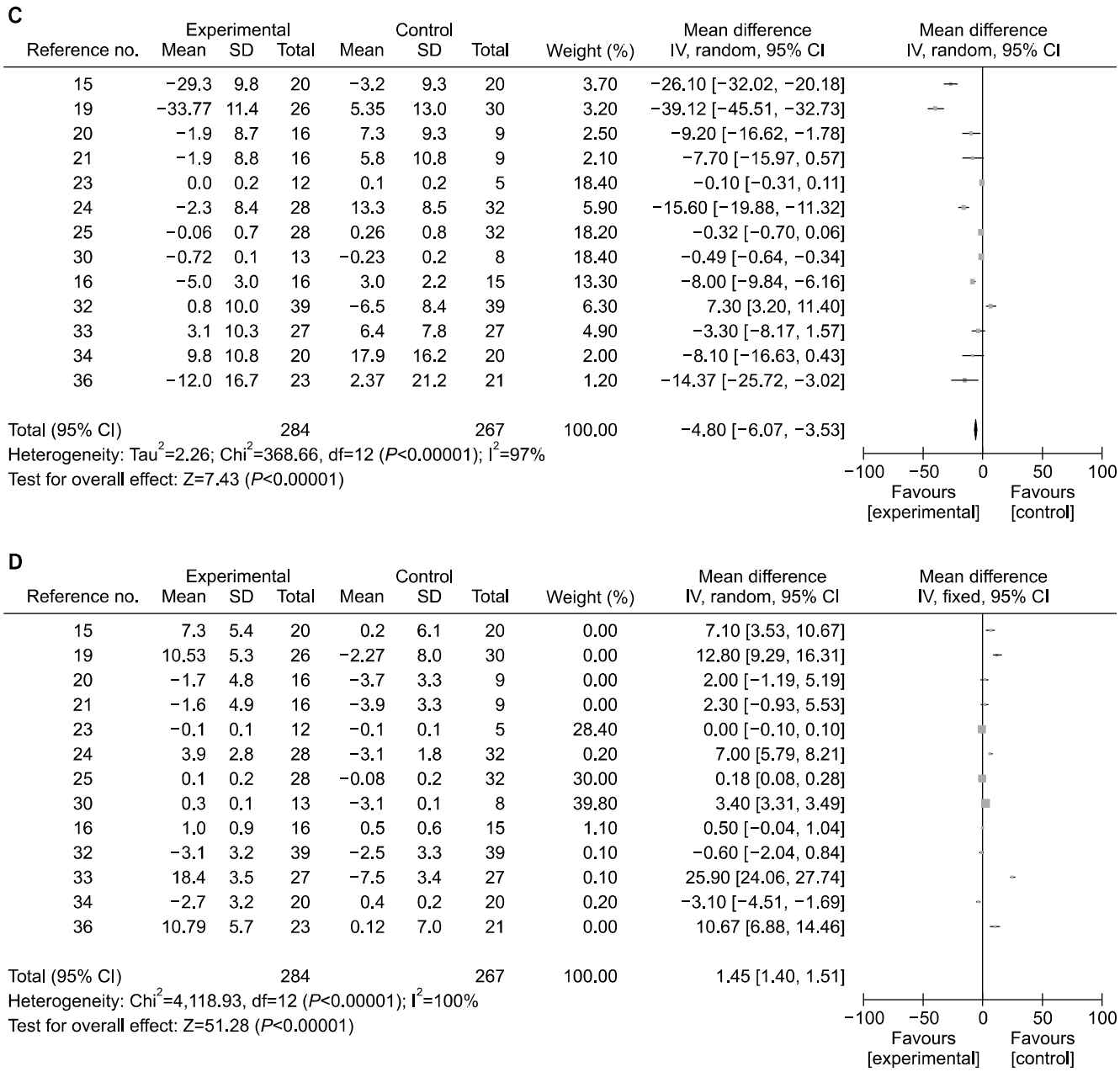


**Fig. 3.** Continued.

−0.96 to −0.10 mg/dL; HDL-c WMD: 1.77 mg/dL, 95% CI: 1.72 to 1.81; FBG WMD: −2.10 mg/dL, 95% CI: −3.57, −0.63), consistent with the overall analysis (Table 2). The "no co-supplement" subgroup analysis demonstrated a significant difference in the mean changes in levels of HDL-c and FBG (HDL-c WMD: 5.38 mg/dL, 95% CI: 4.56 to 6.19; FBG WMD: −28.20 mg/dL, 95% CI: −44.32, −12.08) (Table 2).

### Effect of study quality

The subgroup analysis for high-quality studies confirmed a significant difference in the mean change of LDL-c, HDL-c, and FBG (LDL-c WMD: −2.22, 95% CI: −4.16, −0.27; HDL-c WMD: 0.09, 95% CI: 0.02, 0.16; FBG WMD: 0.52, 95% CI: 0.11, 0.93). The low-quality studies showed a significant increase in all indices except for TG, which was consistent with the overall results (TC WMD: −17.66 mg/dL, 95% CI: −20.17, −15.15; LDL-c WMD: −20.37 mg/dL, 95% CI: −22.32, −18.43; HDL-c WMD: 2.60 mg/dL, 95% CI: 2.55, 2.65; FBG WMD: −27.35 mg/dL, 95% CI: −41.38, −13.32; HbA1c WMD: −0.54%, 95% CI: −0.92, −0.15). However, compared with the overall results, heterogeneity was not related to decreases in the subgroup analysis of interventions and quality assessment of trials (Table 2).

### Effect size

To explore the effectiveness of zinc supplementation, the size of the effect within the 20 studies included in this meta-analysis was explored. Zinc supplementation great-

**Table 2.** Subgroup analysis

| Subgroup | Intervention | | Quality of study | |
|---|---|---|---|---|
| | Co-supplement | No co-supplement | Low quality | High quality |
| TG | | | | |
| WMD (95% CI) | −0.24 (−0.63, 0.15) | −4.21 (−40.59, 32.18) | −0.43 (−1.03, 0.17) | −0.01 (−0.63, 0.61) |
| Test for heterogeneity ($I^2$, $P$) | 96%, $P$<0.00001 | 97%, $P$<0.00001 | 94%, $P$<0.00001 | 92%, $P$<0.00001 |
| Test for overall effect | $P$=0.23 | $P$=0.82 | $P$=0.04 | $P$=0.97 |
| Cohen's d (95% CI) | −0.14 (−1.31, 0.32) | −0.18 (−1.24, 0.87) | −0.49 (−1.30, 0.31) | −0.19 (−1.23, 0.86) |
| TC | | | | |
| WMD (95% CI) | −2.31 (−3.35, −1.27) | −37.79 (−79.91, 4.34) | −17.66 (−20.17, −15.15) | −0.66 (−2.07, 0.75) |
| Test for heterogeneity ($I^2$, $P$) | 98%, $P$<0.00001 | 97%, $P$<0.00001 | 99%, $P$<0.00001 | 94%, $P$<0.00001 |
| Test for overall effect | $P$<0.0001 | $P$=0.08 | $P$<0.0001 | $P$=0.36 |
| Cohen's d (95% CI) | −1.68 (−2.81, −0.54) | −0.73 (−1.17, −0.63) | −2.35 (−3.35, −1.35) | −0.24 (−1.44, 0.95) |
| LDL-c | | | | |
| WMD (95% CI) | −0.53 (−0.96, −0.10) | −13.89 (−28.97, 1.19) | −20.37 (−22.32, −18.43) | −2.22 (−4.16, −0.27) |
| Test for heterogeneity ($I^2$, $P$) | 90%, $P$<0.00001 | 97%, $P$<0.00001 | 99%, $P$<0.00001 | 97%, $P$<0.00001 |
| Test for overall effect | $P$<0.02 | $P$=0.07 | $P$<0.0001 | $P$=0.03 |
| Cohen's d (95% CI) | −1.31 (−2.04, −0.59) | −0.39 (−2.20, −0.13) | −2.03 (−2.58, −1.47) | 0.81 (0.33, 0.98) |
| HDL-c | | | | |
| WMD (95% CI) | 1.77 (1.72, 1.81) | 5.38 (4.56, 6.19) | 2.60 (2.55, 2.65) | 0.09 (0.02, 0.16) |
| Test for heterogeneity ($I^2$, $P$) | 100%, $P$<0.00001 | 99%, $P$<0.00001 | 100%, $P$<0.00001 | 100%, $P$<0.00001 |
| Test for overall effect | $P$<0.00001 | $P$<0.00001 | $P$<0.0001 | $P$=0.02 |
| Cohen's d (95% CI) | 1.11 (0.83, 1.40) | 0.90 (0.64, 1.16) | 1.12 (0.89, 1.35) | 0.81 (0.33, 0.98) |
| FBG | | | | |
| WMD (95% CI) | −2.10 (−3.57, −0.63) | −28.20 (−44.32, −12.08) | −27.35 (−41.38, −13.32) | 0.52 (0.11, 0.93) |
| Test for heterogeneity ($I^2$, $P$) | 95%, $P$<0.00001 | 99%, $P$<0.00001 | 99%, $P$<0.00001 | 57%, $P$=0.05 |
| Test for overall effect | $P$=0.005 | $P$=0.0006 | $P$=0.0001 | $P$=0.01 |
| Cohen's d (95% CI) | −0.90 (−1.89, 0.10) | −2.54 (−3.61, −1.48) | −2.48 (−3.40, −1.56) | 0.82 (0.27, 1.26) |
| HbA1c | | | | |
| WMD (95% CI) | −0.35 (−0.84, 0.14) | −0.44 (−0.86, −0.01) | −0.54 (−0.92, −0.15) | 0.05 (−0.12, 0.21) |
| Test for heterogeneity ($I^2$, $P$) | 98%, $P$<0.00001 | 99%, $P$<0.00001 | 99%, $P$<0.00001 | 71%, $P$=0.02 |
| Test for overall effect | $P$=0.16 | $P$=0.07 | $P$=0.007 | $P$=0.59 |
| Cohen's d (95% CI) | −0.34 (−1.72, 0.84) | −0.22 (−1.17, 0.47) | −2.12 (−3.26, −0.98) | 0.35 (−0.45, 1.14) |

WMD, weighted mean difference; CI, confidence interval; TG, triglycerides; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, hemoglobin A1c.

ly impacted on levels of FBG (d=−1.73, 95% CI: −2.53, −0.94), HbA1c (d=−1.63, 95% CI: −2.55, −0.71), HDL-c (d=1.44, 95% CI: 0.56, 2.33), LDL-c (d=−1.28, 95% CI: −1.95, −0.61), and TC (d=−1.99, 95% CI: −2.87, −1.11) but only had a small, non-significant effect on levels of TG (d=−0.15, 95% CI: −0.79, 0.49) (Fig. 4).

We conducted further subgroup analysis based on intervention and study quality. In studies analyzing the effects of zinc with co-supplements, a large effect size was found for TC (d=−1.68, 95% CI: −2.81, −0.54), LDL-c (d=−1.31, 95% CI: −2.04, −0.59), and HDL-c (d=1.11, 95% CI: 0.83, 1.40). Only FBG had a large and significant effect size in the no co-supplement group (d=−2.54, 95% CI: −3.61, −1.48) (Table 2).

In high quality studies, all outcomes showed small non-significant effect sizes in the intervention group compared with the control group. However, low quality studies showed large effect sizes for HDL-c (d=1.12, 95% CI: 0.89, 1.35), LDL-c (d=−2.03, 95% CI: −2.58, −1.47), TC (d=−2.35, 95% CI: −3.35, −1.35), FBG (d=−2.48, 95% CI: −3.40, −1.56), and HbA1c (d=−2.12, 95% CI: −3.26, −0.98), but small effect sizes for the remaining parameters (Table 2).

### Publication bias

In this meta-analysis, publication bias was assessed by examining funnel plot of the effects on LDL-c as a representative index for the lipid profile, and FBG as a representative index for glycemic status. Based on visual inspection of the plots, there was some evidence of publishing bias regarding studies of zinc supplementation on both LDL-c and FBG. This was confirmed by Egger's linear regression (LDL-c: intercept: −3.9; standard error: 1.41; 95% CI: −7.03, −0.79; t=2.75, df=11; two-tailed $P$=0.01; FBG: intercept: −8.2; standard error: 3.11; 95% CI: −14.90, −1.53; t=2.63, df=14; two-tailed $P$=0.01) (Fig. 5).

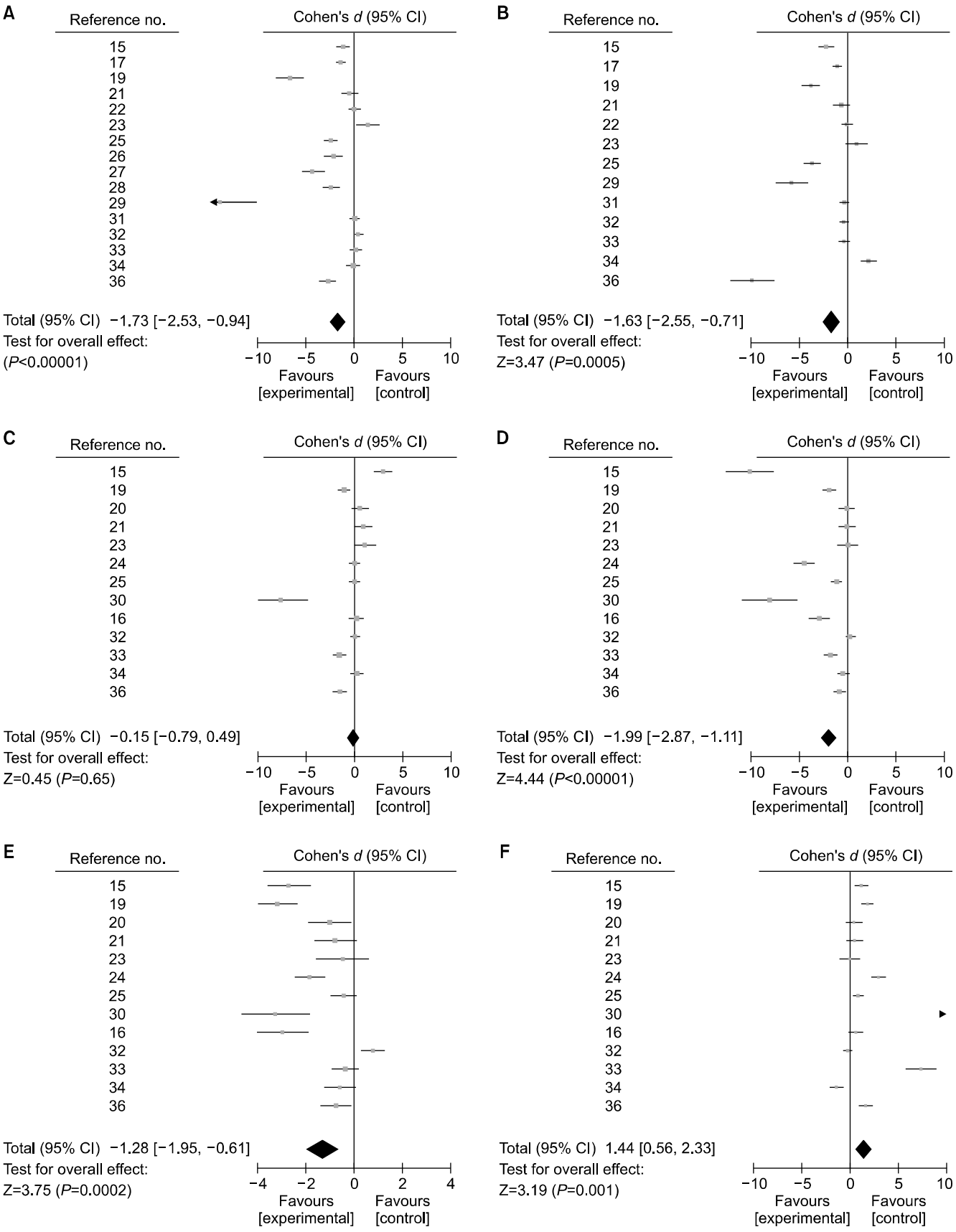


**Fig. 4.** Results of meta-analysis, Forest plot of point estimate effect sizes reported as Cohen's d (X-axis) evaluating zinc supplementation on (A) fasting blood glucose (FBG), (B) hemoglobin A1c (HbA1c), (C) triglyceride (TG), (D) total cholesterol (TC), (E) low-density lipoprotein cholesterol (LDL-c), and (F) high-density lipoprotein cholesterol (HDL-c) using the random effects model. Points represent weighted effect size, lines represent 95% confidence intervals (CIs). Triangle indicates overall effect size and 95% CI.

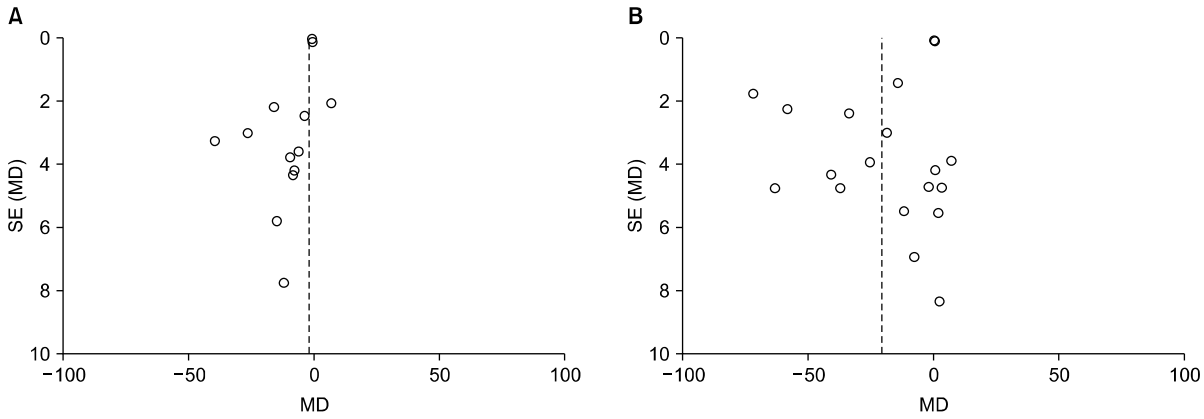


**Fig. 5.** Funnel plot of studies included in the meta-analysis for the outcome of (A) low-density lipoprotein cholesterol (LDL-c) and (B) fasting blood glucose (FBG). MD, mean difference; SE, standard error.

## DISCUSSION

Our meta-analysis of 20 clinical trials demonstrated that zinc supplementation leads to a significant reduction in the concentration of all diabetic markers measured except TG. Using Cohen's criteria for effect size categorization (13), we showed that the effect of zinc supplementation was large for FBG, HbA1c, HDL-c, LDL-c, and TC and small for TG. The effects of zinc supplementation were investigated in trials that supplemented zinc as an investigated intervention alone or in combination with the other micronutrients. This meta-analysis showed zinc supplementation significantly reduces overall serum glucose concentrations. Moreover, the analyzed studies indicated that zinc supplementation significantly decreases serum glucose concentration, levels of HbA1c, LDL-c, and TC, and increases concentrations of HDL-c, while it did not significantly effect TG.

Our data demonstrates positive clinical and therapeutical effects of zinc supplements for patients with DM. It suggests that zinc is responsible for improving glycemic and lipid profile controls. In general, these findings are consistent with results of most of the individual studies; of the 20 included studies, only four trials reported no beneficial effects of zinc supplementation on glycemic and lipidemic statuses. The reasons provided are: small sample sizes and low dosages of zinc supplements used (16,23,31,34). Moreover, the diversity of zinc compounds may have affected the results.

The data showed that heterogeneity among studies was significant. Subgroup analysis revealed that the effects of zinc supplement may differ by factors such as intervention regimens (zinc supplements alone or in combination with the other co-supplements) and quality assessment. Subgroup analysis based on quality assessment reduced the high heterogeneity of mean changes of FBG in subgroups of high quality studies.

### Subgroup analysis by intervention regimens

Subgroup analysis of intervention regimens (zinc supplements in combination with the co-supplements) indicated that the result of zinc supplementation on metabolic indicators is consistent with the overall analysis, with the exception of for serum HbA1c. There is therefore a discrepancy between the overall results and the subgroup analysis of "co-supplements" and "no co-supplements". Magnesium, vitamin C, and vitamin E were the co-supplements used in most of the included trials and their co-ingestion with zinc could promote further effects on markers of interest. A meta-analysis of 9 randomized controlled trials reported that oral magnesium supplementation was effective in reducing fasting plasma glucose and rising HDL-c in type 2 diabetic subjects, but without inducing significant effects on TC, TG, and LDL-c (41). Paolisso et al. (42) suggested that chronic administration of vitamin C exerts beneficial effects upon glucose and lipid metabolism in elderly type 2 diabetic subjects, however the supporting trials are limited in number. The other most frequently administrated co-supplement was vitamin E; a systematic review and meta-analysis in 2011 suggested no beneficial effects of vitamin E supplementation on glycemic control. However, authors of this study suggested that HbA1c could decrease with vitamin E supplementation in subjects with poor glycemic control or low vitamin E levels (43). Other components analyzed were used sporadically in the trials and were therefore found to have the least effect. However, the roles of these compounds cannot be ignored, especially for vitamin D and chromium.

A previous study has demonstrated a positive relationship between FBS and HbA1c (44), however this association was not supported in others studies, possibly due to individual study designs. Derakhshan et al. (45) did not observe any association between HbA1c and blood glucose in type 1 diabetic patients; this may be explained by the younger ages of subjects in the study and its low

power. Another study investigating subjects with diabetics and impaired blood glucose levels showed that the sensitivity and the specificity of HbA1c were 88% and 93.75%, respectively (46). This was similar to the findings by Ghazanfari et al. (47), which concluded that FBS is more reliable than HbA1c for separating diabetic from non-diabetic subjects.

Subgroup analysis based on zinc supplements alone showed significant improvements in HDL-c and FBG levels. Combination of zinc supplemention with other vitamin/mineral supplements exhibited favorable effects on nearly all metabolic indicators. Zinc supplementation alone may therefore affect FBG and HDL-c, but changes to the other investigated metabolic markers may depend on the addition of other co-supplements.

Results from the effect size analysis showed that zinc supplementation in combination with other supplements can induce large changes to levels of TC, HDL-c, and LDL-c, however zinc supplementation alone is likely to only induce a large effect on FBG. In clinical practice, zinc supplements should be combined with other supplements to improve lipid markers in addition to serum FBG.

**Subgroup analysis by quality assessment**

Another analysis was conducted based on quality assessment. Low quality studies showed significant differences in the mean changes of all investigated indicators. However, in high quality studies, significant differences were found in the mean changes of levels of LDL-c, HDL-c, and FBG. After carrying out analysis of effect size, low quality studies showed large effects for zinc supplementation on glycemic markers and levels of serum LDL-c, HDL-c, and TC; however, high quality studies did not show any significant effects on the outcomes of interest. These results indicate that high quality studies did not show large effects of zinc supplementation on lipid or glycemic markers, however low quality studies were able to confirm some clinical benefits.

Overall, the analysis carried out in this study showed that FBG and HDL-c are the most significantly affected markers by zinc supplementation. Diabetic subjects supplemented with zinc (with or without other co-supplements), should expect a significant reduction in serum FBG, and elevation in HDL-c. This result is consistent with our subgroup analysis of high quality studies, with the exception of LDL-c.

However, subgroup analysis did not reduce high heterogeneity for mean changes of all markers (except for FBG) in the high quality studies. The source of heterogeneity therefore remains unknown.

Several meta-analyses studies have investigated the effects of zinc supplementation on diabetic or healthy subjects. Jayawardena et al. showed a significant reduction in systolic and diastolic blood pressures following zinc supplementation. The study demonstrated the beneficial effects of zinc supplementation on glycemic control and healthy lipid parameters in patients with diabetes (8). The review consisted of 12 studies which compared the effects of zinc supplementation on FBG in patients with type 2 diabetes, and 8 studies comparing the effects of zinc supplementation on serum lipid profiles. In the current review, we included 4 additional studies investigating the effects of zinc supplementation on glycemic status (19,23,31,36) and 5 additional studies on the effects of serum lipid profiles (16,19,23,25,36).

A further review showed a significant, albeit modest, reduction in glucose concentrations following zinc supplementation, and a tendency for reductions in mean levels of HbA1c. The authors suggested that zinc may contribute to the management of hyperglycemia in individuals with chronic metabolic disease (48).

In the recent meta-analysis, Ranasinghe et al. showed that zinc supplementation had significantly reduces total serum cholesterol, LDL-c, and TG on plasma lipid parameters in patients with different health statuses (49). The authors analyzed 14 trials which included healthy patients and patients with various health conditions such as chronic metabolic diseases (types 1 and 2 DM, metabolic syndrome, and obesity). A total of 8 studies, which included subjects with type 2 diabetes, were also included in the current meta-analysis (17,20,21,24,26,31, 33,34); an additional 8 studies were added in this updated study (15,19,23,27-29,32,36). This study is therefore the most comprehensive meta-analysis to date, evaluating whether zinc supplementation impacts serum lipid profiles and glycaemic status in diabetic patients. Furthermore, this is the first meta-analysis to investigate the effects of zinc supplementation based on distinct subgroups, intervention and quality assessment.

Several studies have suggested that supplementation with vitamins and minerals such as vitamins C and E, and magnesium may ameliorate the severity of many diabetic symptoms in patients (24,35,50). Moreover, that zinc supplementation improves the symptoms of T2DM and may lead to improvement of factors such as microalbuminuria, insulin secretion, homocsteine concentration, glucagon, glucose-6-phosphate, vitamin $B_{12}$, and folate ($BH_5$) (22,24). However, cohort studies have revealed different outcomes for the association between zinc intake and serum glucose concentrations (51) and the risk of T2DM (52); multiple studies have demonstrated that zinc is inversely associated with cardiovascular disease (CVD) risk factors in diabetic subjects (50,53). These findings are consistent with the conclusions presented in the present meta-analysis.

Multiple molecular mechanisms are known to affect glycaemic status after zinc supplementation of patients

with T2DM, including interactions between zinc and the insulin receptors, the structural integrity of insulin, and insulin signaling pathways (1,37,54). Zinc exerts insulin-like effects by stimulating phosphorylation of the insulin receptor β-subunit. Zinc can therefore influence phosphorylation of glucose receptors. Zinc can additionally mediate PI3K/Akt insulin-signaling pathway (1,37,54). Two families of zinc transporters are involved in maintaining intracellular zinc homoeostasis. These transporters onsist of the ZnT (SLC30) and ZiP (SLC390) transporter families (55). ZnT transporters act to elevate cellular zinc efflux and sequestration of zinc into intra-cellular organelles, and ZiP transporters transport zinc from outside the cells and from in intracellular compartments into the cytoplasm (55). ZnT8 co-localizes with insulin in human pancreatic islets is thought to be involved in both insulin granule zinc accumulation and regulation of insulin secretion in β-cells (56). Studies suggest that zinc transporters can affect both α- and β-cell function (56,57). Reducing insulin resistance and improving insulin secretion inhibits lipolysis in adipose tissues, reducing free fatty acid release and its availability to the liver, which prevents excessive lipoprotein synthesis. Moreover, Ginsberg et al. demonstrated that zinc deficiency downregulates fatty acid utilization in mitochondria and peroxisomes, and upregulates lipid synthesis in the liver of rat (58). Zinc can further regulate the activity of inducible nitric oxide syntnase, reversing the adverse effects of inflammation on the endothelium (59), and may reduce atheroma formation and plasma and arterial wall lipid peroxidation in rabbits fed on a high lipid and cholesterol diet (5). These animal models provide biological plausibility for a beneficial role of zinc in CVD prevention. Rodent models have further demonstrated that zinc may play important roles in the synthesis, secretion and function of insulin under normal physiological conditions, and that zinc supplementation may be protective in animal models of type 2 diabetes (60). In human, low serum zinc has been associated with diabetes, but this is thought likely due to hyperzincuria and impaired zinc absorption (61). One study reported a lower incidence of type 2 diabetes in patients with higher intakes of dietary zinc (62). However, oxidative stress, which is common in diabetic patients, may be reduced by zinc supplementation (52). Other supplements, such as selenium and magnesium, are indicated for relieving diabetes complications, similar to zinc supplements. However, the association between selenium and glucose metabolism has yielded inconsistent results within several studies: a prospective epidemiology study has linked high selenium status with a reduced risk of diabetes progression (63), while a study by the US National Health and Nutrition Examination associated high serum selenium with increased incidence of type 2 diabetes (64). A further study by Gao et al. did not find an association between selenium status with insulin secretion, insulin sensitivity, or risk of type 2 diabetes (65). Therefore, the exact role of selenium in progression of diabetes remains uncertain.

A further study by Guerrero et al. showed an association between hypomagnesaemia, impaired glucose tolerance and type 2 diabetes, but not with impaired fasting glucose (66). However, several reports have shown that patients with pre-diabetic and type 2 diabetic may have significant magnesium deficiencies (67). A study by Hruby et al. concluded that participants with higher magnesium intakes are about 32 to 47 percent less likely to develop incident diabetes, therefore supporting a role of magnesium intake for protection against development of overt diabetes (6). However, the mechanism of action remains inconclusive. Our studies suggest that zinc supplementation may be one of the most important factors for alleviating complications in diabetes, next to other trace elements such as selenium and magnesium.

In some trials, the dosage of zinc was greater than the recommended upper limit of 40 mg/d (15,26,27,29-31, 33,34,36); high dosages of zinc may cause copper deficiencies and adversely affect antioxidant enzymes such as superoxide dismutase (68). It has been suggested that zinc supplementation may lead to iron deficiency in females, especially those with low levels of iron storage (69). In another study, zinc supplementation was linked to abdominal pain (15), however the cause and effect relationship was not proved (8). In addition, a meta-analysis revealed that zinc supplementation may lead to attenuation of plasma HDL-c levels (9) after administration of zinc dosages higher than 50 mg/d for longer than 3 months (68). Doses of zinc $\geq$150 mg/d may further result in immune dysfunction (70). In this study, we noticed that the observed metabolic results of the 20 mg/d zinc dose are closest to the overall findings. Therefore, we can assume 20 mg/d is the optimal zinc dosage for improvement of metabolic indices. Despite the noted benefits of zinc supplementation on metabolic indices of diabetic patients, further research may be required before the benefits of zinc supplementation are concluded.

Limitations in the present meta-analysis include exclusion of papers not written in English and those only found on other electronic databases. As the authors of this paper only spoke English, we were unable to include papers that published in other languages; future meta-analyses should include these papers to increase confidence in the conclusions. A further limitation of the study was that we had insufficient data from some of papers for the meta-analysis, despite attempts to obtain the data from the authors.

Residual confounders are considered a further limitation. We were unable to rule out potential confounding

due to unmeasured variables in the included studies, such as patient selection, family history, type of test used, patient selection, clinical setting, and formulation of supplements. Moreover, dietary factors (such as restricted access to data of dietary intake of zinc, energy, vegetables, fat) differed between studies, which may increase confounding bias. Furthermore, there may be potential publication bias since there was remarkable heterogeneity among the included studies. The observed funnel plot asymmetry could be partly defined by the heterogeneity in the measurements. This variation may be caused by chance alone (small sample sizes) or errors in calculating measures of accuracy statistics, but could also reflect true heterogeneity.

Contrary to these limitations, the current meta-analysis has considerable strengths including the quantity of subjects included, lack of publication bias, and the use of a random effects model of meta-analysis for assessing study heterogeneity. In addition, studies were assessed using subgroup analysis based on intervention and quality assessment.

In conclusion, this meta-analysis found that administration of zinc supplements may improve lipid metabolism and glucose homeostasis in patients with type 2 diabetes. Since the calculated effect sizes were categorized as large effects for most of the parameters studies, the significant effects should be considered clinically. Although the overall analysis showed significant changes in nearly all indicators, subgroup analyses found that changes that are more noticeable for FBG, LDL-c, and HDL-c. Further research is warranted on larger sample sizes to determine the effectiveness, optimal dosage, and duration of zinc supplementation to induce maximal positive effects.

## AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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