

The Effect of Zinc Supplementation on Circulating Levels of Brain-Derived Neurotrophic Factor (BDNF): A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Abstract

Background: There are randomized controlled trials (RCTs) about the zinc supplementation effect on circulating levels of brain-derived neurotrophic factor (BDNF). However, the findings of these studies are inconsistent. The purpose of this systematic review and meta-analysis was to determine the zinc supplementation effect on BDNF and zinc levels in published RCTs. **Methods:** We searched PubMed/Medline, Cochrane, Scopus, ISI Web of Science, EMBASE, "Clinicaltrials.gov", "Cochrane Register of Controlled Trials", "IRCT" and also key journals up to 2019. RCTs with two intervention (zinc) and control (placebo) groups that evaluated zinc supplementation efficacy on BDNF levels were included. Study heterogeneity was assessed, and then, meta-analysis was performed using the fixed-effects model. **Results:** Four studies were included in the present secondary analysis. Compared with placebo, zinc supplementation significantly enhanced circulating levels of BDNF [(SMD): 0.31, 95% confidence interval (CI): (0.22, 0.61)] and zinc [(SMD): 0.88, 95% CI: (0.54, 1.22)] with no considerable heterogeneity among the studies [($Q = 3.46$; $P = 0.32$; $I^2\% = 13.4$); ($Q = 2.01$; $P = 0.37$; $I^2\% = 0.5$), respectively]. **Conclusions:** Our results propose that zinc supplementation can increase the circulating levels of BDNF and zinc. This study was registered at PROSPERO as CRD42020149513.

Keywords: Brain-derived neurotrophic factor, meta-analysis, randomized controlled trial, systematic review, zinc

Introduction

Neurodegenerative diseases (NDs) are a major concern in a quickly aging world.^[1,2] Increasing evidence suggests that the change in BDNF expression, peripheral levels and signaling can be involved in NDs pathogenesis.^[3,4]

BDNF is a member of the neurotrophin family.^[5] It plays a critical role in neuron survival, such as dorsal root ganglion subpopulation,^[6] central serotonergic (5-HT) neurons function,^[7] reducing hippocampus neuroinflammation^[8], increased synaptic transmission^[9] and neurogenesis.^[10,11] According to the rat model of stroke, BDNF can alleviate local inflammation by reducing proinflammatory cytokine and also enhancing anti-inflammatory cytokine.^[12]

Decreased BDNF expression has been reported in Alzheimer's disease (AD),^[13]

Parkinson's disease (PD),^[14] dementias,^[15] multiple sclerosis (MS)^[16] and amyotrophic lateral sclerosis (ALS).^[17] Several conditions, including antidepressant medications^[18] and anthocyanin supplementation^[19] can increase the BDNF gene expression. Its blood concentration can also be enhanced by environmental factors such as exercise,^[20] omega-3 fatty acids,^[21] resveratrol^[22] and zinc supplementation.^[23]

Zinc is the second most abundant trace element in the brain.^[24] In addition to its anti-inflammatory and antioxidant properties,^[25,26] it can affect BDNF expression and activity.^[27] Recently, RCTs have been performed to designate the zinc supplement efficacy on BDNF levels (serum or plasma). However, in these RCTs, the impact of zinc supplementation on BDNF levels was inconsistent and uncertain. So, this meta-analysis was conducted to evaluate the zinc supplement effect on circulating levels of BDNF in adults.

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Methods

Protocol

The present systematic review and meta-analysis were accomplished based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline and registered in PROSPERO with the registration number CRD42020149513.

Search strategy

To ensure access to all available relevant evidence, Medical Subject Headings (MeSH) terms were used during the search strategy to recognize scientific literature between 1980 and 2019 within the international databases of PubMed/Medline, Scopus, ISI Web of Science, Cochrane, and EMBASE. Gray literature searching was “Clinicaltrials.gov”, “Cochrane Register of Controlled Trials”, “IRCT”, and also key journals in Nutrition and Neuroscience [Appendix 1]. The search was performed without any restrictions in language. PICO was defined as a structured question describing the Population (healthy adults and adults with any medical disorders), Intervention (oral zinc supplement), Comparison (placebo) and Outcome (BDNF and zinc levels). The search terms were focused on zinc or “zinc supplement”; together with the “BDNF”, and “brain-derived neurotrophic factor”. Relevant mesh terms and main words are added to search queries that are attached in Appendix 2.

Inclusion and exclusion criteria

Regarding the study design, RCTs with at least two groups, zinc (as an intervention group) and placebo (as a control group) were included. There were no restrictions for the type and doses of zinc supplement, intervention duration, placebo type, BDNF and zinc assessment method; and nor for the participants' health status. We included studies where zinc was applied as a single therapy. The primary outcome was to compare BDNF level changes between an intervention and control group. Serum zinc change in response to zinc supplementation also was a secondary outcome. Duplicate and non-relevant publications were excluded.

Data collection and data extraction

The bibliographic data of searching articles were saved using the Endnote software libraries. Duplicate records were removed. To assess the article's eligibility and relevancy, three-step process titles, abstracts and full text were conducted by two independent researchers. Quality assessment and data extraction were performed with two independent reviewers. Probable differences of opinions were solved by the third researcher. First author, publication year; study place; mean age (year); male and female percentage in each group; participants' health status, type and the dose of zinc supplement; intervention duration; placebo type; BDNF and zinc assessment method, sample size; BDNF and zinc levels change; effect size and article quality were extracted from included articles, and then, recorded in Excel.

Quality assessment of selected studies

Two investigators have independently evaluated the article's methodological quality with the Cochrane Risk of Bias Tool for RCTs.^[28] Evaluated criteria of included RCTs generation, allocation concealment, selective reporting, other bias, incomplete outcome data, blinding of participants and personnel, and also outcome assessment. A study that met all criteria received good quality, otherwise, based on the Cochrane tool guidance, it was classified as a fair quality or poor-quality study.

Statistical analysis

The zinc supplementation efficacy on BDNF and zinc levels was assessed as the standard mean difference (SMD) of change in peripheral blood levels and 95% CI which was used to compute the difference of the mean value of the final mean from the baseline for each study group. The pooled SMD was estimated using the fixed effect meta-analysis of the BDNF level without severe heterogeneity between studies in terms of reported effect size, respectively.^[29] The heterogeneity amount was computed with I^2 statistics, which is an estimation of the total variation across investigations due to heterogeneity.^[30] The analyses were conducted using STATA 14 software. P value ≤ 0.05 was contemplated as statistically significant. Publication bias

Publication bias was assessed by Begg and Egger's test. In the Egger's test, 0.1 was regarded as statistically significant.

Sensitivity analysis

There was not substantial heterogeneity among the included RCTs; therefore, we did not conduct sensitivity analysis.

Subgroup analyses

We did subgroup analyses for intervention duration, supplemental dosage and quality of the included RCTs to assay the zinc supplementation efficacy on BDNF levels.

Results

Search results

Our search strategy resulted in 12,064 records through database searching. The detailed search processes and article selection have been presented in the flow chart [Figure 1]. Finally, four RCTs that meet the present study's inclusion/exclusion criteria were included in the present secondary analysis [Table 1].

Specifications of selected studies

The important features of the four RCTs which reported the zinc supplementation efficacy on BDNF levels and other variables have been summarized in Table 1. All selected RCTs with publication dates between 2015 and 2019 had been conducted in Iran. In the present meta-analysis, all of the included original studies described serum or plasma BDNF levels as an outcome with a total of 185 participants (intervention group = 92, control group = 93),

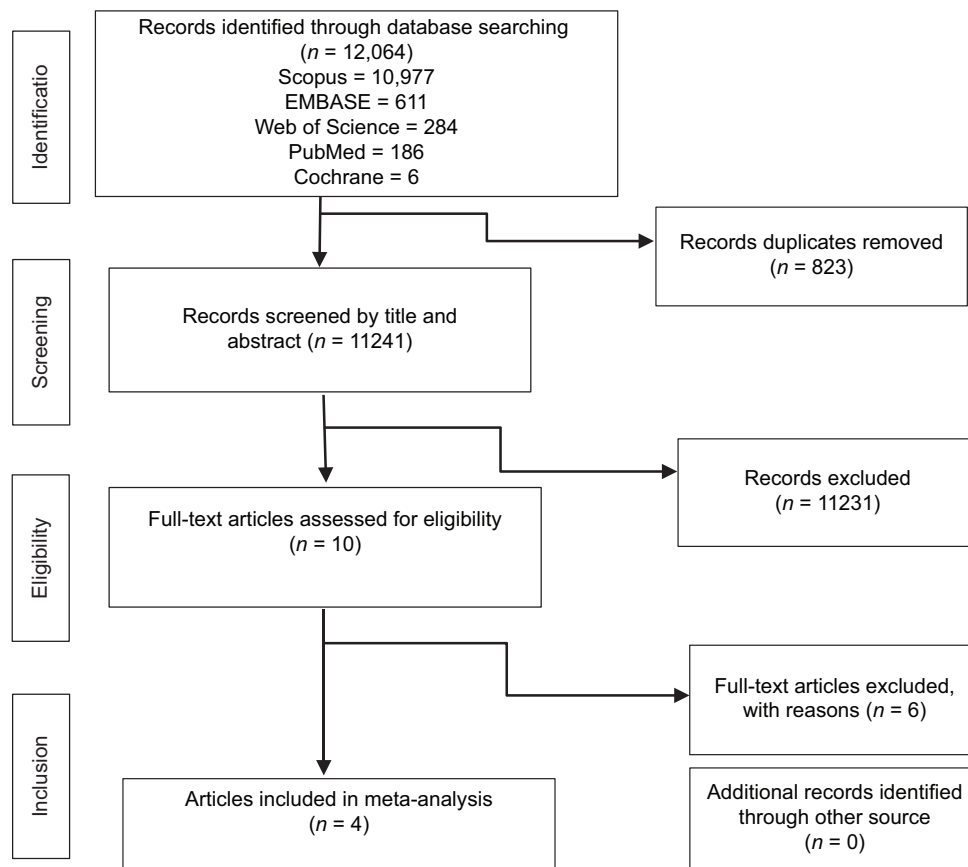


Figure 1: Flowchart of the articles selected for meta-analysis of zinc supplementation on circulating levels of BDNF

Table 1. Demographic and clinical characteristics of included randomized controlled trials for meta-analysis of zinc supplementation on circulating levels of BDNF

Country	Health status of participants and sex	Number of participant (I/C)	Age range (year)	Intervention		Duration of intervention	Outcome assessment method	
				Intervention (name and dose)	Control (name and dose)		BDNF	Serum Zn
Iran	Premenstrual syndrome Female	I=27 C=30	18-30	Zinc gluconate 30 mg	-	12 weeks	ELISA Serum	Colorimeter
Iran	Non-proliferative diabetic retinopathy Male/Female	I=23 C=22	20-40	Zinc gluconate 30 mg	Maltodextrin 30 mg	3 months	ELISA Serum	Atomic absorption spectrophotometry
Iran	Overweight or obese Male/Female	I=22 C=24	18-35	Zinc gluconate 30 mg	Starch	12 weeks	ELISA Serum	Atomic absorption spectrophotometry
Iran	Major depressive disorder Male/Female	I=20 C=17	18-55	Zinc sulfate 25 mg	Malto dextrose	12 weeks	Immuno assay kits Plasma	-

whereas, Three RCTs, which used a total of 148 participants (intervention group = 72, control group = 76) reported serum zinc alteration as an outcome measure as a result of zinc supplementation.^[23,31,32] All trials were double-blinded placebo controlled. One RCT included only women^[23] and others recruited both men and women.^[31-33] In all four included RCTs, the dietary zinc intake did not change during the intervention period. The participants' age ranged from 18 to 55 years. In all the studies, zinc

supplement had been prescribed alone. The daily oral zinc doses in the intervention group of Three RCTs were 30 mg^[23,31,32] and one study used 25 mg/day.^[33] The supplement was administered orally in all research. The intervention period was 84 days in three studies^[23,31,33] and 90 days in one study.^[32] Selected studies had enrolled participants with major depressive disorder,^[33] obese or overweight populations,^[31] non-proliferative diabetic retinopathy^[32] and young women with premenstrual syndrome (PMS).^[23]

Quality assessment

According to the Cochrane Risk of Bias Tool for RCTs, two studies were considered as good quality^[23,33] while the other two RCTs were classified as poor quality.^[31,32]

The impact of zinc supplementation on circulating levels of BDNF

Four RCTs reported changes in BDNF levels as research findings. The overall zinc supplement efficacy on BDNF

enhancement was statistically significant. The pooled SMD using the fixed effect suggested that zinc supplementation is correlated with a significant increased circulating BDNF levels in the intervention group compared with the placebo group [(SMD): 0.31, 95% ; CI: (0.22, 0.61)] [Table 2 and Figure 2] with no considerable heterogeneity among studies ($Q = 3.46, P = 0.32, I^2 = 13.4$) [Table 2].

Subgroup analyses

As a result of subgroup analysis, increased peripheral blood

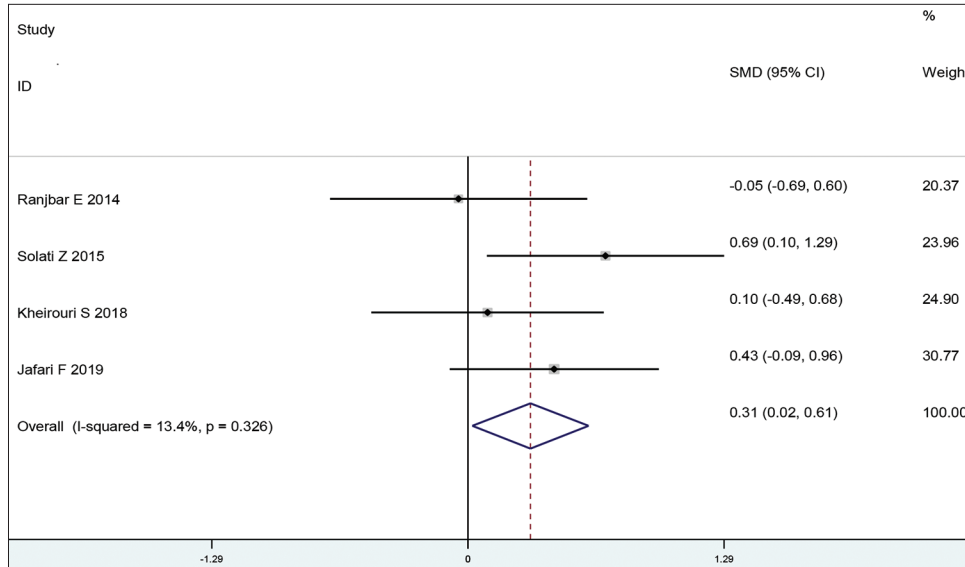


Figure 2: Forest plot of randomized-controlled trials to investigate the effect of zinc supplementation on circulating levels of BDNF

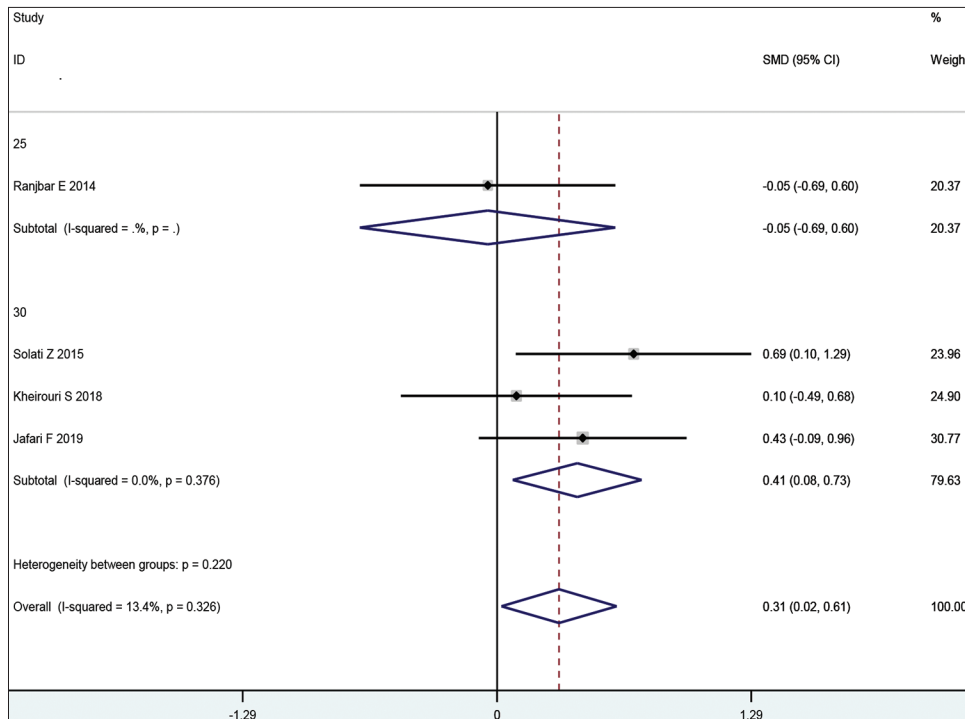


Figure 3: Forest plot of randomized-controlled trials to investigate the effect of zinc supplementation on circulating levels of BDNF (subgroup analysis by zinc doses).

Table 2: Meta-analysis of zinc supplementation on circulating levels of BDNF and zinc

Number of participants	Number of studies	SMD (95% CI)	Model	Heterogeneity assessment		
				I ² %	Q test	P
BDNF						
I=92, P=93	4	0.31 (0.22, 0.61)*	Fixed	13.4	3.46	0.32
Zinc						
I=72, P=76	3	0.88 (0.54, 1.22)*	Fixed	0.5	2.01	0.37

*Statistically significant. BDNF: Brain-derived neurotrophic factor; SMD: Standard mean difference

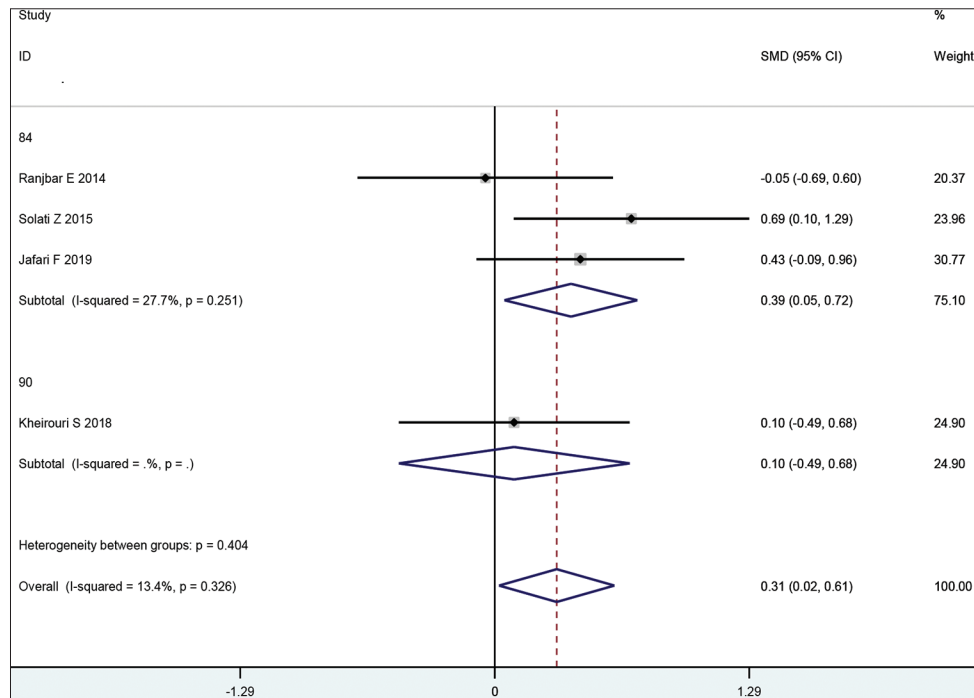


Figure 4: Forest plot of randomized-controlled trials to investigate the effect of zinc supplementation on circulating levels of BDNF (subgroup analysis by intervention duration)

BDNF levels were significant at 30 mg supplementary dosages. (Three studies, SMD: 0.41, 95% CI: 0.08 to 0.61; $P < 0.001$, $I^2 = 0.0\%$) and not significant with 25 mg supplementary dosages (One study, SMD: -0.04, 95% CI: -0.69 to 0.6, $P = 0.21$) [Figure 3].

With regard to intervention duration, both 84 days (Three RCTs, SMD: 0.38, 95% CI: 0.049 to 0.72; $P < 0.001$; $I^2 = 27.7\%$) and 90 days zinc supplementation (One RCT, SMD: 0.1, 95% CI: 0.022 to 0.61, $P < 0.001$) elevated BDNF levels [Figure 4].

The study quality did not significantly affect the BDNF levels [(Two poor quality studies, SMD: 0.24, 95% CI: -0.16 to 0.65, $P = 0.26$; $I^2\% = 21.8$); (Two good quality studies, SMD: 0.39, 95% CI: -0.28 to 0.81, $P = 0.16$; $I^2\% = 48.4$)]; while this effect was significant in combining all studies together (SMD: 0.31, 95% CI: 0.022 to 0.61) [Figure 5].

The impact of zinc supplementation on serum zinc levels

The zinc supplement influence on serum zinc was analyzed in Three RCTs of four included studies [Figure 6]. Zinc supplementation brought about a significant increase in serum zinc level of intervention group compared with the

control group [(SMD): 0.88, 95% CI: (0.54, 1.22)] [Table 2]. There was no obvious heterogeneity in the reviewed articles ($Q = 2.01$; $P = 0.37$; $I^2\% = 0.5$) [Table 2].

Publication bias

There was no significant publication bias among RCTs investigating the zinc supplementation impact on BDNF (coefficient = -1.82, standard error = 0.25, $P = 0.59$, 95% CI = -3.52, 0.36) and zinc levels (coefficient = -1.35, standard error = 0.12, $P = 0.6$, 95% CI = -2.89, 0.18).

Discussion

Main findings

However, to the best of the author’s knowledge, this is the first secondary analysis of RCTs assessing the zinc supplementation efficacy on BDNF levels. The result of our study showed that zinc supplementation is associated with enhanced circulating levels of BDNF. This beneficial effect is in line with growing evidence indicating that the BDNF levels have a significant positive association with serum zinc.^[31]

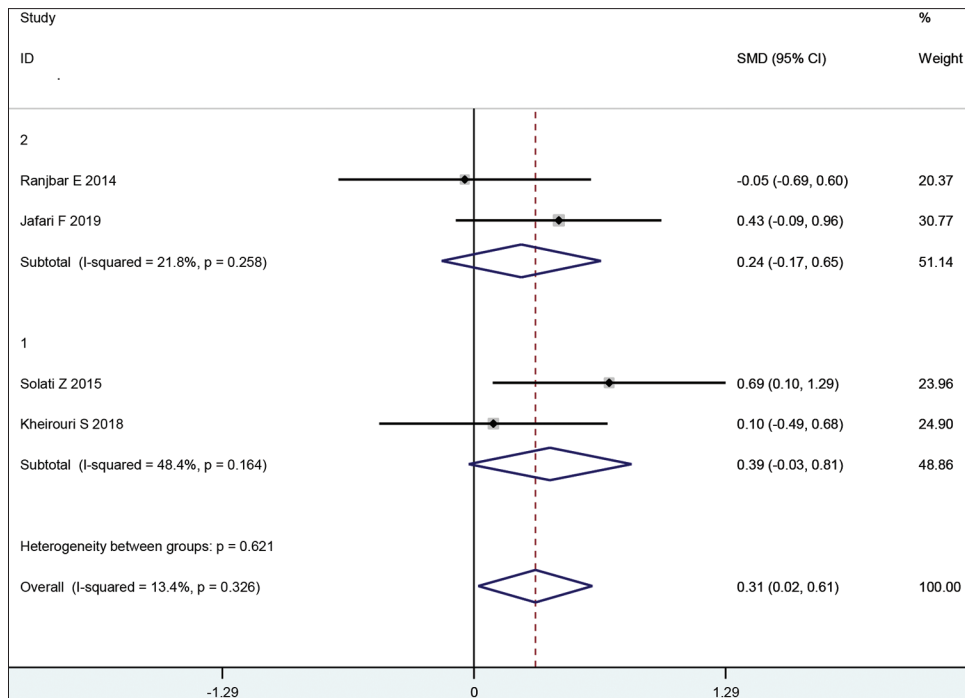


Figure 5: Forest plot of randomized-controlled trials to investigate the effect of zinc supplementation on circulating levels of BDNF (subgroup analysis by study quality)

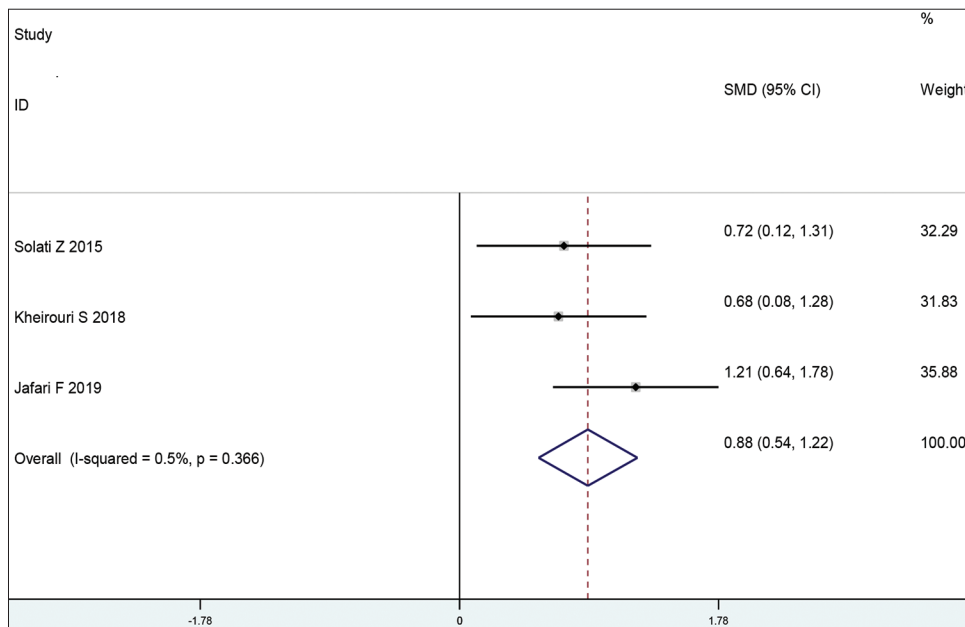


Figure 6: Forest plot of randomized-controlled trials to investigate the effect of zinc supplementation on serum zinc levels

The supportive effect of zinc supplementation on increasing BDNF levels suggests its possible benefit for ND that correlates with low BDNF levels. A large body of evidence indicated BDNF as an important predictive factor for following the beginning, progress and cure of brain disorders due to its main role in brain neurogenesis and neuroplasticity.^[5,34] Previous published systematic reviews and/or meta-analysis have shown that peripheral BDNF levels reduce in bipolar disorder (BD),^[35] patients with suicidal behavior,^[36] AD,^[37] PD,^[38] first-episode

psychosis (FEP)^[39] and schizophrenia.^[40] Decreased BDNF levels, in turn, are considerably associated with cognitive impairment in schizophrenia patients.^[41]

The effectiveness of various strategies such as exercise,^[42] nutritional interventions including high-flavonoid fruit and vegetable intake,^[43] dietary antioxidant^[44] and zinc supplementation^[23] has been shown to elevate BDNF. The precise molecular mechanism by which zinc supplementation enhances BDNF levels is beyond this study, but in short, one of

the proposed mechanisms is increasing matrix metalloproteinases 2 (MMP-2) and MMP-9 activation.^[45] MMPs activation, in turn, is involved in converting biologically inactive form (pro-BDNF) to mature BDNF.^[45] Huang *et al.* showed that zinc activates tyrosine kinase receptor (TrkB), and its downstream signaling pathways via a BDNF-independent method. TrkB receptor is one of the important signals involved in nervous system function.^[46]

The results of Mc Murphy's study to promote healthy aging through targeting hypothalamic BDNF^[47] and this study supports the idea that zinc supplementation may be an effective and safe nutritional strategy in delaying and decelerating age-related disorders and having healthy aging.

Three studies, included in our meta-analysis, measured changes in serum zinc levels as a research outcome, which demonstrated that zinc supplement considerably increases serum zinc levels in the intervention group compared with the placebo group.

Strengths and limitations

Our study had several strengths and limitations that should be contemplated when analyzing the results. One of our meta-analysis strengths was the low heterogeneity of the selected studies. There were a limited number of RCTs investigates the zinc supplementation effect on circulating BDNF levels. Inevitably, our results were based on only four available RCTs in this regard with a small sample size. So, more RCTs are necessary to reveal the zinc supplementation effect on BDNF levels conclusively.

In included RCTs, zinc supplement impact on elevating BDNF levels was investigated in healthy persons and individuals with medical problems (premenstrual syndrome, non-proliferative diabetic retinopathy and major depressive disorder) that affect the finding generalizability to people with different health status. All included studies were carried out in Iran, with identical culture, ethnicity and genetic, which may limit the result's generalizability to other communities and ethnicities.

Previous articles indicated both gender and age affect the BDNF levels. BDNF levels are higher in men than women and decrease after the age of 65.^[43] In reviewed RCTs, the participants' age range was 18-55. The question that arises is whether these beneficial effects can be expected in people over 65? That needs to be surveyed in the future researches. Thus, future well-designed RCTs with a large sample size, participants' homogeneity in health status and different age groups of men and women are needed to prospectively investigate the zinc supplement impact on increasing BDNF levels as well as supplementation efficacy as adjunct therapeutic strategies for reducing and delaying age-related disorders in an aging population.

Conclusions

This secondary analysis of RCTs illustrated the significant enhancing effect of oral zinc supplementation on peripheral

BDNF and zinc levels in adults. Increased circulating levels of BDNF as a result of zinc supplementation suggest that zinc supplementation may be a safe and effective strategy to counteract NDs that are correlated with low BDNF levels.

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Conflicts of interest

There are no conflicts of interest.

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 45. Corona C, Masciopinto F, Silvestri E, Viscovo AD, Lattanzio R, Sorda RL, *et al.* Dietary zinc supplementation of 3xTg-AD mice increases BDNF levels and prevents cognitive deficits as well as mitochondrial dysfunction. *Cell Death Dis* 2010;1:e91. doi: 10.1038/cddis.2010.73.
 46. Huang YZ, Pan E, Xiong Z-Q, McNamara JO. Zinc-mediated transactivation of TrkB potentiates the hippocampal mossy fiber-CA3 pyramid synapse. *Neuron* 2008;57:546-58.
 47. McMurphy T, Huang W, Liu X, Siu JJ, Queen NJ, Xiao R, *et al.* Hypothalamic gene transfer of BDNF promotes healthy aging in mice. *Aging Cell* 2019;18:e12846.

Appendix 1: Searched key journals for meta-analysis of zinc supplementation on circulating levels of BDNF

Nature neuroscience	Neurological Science Journal
Neurology Research International	Acta Psychopathologica
Journal of Neuropsychiatry	Insights in Neurosurgery
Journal of Neurology and Neuroscience	Advances in Nutrition
Journal of Alzheimer's & Dementia	Nutritional Neuroscience
Journal of Neurological Disorders	Journal of Clinical Nutrition & Dietetics
Journal of the Neurological Sciences	Journal of Human Nutrition and Dietetics
Psychology and Brain Studies	The American Journal of Clinical Nutrition
Journal of Brain, Behaviour and Cognitive Sciences	

Appendix 2: Search strategy for meta-analysis of zinc supplementation on circulating levels of BDNF

Pubmed

(Zinc OR Zn OR "Zinc gluconate" OR "Gluconic acid zinc (II) salt" OR "D-Gluconic acid zinc" OR "Zinc acetate" OR "Galzin" OR "Zinc Acetate Dihydrate" OR "Anhydrous Zinc Acetate" OR "Dicarbomethoxyzinc" OR ("Zinc Acetate" AND Anhydrous) OR "Zinc Acetate Anhydrous" OR ("Acetic acid" AND zinc salt) OR "Zinc (II) acetate" OR "Zinc sulfate" OR (Sulfate AND Zinc) OR "Zincteral" OR (Zinc Sulfate AND Heptahydrate) OR "Zinc picolinate" OR "Zinc orotate" OR "Zinc citrate" OR "Zinc oxide") AND ("Brain Derived Neurotrophic Factor" OR (Factor AND "Brain-Derived Neurotrophic") OR ("Neurotrophic Factor" AND "Brain-Derived") OR BDNF OR Neurotrophin) AND (1980/01/01: 2019/08/31).

EMBASE

(Zinc OR Zn OR "Zinc gluconate" OR "Gluconic acid zinc (II) salt" OR "D-Gluconic acid zinc" OR "Zinc acetate" OR "Galzin" OR "Zinc Acetate Dihydrate" OR "Anhydrous Zinc Acetate" OR "Dicarbomethoxyzinc" OR ("Zinc Acetate" AND Anhydrous) OR "Zinc Acetate Anhydrous" OR ("Acetic acid" AND zinc salt) OR "Zinc (II) acetate" OR "Zinc sulfate" OR (Sulfate AND Zinc) OR "Zincteral" OR (Zinc Sulfate AND Heptahydrate) OR "Zinc picolinate" OR "Zinc orotate" OR "Zinc citrate" OR "Zinc oxide") AND ("Brain Derived Neurotrophic Factor" OR (Factor AND "Brain-Derived Neurotrophic") OR ("Neurotrophic Factor" AND "Brain-Derived") OR BDNF OR Neurotrophin).

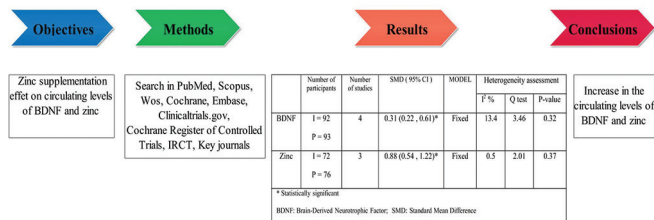
Scopus

(ALL (Zinc OR Zn OR "Zinc gluconate" OR "Gluconic acid zinc (II) salt" OR "D-Gluconic acid zinc" OR "Zinc acetate" OR Galzin OR "Zinc Acetate Dihydrate" OR "Anhydrous Zinc Acetate" OR "Dicarbomethoxyzinc" OR "Zinc Acetate" AND Anhydrous OR "Zinc Acetate Anhydrous" OR "Acetic acid" AND "zinc salt" OR "Zinc (II) acetate" OR "Zinc sulfate" OR (Sulfate Zinc) OR Zincteral OR ((Zinc Sulfate) AND Heptahydrate) OR "Zinc picolinate" OR "Zinc orotate" OR "Zinc citrate" OR "Zinc oxide")) AND (ALL ("Brain Derived Neurotrophic Factor" OR (Factor AND "Brain-Derived Neurotrophic") OR ("Neurotrophic Factor" AND "Brain-Derived") OR BDNF OR Neurotrophin)).

ISI/WOS

(ALL = (Zinc OR Zn OR "Zinc gluconate" OR "Gluconic acid zinc (II) salt" OR "D-Gluconic acid zinc" OR "Zinc acetate" OR Galzin OR "Zinc Acetate Dihydrate" OR "Anhydrous Zinc Acetate" OR "Dicarbomethoxyzinc" OR "Zinc Acetate" AND Anhydrous OR "Zinc Acetate Anhydrous" OR "Acetic acid" AND "zinc salt" OR "Zinc (II) acetate" OR "Zinc sulfate" OR (Sulfate Zinc) OR Zincteral OR ((Zinc Sulfate) AND Heptahydrate) OR "Zinc picolinate" OR "Zinc orotate" OR "Zinc citrate" OR "Zinc oxide")) AND (ALL = ("Brain Derived Neurotrophic Factor" OR (Factor AND "Brain-Derived Neurotrophic") OR ("Neurotrophic Factor" AND "Brain-Derived") OR BDNF OR Neurotrophin)).

Zinc supplementation on BDNF levels



This is a graphical abstract