# **Review Paper**

# Association Between Zinc and Pediatric Metabolic Syndrome: 🔒 🧑 A Systematic Review and Meta-analysis





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#### **ABSTRACT**

Background: The increasing prevalence of metabolic syndrome (MetS) in the pediatric population underscores a critical need for understanding dietary and micronutrient factors, including the role of zinc in metabolic regulation. Despite the well-known importance of zinc in metabolic functions, there are contradictory results regarding its association with

Objectives: We aimed to perform a comprehensive review of the studies on the association between serum zinc level and dietary zinc intake with MetS in children and adolescents.

Methods: This is a systematic review and meta-analysis study conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The related studies in English published up to the end of May 2024 were searched in PubMed, Scopus, and Web of Science. The observational studies with high quality (assessed using the Newcastle-Ottawa scale [(NOS)]) were included. Odds ratios (ORs) and 95% confidence intervals (CIs) comparing the risk of MetS in lower levels of zinc versus higher levels were also extracted from each study.

Results: Of 444 initially identified records, four eligible studies were selected for the review. The pooled analysis revealed no significant association between zinc levels (food intake or serum level) and the presence of MetS (P=0.41; OR=1.22, 95% CI, 0.92%, 1.62%). Heterogeneity was not substantial (I2=0.00).

Conclusions: The non-significant association of serum zinc level and dietary zinc intake with MetS in children and adolescents, coupled with substantial heterogeneity across included studies, highlights the complexity of the association between zinc and MetS among youths. This underscores the necessity for further longitudinal studies on the association of low zinc levels and the risk of MetS in children and adolescents.

#### **Key Words:**

Metabolic syndrome (MetS), Pediatrics, Zinc, Meta-analysis

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# Introduction

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etabolic syndrome (MetS) is a known medical condition. It is characterized by the presence of abdominal obesity, insulin resistance, high blood pressure, and elevated lipid levels, thereby increas-

ing the risk of cardiovascular diseases [1, 2]. It is characterized by at least three of the following conditions: increased waist circumference, elevated triglyceride levels, reduced HDL cholesterol levels, elevated blood sugar levels, and increased blood pressure [3, 4]. The global prevalence of MetS ranges from 11.6% to 62.5% [5].

While the precise etiology remains incompletely elucidated, some trace elements, including zinc, have been postulated to play a pivotal role. Emerging evidence has suggested an association between zinc deficiency and metabolic disorders [6, 7]. Trace elements are essential cofactors in various metabolic processes, facilitating enzyme reactions and supporting overall cellular function [8, 9]. Zinc ranks as the second most prevalent trace metal in the human body, playing a crucial role in DNA functions, protein synthesis, cell division, and preserving cellular and endothelial integrity. It can reduce oxidative stress, chronic inflammation, and insulin resistance [10, 11]. Epidemiological investigations have indicated an inverse relationship between dietary zinc intake and MetS-related conditions such as diabetes [12, 13]. It was assumed that higher dietary zinc intake could have an inverse effect on the occurrence of MetS [14]. However, the findings of some observational studies have shown an inconsistent association between dietary zinc intake and MetS in children and adolescents [15, 16]. This study aims to review the studies that examined the association of dietary zinc intake and serum zinc levels with MetS among children and adolescents.

### **Methods**

This is a systematic review and meta-analysis study conducted according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) 2020 guidelines [17]. We conducted searches in online databases, including PubMed, Web of Science, and Scopus, for related studies published up to May 2024. Search terms related to MetS ("metabolic syndrome," "metabolism syndrome") and zinc ("zinc," "Zn"), targeting children and adolescents were used for the search. Initially, the titles and abstracts of articles were screened to find relevant studies, followed by an in-depth review of the full texts to select eligible studies. Furthermore, we examined the reference lists of included articles to

find additional relevant studies. Two authors (Kasra Talebi Anaraki and Motahar Heidari-Beni) independently screened the titles, abstracts, and full texts. Any discrepancies were settled through discussion and mutual consultation. Observational studies that investigated the association between serum zinc levels or dietary zinc intake with MetS in children and adolescents were included. Only English-language articles and human studies were included. Irrelevant studies, review studies, letters to the editor, case reports, randomized controlled clinical trials; and animal studies were excluded.

Data extraction was performed independently by two authors (Motahar Heidari-Beni and Sepideh Moalem), with any discrepancies addressed through discussion and mutual agreement. The information extracted included the first author's name, year of publication, study location, age, gender, sample size, study design, adjustments made, serum zinc assessment, dietary zinc intake, effect estimates, and the diagnostic criteria for MetS.

For quality assessment, we used the Newcastle-Ottawa scale (NOS), applicable to non-randomized studies [18]. This tool has three main elements: The process of selecting study cohorts, the comparability of various cohorts, and the determination of exposure or outcome in the study cohorts. Any disputes concerning methodological quality were addressed through dialogue and collaborative consultation between authors.

Odds ratios (ORs) and 95% confidence intervals (CIs) comparing the risk of MetS in people with lower levels of zinc versus those with higher levels were extracted from each study. The subgroup analysis was done based on dietary intake or serum zinc level. A fixed-effects meta-analysis was employed to derive effect estimates due to the inherent study design and varied methodologies. The assessment of population bias was not conducted due to the insufficient number of studies available. The heterogeneity between studies was assessed by the I² statistic. All statistical analyses were carried out in Stata software, version 17 (StataCorp LP), with a significance level set at 0.05 for all tests.

#### Results

During the initial search, 444 records were identified. After removing 148 duplicates, the remaining 296 articles underwent screening based on titles and abstracts, which led to the exclusion of 213 irrelevant studies. Subsequently, 79 studies, including review studies, case reports, letters to the editor, animal studies, or randomized controlled clinical trials, were excluded. Finally,

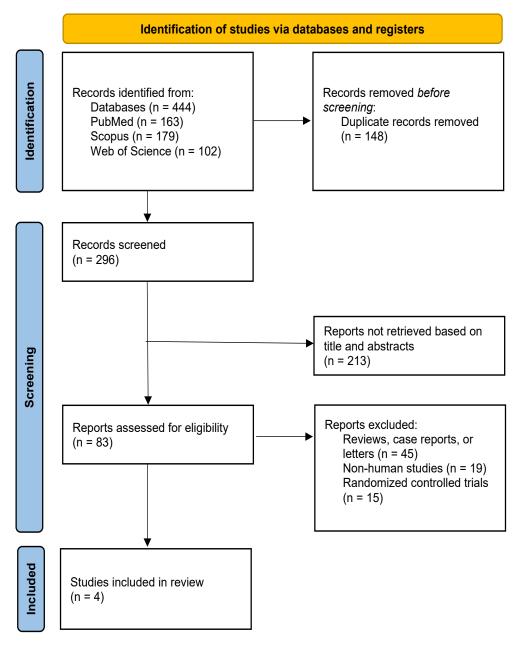


Figure 1. Flowchart of the study selection

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four articles [15, 16, 19, 20] were included in this metaanalysis. Figure 1 illustrates a comprehensive diagram of these articles and Table 1 presents their key characteristics. These studies, published between 2013 and 2024, were cross-sectional studies. The studies were conducted in Iran [15], China [20], Colombia [19], and Brazil [16]. The sample size ranged from 327 to 3701, for a total of 6710 participants.

Qorbani et al. [15] in a cross-sectional study on Iranian children and adolescents, revealed no significant association between serum zinc levels and MetS. Batista et al. [16] in a cross-sectional study on 327 adolescents dem-

onstrated a significant association between MetS and its components with the intake of antioxidant nutrients in Brazilian adolescents. Suarez-Ortegon et al. [19] in a cross-sectional study among 1311 adolescents, showed a negative correlation between the highest quartile of zinc intake and MetS in males. They found no significant association in females. Yang et al. [20] in a cross-sectional study on 3701 adolescents in China found no significant association between levels of zinc intake and MetS risk.

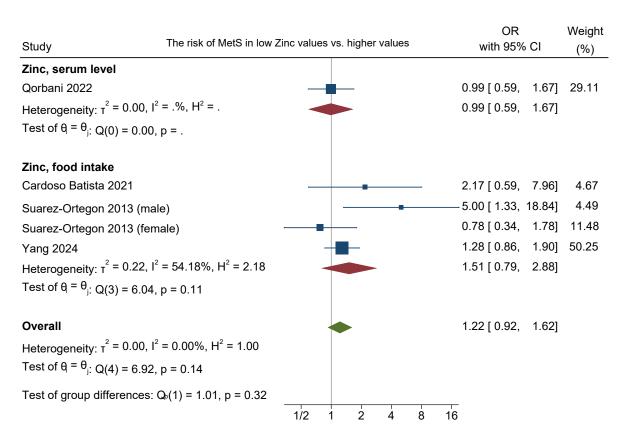


Figure 2. The ORs and 95% CIs for the MetS risk in low values of Zinc vs higher values

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Figure 2 shows the ORs and 95% CIs of the MetS risk in low values of zinc vs higher values. There was no significant association between zinc (dietary intake or serum level) and MetS (OR=1.22, 95% CI, 0.92%, 1.62%). Heterogeneity was not substantial (I<sup>2</sup>=0.00).

#### Discussion

A meta-analysis conducted on adults revealed that elevated serum zinc levels were linked to an increased risk of MetS. The findings indicated that participants diagnosed with MetS exhibited higher serum zinc levels compared to the control group [21]. Zinc content has been assessed in various tissues like serum, blood cells, hair, and nails [22]. Factors such as stress, infection, and hormonal changes can influence serum zinc levels. Thus, serum zinc is considered the best gauge of zinc status [23]. The presence of phytates in foods like nuts and grains may affect the absorption of dietary zinc [24]. Therefore, randomized controlled trials using zinc supplements are necessary. Dietary sources, such as meat, nuts, and whole grains, contain zinc. However, modern nutritional patterns are often deficient in this essential nutrient [25]. Zinc, an indispensable trace metal in the human body, has critical roles in DNA replication, transcription, protein synthesis, and various cellular

processes. It serves as a cofactor in enzymatic reactions associated with superoxide dismutase, catalase, and glutathione peroxidase [26, 27].

Childhood obesity has adverse effects on erythroid antioxidant levels. This accentuates the role of oxidative stress in MetS [28]. There are significant variations in zinc levels among children with MetS. This indicates a potential imbalance that may exacerbate metabolic dysregulation. Some studies investigated the role of zinc concentrations in the morbidity of obese children, with or without MetS [29, 30]. Their findings showed that zinc levels correlated with the health status of these children. Chronic inflammation is a potential underlying factor for MetS [31]. Zinc acts as a cofactor for antioxidant enzymes, thereby diminishing the production of inflammatory cytokines [32].

The connection between serum zinc and MetS is debated. The connection has been reported in the adult population. Two prospective cohort studies have shown a significant association between higher serum zinc levels and an increased risk of hypertension [33] and diabetes [34]. Two meta-analysis studies on adults suggested a significant inverse association between zinc dietary intake and MetS. However, results in adolescents

Table 1. Characteristics of included studies

Author(s), Year	Location	Sample Size	Age (y)	Study Design	Sample	Effect Estimates	Diagnostic Criteria for MetS	NOS Score
Qorbani, 2022 [15]	Iran	1371	Mean: 12.2±3.2	Cross- sectional	Whole blood zinc	OR: 1.01 (95% CI, 0.6%, 1.7%)	NHANES III criteria	6
Suarez-Ortegón, 2013 [19]	Colombia	664	6-11 (girl)	Cross- sectional	Whole blood zinc	OR: 1.29 (95% CI, 0.56%, 2.94%)	Ferranti's criteria	7
		647	6-11 (boy)			OR: 0.2 (95% CI, 0.05%, 0.71%)		
Batista, 2021 [16]	Brazil	327	<18	Cross- sectional	Whole blood zinc	OR: 2.17 (95% CI: 0.59%, 7.94%)	Cook's criteria	7
Yang, 2024 [20]	China	3701	Mean: 15.5±0.06	Cross- sectional	Zinc intake	OR=1.28 (95% CI, 0.86%, 1.9%)	ATP III criteria	8

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Abbreviations: OR: Odds ratio, NOS: Newcastle-Ottawa scale; NHANES III: Third national health and nutrition examination survey.

were non-significant [21, 35]. This association may underscore the importance of collaboration between physicians and nutritionists in managing metabolic disorders. Of course, the adverse effects of excess zinc intake should not be ignored.

Zinc status should be considered in the broader context of metabolic regulation, as it affects insulin signaling, lipid metabolism, and inflammatory pathways. Zinc plays a key role in insulin crystallization and secretion via transporters such as ZnT8 (critical for pancreatic  $\beta$ -cell function), and modulates the PI3K/Akt pathway, enhancing insulin sensitivity and glucose uptake [36]. Additionally, zinc influences lipid metabolism by regulating adipokines (e.g. leptin, ZAG), PPAR $\gamma$  activation, and antioxidant defenses, thereby mitigating oxidative stress and inflammation [12]. Clarifying these mechanisms in pediatric populations may open new avenues for MetS prevention and treatment.

The findings of the present study, however, revealed no significant correlation between zinc levels and the risk of MetS in youths. The high degree of heterogeneity between reviewed studies suggests that the studies may not be enough to draw a definitive conclusion. Therefore, well-designed longitudinal studies are needed. This is the first meta-analysis study on the association between serum zinc levels and dietary intake with MetS among children and adolescents. However, the small number of included papers was a disadvantage. It highlights the necessity for further research with larger sample sizes and standardized zinc measurement techniques in the pediatric population. Future studies

should also explore the impact of dietary patterns and nutritional interventions.

#### Conclusion

The current study does not confirm a definitive association of serum zinc levels or dietary zinc intake with pediatric MetS. This study provides a comprehensive understanding and evidence-based guidance for clinical practice in pediatric MetS and public health strategies.

## **Ethical Considerations**

#### **Compliance with ethical guidelines**

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran (Code: IR.MUI.MED.REC.1402.276).

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#### **Authors contributions**

Conceptualization: Motahar Heidari-Beni and Majid Khademian; Investigation and project administration: Roya Kelishadi; Data curation: Sepideh Moalem and Kasra Talebi Anaraki; Formal analysis: Maryam Yazdi; Methodology: Kasra Talebi Anaraki and Motahar Heidari-Beni; Writing the original draft: Kasra Talebi Anaraki, Sepideh Moalem, and Maryam Yazdi; Review and editing: Motahar Heidari-Beni, Majid Khademian, and Roya Kelishadi.

#### **Conflicts of interest**

The authors declared no conflict of interest

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