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THE ZINC STATUS IN CHILDREN WITH ALLERGIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Allergies pose significant health concerns, particularly in children, where they can adversely affect growth and quality of life. Recent studies have suggested that zinc deficiency may play a critical role in the immune dysregulation associated with allergies. The method used in This systematic review followed the PRISMA guidelines and analyzed studies on the relationship between zinc levels and allergies in children, using data from PubMed, Science Direct, EBSCO, and Cochrane Library, and a meta-analysis was conducted to evaluate the effect size and risk of bias assessed using the Newcastle-Ottawa Scale to examine the relationship between zinc levels and allergies in children. Our findings indicate that children with allergies may exhibit different zinc levels compared to healthy controls, with a pooled effect size of -0.56 (95% CI: [-0.99, -0.13]). The analysis revealed significant heterogeneity ($Tau^2 = 0.39$; $Chi^2 = 79.41$, $df = 8$, $p < 0.00001$; $I^2 = 90\%$), highlighting the variability across studies and the necessity for further research to standardize the methodologies. These results were statistically significant ($Z = 2.54$, $p = 0.01$), suggesting a potential association between zinc levels and allergies in children. Further investigations are needed to explore whether zinc supplementation can support immune function and alleviate allergic symptoms.

Keywords: *zinc deficiency, allergic, children, Immune dysregulation, Zinc supplementation*

INTRODUCTION

Allergies are increasingly recognized as a significant health concern, particularly in children, where they can affect the growth, development, and overall quality of life (Mehta et al., 2013). Among the various factors that influence allergic responses, micronutrient status has emerged as a critical area of study as zinc plays a potentially important role. Zinc is essential for immune system function, and evidence suggests that zinc deficiencies may predispose children to allergic conditions. Recent research has indicated that children with allergies often have lower zinc levels than their healthy peers, and hair sample analysis frequently reveals these deficiencies (Zakharova et al., 2023). The increase in allergic diseases in recent decades may be partly attributed to dietary factors, including zinc intake (Maywald & Rink, 2024). This emerging relationship underscores the importance of further exploration of the role of zinc in immune regulation and its potential as a modifiable factor in managing or even preventing allergies in the pediatric population (Di Toro et al., 1987; Kamer et al., 2012).

Zinc deficiency is associated with severe and extensive eczema lesions in patients (Endre et al., 1989). Additionally, Zn plays a crucial role in the immune system and antioxidant defense, with food-allergic children showing weakened antioxidative barriers (Kamer et al., 2012). Zn supplementation has been shown to improve lymphocyte function in patients (Endre et al., 1989). The relationship between zinc and allergies may be due to its anti-inflammatory, antioxidant, and anti-allergic properties (Ozdemir, 2014). These findings suggest that maintaining adequate Zn levels could potentially reduce the risk of developing or exacerbating allergic diseases in children, particularly those with existing hypozincemia (Ozdemir, 2014). Gunaydin et al.,(Cigerci Gunaydin et al., 2023) reported lower zinc levels in the erythrocytes of children with allergic proctocolitis than in a healthy control group. This study aimed to examine the zinc profiles of children with allergies through a systematic review and meta-analysis.

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Pathophysiology of Zinc Deficiency in Immune Function and Allergic Responses

Nutrition, especially that of zinc, is crucial for a healthy immune system. Zinc deficiency can impair immune function and increase susceptibility to immune disorders, particularly among the elderly, those with chronic diseases, and individuals who implement restrictive diets, such as vegetarians, vegans, pregnant women, and athletes. Zinc supports both innate and adaptive immunity and helps maintain immune tolerance. Deficiency may lead to weakened immunity, recurrent infections, and growth issues, often due to low intake of substances, such as phytate, that block absorption. Zn is essential for T cell development and maintains the Th1/Th2 balance in cellular immunity and allergic responses. A lack of zinc can heighten Th2 responses, *fueling eosinophilic inflammation* and type 2 inflammation seen in conditions such as allergic asthma. Zinc also affects dendritic cells (DCs), which process allergens and promote Th2 responses. Deficiency can increase the cytokine IL-4 and boost IgE production, which binds to receptors on mast cells. When exposed to allergens, mast cells release histamine, which triggers allergic symptoms. However, the full effect of zinc on allergies remains partially unclear, with some studies suggesting that it may even inhibit histamine release under certain conditions.

Chronic Respiratory allergic diseases, such as asthma and rhinosinusitis (CRS), significantly impact quality of life and often require multiple medications; however, treatment remains challenging due to unclear etiology. Long-known risk factors include family history, air pollution, and obesity, whereas recent findings highlight micronutrient imbalances, particularly zinc deficiency, as exacerbating factors. Zinc deficiency can weaken immune defense, increase Th2 cell responses, eosinophilia, and pro-inflammatory cytokines (e.g., IL-4, IL-6), reduce antioxidant defense, heighten airway sensitivity, and weaken epithelial barrier function, followed by inflammation and worsened asthma symptoms. Zinc supplementation can mitigate these effects, restore immune balance, reduce histamine production, support antioxidant defenses, and strengthen the pulmonary and gastrointestinal barriers. Clinically, adequate zinc level during pregnancy are linked to better lung function and reduce childhood asthma risk, whereas deficiency is associated with elevated bronchial

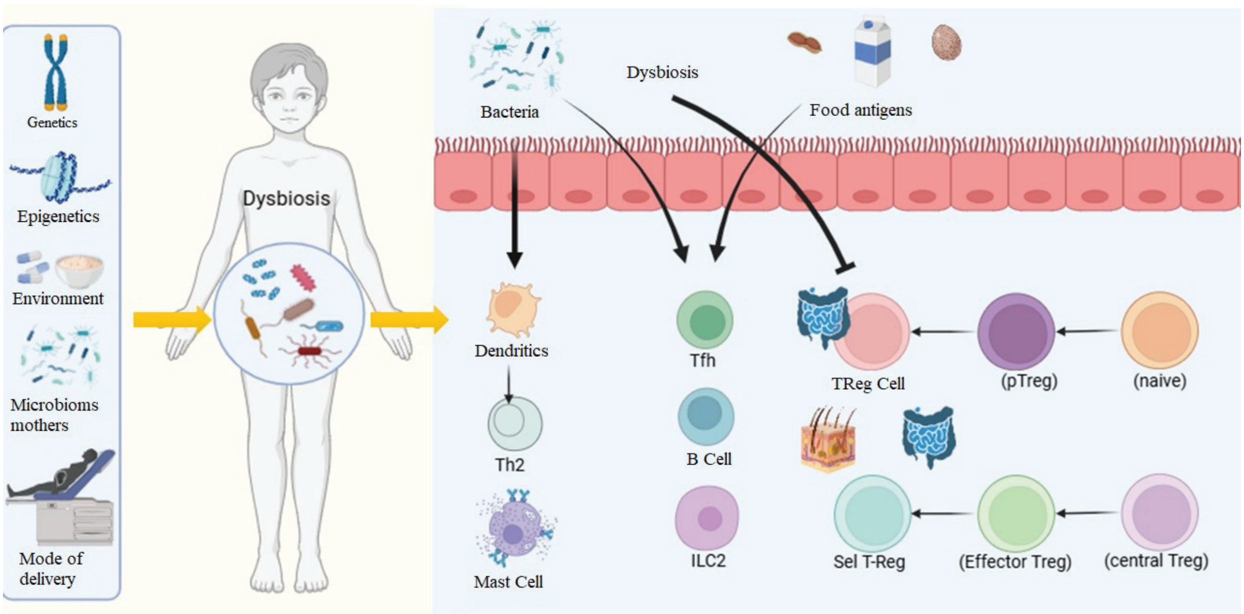

Figure 1. In childhood, a combination of maternal microbiome, delivery mode, genetics, and environmental factors shape human microbiota. Dysbiosis, or disruption of gut microbiota, impairs Treg cell differentiation, leading to an imbalance between Treg and Th2 cells. This imbalance, together with allergens and microbiota, activates T follicular helper (Tfh) cells, which stimulate B cells to produce IgE via IL-4 and IL-13 cytokines, triggering allergic reactions (rendered with biorender.com).

reactivity, severe asthma, and decreased lung function(Maywald & Rink, 2024).

In CRS, zinc deficiency affects epithelial health, as seen in both CRSwNP and CRSsNP types, although serum zinc levels do not significantly differ between these subtypes. Altered zinc transporter expression, such as ZIP downregulation and ZnT1 upregulation in CRSsNPs, contributes to disrupted intracellular zinc. Zinc plays a role in maintaining epithelial barriers, especially through proteins such as E-cadherin and claudin, mitigating inflammation, and strengthening cell junctions. Zinc supplementation can stabilize tight junctions, reduce inflammation, and improve CRS patient health, as demonstrated by the increase in serum zinc and barrier stability post-supplementation, despite ongoing research to clarify the precise effects of zinc on respiratory diseases(Maywald & Rink, 2024).

Children with acquired zinc deficiency should receive elemental zinc at a dosage of 0.5 to 1 mg/kg/day to replenish zinc stores. Children with conditions that lead to excessive zinc loss may require higher doses. For children with acrodermatitis-like eruptions (AELE), a dosage of 3 mg/kg/day of elemental zinc may be necessary, with regular monitoring through serum zinc measurement every 3 to 6 months. It is also important to assess copper and iron levels because these minerals interact with zinc. With proper supplementation, symptoms typically begin to improve within 1–2 days. For dietary zinc deficiency, treatment should include reducing fiber, phytate, and cadmium intake while introducing zinc-rich foods such as meat and liver. In most cases, addressing the underlying condition leads to symptom resolution of symptoms (Corbo & Lam, 2013). Plasma zinc considered to be deficient if the value is below 70 µg/dL (10.71 µmol/L) for morning fasting samples and below 65 µg/dL (9.95 µmol/L) for nonfasting samples (Domellöf et al., 2009; Semba et al., 2008). A serum zinc level <65 µg/dL was considered subclinical zinc deficiency for children <10 years of age. For children ≥10 years of age, the cutoff for serum zinc concentration was set at 66 µg/dL for females and 70 µg/dL for males (Vuralli et al., 2017)

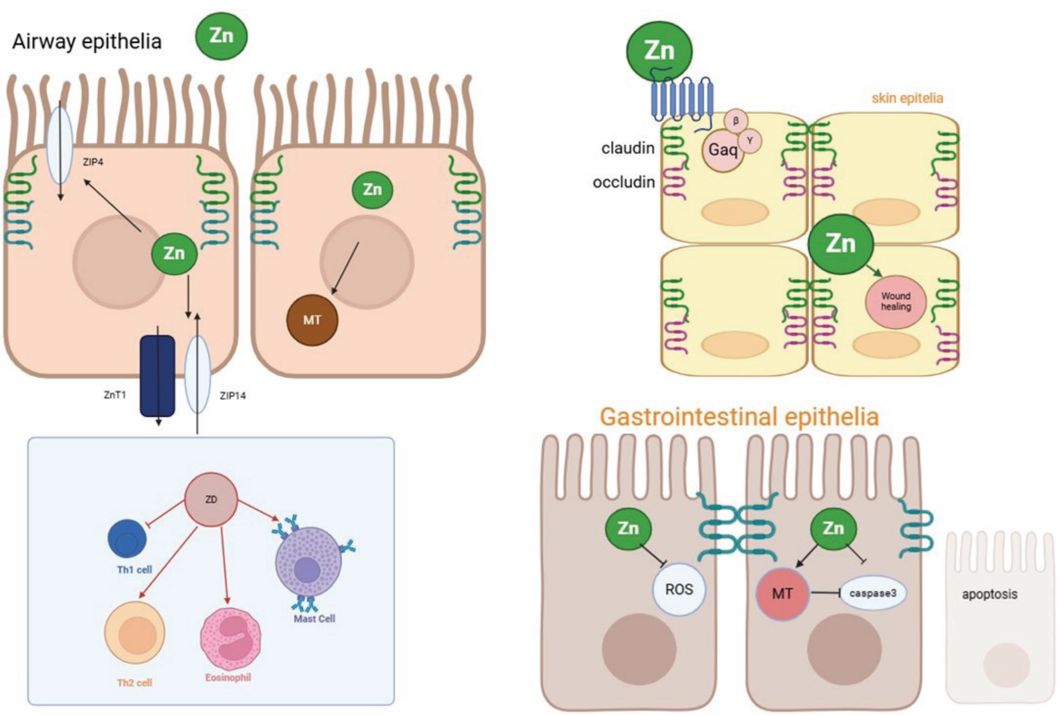

Figure 2. Zinc supplementation supports cellular repair and stability in the airway, skin, and gastrointestinal epithelia by normalizing zinc transporter levels, enhancing tight junctions through GPR39 activation, and reducing inflammation via the antioxidant effects of metallothionein. In contrast, zinc deficiency disrupts the immune balance by increasing mast cell activity and Th2 responses, resulting in higher eosinophil levels and altered antibody production linked to allergies (rendered with Biorender.com).

METHODS

Data Collection

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant articles were systematically searched in the PubMed (PMC Central MEDLINE), Science Direct, EBSCO, and Cochrane Library databases. The search strategy included keywords such as (effect OR impact OR association) AND (allergy) AND (infection) AND (zinc) AND (immune response). The inclusion criteria included articles using human subjects, written in English, available in full text, published between 1987 and 2024, examining the relationship between zinc level and allergy in children, and providing quantitative data suitable for meta-analysis (e.g., mean ± SD, median, odds ratio, and risk ratio). Studies were excluded if they were included as non-original research, focused on non-human populations, or were available only as abstracts. Independent reviewers screened and selected articles, and the results were managed using Zotero software.

Data Selection

The selection process involved identifying relevant articles by entering keywords into databases, followed by the removal of duplicate studies. The titles and abstracts were screened, and full-text assessment was conducted to confirm the eligibility of the articles. The inclusion criteria for the articles were published between 1987 and 2024. Studies that provided relevant information were systematically reviewed and included in this meta-analysis. This process was visualized using a PRISMA flow diagram (Figure 3). Data extraction included details, such as references, setting, sample size, patient age, allergic type, zinc level, and study conclusion. Two reviewers independently conducted each step of the selection and data extraction.

Meta-Analysis

A meta-analysis was conducted to combine the effect sizes and evaluate the relationship between zinc levels and allergies. Heterogeneity between studies was analyzed using the I^2 statistic, and an appropriate model (random effects) was chosen based on the degree of heterogeneity. Sensitivity analyses were performed to test the robustness of the results, whereas subgroup analyses explored variations across sample groups, including pediatric vs. adult populations and those with different types of allergies. The meta-analysis results were visualized in forest plots generated using Revman 5.4.1 software.

Quality Assessment

The risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS), which assesses studies based on three domains: selection, cohort comparability, and outcome comparability. Each domain included specific criteria, and studies were scored based on criteria fulfilment. Two independent reviewers assessed the risk of bias for each study. Any disagreements were resolved through discussion and consensus. The NOS assessment results are shown in Fig. 4.

RESULTS

Article Identification and Screening

A systematic search of PubMed, Science Direct, JSTOR, the Cochrane Library, LILACS, and DOAJ identified 606 records. After the removal of 2 duplicate records, 604 articles remained for screening. Screening of titles and abstracts resulted in the exclusion of 404 records, including 90 non-original research articles and 314 articles without full-text availability, leaving 200 articles for full-text assessment. After further evaluation, 190 articles were excluded because they were not relevant to the topic. Ultimately, 9 studies were included in the final review and meta-analysis (Figure 3).

Key Findings from Analyzed Studies

Measurement Techniques and Population Characteristics

Atomic absorption spectrophotometry was utilized in studies conducted by (Abdulwahab et al., 2018), Qatar, (Alkholy et al., 2024), Egypt), and Gunaydin et al., 2023), Turkey), underscoring the reliability of the method for accurately measuring zinc levels. (Abdulwahab et al., 2018)

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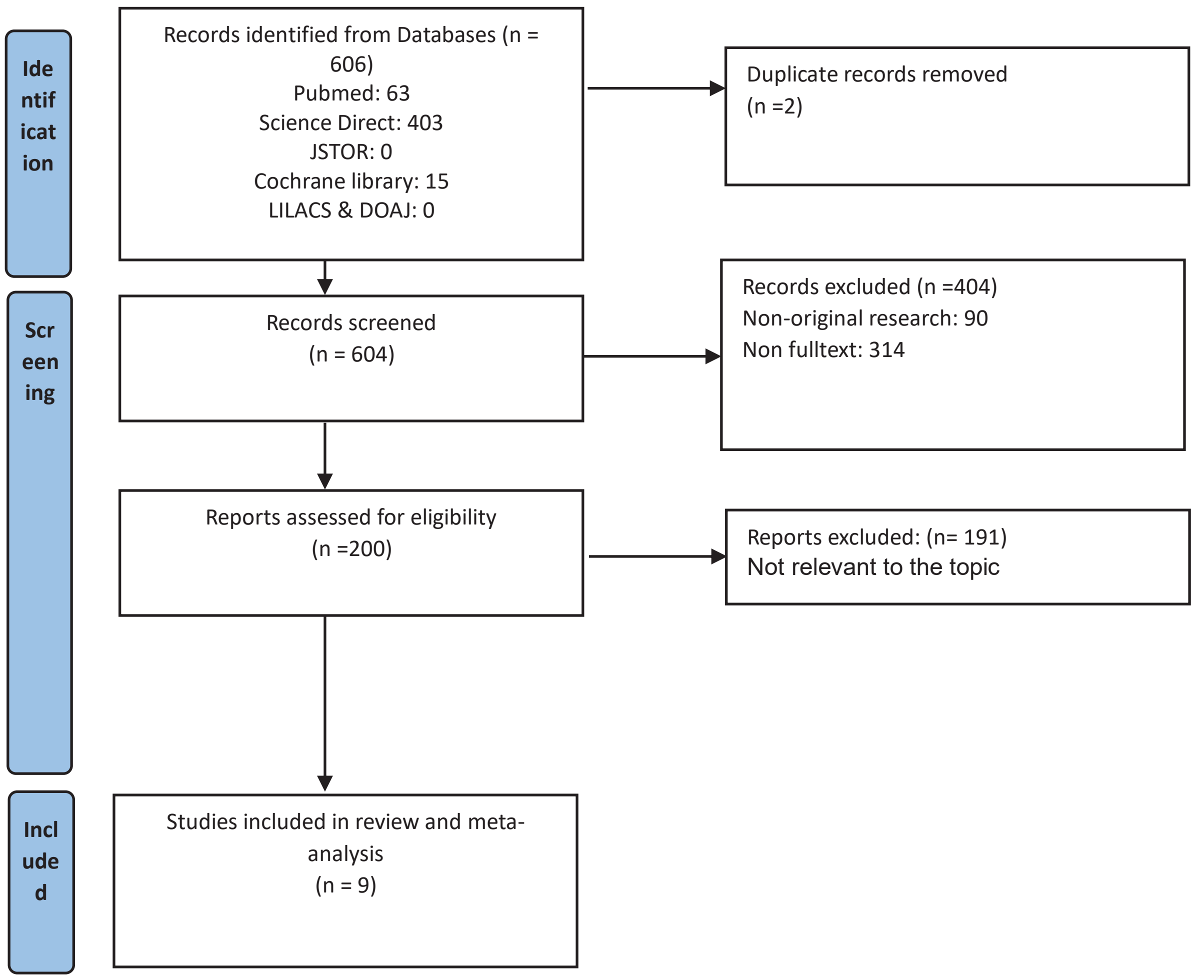

Figure 3. PRISMA chart of the study.

demonstrated that asthmatic children exhibited lower zinc levels than their healthy peers, even after adjusting for the BMI Z-score, suggesting a potential link between zinc deficiency and asthma. Similarly, Alkholy (2024) found reduced zinc levels in asthmatic children compared to controls, with adjustments made for age, weight, and height, indicating that these factors could influence zinc status and its association with asthma.

Zinc Level and Asthma Control

Rajkumar (2023) found no significant correlation between zinc levels and asthma control; however, the study emphasized the importance of monitoring zinc levels in children with asthma as part of managing inflammation. In contrast, Srivastava (2023 in India) suggested that zinc supplementation could potentially enhance asthma control, indicating its potential as an adjunctive therapy to reduce asthma symptoms and improve overall management.

Influence of Sociodemographic Factors

Carneiro (2011) analyzed zinc levels in children's fingernails, adjusting for factors such as socioeconomic status, mother's education, and age, which revealed disparities likely tied to environmental and nutritional influences. Similarly, Podlecka (2022, Poland) accounted for maternal education and income in their analysis, even though age and sex were not explicitly controlled. This study also identified socioeconomic factors as potential contributors to asthma prevalence, highlighting the broader impact of social determinants on health outcomes.

Techniques Beyond Spectrophotometry

The Proton-Induced X-ray Fluorescence Technique (PIXE) was used by Toro (1987, Italy) to assess zinc levels, revealing no significant correlation with age, which suggests that other factors may influence zinc bioavailability in children with asthma. In contrast, the Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method employed by Srivastava (2023) and Carneiro (2011) demonstrated high precision in detecting trace elements, such as zinc. These studies have confirmed the effectiveness of ICP-MS for pediatric sample assessment, highlighting its value in accurately measuring micronutrient levels and understanding their impact on health.

The presentation of the meta-analysis in Figure 5 evaluates the association between zinc levels and allergies across various studies, highlighting the potential difference in zinc levels between allergic individuals and healthy controls. The pooled analysis showed a combined effect size of -0.56 [-0.99, -0.13], suggesting that individuals with allergies may have lower zinc levels than non-allergic controls. The high heterogeneity value ($Tau^2 = 0.39$; $Chi^2 = 79.41$, $df = 8$, $P < 0.00001$; $I^2 = 90\%$) indicated substantial variability among the included studies, likely driven by factors such as diverse allergy types, varying sample sizes, and

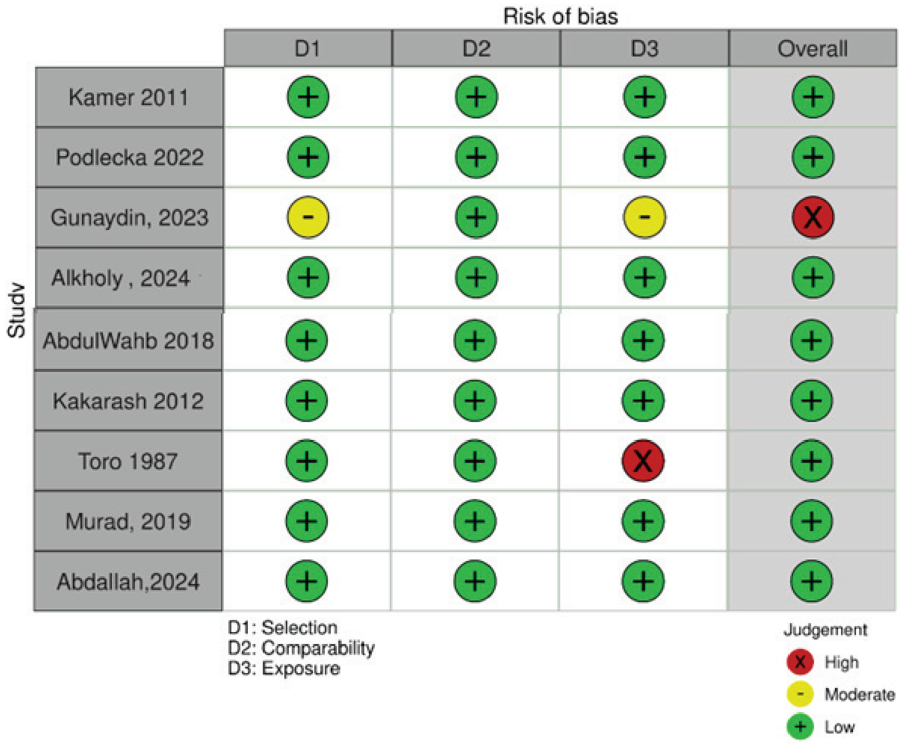

Figure 4. Newcastle–Ottawa risk of bias analysis of included studies

	Allergy			Healthy				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Abdallah 2024	0.81	0.3	134	0.85	0.26	36	11.4%	-0.14 [-0.50, 0.23]
Abdul Wahab 2018	88.57	18.05	40	81.06	11.84	40	11.0%	0.49 [0.04, 0.93]
Alkholy 2024	495.5	134	50	567.3	154.4	50	11.3%	-0.49 [-0.89, -0.09]
Gunaydin 2023	70.44	9.51	62	89.3	15.01	62	11.2%	-1.49 [-1.89, -1.09]
Kakarash 2012	51	12.8	100	60	18.2	75	11.7%	-0.58 [-0.89, -0.28]
Kamer 2011	12.69	1.8	40	13	1.52	40	11.0%	-0.18 [-0.62, 0.25]
Murad 2019	70.02	7.78	50	84.94	10.08	50	10.9%	-1.64 [-2.10, -1.19]
Podlecka 2022	16.2	0.5	43	16.2	0.8	19	10.4%	0.00 [-0.54, 0.54]
Toro 1987	87.85	7.79	45	98.45	13.2	45	11.0%	-0.97 [-1.41, -0.53]
Total (95% CI)			**564**			**417**	**100.0%**	**-0.56 [-0.99, -0.13]**

Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 79.41$, $df = 8$ ($P < 0.00001$); $I^2 = 90\%$
Test for overall effect: $Z = 2.54$ ($P = 0.01$)

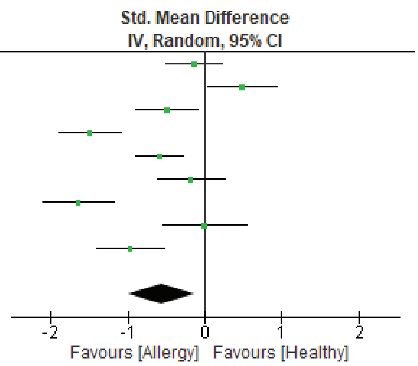

Figure 5. Forest plot comparing allergy and healthy children group vs. control based on standard mean difference and random effects model study.

different populations. Despite this variability, the overall test for effect (Z = 2.54, P = 0.01) reached statistical significance, indicating a potential association between zinc levels and allergies, although further research is required to confirm these findings.

DISCUSSION

The high prevalence of low zinc levels in individuals with allergies indicates a possible role of zinc in immune function and allergy modulation. Studies by Kamer (Kamer et al., 2012) and Seo (Seo et al., 2017) contributed to a substantial portion of the weight, both of which showed significantly lower zinc levels in allergic individuals. Kamer (Kamer et al., 2012) focused on IgE-dependent allergies, while Seo (Seo et al., 2017) studied common allergens, such as dust mites and pet danders. Both studies highlighted the prevalence of hypozincaemia in allergic groups, linking lower zinc levels to immune dysregulation, as reflected by elevated IgE levels. Gunaydin (Cigerci Gunaydin et al., 2023) and Podlecka (Podlecka et al., 2022) focused specifically on allergies in children, such as Food Protein-Induced Allergic Proctocolitis (FPIAP) and milk, egg, and peanut allergies. Although these studies had smaller sample sizes, they supported the overall trend, suggesting a correlation between zinc deficiency and allergy prevalence, particularly in pediatric populations. Meanwhile, Seppo (Seppo et al., 2005) studied cow milk allergy and observed slight differences in zinc intake among infants consuming soy or hydrolyzed whey formula. Although no significant impact on growth was noted, Seppo's (Seppo et al., 2005) findings suggested that zinc may influence immune health rather than physical development, in agreement with other studies on the role of zinc in immune regulation in allergic conditions.

Zn is known to support immune homeostasis by influencing T-cell activity, cytokine production, and inflammation control. Therefore, zinc deficiency may exacerbate immune dysregulation, as evidenced by the elevated total and allergen-specific IgE levels, potentially intensifying allergic reactions. Zinc plays a crucial role in immune homeostasis and regulation, and influences various aspects of the immune response (Maywald & Rink, 2024; Ozdemir, 2014). Zinc deficiency is associated with an increased prevalence of allergic diseases, characterized by elevated IgE levels and Th2 cytokine production (Maywald & Rink, 2024). This deficiency affects both innate and adaptive immunity, and alters the survival, proliferation, and differentiation of immune cells (Bonaventura et al., 2015). Chronic zinc deficiency can lead to increased inflammation and pro-inflammatory cytokine production, potentially exacerbating inflammatory diseases, such as rheumatoid arthritis (Bonaventura et al., 2015). In allergic conditions, such as atopic dermatitis, asthma, and chronic rhinosinusitis, a decrease in zinc levels may enhance inflammatory activation (Suzuki et al., 2021). Conversely, zinc supplementation has shown potential in modulating the immune system and reducing allergic symptoms, although the results vary due to differences in supplement bioavailability and study design (Maywald & Rink, 2024).

Expanding on this, additional studies have highlighted the significance of zinc levels in pediatric asthma management. For instance, Abdulwahab (AbdulWahab et al., 2018) and Alkholy (Alkholy et al., 2024) utilized atomic absorption spectrophotometry and found that asthmatic children generally had lower zinc levels than their healthy peers, even after adjusting for variables such as BMI Z-score, age, weight, and height. These findings suggest that zinc deficiency might contribute to increased asthma severity and indicate the need for careful nutritional assessment in children with asthma. Rajkumar (Rajkumar et al., 2022), but did not find a significant correlation between zinc levels and asthma control, emphasized the importance of monitoring zinc levels to manage inflammation. Conversely, Srivastava (Srivastava et al., 2023) observed that zinc supplementation could improve asthma control, indicating its potential as an adjunctive therapy.

Toro (Di Toro et al., 1987), using the Proton-Induced X-ray Fluorescence Technique (PIXE), found no significant age-related correlation with zinc levels, suggesting that factors beyond age could influence zinc bioavailability in children with asthma. In contrast, studies employing

Inductively Coupled Plasma Mass Spectrometry (ICP-MS), such as those performed by Srivastava (Srivastava et al., 2023) and Carneiro (Carneiro et al., 2011) confirmed the precision of the method for detecting trace elements, showing its effectiveness in pediatric nutritional assessments. Carneiro et al. ‘s study, which adjusted for socioeconomic status, maternal education, and age, underscored the impact of environmental and nutritional factors on zinc levels, which may influence both asthma and allergy prevalence.

Collectively, these findings highlight the role of zinc in supporting immune homeostasis and influencing T-cell activity, cytokine production, and inflammation control. Zn deficiency can exacerbate immune dysregulation, as evidenced by the elevation of total and allergen-specific IgE levels, potentially intensifying allergic reactions. Moreover, chronic Zn deficiency may enhance inflammatory responses, contributing to conditions such as asthma and allergic rhinitis. Thus, monitoring zinc levels in children with allergic and asthmatic conditions could provide insights into potential therapeutic interventions. Zinc supplementation, although variable in its outcomes owing to differences in bioavailability and study design, has shown promise in modulating the immune response and reducing symptoms.

CONCLUSION

In summary, the role of zinc in immune regulation, including its impact on T cell activity, cytokine production, and inflammation control, underscores its potential therapeutic value in managing allergic conditions. While the results support the need to monitor zinc levels in children with allergies and asthma, further research is necessary to standardize methodologies and assess the effectiveness of zinc supplementation as an adjunctive therapy.

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Author (year)	Country of origin	Children, adults, or both	Mean age	n cases	n total	Type of control	Method of zinc determination	Matching or adjusment factors
Abdallah (2024)	Iraq	Children	10 years	45	90	Healthy individual	ELISA	Age, gender, and residence
Abdulwahab (2018)	Qatar	Children	10.92 years for asthmatic children, 10.89 years for non-asthmatic children	40	80 (40 asthmatic, 40 non-asthmatic)	Healthy non-asthmatic school children, matched for age, gender, and BMI Z score	Atomic absorption spectrophotometry	Age, gender, and BMI Z-score
Alkholy (2024)	Egypt	Children	Five to fourteen years old	62 asthmatic children	124	Healthy control	Atomic absorption spectrophotometry	Healthy control matched by age, weight, and height
Gunaydin (2023)	Turkey	Children	7 months	50	100	Healthy children without malnutrition, age and sex paired whenever possible	Atomic absorption spectrophotometry	Paired for age whenever possible and paired for sex whenever possible
Kakarash (2012)	Iraq	Children	Three groups: 1–4-year-old, 5–8-year-old, and 9–12-year-old	50 asthmatic children	100 (50 asthmatic children + 50 healthy controls)	Healthy children, matched for age and gender, without chronic disease	Spectrophotometry (CE 2021), using LTA reagents at a wavelength of 578 nm	Matched for age and gender between the asthmatic and control group
Kamer (2012)	Poland	Children	15.4 months	134	170	Healthy children without malnutrition, age and sex paired whenever possible	Flame atomic absorption spectrophotometry	Paired for age whenever possible and paired for sex whenever possible
Murad (2019)	Iraq	Children	2 to 12 years	47 asthmatic children	94	Healthy control	Not mentioned	Zinc levels and age, gender, BMI, or family history of asthma

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Podlecka (2022)	Poland	Children	9-12 years old	40	80	Children without allergy/asthma diagnosis	Flame atomic absorption spectrometry	Age: Not explicitly mentioned if age was matched, but mother's age was included as a covariate in adjusted models. Sex: Not mentioned if sex was matched. Other: Mother's education and income were also included as covariates in adjusted model.
Srivastava (2023)	India	Children	9 years old	100	175	Healthy, age- and sex-matched children	Inductively Coupled Plasma Mass Spectrometry (ICPMS)	Age and sex were matched between cases and controls
Toro (1987)	Italy	Children	2-14 years old	43	62	Healthy children from similar socioeconomic backgrounds	Proton-induced X-ray fluorescence technique (PIXE)	Age and sex were not explicitly stated as matching factors, but the results were analyzed without regard to sex as no significant differences were found. Age did not significantly correlated with zinc or copper levels