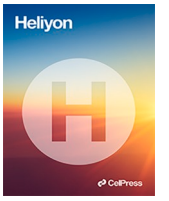
Heliyon 10 (2024) e33686

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Zinc status in cystic fibrosis patients; a systematic review and meta-analysis

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A R T I C L E I N F O

Keywords:
Cystic fibrosis
Zinc deficiency
Trace element
Zinc status
Adult
Children
Adolescent

A B S T R A C T

Background: Cystic fibrosis (CF) is an autosomal recessive hereditary disease causes concentration of secretions and this affects the lungs and digestive system. These patients are exposed to zinc (zn) deficiency. In this review, we decided to investigate the status of zn in CF patients compared to control group. Also, the clinical trials that have so far performed zinc supplementation in these patients are examined.

Method: ISI Web of Science, Scopus, PubMed/Medline, and Cochrane database were searched, up to December 2023, for studies that reported the association between zn levels of CF patients compared to a healthy control group. A random-effect model was used to compute the pooled weighted mean difference (WMD) with 95 % confidence intervals (CI). Subgroup analysis was done for region, sample and method of measurement, zinc supplementation and age.

Result: Overall, meta-analysis of 9 studies (n = 383 participants) revealed that the zn levels were significantly lower in children and adolescents with CF compared with healthy subjects (WMD = −11.97 μg/dL, 95 % CI: −22.57 to −1.37; I^2 = 92.83 %). Meta-analysis of 8 studies (n = 320 participants) revealed that the serum and plasma level of zn was significantly lower in CF patients compared with healthy subjects (WMD = −14.31 μg/dL, 95 % CI: −25.09 to −3.53; I^2 = 88.14 %, P-heterogeneity <0.001) While the zn level in saliva and sputum was significantly higher in CF patients.

Conclusion: CF patients have decreased zn levels in circulatory reservoirs. zn may effective for the diminish the respiratory and gastrointestinal symptoms in CF patients, further well-designed clinical trial studies is required to prove these effects.

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https://doi.org/10.1016/j.heliyon.2024.e33686
Received 14 August 2023; Received in revised form 20 June 2024; Accepted 25 June 2024
Available online 28 June 2024

1. Introduction

Cystic fibrosis (CF) is one of the life-shortening hereditary diseases [1]. This is an autosomal recessive hereditary disease characterized by mutations in the CFTR (CF transmembrane conductance regulator) gene [2]. The most common type of mutation, which includes about 70 % of patients, is the deletion of three base pairs of CTT in exon 10 [3]. This mutation, which is related to the deletion of a phenylalanine residue (DF508), causes the absence of a cAMP-dependent chloride channel in the apical surface of secretory epithelial cells [4]. As a result, it causes concentration of secretions and this increases the risk of lung infection [1,5]. This chronic disease affects the lungs and digestive system [3]. Clinical manifestations in the digestive system are pancreatic exocrine dysfunction and intestinal mucus disorder.

It is estimated that around 70,000 cases worldwide are suffering from this disease [2]. Its incidence in Europe is one in every 3500 births among whites [3]. The rate of prevalence in USA and Europe is similar [2]. Finally, frequent lung infections in these patients become chronic and it becomes more difficult to treat [1]. Inflammation, infection, and airway obstruction are associated with structural damage to the airways, which ultimately leads to respiratory failure [6,7]. Despite progress in the treatment of this disease, lung infections are still the main cause of death in these patients [1]. The average lifespan of these patients is estimated to be 59 years [5].

The growth and development of these patients during childhood and adolescence, as well as the functioning of their immune system during adulthood, are influenced by various factors, including nutritional status and especially zinc (zn) status [8]. As an essential trace element, zn has various functions in the body, including the role of cofactor, regulator, and structural function [9]. Zn regulates gene expression through the metal response element (MRE) that binds to the transcription factor (MTF-1) [3]. Also, zn regulates cell signaling by regulating the activity of kinases and phosphorylases [3]. Cells that have high turnover, such as the cells of the digestive system, the immune system, and the skin, are more sensitive to zn deficiency [3]. Zn is distributed in different tissues. Its highest concentration is found in prostate, pancreas and bone (up to 200 μg/g) [3]. The concentration of zn in the heart, brain and plasma is the lowest (1–23 μg/g) [3]. Although plasma has the lowest concentration of zinc among tissues (1 μg/g), it plays the most important role in its homeostasis [10].

Since CF patients are exposed to zn deficiency due to malabsorption and reduced intake, and on the other hand, zn deficiency, due to its role in various aspects of health mentioned above, can worsen the condition of CF patients and also in order to delay growth in children and increase the possibility of lung infections, many studies have investigated the status of zn in CF patients and its level in various tissues such as white and red blood cells (WBC and RBC), plasma, serum, hair, pancreas, teeth and secretions such as sputum, and saliva have reported [11–17]. Based on this, in this systematic review and meta-analysis study, we decided to investigate the status of zn in different tissue especially circulatory reservoirs in CF patients compared to healthy control group. Also, the clinical trials that have so far performed zn supplementation in these patients with all clinical outcome such as respiratory function, inflammation, infection and antibiotic prescription are examined.

2. Method

The current meta-analysis addressing the zinc status in cystic fibrosis patients, was performed based on the preferred reporting items for systematic review and meta-analysis (PRISMA) guideline [18]. We registered the protocol of this meta-analysis in the PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=445624, ID: CRD42023445624).

2.1. Search strategy

Two independent investigators (SS & MM) searched all published papers up to19 December 2023 through ISI Web of Science, Scopus, PubMed/Medline, and Cochrane database with limited English language. The keywords including MESH and non-MESH terms used were showed in Supplementary Table 1. The reference list of all eligible case-control studies and clinical trials was reviewed. In addition, manual searches of reference lists of related reviews were also performed to identify other eligible studies. The full text of papers that were published before 2000 and did not have a “doi “were taken from the university library.

2.2. Inclusion and exclusion criteria

Case-control studies were included in this meta-analysis if they met the following inclusion criteria: 1) Publications with cystic fibrosis patients as case group and healthy individuals as control group, 2) studies carried out on human models; 3) investigating the zinc level in tissues and circulatory reservoirs such as serum, plasma, WBC, RBC and secretions such as saliva and sputum) reporting aadequate data based on convertible units in case and control groups.

Clinical trial studies that have investigated the effect of zn supplementation on all clinical outcome such as respiratory function, inflammation, infection and antibiotic prescription in CF patients and had both intervention and control groups were systematically reviewed. In addition, neither in trial studies nor in case-control studies, the age of the participants was not restricted. Cohort studies, case reports, cross-sectional studies, letters, short communications, comments, case reports, conference abstracts, reviews, and meta-analyses were excluded.

2.3. Data extraction

Two investigators (MM & ES) independently checked out the title and abstract of the searched papers and based on the inclusion and exclusion criteria, checked out the selected studies with full text and extracted the following data: 1) study characteristics: first authors' last name, publication year, country, study design, exposure, case and control group size, age and sex; 2) Outcome characterizes: means and standard deviations of zn level in case and control groups. 3) Clinical trials outcomes, duration, dosage and type of intervention.

2.4. Quality assessment of studies

The quality assessment of the studies entered meta-analysis, was based on the Newcastle-Ottawa Scale (NOS) tool [19], which includes 7 items in 3 domains: selection, comparability, and outcome with a maximum score of 10. Studies with a total score of $\geq$6 were considered high quality, and studies with a score between 4 and 6 were classified as moderate and $\leq$4 as poor.

The risk of bias of RCTs assessed based on the Cochrane risk of the bias assessment tool [20]. which includes 7 items: random sequence generation, allocation concealment, incomplete data outcome, selective outcome reporting, blinding of participants, investigators, and other sources of bias. The overall standard of the RCT was considered poor if they had less than four points for a low risk of bias. They were classified as fair if they had four points and good if they had more than four points for low risk of bias.

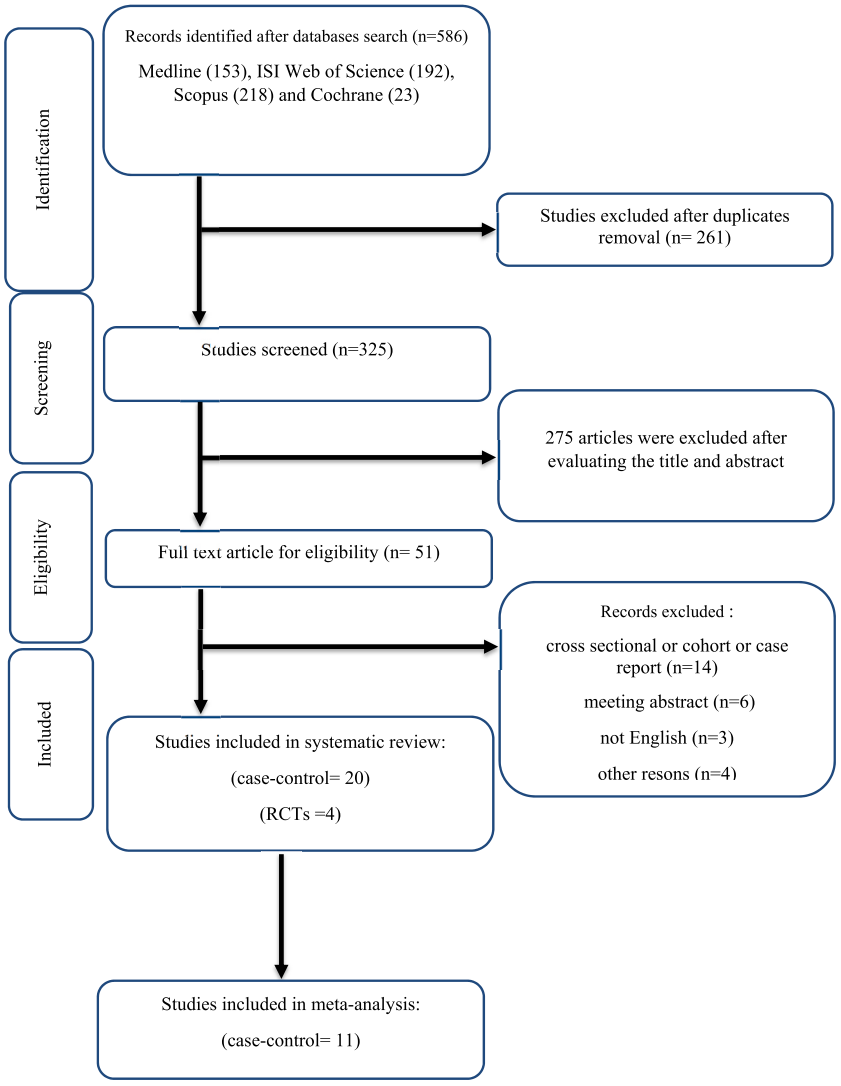

Fig. 1. Study selection.

2.5. Statistical analysis

The means and their corresponding SD of zinc concentrations in cases with CF and their controls were used to calculate the effect size. Calculations for zn level in all studies were considered based on μg/dl, so in the studies that were expressed with other units, the unit was converted. In cases where the concentration was reported based on median and standard error or inter quartile range, with statistical methods it was converted to mean and SD. In the studies where the level of zn has been reported in several different tissues, only the serum or plasma level of that study was included in the analysis based on age. With random effects model, the weighted mean differences (WMD), with the corresponding 95 % CI, were calculated [21]. To assess statistical heterogeneity, Cochran's Q test and I^2 were applied [22]. Subgroup analyses for age of participants (Children & adolescent and adult), the type of sample in which the level of zinc was measured (granulocyte, lymphocyte, erythrocyte, platelet, plasma, saliva and sputum), method of measurement (atomic absorption spectrophotometry, Optical emission spectrometry and Mass-spectrometry), region of study (USA, Europe, India and Australia) and zinc supplementation (yes or no) were performed to identify the possible sources of heterogeneity. To describe the effect of individual studies on pooled analysis, sensitivity analysis was carried out. publication bias was not evaluated because the number of included studies were <10 and as a result, the obtained results will not have the necessary validity [23]. STATA version 17 (STATA Corp., College Station, TX, USA) was used to statistical analyses. P values ≤ 0.05 were considered statistically significant.

3. Result

A total of 586 articles were obtained through searching databases. After removing duplicate articles, 325 studies were reviewed in terms of title and abstract, and finally, the full text of 51 studies was reviewed in terms of inclusion criteria. Among the above studies, 12 were cross-sectional studies without control group [3,8,11,12,24–31], 6 were meeting abstracts and conference papers [32–37], 3 were non-English [38–40], one was a cohort [41], one was an in vitro study [42], one was a case report [43], and one was a study on absorption and retention [44], two was trial study without a control group [41,45], and 4 were clinical trials [46–49]. Finally, 20 studies with case and control groups were included in the qualitative analysis of zinc status in CF patients. 3 studies were excluded from the quantitative analysis due to the impossibility of converting the measured zn unit to the unit of other studies [50–52]. In two studies SD could not be calculated [53,54]. Also, one study in teeth [15], one in cervical mucus [55], one in pancreatic tissue [17], three in hair [16,56,57] were not included in the quantitative analysis, and finally 11 studies were included in the meta-analysis to check the zinc status in circulatory reservoirs (Fig. 1).

Table 1
Study characteristics.

Author	year	Country	Exposure	Case (CF)/ctrl (normal)	Age case/ctrl (years)	Male/female
Abdulhamid	1999	USA	Lymp, Gran, Platelet, plasma	16/16	13.5 (±3.28)/13.2 (±3.67)	
Blomfield	1973	Australia	Saliva	35/28	4–21	39/24
Brand-Auraban	1972	Israel	Cerumen	7/12	4–17	case: 5/2
Cua	1991	USA	Teeth	32/23	Children and adolescents	
Foucard	1991	Sweden	Erythrocytes	8/8	3–19	3/5 case 3/5 ctrl
Gray	2010	UK	Sputum	23/20	CF26.3 (2.0) ctrl 36.9 (2.5) (sem)	CF 14/9 ctrl 6/14
Halsted	1970	USA	Plasma	10/26 cf with normal groth 10/26 cf with growth retarded	CF 3–16 ctrl 3-13	
Holt	1984	Australia	Hair	7/8	4–14	
Kopito	1973	USA	Cervical mucus	3/6	19–32	Female
Kopito	1976	USA	Sections of pancrea	35/17	CF 15 days-21 years ctrl 3 days-13 years	CF 19/16 ctrl 12/5
Marin	2004	Chile	Hair	15/15	2–15	9/6 in case group
Mocchegiani	1995	Italy	plasma	15/15	2–13	7/8 in case group
Neve	1983	Belgium	Plasma and erythrocyte	29/20	case 7–19 ctrl 5-20	13/7 in case group
Rule	1970	USA	Seminal Plasma	18/13	>18	Male
Smith	2014	Austrailia	Sputum supernatant	45/8	29 ± 12/57 ± 7	28/17 in case group
Solomons	1981	USA	Plasma and hair	19/40	6–17	12/7 in case group
Van Caillie-Bertrand	1982	Netherlands	Serum	13/12	6–15	
Van Biervliet	2007	Belgium	serum	101/174	median:16	53/48 in case group
Vormann	1992	Germany	plasma and erythrocyte	15/8	5-22, mean:16	6/9 in case group
Yadav	2014	India	Plasma	27/27	3 month- 5 year	

Ctrl = conttol

3.1. Study characteristic

A total of 20 studies were included in the systematic review, of which 11 studies met the criteria for entering the meta-analysis [13,14,51,56–63]. 7 studies have been conducted in the USA [14,15,17,52,55–57], 3 studies in Australia [16,58,62], one in Israel [50], one in Chili [64], one in India [61] and 7 studies in Europe [13,51,53,59,60,63,65]. One study assessed zinc level in platelets, granulocytes and lymphocytes [14], 3 studies in erythrocytes [51,53,60], one in saliva [58], 2 studies in sputum [13,62], 3 studies in hair [16,57,64], one in teeth [15], one in cerumen [50], one in cervical mucus [55], one in the pancreas [17] and 10 other studies in serum and plasma. 4 studies have been conducted in adults [13,52,55,62] and 16 other studies in children and adolescents. The characteristics of the studies are summarized in Table 1.

Among the 4 clinical trial studies included in this systematic review. Two study are RCTs [46,48]. Three studies have been conducted in the USA and one in India [46]. 3 studies were conducted in children and adolescents, while one study included adults [49]. The age range of the participants was 5–48 years. In 3 studies a dose of 30 mg/day and in one study [47] a dose of 100 mg/day of zinc has been investigated. The duration of the intervention was between 6 weeks and one year. The summary of the results and characteristics of the studies are shown in Table 2.

3.2. Meta analysis

Overall, meta-analysis of 9 studies (n = 383 participants) revealed that the zn levels were significantly lower in children and adolescents with CF compared with healthy subjects (WMD = −11.97 μg/dL, 95 % CI: −22.57 to −1.37; I^2 = 92.83 %, P-heterogeneity <0.001), while in adults (2 studies, n = 96 participants) the zn levels were significantly higher in CF patients compared with healthy subjects (WMD = 107.50 μg/dL, 95 % CI: 66.77 to 148.22; I^2 = 0.00 %, P-heterogeneity = 0.64) (Fig. 2).

Meta-analysis of 8 studies (n = 320 participants) revealed that the serum and plasma level of zn was significantly lower in CF patients compared with healthy subjects (WMD = −14.31 μg/dL, 95 % CI: −25.09 to −3.53; I^2 = 88.14 %, P-heterogeneity <0.001) (Fig. 3). While, the zn level in saliva (one studies, n = 63 participants) (WMD = 3.94 μg/dL, 95 % CI: 0.75 to 7.13) and sputum (2 studies, n = 96 participants) (WMD = 107.50 μg/dL, 95 % CI: 66.77 to 148.22; I^2 = 0.00 %, P-heterogeneity = 0.64) was significantly higher in CF patients in comparison to healthy subjects.

Subgroup analysis showed that zinc levels in patients with CF were significantly lower in studies conducted in the USA compared to healthy individuals, and heterogeneity was also reduced (WMD = −5.668 μg/dL, 95 % CI: −10.378 to −0.958; I2 = 0.0 %, P-heterogeneity = 0.432). Also, in all the studies, the zinc level was measured by atomic absorption spectrophotometry, except for two studies that examined the sputum sample [13,62]. By atomic absorption spectrophotometric method, the level of zinc in CF patients was significantly lower than that of healthy individuals (WMD = −11.970 μg/dL, 95 % CI: −22.568 to −1.372; I2 = 92.8 %, P-heterogeneity≤ 0.001). In three studies [14,56,60], CF patients used zinc supplements, which was one of the reasons for the high heterogeneity (Table 3).

Sensitivity analysis indicated after removal of each study, individually, from the analysis results remained stable. No asymmetry in

Table 2
Study characteristics of clinical trials.

Author	Year	Country	Study	Age year	Int/ctrl number	Int	Ctrl	Type of zinc	Dose mg/day	Duration	Results
Abdulhamid	2008	USA	RCT	8–18	5/7	Children With CF	Children With CF	Zn gluconate	30	12 months	Percentage change of plasma zn, sIL-1ra, sTNFR1, IL-1b, TNF-a ↔ Percentage change of ex-vivo generation of IL-2 ↑ Percentage increase of plasma IL-6 and 8 and the number of days oral antibiotics ↓
Best	2004	USA	Trial	12–48	10/8	CF patients	CF patients	Zinc glycinate	30	6 weeks	Activity of peroxide dismutase and plasma diamine oxidase ↔
Palin	1976	USA	Trial	8–21	36/17	CF patients	Their Sibling	Zinc sulfate	100	8 weeks	Serum vitamin A, zn, RBP and growth status ↔
Sharma	2016	India	DB RCT	5–15	18/19	children with CF	Children with CF		30	12 months	Percent-of-predicted and change in FEV1, average days of systemic antibiotics, rate of colonisation Pseudomonas, height, weight and height for age and BMI, median Z score and serum zn ↔ Weight ↑

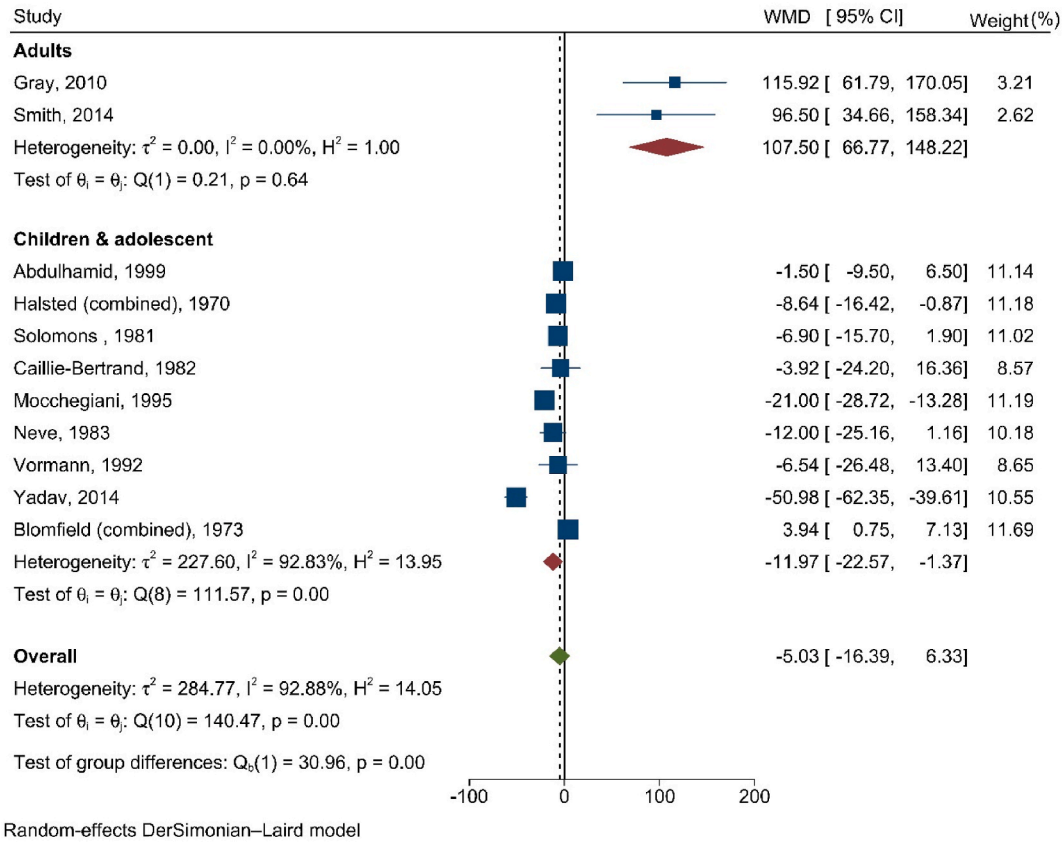

Fig. 2. Forest plot demonstrating meta-analysis of studies evaluating zn levels in adults, children and adolescents with CF compared to control group. (The analysis was done using random effects model. P-value of effect <0.05).

the funnel plots was identified as assessed by visual inspection. Using asymmetry tests for meta-analysis (Begg's test, P = o.474; Egger's test, P = 0.803) no significant publication bias was detected.

3.3. Quality assessment

The results of quality assessment, based on the Newcastle-Ottawa scale, suggested that no studies had high quality. Seven studies were moderate, and four had low quality [51,56,58,60] (Table 4). Among the examined items, the most bias was in the control definition and selection of control group. Also, the non-response rate item did not meet the promising conditions in any of the studies. While the assessment of exposure and same method of ascertainment in all studies were acceptable.

Based on Cochrane collaboration tools, three RCTs had fair quality and one was poor (Table 5). In three studies, dietary zinc intake wasn't assessed so, this was considered as potential other biases.

4. Discussion

In the present meta-analysis, we examined the findings of studies comparing zn levels in CF patients and control groups in different circulatory reservoirs. To the best of our knowledge, this is the first systematic review and meta-analysis that assessing zn levels in CF patients in comparison with healthy control group. Our results showed the significantly lower mean serum zn level in children and adolescents with CF in comparison with healthy control group. However, this relationship was reversed in studies that examined zn level in saliva amd sputum in adults.

As one of the most abundant and influential elements in the human body, zn has three main roles include catalytic, structural, and regulatory and also plays main a role as an essential element in the catalyst site of 300 enzymes, as well as has the essential role in nucleic acid metabolism, cellular integrity, protein synthesis, contributing to cell growth, differentiation proliferation and death [66,67]. Although zn is present in the amount of 2–4 g in various tissues and fluids of the body, it cannot be stored in the body for a long time and must be continuously received through the diet [68]. According to the results of a recent review, zn in the respiratory system can have anti-inflammatory, antiviral, anti-oxidative stress and immune system strengthening roles, and in this way it can help improve the function of the respiratory system [69]. It seems that the protective role of zn against apoptosis and oxidative stress in the

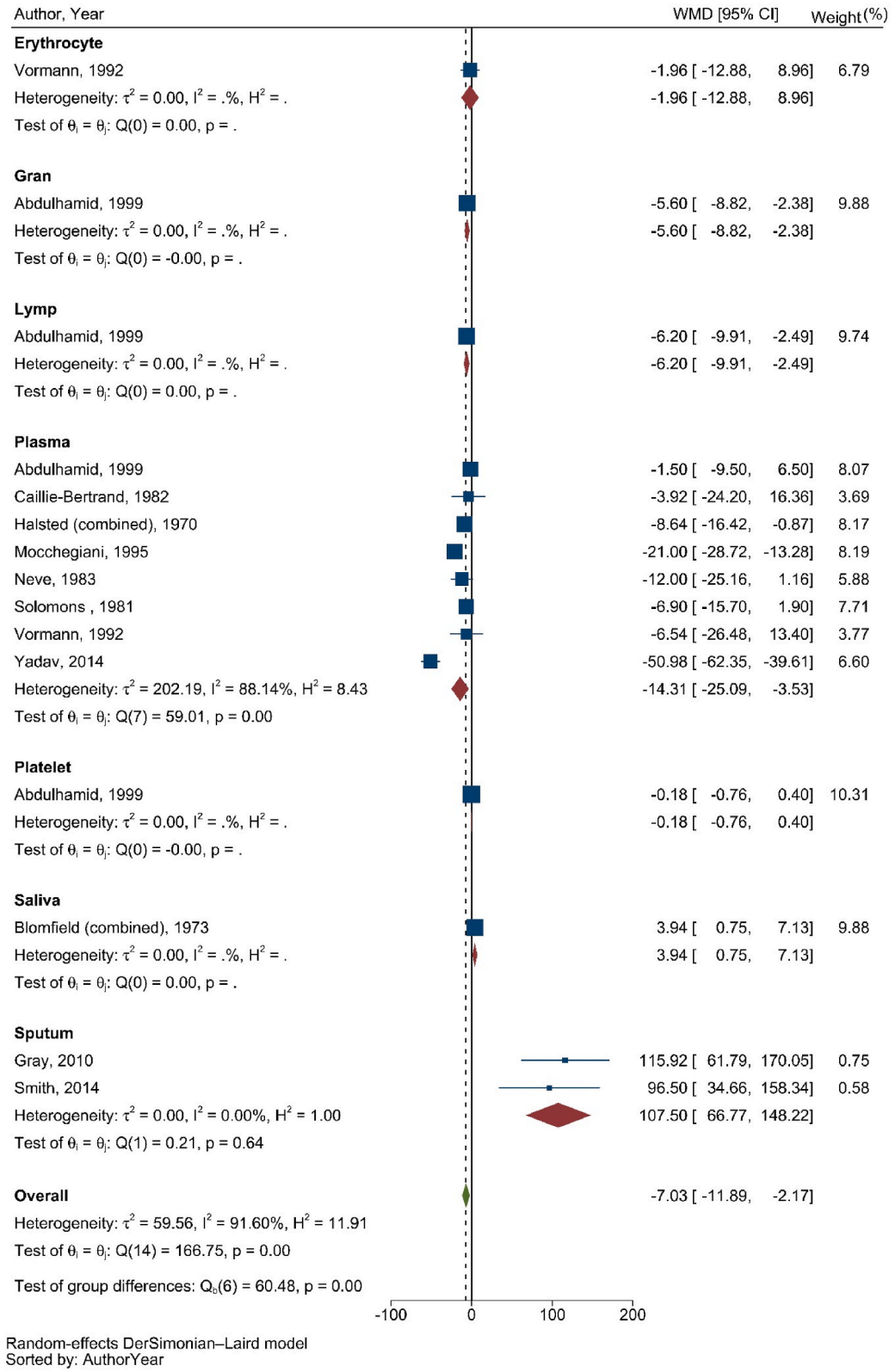

Fig. 3. Forest plot demonstrating meta-analysis of studies evaluating zn levels in different circulatory reservoirs of CF participants compared to control group. (The analysis was done using random effects model. P-value of effect <0.05).

Table 3
Subgroup analysis of zinc status in CF patients compared to control group.

Overall	Study, n	Meta- analysis			Heterogeneity	
		WMD (95 % CI)	P effect	Q statistic	P within group	I2, %
	11	−5.034 (−16.393, 6.326)	0.385	140.47	≤0.001	92.9
Subgroup						
Region						
USA	3	−5.668 (−10.378, −0.958)	0.018	1.68	0.432	0.0
Europe	5	−0.316 (−45.239, 134.953)	0.975	26.82	≤0.001	85.1
India	1	−50.980 (−62.354, −39.606)	≤0.001	0.00	–	–
Australia	2	44.857 (−45.239, 134.953)	0.329	8.58	0.003	88.4
Sample						
Granulocyte	1	−5.600 (−8.825, −2.375)	≤0.001	0.00	–	–
Lymphocyte	1	−6.200 (−9.907, −2.493)	≤0.001	0.00	–	–
Erythrocyte	1	−1.960 (−12.875, 8.955)	0.725	0.00	–	–
Plasma & serum	8	−14.309 (−25.092, −3.526)	0.009	59.01	≤0.001	88.1
Platelet	1	0.180 (−0.755, 0.395)	0.540	0.00	–	–
Saliva	1	3.940 (0.748, 7.131)	0.016	0.00	–	–
Sputum	2	107.496 (66.768, 148.224)	≤0.001	0.21	0.643	0.0
Method of measurement						
Atomic absorption spectrophotometry	9	−11.970 (−22.568, −1.372)	0.027	111.57	≤0.001	92.8
Optical emission spectrometry	1	115.920 (61.794, 170.046)	≤0.001	0	–	–
Mass-spectrometry	1	96.500 (34.662, 158.338)	0.002	0	–	–
Zinc supplement						
Yes	3	−5.273 (−10.643, 0.096)	0.054	1.59	0.451	0.0
No	8	−1.628 (−18.473, 15.217)	0.850	138.42	≤0.001	94.9
Age						
Children & adolescent	9	−11.970 (−22.568, −1.372)	0.027	111.57	≤0.001	92.8
Adults	2	107.496 (66.768, 148.224)	≤0.001	0.21	0.643	0.0

WMD, Weighted Mean difference.
Int = intervention, ctrl = control, RCT = randomized controlled trial, RBP = retinol binding protein, ↔ not changed, ↑ increased significantly, ↓ decreased significantly.

gastrointestinal system and liver can express the effects of this trace element [70]. Considering that the symptoms of zn deficiency are non-specific and include growth delay, loss of appetite and immune functions disorder, according to these symptoms because of similar symptoms in CF individuals, it is necessary to check CF patients for zn deficiency or low circulatory reservoirs zn levels [71,72]. In CF patients, if the nutritional status is not paid attention, they become malnourished and their serum albumin level decreases, and considering that most of the zn in the plasma is transported by albumin, it can be said that one of the reasons for the decrease in zn levels in different tissues is malnutrition in these patients [66]. Escobedo-Monge et al.'s study showed that CF patients are at high risk of zn deficiency and food sources of this trace element should be obtained [73]. Although a number of studies reported conflicting results on the relationship between zn status, malabsorption and growth impairment in CF patients [25,29,30,63,74], the present meta-analysis showed that there is a deficiency of circulating zn in CF patients and it is necessary to pay attention to zn intake. Although the results of our two included studies that were conducted on adults showed that the zn level in CF patients is higher than healthy individuals (control groups) [13,62], the reason for these conflicting results is due to the fact that in these two studies, the level of zn in the sputum was measured, and because probably one of the ways to excrete zn in CF patients is sputum, so its level is shown to be higher. Although some studies did not report a significant relationship between zn levels and pulmonary problems [25,30], probably because these studies were cross-sectional and CF patients received nutritional supplements containing zn, and there was no control group for comparison. However some of them showed that low zn levels were associated with pulmonary problems and moderate to severe growth retardation in CF patients [51,75]. Considering the high prevalence of respiratory infections in CF patients [76], as well as the undeniable role of zn in improving the condition of the immune system and reducing infection [77], it seems that receiving enough zn can help improve the condition of CF patients. A decrease in the plasma level of zn in CF patients has been associated with a decrease in the level of interleukin 2 and also diminish in the activity of natural killer (NK) cells [63]. According to the one study result, plasma zn level less than 90 μg/dL has been associated with increased risk of respiratory tract infections, so it should be tried to maintain plasma zn level in CF patients by improving nutritional status above 90 μg/dL [48]. It seems that one of the ways that zn can be effective in reducing the release of pro-inflammatory cytokines and infection is at the mRNA level and its inhibitory effect on NF-κB [78]. Also, another effect of zn on the respiratory function is the inhibitory effect of this trace element on NADPH oxidase, which produces superoxide anions [79]. On the other hand, sufficient amounts of zn are needed for normal pancreas function include glucagon secretion, digestive enzyme activity, and insulin packaging, secretion, and signaling, and therefore, the normal level of zn in the body is related to the improvement of digestion and absorption in CF patients [80–82]. Therefore, zn supplementation in CF patients whose zn levels are lower than normal can help improve the digestive and respiratory symptoms of these patients.

According to the findings of meta-analysis on case-control studies and the appearance low circulatory reservoirs zn levels in CF patients, intervention with zn can be effective in improving the function and reducing the pulmonary and gastrointestinal symptoms of these patients, therefore, we conducted a systematic review on four clinical trial studies that had a control group [46–49], although

Table 4
Quality assessment of case control studies.

Author, Year	Selection				Comparability	Exposure			Overall quality
	Case definition	Representativeness	Selection of control	Control definition	Comparability	Ascertainment of exposure	Same method of ascertainment	Non-Response rate	
Abdulhamid, 1999	*	*	–	–	*	*	*	–	Moderate
Blomfield, 1973	–	–	–	–	–	*	*	–	Low
Gray, 2010	*	*	–	–	–	*	*	–	Moderate
Halsted, 1970	–	–	–	–	–	*	*	–	Low
Mocchegiani, 1995	*	*	*	*	–	*	*	–	Moderate
Neve, 1983	–	–	–	–	*	*	*	–	Low
Smith, 2014	*	*	–	–	–	*	*	–	Moderate
Solomons, 1981	*	*	–	–	*	*	*	–	Moderate
van Bertrand, 1982	*	*	–	–	–	*	*	–	Moderate
Vormann, 1992	–	–	–	–	–	*	*	–	Low
Yadav, 2014	*	*	–	*	*	*	*	–	Moderate

Table 5
Study quality and risk of bias assessment using Cochrane Collaboration's tool.

Author, year	Random sequence generation	Allocation concealment	Blinding	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall quality
Abdulhamid, 2008	Low	Unclear	Low	Unclear	Low	Low	High	Fair
Best, 2004	Low	Unclear	High	High	Low	Low	High	Poor
Palin, 1976	unclear	Unclear	Low	Unclear	Low	Low	Low	Fair
Sharma, 2016	Low	Unclear	Low	Unclear	Low	Low	High	Fair

their results were not decisive based on the type of study design and the investigated outcomes. Future interventional studies should be conducted with specific doses of zn and by examining comprehensive factors related to growth, clinical symptoms in the digestive and respiratory systems, and infection, inflammation and oxidative stress status on children and adults with CF.

5. Limitations

The present study have some limitations. First, the variety of sample used in reporting the measuring of zn levels. Second, the limited number of studies that included in analysis. Third, most bias was in the control definition and selection of control group. In addition, moderate or low quality of included studies was another limitation of this study. Another limitation of this review is that in some studies, dietary zinc intake and serum zinc levels were not checked and controlled.

6. Conclusion

According to our findings, we noted that zn levels is significantly lower in CF patients which is probably due to the thickening of the secretions in the digestive and the respiratory system, as well as possible secretion and excretion through sputum and saliva. Considering the low levels of zn in serum of CF patients and the well designed of clinical trials, there is a need for more well-designed studies to clarify the zn supplementation effects on CF patients.

Funding

Not.

Availability of data and materials

The datasets can be made available by the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Mahsa Malekahmadi: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Sepideh Soltani:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Naseh Pahlavani:** Writing – original draft. **Elham Sharifi Zahabi:** Data curation. **Hossein Kazemizadeh:** Supervision. **Shima Hadavi:** Writing – original draft. **Gholamreza Mohammadi Farsani:** Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We sincerely thank Dr. Soheila Mirzaeian and the library of university of Manitoba for providing us with the full text of the articles

that we did not have access to.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33686.

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