Review Paper

A Systematic Review and Meta-analysis on the Prevalence of Zinc Deficiency in Iranian Population

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ABSTRACT

Objectives: This study aims to assess the zinc deficiency prevalence in Iran during the past two decades and compare it with other countries.

Methods: We searched PubMed, Google Scholar, Web of Sciences, Scientific Information Database (SID), and Magiran for English and Persian reports on zinc deficiency prevalence in Iran. The search terms were "zinc", zinc deficiency", "low zinc level", "low zinc concentration", "prevalence", "epidemiology", "status", "Iran", "Iranian", and "Persian", using Boolean operators 'AND' or 'OR.' The preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist were applied during the review. Two authors reviewed the articles independently. We included all articles published from 2001 to 2021 that reported zinc deficiency prevalence based on serum zinc levels (µg/dL) in the Iranian population. We excluded clinical intervention studies and studies on pregnant women, children with stunting or malnutrition, and patients with a particular disease. The effect sizes of prevalence rates were extracted from original studies. Meta-analysis with the random-effects model was used to estimate the pooled prevalence of zinc deficiency. Publication bias was evaluated by Egger's test and the Funnel plot.

Results: This systematic review and meta-analysis included 20 studies (12 for males, 13 for females, and 18 for both that involved 16138 participants; 8424 males and 9053 females). Using the random effect model, the overall prevalence of zinc deficiency in the general population was 16% (95% CI, 11%-20%), and in males and females, 18.4% (95% CI, 0.12%-0.24%) and 15% (95% CI, 10%-20%), respectively. In subgroup analysis, the prevalence rates of zinc deficiency for 6 years old children and adolescents were 29% and 12%, respectively.

Conclusions: The overall prevalence of zinc deficiency in the Iranian population was 16%, lower than the 20% set by IZiNCG (the International Zinc Nutrition Consultative Group) to indicate the need for national intervention programs. However, the COVID-19 pandemic and climate changes threaten this fragile margin. Dietary diversification/modifications, supplementation programs, fortification, and bio-fortification can be used to minimize the problem in high-risk populations. Since this study evaluates the adult healthy population of Iran, we should be cautious about generalizing its results on other population groups like children.

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Introduction

Zinc deficiency occurs due to low dietary intake, malabsorption, and chronic illnesses [1]. It causes various problems, including skin disorders, delayed wound healing, increased susceptibility to bacterial infections [1], atherosclerosis, and insulin resistance [1, 2]. Children and adolescents with zinc deficiency are more susceptible to stunting and delayed sexual maturation because of the body's substantial need for zinc at growth ages [3].

Substantial amounts of zinc are readily absorbed in animal resources like red meat [4]. On the other hand, some diets based on plant foods are rich in phytate, a potent zinc absorption inhibitor. Therefore, many low-income families in developing countries will likely receive insufficient amounts of zinc due to a high amount of phytate in their diet. However, it is not only a concern of impoverished areas but also a global issue [5, 6].

The prevalence of zinc deficiency ranges from 20% to 40% worldwide [7, 8]. In 2002, World Health Organization (WHO) reported that zinc deficiency ranks 5 out of 10 leading risk factors of illnesses and diseases in low-income countries and attributed 800000 deaths worldwide to this issue annually. Following the same report, the number of disability-adjusted life years (DALYs) lost due to zinc deficiency has been estimated at 29 million, with 90% affecting developing countries [9].

The first unequivocal cases of zinc deficiency were found in Middle East countries [10]. Today, zinc deficiency is a concern in these countries [11]. Iran is a large country with over 80 million people of different ethnicities. Several studies reported significant variations in the prevalence of zinc deficiency in Iran, ranging from 2% to 55.1% [12, 13].

This study aims to analyze all available research data to determine the prevalence of zinc deficiency in the healthy population of Iran, given the lack of systematic review studies. Additionally, by gaining a more accurate picture of the disease's epidemiology, healthcare policymakers can make informed decisions on addressing the issue at a larger scale.

Methods

Data sources

We identified studies by searching multiple international (MEDLINE through PubMed, Google Scholar, and Web of Sciences) and Iranian scientific databases (Scientific Information Database [SID], Magiran) for English and Persian language studies published between 2001 and 2021 that contained data on the zinc deficiency prevalence among the Iranian population. The date of our last search was on January 2022. We searched the literature by combining the following keywords to find all relevant studies in the search database: "Zinc", zinc deficiency", "low zinc level", "low zinc concentration", "prevalence", "epidemiology", "status", "Iran", "Iranian", and "Persian". We constructed the search strategy for Iranian databases according to the Persian equivalents of the English keywords.

Screening and study selection

After removing duplicates, we selected the relevant articles in three phases. To assess the quality, we used the JBI (The Joanna Briggs Institute) critical appraisal checklist for prevalence studies. During the review, we used the preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist. We screened papers by titles and abstracts in the first and second phases, respectively, and irrelevant ones were excluded. In the third phase, we deeply explored the articles' full text to select only the relevant papers. Two reviewers (MJE and MK) performed this phase independently, and discrepancies were resolved by consultation and consensus.

In the next step, we evaluated the eligibility of relevant papers. We included all articles that reported zinc deficiency prevalence based on serum zinc levels (µg/dL) in the Iranian population. We excluded clinical intervention studies and studies on certain groups, including pregnant women, children with stunting or malnutrition, and patients with a particular disease. However, we used the data of healthy control groups in the studies of zinc deficiency in patients. We also excluded the Persian version of a paper if it repeated the same result in English. The study selection process of the systematic review is shown in the flowchart (Figure 1).

Data extraction

The required data extracted from eligible studies are as follows: General characteristics of the study (first author's name, year of study and publication, and study design, study location [i.e. province, city/town name] or national), general characteristics of the study participants (age and sex study population and the sample size), serum zinc cut-off point for deficiency (µg/dL), prevalence of zinc deficiency (total and by gender), and serum zinc level (µg/dL, total and by gender).

Statistical analysis

The effect sizes of prevalence rates were extracted from original studies. The standard error of the prevalence of zinc deficiency was calculated in every study according to the binomial distribution formula. The potential heterogeneity across studies was assessed using Cochran's Q-test and expressed using the I^2 index. A random-effects model was used to estimate the pooled prevalence of zinc deficiency. Subgroup analyses based on geographical regions of the country (Tehran, National, Others), mean age groups (6 y, 7-18 y, ≥18 y), year of publication (≤2010, >2010), and language of publication (English, Persian) were performed to seek the reasons for heterogeneity. In addition, meta-regression analysis was used for assessing continuous variables of the mean age, sample size, and year of publication of studies as the possible sources of heterogeneity. The sensitivity analyses were performed by excluding one or several studies at a time to gauge the robustness of our results. Publication bias was evaluated by the Funnel plot and Egger's test. All statistical analyses were conducted using the software STATA software, version 12 (STATA Corp, College Station, Texas, USA).

Results

Study selection

We initially found 716 records in the database search. After removing the duplicates, we screened the titles and abstracts of 655 studies, and 622 were excluded. Thirty-three full-text articles were assessed for eligibility; 13 were excluded because zinc deficiency prevalence was not reported, and 20 studies remained. The search process and results are summarized in Figure 1.

Characteristics of the studies

The main characteristics of selected studies are represented in Table 1. Eighteen studies were included in the meta-analysis for both genders, 12 for males, and 13 for females, which involved 16138 participants (8424 males and 9053 females). All studies were published between 2001 and 2021, and 8 were published after 2010. Three studies were conducted in Tehran, the capital of Iran, and three at a national level. Participants ranged from 3 to 94 years, and 13 studies were conducted specifically on the child and adolescent population. Eighteen studies were cross-sectionally designed, and we used the healthy control group in two case-control studies.

Prevalence of zinc deficiency in general Iranian population

The meta-analysis findings using the random-effect model on 18 studies showed that the overall prevalence rate of zinc deficiency was 16% (95% CI, 11%-20%) (Figure 2). There was high and significant heterogeneity between studies (I^2=98.9%, P<0.001). The funnel plot was asymmetry, and Egger's test was significant (P=0.010). Therefore, there was publication bias among these studies (Figure 3). Trim-and-Fill method was conducted, but no investigation was filled, implying that the publication bias had a non-significant effect on the results.

Prevalence of zinc deficiency in Iranian male population

Twelve studies were included in the analysis to estimate the prevalence of zinc deficiency among the Iranian male population. Using the random effect model, the prevalence of zinc deficiency was 18.4% (95% CI, 0.12-0.24) (Figure 4). However, the heterogeneity was high among these 12 studies (I^2=98.6%, P<0.001). The funnel plot was asymmetry, and Egger's test was significant (P=0.015). Therefore, there was publication bias among these studies. Trim-and-Fill method was conducted, but no investigation was filled, which means that the publication bias non-significantly affects the results (Figure 5).

Prevalence of zinc deficiency in Iranian female population

The random-effect model on 13 studies demonstrated that the prevalence of zinc deficiency in the Iranian female population was 15% (95% CI, 10%-20%) (Figure 6). The studies' heterogeneity was high (I^2=98.3%, P<0.001). The funnel plot was asymmetrical, and Egger's test was significant (P=0.008), so there was publication bias among these studies (Figure 7). Trim-and-fill method was conducted, but no investigation was filled, representing that the publication bias had a non-significant effect on the results.

Subgroup analysis

Results of subgroup analysis based on age groups demonstrated the prevalence of zinc deficiency for 6 years old children was estimated at 29% (95% CI, 14%-43%). Furthermore, the prevalence rates for adolescent girls and boys were 12% (95% CI, 8%-16%) and 16% (95% CI, 8%-23%), respectively. Moreover, the prevalence rates of zinc deficiency for adult males and females were estimated at 24% (95% CI, 4%-43%) and 22% (95% CI, 4%-49%), respectively (Table 2). Results of subgroup analysis based on geographical regions, year of publication, and language of studies are shown in Table 2.

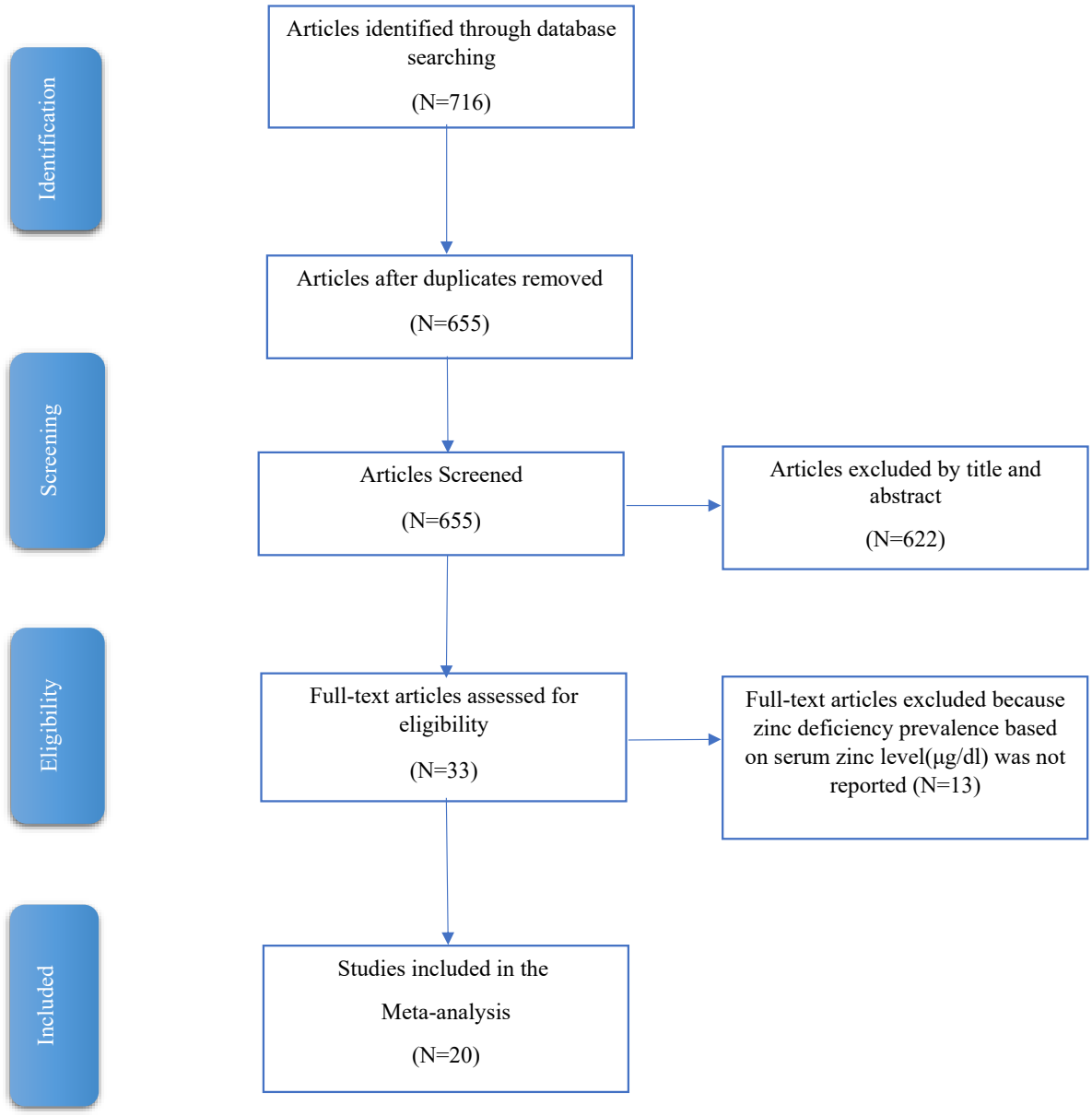

Figure 1. Flow Chart of studies included in the systematic review and meta-analysis

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Results of meta-regression

The meta-regression results indicated that the mean age of subjects in the study, sample size, and year of publication of studies were not significantly associated with the prevalence of zinc deficiency in the general Iranian population, males and females (P>0.05).

Results of sensitivity analysis

Results of sensitivity analysis showed that excluding one or several studies did not significantly change the pooled prevalence of zinc deficiency and heterogeneity for the Iranian population of general, males and females. After dropping case-control studies, the prevalence rates of zinc deficiency in the general population and females were 17% (95% CI, 12%-22%) and 15% (95% CI, 10%-21%), respectively. The heterogeneity values between cross-sectional studies were estimated at 99.4% and 98.3%, with P<0.001 for general and female populations. All studies of the zinc deficiency prevalence for the male population were cross-sectional.

Discussion

This investigation is the first systematic review and meta-analysis summarizing the strongest evidence to estimate the prevalence of zinc deficiency in the Iranian

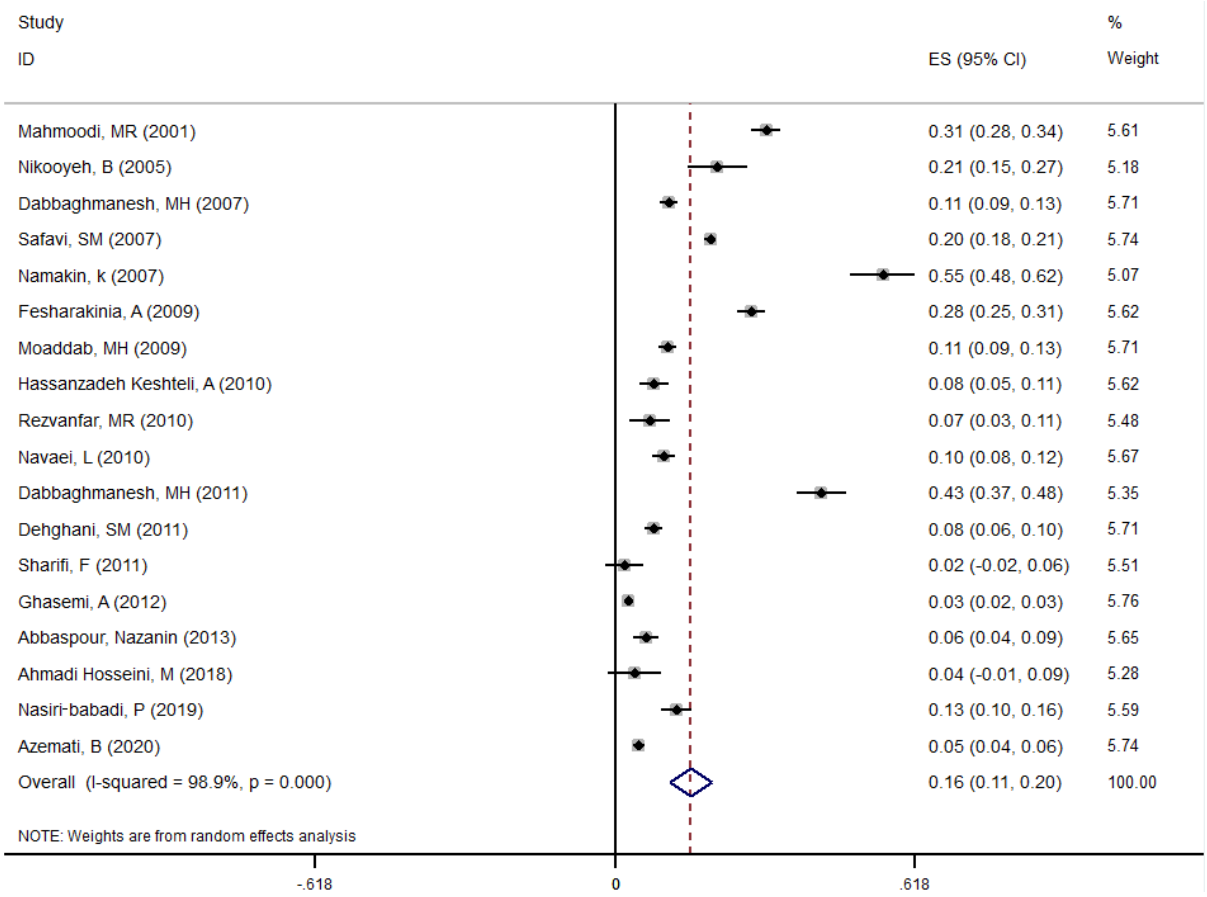

Figure 2. Forrest plot for the prevalence of zinc deficiency in general Iranian population

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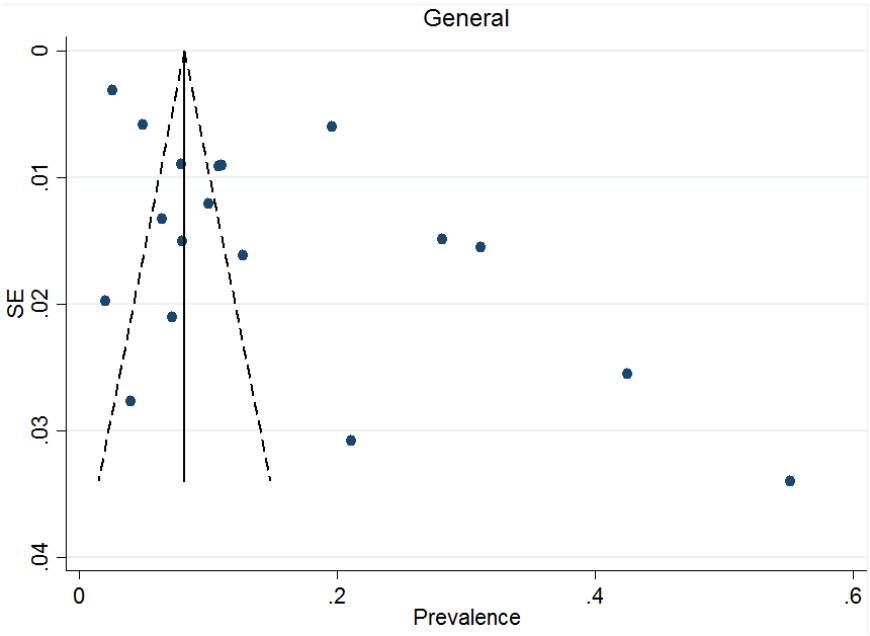
population. As shown in Table 2, the estimated pooled prevalence rates of zinc deficiency in the general, male, and female Iranian populations were 16%, 18.4%, and 15%, respectively. This outcome is lower than the result of reports from other low- and middle-income countries, including Nigeria (28%), Mexico (34%), Afghanistan (23%), Iraq (55%), Pakistan (42%), India (52%), Bangladesh (57%), and Philippines (31%) [14-21].

In subgroup analysis, based on age groups, the estimated prevalence rates of zinc deficiency in children aged 6, adolescents, and adults were 29%, 12%, and 19%, respectively. Our findings showed a higher prevalence of zinc deficiency in the young-aged group than in Iran's National Integrated Micronutrient Survey (NIMS-II), which reported 13.6% and 11.4% in 6-year-old children and adolescents, respectively [22]. Compared to the other countries, this prevalence in children aged 6 (29%) is higher than the prevalence among children in Nigeria (20%), Afghanistan (15%), Azerbaijan (11%), Nepal (21%), Sri Lanka (5%), and China (4%) [15, 17, 23-25], but lower than the findings from India (43%), Senegal (50%), Colombia (43%), Pakistan (37%), Bangladesh (45%), Cambodia (68%), and Philippines (31%) [16, 21, 26-30].

Different socioeconomic statuses and nutritional practices may explain the differences in findings in Iran and other countries. In developing countries, it is less likely for an individual to receive adequate zinc-rich food resources and more likely to consume whole-grain cereals that contain high amounts of phytates that may interfere with zinc absorption. Moreover, young children and adolescents are at a greater risk of zinc deficiency due to the higher zinc requirements during early growth and development and pubertal growth spurt, respectively [31, 32]. Thus, children of developing countries are twice as at higher risk of being deprived of sufficient zinc intake and are more likely to become deficient. On the other hand, the cut-off point used to define zinc deficiency in each survey may also explain the other part of the discrepancies. Studies in Afghanistan and Pakistan used a <60 µg/dL cut-off point. In contrast, in this systematic review and meta-analysis, studies on children aged 6 used the cut-off point of 65 [33] and 70 µg/dL [12, 34]. In the current survey, zinc deficiency among children aged 6 was considerable. However, our zinc status information in this age group was identified based on 3 studies [12, 33, 34], and we need to be cautious of generalizing the findings.



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Fiigure 3. Funnel plot for assessment of publication bias among studies included estimating the pooled prevalence of zinc deficiency among the general Iranian population

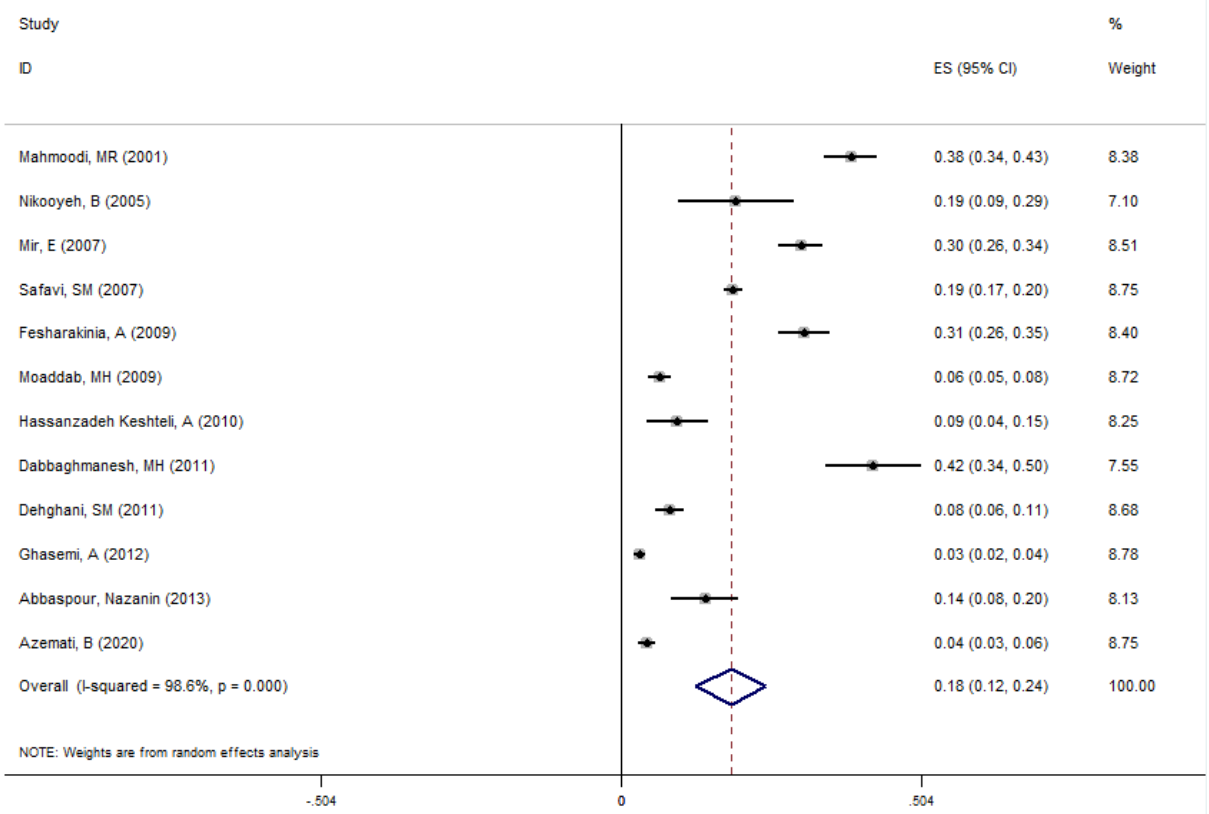

Figure 4. Forrest plot for the prevalence of zinc deficiency in Iranian male population

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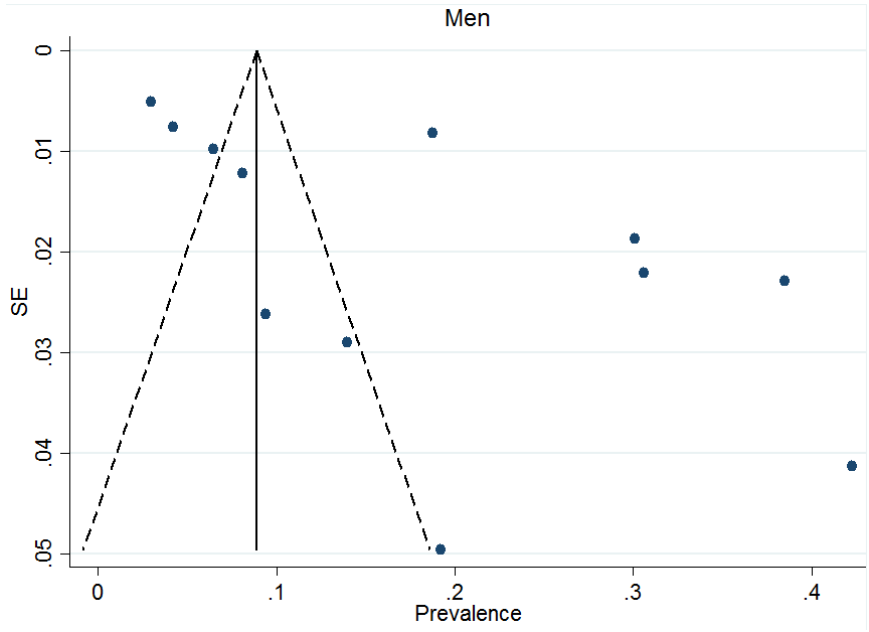

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Figure 5. Funnel plot for assessment of publication bias among studies included estimating the pooled prevalence of zinc deficiency among the Iranian male population

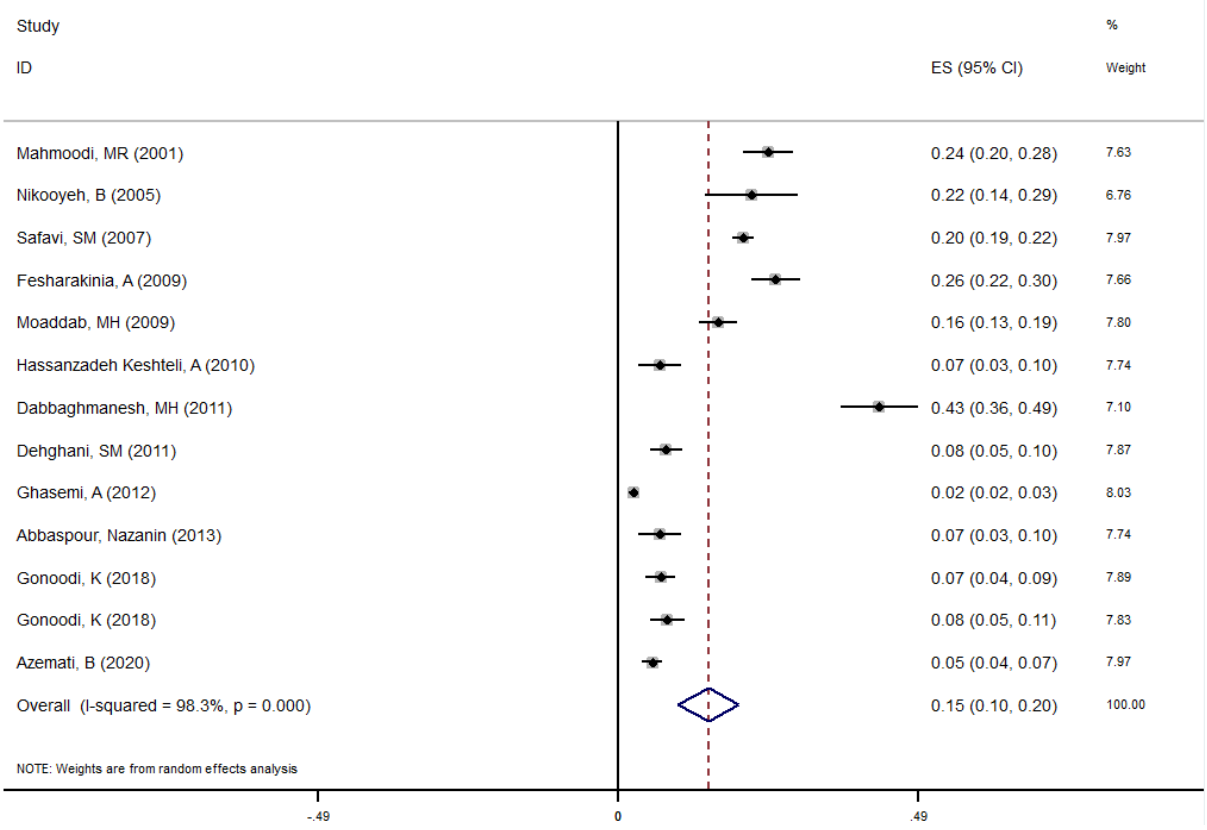

Figure 6. Forrest plot for the prevalence of zinc deficiency in Iranian female population

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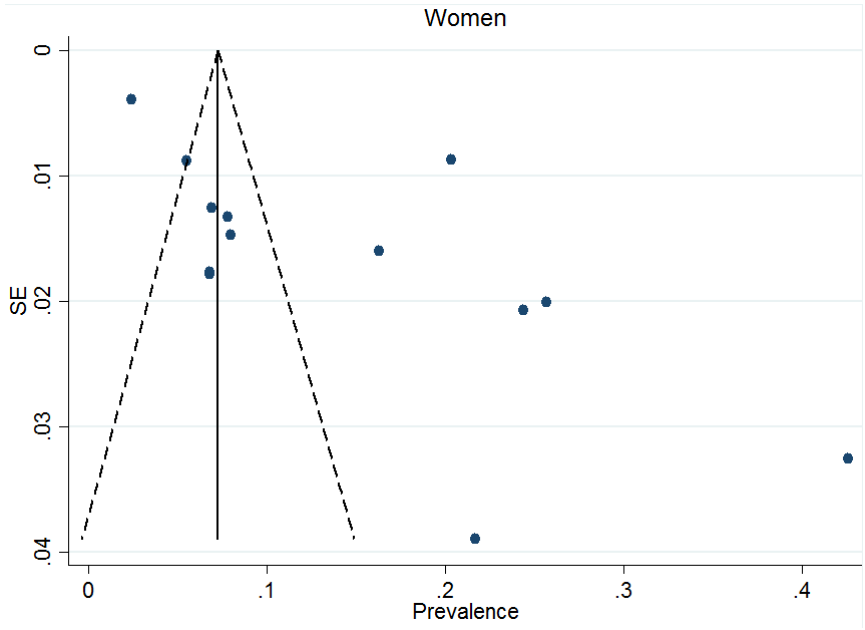

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Figure 7. Funnel plot for assessment of publication bias among studies included estimating the pooled prevalence of zinc deficiency among the Iranian female population

Though our findings suggest that zinc deficiency prevalence in the general Iranian population (16%) was lower than the 20% set by the International Zinc Nutrition Consultation Group (IZiNCG) to indicate the need for national intervention programs [35], it should still be considered as a health concern. Hoshyarrad et al. (2013) showed that Iranian households, on average, receive 79% of the reference nutrition intake recommended by FAO/WHO and estimated a relatively significant prevalence of zinc deficiency [36]. Moreover, a recently published study [37] has warned that in the coming decades, as a result of anthropogenic CO_2 emission and climate changes, the food corps will become more impoverished. This situation can threaten the diet and nutritional sufficiency of vulnerable regions' populations, including the middle east and Iran, and is estimated to increase the prevalence of zinc deficiency by up to 2.9% by 2050. On the other hand, the spread of COVID-19 has enormously impacted the food sector and resulted in economic and food crises [38]. Poor and isolated rural people are the most vulnerable group like zinc deficiency. Therefore, zinc deficiency malnutrition can be multiplied in this group. Governments, industries, and individuals should collaborate effectively to minimize the risks of malnutrition, specifically zinc deficiency, during and after the pandemic. However, many Iranian families have been affected by the benefits of using zinc supplementation for their children. Everyone should be cautious of the harmful adverse effects of excessive zinc on human organs, including the brain, prostate, respiratory and gastrointestinal tract, and so on [39].

Our survey is the first systematic review and meta-analysis providing comprehensive information about zinc deficiency prevalence in Iran. Our study's strong point was to strictly follow the PRISMA guideline on each step during the review process and write-up. Moreover, we conducted a subgroup analysis using the parameter of age to provide additional valuable information on children, adolescents, and adults. But our work has some limitations as well. First, serum zinc has been used to evaluate zinc deficiency in the studies included in our review. Since zinc hemostasis is tightly controlled to sustain metabolic functions over a wide range of zinc intakes, evaluating body zinc status using serum zinc levels is in the debate. However, several expert committees have endorsed the usefulness of serum zinc level as an indicator to determine the risk of zinc deficiency in populations [40-42]. Second, there were limited studies on children as a vulnerable age group for zinc deficiency; therefore, caution is required in interpreting and generalizing the results. Third, the heterogeneity level of articles was significant, limiting the data's ability to be pooled to provide a complete overview of the evidence-based. However, further analysis showed that it has not significantly affected the results.

Table 1. Prevalence of zinc deficiency based on the assessment of plasma/serum zinc concentration in studies among Iranian populations

No	Author	Year of Study, Publication	No.		Study Design	Province, City	Mean±SD	%	Serum Zinc Cut-off for Deficiency (µg/dL)	%	Serum Zinc Level, Total (µg/dL) Total Male Female
			Sample Size	Sample Size by Gender			Age	Proportion of male		Prevalence of Zinc Deficiency Total Male Female	
1	Dabbaghmanesh	2010	374	M: 143 F: 231	CS	Fars, Shiraz	38±13.37 19-82	38.2	100	42.5 42.3 42.6	103.66±18.06 105.05±19.6 102.9±16.9
2	Hassanzadeh Keshteli	2010	326	---	CS	Isfahan, Isfahan	--- 6-13	66.3	65	8.0 9.4 6.8	96.00±25.79 95.41±30.49 96.49±21
3	Rezvanfar	2010	151	M: 92 F: 59	CS	Markazi, Arak	8.90±1.35 6-11	60.9	65	7.2 --- ---	89±17.0 --- ---
4	Azemati	2004	1370	M: 695 F: 675	CS	National	12.4±3.0 7-18	50.7	75	4.9 4.2 5.5	107.23±25.81 109.03±26.12 105.41±25.30
5	Dehghani	2011	902	M:496 F: 406	CS	Fars, Shiraz	--- 3-18	55	70	7.9 8.1 7.8	122.3±55 119.6±43.9 125.7±67.2
6	Mahmoodi	2001	889	M: 452 F: 429	CS	Tehran, Tehran	13.2±1.0 11-16	50.8	100	31.1 38.5 24.4	95.2±17.7 94.7±16.7 95.6±18.6
7	Abbaspour	2013	341	---	CS	Khomeini Shahr & Rooran, Isfahan	---	---	65 and 70	6.4 14.0 6.8	91.1±15.5 --- ---
8	Ahmadi Hosseini	2018	50	M: 10 F: 40	CC	Birjand, South Khorasan	---	20	---	4 --- ---	96.57±21.25 --- ---
9	Dabbaghmanesh	2008	1188	M: 598 F: 590	CS	Marvdasht, Fars	--- 8-13	50.3	65	11 --- ---	84.1±20.7 86.6±22.7 82±18.7
10	Fesharakinia	2009	908	M: 434 F: 474	CS	Birjand, South Khorasan	--- 9-11	47.8	70	28.1 30.6 25.7	87.7±32.7 83.7±29.9 91.3±34.8
11	Ghasemi	2012	2632	M:1119 F: 1513	CS	Tehran, Tehran	47.3±16.8 (males) 45.5±15.6 (females) 20-94	42.5	---	--- 3.0 2.4	110.4±35.9 113.1±35.9 108.5±35.3
12	Gonoodi	2018	408 (girls)	F: 408	CS	Mashhad, Khorasan Razavi	15.07±1.52 12-18	0	67.9	6.9	95.5±17.7
13	Mir	2007	600 (males)	M: 600	CS	Tehran, Mashad, Shiraz, Tabriz and Boushehr	40.83±15.06 20-69	100	75	30.1	92.15±35.15
14	Moaddab	2009	1157	M: 626 F: 531	CS	Semirom, Isfahan	9.3±1.0 7-13	54.1	65	10.8 6.5 16.3	83.38 ±16.25 88.42±17.50 77.00±11.91
15	Navaei	2010	612	M: 265 F: 347	CS	Tehran, Tehran	32.5±19 3-83	43	---	10% --- ---	120±39.7 --- ---
16	Nasiri-babadi	2020	425	M:200 F: 225	CS	National	--- 5-7	47.1	70	12.7 --- ---	---
17	Safavi	2007	4374	M: 2235 F: 2139	CS	National	--- 6-7	51	65	19.6 18.75 20.35	81.72±15.03 81.98±25.95 81.39±25.10
18	Nikooyeh	2005	175	M: 63 F: 112	CS	Tabriz, East Azerbaijan	--- 18-25	36	---	19.2 21.7	--- 91.98±20.66 89.57±16.14
19	Sharifi	2011	50	M: 25 F: 25	CC	Zanjan, Zanjan	10.2±3 ---	50	75	2 --- ---	110.9±12.4 --- ---
20	Namakin	2007	214	M: 104 F: 111	CS	Birjand, South Khorasan	6	48.5	70	55.1 --- ---	75.56±29.84 --- ---

Table 2. Results of subgroup analysis of the prevalence of zinc deficiency by gender

Overall	Total				Male				Female			
	n	Pooled Prevalence 95% CI	I2 (%)	P	n	Pooled Prevalence 95% CI	I2 (%)	P	n	Pooled Prevalence 95% CI	I2 (%)	P
	18	16 (11, 20)	98.90	<0.001	12	18 (12, 24)	98.6	<0.001	13	15 (10, 20)	98.30	<0.001
Geographical Regions of the Country												
Tehran	3	14 (-0.4, 29)	99.40	<0.001	2	21 (-14, 46)	99.60	<0.001	2	13 (-8, 35)	99.10	<0.001
National	3	12 (2, 23)	99.40	<0.001	2	12 (-3, 26)	99.40	<0.001	2	13 (-2, 28)	99.30	<0.001
Others	12	17 (11, 22)	97.90	<0.001	8	20 (12, 28)	97.30	<0.001	9	15 (10, 21)	96.00	<0.001
Mean Age Groups (y)												
6	3	29 (14, 43)	98.40	<0.001	1	19 17, 20)	-		1	20 (19, 22)	-	-
7-18	10	12 (7, 17)	98	<0.001	7	16 (8, 23)	98.10	<0.001	9	12 (8, 16)	95.2	<0.001
≥18	4	19 (6, 32)	99.4	<0.001	4	24 (4, 43)	38.9	<0.001	3	22 (-4, 49)	98.80	<0.001
Year of Publication												
≤2010	10	20 (14, 25)	98.10	<0.001	7	22 (13, 30)	98.00	<0.001	6	19 (14, 24)	93.00	<0.001
>2010	8	10 (6, 14)	97.70	<0.001	5	12 (7, 17)	96.40	<0.001	7	11 (6, 15)	96.70	<0.001
Language of Publication												
English	13	15 (10, 20)	99.10	<0.001	11	18 (12, 24)	98.70	<0.001	12	14 (9, 19)	98.40	<0.001
Persian	5	18 (4, 32)	98.10	<0.001	1	19 (10, 29)	-	-	1	22 (14, 29)	-	-

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Conclusion

In summary, our findings revealed that although zinc deficiency is still of concern in Iran, its average prevalence of 16% is lower than the 20% set by IZiNCG. Adopting policies including dietary diversification/modifications, supplementation programs, fortification, and bio-fortification [6] can be used complementary, helping minimize the problem among high-risk populations.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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