Review Article:

The Association Between Antioxidant Status and Excess Weight in Children: A Systematic Review and Meta-analysis

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ABSTRACT

Background: The prevalence of childhood obesity with its complications has increased in the world. Obesity, along with antioxidants deficiency (due to an unhealthy diet), might change the balance in favor of oxidative stress.

Objectives: The current study aims to assess the literature on the relationship between obesity and antioxidant status through a systematic review and meta-analysis

Results: β-Carotene levels was significantly lower in obese children than non-obese ones (mean difference: 0.13, 95%CI: 0.09-0.16, P<0.001), with significant heterogeneity (P<0.001, I^2=85%). There was a significant difference between obese and non-obese children in both α-tocopherol (pooled mean difference respectively: 0.36, 95% CI: 0.04-0.96, P<0.001) with non-significant heterogeneity (P>0.05, I^2=0.0%) and α-tocopherol per lipoid (pooled mean difference: 0.42, 95%CI: 0.28-0.55, P<0.001), with significant heterogeneity (P=0.048, I^2=58.8%). There was no significant association between vitamin E level and obesity (pooled mean difference: 0.40, 95%CI: -0.05-0.85, P>0.05), with significant heterogeneity (P<0.001, I^2=84.5%). There was significant association between zinc, magnesium, copper, and selenium level and obesity (P>0.05), with significant heterogeneity (P<0.001).

Conclusions: This review revealed a significant inverse relationship between childhood obesity and serum antioxidant levels. More studies are necessary to find the underlying mechanisms and clinical impacts of this finding. Data Sources: This systematic review and meta-analysis were performed among English language articles published until September 2020 without any time limit. An electronic search was conducted in international databases of Google Scholar, PubMed, Web of Science, Scopus, Medline, and Cochrane. Study Selection: First, 1255 papers were found. After removing duplicates and quality assessment, 46 were used in the systemic review, and 19 articles were entered into the meta-analysis. Data Extraction: Two researchers independently searched the following keywords in the databases: “Vitamin C”, “Vitamin E”, “Vitamin A”, “Carotenoids”, “Antioxidants”, “Selenium”, “Magnesium”, “Copper”, “Zinc”, “Ascorbic acid”, “Tocopherol”, “Obesity”, “Overweight”, “Childhood”, “Pediatric”, and “Adolescence”. Articles that examined the

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association between obesity and antioxidant status were included in the study. The research on animals, interventional studies, case studies, case reports, and irrelevant studies were excluded. The research team determined the quality of studies using the STROBE (strengthening the reporting of observational studies in epidemiology) checklist. Heterogeneity of studies was evaluated using index (I2) and probability of diffusion bias by funnel plot and Begg's and Egger's tests.

1. Introduction

Obesity and overweight are dramatically increasing worldwide [1]. Obesity is associated with several chronic life-long diseases [2]. During the last three decades, the prevalence of obesity in children has increased worldwide [3], including in Iran, which is the seventh country in terms of having obese children [4]. The prevalence rates of overweight and obesity among Iranian children have reached 10.8% and 5.1%, respectively, between 2007 and 2012 [5]. Childhood obesity increases the risk of morbidity due to obesity in adulthood [6]. Obesity in children is associated with various factors such as genetics, environment, nutrition, and physical inactivity, especially screen time [7].

Reactive species of oxygen and nitrogen are unstable and highly reactive molecules. These molecules oxidize various macromolecules to reach a stable state [8, 9]. Free radicals destroy fats, proteins, and cellular DNA [10]. Antioxidants are generally regenerative substances found inside and outside the cell and can react with free radicals and active species. Antioxidants reduce or prevent oxidative stress by reacting with free radicals and active species [10, 11]. Antioxidants are synthesized both in the body and absorbed through food. Antioxidants are generally divided into two categories: enzymatic and non-enzymatic. The most important antioxidants are Superoxide Dismutase (SOD), Glutamine Peroxidase (GPX), and Catalase (CAT) [10, 11]. Vitamins C, A, E, and β-carotene are non-enzymatic antioxidants, and magnesium, zinc, selenium, and copper are mineral antioxidants [12].

Oxidative stress might change the balance between the production of free radicals and the antioxidant defense system in favor of free radicals, which would cause oxidative damage and worsen the pathological status [13]. On the one hand, obesity is usually associated with micronutrient deficiency as a result of an unhealthy diet and low antioxidants intakes, and on the other hand, it can change the balance towards oxidative stress [14].

Magnesium is related to the enzymatic activity of cells and glucose metabolism; a significant relationship is reported between magnesium deficiency and obesity [15]. Zinc is one of the most important elements in several health issues. Some studies found a significant relationship between low levels of zinc and high levels of leptin [15]. Selenium is a mineral antioxidant that prevents the damaging effects of radicals and strengthens the immune system and metabolic processes, and decreases obesity status [16]. Copper is a mineral and one of the components of antioxidant enzymes in the body that plays an essential role in upsetting the balance in favor of antioxidants and has an inverse relationship with obesity [17].

In recent years, many studies assessed the relationship between antioxidant levels and obesity in adults [18], but few studies have been conducted in the pediatric age group [19, 20]. These studies have reported controversial findings. Therefore, this study aims to assess the current literature on the relationship between childhood obesity and antioxidant status through systematic review and meta-analysis.

2. Materials and Methods

In this systematic review, the following keywords and their equivalents were searched separately and together: "Vitamin C", "Vitamin E", "Vitamin A", "Carotenoids", "Selenium", "Magnesium", "Copper", "Zinc", "Ascorbic acid", "Tocopherol", "Antioxidants", "Childhood", "Pediatric Adolescence", "Overweight", and "Obesity". These words were searched in international databases of Google Scholar, PubMed, Web of Science, Scopus, Medline, and Cochrane. This research was conducted without time or gender restrictions until September 2020.

The search was performed by two researchers independently. Examining the agreement between the search results was performed by a third person, where eventually, duplicates were omitted. This study includes case-control, cross-sectional, and prospective articles with control groups. These English language full-text articles evaluated the association between antioxidant status and overweight/obesity. Overweight and obesity were confirmed by anthropometric indices: Body Mass Index (BMI), weight for height, and waist circumference. Research on animals, interventional studies, case studies, case reports, and irrelevant studies were excluded.

Data extraction

Initially, 1255 articles were extracted from the mentioned databases. Then, 360 duplicate articles were removed by reviewing the titles (those extracted by the two researchers whose titles of the authors and the published journal are the same). Next, the abstracts of the remaining 895 articles were reviewed, where 380 articles were omitted because the studies were case study, animal research, or their interventions were irrelevant. Afterward, the full texts of the remaining 515 articles from the previous step were read, and unrelated articles were excluded because of lacking the inclusion criteria. Finally, 46 articles were included in the systematic review after examining the inclusion and exclusion criteria, and 19 competent articles in the meta-analysis (Figure 1).

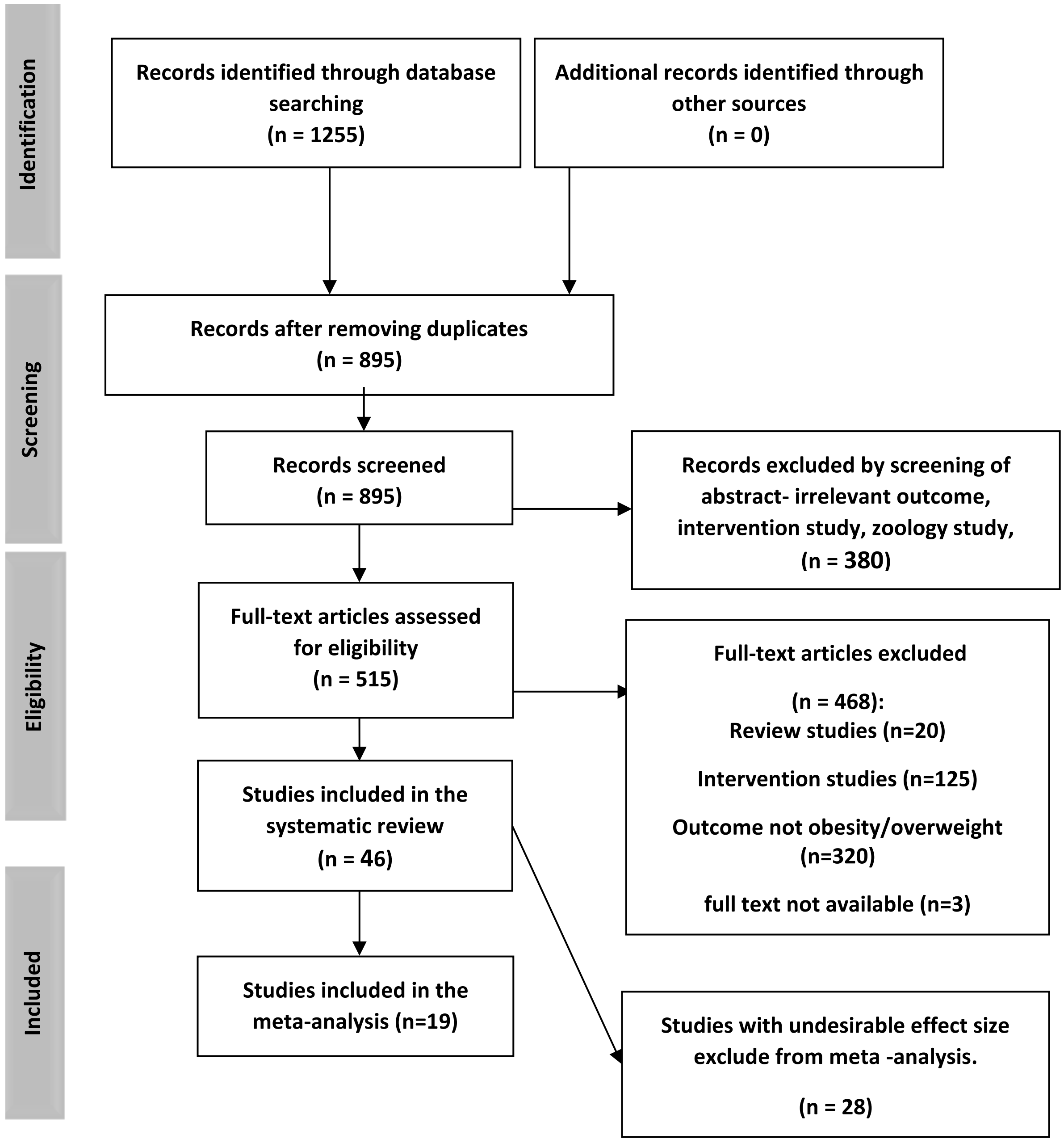

Figure 1. Flowchart of study selection for systemic review and meta-analysis

Journal of Pediatrics Review

Quality of studies

All articles included in the current review were extracted using a pre-prepared checklist. It included the author's last name, year of publication, country of origin, age, sex, and sample size. After reviewing the inclusion and exclusion criteria and determining the related studies, the quality of the articles was independently assessed by two researchers using the checklist of STROBE (strengthening the reporting of observational studies in epidemiology). This checklist has 22 sections and various methodological aspects, including sampling and measuring methods, variables, statistical analysis, and study objectives. In this checklist, the minimum and maximum scores were 1 and 22. The studies with a score of 11 and above were entered into this review study, and the data related to them were selected for the meta-analysis process. A third researcher examined any disagreement between the two researchers (Figure 1).

Data analyses

The desired pooled effect size was considered a mean difference with a 95% Confidence Interval (CI). We used the forest plot to investigate the association between antioxidants levels and obesity among children and adolescents. The fixed-effects model was used according to the nonexistence of significant heterogeneity. The z-statistics was used to assess the significance of the pooled effect size; a P value of less than 0.05 was considered as statistically significant. Heterogeneity between the included studies was assessed by Cochran's Q statistic, which was quantified by calculating the inconsistency index (I^2). In cases with high heterogeneity among studies (substantial heterogeneity considered as I^2>50%), the random-effects model with Der Simonian and Liard method was used. We assessed potential publication bias using funnel plots (not shown) and both Begg's and Egger's tests. P values of less than 0.05 from both Begg's and Egger's tests and the asymmetrical shape of the funnel plot showed statistically significant publication bias. The sensitivity analysis was conducted to assess the extent of the influence of omitting individual studies on the pooled mean difference. The analysis was conducted by the Stata software, version 11.2 (STATA Corp, College Station, TX, USA).

3. Results

Figure 1 shows that 46 articles were reviewed, and finally, 19 articles met the inclusion criteria and were entered into the analysis. Table 1 shows a summary of reviewed articles. The associations of following antioxidants and childhood obesity were assessed:

Association between obesity and β-carotene

The forest plot for the association between antioxidants level and obesity according to the type of antioxidants is shown in Figures 2, 3, 4, 5, 6 and 7. The pooled mean difference of β-carotene level between obese and non-obese children was significantly different (mean difference: 0.13, 95% CI: 0.09-0.16, P<0.001), with significant heterogeneity (P<0.001, I^2=85%) (Figure 2). We used the funnel plot and Egger's test to assess the publication bias. Based on the funnel plot (figures not shown) and Egger's test, there was no evidence of publication bias (Egger's test: P=0.27).

Subgroup meta-analysis according to α-tocopherol type

Results of subgroup meta-analysis according to α-tocopherol type are shown in Figure 3. There was a significant difference between obese and non-obese children in both α-tocopherol (pooled mean difference respectively: 0.36, 95%CI: 0.04-0.96, P<0.001) with non-significant heterogeneity (P>0.05, I^2=0.0%) and α-tocopherol per lipoid (pooled mean difference: 0.42, 95%CI: 0.28-0.55, P<0.001), with significant heterogeneity (P=0.048, I^2=58.8%) (Figure 3).

We used the funnel plot and Egger's test to assess the publication bias. Based on the funnel plot (figures not shown) and Egger's test, there was no evidence of publication bias (Egger's test: P=0.91).

Association between obesity and vitamin E

The forest plot for the association between vitamin E level and obesity is shown in Figure 4. There was no significant association between vitamin E level and obesity (pooled mean difference: 0.40, 95%CI: -0.05-0.85, P>0.05), with significant heterogeneity (P<0.001, I^2=84.5%) (Figure 4). We used the funnel plot and Egger's test to assess the publication bias. Based on the funnel plot (figures not shown) and Egger's test, there was no evidence of publication bias (Egger's test: P=0.18).

Association of obesity with zinc, magnesium, copper, and selenium

The forest plot for the association between obesity and variables of zinc, magnesium, copper, and selenium level are shown in Figures 5, 6 and 7. There were significant associations between zinc, magnesium, copper, and selenium level and obesity (P>0.05), with significant heterogeneity (P<0.001). We used the funnel plot and Egger's test to assess the publication bias. Based on the funnel plot (figures not shown) and Egger's test, there was no evidence of publication bias (Egger's test: zinc studies, P=0.65; magnesium studies, P=0.07; selenium and copper studies, P=0.98).

Sensitivity analysis

The sensitivity analysis showed that eliminating any individual studies did not significantly change the pooled effect size and heterogeneity among magnesium, copper, and selenium studies (P>0.05). Regarding other antioxidant studies, the results of sensitivity analysis are presented in Table 2.

DiscussionThis systematic review and meta-analysis study was performed to determine the relationship between childhood obesity and anthropometric indices with antioxidant status. After completing the search, 46 articles were systematically reviewed (Table 1), and 19 were entered into the meta-analysis. The results showed that vitamins A, C, and their components, including α-tocopherol and β-carotene, as well as selenium, copper, magnesium, and zinc, were inversely related to childhood obesity. But vitamin E is not significantly associated with obesity.

Eighteen studies examined the relationship between vitamins A, E, C and obesity separately or together. In these studies, dietary intake of antioxidants or their serum levels or both have been investigated. In some studies, dietary intake of antioxidants predicted their serum levels, but in some studies, despite dietary intake of antioxidants, their serum levels were low, which suggests that serum levels of antioxidants may depend on various factors. In each article, a different hypothesis is addressed.

Strauss et al. reported that serum levels of α-tocopherol and β-carotene were significantly lower in obese children compared with the control group (P<0.001). It is hypothesized that the breakdown of α-tocopherol from adipose tissue in obese children is limited, leading to reduced access to other organs and thus its reduced serum levels [25]. Gillis et al. analyzed the diets of 156 obese children and 90 non-obese controls aged 4-17 years. The results showed that inadequate intake of vitamins E, A, magnesium, and zinc did not differ significantly between the two groups; however, in obese children, this inadequate intake was higher, indicating that all children should receive adequate vitamins as they grow [31].

Obese children may have inadequate food intake due to low intake of vitamins A, E, and C but may not have

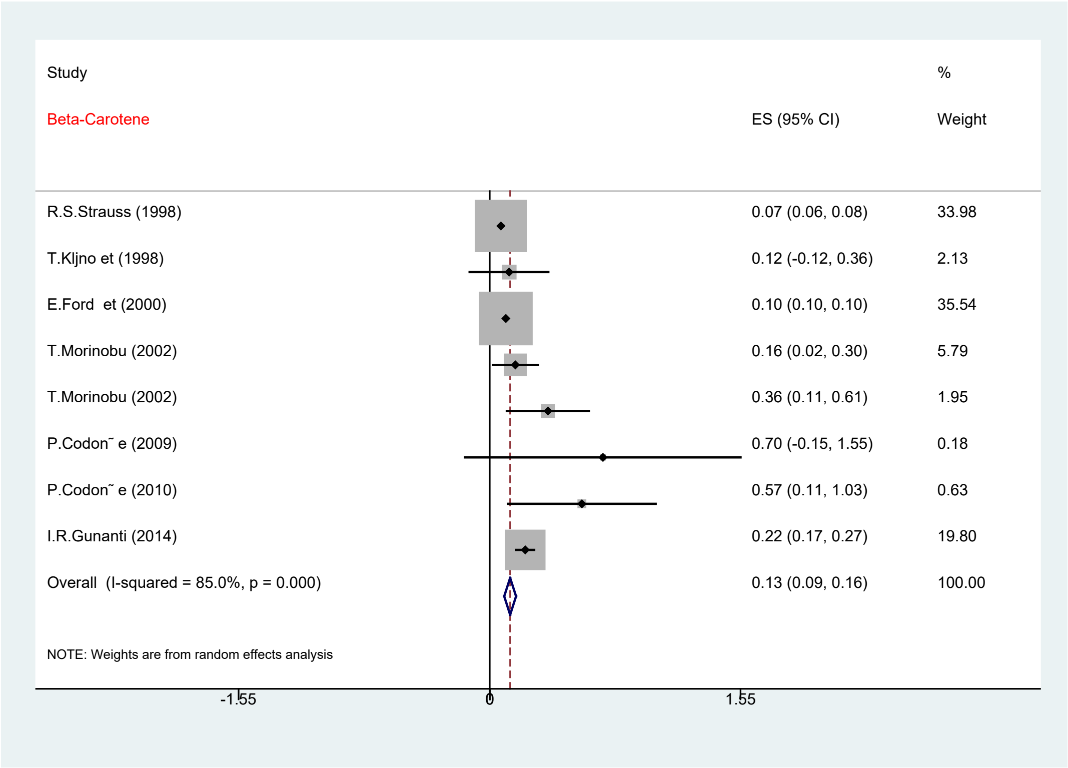

Figure 2. Association of β-carotene with obesity (weights are from random effect analysis)

Journal of Pediatrics Review

Table 1. General characteristics of studies examining the association between antioxidant status and obesity

ID	Authors	Year of Publication	Type of Study	Sample Size	Age Group, y	Gender (F/M)	Outcome	Antioxidant	Adjusted Co-variates	Results
1	Hongo et al. Japan [21]	1992	Cross- sectional	66	7-11	F/M	Mean ± SD of BMI	Intake zinc and zinc concentration	Sex and age	Serum zinc concentration and daily zinc intake were not significantly correlated with weight.
2	Marotta et al. Naples [22]	1995	Case-control	48	5-15	F/M	Mean ± SD of obesity and BMI	Zinc content in cell subsets of lymphomonocytes (LMs) and polymorphonuclear cells (PMNc), in plasma and erythrocytes	Sex and age	The mean level of LMs zinc content was significantly lower in obese children than in controls. The zinc content of PMNc, plasma, and erythrocytes were not significantly different.
3	Yakinci et al. Turkey [23]	1997	Case-control	82	7-11	F/M	Mean ± SD of obesity and BMI	Serum zinc, copper, magnesium	Sex and age	Serum zinc and copper levels of obese children were significantly higher than those of the control group (P<0.01). serum magnesium levels were significantly lower in obese children than in the healthy children (P<0.01).
4	Perrone et al. Italy [24]	1998	Case-control	307	7-13	F/M	Mean ± SD of obesity and BMI	Zinc, copper Serum	Sex and age	Serum zinc levels and copper were lower in obese than in the normal group.
5	Strauss et al. [25]	1999	Cross-sectional	6139	6-19	F/M	Mean ± SD of obesity and BMI	Serum levels of α-tocopherol and β-carotene	Serum triglyceride and cholesterol	Serum levels of β-carotene and α-tocopherol were significantly lower in obese children than normal group (P<0.001).
6	Kljno et al. Japan [19]	1998	Case-control	24	8-14	F	Mean ± SD of obesity and BMI	β-carotene and a-tocopherol serum level	Sex	Plasma β-carotene level and a-tocopherol were significantly lower in obese children than in normal control (P<0.05)
7	Ford et al. The USA [26]	2002	Cross-sectional	4231	6-16	F/M	Mean ± SD of obesity, BMI, and overweight	Serum concentrations of α-carotene, β-carotene	Age, sex, race, or ethnicity	BMI was inversely associated with all concentrations of all carotenoids (P ≤ 0.001) except lycopene. Significant positive associations between fruit and vegetable intake and the concentrations of all carotenoids except lycopene.

ID	Authors	Year of Publication	Type of Study	Sample Size	Age Group, y	Gender (F/M)	Outcome	Antioxidant	Adjusted Co-variates	Results
8	Gibson et al. New Zealand [27]	2000	Cross-sectional	453	11	F/M	Mean ± SD of obesity and BMI	Hair zinc concentration serum zinc	Sex and age	Low hair zinc values were associated with a higher BMI.
9	Morinobu et al. Osaka Japan [28]	2002	Cross-sectional	93	6-15	F/M	Mean ± SD of obesity and BMI	Β-carotene, α-tocopherol, retinol	Age, height, total lipids	The plasma β-carotene concentration and the ratio of β-carotene to plasma total lipids (β-carotene/t. lipids ratio) were significantly lower in the obese children than in the control group, the α-tocopherol level, and α-tocopherol/t. Lipids ratios were not significantly different. The plasma retinol concentration was not different between the two groups.
10	Molnár et al. [29]	2004	Cross-sectional	48	11-17	F/M	Mean ± SD of obesity and BMI	α-Tocopherol, and β-carotene levels	Sex and age	Plasma α-tocopherol and β-carotene levels were significantly (P<0.05) lower in obese children.
11	Erdeve et al. Turkey [30]	2004	Case-control	59	7-12	F/M	Mean ± SD of obesity and BMI	Cu/Zn-SOD (superoxide dismutase)	Sex and age	Cu/Zn-SOD was significantly higher in the obese group (P<0.05).
12	Gillis et al. [31]	2005	Cross-sectional	246	4-17	F/M	Mean ± SD of obesity and BMI	Intake of food vitamin A, E, zinc, mg	Sex and age	A similar prevalence of inadequate intake of vitamin E93% magnesium 29% was in non-obese children compared with normal children.
13	Huerta et al. America [32]	2005	Cross control	48	8-17	F/M	Mean ± SD of obesity and BMI	Dietary magnesium intake, serum magnesium,	Sex and age	Serum and dietary magnesium intake were significantly lower in obese children (P=0.009, P=0.003)
14	Sarni et al. Brazil [33]	2005	Case-control	46	4-9	F/M	Mean ± SD of obesity and BMI	serum retinol and total carotene concentration	Sex and age	Serum retinol was not significantly lower in obese children (P=0.38). Low carotenoid levels were found in the obese concerning the non-obese (P=0.0054)

ID	Authors	Year of Publication	Type of Study	Sample Size	Age Group, y	Gender (F/M)	Outcome	Antioxidant	Adjusted Co-variates	Results
15	Aeberli et al. [34]	2006	Cross-sectional	79	6-14	F/M	Mean ± SD of obesity, BMI, overweight, and waist-hip ratio	vitamins E and C and β-carotene intake	Sex and age	Intake of vitamins E, C, and β-carotene were not significant differences between normal-weight and overweight and obese children (P>0.05).
16	Shin et al. Korean [35]	2006	Cross-sectional	103	10-11	F/M	Mean ± SD of obesity, BMI, and waist circumference	Plasma α-tocopherol β-carotene	Ideal body weight, waist circumference, gender, blood lipids, and leptin levels	α-Tocopherol and β-carotene are lower in the highest homeostasis model assessment of insulin resistance (HOMA-IR) (P=0.004, P=0.008)
17	Lima et al. Brazil [36]	2006	Case-control	66	6-16	F/M	Mean ± SD of obesity, BMI, and waist circumference	Plasma copper concentration	Sex and age	The plasma copper concentrations were significantly higher in the obese group than in the control group (P=0.0006).
18	López-Sobaler et al. Spain [37]	2007	Cross-sectional	181	10-12	F/M	Mean ± SD of obesity, BMI, and overweight	α-Tocopherol, selenium, zinc, β-carotenes, vitamin E, Vitamin A level and intake	Sex and age	Intakes of vitamin E, selenium, and zinc were higher in overweight. Intakes of vitamin A or beta carotenes were similar. α-Tocopherol and selenium levels are lower in obese children.
19	Weisstaub et al. [15]	2007	Cross-sectional	72	1-3	F/M	Mean ± SD of obesity, BMI, and waist circumference	Zinc plasma and intake	Sex and age	Plasma zinc level was not significantly associated with weight or waist circumference (P<0.001).
20	de Souza Valente da Silva et al. Brazil [38]	2007	Case-control	471	7-17	F/M	Mean ± SD of obesity, BMI, and overweight	The serum concentration of retinol and carotenoids	Sex and age	The average carotenoids were significantly lower in overweight (P=0.001)—no significant difference in the average of retinol between overweight and non-overweight (P=0.0304).
21	Linardakis et al. Greece [39]	2008	Cross-sectional	1209	3-17	F/M	Mean ± SD of obesity, BMI, and waist circumference	Diet quality mg vitamin A E C	Sex and age	Increasing BMI and waist/height ratio were strongly associated with poor diet quality.

ID	Authors	Year of Publication	Type of Study	Sample Size	Age Group, y	Gender (F/M)	Outcome	Antioxidant	Adjusted Co-variates	Results
22	Codoñer-Franch et al. Spain [40]	2010	Cross-sectional	58	8-13	F/M	Mean ± SD of obesity and BMI	Levels and intake of Vitamin A, C, and E, α- tocopherol, β-carotene	Sex and age	Levels of β-carotene were similar in control children and T1D (Type 1 diabetes) patients but significantly increased in obese individuals.
23	Bouglé et al. Paris [41]	2009	Case-control	242	2-17	F/M	Mean ± SD of obesity and BMI	Zinc and Selenium plasma	Sex and age	Plasma zinc or Selenium was not associated with increasing BMI.
24	Puchau et al. Spain [20]	2010	Cross-sectional	369	6-18	F/M	Mean ± SD of obesity and BMI	Vitamin A, C, E magnesium intake	Sex and age	Dietary total antioxidant capacity (TAC) showed positive associations with magnesium, vitamins A, C, and E intake. BMI was inversely associated with dietary TAC in the obese group.
25	Tascilar et al. Turkey [42]	2011	Case-control	67	8-12	F/M	Mean ± SD of obesity and BMI	Serum levels of selenium, zinc, vanadium, molybdenum, iron, copper, beryllium, boron, chromium, manganese, cobalt, silver, barium, aluminum, nickel, cadmium, mercury, and lead	Sex and age	Trace elements levels were not different between the case and control groups (P<0.001).
26	Codoñer-Franch et al. Spain [43]	2010	Cross-sectional	68	6-14	F/M	Mean ± SD of obesity BMI, and overweight	Serum α-tocopherol and β-carotene	Sex and age	There were no differences in serum α-tocopherol and β-carotene levels between groups.
27	Çelik et al. Turkey [44]	2011	Case-control	203	8-14	F/M	Mean ± SD of obesity and BMI	Serum magnesium	Sex and age	Serum levels of magnesium were significantly lower in the (insulin resistance) IR (+) obese group than controls (P=0.014). A positive correlation between serum magnesium levels and body mass index-standard deviation score (BMI-SDS) (r=–0.28, P=0.03) in the IR (–) obese group was found.
28	Jose et al. [45]	2012	Cross-sectional	108	4-14	F/M	Mean ± SD of obesity, BMI, waist circumference, and overweight	Serum magnesium and intake	Sex and age	Serum magnesium levels were inversely correlated with body mass index, waist circumference. The serum magnesium levels were significantly lower in overweight compared to the normal weight group (P<0.001), while the dietary intake of magnesium was higher in the overweight group compared to normal weight (P=0.005).

ID	Authors	Year of Publication	Type of Study	Sample Size	Age Group, y	Gender (F/M)	Outcome	Antioxidant	Adjusted Co-variates	Results
29	Ortega et al. Madrid Spain [46]	2012	Cross-sectional	573	8-13	F/M	Mean ± SD of obesity, BMI, overweight, and waist-hip ratio	Serum selenium and intake	Sex and age	The intake and serum selenium were lower in obese children than normal group (P<0.001). A negative relationship was seen between serum selenium and all the anthropometric indices (P<0.05).
30	Błażewicz et al. Lublin [47]	2013	Case-control	81	6-17	F/M	Mean ± SD of obesity and BMI	Cu, Zn, in whole blood, plasma, and urine	Sex and age	Negative correlations between BMI and Zn, Cu in blood, plasma, and urine were found.
31	García et al. Mexican [48]	2013	Cross-sectional	197	6-10.5	F/M	Mean ± SD of obesity, BMI, and waist-to-height ratio (WHR)	Zinc, vitamins A, C, and E serum and intake	Sex and age	Vitamin C and vitamin E: lipids were negatively associated with BMI, waist-to-height ratio (WHR), and body and abdominal fat (P<0.05). Vitamin A concentration was positively associated with BMI, BMI-for-age, waist circumference, waist/height ratio, and abdominal fat (P<0.05). Low zinc concentrations were associated with higher insulin concentrations (P<0.05).
32	Niranjan et al. India [49]	2014	Cross-sectional	122	8-11	F/M	Mean ± SD of obesity, BMI, waist-to-height ratio (WHR), and waist circumference (WC)	Serum magnesium levels	Sex and age	Serum magnesium levels were low in obese children (P=0.001).
33	Gunanti et al. Mexican American [50]	2014	Cross-sectional	1154	8-15	F/M	Mean ± SD of obesity, BMI, and overweight	Carotenoids, retinol, vitamin E	Sex and age	Serum concentrations of α-carotene (P<0.05), trans β-carotene (P<0.01), cis β-carotene (P<0.01), retinol (P<0.01) were inversely associated with BMI.
34	Teske et al. Brazil [51]	2014	Cross-sectional	61	8-12	F/M	Mean ± SD of obesity and BMI	Plasma concentrations of retinol	Sex and age	Plasma retinol levels are inversely related to glucose tolerance and obesity.

ID	Authors	Year of Publication	Type of Study	Sample Size	Age Group, y	Gender (F/M)	Outcome	Antioxidant	Adjusted Co-variates	Results
35	Azab et al. Egypt [52]	2014	Case-control	160	6-9	F/M	Mean ± SD of obesity, BMI, and waist-to-height ratio (WHR), and waist circumference (WC)	Zinc copper selenium Serum	Sex and age	Serum Zn, Se levels were lower in obese children. Cu level was significantly higher in the obese group (P<0.01).
36	Cayir et al. Turkey [53]	2014	Case-control	105	6-17	F/M	Mean ± SD of obesity and BMI	Serum zinc (Zn), copper (Cu), and selenium (Se)	Sex and age	Serum Se and Cu were higher in the obese group (P<0.05, r=0.31). Serum zinc was low in the obese group (P<0.05).
37	Zaakouk et al. Egypt [54]	2016	Cross-sectional	100	2-16	F/M	Mean ± SD of obesity and BMI	Serum magnesium	Sex and age	Serum magnesium was significantly low in obese children than in the control group (P<0.001).
38	Błażewicz et al. Lublin [55]	2015	Cross-sectional	80	6-17	F/M	Mean ± SD of obesity and BMI	Serum and urinary selenium	Sex and age	Obese children have lower selenium content in serum and urine (P=0.001; OR 0.74, 95%CI: 0.62-0.88).
39	Habib et al. Egypt [56]	2015	Case-control	112	5-17	F/M	Mean ± SD of obesity and BMI	Serum zinc and Cu	Sex and age	Zinc serum was lower, and copper was higher in obese children than in the control group (P<0.001).
40	Ul Hassan et al. Peshawar [57]	2017	Case-control	140	2-14	F/M	Mean ± SD of obesity, BMI, and overweight	Serum Magnesium	Sex and age	The serum magnesium levels were significantly lower in the overweight and obese group than in the control group (P<0.001).
41	Fan, et al. United State [58]	2017	Cross-sectional	5404	6-19	F/M	Mean ± SD of obesity BMI, and overweight	Copper zinc selenium serum	Sex and age	In obesity, copper concentrations in blood were higher. Selenium and zinc levels were inversely associated with BMI.

ID	Authors	Year of Publication	Type of Study	Sample Size	Age Group, y	Gender (F/M)	Outcome	Antioxidant	Adjusted Co-variates	Results
42	Xu et al. China [59]	2018	Cross-sectional	127	7-13	F/M	Mean ± SD of obesity and BMI	Fingernail selenium	Sex and age	Selenium level is higher in the normal group but without statistical significance (P=0.79).
43	Gonoodi et al. Iran [60]	2018	Cross-sectional	408	12-18	F	Mean ± SD of obesity and BMI	Dietary and serum concentrations of zinc, copper	Sex and age	There was a weak correlation between serum and dietary zinc intake (r=0.117, P=0.018). The correlation between serum and dietary copper approached significance (r=−0.094, P=0.056). A significant relationship was not seen between serum zinc and copper or their dietary intake with obesity.
44	Gaber et al. Egypt [61]	2019	Case-control	60	2-14	F/M	Mean ± SD of obesity and BMI	Serum zinc, magnesium, and copper	Sex and age	In obesity status, serum copper levels increase, and serum levels of zinc and magnesium reduce (P<0.001).
45	Chen et al. China [62]	2021	Cross- sectional	443	6-9	F/M	Mean ± SD of obesity and BMI	Plasma copper, magnesium	Sex and age	Higher plasma Cu concentration was positively correlated with BMI (P<0.01).
46	Vivek et al. India [63]	2020	Case-control	173	6-16	F/M	Mean ± SD of obesity, BMI, and waist circumference	Serum copper and zinc	Sex and age	The serum and whole blood concentrations of zinc and copper were significantly lower in children with obesity than controls (P=0.0001).

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a poor diet due to overeating. Therefore, controversial results have been obtained regarding the relationship between serum levels of antioxidants and intake.

Aeberli et al. examined the food intake of the last 48 hours of 3 groups of normal, overweight, and obese children. They found that the intake of vitamins C, E, and carotene in the three groups was not significantly differ-

Table 2. Antioxidants level and obesity, sensitivity analysis

Authors	β-Carotene	Vitamin E	Zinc
Exclusion of the Strauss study (1998)	0.19 (0.1/0.28) I^2=79.3%	-	-
Exclusion of the Gunanti et al. study (2014)	-	0.04 (-0.08/0.17) I^2=0.0%	-
Exclusion of the Gunanti et al. study (2014)	-	-	16.7 (10.4/23.6) I^2=84.4%

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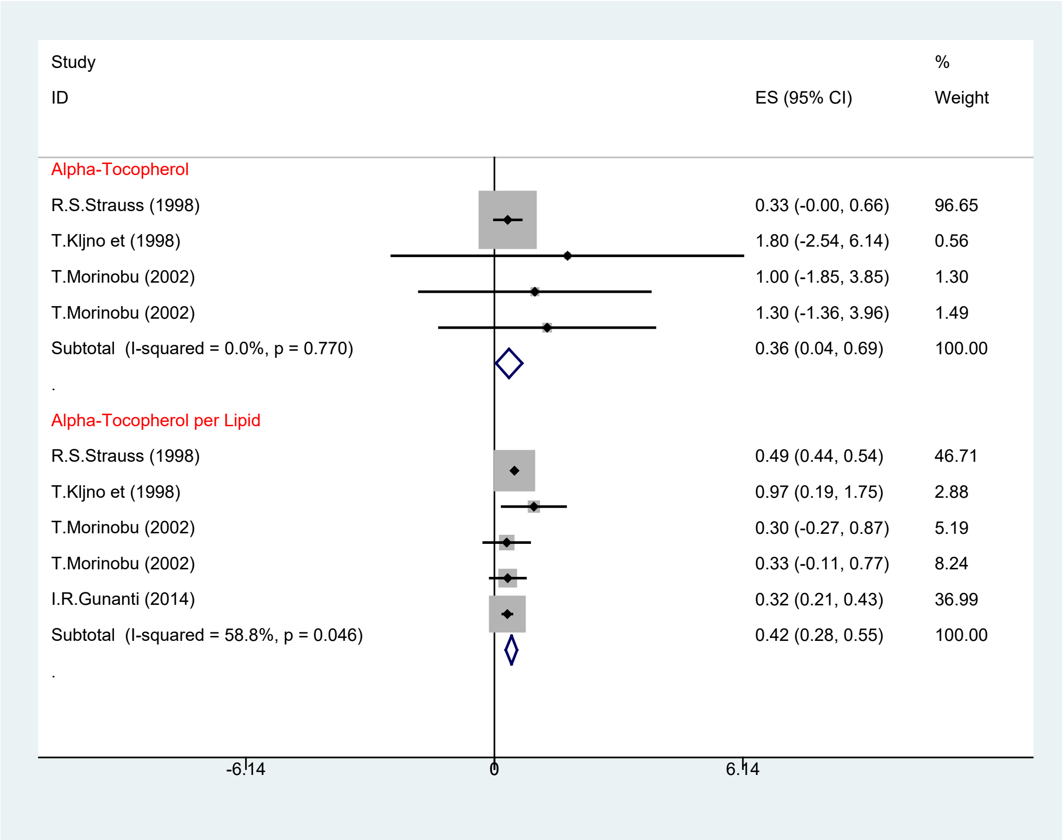

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Figure 3. Association of α-tocopherol with obesity (weights are from fixed [α-tocopherol] and random effect [α-tocopherol per lipid] analysis)

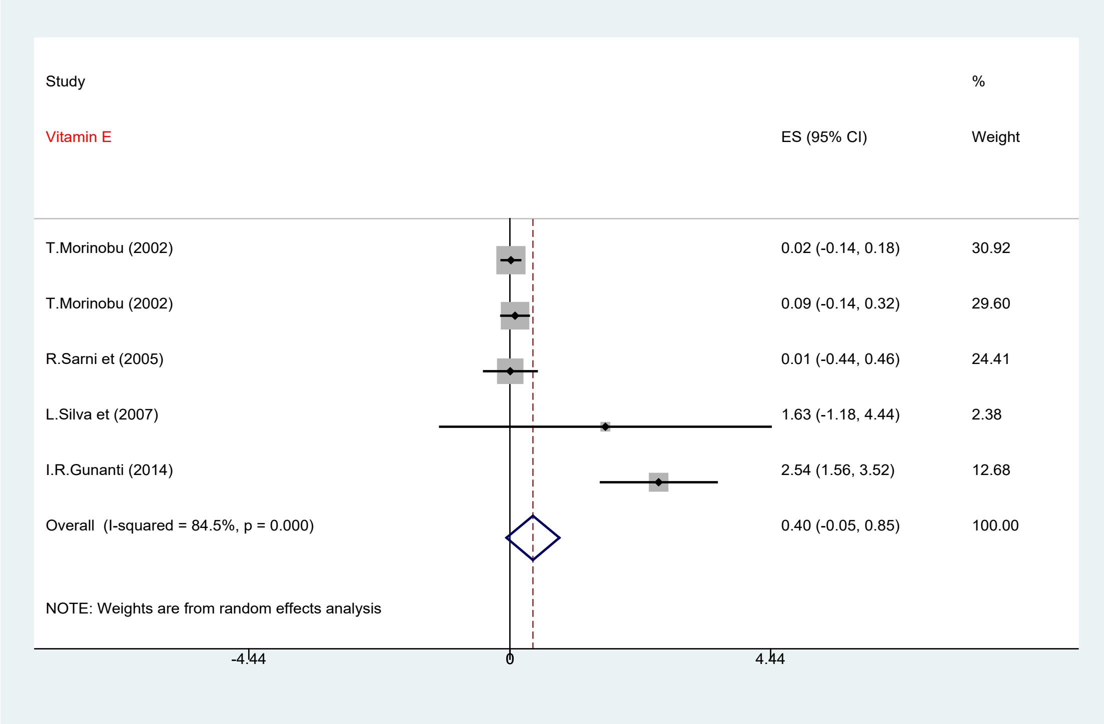

Figure 4. Association of vitamin E with obesity (weights are from random effect analysis)

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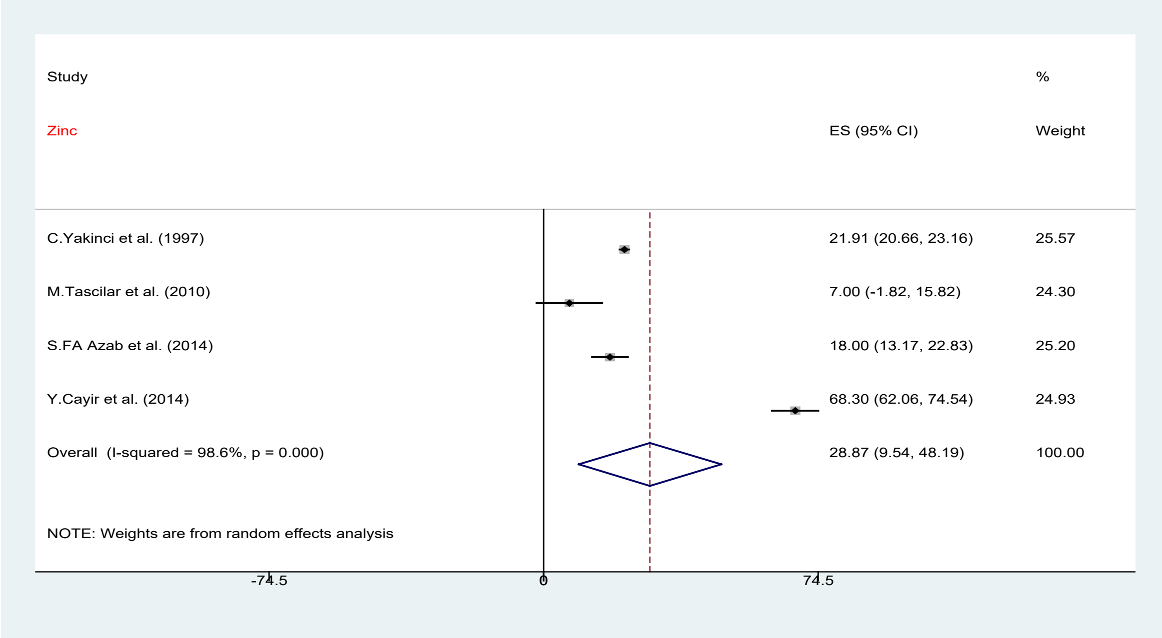

Figure 5. Association of zinc with obesity (weights are from random effect analysis) *Journal of Pediatrics Review*

ent, and only the amount of protein and meat intake was different between the two groups. The researchers proposed that mentioning food items in the food questionnaire in children may have some shortcomings and is not effective as adults [34]. Lopez-Sobaler et al. studied the 3-day dietary intake of 10-12 years old children. They found that the intake of vitamin E, selenium, and zinc is higher in obese and overweight children, but vitamin A or β-carotene intake did not differ between obese and control groups. Serum levels of α-tocopherol and selenium were lower in obese children [37]. Codone R-Franch et al. compared the dietary intake of

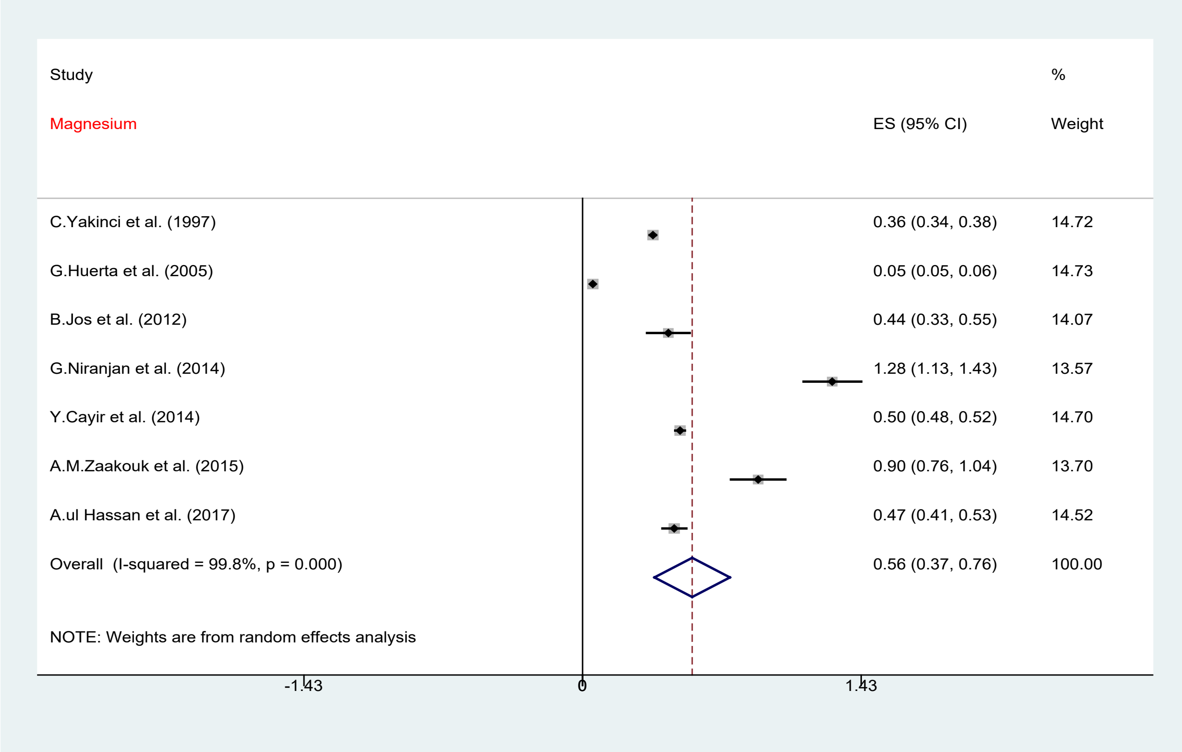

Figure 6. Association of magnesium with obesity (weights are from random effect analysis) *Journal of Pediatrics Review*

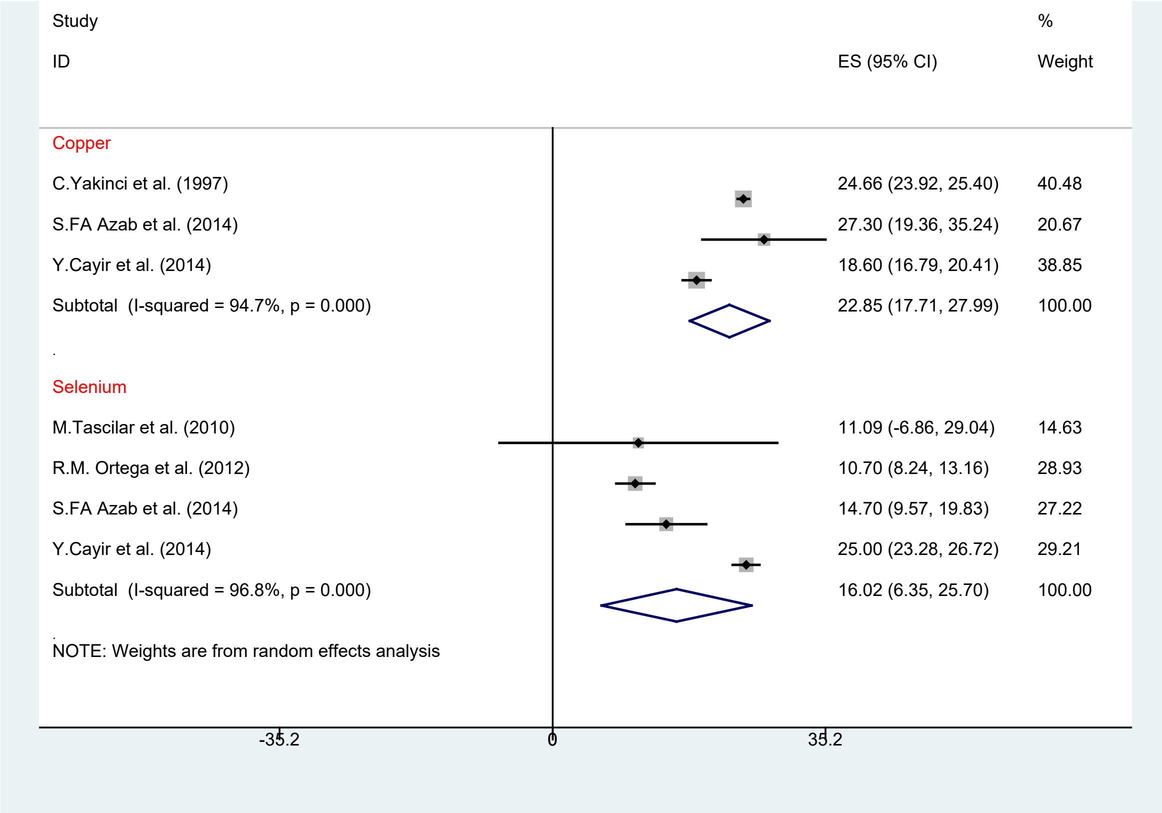

Figure 7. Association of copper and selenium with obesity (weights are from random effect analysis) *Journal of Pediatrics Review*

two groups of children with Type 1 diabetes and obese children without disease with the control group. They showed that the intake of vitamins A, E, C, and fruits and vegetables was not different, and contrary to expectations, serum β-carotene levels were similar in diabetic children and the control group, but it was higher in the obese children. This finding may be because the obese children in this study had a normal diet [40].

Food questionnaires and their items and also the duration of recall varied in different articles, which makes it difficult to compare their results and draw conclusions.

Puchau et al. showed that dietary Total Antioxidant Capacity (TAC) is directly related to vitamins A.E, C and is inversely related to BMI [20]. Linardakis et al. reported that the group that received a nutritious diet of vitamins A, E, C, and minerals had lower metabolic syndrome indices such as BMI and waist/height ratio [39]. Ford et al. conducted a study on participants in the Third National Health and Nutrition Examination Survey (NHANES III). They found that all carotenoids from vitamin A compounds except lycopene were inversely related to BMI (P<0.001). There was also a direct relationship between dietary intake of fruits and vegetables and carotenoids [26].

In some reviewed articles, as expected, the levels of β-carotene and α-tocopherol and other components of vitamins A and E are inversely related to obesity and anthropometric indices, but in some articles, no significant relationship was found. In our study, we found no significant relationship between vitamin E with obesity, but α-tocopherol is a significant component of vitamin E and is significantly lower in obese children.

Because obese individuals are prone to hyperlipidemia and insulin resistance, Kljno et al. measured plasma levels of β-carotene and α-tocopherol in plasma and LDL. They wanted to assess antioxidant intake capacity and showed that the levels of β-carotene and α-tocopherol are lower in plasma and LDL of obese girls, and this low amount can make obese girls more prone to future atherosclerotic events [19]. A study by Gunanti et al. on children aged 8-15 years showed that plasma concentrations of α-tocopherol (β=–0.88, P<0.05), trans β-carotene (β=–2.21, P<0.01), cis β-carotene (β=–2.10, P<0.01), and α-tocopherol (β=–3.66, P<0.01) were inversely related to BMI [50]. Molnar et al. found that plasma β-carotene and α-tocopherol were significantly lower in obese children (P<0.005) [29]. Shin et al. showed a significant inverse relationship between HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) and β-carotene (r=-0.233, $P<0.05$) and α-tocopherol (r=-0.370, $P<0.0001$) [35].

Different hypotheses have been suggested for the association of vitamin A and E with obesity. There is a hypothesis that in obesity, antioxidant levels rise due to an increase in the levels of oxidative stress. In other words, the defense system in the body is activated against antioxidants. Contrary to expectations, it leads to increase levels of antioxidants in obesity [64].

Codoñer-Franch et al. reported that β-carotene and α-tocopherol were not significantly associated with obesity. Because these two vitamins are fat-soluble, obese children in this study had normal lipid profiles to justify the result [43]. García et al. studied 197 children aged 6-10.5 years and found that vitamin A was positively correlated with BMI and Waist to Height Ratio (WHR) ($P<0.05$). Vitamins E and C were inversely related to BMI waist/height ratio ($P<0.05$). This finding may result from the direct relation of vitamin A, which is a fat-soluble vitamin, to the storage of adipose tissue [48]. Because vitamins A and E are fat-soluble and obese children have high-fat tissues, these vitamins can increase with obesity [65].

Another component of vitamin A is retinol, which has an antioxidant role [66], but different results are published in various articles on obesity. Mobinobu et al. showed that levels of plasma β-carotene were significantly lower in obese children compared with control groups. However, no significant differences were found in plasma levels of α-tocopherol and retinol, which may result from closer relation of β-carotene levels to adipose tissue than retinol [28]. Sarni et al. reported that serum carotene levels were significantly lower in obese children compared with the control group but did not differ significantly in retinol levels, although they were lower in obese children [33]. de Souza Valente da Silva et al. argued that overweight children had lower carotenoid serum ($P<0.001$), but there was no significant difference between BMI and retinol ($P=0.304$). This fact may indicate that retinol plays a lower role in antioxidant activity [38]. Teske et al. showed that plasma retinol levels were inversely related to obesity and glucose tolerance (fasting blood sugar and 2 hours later). In other words, it measured the association of retinol with metabolic syndrome [51]. However, few studies have linked retinol to obesity. Future studies may further consider the role of retinol in antioxidants activities.

Regarding the relationship between childhood obesity and variables of copper and selenium, zinc, magnesium status, we found 29 articles on the relationship of zinc, copper, magnesium, and selenium to obesity separately or in combinations. Some articles revealed an inverse relationship between obesity and the levels of these elements, which might be because of the antioxidant properties of these elements that can be reduced in obesity.

Various studies have been performed on the role of zinc in obesity, and the association between zinc and leptin has been considered. Leptin is a hormone produced by adipose tissue. In zinc deficiency, a decrease in zinc is associated with a decrease in leptin. Decreased leptin leads to increased appetite and obesity [15].

Magnesium, copper, selenium are essential trace elements. They play an essential role in the growth and regulation of various enzymes in metabolic processes [67]. Some studies have shown that obesity is associated with reduced trace elements.

Vivek et al. showed that zinc and copper levels are significantly lower in obesity among Indian children aged 6-16 years [63]. In a study by Perrone et al. serum zinc and copper levels were lower in obese, overweight children [24]. Błażewicz et al. reported that levels of zinc and copper of plasma are inversely related to BMI [47]. Erdeve et al. reported that Cu/Zn-SOD (superoxide dismutase) enzymes in obese children are significantly higher, indicating that the balance is changed in favor of the oxidative status in obesity ($P<0.05$) [30].

In some studies, the levels of antioxidants were searched in other body components like hair, nail, and urine. Gibson et al. showed that obese children with higher BMIs in New Zealand had lower hair zinc levels [27]. Xu et al. showed that nail selenium levels are lower in obese people, although there is no significant difference [59]. Błażewicz et al. found that obese people had lower serum and urine selenium [55].

In the Huerta et al. study, serum magnesium levels, as well as magnesium intake from food, were significantly lower in obese children ($P=0.009$) [32]. Zaakouk et al. concluded that serum magnesium levels were significantly lower in obese people (r=-0.8, $P<0.001$) [54]. Niranjan et al. also showed that obese people had lower magnesium levels [49]. Ul Hassan et al. reported that serum magnesium levels were significantly lower in obese and overweight individuals ($P<0.001$) [57]. Ortega et al. showed that dietary selenium intake was directly related to selenium levels and was lower in obese children and inversely related to BMI. This finding indicates that obese children had worse antioxidant status than other children [46].

However, in several reviewed articles, different results were obtained. They reported that the levels of zinc, copper, magnesium, and selenium are directly related to obesity, or at least there is no significant difference. Gonoodi et al. examined 408 Iranian girls aged 12-18 years, found that serum levels and intake of zinc and copper were not associated with obesity [60]. Studies show a correlation between serum zinc level and appetite which can lead to obesity. In other words, there is a direct link between zinc and increased appetite [68]. Hongo et al. conducted a study of 66 boys and girls in Tokyo, Japan. They reported that dietary zinc intake in the 3-day diet questionnaire was not related to serum zinc concentration. In other words, zinc food intake was not a predictor of serum level, and zinc status was not related to weight and height ($P<0.01$). That is, this study, which showed zinc deficiency in Japanese children, hypothesized that borderline serum deficiency could not affect children's height and BMI [21].

In the study of Weisstaub et al. on 18- to 36-month-old children of Chile, no relationship was found between zinc of plasma, height, and waist circumference, which may be due to borderline zinc deficiency [15]. A study by Yakinci et al. on children aged 7 to 11 years in Turkey showed that zinc and copper levels in obese children were significantly higher than in control groups ($P<0.01$), which may be due to the high appetite of obese children. Dietary intake of zinc and copper was associated with serum levels, but magnesium levels were lower in obese children ($P<0.01$) [23].

Zinc is involved in the cellular defense of lymphocytes. In this regard, Marotta et al. examined two groups of obese children and control groups of 5 to 17 years old in Nepal and found that the level of zinc content in lymphocytes was lower in obese children, but there was a significant difference in plasma zinc and erythrocytes and polymorphonuclear. According to the hypothesis of this article, zinc deficiency in lymphocytes can be an indicator of zinc deficiency in obese children [22].

Bouglé et al. study did not find any significant relationship between zinc and selenium levels and BMI. In other words, this study showed that obese children are not always deficient in micronutrients [41]. Tascilar et al. who studied the serum levels of various trace elements in obese children, concluded that serum zinc, copper, and selenium were lower in obese people but did not differ significantly from the control group. This finding may be due to the diet of obese children, which is not nutritious and in nutrients such as trace elements, and obese children are deficient in these substances [42].

Çelik et al. reported that serum magnesium levels in obese people with insulin resistance are very low, but the two obese groups without insulin resistance and the control group are not different. On the other hand, serum magnesium levels are directly related to BMI. The researchers may believe that this finding is due to the study's limitations in measuring total magnesium, including intracellular magnesium, but in this study, serum magnesium was measured [44]. Jose et al. concluded that although dietary magnesium intake was higher in obese Indian children, serum magnesium levels were lower in obese children and were inversely related to BMI due to decreased reabsorption or increased urinary magnesium excretion. Magnesium excretion increase has been previously reported in obese adults and hypertension and Type 2 diabetes [45]. However, several studies have shown that copper levels are directly related to obesity. One of the hypotheses is that copper levels rise in obesity due to the reduction of zinc and the antagonist properties of zinc and copper in the body.

Chen et al. concluded that levels of plasma copper are directly related to BMI [62]. Gaber et al. found that obesity is associated with increased copper levels and decrease zinc and magnesium levels [61]. In the study of Lima et al. plasma copper levels in obese children were higher than that in the control group, but the copper concentration of erythrocytes did not differ [36]. In the study of Azab et al. serum levels of zinc and selenium are lower in obese people, but copper levels were higher in obese people due to the antagonist effect of zinc and copper in the body [52]. In the study by Habib et al. plasma zinc levels were lower in obese Egyptian children ($P<0.001$), but plasma copper levels were significantly higher in obese individuals, possibly due to zinc and copper interactions. In other words, dietary zinc intake may be associated with some degree of copper deficiency [56].

In the study by Fan et al. zinc and selenium levels were inversely related to the BMI of American children, but serum copper levels were directly related to BMI, which could still be due to zinc-copper interactions [58]. Cayir et al. showed that selenium and copper are higher in obese people, but zinc levels are lower, again due to the antagonist effects of zinc and copper. The study researchers suggested that this is due to the specific eating habits of the participants in this article, which is not included in this study. On the other hand, selenium in obese people increases due to its antioxidant defense mechanism against oxidative stress and is reduced if the balance gets upset in favor of the oxidative status [53].

Articles in this study have case-control or cross-sectional designs. The absence of a cohort study is one of the limitations of this study. Food questionnaire collection for evaluation of intake antioxidants was different in the studies. The definition of obesity and overweight, measurement parameters, how to choose the control and case group, and size of them were different in studies. The main strength in this study is the consideration of the most antioxidants, while in the previous review studies, only one or two antioxidants had been discussed. This study examined the population of children. While few review studies have researched individual children.

4. Conclusion

We showed that antioxidants decrease obesity and are inversely related to each other by reviewing existing studies. Because of the increasing prevalence of obesity in children and its complications, interventional and cohort studies are suggested in the future. Future studies based on cohort will show cause and effect relationship between obesity and antioxidants. That relationship can be used to prevent or plan intervention strategies to deal with obese children.

Ethical Considerations

Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

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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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